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# Premature Myocardial Infarction: Are We Looking Deep Enough to Understand and Manage It?

## Prematür Miyokard Enfarktüsü: Anlamak ve Yönetmek İçin Yeterince Derinlemesine İnceliyor muyuz?

**ABSTRACT**

Premature myocardial infarction (MI) is no longer an uncommon presentation but a growing clinical and public health concern, particularly in Türkiye, where coronary events occur at younger ages than in most European countries. Rising cardiometabolic risk, smoking, inherited lipid disorders, substance use, and psychosocial stress contribute to this burden, while conventional risk scores often fail to identify young individuals at risk. This Young MI focus issue of the Archives of the Turkish Society of Cardiology attracted numerous submissions, reflecting how frequently clinicians now encounter young patients with MI. These submissions also revealed recurring gaps in practice. Key lipid parameters, including lipoprotein(a) and non-HDL cholesterol, were often not assessed; family screening was rarely considered; and non-atherosclerotic causes, substance and energy drink use, and long-term outcomes received limited attention. This editorial discusses the burden and drivers of premature MI, summarizes the contributions to this issue, and highlights areas for future research. Every young patient with MI deserves a complete lipid assessment, a careful search for the underlying cause, questioning about substance use, and early cascade screening of first-degree relatives. Treating each young MI as a question to be answered, not only as an event to be managed, may help prevent further events in patients and their families.

**Keywords:** Cascade screening, LDL-cholesterol, premature myocardial infarction, young adults

**EDITORIAL**
EDİTORYAL

Some research endeavors begin with a scientific question; others are born from deeply personal experiences. This project began with a loss that profoundly shaped both my life and my professional journey. While preparing for the national medical specialty examination (TUS), long before I had chosen cardiology as my specialty, I lost my brother unexpectedly in his sleep at the age of 38. His sudden death left us with unanswered questions. We never learned what had caused it, nor was our family offered an evaluation for potential inherited cardiovascular risks. Over time, those unanswered questions became a driving force behind my decision to pursue cardiology and my determination to better understand cardiovascular events occurring at a young age. What began as a personal search for answers ultimately evolved into the young myocardial infarction (MI) project and, eventually, this special issue dedicated to understanding and addressing MI in young adults.

I share this personal experience because it reflects a reality familiar to every clinician who has cared for a young patient with acute coronary syndrome (ACS): when myocardial infarction (MI) strikes in the third or fourth decade of life, or even earlier, its consequences extend far beyond the coronary arteries. Families may lose a parent, a sibling, or a child; society loses decades of human potential and productivity; and those who survive face a lifetime of cardiovascular risk and secondary prevention, often with limited age-specific evidence to guide their long-term care.

### What Is the Burden of MI in Young Adults?

Premature MI is no longer an uncommon presentation but a growing clinical and public health concern. In the Atherosclerosis Risk in Communities (ARIC) surveillance study, the proportion of MI hospitalizations among patients aged 35–54 years increased from 27% in 1995–1999 to 32% in 2010–2014, with the steepest increase observed among young women.[1] The burden appears to be even greater in Türkiye. In

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the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) III survey, 20% of Turkish patients with coronary artery disease were younger than 50 years, compared with 12.7% across Europe.[2] In EUROASPIRE IV, the median age at the index event in Türkiye was 58.8 years, compared with a European mean of 62.5 years, with 19.3% of patients younger than 50 years.[3] In the nationwide Turkish Myocardial Infarction (TURKMI) registry, 235 of 1,930 patients (12.2%) experienced MI at a young age (younger than 45 years in men and 55 years in women), representing approximately one in eight acute MI cases.[4] These findings highlight a burden that can no longer be ignored.

### Is the Incidence of Myocardial Infarction Increasing Among Young Adults?

Although MI rates have declined in older populations, they have plateaued or even increased among younger individuals, attracting attention from clinicians and the public alike. In the Young Myocardial Infarction (YOUNG-MI) study, the proportion of patients aged 40 years or younger increased by approximately 2% annually during the final decade of the study.[5] In the INTERHEART study, the median age at first MI was approximately a decade lower in the Middle East (51 years) than in Western Europe (63 years).[6] Similarly, the mean age was 53.0 years in South Asia, compared with 58.8 years elsewhere.[7] MI in young adults is therefore particularly common and increasingly prevalent in Middle Eastern countries, such as Egypt, and in India, which share many characteristics with Türkiye.

A major contributing factor is a cardiometabolic pandemic that begins earlier in life: obesity, insulin resistance, hypertension, and dyslipidemia now frequently coexist in young adults, and cumulative exposure to these risk factors accelerates vascular aging. The recent REACT study clearly illustrated this phenomenon. Among 16,808 adults aged 18–70 years without known cardiovascular disease in Denmark and Spain, vascular ultrasonography and coronary computed tomography (CT) angiography detected subclinical atherosclerosis in 57.1%, including approximately one in 13 individuals aged 18–29 years and 34.6% of men and 21.3% of women in their 30s, with men showing a 5–10-year lead over women in the development of atherosclerosis. However, Systematic Coronary Risk Evaluation 2 (SCORE2) classified only a small minority of these individuals as being at high risk, particularly among younger adults.[8] Atherosclerosis begins early in life and largely escapes detection by conventional risk estimation methods. Inflammation, infections, increasing smoking rates among young women, recreational drug and stimulant use, and possibly energy drink consumption further contribute to this burden (Table 1, Figure 1). Three studies in this issue describe distinct clinical, inflammatory, lipid, metabolic, and angiographic profiles in younger patients compared with middle-aged and older patients.[9–11]

Several characteristics of the Turkish population further amplify this risk. First, genetic dyslipidemias, such as familial hypercholesterolemia (FH), are common: according to the national health database, the prevalence of probable or definite FH was 0.61% (approximately 1 in 164 individuals) in the overall population, and 4.56% of adults (1 in 22) had low-density lipoprotein (LDL) cholesterol levels above 190 mg/dL.[12] Second, consanguineous marriage, reported among 18.5%

**Table 1.** Main drivers of the rising burden of myocardial infarction in young adults

| Driver | Comment |
|---|---|
| Rising cardiometabolic risk at younger ages | Obesity, insulin resistance, diabetes, and hypertension develop earlier and cluster together, resulting in cumulative exposure and premature vascular aging; in ARIC, the prevalence of hypertension increased from 59% to 73% and that of diabetes from 25% to 35% among young patients with MI over two decades.[1] |
| Tobacco use in traditional and emerging forms | Cigarette, waterpipe, and e-cigarette use are increasingly prevalent among young women; smoking remains the most common risk factor for MI in young adults. |
| Recreational drugs and stimulants | Cocaine and/or cannabis use in approximately 1 in 10 young patients with MI; anabolic steroid use and consumption of high-caffeine energy drinks.[37] |
| Underrecognized genetic dyslipidemias | FH affects approximately 1 in 10 young patients with MI; elevated Lp(a) levels are rarely assessed.[21] |
| Limitations of conventional risk prediction | Most young adults with MI would not have qualified for statin therapy before their event under risk score-based guidelines; in REACT, SCORE2 failed to identify most young adults with subclinical atherosclerotic plaques.[8,58] |
| Lifestyle factors | Sedentary behavior, unhealthy dietary habits, and poor sleep quality. |
| Psychosocial and environmental stress | Economic hardship, occupational stress, and natural disasters.[15,16] |
| Improved detection | High-sensitivity troponin testing, greater access to coronary angiography, and increased recognition of SCAD and MINOCA. |
| Inflammation and infections | Chronic inflammatory and autoimmune diseases, HIV infection, and acute infections, including COVID-19, contribute to increased coronary risk. |

ARIC, Atherosclerosis Risk in Communities; COVID-19, coronavirus disease 2019; FH, familial hypercholesterolemia; HIV, human immunodeficiency virus; Lp(a), lipoprotein(a); MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructive coronary arteries; SCAD, spontaneous coronary artery dissection; SCORE2, Systematic Coronary Risk Evaluation 2.

of women, increases the likelihood of homozygous and other inherited lipid disorders.[13] Third, atherogenic dyslipidemia, smoking, and metabolic risk factors are highly prevalent.[14] In the TURKMI registry, hypercholesterolemia (60.2%), hypertension (49.5%), smoking (48.8%), and diabetes (37.9%) were the predominant risk factors.[4]

Natural disasters represent an additional, often overlooked trigger of ACS. Major earthquakes increase the incidence of ACS and cardiovascular mortality.[15] Following the February 2023 Kahramanmaraş earthquakes, ACS was particularly common among young patients, often resulting from SCAD or stress-induced vasospasm.[16] Economic hardship and chronic psychosocial stress likely compound these risks, although data on younger populations remain limited.

Nevertheless, our diagnostic and therapeutic approaches remain largely based on evidence derived from older patients. The questions are therefore straightforward: Are we sufficiently aware of the true burden of premature MI in our population, and are we looking deeply enough to understand and manage it?

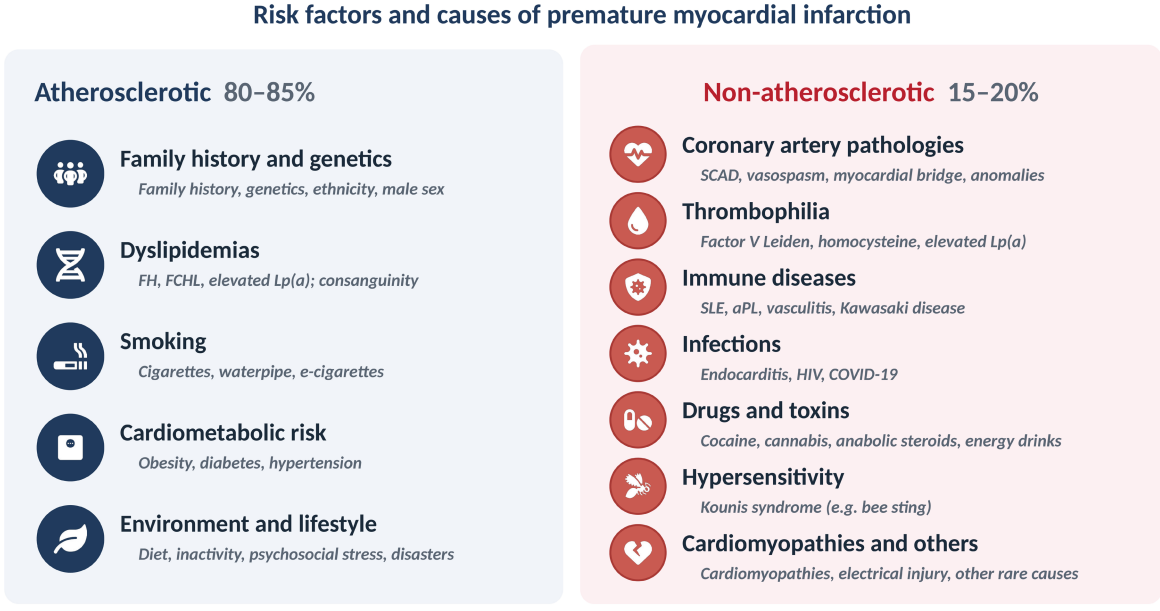
## An Overwhelming Response to the Young MI Focus Issue

Within three months of the call for papers, we received 83 manuscripts: 46 case reports, 33 original research articles, and 4 reviews or letters to the editor. This issue includes 14 original research articles, 7 case reports, and 3 reviews, two of which evolved from case reports into systematic reviews. Unfortunately, we were unable to publish all the submitted manuscripts, but we thank every author for sharing their work with us. This remarkable level of interest is itself informative: it suggests that MI in young adults is encountered more frequently in everyday clinical practice than is generally assumed and that clinicians across the country are seeking guidance on its evaluation and management.

## What the Submissions Taught Us

The most consistent observation was the incomplete assessment of lipid profiles. Although all 52 young patients with MI described in the submitted case reports underwent coronary angiography, LDL cholesterol levels were reported in only 23 (44.2%), while lipoprotein(a) [Lp(a)] and non-high-density lipoprotein (non-HDL) cholesterol levels were reported in only 11 (21.2%), despite their central role in quantifying the atherogenic lipoprotein burden. A young patient with MI has, by definition, either accumulated sufficient atherogenic exposure or developed an alternative pathology to experience a coronary event decades earlier than expected. Non-HDL cholesterol reflects the burden of all atherogenic lipoproteins and can be calculated from a standard lipid panel at no additional cost. As Corral argues in this issue, the evaluation of premature MI should extend beyond LDL cholesterol while maintaining a focus on atherogenic lipoproteins.[17]

Lp(a) warrants particular emphasis. More than 90% of its plasma concentration is genetically determined, its levels are not reduced by lifestyle modifications or statin therapy, and its association with cardiovascular risk is continuous.[18] The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines and the 2022 EAS consensus statement recommend measuring Lp(a) at least once during every adult's lifetime.[18,19] The 2025 ESC/EAS focused update identifies Lp(a) levels above 50 mg/dL (105 nmol/L) as a risk-enhancing factor.[20] In young patients with MI, failure to measure Lp(a) represents a missed diagnostic opportunity for both the patient and their family. The same applies to FH. In the YOUNG-MI study, nearly 1 in 10 of 1,996 patients experiencing their first MI at age 50 years or younger met the criteria for probable or definite FH, and 42.8% of these patients were not receiving statin therapy before the event.[21] These are precisely the patients in whom the first cardiovascular




*Modified from Kayıkçıoğlu M, et al. Balkan Med J 2022;39:83–95.*

aPL, antiphospholipid antibodies; FCHL, familial combined hyperlipidemia; FH, familial hypercholesterolemia; Lp(a), lipoprotein(a); SCAD, spontaneous coronary artery dissection; SLE, systemic lupus erythematosus.

**Figure 1.** Risk factors and underlying causes of premature myocardial infarction.

event should have been prevented. The lipid profiles of adults younger than 45 years with MI, as reported in this issue, further reinforce this point.[22]

A second pattern emerged from the research submissions: many studies focused on novel inflammatory, hematologic, or composite indices. In this issue, the non-HDL cholesterol to high-density lipoprotein (HDL) cholesterol ratio,[23] Castelli risk index II,[24] eosinophil-to-monocyte ratio,[25] and inflammatory prognostic index[26] are investigated as predictors of adverse events, repeat revascularization, ST-segment resolution, and the no-reflow phenomenon, while a cluster analysis explores lipid-derived phenotypes.[27] Tanrıverdi et al.[9] found higher hemoglobin, albumin, lymphocyte, and platelet (HALP) scores and lymphocyte-to-monocyte ratios in younger patients, whereas systemic inflammation response indices, platelet-to-lymphocyte ratios, and Naples prognostic scores were higher in older patients. Such retrospective studies are attractive to young researchers because they use existing data and can be conducted and published relatively quickly and easily. As Başaran and Güngör ask, the key issue is whether these indices provide additional value beyond the parameters we already measure.[28] Arya's methodological comments on the cluster analysis are equally instructive.[29]

This is the paradox: while we search for the next ratio, the basics are often missing. A comprehensive lipid profile, a one-time Lp(a) measurement, and a thorough family history may not be particularly novel, but they provide actionable information today, and emerging biomarkers should complement rather than replace these essential assessments. Clearly, further research is needed in this field, but the most pressing question may be why we fail to implement what we already know.

## Where We Need to Look Deeper?

Reviewing the submissions to this issue revealed six important gaps in how we evaluate and manage young patients with MI.

### *1. Etiological workup is insufficient*

We do not investigate the underlying causes of MI in young patients thoroughly enough. Nonatherosclerotic causes warrant particular consideration in younger patients, including spontaneous coronary artery dissection (SCAD), coronary embolism, vasospasm, MI with nonobstructive coronary arteries (MINOCA), thrombophilia, autoimmune and inflammatory diseases, and substance use. SCAD may account for up to 35% of ACS/MI presentations in women aged ≤50 years and is the most common cause of pregnancy-associated MI (43%).[30] This condition is reviewed in the current issue.[31] The case reports presented here illustrate this etiological diversity: late stent thrombosis with cardiac arrest in primary antiphospholipid syndrome,[32] coronary thrombosis associated with newly diagnosed human immunodeficiency virus (HIV) infection,[33] ST-segment elevation following high-voltage electrical injury,[34] and bee sting-associated Kounis syndrome.[35] As Canpolat

**Table 2.** Suggested etiological workup in young patients with myocardial infarction

| Domain | What to assess | Examples |
|---|---|---|
| Lipids and lipoproteins | Baseline lipid profile at presentation, before the effects of statin therapy | Total cholesterol, LDL-C, HDL-C, triglycerides, non-HDL-C, apolipoprotein B, and Lp(a) (measured at least once) |
| Familial hypercholesterolemia | Structured clinical scoring; genetic testing when indicated | Dutch Lipid Clinic Network score, physical signs, and family history |
| Family history | Premature ASCVD and sudden cardiac death among first-degree relatives | Family pedigree assessment and cascade screening of relatives |
| Substances and stimulants | Proactive, nonjudgmental questioning; toxicology screening when substance use is suspected | Cocaine, amphetamines, cannabis, anabolic steroids, energy drinks, and synthetic cannabinoids |
| Nonatherosclerotic coronary causes | Careful review of coronary angiography; intracoronary imaging when findings are inconclusive | SCAD, coronary vasospasm, coronary embolism, anomalous coronary arteries, and myocardial bridging |
| MINOCA workup | Cardiac magnetic resonance imaging and further evaluation in the absence of obstructive coronary artery disease | Myocarditis, Takotsubo syndrome, and coronary microvascular dysfunction |
| Thrombophilia and embolic sources | Evaluation when thrombus burden is high or atherosclerosis is minimal | Antiphospholipid syndrome, inherited or acquired thrombophilias, patent foramen ovale, atrial fibrillation, and left ventricular thrombus |
| Hematologic and systemic diseases | Targeted screening guided by the clinical context | Myeloproliferative neoplasms, autoimmune diseases, vasculitis, HIV infection, and chronic kidney disease |
| Metabolic and endocrine factors | Assessment beyond blood glucose measurement alone | HbA1c, thyroid function, homocysteine levels when indicated, obesity, and insulin resistance |
| Pregnancy-related factors (women) | Pregnancy and postpartum status; reproductive history | Pregnancy-associated SCAD, history of preeclampsia, and hormonal therapy |

ASCVD, atherosclerotic cardiovascular disease; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MINOCA, myocardial infarction with nonobstructive coronary arteries; SCAD, spontaneous coronary artery dissection.

emphasizes, the first event provides a critical opportunity for etiological evaluation.[36] Identifying the underlying mechanism is essential for determining treatment, antithrombotic strategy, recurrence risk, and implications for family members; Table 2 summarizes a practical diagnostic workup.

***2. Family screening is almost entirely absent***

None of the submitted case reports or studies mentioned family screening. FH is common, heritable, and treatable, while elevated Lp(a) identifies inherited cardiovascular risk that can guide preventive strategies. Every young patient with MI should therefore be considered a potential index case. Cascade screening of first-degree relatives, as recommended for both FH and elevated Lp(a), can prevent subsequent cardiovascular events among family members and is particularly important in populations with high rates of consanguinity.[13,18,19] Because atherosclerosis is already detectable in young adulthood, screening of families affected by MI in young individuals or premature coronary artery disease should begin early.[8] Siblings and children should undergo lipid profiling, including non-HDL cholesterol measurement, a one-time Lp(a) measurement, and FH assessment beginning in childhood or early adulthood, with imaging for subclinical atherosclerosis considered in selected cases. Relying solely on conventional risk scores to identify at-risk relatives may result in missed opportunities for effective prevention.

***3. Drugs, substances, and energy drinks are underrecognized***

Awareness of the cardiovascular risks associated with illicit drugs, stimulants, anabolic steroids, and high-caffeine energy drinks must increase among physicians and the public. In the YOUNG-MI study, cocaine and/or marijuana use was documented in 10.7% of patients experiencing their first MI at age 50 years or younger and was associated with approximately twofold higher all-cause (adjusted hazard ratio [HR], 1.99) and cardiovascular (adjusted HR, 2.22) mortality over a median follow-up of 11.2 years.[37] This issue places particular emphasis on this topic. Üresin et al.[38] review substance abuse as an underrecognized trigger of MI in young adults, while our group presents two cases alongside a patient-level systematic review of 31 energy drink-associated premature coronary events.[39] Case reports describe ST-segment elevation myocardial infarction (STEMI) following chronic anabolic-androgenic steroid use,[40] further discussed by Dinç Asarcıklı and Şen,[41] and anterior STEMI followed by acute popliteal artery occlusion in a 25-year-old smoker who used cannabis.[42] Substance use and high-caffeine beverage consumption should be assessed proactively and nonjudgmentally in every young patient with MI; their contribution is likely substantially greater than currently recognized, precisely because we rarely ask about them.[39]

***4. Does management differ in young patients?***

We know little about whether young patients should receive different treatment approaches. Should interventional strategies, stent selection, antithrombotic therapy, and lipid targets be tailored to individuals who may live another 40–50 years? Young patients are underrepresented in clinical trials, and treatment recommendations are largely extrapolated from studies involving older populations.[43] High thrombus burden is one example: in this issue, it was associated with STEMI presentation, impaired coronary flow, and systemic inflammation in premature type 1 MI,[44] as discussed by Yurtseven,[45] while a four-case series describes a stent-free treatment strategy.[46] Dedicated studies involving young patients are needed to determine whether management should differ in this age group and, if so, how.

***5. Long-term prognosis is essentially unknown***

The available literature focuses primarily on in-hospital and short-term outcomes; consequently, the relatively low early mortality observed in young patients may underestimate their long-term risk. Long-term data suggest an unfavorable prognosis. In the YOUNG-MI registry, very young patients (≤40 years) had long-term mortality comparable to that of patients aged 41–50 years over a median follow-up of 11.2 years, despite being a decade younger.[5] Moreover, young women had a 63% higher adjusted all-cause mortality risk than young men.[47] Articles in this issue report long-term follow-up of SCAD in young women,[48] recurrent SCAD requiring left ventricular assist device implantation,[49] with Ildızlı-Demirbaş emphasizing the need to look beyond the coronary lumen,[50] 1-year outcomes following emergency angiography for suspected STEMI,[51] the prognostic impact of early acute kidney injury,[52] and sex differences in outcomes among adults aged 18–50 years.[53] Outcomes over 20–30 years, including recurrent events, heart failure, treatment adherence, return to work, and quality of life, remain largely unknown, and data from Türkiye are virtually nonexistent. As Okyay concludes, intracoronary imaging and long-term follow-up are essential for clarifying the mechanisms and prognostic implications of premature MI.[54]

***6. A national health problem that must be quantified***

Premature MI represents a major public health challenge in Türkiye, and its burden must be accurately quantified. Beyond the Turkish Adult Risk Factor (TEKHARF) study estimate of approximately 480,000 new coronary heart disease cases annually, national data on MI in young adults remain limited, and the findings from the TURKMI registry, collected shortly before the coronavirus disease 2019 (COVID-19) pandemic, require updating.[4,55]

**Looking Deeper, Together!**

The message of this issue is not that we lack the necessary tools, but that we fail to use those already available to us. As Tokgözoğlu emphasizes, MI in a young patient is a warning that preventive measures have come too late.[56] Similarly, as Sabouret and colleagues stress, residual cardiovascular risk extends beyond the culprit lesion and traditional risk factors.[57] Every young patient with MI deserves a comprehensive lipid assessment, including Lp(a) measurement, an open and nonjudgmental discussion about substance use, a thorough investigation of the underlying cause, and family screening. None of these measures requires new technology, but rather a shift in mindset: viewing every MI in a young patient not merely as an event to manage, but also as a question that demands an answer.

Much is still unknown. We hope this issue will serve both as a reminder of what we should already be doing and as an invitation to study what we do not yet understand.

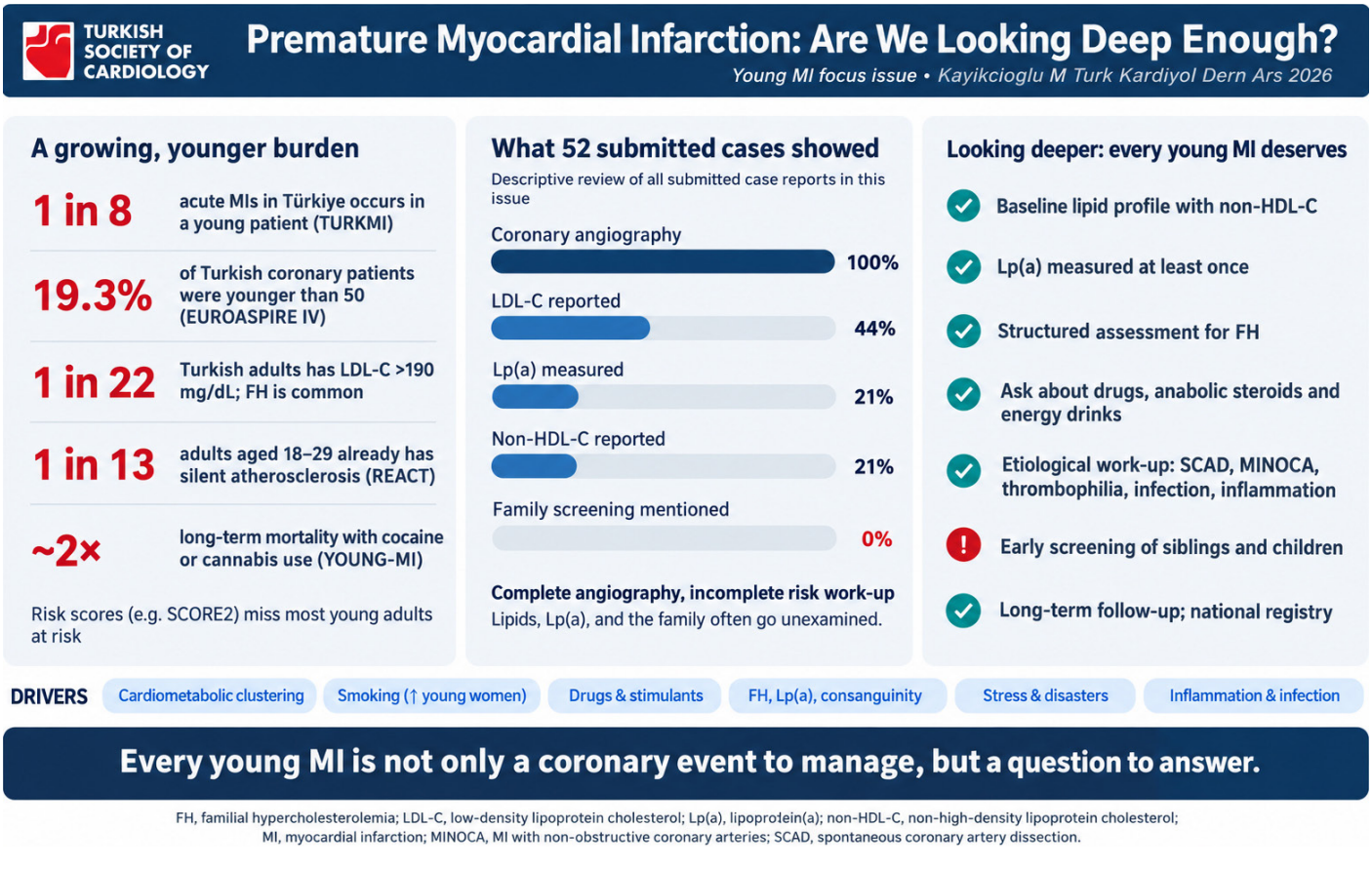
When I reflect on my brother's loss, I cannot help but wonder what a closer examination might have uncovered. I may never know the answer, but I firmly believe that for many young patients and their families, the answers we seek are already within reach—if only we take the time to look deeper.

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# Prognostic Value of the Non-HDL-C/HDL-C Ratio for Predicting One-Year Major Adverse Cardiac and Cerebrovascular Events in Young Patients with Myocardial Infarction

## Genç Miyokard Enfarktüsü Hastalarında Non-HDL-C/HDL-C Oranının 1 Yıllık Majör Advers Kardiyak ve Serebrovasküler Olayları Öngörmedeki Prognostik Değeri

**ABSTRACT**

**Objective:** Young patients with myocardial infarction (MI) remain at risk for recurrent cardiovascular events despite favorable short-term outcomes. The prognostic significance of the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol (non-HDL-C/HDL-C) ratio in this population remains insufficiently studied. We aimed to evaluate its association with 1-year major adverse cardiac and cerebrovascular events (MACCE).

**Method:** This retrospective, single-center study included 856 consecutive patients aged ≤50 years who were hospitalized with acute MI between January 2022 and January 2025, including 302 (35.3%) with STEMI and 554 (64.7%) with NSTEMI. The primary outcome was 1-year MACCE, defined as a composite of all-cause mortality, ischemic stroke, recurrent MI, and unplanned repeat coronary revascularization. Patients were categorized into low- and high-ratio groups using a receiver operating characteristic (ROC)-derived cutoff based on the Youden index. Associations were assessed using multivariable Cox proportional hazards models.

**Results:** During follow-up, 129 patients (15.0%) experienced MACCE. The optimal non-HDL-C/HDL-C cutoff was 4.43. The ratio was independently associated with 1-year MACCE (HR=1.568, 95% CI=1.463–1.681; P < 0.001), with consistent effects across the STEMI and NSTEMI subgroups (p for interaction=0.545). The non-HDL-C/HDL-C ratio showed the highest discriminatory performance among the lipid parameters (AUC=0.864), outperforming LDL-C, non-HDL-C, and the atherogenic index of plasma (DeLong P < 0.001).

**Conclusion:** In this retrospective observational cohort, a higher non-HDL-C/HDL-C ratio was independently associated with an increased risk of 1-year MACCE in young patients with MI. Prospective multicenter studies are warranted to confirm these findings.

**Keywords:** Cholesterol, HDL, lipoproteins, myocardial infarction, risk assessment, young patients.

**ÖZET**

**Amaç:** Genç yaşta miyokard enfarktüsü (MI) geçiren hastalarda kısa dönem sonuçlar daha iyi olsa da tekrarlayan kardiyovasküler olay riski devam etmektedir. Non-HDL-C/HDL-C oranının bu popülasyondaki prognostik değeri yeterince araştırılmamıştır. Bu çalışmada, söz konusu oranın 1 yıllık majör advers kardiyak ve serebrovasküler olaylarla (MACCE) ilişkisi değerlendirildi.

**Yöntem:** Bu retrospektif, tek merkezli çalışmaya Ocak 2022–Ocak 2025 tarihleri arasında akut MI nedeniyle hastaneye yatırılan ≤50 yaşındaki 856 ardışık hasta dahil edildi; bunların 302'si (%35,3) STEMI, 554'ü (%64,7) NSTEMI idi. Birincil sonlanım noktası, tüm nedenlere bağlı ölüm, iskemik inme, tekrarlayan MI ve plansız koroner revaskülarizasyonu içeren 1 yıllık MACCE olarak tanımlandı. Hastalar, ROC analiziyle belirlenen eşik değere (Youden indeksi) göre düşük ve yüksek oran gruplarına ayrıldı. İlişkiler çok değişkenli Cox regresyon analizleriyle değerlendirildi.

**Bulgular:** Takip süresince 129 hastada (%15,0) MACCE gelişti. Optimal non-HDL-C/HDL-C eşik değeri 4,43 olarak belirlendi. Non-HDL-C/HDL-C oranı, 1 yıllık MACCE ile bağımsız olarak ilişkili bulundu (HR=1,568; %95 GA=1,463–1,681; P < 0,001). Bu ilişki STEMI ve NSTEMI alt gruplarında tutarlıydı (etkileşim için P = 0,545). Non-HDL-C/HDL-C oranı, incelenen lipid parametreleri arasında en yüksek ayırt edici gücü gösterdi (AUC=0,864) ve LDL-C, non-HDL-C ve aterojenik plazma indeksinden anlamlı olarak üstün bulundu (DeLong P < 0,001).

**Sonuç:** Bu gözlemsel kohortta, daha yüksek non-HDL-C/HDL-C oranı genç MI hastalarında artmış 1 yıllık MACCE riski ile ilişkili bulundu. Bu bulguların doğrulanması için prospektif, çok merkezli çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Kolesterol, HDL, lipoproteinler, miyokard enfarktüsü, risk değerlendirmesi, genç hastalar.

**ORIGINAL ARTICLE**
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Acute myocardial infarction (MI) continues to rank among the most common causes of morbidity and mortality worldwide.[1,2] Although the incidence of MI increases with age, recent data suggest a noticeable rise in MI occurring at younger ages, commonly referred to as premature MI.[3,4] Moreover, although short-term outcomes are generally more favorable in younger individuals, the long-term prognosis remains concerning; early-onset MI has been associated with a substantial long-term survival disadvantage, underscoring the cumulative burden of recurrent events over time.[5]

Dysregulated lipid metabolism plays an important role in the pathophysiology of atherosclerotic cardiovascular disease. Although low-density lipoprotein cholesterol (LDL-C) is the primary therapeutic target in current guidelines, reliance on LDL-C alone may not fully capture the burden of atherogenic lipoproteins, particularly in the setting of residual cardiovascular risk.[6-8] Non-high-density lipoprotein cholesterol (non-HDL-C), which encompasses all apolipoprotein B-containing atherogenic lipoproteins, is increasingly recognized as a more comprehensive measure of lipid-related cardiovascular risk.[6,9,10] More recently, composite lipid measures that integrate both proatherogenic and protective components have been proposed to better characterize the complex lipid milieu.[11] Among these, the non-HDL-C/HDL-C ratio has emerged as a promising marker that reflects the balance between atherogenic and atheroprotective lipid fractions.[12-14]

Younger individuals with MI often exhibit an unfavorable metabolic profile and a high prevalence of dyslipidemia, which may not be fully captured by conventional lipid parameters.[15,16] As a result, traditional lipid metrics may underestimate the true cardiovascular risk in this population.

However, data regarding the prognostic significance of the non-HDL-C/HDL-C ratio in young patients with MI remain limited. A better understanding of this association may improve early risk stratification and facilitate more individualized cardiovascular care in this high-risk population. Therefore, the present study aimed to evaluate the prognostic value of the non-HDL-C/HDL-C ratio for predicting 1-year major adverse cardiac and cerebrovascular events (MACCE) in young patients with MI. We hypothesized that a higher non-HDL-C/HDL-C ratio would be independently associated with an increased risk of adverse cardiovascular outcomes and would provide superior prognostic discrimination compared with conventional lipid parameters.

## Materials and Methods

### Study Population

This retrospective, single-center observational study was conducted at a tertiary referral cardiovascular center. Consecutive patients aged ≤50 years who were hospitalized with a diagnosis of acute MI between January 2022 and January 2025 were screened for eligibility.

The definition of "young" or "premature" MI was based on prior literature, in which age thresholds ranging from 40 to 55 years have been used. A uniform age cutoff of ≤50 years was selected to represent a relatively early-onset MI population while maintaining a consistent and clinically homogeneous study cohort.

## ABBREVIATIONS

| | |
|---|---|
| AIP | Atherogenic index of plasma |
| AUC | Area under the curve |
| DCA | Decision curve analysis |
| eGFR | Estimated glomerular filtration rate |
| HDL-C | High-density lipoprotein cholesterol |
| HR | Hazard ratio |
| LDL-C | Low-density lipoprotein cholesterol |
| LVEF | Left ventricular ejection fraction |
| MACCE | Major adverse cardiac and cerebrovascular events |
| MI | Myocardial infarction |
| NSTEMI | non-ST-segment elevation myocardial infarction |
| non-HDL-C | Non–high-density lipoprotein cholesterol |
| RCS | Restricted cubic spline |
| ROC | Receiver operating characteristic |
| STEMI | ST-segment elevation myocardial infarction |
| VIF | Variance inflation factor |

Eligible patients were required to fulfill all of the following criteria: (1) age ≤50 years at the time of presentation; (2) diagnosis of acute MI according to the Fourth Universal Definition of Myocardial Infarction; (3) availability of baseline clinical and laboratory data, including a complete lipid profile obtained within the first 24 hours of admission; and (4) availability of complete 1-year clinical outcome ascertainment.

The diagnosis of MI was established by the presence of acute myocardial injury, demonstrated by a rise and/or fall in cardiac troponin values, together with clinical evidence of myocardial ischemia. The study cohort included both STEMI and NSTEMI presentations. Patients with type 2 MI were excluded. Patients with MINOCA or other nonatherosclerotic mechanisms of MI (e.g., spontaneous coronary artery dissection, coronary vasospasm, coronary embolism, myocardial bridging, or coronary artery anomalies) were not systematically excluded, provided that they fulfilled the diagnostic criteria for acute MI and were not classified as having type 2 MI. Angiographic confirmation of a culprit lesion was not required as an inclusion criterion. All patients underwent coronary angiography, and revascularization strategies were applied according to contemporary guideline recommendations.[17]

Patients were excluded if they had missing laboratory data required for calculation of the study lipid parameters, active inflammatory or infectious diseases at presentation, known chronic liver disease, active malignancy, or incomplete follow-up information. These exclusion criteria were applied to minimize potential confounding and ensure reliable assessment of the relationship between lipid-derived markers and clinical outcomes. After application of the eligibility criteria, 856 patients were included in the final analysis (Figure 1).

The study protocol was approved by Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2026/09/1464, Date: 05.05.2026) and conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design of the study, the requirement for written informed consent was waived by the ethics committee.

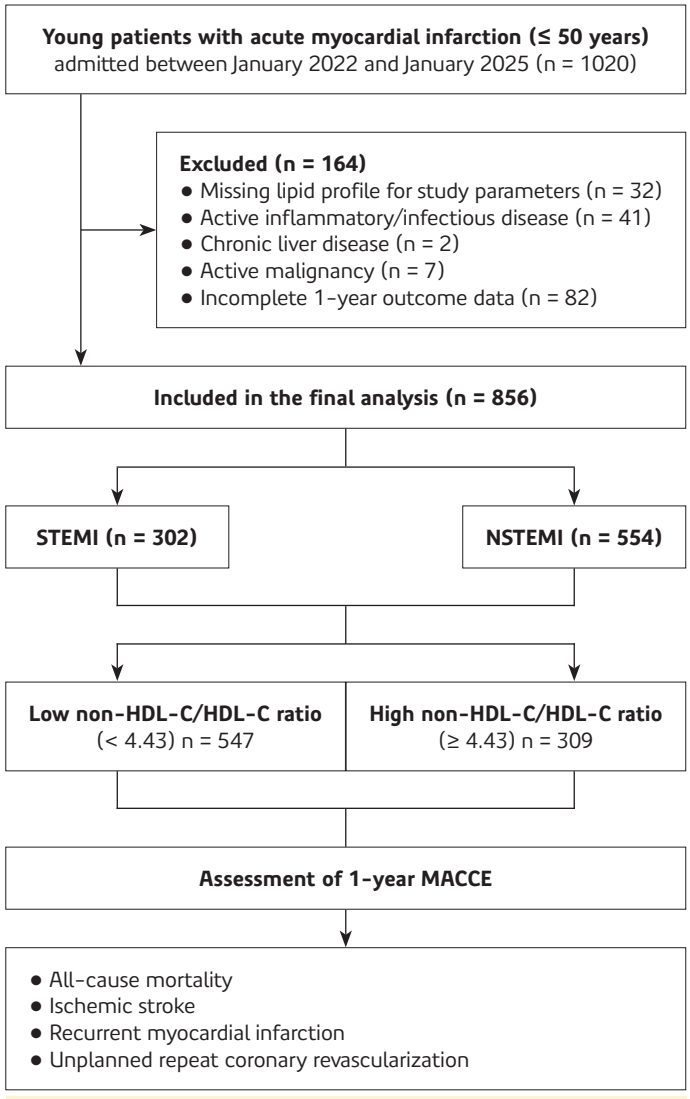



**Figure 1.** Study flowchart of patient selection and cohort stratification. Flow diagram illustrating patient screening, exclusion criteria, final cohort selection, stratification according to the non-HDL-C/HDL-C ratio cutoff value of 4.43, and assessment of 1-year major adverse cardiac and cerebrovascular events (MACCE).

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; MI, myocardial infarction; MACCE, major adverse cardiac and cerebrovascular events.

### Clinical Definitions

Patients were classified as having STEMI or NSTEMI according to electrocardiographic findings and clinical presentation, in accordance with the Fourth Universal Definition of Myocardial Infarction.

Hypertension was defined as a documented history of hypertension, use of antihypertensive medication, or a previous physician diagnosis. Diabetes mellitus was defined as a documented history of diabetes, use of glucose-lowering medication, or a previous physician diagnosis. Hyperlipidemia was defined as a documented history of dyslipidemia, prior lipid-lowering therapy, or a previous physician diagnosis. Chronic kidney disease was defined as a documented history of chronic kidney disease or an estimated glomerular filtration rate <60 mL/min/1.73 m$^2$. Prior coronary artery disease was defined as a documented history of MI, percutaneous coronary intervention, or coronary artery bypass graft surgery.

Current smokers were defined as patients who were actively smoking cigarettes at the time of hospital admission. Former smokers were defined as patients with a history of cigarette smoking who had quit before admission. Never smokers were defined as patients who had never smoked cigarettes.

The non-HDL-C value was calculated by subtracting HDL-C from total cholesterol, and the non-HDL-C/HDL-C ratio was calculated by dividing non-HDL-C by HDL-C. For descriptive and graphical analyses, patients were categorized according to the receiver operating characteristic (ROC)-derived non-HDL-C/HDL-C ratio cutoff value of 4.43.

### Laboratory Measurements and Data Collection

Laboratory, clinical, and demographic data were obtained from the electronic health record system. Venous blood samples were obtained as part of routine clinical care at hospital presentation or within the first 24 hours of hospitalization, and the first available lipid profile was used for analysis. Standard biochemical analyses were performed using automated laboratory systems.

Total cholesterol, triglyceride, HDL-C, and LDL-C levels were recorded. non-HDL-C was calculated using the following formula:

non-HDL-C = Total cholesterol − HDL-C

The non-HDL-C/HDL-C ratio was subsequently calculated as follows:

non-HDL-C/HDL-C ratio = non-HDL-C ÷ HDL-C

In addition, the atherogenic index of plasma (AIP) was calculated using molar concentrations as AIP = log10[(triglycerides/88.57)/(HDL-C/38.67)], where 88.57 and 38.67 are the mg/dL-to-mmol/L conversion factors for triglycerides and HDL-C, respectively.

At discharge, all patients were prescribed contemporary guideline-directed secondary prevention therapy, including aspirin, a P2Y12 inhibitor, and high-intensity statin therapy. The prescribed P2Y12 inhibitor was ticagrelor, clopidogrel, or prasugrel, according to clinical characteristics and physician discretion. Two patients who had been receiving ezetimibe before admission continued this treatment at discharge. No patient was discharged on a PCSK9 inhibitor.

### Outcome

The primary outcome was the occurrence of 1-year MACCE, defined as a composite of all-cause mortality, ischemic stroke, recurrent MI, and unplanned repeat coronary revascularization. Repeat revascularization was defined as any unplanned coronary revascularization during follow-up, irrespective of the target vessel. Staged revascularization procedures performed as part of a prespecified treatment plan were not considered outcome events.

Clinical outcomes were ascertained through review of the institutional electronic medical records, follow-up documentation available within the hospital information

system, and the national electronic health record system (e-Nabız), which was used to verify outcomes occurring outside our institution. Only patients with complete ascertainment of the predefined 1-year clinical outcome were included in the study; patients without available 1-year outcome information were excluded before cohort entry. No patient was lost to follow-up after study inclusion. Patients who died during follow-up were considered to have experienced the study endpoint on the date of death rather than being treated as lost to follow-up. Recurrent MI and ischemic stroke were identified based on documented clinical diagnoses and confirmed through review of the available medical records. All-cause mortality was determined from institutional medical records and follow-up documentation. For the composite endpoint, only the first MACCE event was considered in the time-to-event analyses. If multiple MACCE components occurred during the same clinical episode, a hierarchical classification strategy was applied to avoid duplicate counting, and the event was classified according to the primary clinical event documented in the medical records. In addition to the composite endpoint, the individual first-event components of MACCE were recorded and analyzed separately.

**Statistical Analysis**

Statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Data distribution was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean±standard deviation or median (interquartile range), as appropriate, whereas categorical variables are expressed as counts and percentages.

ROC analysis with the Youden index was used to identify an optimal non-HDL-C/HDL-C ratio cutoff of 4.43 (AUC=0.864, 95% CI=0.834–0.894), which was used solely for descriptive and graphical analyses, including Kaplan–Meier analyses. Because complete 1-year outcome ascertainment was available for all patients included in the final analysis, ROC analysis was performed using the predefined binary 1-year MACCE endpoint rather than censored survival data. Group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate. In addition, the ROC-derived non-HDL-C/HDL-C cutoff underwent a dedicated internal validation procedure using 2,000 bootstrap resamples. Within each bootstrap sample, the optimal threshold was rederived *de novo* using the Youden index, and its performance was evaluated to estimate the optimism-corrected AUC, sensitivity, and specificity. The distribution of bootstrap-selected thresholds was also examined to assess threshold stability.

Time-to-event analyses were performed using Kaplan–Meier survival curves and compared using the log-rank test. Associations between lipid parameters and 1-year MACCE were evaluated using Cox proportional hazards regression models. Only the first MACCE event was included in the time-to-event analyses. If multiple MACCE components occurred during the same clinical episode, a hierarchical classification strategy was applied, and only the primary clinical event was recorded as the composite endpoint. Subsequent events were not included in the survival analyses. Variables with established clinical relevance and significant associations in univariable analyses were entered into the multivariable models. The multivariable models included age, sex, hypertension, diabetes mellitus, current smoking, chronic kidney disease, albumin, lymphocyte count, C-reactive protein, and left ventricular ejection fraction. To avoid multicollinearity among lipid parameters, four separate multivariable Cox models were constructed, including the non-HDL-C/HDL-C ratio, AIP, LDL-C, and non-HDL-C, respectively. No missing data were present for any variable included in the multivariable Cox models; therefore, all four models included the entire cohort of 856 patients and 129 MACCE events, and no imputation was required. The non-HDL-C/HDL-C ratio was modeled as a continuous variable in the primary analyses, and other continuous covariates were entered as linear terms. Multicollinearity was assessed using variance inflation factors (VIFs).

The proportional hazards assumption was evaluated using Schoenfeld residuals (cox.zph), and no significant violations were detected. A total of 129 MACCE events were observed, yielding approximately 11.7 events per variable in the primary multivariable model.

Subgroup analyses were performed according to MI presentation (STEMI vs. NSTEMI), and a multiplicative interaction term (MI type × non-HDL-C/HDL-C ratio) was tested to evaluate effect modification. To account for the limited number of events within each subgroup and maintain an adequate events-per-variable ratio, the subgroup Cox models were restricted to the non-HDL-C/HDL-C ratio and a parsimonious set of covariates selected based on clinical relevance and event frequency. Accordingly, the STEMI subgroup model included fewer covariates than the NSTEMI subgroup model because of the lower number of observed events.

The discriminatory performance of lipid parameters for predicting 1-year MACCE was assessed using ROC analysis, and pairwise comparisons between AUCs were performed using the DeLong method. Model calibration and discrimination were assessed using calibration plots and bootstrap internal validation with 1,000 resampling iterations, from which optimism-corrected calibration intercepts, calibration slopes, Brier scores, and Harrell's C-statistics were derived.

Restricted cubic spline (RCS) analysis with four prespecified knots was performed within the Cox proportional hazards framework to examine the potential nonlinear association between the non-HDL-C/HDL-C ratio and the risk of 1-year MACCE. Nonlinearity was assessed using the Wald test.

Decision curve analysis (DCA) was performed primarily by entering each lipid parameter individually as the sole predictor of 1-year MACCE to provide a head-to-head comparison of the lipid markers. As sensitivity analyses, DCA was repeated after adding each lipid parameter separately to the fully adjusted multivariable model and using a survival-compatible approach based on Cox model-derived 1-year predicted risks.

All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

## Results

The final study cohort comprised 856 patients, with 547 (63.9%) classified into the low-ratio group and 309 (36.1%) into the high-ratio group. Of the 856 patients included in the study, 302 (35.3%) presented with STEMI and 554 (64.7%) with NSTEMI. The distribution of MI subtype did not differ significantly between the low- and high-non-HDL-C/HDL-C-ratio groups (STEMI: 35.1% vs. 35.6%; NSTEMI: 64.9% vs. 64.4%; P = 0.943).

Most baseline clinical and nonlipid laboratory characteristics were comparable between the groups; however, the lymphocyte count was modestly higher in the high-non-HDL-C/HDL-C-ratio group. Patients in the high-non-HDL-C/HDL-C-ratio group demonstrated a less favorable lipid profile, characterized by higher total cholesterol, LDL-C, triglyceride, and non-HDL-C concentrations, together with lower HDL-C levels (all P < 0.001) (Table 1).

At discharge, all patients received aspirin and a P2Y12 inhibitor. Specifically, ticagrelor was prescribed to 388 patients (45.3%), clopidogrel to 395 (46.1%), and prasugrel to 73 (8.5%). All 856 patients (100%) were discharged on high-intensity statin therapy. Two patients (0.2%) who had been receiving ezetimibe before admission continued ezetimibe after discharge. No patient was discharged on a PCSK9 inhibitor.

Patients with higher non-HDL-C/HDL-C ratios exhibited a significantly higher incidence of 1-year MACCE than those in the low-ratio group (28.1% vs. 7.7%; P < 0.001). When the individual components of the composite endpoint were examined separately, all-cause death occurred in 8 patients (0.9%), ischemic stroke in 4 (0.5%), recurrent MI in 61 (7.1%), and unplanned repeat coronary revascularization in 56 (6.5%) (Table 1).

Multivariable Cox proportional hazards analysis, adjusted for clinically relevant covariates, demonstrated that the non-HDL-C/HDL-C ratio remained independently associated with 1-year MACCE (HR=1.568, 95% CI=1.463–1.681; P < 0.001). When lipid-related parameters were evaluated in separate multivariable Cox models to avoid collinearity, AIP (per IQR increase; HR=2.140, 95% CI=1.722–2.659; P < 0.001), LDL-C (per 10 mg/dL increase; HR=1.188, 95% CI=1.143–1.234; P < 0.001), and non-HDL-C (per 10 mg/dL increase; HR=1.195, 95% CI=1.153–1.239; P < 0.001) were also independently associated with the occurrence of 1-year MACCE (Table 2). Kaplan–Meier analysis demonstrated significantly lower event-free survival among patients with a non-HDL-C/HDL-C ratio ≥4.43 than among those with a ratio <4.43 (log-rank P < 0.001) (Figure 2). Internal validation of the primary multivariable Cox model, in which the non-HDL-C/HDL-C ratio was analyzed as a continuous variable, was performed using bootstrap resampling with 1,000 iterations. The optimism-corrected Harrell's C-statistic was 0.781 (apparent C-statistic=0.804; optimism=0.023), indicating good internal discriminative performance with limited apparent optimism on internal validation (Supplementary Table 1). All VIFs were below 1.20, indicating no evidence of problematic multicollinearity (Supplementary Table 2).

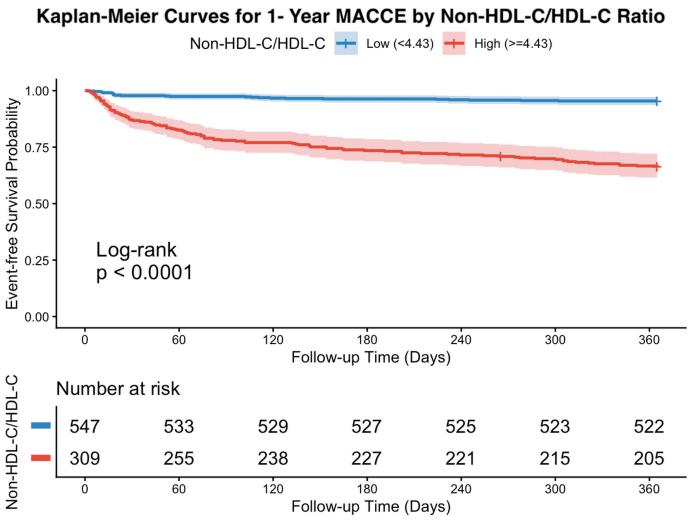



**Figure 2.** Kaplan–Meier analysis of 1-year MACCE according to the non-HDL-C/HDL-C ratio. Kaplan–Meier curves demonstrating event-free survival stratified by the ROC-derived non-HDL-C/HDL-C ratio cutoff value of 4.43. Patients with a non-HDL-C/HDL-C ratio ≥4.43 exhibited significantly lower event-free survival than those with a ratio <4.43 (log-rank P < 0.0001).

MACCE, major adverse cardiac and cerebrovascular events; ROC, receiver operating characteristic.

Subgroup analyses according to MI presentation demonstrated that the non-HDL-C/HDL-C ratio remained independently associated with 1-year MACCE in both patients with STEMI and those with NSTEMI. In the STEMI subgroup, the non-HDL-C/HDL-C ratio was independently associated with 1-year MACCE (HR=1.636, 95% CI=1.437–1.862; P < 0.001). Similarly, in the NSTEMI subgroup, the non-HDL-C/HDL-C ratio remained a significant predictor of 1-year MACCE (HR=1.574, 95% CI=1.438–1.724; P < 0.001) (Table 3). Formal interaction testing revealed no significant interaction between MI subtype and the prognostic effect of the non-HDL-C/HDL-C ratio (p for interaction=0.545), indicating a consistent association across both STEMI and NSTEMI presentations (Table 3).

Sex-specific analyses showed no evidence of effect modification by sex (p for interaction=0.205 by likelihood ratio test; Wald P = 0.208). The non-HDL-C/HDL-C ratio remained significantly associated with 1-year MACCE in both men (HR=1.653, 95% CI=1.501–1.821; P < 0.001) and women (HR=1.527, 95% CI=1.377–1.693; P < 0.001) in the parsimonious sex-stratified models. One-year MACCE occurred in 73 of 502 men (14.5%) and 56 of 354 women (15.8%), with no significant difference in crude event rates (P = 0.676) or event-free survival (log-rank P = 0.650) (Supplementary Table 3).

In ROC curve analysis, the non-HDL-C/HDL-C ratio yielded the greatest discriminatory ability for identifying 1-year MACCE (AUC=0.864). Moreover, DeLong pairwise comparisons demonstrated that its predictive performance was significantly superior to that of non-HDL-C, AIP, and LDL-C (all P < 0.001). By contrast, no statistically significant difference was observed between AIP and LDL-C in terms of discriminative performance (P = 0.502) (Figure 3). In a dedicated bootstrap analysis of the ROC-derived cutoff, the complete threshold-selection procedure using the Youden index was repeated

**Table 1.** Baseline clinical and laboratory characteristics stratified by non-HDL-C/HDL-C

| Variables | Total, n=856 (100%) | Low non-HDL-C/HDL-C, n=547 (63.9%) | High non-HDL-C/HDL-C, n=309 (36.1%) | *P* |
|---|---|---|---|---|
| Age, years | 43.0 (40.0–47.0) | 43.0 (40.0–47.0) | 43.0 (39.0–46.0) | 0.151 |
| Female, n (%) | 354 (41.4) | 221 (40.4) | 133 (43.0) | 0.367 |
| MI type | | | | |
| STEMI, n (%) | 302 (35.3) | 192 (35.1) | 110 (35.6) | 0.943 |
| NSTEMI, n (%) | 554 (64.7) | 355 (64.9) | 199 (64.4) | 0.943 |
| Hypertension, n (%) | 452 (52.8) | 279 (51.0) | 173 (55.9) | 0.161 |
| Diabetes mellitus, n (%) | 167 (19.5) | 102 (18.6) | 65 (21.0) | 0.397 |
| Current smoker, n (%) | 331 (38.7) | 215 (39.3) | 116 (37.5) | 0.611 |
| Former smoker, n (%) | 45 (5.25) | 29 (5.3) | 16 (5.1) | 0.938 |
| Hyperlipidemia, n (%) | 287 (33.5) | 127 (23.2) | 160 (51.8) | **<0.001** |
| Prior coronary artery disease, n (%) | 175 (20.4) | 109 (19.9) | 66 (21.4) | 0.618 |
| Chronic kidney disease, n (%) | 35 (4.1) | 19 (3.5) | 16 (5.2) | 0.281 |
| Cerebrovascular disease, n (%) | 6 (0.7) | 2 (0.4) | 4 (1.3) | 0.255 |
| Peripheral artery disease, n (%) | 16 (1.9) | 11 (2.0) | 5 (1.6) | 0.885 |
| Medications | | | | |
| Prior statin use, n (%) | 136 (15.9) | 83 (15.2) | 53 (17.2) | 0.507 |
| Discharge treatment, n (%) | | | | |
| Aspirin | 856 (100) | 547 (100) | 309 (100) | 1.000 |
| Ticagrelor | 388 (45.3) | 250 (45.7) | 138 (44.7) | 0.823 |
| Clopidogrel | 395 (46.1) | 252 (46.1) | 143 (46.3) | 1.000 |
| Prasugrel | 73 (8.5) | 45 (8.2) | 28 (9.1) | 0.770 |
| High-intensity statin | 856 (100) | 547 (100) | 309 (100) | 1.000 |
| Left ventricular ejection fraction, % | 52 (44–60) | 50 (44–60) | 52 (45–60) | 0.438 |
| Fasting blood glucose, mg/dL | 118 (103–145) | 119 (103–145) | 117 (103–142) | 0.984 |
| Creatinine, mg/dL | 0.82 (0.74–0.99) | 0.81 (0.73–0.96) | 0.84 (0.75–1.00) | 0.080 |
| Estimated glomerular filtration rate (eGFR), mL/min/1.73 $m^2$ | 98.6 (84.5–112) | 99.0 (85.9–112) | 97.2 (82.5–111) | 0.159 |
| C-reactive protein, mg/L | 3.40 (1.17–7.73) | 3.50 (1.10–7.60) | 3.20 (1.20–7.85) | 0.693 |
| Albumin, g/dL | 3.90 (3.60–4.15) | 3.90 (3.54–4.14) | 3.90 (3.60–4.16) | 0.131 |
| Hemoglobin, g/dL | 14.1 (13.0–15.0) | 14.1 (13.1–14.9) | 14.1 (13.0–15.1) | 0.532 |
| White blood cell count, $\times10^3$/μL | 10.7 (8.38–13.3) | 10.5 (8.29–13.1) | 10.8 (8.49–13.4) | 0.251 |
| Neutrophil count, $\times10^3$/μL | 7.40 (5.28–10.4) | 7.40 (5.29–10.5) | 7.40 (5.28–10.3) | 0.955 |
| Lymphocyte count, $\times10^3$/μL | 1.90 (1.40–2.52) | 1.86 (1.38–2.44) | 2.02 (1.43–2.61) | **0.011** |
| Monocyte count, $\times10^3$/μL | 0.60 (0.46–0.78) | 0.60 (0.46–0.78) | 0.60 (0.45–0.78) | 0.785 |
| Platelet count, $\times10^3$/μL | 197 (161–243) | 197 (160–245) | 198 (162–243) | 0.738 |
| Lipid parameters | | | | |
| Total cholesterol, mg/dL | 184 (156–209) | 168 (145–194) | 207 (187–243) | **<0.001** |
| HDL-C, mg/dL | 37.0 (31.0–43.0) | 40.0 (35.0–45.0) | 32.0 (28.0–36.0) | **<0.001** |
| LDL-C, mg/dL | 110 (86–136) | 98 (80–121) | 135 (108–158) | **<0.001** |
| Triglycerides, mg/dL | 134 (101–187) | 123 (93–161) | 166 (121–231) | **<0.001** |
| AIP | 0.21 (0.05–0.39) | 0.14 (−0.02–0.27) | 0.37 (0.22–0.53) | **<0.001** |
| Non-HDL-C, mg/dL | 146 (119–170) | 127 (107–151) | 175 (157–206) | **<0.001** |
| Non-HDL-C/HDL-C ratio | 3.95 (3.12–4.89) | 3.39 (2.74–3.89) | 5.35 (4.79–6.27) | **<0.001** |
| Follow-up and outcomes | | | | |
| All-cause death, n (%) | 8 (0.9) | 3 (0.5) | 5 (1.6) | 0.146 |
| Ischemic stroke, n (%) | 4 (0.5) | 0 (0.0) | 4 (1.3) | **0.017** |
| Recurrent MI, n (%) | 61 (7.1) | 23 (4.2) | 38 (12.2) | **<0.001** |
| Repeat revascularization, n (%) | 56 (6.5) | 16 (2.9) | 40 (12.9) | **<0.001** |
| 1-year MACCE, n (%) | 129 (15.0) | 42 (7.7) | 87 (28.1) | **<0.001** |

Continuous variables are presented as median (interquartile range) unless otherwise specified. AIP is presented as median (interquartile range) and was compared between groups using the Mann–Whitney U test because of its nonnormal distribution. Other continuous variables were compared using the Mann–Whitney U test. Categorical variables are presented as n (%) and were compared using the chi-square test or Fisher's exact test, as appropriate. Bold p-values indicate statistical significance ($P < 0.05$). AIP, atherogenic index of plasma; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; non-HDL-C, non-high-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

**Table 2.** Multivariable Cox proportional hazards regression analyses for predictors of 1-year MACCE

| Variables | Model 1: Non-HDL-C/HDL-C HR (95% CI) | *P* | Model 2: AIP (per IQR) HR (95% CI) | *P* | Model 3: LDL-C (per 10 mg/dL) HR (95% CI) | *P* | Model 4: Non-HDL-C (per 10 mg/dL) HR (95% CI) | *P* |
|---|---|---|---|---|---|---|---|---|
| Primary lipid marker | **1.568 (1.463–1.681)** | **<0.001** | **2.140 (1.722–2.659)** | **<0.001** | **1.188 (1.143–1.234)** | **<0.001** | **1.195 (1.153–1.239)** | **<0.001** |
| Age, years | 1.005 (0.965–1.046) | 0.822 | 1.006 (0.966–1.046) | 0.783 | 1.007 (0.969–1.047) | 0.708 | 1.010 (0.971–1.050) | 0.631 |
| Male sex | 1.003 (0.692–1.454) | 0.988 | 0.925 (0.637–1.341) | 0.679 | 1.196 (0.830–1.722) | 0.336 | 1.167 (0.811–1.681) | 0.406 |
| Hypertension | 0.773 (0.523–1.144) | 0.198 | 0.790 (0.535–1.166) | 0.235 | 0.701 (0.476–1.034) | 0.073 | 0.711 (0.482–1.048) | 0.085 |
| Diabetes mellitus | 0.963 (0.620–1.498) | 0.869 | 0.906 (0.585–1.402) | 0.657 | 0.853 (0.546–1.333) | 0.485 | 0.880 (0.565–1.371) | 0.572 |
| Current smoking | 1.195 (0.833–1.712) | 0.333 | 1.165 (0.811–1.671) | 0.409 | 1.046 (0.730–1.498) | 0.806 | 1.087 (0.759–1.555) | 0.650 |
| LVEF, % | 0.996 (0.980–1.013) | 0.672 | 0.997 (0.980–1.013) | 0.683 | 0.999 (0.983–1.015) | 0.870 | 0.996 (0.980–1.012) | 0.618 |
| Albumin, g/dL | 1.211 (0.818–1.793) | 0.338 | 1.223 (0.837–1.787) | 0.298 | 1.168 (0.808–1.689) | 0.407 | 1.155 (0.802–1.664) | 0.439 |
| Lymphocyte count, $\times 10^3/\mu L$ | 1.000 (0.968–1.033) | 0.989 | 1.015 (0.985–1.047) | 0.328 | 1.015 (0.987–1.044) | 0.301 | 1.011 (0.981–1.041) | 0.487 |
| CRP, mg/L | 1.000 (0.962–1.040) | 0.991 | 1.027 (0.988–1.067) | 0.177 | 1.040 (0.999–1.083) | 0.055 | 1.026 (0.986–1.068) | 0.199 |
| CKD | 2.237 (1.047–4.780) | **0.038** | 1.818 (0.854–3.871) | 0.121 | 2.042 (0.960–4.343) | 0.064 | 2.049 (0.963–4.356) | 0.062 |
| C-statistic | **0.804** | | **0.689** | | **0.717** | | **0.738** | |

All models were adjusted for age, sex, hypertension, diabetes mellitus, current smoking, LVEF, albumin, lymphocyte count, CRP, and CKD. To avoid collinearity among lipid parameters, four separate multivariable Cox proportional hazards models were constructed, each including one lipid marker (Model 1: non-HDL-C/HDL-C ratio; Model 2: AIP; Model 3: LDL-C; Model 4: non-HDL-C). The C-statistic represents the apparent discriminative performance of the full multivariable Cox model and is therefore not directly comparable with the single-marker ROC AUC values reported elsewhere. Hazard ratios are expressed per unit increase in the non-HDL-C/HDL-C ratio, per interquartile-range increase in AIP, and per 10 mg/dL increase in LDL-C and non-HDL-C; accordingly, the magnitudes of the hazard ratios should not be compared directly across models. AIP, atherogenic index of plasma; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; non-HDL-C, non-high-density lipoprotein cholesterol.




**Figure 3.** Discriminative performance of lipid parameters for 1-year MACCE. Receiver operating characteristic (ROC) curves comparing the predictive performance of the non-HDL-C/HDL-C ratio, non-HDL-C, LDL-C, and AIP. The non-HDL-C/HDL-C ratio showed the highest discrimination (AUC=0.864), significantly outperforming the other parameters (DeLong P < 0.001).

AUC, area under the curve; ROC, receiver operating characteristic; MACCE, major adverse cardiac and cerebrovascular events; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AIP, atherogenic index of plasma.

within 2,000 bootstrap resamples. The optimism-corrected AUC was 0.865 (95% CI=0.835–0.892), compared with an apparent AUC of 0.864. The median bootstrap-selected cutoff was 4.49 (range=3.98–5.18; SD=0.27), and 26.1% of bootstrap samples yielded a threshold differing by more than 10% from the originally derived value of 4.43. The optimism-corrected sensitivity and specificity were 0.825 and 0.731, respectively, compared with apparent values of 0.844 and 0.734. Thus, although the discriminatory performance of the marker remained stable under resampling, the data-derived threshold showed greater sampling variability and was therefore considered exploratory.

Calibration analysis showed acceptable visual agreement between predicted and observed event rates, without marked evidence of systematic over- or underestimation (Figure 4). Bootstrap internal validation using 1,000 resampling iterations demonstrated good calibration and limited optimism. The optimism-corrected calibration slope was 0.883 (95% CI=0.613–1.157), the calibration intercept was −0.162 (95% CI=−0.637 to 0.345), and the Brier score was 0.107 (95% CI=0.091–0.122), indicating acceptable calibration and good predictive accuracy with limited apparent optimism on internal validation. The confidence interval for the calibration slope was relatively wide (0.613–1.157), and the results should therefore be interpreted with corresponding caution.

The association appeared relatively flat at lower ratio values, followed by a progressive increase in the hazard ratio above approximately 4.0, supporting a graded association between higher non-HDL-C/HDL-C ratio values and the risk of 1-year MACCE (Figure 5).

Lastly, DCA demonstrated that the non-HDL-C/HDL-C ratio provided the greatest net benefit across the evaluated threshold

**Table 3.** Multivariable Cox regression analysis of predictors of 1-year MACCE in the STEMI and NSTEMI subgroups

| Variables | STEMI (n=302, events=42), HR | 95% CI | *P* | NSTEMI (n=554, events=87), HR | 95% CI | *P* |
|---|---|---|---|---|---|---|
| Non-HDL-C/HDL-C ratio | 1.636 | 1.437–1.862 | **<0.001** | 1.574 | 1.438–1.724 | **<0.001** |
| Age, years | 0.933 | 0.884–0.986 | **0.013** | 1.099 | 1.027–1.176 | **0.006** |
| CKD | 2.734 | 0.933–8.011 | 0.067 | 1.223 | 0.435–3.435 | 0.702 |
| Diabetes mellitus | 0.559 | 0.231–1.353 | 0.197 | 1.268 | 0.765–2.102 | 0.357 |
| PAD | – | – | – | 0.847 | 0.251–2.861 | 0.790 |
| CRP, mg/L | – | – | – | 1.016 | 0.971–1.063 | 0.488 |
| Albumin, g/dL | – | – | – | 1.386 | 0.838–2.292 | 0.204 |
| Lymphocyte count, ×10³/μL | – | – | – | 0.891 | 0.720–1.102 | 0.288 |

P for interaction (MI type × non-HDL-C/HDL-C ratio) = 0.545. Bold p-values indicate statistical significance (P < 0.05). The STEMI and NSTEMI subgroup models were not identically adjusted. Because of the smaller number of events in the STEMI subgroup, a more parsimonious covariate set was used to preserve an adequate events-per-variable ratio. The STEMI model was adjusted for the non-HDL-C/HDL-C ratio, age, chronic kidney disease, and diabetes mellitus, whereas the NSTEMI model was additionally adjusted for peripheral artery disease, C-reactive protein, albumin, and lymphocyte count. The interaction p-value of 0.545 indicates no significant difference in the association between the non-HDL-C/HDL-C ratio and 1-year MACCE across the STEMI and NSTEMI subgroups. Because the two models were not identically adjusted, the subgroup hazard ratios should be interpreted with caution and should not be directly compared. The non-HDL-C/HDL-C ratio was modeled as a continuous variable, with the hazard ratio expressed per unit increase. CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; non-HDL-C, non-high-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; STEMI, ST-segment elevation myocardial infarction.

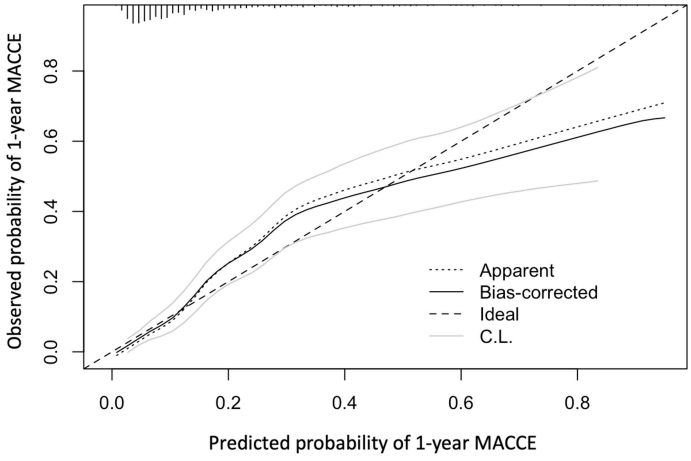



**Figure 4.** Calibration plot of the primary multivariable Cox model for predicting 1-year MACCE. Calibration plot showing agreement between the predicted and observed probabilities of 1-year major adverse cardiac and cerebrovascular events (MACCE). The bias-corrected calibration curve demonstrated acceptable agreement with the ideal reference line, indicating good calibration and limited optimism after bootstrap internal validation.

MACCE, major adverse cardiac and cerebrovascular events; C.L., confidence limits.

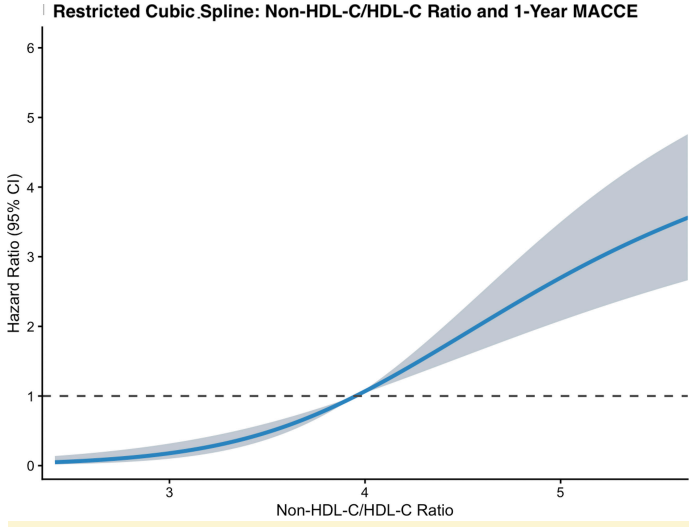



**Figure 5.** Association between the non-HDL-C/HDL-C ratio and 1-year MACCE. Restricted cubic spline illustrating the association between the non-HDL-C/HDL-C ratio and the risk of 1-year MACCE. The hazard ratio remained relatively low at lower ratio values and increased progressively above approximately 4.0, without evidence of attenuation at higher values (p for nonlinearity<0.001). The solid line represents the estimated hazard ratio, and the shaded area represents the 95% confidence interval. The dashed horizontal line indicates a hazard ratio of 1.0.

MACCE, major adverse cardiac and cerebrovascular events; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

probabilities compared with the other lipid parameters, particularly between approximately 10% and 40%. The non-HDL-C/HDL-C ratio also showed greater net benefit than the treat-all and treat-none reference strategies across a broad range of threshold probabilities (Figure 6). Sensitivity analyses yielded consistent findings. When each lipid parameter was added to the fully adjusted multivariable model, net benefit estimates remained broadly similar, and the ranking of the lipid markers was unchanged (Supplementary Table 4). Likewise, survival-compatible DCA based on Cox model-derived 1-year predicted risks produced results consistent with the binary analysis, with the non-HDL-C/HDL-C ratio maintaining the greatest net benefit (Supplementary Table 5).

## Discussion

In this study, we demonstrated that the non-HDL-C/HDL-C ratio was independently associated with 1-year MACCE in young patients (≤50 years) with MI. Patients with higher ratios had a substantially increased risk of adverse outcomes, and this association remained significant in multivariable Cox proportional hazards analyses after adjustment for clinically relevant covariates. The non-HDL-C/HDL-C ratio also demonstrated greater discriminative ability than

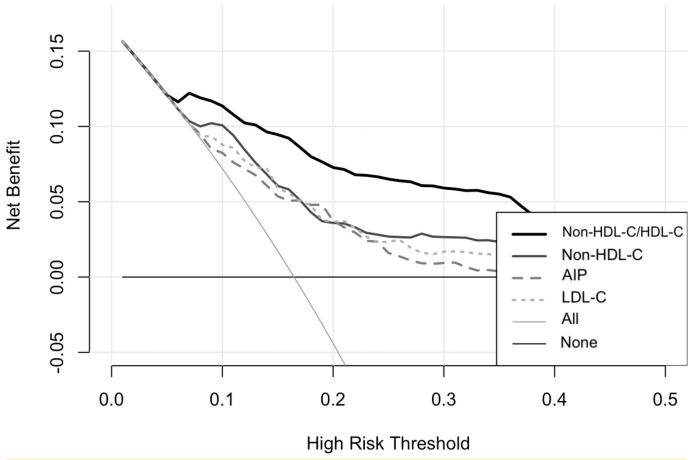



**Figure 6.** Decision curve analysis for prediction of 1-year MACCE. Decision curve analysis illustrating the net benefit of the non-HDL-C/HDL-C ratio, non-HDL-C, LDL-C, and AIP across a range of threshold probabilities. The non-HDL-C/HDL-C ratio consistently provided the greatest net benefit across the evaluated threshold probabilities compared with the other lipid parameters. The treat-all and treat-none strategies are shown as reference lines.

MACCE, major adverse cardiac and cerebrovascular events; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AIP, atherogenic index of plasma.

conventional lipid parameters, including LDL-C, non-HDL-C, and the AIP. Consistent with these findings, Kaplan–Meier analysis revealed significantly lower event-free survival among patients with elevated non-HDL-C/HDL-C ratios. Calibration and decision curve analyses provided complementary support for the predictive performance of the model.

Despite advances in contemporary management, younger patients with MI continue to experience a substantial burden of adverse cardiovascular events.[3,4] Although early outcomes are often perceived as more favorable in this population, the cumulative lifetime risk of recurrent events remains substantial and may even exceed that of older individuals because of prolonged exposure to cardiovascular risk factors.[5] In line with prior reports, the incidence of 1-year MACCE in our cohort was also notable, underscoring the need for improved risk stratification in this population.[18] As atherosclerotic cardiovascular disease is the principal underlying mechanism, the observed association likely reflects the cumulative burden of atherogenic lipoproteins rather than a direct causal relationship. RCS analysis further supported this relationship, demonstrating relatively low risk at lower ratio values followed by a progressive increase in the risk of 1-year MACCE at higher non-HDL-C/HDL-C ratio levels. This pattern is consistent with a graded association between lipid-related atherogenic burden and adverse cardiovascular outcomes. Notably, the confidence intervals widened at the upper range of the non-HDL-C/HDL-C ratio, reflecting the smaller number of patients with very high values; accordingly, the spline estimates at these extremes should be interpreted with caution. Thus, identifying reliable markers that reflect the overall atherogenic burden is of particular importance in younger patients.[3,4,15,16,19]

Our cohort included a higher proportion of female patients (41.4%) than most previously published young MI registries. This finding may be related to regional differences in the clinical characteristics of premature coronary artery disease, as well as to the broader age definition (≤50 years) adopted in the present study. The definition of young or premature MI remains heterogeneous across the literature, with some studies applying sex-specific age thresholds and others using a uniform age cutoff. In addition, very young MI is frequently considered a distinct subgroup, often defined using substantially lower age thresholds. However, no universally accepted age definition currently exists. In the present study, a single threshold of ≤50 years was selected to ensure a consistent and clinically homogeneous study population, preserve statistical power, and facilitate interpretation of the overall cohort. Although sex-specific age definitions may better account for differences in the age of MI onset between women and men, the use of a uniform threshold allowed evaluation of the prognostic value of the non-HDL-C/HDL-C ratio within a single contemporary young MI population. Nevertheless, alternative age definitions may identify different risk profiles, particularly among women and very young patients, and this methodological heterogeneity should be considered when interpreting the findings and comparing them with those of other premature MI cohorts. It should nonetheless be recognized that premature MI represents a heterogeneous clinical entity encompassing both atherosclerotic and nonatherosclerotic mechanisms, and a structured etiologic assessment has been advocated in this population.[4] Furthermore, detailed information regarding menopausal status, hormonal exposure, and pregnancy-related risk factors was not systematically available in the present cohort; therefore, their potential contribution to the relatively high proportion of female patients in the cohort could not be evaluated. Although the present analysis focused on the prognostic value of lipid-derived indices rather than etiologic classification, these broader mechanisms warrant systematic evaluation in future prospective studies.

Although LDL-C remains the primary therapeutic target in current guidelines, non-HDL-C has emerged as an important secondary therapeutic target, particularly in individuals with elevated residual risk.[6,9,15,20,21] Unlike LDL-C, which reflects only a single component of circulating atherogenic lipoproteins, non-HDL-C represents the overall burden of apoB-containing particles, including very-low-density lipoproteins and remnant lipoproteins, both of which are implicated in the initiation and progression of atherosclerosis.[22–25] Moreover, non-HDL-C can be reliably assessed irrespective of fasting status and is less susceptible to fluctuations in triglyceride levels than LDL-C, making it particularly practical in routine clinical settings. This more comprehensive representation of atherogenic load may be particularly relevant in younger patients, who often exhibit more complex metabolic profiles and prolonged exposure to dyslipidemia. Consistent with this, large-scale observational data, including findings from the SWEDEHEART registry, have demonstrated the clinical relevance of non-HDL-C in heterogeneous cardiovascular populations.[8,9]

Combined lipid indices that integrate both atherogenic and antiatherogenic lipoprotein components may provide a more comprehensive assessment of cardiovascular risk than isolated lipid measurements alone.[11] Among these, the non-HDL-C/HDL-C ratio has been proposed as a marker reflecting the balance between proatherogenic and antiatherogenic lipid

fractions.[26] Population-based cohort studies have demonstrated a strong association between this ratio and the development of cardiovascular disease, with particularly pronounced associations observed in younger individuals.[13,14]

Evidence derived from acute coronary syndrome cohorts further reinforces these observations. For instance, previous studies in NSTEMI populations have reported that elevated non-HDL-C/HDL-C ratios were independently associated with both more severe coronary artery involvement and an increased risk of MACCE.[27] Similarly, studies involving patients undergoing percutaneous coronary intervention have shown that this ratio may also be associated with the development of nonculprit coronary lesions, suggesting that the ratio may reflect the extent and progression of the underlying atherosclerotic process.[28] However, the relatively limited sample sizes and heterogeneous study populations in these investigations may restrict the generalizability of their findings. Although STEMI and NSTEMI represent distinct clinical entities, the prognostic association between the non-HDL-C/HDL-C ratio and 1-year MACCE was consistent across both subgroups, with no significant interaction according to MI presentation. This finding suggests that the relationship between lipid-related atherogenic burden and adverse outcomes is broadly consistent across different acute MI phenotypes.

Overall, the non-HDL-C/HDL-C ratio showed stronger discrimination than the other lipid parameters evaluated, with consistent associations in multivariable Cox and Kaplan–Meier analyses. However, given the observational design, these findings should not be interpreted as evidence of causality, and residual confounding may have influenced the results.

Our findings may have clinical implications. The non-HDL-C/HDL-C ratio is readily derived from routine lipid measurements and may help identify young patients with MI who are at higher risk of subsequent events. However, prospective multicenter validation is required before routine clinical use. All patients were discharged on high-intensity statin therapy; however, repeat lipid measurements were not systematically available, and our findings therefore primarily reflect the prognostic value of the lipid profile obtained during the index hospitalization.

This study has several limitations. Its single-center retrospective design may limit generalizability and introduce selection bias and residual confounding, while the relatively short follow-up may not fully capture long-term outcomes. ApoB and lipoprotein(a) levels were not routinely available. Lipid parameters were assessed only once using the first available profile obtained at presentation or within 24 hours, without standardized fasting status or timing relative to PCI or heparin administration; therefore, particularly for triglyceride-related measures, some influence of sampling conditions cannot be excluded. Repeat lipid measurements were not systematically available, precluding assessment of longitudinal lipid changes after the index MI.

A comprehensive etiologic evaluation of young MI was also not feasible. Although type 2 MI was excluded, MINOCA and other nonatherosclerotic mechanisms could not be systematically analyzed, and information regarding family history of premature ASCVD, familial hypercholesterolemia, inherited thrombophilia, substance use, hormonal or pregnancy-related factors, and inflammatory or autoimmune disorders was not systematically available. Although discharge antiplatelet and lipid-lowering therapies were available, longitudinal treatment changes and medication adherence were not systematically captured. Reliable patient-level discharge data regarding ACE inhibitors, ARBs, ARNI, and beta-blockers were also unavailable. In addition, several potentially relevant clinical and angiographic variables, including body mass index, culprit vessel characteristics, multivessel coronary disease burden, symptom-to-revascularization and door-to-balloon times, and detailed revascularization strategies, could not be incorporated into the analyses. Finally, the cutoff of 4.43 was derived and evaluated in the same cohort and should therefore be considered exploratory. Although bootstrap resampling demonstrated stable discrimination, some variability in the rederived threshold remained, and external validation is required before clinical application.

## Conclusion

The non-HDL-C/HDL-C ratio demonstrated greater discriminative ability than conventional lipid parameters and was independently associated with an increased risk of 1-year MACCE in young patients with myocardial infarction. As an easily obtainable marker derived from routine lipid measurements, it may provide additional value for risk stratification in this population. Nevertheless, these findings require confirmation in larger prospective multicenter studies before routine clinical implementation can be considered.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-30998/TKDA-30998_(0)_Supplementary_Tables.pdf

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**Author Contributions:** Concept – M.F.K.; Design – M.F.K., K.B.; Supervision – M.F.K.; Resource – K.B.; Materials – K.B.; Data Collection and/or Processing – M.F.K.; Analysis and/or Interpretation – M.F.K., K.B.; Literature Review – K.B.; Writing – M.F.K.; Critical Review – M.F.K.

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# Premature Myocardial Infarction: Beyond LDL-C, but Not Beyond Atherogenic Lipoproteins

## Prematür Miyokard Enfarktüsü: LDL-Kolesterolün Ötesinde, Ancak Aterojenik Lipoproteinlerin Sınırları İçinde

**EDITORIAL COMMENT**
EDİTÖRYAL YORUM

I read with great interest the study by Keten and Bıyıklı[1] evaluating the prognostic value of the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol (non-HDL-C/HDL-C) ratio in young patients with myocardial infarction (MI). The study addresses a clinically relevant challenge: identifying patients at increased residual cardiovascular risk after experiencing MI at a young age. Premature MI represents a particularly important clinical phenotype because an early event may reflect accelerated exposure to atherogenic, metabolic, genetic, and behavioral risk factors while also placing patients at an increased lifetime risk of recurrent cardiovascular disease.

Previous studies have shown that young patients with MI frequently have a substantial burden of modifiable and inherited cardiovascular risk factors. In the YOUNG-MI Registry, patients aged ≤40 years had risk profiles broadly similar to those aged 41–50 years and experienced comparable long-term all-cause and cardiovascular mortality despite being approximately a decade younger.[2] Importantly, inherited lipid disorders warrant particular attention in this setting. Clinically defined familial hypercholesterolemia (FH) was identified in approximately 9% of patients who experienced MI at ≤50 years of age in the same registry.[3] Premature MI therefore represents not only an acute coronary event but also an opportunity to identify previously unrecognized determinants of accelerated atherosclerosis.

Recent evidence has reinforced the importance of looking beyond low-density lipoprotein cholesterol (LDL-C) alone when characterizing the atherogenic lipoprotein burden. Non-HDL-C captures cholesterol transported by a broad spectrum of apolipoprotein B (apoB)-containing lipoproteins, whereas apoB more directly reflects the number of circulating atherogenic particles.[4] Similarly, lipoprotein(a) [Lp(a)], a largely genetically determined cardiovascular risk factor, appears particularly relevant in premature atherosclerotic cardiovascular disease (ASCVD). A systematic review and meta-analysis comprising 51 studies and 100,540 participants found that elevated Lp(a) levels were associated with premature ASCVD, with a particularly strong association observed for premature coronary artery disease.[5]

The investigators retrospectively evaluated 856 consecutive patients aged ≤50 years with acute MI, including 302 with ST-segment elevation MI (STEMI) and 554 with non-ST-segment elevation MI (NSTEMI). During the one-year follow-up, 129 patients (15.0%) experienced major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause mortality, ischemic stroke, recurrent MI, or unplanned repeat coronary revascularization.[1] The non-HDL-C/HDL-C ratio was independently associated with MACCE (hazard ratio [HR], 1.568; 95% confidence interval [CI], 1.463–1.681), and this association was consistent across both STEMI and NSTEMI presentations. Most notably, the ratio demonstrated an area under the receiver operating characteristic curve of 0.864, which was significantly greater than those observed for LDL-C, non-HDL-C, and the atherogenic index of plasma.[1]

These findings extend previous observations linking the non-HDL-C/HDL-C ratio to coronary artery disease and adverse cardiovascular outcomes. In a study of 426 patients with first-onset NSTEMI, Mao et al.[6] reported that the ratio was independently associated with severe coronary lesions and subsequent major adverse cardiovascular events. More recently, Liu et al.[7] evaluated 329 patients with acute coronary syndrome who underwent percutaneous coronary intervention and found that a higher non-

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HDL-C/HDL-C ratio was independently associated with the progression of nonculprit coronary lesions during follow-up. The present study extends these observations specifically to a young MI population and provides further support through a comprehensive statistical evaluation incorporating multivariable analyses, calibration, bootstrap validation, restricted cubic splines, and decision curve analysis.

The simplicity of this marker represents an important strength, as the non-HDL-C/HDL-C ratio requires no additional laboratory testing, can be calculated from a conventional lipid profile, and incurs no additional cost. This characteristic may be particularly relevant in clinical settings where apoB, Lp(a), and other advanced lipid measurements are not routinely available.

Nevertheless, the biological interpretation of the ratio warrants consideration. Non-HDL-C reflects the cholesterol contained in LDL and other apoB-containing atherogenic lipoproteins. In contrast, HDL-C has a different relationship with cardiovascular disease causality. Although low HDL-C levels are strongly associated with ASCVD in observational studies, evidence from human genetics and randomized clinical trials does not support HDL-C concentration itself as a therapeutic target for ASCVD prevention.[8] Accordingly, the non-HDL-C/HDL-C ratio may be more appropriately interpreted as an integrated prognostic marker rather than a specific therapeutic target. Its potential clinical value lies in identifying risk rather than establishing a treatment goal based on the ratio itself.

Several limitations should be considered when interpreting these findings. First, this was a retrospective, single-center study, and external validation remains essential. The proposed cutoff value of 4.43 was derived from the same population in which its prognostic performance was evaluated; therefore, this value should currently be regarded as exploratory rather than as a definitive clinical cutoff.

Second, lipid measurements were obtained at presentation or within the first 24 hours after MI, using the first available lipid profile.[1] The timing of sampling, fasting status, acute treatment, and metabolic and inflammatory responses accompanying an acute coronary event may influence individual lipid measurements. Furthermore, longitudinal lipid measurements were unavailable, precluding assessment of whether the prognostic value of the ratio persists after clinical stabilization and intensive lipid-lowering therapy. This is particularly relevant because all patients were discharged on high-intensity statin therapy.[1]

Third, apoB and Lp(a) measurements were not routinely available, a limitation of particular importance in a young MI population. A recent systematic review of 15 discordance studies involving 593,354 participants found that apoB outperformed LDL-C in all nine direct comparisons and non-high-density lipoprotein cholesterol (non-HDL-C) in seven of nine comparisons.[4] Whether the non-HDL-C to high-density lipoprotein cholesterol (HDL-C) ratio provides incremental prognostic information when apoB measurements are available therefore remains an important question for future studies.

The absence of Lp(a) measurements is similarly important. In the meta-analysis by Tian et al.,[5] elevated Lp(a) levels were associated with more than twice the odds of premature ASCVD (odds ratio [OR], 2.15; 95% confidence interval [CI], 1.53–3.02) and an even stronger association with premature coronary artery disease (OR, 2.44; 95% CI, 2.06–2.90). Evaluating the non-HDL-C/HDL-C ratio alongside apoB and Lp(a) would therefore allow a more comprehensive assessment of its incremental prognostic value.

Systematic characterization of FH and family history of premature ASCVD was also unavailable, an important limitation in patients aged ≤50 years, among whom FH is substantially more prevalent than in the general population.[3] The study appropriately acknowledges the lack of information on FH, family history, inherited thrombophilia, substance use, hormonal and pregnancy-related factors, and inflammatory or autoimmune disorders among its limitations.[1]

Another consideration is the etiologic heterogeneity of MI in younger individuals. In addition to conventional atherosclerotic mechanisms, premature MI may involve spontaneous coronary artery dissection, coronary vasospasm, coronary embolism, substance-related events, thrombophilia, coronary anomalies, and other mechanisms.[9] In the present study, although type 2 MI was excluded, myocardial infarction with nonobstructive coronary arteries (MINOCA) and nonatherosclerotic mechanisms were not systematically excluded when patients met the diagnostic criteria for acute MI.[1] This issue may be particularly relevant given the relatively high proportion of women in the cohort.

Finally, interpretation of the composite endpoint warrants some caution. Among the 129 MACCE, recurrent MI accounted for 61 events and unplanned repeat coronary revascularization for 56, whereas only eight deaths and four ischemic strokes occurred.[1] Thus, the prognostic performance of the ratio primarily reflects its association with recurrent coronary events and revascularization rather than an equivalent ability to predict each component of the composite outcome.

These considerations should, however, be weighed against the important strengths of the study. The investigators evaluated a sizeable and clinically relevant cohort of young patients with MI, examined an inexpensive and universally available lipid parameter, achieved complete one-year outcome ascertainment, and applied a comprehensive statistical approach.[1] Importantly, the association between the non-HDL-C/HDL-C ratio and subsequent events remained consistent in patients with both STEMI and NSTEMI, with no significant interaction according to MI presentation. The association was also observed in both men and women.[1]

I therefore agree with the authors that the non-HDL-C/HDL-C ratio may provide additional prognostic information beyond conventional lipid parameters in young patients with MI. Its simplicity and universal availability make it an attractive candidate for risk stratification, particularly in settings where advanced lipid testing is unavailable. Nevertheless, the aforementioned limitations underscore the need for prospective validation in larger, multicenter, and more diverse populations.

Future studies should determine whether this association remains robust in the setting of contemporary intensive lipid-lowering therapy and, importantly, whether the ratio provides incremental prognostic information when apoB, Lp(a), and

other determinants of premature ASCVD are incorporated into risk assessment. Ultimately, one of the principal strengths of the present study is its demonstration that clinically meaningful prognostic information can still be obtained from a simple and universally available lipid profile. The non-HDL-C/HDL-C ratio appears to be a promising and pragmatic marker for risk stratification in young patients with MI, and the present findings provide a strong rationale for prospective external validation.

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# Young Patients Presenting with Suspected ST-Elevation Myocardial Infarction Undergoing Emergency Coronary Angiography: Clinical Characteristics and 1-Year Outcomes

## ST-Segment Yükselmeli Miyokard Enfarktüsü Şüphesiyle Başvuran ve Acil Koroner Anjiyografi Uygulanan Genç Hastalar: Klinik Özellikler ve 1 Yıllık Sonlanımlar

**ABSTRACT**

**Objective:** This study aimed to determine the demographic and clinical profiles, cardiovascular risk factors, and variables independently associated with major adverse cardiovascular events (MACE) during 1-year follow-up in young patients aged 45 years or younger who presented with suspected ST-segment elevation myocardial infarction (STEMI) and underwent emergency coronary angiography.

**Method:** This retrospective, single-center, observational study included 126 young patients presenting with suspected STEMI who underwent underwent emergency coronary angiography, with percutaneous coronary intervention when indicated at a high-volume tertiary cardiovascular center between January 2021 and April 2025. Patients were classified into two groups according to the occurrence of MACE during 1-year follow-up: the MACE group (n=28) and the non-MACE group (n=98). HbA1c levels were assessed based on a single measurement obtained during the index MI admission. Logistic regression analyses were performed to identify variables independently associated with MACE.

**Results:** The median age of the overall cohort was 40 years (38–42), and 7.9% of the patients were female. During follow-up, MACE occurred in 22.2% of the patients. The all-cause mortality rate was 4.0%. Multivariable logistic regression analysis demonstrated that higher HbA1c levels (aOR: 1.57; 95% CI: 1.10–2.24; P = 0.014), a history of CAD (aOR: 3.93; 95% CI: 1.15–13.37; P = 0.029), and lower LVEF (aOR: 0.94; 95% CI: 0.88–0.99; P = 0.029) were independently associated with MACE. Notably, among patients without previously known diabetes, HbA1c levels ≥6.5% were significantly associated with an increased risk of MACE.

**Conclusion:** Young patients presenting with suspected STEMI who undergo emergency coronary angiography may have a notable risk of MACE during the first year of follow-up. A history of CAD, lower LVEF, and elevated HbA1c levels appear to be associated with adverse clinical outcomes.

**Keywords:** HbA1c, major adverse cardiovascular events, premature coronary artery disease, young STEMI.

**ÖZET**

**Amaç:** Bu çalışmada, 45 yaş ve altındaki ST-segment elevasyonlu miyokard enfarktüsü (STEMI) şüphesiyle acil koroner anjiyografi yapılan genç hastaların demografik ve klinik profillerinin, kardiyovasküler risk faktörlerinin ve 1 yıllık takip süresince majör advers kardiyovasküler olaylar (MACE) ile bağımsız olarak ilişkili değişkenlerin belirlenmesi amaçlandı.

**Yöntem:** Bu retrospektif, tek merkezli ve gözlemsel çalışma, Ocak 2021 ile Nisan 2025 tarihleri arasında yüksek hacimli bir üçüncü basamak kardiyovasküler merkeze STEMI şüphesiyle başvuran ve acil koroner anjiyografi ve gerektiğinde perkütan koroner girişim uygulanan uygulanan 126 genç hastayı kapsadı. Hastalar, 1 yıllık takip süresince MACE gelişimine göre iki gruba sınıflandırıldı: MACE grubu (n=28) ve MACE olmayan grup (n=98). HbA1c düzeyleri, indeks miyokard enfarktüsü yatışı sırasında elde edilen tek bir ölçüme dayanarak değerlendirildi. MACE ile bağımsız olarak ilişkili değişkenleri belirlemek amacıyla lojistik regresyon analizleri yapıldı.

**Bulgular:** Genel kohortun ortanca yaşı 40 (38–42) yıl olup hastaların %7,9'u kadındı. Takip süresince hastaların %22,2'sinde MACE gözlendi. Tüm nedenlere bağlı mortalite oranı %4,0'dı. Çok değişkenli lojistik regresyon analizinde yüksek HbA1c düzeyleri (aOR: 1,57; %95 GA: 1,10–2,24; P = 0,014), koroner arter hastalığı (KAH) öyküsü (aOR: 3,93; %95 GA: 1,15–13,37;

**ORIGINAL ARTICLE**
ARAŞTIRMA MAKALESİ

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P = 0,029) ve düşük sol ventrikül ejeksiyon fraksiyonu (LVEF) (aOR: 0,94; %95 GA: 0,88–0,99; P = 0,029) MACE ile bağımsız olarak ilişkili değişkenler olarak belirlendi. Dikkat çekici olarak, daha önce diyabet tanısı olmayan hastalarda bile %6,5 ve üzerindeki HbA1c düzeyleri, artmış MACE riski ile anlamlı düzeyde ilişkili bulundu.

**Sonuç:** STEMI şüphesiyle acil koroner anjiyografi yapılan genç hastalar, 1 yıllık takip süresi boyunca belirgin bir MACE riskiyle karşı karşıya kalabilmektedir. KAH öyküsü, düşük LVEF ve yüksek HbA1c düzeyleri olumsuz klinik sonuçlarla ilişkili görünmektedir.

**Anahtar Kelimeler:** HbA1c, majör advers kardiyovasküler olaylar, prematür koroner arter hastalığı, genç STEMI.

Acute myocardial infarction (MI) remains a leading cause of global cardiovascular morbidity and mortality; however, its rising or stagnating incidence among young adults has emerged as an important public health concern.[1,2] For decades, clinical attention and primary prevention guidelines have predominantly focused on older adults, in whom coronary artery disease (CAD) develops as a consequence of progressive, age-related vascular degeneration. Conversely, contemporary data from large-scale multicenter studies, such as the YOUNG-MI registry, underscore a concerning epidemiological shift characterized by a disproportionate burden of ST-elevation myocardial infarction (STEMI) among young patients despite a substantial global decline in CAD rates among older populations.[3] The literature remains inconsistent because of the lack of consensus regarding a universally accepted age threshold for defining young patients with myocardial infarction; some studies have used cutoffs ranging from ≤40 to ≤55 years, whereas ≤45 years is the most commonly used threshold for assessing premature CAD in contemporary cardiovascular studies.[4,5] STEMI in this younger population represents not only a clinical challenge but also a substantial socioeconomic burden, as it affects individuals during their most productive years and may result in profound long-term psychological, familial, and societal consequences.

The pathophysiological and angiographic profiles of young patients with STEMI differ substantially from those observed in older populations. Although traditional cardiovascular risk factors-most notably heavy tobacco use, a family history of premature CAD, hyperlipidemia, and metabolic syndrome-remain highly prevalent, the classical atherosclerotic cascade does not fully explain premature coronary syndromes.[6] Accumulating molecular and clinical evidence indicates a shift toward a more complex interplay of nonatherosclerotic etiologies and novel triggering mechanisms in young patients.[7] These include hypercoagulable states, autoimmune-mediated chronic low-grade vascular inflammation, substance abuse, and structural coronary anomalies, along with alternative mechanisms such as spontaneous coronary artery dissection (SCAD) and severe coronary vasospasm.[1,4]

Notably, young patients presenting with suspected STEMI generally have excellent short-term and in-hospital survival rates compared with older cohorts, a finding largely attributed to a higher prevalence of single-vessel disease, preserved left ventricular ejection fraction, and fewer debilitating age-related comorbidities. However, this favorable initial presentation may mask an unfavorable long-term prognosis. Recent longitudinal follow-up registries have demonstrated that young MI survivors carry a high cumulative lifetime risk of major adverse cardiovascular events (MACE), including recurrent ischemic events, progressive heart failure, and target-vessel revascularization over subsequent decades.[2,8] This clinical vulnerability is reflected in the latest European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes, which emphasize intensive, individualized risk-factor modification and comprehensive secondary prevention strategies.[9]

Although multinational registries have provided important insights into premature acute coronary syndromes, the external generalizability of their findings remains limited by substantial regional differences in sociodemographic characteristics, healthcare accessibility, ethnic predispositions, and lifestyle-related risk factors. Furthermore, the current literature lacks studies that simultaneously evaluate baseline clinical characteristics, emergency department presentation patterns, detailed angiographic findings, and MACE outcomes in a homogeneous and specific group of young patients hospitalized with suspected STEMI and managed exclusively with primary coronary angiography (CAG).

To expand on these findings, the present study aimed to evaluate the demographic and clinical profiles, cardiovascular risk factors, and clinical outcomes of young patients aged 45 years or younger who presented with suspected STEMI and underwent primary CAG at a high-volume tertiary referral center.

## ABBREVIATIONS

| | |
|---|---|
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CAG | Coronary angiography |
| ESC | European Society of Cardiology |
| LAD | Left anterior descending artery |
| MACE | Major adverse cardiovascular events |
| MI | Myocardial infarction |
| NSTEMI | Non-ST-elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| RCA | Right coronary artery |
| SCAD | Spontaneous coronary artery dissection |
| USAP | Unstable angina pectoris |

## Methods

### Study Design and Setting

This single-center, retrospective cohort study was conducted at a high-volume tertiary cardiovascular referral center to evaluate the clinical characteristics and outcomes of young patients presenting to the emergency department or cardiology clinic with suspected STEMI between January 2021 and April 2025. The study period was selected to ensure that all included patients had a minimum follow-up duration of 12 months for assessment of clinical outcomes. The study protocol was formally reviewed and approved Dokuz Eylül University Non-Interventional Research Ethics Committee (Approval Number: 2026/20-47, Date: 01.06.2026). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

### Study Population and Sample Size Strategy

A total of 138 consecutive patients were initially screened for eligibility. Patients with missing critical angiographic, echocardiographic, or baseline laboratory data (n=3), those with missing 1-year follow-up data (n=5), and those who experienced preprocedural or procedural mortality (n=4) were excluded from the study cohort and final analysis. Consequently, the final study population comprised 126 young adults aged 18–45 years (inclusive) who presented to the emergency department, were admitted to the coronary care unit, received an initial diagnosis of suspected STEMI between January 2021 and April 2025, and had complete baseline and follow-up data. Because there is no universally accepted age cutoff in the literature for defining young patients with MI, with thresholds ranging from ≤40 to ≤55 years, the ≤45-year cutoff, which is commonly used in contemporary cardiovascular studies, was selected to facilitate comparability with available epidemiological data.[5]

This cohort was intentionally designed to reflect a real-world, unselected population of young adults presenting with an initial working diagnosis of suspected STEMI who underwent emergency invasive evaluation, thereby encompassing both true atherosclerotic type 1 myocardial infarction and alternative diagnoses subsequently established after angiography, such as MINOCA, SCAD, and STEMI mimickers. Patients were stratified into two groups according to the occurrence of MACE during the 1-year follow-up period: the MACE and non-MACE groups.

All eligible patients presenting during the study period were consecutively included, reflecting our institution's annual volume of premature cardiovascular events. To ensure adequate statistical power for the evaluation of clinical outcomes, a formal sample size rationale was established based on effect sizes derived from contemporary premature MI literature, including the PARTNERS YOUNG-MI registry. It was determined that a minimum sample size of 120 patients would provide 80% statistical power with a two-sided type I error rate of 5% (alpha=0.05) to detect statistically significant differences in clinical characteristics and MACE, assuming a conservative estimated MACE incidence of 20% and an anticipated odds ratio of approximately 2.5 for key variables, representing a clinically meaningful risk threshold reported for high-risk prognostic markers in young STEMI cohorts. A study cohort exceeding this minimum threshold was ultimately included.

### Eligibility and Screening Criteria

Candidate participants were systematically screened according to predefined eligibility criteria. The study flowchart is summarized in Figure 1.

The inclusion criteria were defined as follows:

Documented age between 18 and 45 years (inclusive) at the time of the index hospital admission.

A definitive diagnosis of STEMI established in accordance with current ESC guidelines; this diagnosis was based on a combination of characteristic ischemic chest pain or equivalent symptoms, electrocardiographic findings showing persistent ST-segment elevation in at least two contiguous leads or a new left bundle branch block, and biochemical evidence of myocardial necrosis demonstrated by a significant rise and/or fall in cardiac troponin values above the 99$^{th}$-percentile upper reference limit.

In addition, inclusion required that all patients undergo urgent CAG, with primary percutaneous coronary intervention (PCI) performed for the infarct-related artery (culprit vessel) when indicated, or that they be immediately referred to the cardiac catheterization laboratory for intended primary PCI.

The exclusion criteria consisted of:

Patients presenting with non-ST-elevation myocardial infarction (NSTEMI) or unstable angina pectoris (USAP).

Patients outside the 18–45-year age range.

Cases with missing critical angiographic, echocardiographic, or baseline laboratory data.

Preprocedural or procedural mortality.

Patients with severe hemodynamic instability that precluded primary CAG.

### Interventional Strategies and Revascularization Protocols

Treatment decisions regarding mechanical revascularization and interventional approaches were made at the discretion of the attending interventional cardiologists based on angiographic findings, clinical judgment, and institutional protocols aligned with current guidelines. The anatomical and angiographic characteristics evaluated included identification of the culprit lesion (vessel), classified as the left anterior descending artery (LAD), left circumflex artery (Cx), or right coronary artery (RCA).

### Data Extraction and Variable Definitions

Procedural metrics included specific presentation characteristics, revascularization features, adverse events during the index hospitalization, and outcomes during the 1-year follow-up period. Clinical, procedural, and laboratory parameters were retrospectively extracted from the institutional electronic medical record system (Hospital Information System; HBYS/Probel) using a structured data abstraction tool. Demographic and lifestyle variables included age, sex, and tobacco use status, which was classified as nonsmoker or active smoker based on documentation at admission. Body mass index (BMI) was calculated from height and weight measurements obtained at admission and recorded in the hospital information system. Baseline clinical comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, and a family history of premature CAD, were recorded in the case report form.

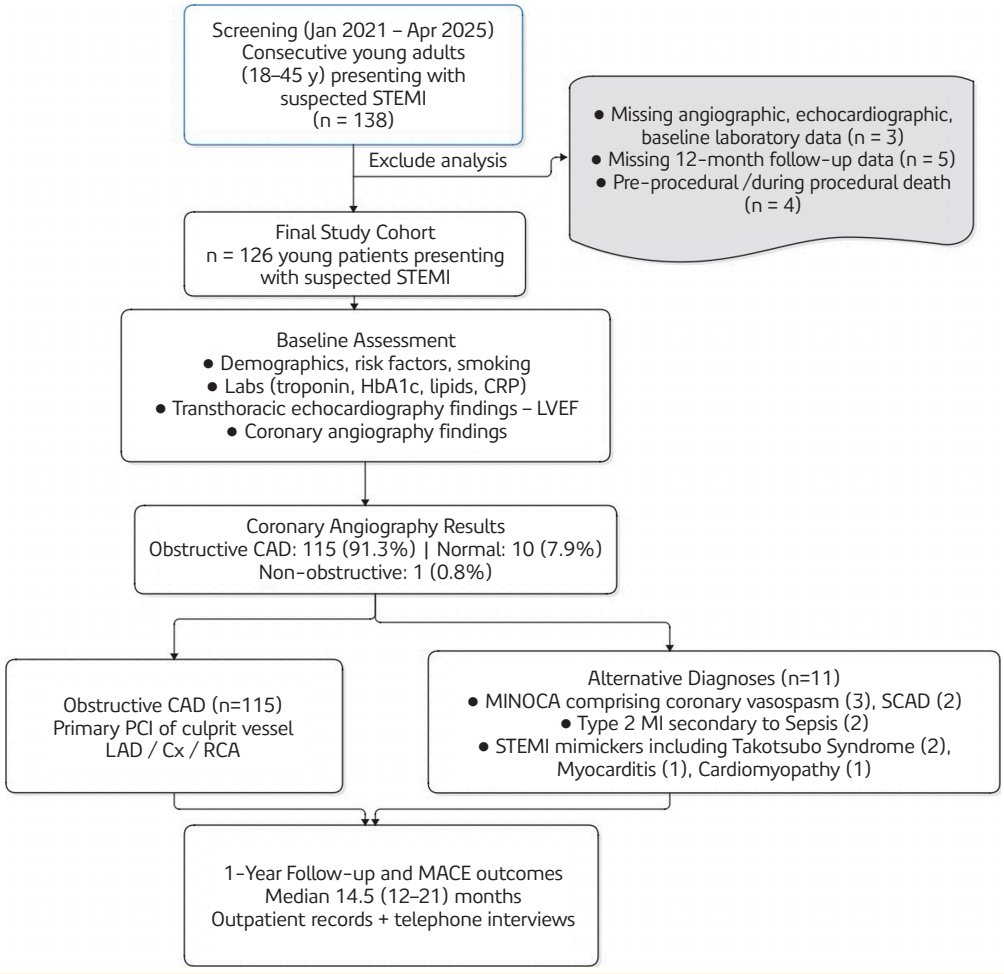



**Figure 1.** Study flow diagram illustrating patient screening, exclusion criteria, angiographic findings, and clinical follow-up.

Hypertension was defined as a documented history of chronic blood pressure elevation (≥140/90 mmHg) or current use of antihypertensive medications.[10] Diabetes mellitus was defined as a prior physician diagnosis of diabetes with use of antidiabetic medications or an HbA1c (glycated hemoglobin) level ≥6.5% at the index admission.[11] Hyperlipidemia was defined as a documented prior diagnosis, use of lipid-lowering therapy, or fasting serum total cholesterol >200 mg/dL, LDL-C >130 mg/dL, or triglyceride levels >150 mg/dL.[12] Participants were defined as smokers if they had used any amount of cigarettes or tobacco products at the time of hospital admission or within the preceding month.[9] Prior CAD was defined as a documented history of myocardial infarction, previous PCI, or coronary artery bypass grafting (CABG).[13] A family history of premature CAD was defined as the presence of premature CAD and/or sudden death in a first-degree male relative aged <55 years or a first-degree female relative aged <65 years.[13]

Laboratory evaluations included complete blood counts, cardiac biomarkers (troponin and CK-MB), renal function tests, blood urea nitrogen, serum creatinine, and fasting lipid profiles. HbA1c was measured once during the index hospitalization, within the first 24 hours of admission when available, using standardized institutional laboratory methods. Conditions potentially interfering with HbA1c interpretation, such as severe anemia, hemoglobinopathies, end-stage renal disease, recent bleeding, or blood transfusion, were carefully considered. New-onset diabetes mellitus was confirmed using standard diagnostic criteria combining baseline HbA1c and fasting plasma glucose levels. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol (non-HDL cholesterol=total cholesterol−HDL-C). Transthoracic echocardiography was performed within 48 hours after the intervention according to standard postprocedural protocols by certified cardiologists blinded to clinical outcomes.

### Clinical Endpoints and Outcome Adjudication

The primary endpoint of the study was the incidence of 1-year MACE, defined as a patient-level composite endpoint comprising cardiovascular mortality, hospitalization for heart failure, recurrent myocardial infarction, and/or unplanned repeat revascularization. Although elective staged revascularization of non-infarct-related arteries was performed when clinically indicated during follow-up, only unplanned repeat revascularizations were considered components of the MACE endpoint. All-cause mortality was evaluated and reported as a separate clinical endpoint outside the composite MACE model.

Event definitions were based on ESC guidelines and clinical trial endpoint definitions reported in the literature. Follow-up data were obtained from institutional electronic medical records

(Hospital Information System; HBYS/Probel), outpatient clinic visits, and structured telephone interviews with patients. All clinical endpoints and adverse events were rigorously verified and adjudicated by two independent cardiologists through detailed review of hospital admission records, discharge summaries, emergency department records, and, where applicable, national registry or death certificate records.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using visual methods (histograms and probability plots) and analytical tests. Normally distributed continuous variables were expressed as mean±standard deviation and compared using Student's t-test. Non-normally distributed continuous variables were presented as median (interquartile range) and compared using the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate.

Variables associated with MACE at a significance level of $P < 0.10$ in univariate comparisons were entered into univariate logistic regression analyses. Variables that remained statistically significant in the univariate logistic regression analyses were subsequently included in a multivariable logistic regression model using the enter method to identify parameters independently associated with MACE. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were reported. A two-sided p-value <0.05 was considered statistically significant.

## Results

### Study Population and Clinical Outcomes

A total of 126 young patients with MI were included in the study. The median age of the overall cohort was 40 (38–42) years, and 10 (7.9%) patients were female. HT, DM, HL, and a history of CAD were present in 31 (24.6%), 12 (9.5%), 36 (28.6%), and 20 (15.9%) patients, respectively. Sixty-nine (54.8%) patients were current smokers. The median LVEF was 45% (40–55), and the median follow-up duration was 14.5

**Table 1.** Baseline characteristics of the overall cohort and patients with and without MACE

| Variables | All patients (n=126) | MACE (+) (n=28) | MACE (–) (n=98) | *P* |
|---|---|---|---|---|
| Age† (years) | 40 (38–42) | 40.5 (38–43) | 40 (38–42) | 0.7 |
| Female, n (%) | 10 (7.9) | 1 (3.6) | 9 (9.2) | 0.3 |
| BMI* (kg/m²) | 29±2.9 | 29±3.2 | 29±2.8 | 0.8 |
| SBP* (mmHg) | 132±19 | 135±16 | 131±20 | 0.5 |
| DBP† (mmHg) | 78 (72–90) | 80 (71–91) | 78 (72–89) | 0.5 |
| HT, n (%) | 31 (24.6) | 7 (25.0) | 24 (24.5) | 0.9 |
| DM, n (%) | 12 (9.5) | 4 (14.3) | 8 (8.2) | 0.3 |
| HL, n (%) | 36 (28.6) | 7 (25.0) | 29 (29.6) | 0.6 |
| History of CAD, n (%) | 20 (15.9) | 8 (28.6) | 12 (12.2) | **0.04** |
| History of stroke, n (%) | 1 (0.8) | 0 (0) | 1 (0.8) | NA |
| CKD, n (%) | 1 (0.8) | 1 (3.6) | 0 (0) | NA |
| COPD, n (%) | 2 (1.6) | 2 (7.1) | 0 (0) | NA |
| PAD, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |
| Chronic inflammatory disease, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |
| Active smoker, n (%) | 69 (54.8) | 21 (75.0) | 48 (49.0) | **0.01** |
| Index MI localization, n (%) | | | | 0.3 |
| Anterior | 70 (55.6) | 13 (46.4) | 57 (58.2) | |
| Inferior | 44 (34.9) | 13 (46.4) | 31 (31.6) | |
| Posterior | 5 (4.0) | 1 (3.6) | 4 (4.1) | |
| Lateral | 7 (5.6) | 1 (3.6) | 6 (6.1) | |
| Coronary angiographic severity, n (%) | | | | 0.7 |
| Normal coronary arteries | 10 (7.9) | 3 (10.7) | 7 (7.1) | |
| Nonobstructive CAD | 1 (0.8) | 0 (0) | 1 (0.8) | |
| Obstructive CAD | 115 (91.3) | 25 (89.3) | 90 (91.8) | |
| Heart rate† (beats/min) | 76 (69–82) | 80 (70–85) | 76 (68–82) | 0.5 |
| LVEF† (%) | 45 (40–55) | 40 (30–55) | 45 (40–51) | **0.02** |
| Follow-up duration† (months) | 14.5 (12–21) | 16 (12–22) | 14 (12–20) | 0.4 |

* Mean±standard deviation. † Median (interquartile range). BMI, Body mass index; CAD, Coronary artery disease; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; DBP, Diastolic blood pressure; DM, Diabetes mellitus; HL, Hyperlipidemia; HT, Hypertension; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiovascular events; MI, Myocardial infarction; PAD, Peripheral artery disease; SBP, Systolic blood pressure.

(12–21) months. Regarding index MI localization, 70 (55.6%) patients had anterior MI, 44 (34.9%) had inferior MI, 7 (5.6%) had lateral MI, and 5 (4.0%) had posterior MI. Obstructive CAD was present in 115 (91.3%) patients, whereas 10 (7.9%) had normal coronary arteries and 1 (0.8%) had nonobstructive CAD on urgent CAG, which had been performed with the intention of primary PCI. In these 11 patients, no culprit obstructive coronary lesion was identified; therefore, primary PCI was not performed. Subsequent evaluation established alternative diagnoses categorized into specific clinical entities: myocardial infarction with nonobstructive coronary arteries (MINOCA), including coronary vasospasm (n=3) and SCAD (n=2); type 2 myocardial infarction secondary to sepsis (n=2); and STEMI mimickers, including Takotsubo syndrome (n=2), myocarditis (n=1), and cardiomyopathy (n=1) (Table 1).

During follow-up, MACE occurred in 28 (22.2%) patients. The most frequent component of MACE was recurrent myocardial infarction and/or unplanned repeat revascularization, which occurred in 25 (19.8%) patients. Cardiovascular mortality occurred in 4 (3.2%) patients, and hospitalization for heart failure occurred in 6 (4.8%) patients. Some patients experienced more than one event during follow-up; therefore, the sum of the individual MACE components exceeded the total number of patients with MACE. All-cause mortality occurred in 5 (4.0%) patients, including 4 cardiovascular deaths and 1 noncardiovascular death.

**Baseline Characteristics According to MACE Status**

The baseline characteristics of patients with and without MACE are presented in Table 1. Patients who developed MACE had a higher prevalence of prior CAD [28.6% vs. 12.2%, P = 0.04] and were more frequently active smokers [75.0% vs. 49.0%, P = 0.01] than those without MACE. In addition, patients with MACE had lower LVEF values [40% (30–55) vs. 45% (40–51), P = 0.02]. No significant differences were observed between the groups in age, sex, HT, DM, HL, MI localization, angiographic severity of CAD, heart rate, or follow-up duration (Table 1).

**Laboratory Findings According to MACE Status**

Laboratory findings according to MACE status are presented in Table 2. Patients who developed MACE had higher HbA1c levels [5.7% (5.5–7.2) vs. 5.6% (5.3–5.8), P = 0.007]. Peak high-sensitivity cardiac troponin T (hs-cTnT) levels did not differ significantly between the groups [12,365 (4,783–29,640) vs. 23,186 (9,067–51,476) ng/L, evaluated per 1,000-ng/L increase, P = 0.06]. No significant differences were observed between the groups in fasting glucose, eGFR, albumin, lipid parameters, hemoglobin, or CRP levels (Table 2).

Complete baseline HbA1c data were available for all 126 patients included in the study. Elevated HbA1c levels (≥6.5%) were further evaluated in the study population. Among the 114 patients without a prior diagnosis of DM, 8 (7.0%) had an admission HbA1c level ≥6.5%. Furthermore, MACE occurred more frequently among patients with HbA1c ≥6.5% than among those with HbA1c <6.5% [44.4% vs. 18.5%, P = 0.028].

**Discharge Treatment According to MACE Status**

Discharge treatment according to MACE status is presented in Table 3. Overall, evidence-based medical therapy at discharge was comparable between patients with and without MACE. High-intensity statins, aspirin, beta-blockers, and ACE inhibitors/ARBs were prescribed at similarly high rates in both groups, with no significant between-group differences. Likewise, the use of P2Y12 inhibitors, mineralocorticoid receptor antagonists, SGLT2 inhibitors, and antidiabetic therapies did not differ significantly according to MACE status (Table 3).

**Variables Associated With MACE**

Univariate and multivariable logistic regression analyses of variables associated with MACE are presented in Table 4. In univariate analyses, a history of CAD [OR 2.87, 95% CI 1.04–7.94, P = 0.04], active smoking [OR 3.13, 95% CI 1.22–8.02, P = 0.02], lower LVEF [OR 0.94, 95% CI 0.90–0.98, P = 0.002], and higher HbA1c levels [OR 1.56, 95% CI 1.14–2.14, P = 0.005] were associated with MACE (Table 4).

**Table 2.** Laboratory characteristics of patients with and without MACE

| Variables | MACE (+) (n=28) | MACE (–) (n=98) | *P* |
|---|---|---|---|
| Fasting glucose† (mg/dL) | 125 (99–175) | 109 (91–129) | 0.1 |
| eGFR† (mL/min/1.73 m²) | 102 (88–111) | 109 (95–113) | 0.25 |
| Albumin* (g/dL) | 4.0±0.4 | 4.1±0.3 | 0.15 |
| LDL-C† (mg/dL) | 138 (118–151) | 128 (104–153) | 0.46 |
| HDL-C* (mg/dL) | 43±11 | 43±10 | 0.9 |
| Total cholesterol† (mg/dL) | 210 (191–235) | 205 (174–235) | 0.29 |
| Triglycerides† (mg/dL) | 142 (100–233) | 146 (98–208) | 0.53 |
| Non-HDL cholesterol (mg/dL) | 165 (149–195) | 164 (134–189) | 0.34 |
| Hemoglobin† (g/dL) | 14.6 (13.5–15.5) | 14.9 (14.0–15.6) | 0.32 |
| Peak hs-cTnT† (ng/L) | 12,365 (4,783–29,640) | 23,186 (9,067–51,476) | 0.06 |
| CRP† (mg/L) | 7.8 (3.6–14.0) | 5.8 (3.4–18.6) | 0.7 |
| HbA1c† (%) | 5.7 (5.5–7.2) | 5.6 (5.3–5.8) | **0.007** |

* Mean±standard deviation. † Median (interquartile range). CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; hs-cTnT, High-sensitivity cardiac troponin T; LDL-C, Low-density lipoprotein cholesterol; MACE, Major adverse cardiovascular events.

**Table 3.** Discharge treatment of patients with and without MACE

| Treatment | MACE (+) (n=28) n (%) | MACE (–) (n=98) n (%) | *P* |
|---|---|---|---|
| ASA | 27 (96.4) | 95 (96.9) | 0.9 |
| Clopidogrel | 6 (21.4) | 10 (10.2) | 0.1 |
| Ticagrelor | 19 (67.9) | 78 (79.6) | 0.2 |
| Prasugrel | 0 (0) | 4 (4.1) | NA |
| High-intensity statin | 27 (96.4) | 94 (95.9) | 0.9 |
| Ezetimibe | 0 (0) | 0 (0) | NA |
| PCSK9 inhibitor | 0 (0) | 0 (0) | NA |
| Beta-blocker | 26 (92.9) | 95 (96.9) | 0.18 |
| Ivabradine | 2 (7.1) | 4 (4.1) | NA |
| ACEI | 22 (78.6) | 83 (84.7) | 0.4 |
| ARB | 2 (7.1) | 10 (10.2) | NA |
| ARNI | 1 (3.6) | 1 (1.0) | NA |
| MRA | 7 (25.0) | 30 (30.6) | 0.5 |
| Diuretic | 2 (7.1) | 3 (3.1) | NA |
| SGLT2 inhibitor | 3 (10.7) | 14 (14.3) | NA |
| Oral antidiabetic therapy | 3 (10.7) | 5 (5.1) | NA |
| Insulin therapy | 3 (10.7) | 3 (3.1) | NA |

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; ARNI, Angiotensin receptor–neprilysin inhibitor; ASA, Acetylsalicylic acid; MACE, Major adverse cardiovascular events; MRA, Mineralocorticoid receptor antagonist; PCSK9, Proprotein convertase subtilisin/kexin type 9; SGLT2, Sodium-glucose cotransporter 2.

In the multivariable logistic regression analysis, higher HbA1c levels [adjusted OR 1.57, 95% CI 1.10–2.24, P = 0.014], a history of CAD [adjusted OR 3.93, 95% CI 1.15–13.37, P = 0.029], and lower LVEF [adjusted OR 0.94, 95% CI 0.88–0.99, P = 0.029] remained independently associated with MACE, whereas the association between active smoking and MACE was no longer statistically significant after adjustment (Table 4). A history of CAD was associated with an approximately fourfold increase in the risk of MACE. Furthermore, each 1% increase in HbA1c was associated with a 57% increase in the risk of MACE, whereas each 1% increase in LVEF was associated with a 6% reduction in the risk of MACE.

## Discussion

In this study, 22.2% of young patients presenting with suspected STEMI experienced MACE during the first year of follow-up. Our analysis identified a history of CAD, lower LVEF, and elevated HbA1c levels as factors associated with adverse clinical outcomes. Although active smoking was significantly associated with MACE in the univariate analysis, this association was not maintained in the multivariable model, suggesting that metabolic factors and pre-existing vascular disease may play a more substantial role in long-term risk. Notably, the predictive value of elevated HbA1c remained significant even in the absence of a formal diabetes diagnosis, highlighting the potential role of glycemic dysregulation in this population despite the relatively low prevalence of known diabetes mellitus.

An important finding of our study is the independent association between elevated HbA1c levels and the incidence of MACE in young patients with STEMI. Patients who experienced MACE had significantly higher baseline HbA1c levels than those who did not. Notably, the markedly higher MACE rate observed in individuals with HbA1c levels ≥6.5% (44.4%) compared with those with levels <6.5% (18.5%) suggests that glycemic status may be associated with adverse clinical outcomes. These findings are consistent with the literature suggesting that subclinical glycemic dysregulation may reflect a proinflammatory and prothrombotic state, even in the absence of a formal diabetes diagnosis.[14] Our observations, which are consistent with studies emphasizing the importance of metabolic profiling in young populations, suggest that even mild glucose intolerance in young adults may contribute to recurrent ischemic events.[14,15] Consequently, these data support consideration of metabolic screening and implementation of more intensive secondary prevention strategies in this population, which is often considered to be at low long-term risk.[15]

In our study, although a formal diagnosis of DM was not significantly associated with MACE, HbA1c levels demonstrated an independent association with MACE, which is a noteworthy finding. This discrepancy may be attributable to HbA1c being a more sensitive marker that reflects not only a clinical diagnosis of DM but also an individual's glycemic exposure and cumulative metabolic burden over the preceding 2–3 months.[10,12] Notably, the identification of HbA1c levels ≥6.5% in 8 (7.0%) of the 114 patients without previously diagnosed diabetes suggests that undiagnosed or subclinical glycemic dysregulation may be more prevalent in this young population than previously recognized and may be associated with clinical outcomes. Although a categorical diagnosis of diabetes may be insufficient to capture early-stage vascular damage, HbA1c as a continuous variable may better reflect the chronic and progressive impact of glycemic burden on the atherosclerotic process.[16] These findings emphasize that, in young patients with MI, HbA1c may provide additional prognostic information beyond a history of DM, and glycemic metabolism may warrant monitoring even in patients without previously known diabetes.

In our study, we found that a pre-existing history of CAD was significantly associated with an approximately fourfold increased risk (OR≈4) of MACE. This finding supports the concept that a history

**Table 4.** Univariate and multivariable logistic regression analyses of variables associated with MACE

| Variables | Univariate OR | 95% CI | *P* | Multivariable OR | 95% CI | *P* |
|---|---|---|---|---|---|---|
| History of CAD | 2.867 | 1.035–7.937 | **0.04** | 3.928 | 1.154–13.369 | **0.029** |
| Active smoker | 3.125 | 1.217–8.021 | **0.02** | 2.212 | 0.700–6.991 | 0.176 |
| LVEF (%) | 0.935 | 0.896–0.976 | **0.002** | 0.937 | 0.884–0.993 | **0.029** |
| Peak hs-cTnT, per 1,000 ng/L | 0.987 | 0.973–1.002 | 0.09 | – | – | – |
| HbA1c (%) | 1.562 | 1.143–2.136 | **0.005** | 1.565 | 1.096–2.235 | **0.014** |

CAD, Coronary artery disease; CI, Confidence interval; HbA1c, Glycated hemoglobin; hs-cTnT, High-sensitivity cardiac troponin T; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiovascular events; OR, Odds ratio.

of CAD before the index MI, even in younger patients, indicates a greater underlying atherosclerotic burden and a more advanced stage of coronary disease. This early atherosclerotic process in young patients often reflects not only involvement of the index vessel but also diffuse vascular disease, leaving patients at residual risk despite successful revascularization.[17,18] Consistent with the literature, the higher frequency of recurrent ischemic events in young individuals with a prior diagnosis of CAD compared with those experiencing their first event demonstrates the aggressive course of systemic atherosclerosis in this population.[18,19] Therefore, in young patients with MI and a prior history of CAD, more intensive, targeted, and sustained implementation of secondary prevention strategies is important for preventing future adverse events.

In our study, LVEF was independently associated with MACE, with each 1% increase in LVEF being associated with an approximately 6% reduction in the risk of MACE. This finding supports the prognostic relevance of preserved left ventricular systolic function in young patients with MI. Low LVEF after the index MI reflects not only the extent of myocardial necrosis (infarct size) but also the ventricular remodeling that occurs during myocardial repair.[20] Progressive ventricular enlargement and scar formation not only increase the incidence of heart failure (HF) but also substantially increase the risk of malignant arrhythmias by altering the electrophysiological substrate.[21] Although young patients may have a high potential for myocardial recovery after reperfusion, those presenting with low LVEF may represent a high-risk phenotype from both hemodynamic and electrical perspectives. Therefore, early initiation of pharmacological therapies, such as beta-blockers, ACE inhibitors/ARBs, and ARNIs, that support preservation of LVEF and attenuate the remodeling process may represent a valuable strategy for preventing long-term adverse events in young patients with STEMI.[9,22,23]

Another noteworthy finding is that smoking was not independently associated with MACE in our study. The relatively high prevalence of smoking (55%) in our young STEMI population may have increased the prevalence and homogeneity of this factor, thereby limiting its statistical discriminatory power. Furthermore, because smoking is strongly associated with the development of CAD and metabolic risk factors, including hyperlipidemia and insulin resistance, its independent effect may have diminished after adjustment for other variables in the multivariable analysis.[24,25] This does not negate the role of smoking as a major trigger of atherosclerosis in young patients but suggests that other clinical variables, particularly HbA1c and a history of CAD, demonstrated more consistent associations with MACE in our young STEMI cohort. In a retrospective study conducted between 2015 and 2020 involving 652 patients with ACS, patients were divided into two groups using an age threshold of 45 years. A positive smoking history and a family history of CAD were significantly more frequent in younger patients (42.2% vs. 27.3%, $P < 0.001$; 22.9% vs. 9.4%, $P < 0.001$, respectively). In-hospital mortality was 0.9% in younger patients compared with 7.4% in older patients ($P = 0.004$).[4] In our study, 54.8% of patients were active smokers, and among the 138 patients initially screened, 4 (2.9%) died before or during the procedure.

Routine assessment of HbA1c levels in young patients with MI, beyond the presence of diabetes, may provide additional value in prognostic assessment. Patients with particularly high HbA1c levels may warrant closer monitoring for recurrent ischemic events, and more intensive secondary prevention strategies, including metabolic control and intensive lipid-lowering therapy, may be prioritized for this group. In conclusion, the absence of a diabetes diagnosis in young patients with STEMI should not be interpreted as indicating low metabolic risk. Routine use of HbA1c as a screening parameter may help identify high-risk young patients and provide additional prognostic information.

Lastly, etiological evaluation of myocardial infarction in young patients requires a comprehensive assessment of both traditional and nontraditional risk factors, as recently emphasized by Kayikcioglu et al.[5] in their standardized assessment framework. Current literature indicates that early atherosclerosis with plaque rupture or plaque erosion is the most common etiology, accounting for almost 90% of AMI cases in young adults. The remaining 10% of cases are attributed to non-plaque-related causes, such as SCAD, coronary vasospasm, hypercoagulable states, coronary embolic events, autoimmune-mediated inflammation, and drug-induced coronary occlusion.[2,26] In our study, alternative diagnoses accounted for 8.73% of cases, including coronary vasospasm (n=3), sepsis (n=2), SCAD (n=2), Takotsubo syndrome (n=2), myocarditis (n=1), and cardiomyopathy (n=1). Although our study assessed available clinical parameters, including a family history of premature CAD, metabolic syndrome parameters, obesity, documented substance use, and detailed angiographic phenotypes identifying nonatherosclerotic conditions such as SCAD, vasospasm, and coronary anomalies, we acknowledge that universal screening for specialized markers, such as lipoprotein(a), ApoB, detailed thrombophilia panels, and comprehensive autoimmune profiles, was not uniformly performed in all patients because of the retrospective study design. Mortality among patients with ACS remains high during both hospitalization and follow-up, indicating that secondary prevention after ACS may remain suboptimal. The prevalence of familial hyperlipidemia among patients with ACS has been reported to be 7.6%, and patients with familial hyperlipidemia have been observed to present with ACS at a younger age than those without familial hyperlipidemia.[27] Future prospective registries incorporating these extended biomarkers may provide deeper etiological insights into premature CAD.[5]

**Limitations**

Several limitations should be considered when interpreting the results of our study. First, this was a single-center, retrospective study, which inherently limits the generalizability of our findings. Because of the retrospective design, some baseline variables, including a family history of premature CAD, details of previous coronary revascularization (PCI/CABG), metabolic syndrome, and preadmission medication use, were not consistently available in the medical records and therefore could not be included in the analyses. Similarly, detailed information regarding treatment adherence during follow-up and specific coronary revascularization strategies, including PCI, CABG, medical management, culprit vessel, number of treated vessels, stent characteristics, and repeat revascularization, was not consistently available for evaluation. Furthermore, specialized biomarkers such as ApoB and lipoprotein(a), which may provide additional information regarding residual lipid-related cardiovascular risk in young patients with myocardial infarction, as well as comprehensive screening for familial hypercholesterolemia

and a systematic etiologic workup for young patients with MI, were not routinely performed and therefore could not be assessed. As a major limitation of our study, the lack of universal screening for these specialized markers and etiologic panels precluded a more detailed evaluation of the causes of premature CAD. Second, the exclusion of patients who experienced preprocedural mortality before CAG introduces potential survival bias, as the most critically ill patients who died before intervention were not captured; therefore, our findings primarily reflect the characteristics of young patients who survived long enough to reach the catheterization laboratory. Third, the sample size, particularly the low proportion of female patients (7.9%), limits the generalizability of the results across sexes. Fourth, the number of MACE observed during the study period (n=28) was relatively low, which may have reduced the statistical power of the multivariable analyses and raises the possibility of overfitting of the multivariable model. Finally, HbA1c levels were measured at only a single time point during the index MI admission, which does not provide comprehensive insight into the long-term glycemic course of the patients. Given that the study findings are largely based on this marker, the lack of serial measurements during postdischarge follow-up precluded assessment of longitudinal changes in glycemic status or the potential influence of acute stress-related responses on HbA1c levels. Despite these limitations, our findings provide preliminary clinical evidence supporting the importance of metabolic risk management in young patients with STEMI.

## Conclusion

Young patients presenting with suspected STEMI who undergo emergency CAG have a notable risk of MACE during the first year of follow-up. A history of CAD, lower LVEF, and elevated HbA1c levels emerged as variables independently associated with adverse clinical outcomes. HbA1c may provide prognostic information beyond a known diagnosis of diabetes and may help identify patients at high risk after MI. These findings emphasize the need for systematic metabolic screening and intensified secondary prevention strategies to improve the long-term prognosis of this young population presenting with suspected STEMI.

**Ethics Committee Approval:** Ethics committee approval was obtained from Dokuz Eylül University Non-Interventional Research Ethics Committee (Approval Number: 2026/20-47, Date: 01.06.2026).

**Informed Consent:** Written informed consent was not required due to the retrospective nature of this study.

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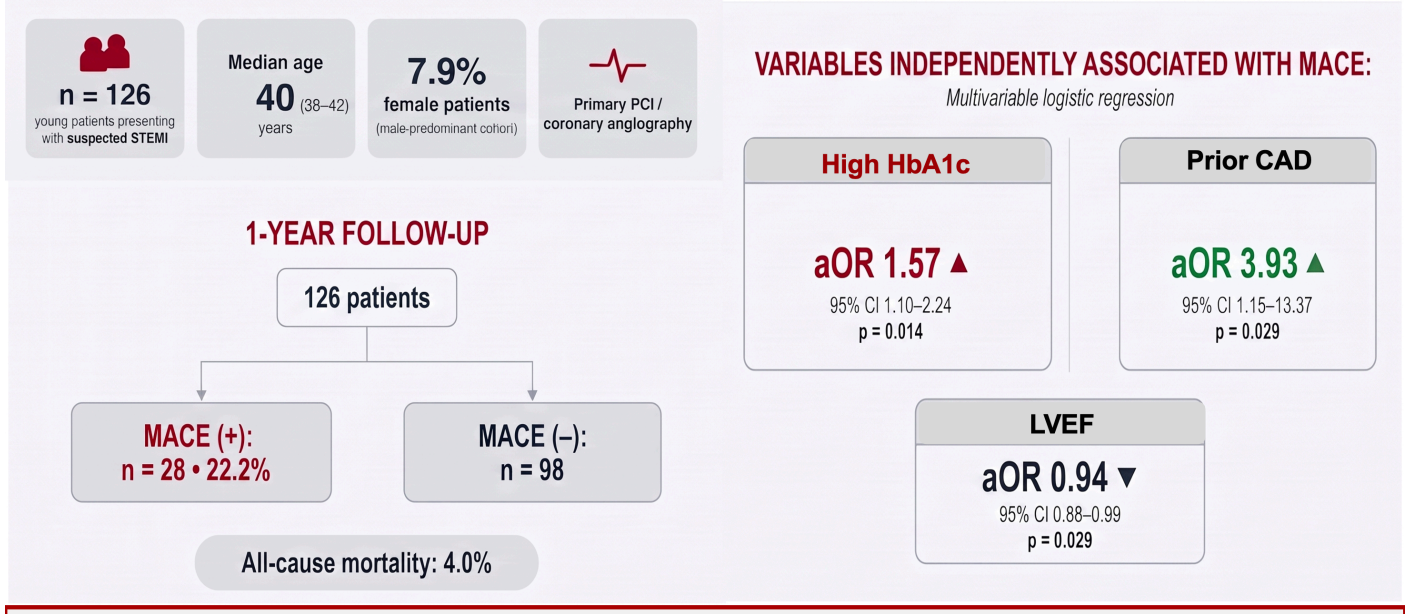
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## Demographic, Clinical Characteristics, and Outcomes of Young Patients Presenting with Suspected STEMI

*Single-centre, retrospective, observational cohort • January 2021 – April 2025*




Young patients presenting with suspected STEMI carry a notably high risk of MACE during 1-year follow-up. A history of CAD, lower LVEF, and elevated HbA1c appear to be associated with adverse clinical outcomes.

***Keywords:*** *HbA1c • major adverse cardiovascular events • premature coronary artery disease • young suspected STEMI*

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# Lipid Profiles, Angiographic Characteristics, and in-Hospital Outcomes in Adults Younger Than 45 Years with Myocardial Infarction

## Kırk Beş Yaş Altı Miyokard Enfarktüsü Geçiren Yetişkinlerde Lipid Profilleri, Anjiyografik Özellikler ve Hastane İçi Sonlanımlar

**ABSTRACT**

**Objective:** To characterize adults younger than 45 years with myocardial infarction (MI) and examine factors associated with multivessel disease.

**Method:** This single-center retrospective study included patients aged 18–44 years who were hospitalized between January 2024 and January 2026 with STEMI, NSTEMI, or a working diagnosis of MI with nonobstructive coronary arteries (MINOCA). Patients with alternative diagnoses or type 2 MI were excluded. Logistic regression analysis was performed among patients with obstructive coronary disease.

**Results:** Among 180 patients, the mean age was 39.0±4.1 years, and 160 (88.9%) were male. Low sex-specific HDL-C levels were present in 78.9%, triglyceride levels ≥150 mg/dL in 56.4%, LDL-C levels ≥130 mg/dL in 44.5%, and LDL-C levels ≥160 mg/dL in 22.0%. Multivessel disease was present in 65 of 164 patients with obstructive disease (39.6%). In the exploratory primary model, each 5-mg/dL decrease in HDL-C was associated with multivessel disease (adjusted odds ratio, 1.35; 95% confidence interval, 1.02–1.77; P = 0.034). In a separately specified alternative model using non-HDL-C as the sole lipid covariate, the adjusted association estimate for non-HDL-C did not reach statistical significance (adjusted odds ratio, 1.13 per 25-mg/dL increase; 95% confidence interval, 0.95–1.35; P = 0.175). The composite in-hospital adverse event occurred in 14 patients (7.8%), and mortality was 1.1%.

**Conclusion:** In the exploratory primary model, lower HDL-C levels were associated with multivessel disease. In a separately specified alternative model, the adjusted association estimate for non-HDL-C did not reach statistical significance. Because the models differed in covariate composition and complete-case populations and were not designed for direct comparison, these findings do not establish the relative importance of HDL-C and non-HDL-C.

**Keywords:** Dyslipidemia, MINOCA, multivessel coronary disease, myocardial infarction, ventricular arrhythmia, young adults.

**ÖZET**

**Amaç:** Kırk beş yaşından genç miyokard enfarktüsü (ME) hastalarının özelliklerini tanımlamak ve çok damar hastalığı ile ilişkili faktörleri incelemek.

**Yöntem:** Bu tek merkezli retrospektif çalışmaya, Ocak 2024 ile Ocak 2026 arasında STEMI, NSTEMI veya obstrüktif olmayan koroner arterlerle seyreden ME (MINOCA) ön tanısıyla hastaneye yatırılan 18–44 yaş arasındaki hastalar dahil edildi. Alternatif tanısı veya tip 2 ME'si bulunan hastalar dışlandı. Obstrüktif koroner hastalığı bulunan hastalarda lojistik regresyon analizi yapıldı.

**Bulgular:** Toplam 180 hastanın ortalama yaşı 39,0±4,1 yıl olup, 160'ı (%88,9) erkekti. STEMI %42,8, NSTEMI %48,3 ve MINOCA %8,9 oranında saptandı. Cinsiyete özgü düşük HDL-C düzeyi %78,9, trigliserid düzeyi ≥150 mg/dL %56,4, LDL-C düzeyi ≥130 mg/dL %44,5 ve LDL-C düzeyi ≥160 mg/dL %22,0 oranında mevcuttu. Çok damar hastalığı, obstrüktif hastalığı bulunan 164 hastanın 65'inde (%39,6) saptandı. Keşifsel birincil modelde, HDL-C düzeyindeki her 5 mg/dL'lik azalma çok damar hastalığı ile ilişkiliydi (düzeltilmiş olasılık oranı, 1,35; %95 güven aralığı, 1,02–1,77; P = 0,034). Non-HDL-C'nin tek lipid kovaryatı olarak kullanıldığı ayrı olarak tanımlanmış alternatif modelde, non-HDL-C için düzeltilmiş ilişki tahmini istatistiksel anlamlılığa ulaşmadı (her 25 mg/dL'lik artış için düzeltilmiş olasılık oranı, 1,13; %95 güven aralığı, 0,95–1,35; P = 0,175). Birlesik hastane içi advers olay 14 hastada (%7,8) görülürken, mortalite orani %1,1'di.

**ORIGINAL ARTICLE**
ARAŞTIRMA MAKALESİ

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**Sonuç:** Keşifsel birincil modelde daha düşük HDL-C düzeyleri çok damar hastalığı ile ilişkiliydi. Ayrı olarak tanımlanmış alternatif modelde ise non-HDL-C için düzeltilmiş ilişki tahmini istatistiksel anlamlılığa ulaşmadı. Modeller farklı kovaryat bileşimlerine ve tam olgu popülasyonlarına sahip olduğundan ve doğrudan karşılaştırma amacıyla tasarlanmadığından, bu bulgular HDL-C ile non-HDL-C'nin göreli önemini ortaya koymamaktadır.

**Anahtar Kelimeler:** Dislipidemi, MINOCA, çok damar koroner arter hastalığı, miyokard enfarktüsü, ventriküler aritmi, genç erişkinler.

Myocardial infarction (MI) in adults younger than 45 years is relatively uncommon but clinically important because affected patients face a prolonged lifetime risk of recurrent cardiovascular events. Although age thresholds vary across studies, an upper age limit of 45 years is frequently used to define MI in younger adults. The same age threshold was applied to both women and men in the present study to ensure a consistent inclusion criterion and because the limited number of women precluded the reliable use of sex-specific age thresholds.[1–3]

MI in younger adults is etiologically heterogeneous. In addition to premature atherosclerotic plaque disruption, potential mechanisms include spontaneous coronary artery dissection, coronary embolism, coronary vasospasm, thrombophilia, substance-associated MI, and myocardial infarction with nonobstructive coronary arteries (MINOCA).[4–6] Accordingly, studies of younger patients should distinguish descriptive cardiovascular risk factor profiles from conclusions regarding the causal importance of individual risk factors.[7]

Low HDL-C and hypertriglyceridemia frequently coexist with smoking, adiposity, diabetes, and insulin resistance. In an uncontrolled cohort of patients hospitalized with MI, the frequency of these abnormalities can be described, but their prevalence or etiologic importance cannot be compared with those of LDL-C or other risk factors.

We therefore aimed to describe the clinical, lipid, angiographic, treatment, and in-hospital outcome characteristics of adults younger than 45 years hospitalized with MI. We also explored factors associated with multivessel coronary disease among patients with obstructive coronary disease.[8]

## ABBREVIATIONS

| | |
|---|---|
| CA-AKI | Contrast-associated acute kidney injury |
| CABG | Coronary artery bypass grafting |
| CMR | Cardiac magnetic resonance imaging |
| IVUS | Intravascular ultrasound |
| LVEF | Left ventricular ejection fraction |
| MI | Myocardial infarction |
| MINOCA | Myocardial infarction with nonobstructive coronary arteries |
| OCT | Optical coherence tomography |
| TIMI | Thrombolysis in Myocardial Infarction |

## Methods

### Study Design and Setting

This was a single-center, retrospective, observational study covering the period from January 2024 to January 2026. The study protocol was approved by Izmir City Hospital Scientific and Medical Research Ethics Committee (Approval Number: 2026/04, Date: 04.06.2026) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective and anonymized nature of the data collection.

### Patient Selection

All patients aged 18–44 years who were admitted to the coronary care unit with suspected acute coronary syndrome or MI were identified from the institutional database. Clinical, electrocardiographic, biomarker, imaging, and angiographic data were retrospectively reviewed. Patients were included if the adjudicated diagnosis was STEMI, NSTEMI, or a working diagnosis of MINOCA. An upper age limit of 44 years was selected because an age threshold of younger than 45 years is frequently used in studies of MI in younger adults, although no universally accepted definition exists. The same threshold was applied to both women and men to provide a consistent inclusion criterion.

Inclusion criteria required a final diagnosis of STEMI or NSTEMI, or a working diagnosis of MINOCA, as defined by the Fourth Universal Definition of Myocardial Infarction.[5] Acute MI was defined by a rise and/or fall in cardiac troponin, with at least one value above the assay-specific 99$^{th}$-percentile upper reference limit, together with clinical evidence of acute myocardial ischemia. Evidence of ischemia included ischemic symptoms, new ischemic electrocardiographic changes, the development of pathological Q waves, imaging evidence of new loss of viable myocardium or a new regional wall-motion abnormality in an ischemic pattern, or identification of a coronary thrombus.

STEMI was classified according to guideline-defined ST-segment elevation criteria, including sex- and age-specific thresholds in leads V2–V3. New or presumed new left bundle branch block alone was not considered diagnostic of STEMI. NSTEMI was defined as acute MI without persistent ST-segment elevation meeting STEMI criteria.[5] Patients with obstructive coronary disease were retrospectively adjudicated as having type 1 MI based on the available clinical, electrocardiographic, biomarker, imaging, and angiographic data. Patients adjudicated as having type 2 MI were excluded.

In patients without obstructive coronary disease, a working diagnosis of MINOCA was assigned when the criteria for acute MI were fulfilled, coronary angiography demonstrated no stenosis ≥50% in a major epicardial coronary artery, and no immediately apparent alternative diagnosis was identified. Patients with a clinically established diagnosis of myocarditis

or pericarditis were excluded. However, because CMR and other etiologic investigations were not systematically performed, occult myocarditis or Takotsubo syndrome could not be systematically excluded in every patient assigned a working diagnosis of MINOCA.

Exclusion criteria were as follows: (1) an alternative final diagnosis that did not meet the criteria for acute MI; (2) myocarditis or pericarditis; (3) type 2 MI; (4) elective admission or procedure; and (5) duplicate records. Forty-six patients were excluded: 22 with myocarditis or pericarditis, 17 with an alternative final diagnosis, 3 with duplicate records, 2 with elective admissions, and 2 with type 2 MI (Figure 1).

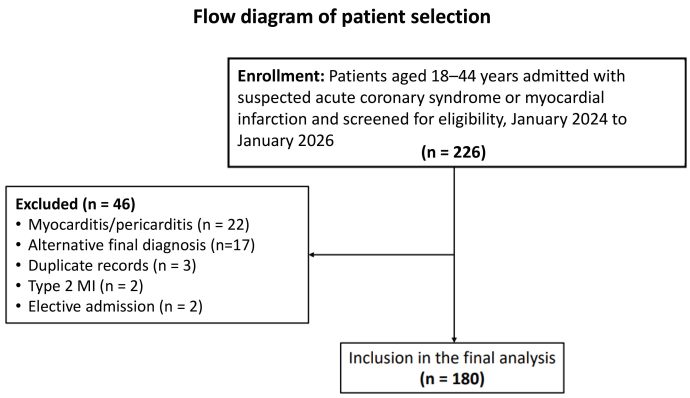



**Figure 1.** Flow diagram of patient selection.

A total of 226 patients aged 18–44 years who were admitted with suspected acute coronary syndrome or myocardial infarction were screened for eligibility. Forty-six records were excluded: 22 patients with myocarditis or pericarditis, 17 with an alternative final diagnosis, 3 duplicate records, 2 elective admissions, and 2 with type 2 myocardial infarction. The final analytical cohort included 180 patients with ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or a working diagnosis of myocardial infarction with nonobstructive coronary arteries.

### Data Collection

Data were extracted from electronic health records and catheterization laboratory logs by two investigators using a prespecified case report form. Clinical variables included age, sex, length of stay, presenting symptom, smoking status, family history of premature coronary artery disease, prior coronary artery disease, prior stroke, hypertension, known diabetes mellitus, chronic kidney disease, documented substance use, thrombophilia or venous thromboembolism, pregnancy, postpartum status, and oral contraceptive use, where applicable. Laboratory variables included peak troponin, admission creatinine, LDL-C, HDL-C, triglycerides, hemoglobin, HbA1c, and left ventricular ejection fraction (LVEF). Lipid values were obtained from the first available lipid panel during the index hospitalization. LDL-C was calculated using the Friedewald formula when triglycerides were <400 mg/dL and measured directly when triglycerides were ≥400 mg/dL. Non-HDL-C was calculated as total cholesterol minus HDL-C. Values coded as missing in the source dataset were treated as missing and excluded from the corresponding analyses. The exact interval from symptom onset, fasting status, timing relative to coronary intervention, and timing relative to the initiation of lipid-lowering therapy were not consistently documented. The calendar day of lipid sampling and whether sampling occurred before or after the initiation of high-intensity statin therapy could not be reliably reconstructed from the retrospective database.

Electrocardiographic and angiographic variables included electrocardiographic abnormalities, MI location, infarct-related artery, culprit segment, preprocedural and final Thrombolysis in Myocardial Infarction (TIMI) flow, number of diseased vessels, coronary spasm, coronary ectasia or aneurysm, and reperfusion strategy. Treatment variables included PCI, coronary artery bypass grafting (CABG), medical treatment, aspiration thrombectomy, glycoprotein IIb/IIIa inhibitor use, intra-aortic balloon pump use, and nonculprit lesion PCI.

The primary objective was the descriptive characterization of the cohort. Secondary exploratory comparisons included sex-based differences and comparisons among STEMI, NSTEMI, and MINOCA. In-hospital outcomes included contrast-associated acute kidney injury, complete atrioventricular block, sustained ventricular tachycardia or ventricular fibrillation, incident atrial fibrillation, cardiogenic shock, major bleeding, death, stroke, mechanical complications, and a composite in-hospital adverse event variable. The composite in-hospital adverse event was defined as any occurrence of sustained ventricular tachycardia or ventricular fibrillation, complete atrioventricular block, cardiogenic shock, major bleeding, or in-hospital death. Information on cardiac magnetic resonance imaging (CMR), optical coherence tomography (OCT), and intravascular ultrasound (IVUS) was not systematically captured in the study database; therefore, the underlying mechanism of MINOCA could not be adjudicated using these modalities.

### Key Definitions

Study-specific composite definition of abnormal in-hospital lipid measurements: The first available lipid panel during the index hospitalization that met at least one of the following criteria: LDL-C ≥130 mg/dL, HDL-C <40 mg/dL in men or <50 mg/dL in women, or triglycerides ≥150 mg/dL. Patients were classified as meeting the composite definition if at least one available lipid component met the corresponding threshold. Classification as not meeting the definition required LDL-C, HDL-C, and triglycerides to all be available and below the corresponding thresholds. Patients with incomplete lipid data and no observed abnormal component were considered unclassifiable and excluded from the denominator. This study-specific composite was used for descriptive purposes and was not intended to represent a guideline-based diagnosis of dyslipidemia.[9]

Multivessel disease: ≥50% stenosis in ≥2 major epicardial vessels or their major branches.

Sustained VT/VF: Ventricular tachycardia lasting >30 seconds or requiring immediate termination, or ventricular fibrillation, occurring during the index hospitalization.

Complete AV block: Third-degree atrioventricular block documented on a rhythm strip or telemetry.

CA-AKI: CA-AKI was defined as an increase in serum creatinine of ≥0.3 mg/dL within 48 hours after contrast exposure or to ≥1.5 times the baseline value within 7 days after exposure, when no alternative explanation for the increase in creatinine was identified.[10]

### Statistical Analysis

Distributional suitability was assessed by visual inspection of histograms and quantile-quantile plots, together with the Shapiro-Wilk test. Approximately normally distributed continuous variables are presented as mean ± standard deviation, whereas skewed variables are presented as median [interquartile range]. Categorical variables are presented as frequencies and percentages. Between-group comparisons across MI subtypes were performed using the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Exploratory unadjusted comparisons according to multivessel disease status were restricted to patients with MI and obstructive coronary artery disease. Comparisons according to multivessel disease status and composite in-hospital adverse event status were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. For variables applicable only to patients with obstructive MI, including infarct-related artery, preprocedural TIMI flow, final TIMI flow, and number of diseased vessels, comparisons were restricted to STEMI versus NSTEMI. Patients with a working diagnosis of MINOCA were excluded from these comparisons. To evaluate factors associated with multivessel disease, exploratory multivariable logistic regression analyses were performed among patients with MI and obstructive coronary artery disease. Patients with MINOCA were excluded because comparison of multivessel disease with single-vessel disease was not applicable. Covariates were selected a priori based on clinical relevance and data availability while limiting model complexity because of the number of multivessel disease cases.

The primary model included age per 5-year increase, male sex, active smoking, hypertension, known diabetes mellitus, LDL-C per 25-mg/dL increase, HDL-C per 5-mg/dL decrease, and triglycerides per doubling. To evaluate non-HDL-C as a single integrated measure of atherogenic cholesterol, the alternative parsimonious model included age per 5-year increase, male sex, active smoking, hypertension, known diabetes mellitus, and non-HDL-C per 25-mg/dL increase; LDL-C, HDL-C, and triglycerides were omitted. Complete-case analysis was used for each model. The models differed in covariate composition and complete-case populations and were not designed to compare the relative importance or superiority of individual lipid measures. Multicollinearity was assessed using variance inflation factors. Linearity in the logit for continuous predictors was evaluated using Box-Tidwell interaction terms. Model discrimination was evaluated using the c-statistic, and calibration was assessed using the Hosmer-Lemeshow test. Potentially influential observations in the primary model were assessed using standardized residuals, leverage, Cook's distance, and leave-one-out refitting. All adjusted analyses were considered exploratory and hypothesis-generating. A sensitivity analysis repeated Primary model after restricting the cohort to men. Because sex was invariant in this subgroup, the male-only model included age per 5-year increase, active smoking, hypertension, known diabetes mellitus, LDL-C per 25-mg/dL increase, HDL-C per 5-mg/dL decrease, and triglycerides per doubling. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are reported. A two-tailed p-value <0.05 was considered statistically significant. Statistical analysis was performed using Python version 3.11 (Python Software Foundation, Wilmington, DE, USA).

No a priori sample size calculation was performed because the study included all eligible patients during the predefined study period. Analyses involving women, patients with MINOCA, and uncommon in-hospital events were considered exploratory because of the limited subgroup sizes and event counts. No post hoc power analysis was performed.

### Results

After applying the exclusion criteria, including myocarditis or pericarditis in 22 patients, an alternative final diagnosis in 17, duplicate records in 3, elective admissions in 2, and type 2 MI in 2, a total of 180 patients were included. Twenty-four patients (13.3%) were younger than 35 years, 55 (30.6%) were aged 35–39 years, and 101 (56.1%) were aged 40–44 years. Age-stratified risk factors, presentation characteristics, and in-hospital events are presented descriptively in Supplementary Table 1. Because of the small numbers of patients and events in the younger age strata, no inferential conclusions were drawn from these subgroup comparisons. Age and sex distributions were comparable across the diagnostic groups. MI subtypes comprised STEMI in 77 patients (42.8%), NSTEMI in 87 (48.3%), and a working diagnosis of MINOCA in 16 (8.9%).

The composite in-hospital adverse event occurred in 14 patients (7.8%). In an exploratory unadjusted comparison, patients with the composite endpoint had higher peak troponin levels than those without the endpoint: 4387.0 [1623.5–10,000.0] ng/L in 14 patients versus 751.0 [244.0–2400.0] ng/L in 165 patients (P = 0.011). LVEF was numerically lower among patients with composite events, but the difference did not reach statistical significance. In exploratory unadjusted comparisons, no statistically significant differences were observed in age, sex, smoking, hypertension, diabetes, the study-specific lipid composite, multivessel disease, or STEMI versus NSTEMI presentation. Prior CAD and CKD were more frequent among patients with composite events, but these findings should be interpreted cautiously because of the sparse event counts. Among the 20 women, no pregnancy, postpartum status, or oral contraceptive use was documented at the index presentation.

### Cardiovascular Risk Factors and in-Hospital Lipid Measurements

Among the 171 patients who could be classified according to the study-specific composite definition of abnormal in-hospital lipid measurements, 161 (94.2%) met at least one component of the definition. Low sex-specific HDL-C was present in 135 of 171 patients (78.9%), triglycerides ≥150 mg/dL in 97 of 172 (56.4%), and LDL-C ≥130 mg/dL in 73 of 164 (44.5%). Median HDL-C was 35.0 [30.0–39.5] mg/dL, median triglycerides were 159.5 [114.0–228.5] mg/dL, and mean LDL-C was 127.9 ± 45.0 mg/dL. Non-HDL-C was available in 165 patients, with a median concentration of 157.6 [131.0–199.6] mg/dL, and did not differ significantly among MI subtypes (P = 0.692). LDL-C was ≥160 mg/dL in 36 of 164 patients (22.0%) and ≥190 mg/dL in 14 of 164 (8.5%), indicating that substantial LDL-C elevation was also clinically relevant in this cohort. Median HDL-C was higher in women than in men (36.5 vs. 34.0 mg/dL; P = 0.034). Using the prespecified sex-specific thresholds, low HDL-C was present in 116 of 151 men (76.8%) and 19 of 20 women (95.0%). Because only 20 women were included,

the sex-specific prevalence estimates should be interpreted descriptively. These findings describe lipid concentrations within the MI cohort and do not establish the relative causal importance of individual lipid fractions.

At least one traditional cardiovascular risk factor was present in 176 of 180 patients (97.8%). Even after excluding the study-specific lipid composite, at least one nonlipid traditional cardiovascular risk factor was present in 126 of 180 patients (70.0%). No illicit substance use was documented in the available medical records; however, substance use history was collected retrospectively, and systematic toxicological screening was not performed.

**Angiographic Findings**

The LAD was the infarct-related artery in 85 patients (51.8% of those with obstructive MI), accounting for 61.0% of STEMI cases. Correspondingly, the predominant MI location among patients with STEMI was anterior (n=45, 58.4%), followed by inferior in 22 (28.6%). The RCA was the infarct-related artery in 19 patients with STEMI (24.7%) and 13 with NSTEMI (14.9%). The circumflex or obtuse marginal territory was more frequently involved in NSTEMI than in STEMI (29.9% vs. 9.1%; P = 0.003).

Multivessel coronary disease was present in 65 of 180 patients (36.1%), corresponding to 65 of 164 patients (39.6%) with angiographically obstructive coronary disease. Among patients with obstructive coronary disease, hypertension [22/65 (33.8%) vs. 20/99 (20.2%); P = 0.067] and known diabetes mellitus [19/65 (29.2%) vs. 16/99 (16.2%); P = 0.053] were numerically more frequent among patients with multivessel disease, although the differences did not reach statistical significance. Patients with multivessel disease had lower HDL-C concentrations (32.5 [28.0–36.8] vs. 36.0 [31.3–41.0] mg/dL; P = 0.009), whereas triglyceride concentrations were numerically higher (198.0 [132.0–271.3] vs. 158.0 [101.0–223.5] mg/dL; P = 0.057). The primary complete-case model included 150 patients with obstructive MI, comprising 61 with multivessel disease and 89 with single-vessel disease. In the exploratory primary model, each 5-mg/dL decrease in HDL-C was associated with higher odds of multivessel disease after multivariable adjustment (aOR 1.35, 95% CI 1.02–1.77; P = 0.034). The adjusted estimates for LDL-C per 25-mg/dL increase (aOR 1.16, 95% CI 0.94–1.42; P = 0.158), triglycerides per doubling (aOR 1.08, 95% CI 0.71–1.65; P = 0.704), hypertension (aOR 1.87, 95% CI 0.78–4.46; P = 0.161), and diabetes mellitus (aOR 1.74, 95% CI 0.64–4.71; P = 0.275) did not reach statistical significance after multivariable adjustment (Table 1). Box-Tidwell interaction terms provided no evidence of nonlinearity for the continuous predictors in the primary model (all p≥0.240). The maximum absolute standardized residual was 2.19, the maximum leverage value was 0.191, and the maximum Cook's distance was 0.081. No observation had an absolute standardized residual >3 or a Cook's distance >1. Across 150 leave-one-out refits, the HDL-C estimate remained directionally consistent, with aORs ranging from 1.30 to 1.43 per 5-mg/dL decrease. However, p values ranged from 0.016 to 0.066 and exceeded 0.05 in 3 of the 150 refits.

The separately specified alternative parsimonious complete-case model included 151 patients, comprising 61 with multivessel disease and 90 with single-vessel disease. In this model, non-HDL-C was the sole lipid covariate. The adjusted association estimate for non-HDL-C did not reach statistical significance (aOR 1.13 per 25-mg/dL increase, 95% CI 0.95–1.35; P = 0.175). The confidence intervals for age, male sex, active smoking, hypertension, and known diabetes mellitus also included the null value, and none of these adjusted estimates reached statistical significance (Table 1). Box-Tidwell interaction terms provided no evidence of nonlinearity for age or non-HDL-C (both p≥0.442). Primary model had a c-statistic of 0.672 and showed no evidence of poor calibration according to the Hosmer-Lemeshow test ($\chi^2$=5.00, 8 df; P = 0.757); the

**Table 1.** Multivariable logistic regression analyses of factors associated with multivessel coronary disease among patients with MI and obstructive coronary artery disease

| Variables | Model 1 aOR | 95% CI | *P* | Model 2 aOR | 95% CI | *P* |
|---|---|---|---|---|---|---|
| HDL-C, per 5-mg/dL decrease | 1.35 | 1.02–1.77 | 0.034 | N/A | N/A | N/A |
| Triglycerides, per doubling | 1.08 | 0.71–1.65 | 0.704 | N/A | N/A | N/A |
| LDL-C, per 25-mg/dL increase | 1.16 | 0.94–1.42 | 0.158 | N/A | N/A | N/A |
| Non-HDL-C, per 25-mg/dL increase | N/A | N/A | N/A | 1.13 | 0.95–1.35 | 0.175 |
| Hypertension | 1.87 | 0.78–4.46 | 0.161 | 1.75 | 0.75–4.10 | 0.197 |
| Diabetes mellitus | 1.74 | 0.64–4.71 | 0.275 | 1.96 | 0.79–4.83 | 0.146 |
| Age, per 5-year increase | 1.06 | 0.67–1.70 | 0.794 | 0.95 | 0.61–1.49 | 0.825 |
| Active smoking | 1.35 | 0.65–2.81 | 0.417 | 1.51 | 0.74–3.05 | 0.255 |
| Male sex | 1.45 | 0.40–5.18 | 0.572 | 1.95 | 0.57–6.66 | 0.288 |

Model 1 included 150 complete cases, comprising 61 patients with multivessel disease and 89 with single-vessel disease. The model included age, male sex, active smoking, hypertension, known diabetes mellitus, LDL-C, HDL-C, and triglycerides. Fourteen patients with obstructive MI were excluded because of incomplete covariate data. Model 2 included 151 complete cases, comprising 61 patients with multivessel disease and 90 with single-vessel disease. The model included age, male sex, active smoking, hypertension, known diabetes mellitus, and non-HDL-C; LDL-C, HDL-C, and triglycerides were omitted to allow non-HDL-C to be evaluated as the sole lipid covariate. Thirteen patients were excluded because of incomplete covariate data. Triglyceride levels in Model 1 were log2-transformed and expressed per doubling. Single-vessel disease was the reference outcome category. All analyses were exploratory. The c-statistic was 0.672 for Model 1 and 0.642 for Model 2; Hosmer–Lemeshow p-values were 0.757 and 0.185, respectively. The models were specified separately, used different complete-case populations, and were not designed for direct comparison of the relative importance of the lipid measures. aOR, Adjusted odds ratio; CI, Confidence interval; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MI, Myocardial infarction; N/A, Not applicable.

maximum variance inflation factor was 1.43. The parsimonious non-HDL-C model had a c-statistic of 0.642 and showed no evidence of poor calibration (Hosmer-Lemeshow $\chi^2$=11.30, 8 df; P = 0.185); the maximum variance inflation factor was 1.28. No problematic multicollinearity was identified in either model. Fourteen patients with MI and obstructive coronary artery disease were excluded from the primary model because of incomplete lipid covariate data. Exploratory comparisons did not identify statistically significant differences between excluded patients and complete cases in age, sex, active smoking, hypertension, diabetes, STEMI presentation, multivessel disease, peak troponin, admission creatinine, or LVEF; however, these comparisons were imprecise because only 14 patients were excluded (all P > 0.05; Supplementary Table 2).

The male-only sensitivity analysis included 135 men with obstructive MI and complete covariate data, comprising 57 with multivessel disease and 78 with single-vessel disease. In this exploratory male-only sensitivity analysis, each 5-mg/dL decrease in HDL-C was associated with higher odds of multivessel disease (aOR 1.50, 95% CI 1.11–2.02; P = 0.009). The model also included age, active smoking, hypertension, known diabetes mellitus, LDL-C, and triglycerides. Complete results of the male-only sensitivity analysis are presented in Supplementary Table 3.

**Reperfusion Strategy and Procedural Outcomes**

PCI was performed in 147 patients (81.7%), with all 77 patients with STEMI undergoing primary PCI. CABG was required in 10 patients (5.6%), all from the NSTEMI subgroup, reflecting the burden of multivessel or left main disease in this subset. Aspiration thrombectomy was used sparingly in 4 patients (2.2%). GP IIb/IIIa inhibitors were administered to 26 patients (14.4%), predominantly those with STEMI. Nonculprit lesion PCI during the index hospitalization was performed in 30 patients (16.7%). CA-AKI occurred in 6 patients (3.3%). Stent thrombosis was documented in 2 patients (1.1%), both in the STEMI group. Complete clinical, laboratory, angiographic, treatment, and in-hospital outcome characteristics according to MI subtype are presented in Table 2.

**In-Hospital Arrhythmic Events**

During hospitalization, sustained VT/VF occurred in 9 patients (5.0%), complete AV block in 5 (2.8%), and new-onset atrial fibrillation in 3 (1.7%). Sustained VT/VF occurred in 6 of 77 patients with STEMI (7.8%), 3 of 87 with NSTEMI (3.4%), and none of the 16 patients with MINOCA; the between-group difference was not statistically significant (P = 0.280). Complete AV block occurred in 4 patients with STEMI and 1 with NSTEMI.

New-onset atrial fibrillation occurred in 3 patients with STEMI (3.9%). Two patients died during hospitalization. Both patients experienced sustained VT/VF, and one also developed cardiogenic shock. Because only 2 deaths occurred and the cause of death was not independently adjudicated, no analysis of mortality predictors or causal attribution was performed. Overall in-hospital mortality was 1.1%.

**Patients with a Working Diagnosis of MINOCA**

Sixteen patients (8.9%) had a working diagnosis of MINOCA. Four were women (25.0%), the mean age was 37.9 ± 5.4 years, 9 (56.2%) were active smokers, and the mean LVEF was 58.1 ± 5.1%. All were managed without coronary revascularization, and no sustained VT/VF or complete AV block was recorded during hospitalization. Because CMR, intracoronary imaging, and coronary functional testing were not systematically performed or captured, specific ischemic and nonischemic mechanisms could not be adjudicated. Comparisons involving this subgroup were considered exploratory.

**STEMI versus NSTEMI**

Compared with NSTEMI, STEMI was associated with a higher peak troponin level: median 2870.0 versus 378.5 ng/L (P < 0.001). LVEF was lower in STEMI than in NSTEMI: median 50.0% versus 60.0% (P < 0.001). LAD culprit involvement was more frequent in STEMI than in NSTEMI: 47 of 77 (61.0%) versus 38 of 87 (43.7%; P = 0.029). PCI was performed in all patients with STEMI compared with 70 of 87 patients with NSTEMI (80.5%; P < 0.001).

There were no statistically significant differences between STEMI and NSTEMI in age, sex, current smoking, study-defined abnormal lipid measurements, triglyceride levels, proximal or ostial culprit involvement, sustained ventricular tachycardia or ventricular fibrillation, complete atrioventricular block, cardiogenic shock, death, or the composite in-hospital adverse event.

**Discussion**

This retrospective study of 180 adults younger than 45 years hospitalized with MI had four principal findings. Abnormal acute-phase lipid measurements and conventional cardiovascular risk factors were common, including low HDL-C, hypertriglyceridemia, and clinically relevant LDL-C elevation. Multivessel disease affected 39.6% of patients with obstructive coronary disease. In the exploratory primary model, lower HDL-C was associated with multivessel disease, with a directionally consistent finding in the male-only sensitivity analysis. In a separately specified alternative model, the adjusted association estimate for non-HDL-C did not reach statistical significance. The models differed in covariate composition and complete-case populations and were not designed to test whether HDL-C was more important than non-HDL-C. The angiographic presentation was predominantly obstructive, with frequent LAD involvement, and PCI was performed in most patients. In-hospital mortality was low, although sustained VT/VF occurred in 5.0% of the cohort.

These adjusted analyses were hypothesis-generating. Model discrimination was modest, and the HDL-C estimate was not uniformly statistically significant in leave-one-out analyses.

**Lipid Profile in Younger Adults With MI: Frequent Low HDL-C, Hypertriglyceridemia, and Relevant LDL-C Elevation**

According to the study-specific composite definition, 161 of 171 classifiable patients (94.2%) had at least one abnormal in-hospital lipid measurement. Sex-specific low HDL-C and hypertriglyceridemia were frequent. Elevated LDL-C was also common: 44.5% had LDL-C ≥130 mg/dL, 22.0% had LDL-C ≥160 mg/dL, and 8.5% had LDL-C ≥190 mg/dL.

This proportion should not be directly compared with registries reporting a prior clinical diagnosis of dyslipidemia because the present definition was based on acute-phase laboratory

**Table 2.** Clinical, laboratory, angiographic, treatment, and in-hospital outcome characteristics of the study population according to myocardial infarction subtype

| Variables | STEMI (n=77) | NSTEMI (n=87) | MINOCA (n=16) | Total (n=180) | *P* |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age (years) | 38.7±4.2 | 39.4±3.7 | 37.9±5.4 | 39.0±4.1 | 0.522 |
| Male sex | 70 (90.9%) | 78 (89.7%) | 12 (75.0%) | 160 (88.9%) | 0.174 |
| Clinical presentation | | | | | |
| Presenting symptom: angina | 76 (98.7%) | 85 (97.7%) | 15 (93.8%) | 176 (97.8%) | 0.473 |
| Presenting symptom: dyspnea | 0 (0.0%) | 2 (2.3%) | 1 (6.2%) | 3 (1.7%) | 0.168 |
| Presenting symptom: out-of-hospital cardiac arrest | 1 (1.3%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0.510 |
| Length of stay (days) | 2 [1–2] | 2 [1–2] | 1.5 [1–3] | 2 [1–2] | 0.499 |
| Cardiovascular risk factors | | | | | |
| Active smoker | 26 (33.8%) | 32 (36.8%) | 9 (56.2%) | 67 (37.2%) | 0.237 |
| Pregnancy, postpartum state, or oral contraceptive use | 0/7 (0.0%) | 0/9 (0.0%) | 0/4 (0.0%) | 0/20 (0.0%) | N/A |
| Hypertension | 22 (28.6%) | 20 (23.0%) | 1 (6.2%) | 43 (23.9%) | 0.157 |
| Diabetes mellitus | 18 (23.4%) | 17 (19.5%) | 2 (12.5%) | 37 (20.6%) | 0.587 |
| Study-specific composite definition of abnormal in-hospital lipid measurements | 70/76 (92.1%) | 77/81 (95.1%) | 14/14 (100%) | 161/171 (94.2%) | 0.610 |
| Family history of premature CAD | 12 (15.6%) | 15 (17.2%) | 4 (25.0%) | 31 (17.2%) | 0.662 |
| Prior CAD | 7 (9.1%) | 10 (11.5%) | 1 (6.2%) | 18 (10.0%) | 0.765 |
| CKD | 3 (3.9%) | 2 (2.3%) | 0 (0.0%) | 5 (2.8%) | 0.642 |
| Thrombophilia/VTE | 1 (1.3%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0.510 |
| Laboratory data | | | | | |
| Peak troponin (ng/L) | 2870 [1545–5273] | 378.5 [176.5–779] | 157.5 [57.5–325.8] | 809 [245–2868] | **<0.001** |
| Admission creatinine (mg/dL) | 0.87 [0.70–1.01] | 0.79 [0.70–0.90] | 0.90 [0.79–0.93] | 0.80 [0.70–0.96] | **0.049** |
| LDL-C (mg/dL) | 125.8±36.9 | 129.8±51.0 | 128.5±49.9 | 127.9±45.0 | 0.948 |
| HDL-C (mg/dL) | 36 [30.5–41] | 34 [29–38] | 35 [33–36.5] | 35 [30–39.5] | 0.403 |
| Triglycerides (mg/dL) | 154.5 [84.8–238.3] | 180 [135–230] | 130 [111–167] | 159.5 [114–228.5] | 0.075 |
| Hemoglobin (g/dL) | 14.2±1.9 | 14.2±1.8 | 14.4±1.2 | 14.2±1.8 | 0.997 |
| HbA1c (%) | 5.55 [5.23–6.18] | 5.70 [5.33–6.30] | 5.20 [5.10–5.68] | 5.60 [5.23–6.10] | 0.183 |
| Echocardiography | | | | | |
| LVEF (%) | 50 [40–52.5] | 60 [50–60] | 60 [60–60] | 55 [45–60] | **<0.001** |
| Electrocardiography | | | | | |
| ST-segment elevation | 77 (100.0%) | 0 (0.0%) | 2 (12.5%) | 79 (43.9%) | N/A |
| ST-segment depression/T-wave abnormality | 0 (0.0%) | 49 (56.3%) | 1 (6.3%) | 50 (27.8%) | N/A |
| No recorded ischemic ECG change | 0 (0.0%) | 38 (43.7%) | 13 (81.3%) | 51 (28.3%) | N/A |
| Angiographic characteristics among patients with obstructive MI | | | | | |
| IRA: LAD | 47 (61.0%) | 38 (43.7%) | – | 85 (51.8%) | **0.029** |
| IRA: RCA | 19 (24.7%) | 13 (14.9%) | – | 32 (19.5%) | 0.170 |
| IRA: CX | 6 (7.8%) | 14 (16.1%) | – | 20 (12.2%) | 0.167 |
| IRA: OM | 1 (1.3%) | 12 (13.8%) | – | 13 (7.9%) | **0.008** |
| IRA: diagonal | 3 (3.9%) | 5 (5.7%) | – | 8 (4.9%) | 0.852 |
| IRA: LMCA | 0 (0.0%) | 1 (1.1%) | – | 1 (0.6%) | 1.000 |
| IRA: PD/PL | 1 (1.3%) | 0 (0.0%) | – | 1 (0.6%) | 0.951 |
| IRA: Culprit not identifiable | 0 (0.0%) | 4 (4.6%) | – | 4 (2.4%) | 0.162 |

**Table 2 (cont).** Clinical, laboratory, angiographic, treatment, and in-hospital outcome characteristics of the study population according to myocardial infarction subtype

| Variables | STEMI (n=77) | NSTEMI (n=87) | MINOCA (n=16) | Total (n=180) | *P* |
|---|---|---|---|---|---|
| Preprocedural TIMI flow grade 0 | 56/77 (72.7%) | 18/77 (23.4%) | – | 74/154 (48.1%) | **<0.001** |
| Preprocedural TIMI flow grade 1 | 5/77 (6.5%) | 6/77 (7.8%) | – | 11/154 (7.1%) | 0.916 |
| Preprocedural TIMI flow grade 2 | 11/77 (14.3%) | 19/77 (24.7%) | – | 30/154 (19.5%) | 0.234 |
| Preprocedural TIMI flow grade 3 | 5/77 (6.5%) | 34/77 (44.2%) | – | 39/154 (25.3%) | **<0.001** |
| Final TIMI flow grade 3 | 75/77 (97.4%) | 74/75 (98.7%) | – | 149/152 (98.0%) | 0.845 |
| Number of diseased vessels | | | | | 0.290 |
| 1-vessel disease | 51 (66.2%) | 48 (55.2%) | – | 99/164 (60.4%) | – |
| 2-vessel disease | 18 (23.4%) | 24 (27.6%) | – | 42/164 (25.6%) | – |
| 3-vessel disease | 8 (10.4%) | 15 (17.2%) | – | 23/164 (14.0%) | – |
| Coronary spasm | 1 (1.3%) | 1 (1.1%) | – | 2 (1.1%) | 0.902 |
| Coronary ectasia/aneurysm | 1 (1.3%) | 1 (1.1%) | – | 2 (1.1%) | 0.902 |
| Reperfusion and procedures | | | | | |
| PCI | 77 (100.0%) | 70 (80.5%) | 0 (0.0%) | 147 (81.7%) | **<0.001** |
| CABG | 0 (0.0%) | 10 (11.5%) | 0 (0.0%) | 10 (5.6%) | **0.003** |
| Medical management | 0 (0.0%) | 7 (8.0%) | 16 (100.0%) | 23 (12.8%) | **<0.001** |
| Aspiration thrombectomy | 2 (2.6%) | 2 (2.3%) | 0 (0.0%) | 4 (2.2%) | 0.812 |
| GP IIb/IIIa inhibitor | 16 (20.8%) | 10 (11.5%) | 0 (0.0%) | 26 (14.4%) | 0.055 |
| Nonculprit lesion PCI | 16 (20.8%) | 14 (16.1%) | 0 (0.0%) | 30 (16.7%) | 0.125 |
| In-hospital outcomes | | | | | |
| Cardiogenic shock | 3 (3.9%) | 0 (0.0%) | 0 (0.0%) | 3 (1.7%) | 0.130 |
| IABP use | 2 (2.6%) | 0 (0.0%) | 0 (0.0%) | 2 (1.1%) | 0.259 |
| Complete AV block | 4 (5.2%) | 1 (1.1%) | 0 (0.0%) | 5 (2.8%) | 0.226 |
| Sustained VT/VF | 6 (7.8%) | 3 (3.4%) | 0 (0.0%) | 9 (5.0%) | 0.280 |
| Atrial fibrillation | 3 (3.9%) | 0 (0.0%) | 0 (0.0%) | 3 (1.7%) | 0.130 |
| Contrast-associated acute kidney injury | 4 (5.2%) | 2 (2.3%) | 0 (0.0%) | 6 (3.3%) | 0.434 |
| Diuretic requirement | 2 (2.6%) | 1 (1.1%) | 0 (0.0%) | 3 (1.7%) | 0.664 |
| Major bleeding | 0 (0.0%) | 1 (1.1%) | 0 (0.0%) | 1 (0.6%) | 0.584 |
| Stent thrombosis | 2 (2.6%) | 0 (0.0%) | 0 (0.0%) | 2 (1.1%) | 0.259 |
| In-hospital death | 1 (1.3%) | 1 (1.1%) | 0 (0.0%) | 2 (1.1%) | 0.902 |

Values are presented as n/N (%), mean±standard deviation, or median (interquartile range), as appropriate for the distribution of each variable. Denominators indicate the number of patients with available and applicable data. Continuous variables were compared using the Kruskal–Wallis test, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All comparisons were exploratory. Preprocedural TIMI flow data were available for 77 patients with STEMI and 77 patients with NSTEMI. Final TIMI flow data were available for 77 patients with STEMI and 75 patients with NSTEMI. Patients with MINOCA were excluded from TIMI flow summaries because no obstructive culprit vessel was identified. Female-specific variables were calculated using the number of women in each diagnostic group as the denominator. "No recorded ischemic ECG change" indicates that no ischemic ST-segment or T-wave abnormality was documented in the extracted ECG field. These patients met the study criteria for MI based on troponin dynamics together with other available clinical or imaging evidence of ischemia. For the number of diseased vessels, the p-value represents the overall comparison of the three-level distribution of 1-, 2-, and 3-vessel disease between STEMI and NSTEMI using Pearson's chi-square test. Patients with a working diagnosis of MINOCA were excluded because this variable was not applicable. AF, Atrial fibrillation; AV, Atrioventricular; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; CA-AKI, Contrast-associated acute kidney injury; CKD, Chronic kidney disease; CX, Circumflex coronary artery; GP, Glycoprotein; HDL-C, High-density lipoprotein cholesterol; IABP, Intra-aortic balloon pump; IRA, Infarct-related artery; LAD, Left anterior descending coronary artery; LDL-C, Low-density lipoprotein cholesterol; LMCA, Left main coronary artery; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; MINOCA, Myocardial infarction with nonobstructive coronary arteries; NSTEMI, Non-ST-segment elevation myocardial infarction; OM, Obtuse marginal branch; PCI, Percutaneous coronary intervention; RCA, Right coronary artery; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction; VTE, Venous thromboembolism; VT/VF, Ventricular tachycardia or ventricular fibrillation.

measurements and differed in ascertainment. Low HDL-C and hypertriglyceridemia may reflect clustering of metabolic risk factors, whereas the observed LDL-C distribution reinforces the clinical relevance of LDL-C in young MI survivors.[1,11]

Low HDL-C remains an established epidemiologic marker of cardiovascular risk and may identify an atherogenic metabolic phenotype, particularly when accompanied by hypertriglyceridemia.[12,13] However, randomized trials have not shown that pharmacologically increasing HDL-C with niacin improves cardiovascular outcomes when added to effective statin therapy, despite increases in HDL-C and reductions in triglycerides.[14,15] Accordingly, HDL-C should not be presented as a direct therapeutic target. Guideline-directed intensive LDL-C lowering remains the foundation of lipid management after MI, whereas low HDL-C may prompt broader clinical evaluation of smoking, physical inactivity, adiposity, glycemic status, triglycerides, and other residual risk markers. This represents a clinical recommendation rather than a description

of the present dataset, which did not include body mass index, waist circumference, apolipoprotein B, lipoprotein(a), or systematic assessment of familial hypercholesterolemia.[9]

**Angiographic and in-Hospital Arrhythmic Findings**

The LAD was the most frequent infarct-related artery, accounting for 51.8% of patients with obstructive coronary disease and 61.0% of patients with STEMI. Sustained VT/VF occurred in 9 patients (5.0%), including 6 patients with STEMI and 3 with NSTEMI. Complete AV block occurred in 5 patients, comprising 4 patients with STEMI and 1 with NSTEMI. Because only 9 sustained ventricular arrhythmic events and 5 complete AV blocks occurred, associations between infarct location, culprit vessel, and arrhythmic events were not evaluated. Both patients who died had experienced sustained VT/VF, but the cause of death was not independently adjudicated.

**MINOCA: Epidemiology and Diagnostic Limitations**

MINOCA accounted for 8.9% of the cohort, a proportion within the range reported in contemporary studies.[16] The subgroup included a higher proportion of women and had preserved LVEF, but its small size limits subgroup inference.[17]

MINOCA is a working diagnosis that requires further evaluation for ischemic and nonischemic mechanisms. Patients with a clinically established diagnosis of myocarditis or pericarditis were excluded from the study. However, occult myocarditis or Takotsubo syndrome could not be systematically excluded among all patients assigned a working diagnosis of MINOCA because CMR was not routinely available. Similarly, plaque disruption, spontaneous coronary artery dissection, vasospasm, and embolic mechanisms could not be comprehensively adjudicated because intracoronary imaging and coronary functional testing were not systematically performed.

**Multivessel Coronary Disease and Cardiometabolic Factors**

In the exploratory primary model, lower HDL-C was associated with multivessel disease, with a directionally consistent association in the male-only sensitivity analysis. In a separately specified alternative model evaluating non-HDL-C as the sole lipid covariate, the adjusted estimate did not reach statistical significance (aOR 1.13 per 25-mg/dL increase, 95% CI 0.95–1.35; P = 0.175). The confidence interval remained compatible with estimates ranging from little association to a potentially clinically relevant positive association. Because the models differed in covariate composition and complete-case populations, these findings should not be interpreted as demonstrating the comparative importance or superiority of HDL-C over non-HDL-C. Neither model establishes a causal effect of the evaluated lipid measures, and residual metabolic or behavioral confounding remains possible.

**Limitations**

This study has several limitations. First, its retrospective, single-center design introduces potential selection, referral, and information biases and limits causal inference and generalizability. The cohort was derived from a single tertiary center and should not be considered representative of populations throughout Türkiye or the Mediterranean region.

Second, the absence of healthy or older MI control groups prevents estimation of the excess prevalence or comparative etiologic importance of individual lipid abnormalities. Lipid concentrations were obtained from the first available panel during acute hospitalization, and fasting status, timing relative to symptom onset or coronary intervention, initiation of lipid-lowering therapy, and preadmission statin exposure were not consistently documented. Acute-phase changes may therefore have influenced the measured concentrations.

Third, body mass index, waist circumference, apolipoprotein B, lipoprotein(a), systematic assessment of familial hypercholesterolemia, and several nontraditional etiologic factors were not available. Substance exposure may also have been underreported because ascertainment relied on retrospective documentation and systematic toxicological screening was not performed.

Fourth, CMR, intracoronary imaging, coronary functional testing, and thrombophilia evaluation were not systematically performed or captured, limiting the classification of patients with MINOCA. The numbers of women and patients with MINOCA were small, and only 2 deaths and a few arrhythmic events occurred. Comparisons involving these groups or outcomes were therefore exploratory and imprecise.

Fifth, missing data were handled using complete-case analysis, and multiple comparisons were performed without adjustment for multiplicity. The primary model included 8 covariates and 61 multivessel disease cases, which may have limited model stability and precision. Residual and unmeasured confounding remain possible. Finally, follow-up ended at hospital discharge, so the study provides no information on postdischarge events, long-term prognosis, treatment adherence, or the effectiveness of secondary prevention strategies.

**Conclusion**

In this single-center cohort of adults younger than 45 years hospitalized with MI, low HDL-C, hypertriglyceridemia, and elevated LDL-C were common, and multivessel disease was present in 39.6% of patients with obstructive coronary disease. In the exploratory primary model, lower HDL-C was associated with multivessel disease, with a directionally consistent finding in the male-only sensitivity analysis. In the separately specified alternative model, the adjusted estimate for non-HDL-C did not reach statistical significance. Because these models differed in covariate composition and complete-case populations and were not designed for direct comparison, the results do not establish the comparative importance or superiority of either lipid measure. These hypothesis-generating findings require confirmation. The absence of a control group and reliance on lipid concentrations measured during acute hospitalization preclude conclusions regarding the comparative etiologic importance of individual lipid fractions.

**Supplementary Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-70716/TKDA-70716_(0)_supplement.docx

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# Young Myocardial Infarction: A Warning that Prevention Came Too Late

## Genç Miyokard Enfarktüsü: Koruyucu Önlemlerin Çok Geç Kaldığına Dair Bir Uyarı

**EDITORIAL COMMENT**
EDİTÖRYAL YORUM

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of mortality worldwide. Advances achieved with modern therapies are increasingly challenged by the cardiometabolic epidemic, which is contributing to myocardial infarction (MI) at younger ages. There is no universally accepted age threshold for young or premature MI; definitions in the literature vary, although cutoffs between 40 and 50 years are commonly used.[1] For the patient, however, the disease may be anything but early: atherosclerosis may have developed over years of exposure to tobacco, atherogenic lipoproteins, and metabolic risk factors.

Türkiye carries a substantial burden of premature coronary disease. In EUROASPIRE IV, MI before the age of 50 years was reported in 19% of the Turkish cohort, compared with 12% of the overall European population.[1,2] The national TURKMI registry likewise showed that patients presenting with acute MI in Türkiye were younger than those in several European registries; hypercholesterolemia and smoking were among the most prevalent risk factors.[3] These observations establish a compelling priority for prevention, although comparisons among coronary cohorts and registries should not be interpreted as population-based estimates of the incidence of young MI.

Two studies in this issue offer complementary perspectives on that priority. Uzun and Ekinci studied 180 adults younger than 45 years who were hospitalized with MI. Nearly 90% were men; low sex-specific high-density lipoprotein (HDL) cholesterol was recorded in 78.9%, triglyceride levels ≥150 mg/dL in 56.4%, and low-density lipoprotein (LDL) cholesterol levels ≥160 mg/dL in 22.0%. Among patients with obstructive disease, 39.6% already had multivessel coronary involvement. These findings illustrate the substantial burden of dyslipidemia and established coronary disease that may already be present at a young age.[4]

Kış and colleagues examined a different clinical population: 126 patients aged 45 years or younger who underwent emergency angiography for suspected ST-elevation myocardial infarction. At approximately one year, 22.2% had experienced the study's composite cardiovascular outcome, and all-cause mortality was 4.0%. Recurrent infarction and/or unplanned repeat revascularization accounted for most composite events. Higher admission glycated hemoglobin (HbA1c), a history of coronary disease, and lower left ventricular ejection fraction were associated with the outcome in the adjusted model. The investigators also identified an admission HbA1c level ≥6.5% in eight patients without previously known diabetes, highlighting an opportunity to detect previously unrecognized dysglycemia during follow-up.[5] Although the cohorts and endpoints differ, the studies converge on an important message: young age should not be equated with low risk after an infarction.

This message is consistent with the Partners YOUNG-MI Registry. Among patients with type 1 MI, those aged 40 years or younger had less extensive coronary artery disease than those aged 41–50 years, yet had similar one-year and long-term outcomes; the median follow-up exceeded 11 years.[6] The consequences of an infarction at a young age also extend across more years of life, work, and family responsibilities.

The other articles in this issue broaden the picture of premature MI. Studies of lipid-derived clusters, lipid ratios, and age-related inflammatory and metabolic profiles examine whether conventional risk-factor categories adequately characterize these

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patients. Reports on acute kidney injury, no-reflow, ST-segment resolution, and repeat revascularization shift attention from who develops an infarction to what determines recovery and subsequent risk. Together, they make a case for studying young MI across the full course of disease, from risk identification to acute care and long-term follow-up.

The most consequential intervention must begin before admission to the coronary care unit. Young adults can accumulate substantial lifetime cardiovascular risk while their short-term predicted risk remains low. Prevention in Türkiye should therefore identify smoking, severe or persistent LDL cholesterol elevation, familial hypercholesterolemia, elevated lipoprotein(a), diabetes and dysglycemia, and a family history of premature ASCVD early enough to permit intervention.[1] After an infarction, prevention must extend beyond conventional risk-factor treatment to include a systematic assessment of why the event occurred. In appropriately selected young patients, this includes consideration of inherited dyslipidemias, substance use, thrombophilia, spontaneous coronary artery dissection, coronary anomalies, inflammatory or immune-mediated disease, and other nonatherosclerotic mechanisms.[1,7] Women require particular attention to sex-specific and reproductive factors, including pregnancy-related disorders and hormonal exposures, as well as mechanisms such as spontaneous coronary artery dissection that may be disproportionately relevant in younger women.[1]

After the index event, sustained smoking-cessation support, cardiac rehabilitation, intensive lipid-lowering therapy and other guideline-directed secondary prevention measures, and monitoring of treatment-goal attainment are essential. Equally important is ensuring that the etiologic evaluation is not abandoned once the acute coronary lesion has been treated.[1,7]

These studies should prompt the development of better national evidence. A prospective, multicenter registry with consistent age definitions, adequate representation of women, adjudicated infarction mechanisms, detailed assessment of lifetime risk exposures, treatment attainment, and long-term outcomes would turn a clinical warning into a measurable public health agenda.

An infarction in a young adult is an acute event within a long disease trajectory. The larger task is to recognize risk years earlier- and prevent the event.

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# Castelli Risk Index-II and Repeat Revascularization After PCI in Young Patients with NSTEMI: A Retrospective Single-Center Study

## Genç NSTEMI Hastalarında Perkütan Koroner Girişim Sonrası Castelli Risk İndeksi-II ve Tekrarlayan Revaskülarizasyon: Retrospektif Tek Merkezli Bir Çalışma

**ABSTRACT**

**Objective:** Repeat revascularization following percutaneous coronary intervention (PCI) remains an important clinical concern in young patients. We evaluated the clinical and atherogenic factors associated with repeat revascularization in patients with premature non-ST-segment elevation myocardial infarction (NSTEMI) undergoing PCI.

**Method:** This retrospective, single-center observational study included 466 consecutive patients younger than 45 years who underwent PCI for NSTEMI between January 2020 and December 2024. Atherogenic markers, including the atherogenic index of plasma (AIP), triglyceride-glucose (TyG) index, remnant cholesterol inflammation index (RCII), and Castelli risk indices I and II (CRI-I and CRI-II), were analyzed. The primary endpoint was repeat revascularization only. A nested multivariable Cox model was used to evaluate the incremental prognostic value of CRI-II beyond that of a baseline model.

**Results:** Repeat revascularization occurred in 73 individuals (16%) over a median follow-up of 37.2 (22.1–51.9) months, predominantly involving non-target vessel revascularization. Patients requiring repeat revascularization had significantly higher CRI-II levels (P = 0.03). CRI-II remained independently associated with repeat revascularization after adjustment, along with hypertension and bifurcation lesions (HR: 1.30, 95% CI: 1.09–1.55, P = 0.003; HR: 2.09, 95% CI: 1.27–3.45, P = 0.004; and HR: 2.26, 95% CI: 1.19–4.27, P = 0.01, respectively); the addition of CRI-II modestly improved discrimination (Harrell's C index: 0.684 to 0.694). High CRI-II was associated with significantly higher repeat revascularization rates in the Kaplan–Meier analysis (log-rank P < 0.0001).

**Conclusion:** Elevated CRI-II was independently associated with repeat revascularization, along with hypertension and bifurcation lesions, in patients with premature NSTEMI undergoing PCI. However, CRI-II showed limited discriminatory performance, and its clinical utility for risk stratification requires external validation.

**Keywords:** Castelli risk index-II, NSTEMI, repeat revascularization, young patients.

**ÖZET**

**Amaç:** Perkütan koroner girişim (PCI) sonrası tekrarlayan revaskülarizasyon ihtiyacı, özellikle genç hastalarda önemli bir klinik sorun olmaya devam etmektedir. Bu çalışmada, ST-segment elevasyonsuz miyokard enfarktüsü (NSTEMI) nedeniyle PCI uygulanan genç hastalarda tekrarlayan revaskülarizasyon ile ilişkili klinik ve aterojenik faktörlerin araştırılması amaçlandı.

**Yöntem:** Bu retrospektif, tek merkezli gözlemsel çalışmada, Ocak 2020-Aralık 2024 döneminde NSTEMI nedeniyle PCI uygulanan 45 yaş altındaki 466 hasta değerlendirildi. Aterojenik plazma indeksi (AIP), remnant kolesterol inflamasyon indeksi (RCII), trigliserid-glukoz (TyG) indeksi, Castelli risk indeksi-I (CRI-I) ve Castelli risk indeksi-II (CRI-II) dahil olmak üzere çeşitli lipitle ilişkili indeksler analiz edildi. Birincil sonlanım noktası yalnızca tekrarlayan revaskülarizasyondu. CRI-II'nin artımsal prognostik değerini değerlendirmek amacıyla, temel modele CRI-II'nin eklendiği çok değişkenli Cox modelleme yaklaşımı kullanıldı.

**Bulgular:** Medyan 37,2 (22,1-51,9) aylık takip süresi boyunca 73 hastada (%16) tekrarlayan revaskülarizasyon gelişti ve bu olayların çoğunluğunu hedef olmayan damar revaskülarizasyonu oluşturdu. Tekrarlayan revaskülarizasyon gelişen hastalarda CRI-II düzeyleri anlamlı olarak daha yüksekti (P = 0,03). CRI-II ile birlikte hipertansiyon ve bifurkasyon lezyonlarının tekrarlayan revaskülarizasyon ile bağımsız olarak ilişkili olduğu saptandı (sırasıyla HR: 1,30, %95 GA: 1,09-1,55, P = 0,003; HR: 2,09, %95 GA: 1,27-3,45, P = 0,004; ve HR: 2,26, %95 GA:

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1,19-4,27, P = 0,01). CRI-II'nin modele eklenmesi, ayırt edici performansta sınırlı bir artış sağladı (Harrell C-indeksi 0,684'ten 0,694'e). Kaplan-Meier analizinde yüksek CRI-II düzeyleri, anlamlı olarak daha yüksek tekrarlayan revaskülarizasyon oranı ile ilişkiliydi (log-rank P < 0,0001).

**Sonuç:** NSTEMI nedeniyle PCI uygulanan genç hastalarda yüksek CRI-II düzeyi, hipertansiyon ve bifurkasyon lezyonları tekrarlayan revaskülarizasyon ile bağımsız olarak ilişkili bulundu. Bununla birlikte, CRI-II'nin ayırt edici performansı sınırlı olup risk sınıflandırmasındaki klinik yararlılığının belirlenmesi için ileri çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Castelli risk indeksi-II, NSTEMI, tekrarlayan revaskülarizasyon, genç hastalar.

Acute coronary syndrome (ACS) continues to be an important global health concern and a major contributor to cardiovascular morbidity and mortality.[1,2] Although ACS predominantly occurs in older individuals, its occurrence among younger adults has become increasingly recognized in recent years. The age definition of premature ACS varies across studies, and young patients are estimated to account for approximately 5%–13% of all ACS presentations.[3-7] Although some studies have proposed sex-specific age thresholds for defining premature ACS, a uniform age threshold of <45 years has also been used in studies evaluating young patients with ACS.[5-7] Among younger individuals, ST-segment elevation myocardial infarction (STEMI) has traditionally been the predominant presentation and has therefore been more extensively investigated in previous studies.[1,5,7,8] In contrast, interest in non-ST-segment elevation myocardial infarction (NSTEMI) has increased because of its rising frequency and potentially distinct clinical characteristics in younger individuals. Traditional cardiovascular risk factors, together with lifestyle-related changes, may contribute to this trend.

Although secondary prevention therapies and contemporary percutaneous coronary intervention (PCI) techniques have improved cardiovascular outcomes, repeat revascularization remains a clinically relevant issue following PCI. Previous studies have reported an association between repeat revascularization and adverse cardiovascular outcomes, as well as an increased healthcare burden.[9,10] In addition to procedural and angiographic factors, residual atherogenic burden may also contribute to recurrent coronary events.[11,12]

Several composite lipid-related indices, such as the atherogenic index of plasma (AIP), remnant cholesterol inflammation index (RCII), triglyceride-glucose (TyG) index, and Castelli risk indices I and II (CRI-I and CRI-II), have been investigated as potential markers of residual atherogenic risk beyond traditional lipid parameters.[12-15] Nevertheless, evidence regarding the relationship between these indices and repeat revascularization in young patients with NSTEMI remains scarce. Accordingly, this study was designed to evaluate the associations of clinical characteristics and lipid-derived atherogenic indices with repeat revascularization in patients with premature NSTEMI undergoing PCI and to identify independent predictors of repeat revascularization.

## ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| AIP | Atherogenic index of plasma |
| CAD | Coronary artery disease |
| CRI | Castelli risk indices |
| CRP | C-reactive protein |
| ECG | Electrocardiography |
| HDL-C | HDL cholesterol |
| HT | Hypertension |
| LDL-C | Low-density lipoprotein cholesterol |
| MACCE | Major adverse cardiac and cerebrovascular events |
| Non-TVR | Non-target vessel revascularization |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| RC | Remnant cholesterol |
| RCII | Remnant cholesterol inflammation index |
| TC | Total cholesterol |
| TG | Triglycerides |
| TLR | Target lesion revascularization |
| TVR | Target vessel revascularization |
| TyG | Triglyceride-glucose |

### Materials and Methods

This retrospective, single-center observational study evaluated 466 young patients who underwent PCI for NSTEMI between January 2020 and December 2024. Individuals younger than 45 years were eligible for inclusion. Patients with cardiogenic shock at presentation, active infectious or inflammatory conditions, active malignancy, advanced renal dysfunction (eGFR <30 mL/min/1.73 $m^2$), or incomplete clinical data were excluded. The patient selection process is shown in Figure 1. Demographic characteristics, laboratory findings, echocardiographic parameters, procedural details, and follow-up data were obtained from hospital records.

Patients presenting with acute chest discomfort in the absence of persistent ST-segment elevation on electrocardiography (ECG) and meeting the criteria for MI according to the Fourth Universal Definition were diagnosed with NSTEMI.[16] All patients had type 1 NSTEMI and underwent coronary angiography followed by PCI. Depending on the procedural strategy, either drug-eluting stent implantation or balloon angioplasty alone was performed. The antiplatelet regimen was administered at the discretion of the interventional cardiologists. During the index procedure, PCI was performed only for the culprit lesion. Elective PCI of non-culprit lesions was performed as a staged procedure before discharge and was not considered a repeat revascularization event. No planned staged PCI procedures were performed after discharge. Bifurcation lesions were defined as true bifurcation lesions according to the Medina classification (Medina 1,1,1; 1,0,1; or 0,1,1). When PCI was indicated, bifurcation lesions were treated using either a

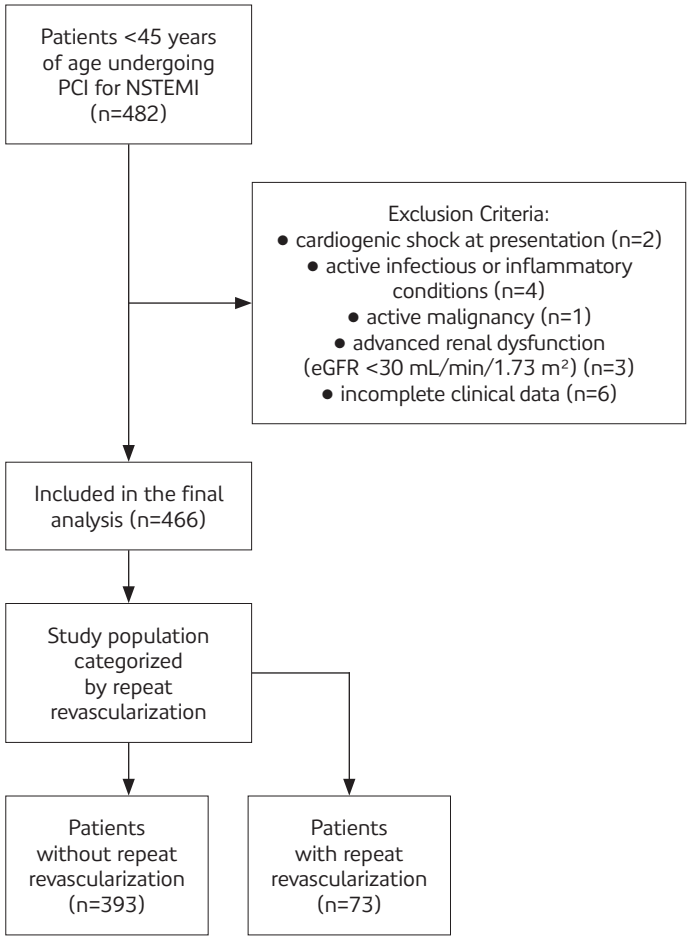



**Figure 1.** Flowchart of the study population and patient selection.

provisional single-stent or a two-stent strategy according to lesion characteristics and operator discretion. New-generation drug-eluting stents were used whenever stent implantation was required. At discharge, patients were prescribed contemporary guideline-recommended therapies, including aspirin plus a P2Y12 inhibitor for a planned duration of 12 months and high-intensity statin therapy. No patients received ezetimibe or PCSK9 inhibitor therapy during the study period. Only clinically indicated (ischemia-driven) repeat revascularizations occurring after hospital discharge were considered study endpoints. Routine surveillance angiography was not performed. Repeat revascularization events were identified from institutional electronic medical records and outpatient follow-up records. Repeat revascularization was categorized as target lesion revascularization (TLR), target vessel revascularization excluding TLR (TVR excluding TLR), or non-target vessel revascularization (non-TVR). TLR was defined as repeat PCI performed for restenosis occurring within the treated segment or within 5 mm of the stent edges. Repeat revascularization occurring in the same coronary vessel outside the target lesion segment was classified as TVR, whereas procedures involving a different coronary artery were categorized as non-TVR. Mortality, recurrent myocardial infarction, and stroke were not predefined study endpoints but were ascertained from available institutional follow-up records and reported descriptively. MACCE was not evaluated as a composite endpoint. Recurrent myocardial infarction was defined as NSTEMI or STEMI during follow-up according to the Fourth Universal Definition of Myocardial Infarction. No cases of unstable angina were identified during follow-up.

The study protocol received approval from Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2026/09/1466, Date: 05.05.2026), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

**Laboratory Measurements and Lipid Indices**

Blood samples were collected after an overnight fast within the first 24 hours of admission and before the index procedure. Serum lipid parameters and fasting plasma glucose were analyzed in the biochemistry laboratory using standard enzymatic methods. Non-HDL cholesterol was calculated as total cholesterol (TC) minus HDL cholesterol (non-HDL-C=TC-HDL-C). Remnant cholesterol (RC) levels were calculated by subtracting HDL-C and low-density lipoprotein cholesterol (LDL-C) from TC, whereas RCII was calculated as RC×C-reactive protein (CRP)/10. The AIP was expressed as log10(TG/HDL-C), with triglyceride and HDL-C concentrations converted from mg/dL to mmol/L, whereas the TyG index was calculated as ln[fasting triglycerides (TG)×fasting plasma glucose/2] using values expressed in mg/dL. CRI-I and CRI-II were calculated as the TC/HDL-C and LDL-C/HDL-C ratios, respectively.

**Statistical Analysis**

Statistical analyses were performed using Jamovi software (version 2.6.2; The Jamovi Project, Sydney, Australia) and R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria). The distributional properties of continuous variables were evaluated using the Shapiro–Wilk test. Normally distributed variables were reported as mean±standard deviation (SD), whereas skewed variables were presented as median with interquartile range (IQR). Categorical variables were expressed as counts and percentages. Between-group comparisons were performed using either Student's t-test or the Mann–Whitney U test for continuous variables. For categorical variables, Pearson's chi-square test or Fisher's exact test was used, as appropriate. Statistical analyses were performed using complete-case data.

The primary outcome was clinically indicated repeat revascularization during follow-up. Time-to-event analyses were performed using Kaplan–Meier survival curves, and intergroup differences were evaluated using the log-rank test. Median follow-up duration was calculated using the reverse Kaplan–Meier approach. To identify factors associated with repeat revascularization, univariable Cox proportional hazards analyses were initially performed. A nested modeling strategy was used to evaluate the incremental prognostic contribution of CRI-II. First, a baseline Cox model including prespecified clinically relevant covariates (smoking, hypertension, diabetes mellitus, prior statin therapy, prior PCI, bifurcation lesion, and balloon-only therapy) was constructed. CRI-II was subsequently added to the baseline model to evaluate its incremental prognostic value. Restricted cubic spline analysis was also performed to assess the potential nonlinear association between CRI-II and repeat revascularization. Multicollinearity was assessed using variance inflation factors (VIFs), and variables showing substantial mathematical overlap were not included simultaneously in the same multivariable model. The proportional hazards assumption

**Table 1.** Baseline clinical, demographic, and procedural characteristics according to repeat revascularization status

| Variables | No repeat revascularization (n=393, 84%) | Repeat revascularization (n=73, 16%) | *P* |
|---|---|---|---|
| Baseline clinical characteristics | | | |
| Age, years | 41.0 (40.0–43.0) | 41.0 (39.0–43.0) | 0.94 |
| Male sex, n (%) | 346 (88.0%) | 69 (94.5%) | 0.10 |
| Hypertension, n (%) | 102 (26.0%) | 30 (41.1%) | **0.01** |
| Diabetes mellitus, n (%) | 85 (21.6%) | 12 (16.4%) | 0.32 |
| Hyperlipidemia, n (%) | 57 (14.5%) | 15 (20.5%) | 0.19 |
| Current smoking, n (%) | 166 (42.2%) | 41 (56.2%) | **0.03** |
| COPD, n (%) | 8 (2.0%) | 4 (5.5%) | 0.09 |
| Heart failure, n (%) | 12 (3.1%) | 3 (4.1%) | 0.64 |
| LVEF, % | 65 (55–65) | 60 (55–65) | 0.52 |
| Prior CAD, n (%) | 79 (20.1%) | 27 (37.0%) | **<0.01** |
| Prior PCI, n (%) | 63 (16.0%) | 21 (28.8%) | **0.01** |
| Chronic kidney disease, n (%) | 7 (2%) | 1 (1%) | 0.80 |
| Cerebrovascular disease, n (%) | 4 (1%) | 0 (0%) | 0.38 |
| Peripheral artery disease, n (%) | 4 (1%) | 0 (0%) | 0.38 |
| Thrombophilia, n (%) | 1 (0.3%) | 0 (0%) | 0.66 |
| Family history, n (%) | 90 (22.9%) | 10 (13.7%) | 0.08 |
| ST-T changes, n (%) | 71 (18.1%) | 14 (19.2%) | 0.82 |
| Baseline medication use | | | |
| Aspirin use, n (%) | 70 (17.8%) | 24 (32.9%) | **<0.01** |
| Beta-blocker use, n (%) | 48 (12.2%) | 16 (21.9%) | **0.03** |
| ACEI/ARB use, n (%) | 66 (16.8%) | 20 (27.4%) | **0.03** |
| Statin use, n (%) | 42 (10.7%) | 10 (13.7%) | 0.45 |
| High-intensity statin use, n (%) | 22 (6%) | 5 (7%) | 0.67 |
| Fenofibrate use, n (%) | 8 (2.0%) | 0 (0%) | 0.22 |
| Insulin use, n (%) | 21 (5.3%) | 4 (5.5%) | 0.96 |
| Procedural characteristics | | | |
| LAD lesion, n (%) | 221 (56.2%) | 36 (49.3%) | 0.28 |
| CX lesion, n (%) | 105 (26.7%) | 16 (21.9%) | 0.39 |
| RCA lesion, n (%) | 130 (33.1%) | 33 (45.2%) | 0.05 |
| Multivessel disease, n (%) | 128 (33%) | 32 (44%) | 0.06 |
| Chronic total occlusion, n (%) | 4 (1%) | 4 (5%) | **0.007** |
| Bifurcation lesion, n (%) | 25 (6.4%) | 12 (16.4%) | **<0.01** |
| Provisional stenting, n (%) | 20 (5%) | 11 (15%) | **0.004** |
| Two-stent strategy, n (%) | 5 (1%) | 1 (1%) | 0.94 |
| Subtotal/total lesion, n (%) | 189 (48.1%) | 38 (52.1%) | 0.53 |
| Balloon angioplasty only, n (%) | 24 (6.1%) | 11 (15.1%) | **0.01** |
| Direct stenting, n (%) | 36 (9.2%) | 3 (4.1%) | 0.15 |
| Predilatation followed by stent implantation, n (%) | 333 (84.7%) | 59 (80.8%) | 0.39 |
| Stent diameter, mm | 3 (2.75–3) | 2.75 (2.5–3) | **0.002** |
| Stent length, mm | 24 (19–33) | 26 (18–38) | 0.36 |
| Thrombectomy, n (%) | 8 (2.0%) | 1 (1.4%) | 0.70 |
| Thrombus burden, n (%) | 79 (20.1%) | 17 (23.3%) | 0.54 |
| GP IIb/IIIa inhibitor use, n (%) | 62 (15.8%) | 15 (20.5%) | 0.31 |

Categorical variables are presented as n (%) and were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Complete data were available for all applicable variables. The denominators were n=393 for the no repeat revascularization group and n=73 for the repeat revascularization group. For stent-related variables, the denominators were n=369 for the no repeat revascularization group and n=62 for the repeat revascularization group. ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; CX, Circumflex artery; GP IIb/IIIa, Glycoprotein IIb/IIIa; LAD, Left anterior descending artery; LVEF, Left ventricular ejection fraction; PCI, Percutaneous coronary intervention; RCA, Right coronary artery.

was evaluated using Schoenfeld residuals. In the Cox time-to-event analysis, follow-up was calculated from the index PCI to the first occurrence of repeat revascularization, death, the last documented clinical contact, or the end of the study period, whichever occurred first. Patients who died before experiencing repeat revascularization were censored at the date of death. Effect estimates were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).

Harrell's concordance index (C-index) was used to evaluate the discriminative performance of the prognostic model. Internal validation was performed using bootstrap resampling with 1,000 iterations to estimate optimism-corrected model performance. In addition, the optimal threshold value for CRI-II was determined using maximally selected rank statistics and should be considered exploratory. Based on regression coefficients derived from the final multivariable model, individualized risk scores were calculated, and participants were subsequently categorized into quartile-based risk categories. Statistical significance was defined as a two-tailed p-value of <0.05.

## Results

### Baseline Characteristics

The clinical and procedural characteristics of the study groups are summarized in Tables 1 and 2.

During follow-up, repeat revascularization occurred in 73 patients (16%). Patients requiring repeat revascularization were more likely to have hypertension (HT), a history of smoking, prior coronary artery disease (CAD), and prior PCI than those in the non-repeat revascularization group (P = 0.01, P = 0.03, P < 0.01, and P = 0.01, respectively). Moreover, baseline use of aspirin, beta-blockers, and ACEIs/ARBs was more frequent in the repeat revascularization group (P < 0.01, P = 0.03, and P = 0.03, respectively). Among procedural findings, bifurcation lesions, provisional bifurcation stenting, balloon angioplasty without stent implantation, and CTO lesions were more common in patients requiring repeat revascularization (P < 0.01, P = 0.004, P = 0.01, and P = 0.007, respectively). Most laboratory parameters showed similar distributions between the groups. In contrast, CRI-II values were significantly higher among patients requiring repeat revascularization during follow-up, whereas other lipid-related indices, including AIP, RCII, the TyG index, CRI-I, and non-HDL cholesterol, were similar between the study groups (P = 0.71, P = 0.92, P = 0.73, P = 0.08, and P = 0.38, respectively).

### Repeat Revascularization Patterns, Cox Regression, and Survival Analyses

The median follow-up duration was 37.2 (22.1–51.9) months. There were no in-hospital deaths, whereas four deaths occurred during long-term follow-up, all among patients without repeat revascularization. The subtypes of repeat revascularization are presented in Table 3. During follow-up, non-TVR (54.8%) was the most frequent subtype of repeat revascularization, followed by TVR excluding TLR (28.7%) and TLR (16.4%). Among TLR events, only one case (1.4%) was related to definite stent thrombosis. Clinical presentation at the time of repeat revascularization, antiplatelet and lipid-lowering therapies, and medication adherence among patients undergoing repeat revascularization are summarized in Supplementary Table 1. Descriptive clinical outcomes during follow-up are summarized in Supplementary Table 2.

**Table 2.** Laboratory findings stratified by repeat revascularization status

| Variables | No repeat revascularization (n=393, 84%) | Repeat revascularization (n=73, 16%) | *P* |
|---|---|---|---|
| WBC, ×10³/μL | 10.0 (8.4–11.8) | 10.0 (8.8–12.0) | 0.29 |
| Hemoglobin, g/dL | 15.0 (13.7–15.8) | 14.9 (13.9–15.9) | 0.42 |
| Platelet count, ×10³/μL | 259 (220–307) | 249 (221–294) | 0.70 |
| Creatinine, mg/dL | 0.83 (0.73–0.97) | 0.86 (0.75–0.95) | 0.10 |
| GFR, mL/min/1.73 m² | 108 (96–116) | 107 (96–115) | 0.29 |
| Glucose, mg/dL | 107 (94–137) | 106 (95–129) | 0.77 |
| Albumin, g/L | 46 (42–47) | 45 (42–47) | 0.75 |
| Triglycerides, mg/dL | 163 (109–264) | 190 (120–259) | 0.83 |
| HDL-C, mg/dL | 36 (31–43) | 34 (30–40) | 0.10 |
| LDL-C, mg/dL | 114±40 | 122±39 | 0.11 |
| Total cholesterol, mg/dL | 192 (163–225) | 198 (171–227) | 0.49 |
| Non-HDL cholesterol, mg/dL | 156 (127.5–186) | 163 (134–189) | 0.38 |
| CRP, mg/L | 3.7 (1.6–7.7) | 3.5 (1.5–7.4) | 0.76 |
| Troponin, ng/mL | 0.07 (0.02–0.45) | 0.05 (0.02–0.29) | 0.40 |
| Remnant cholesterol, mg/dL | 33.0 (20.0–57.0) | 38.8 (22.0–56.0) | 0.82 |
| AIP | 0.30 (0.10–0.52) | 0.33 (0.13–0.54) | 0.71 |
| RCII | 13.9 (7.2–31.5) | 14.9 (7.5–29.1) | 0.92 |
| TyG index | 9.15 (8.74–9.65) | 9.32 (8.65–9.71) | 0.73 |
| CRI-I | 5.10 (4.20–6.51) | 5.4 (4.61–7.04) | 0.08 |
| CRI-II | 3.06 (2.40–3.91) | 3.45 (2.64–4.24) | **0.03** |

Continuous variables are presented as mean±standard deviation or median (interquartile range), according to the data distribution. Complete data were available for all variables; the denominators were n=393 for the no repeat revascularization group and n=73 for the repeat revascularization group. AIP, Atherogenic index of plasma; CRI-I, Castelli risk index I; CRI-II, Castelli risk index II; CRP, C-reactive protein; GFR, Glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; RCII, Remnant cholesterol inflammation index; TyG, Triglyceride-glucose index; WBC, White blood cell count.

**Table 3.** Subtypes of repeat revascularization during follow-up

| Repeat revascularization subtype | n (%) |
|---|---|
| Target lesion revascularization (TLR) | 12 (16.4) |
| Stent thrombosis-related TLR | 1 (1.4) |
| Target vessel revascularization (TVR) excluding TLR | 21 (28.7) |
| Non-target vessel revascularization (non-TVR) | 40 (54.8) |

Percentages were calculated using the total number of patients who underwent repeat revascularization (n=73) as the denominator. TLR, Target lesion revascularization; TVR, Target vessel revascularization; non-TVR, Non-target vessel revascularization.

Nested multivariable Cox regression models and the sensitivity analysis for repeat revascularization are shown in Table 4. In the baseline model (Model 1), smoking, HT, prior PCI, and bifurcation lesions were independently associated with repeat revascularization (HR: 1.67, 95% CI: 1.04–2.67, P = 0.03; HR: 1.99, 95% CI: 1.21–3.26, P = 0.007; HR: 1.88, 95% CI: 1.01–3.49, P = 0.04; and HR: 2.13, 95% CI: 1.13–4.04, P = 0.02, respectively). After the addition of CRI-II (Model 2), CRI-II remained independently associated with repeat revascularization, along with HT and bifurcation lesions (HR: 1.30, 95% CI: 1.09–1.55, P = 0.003; HR: 2.09, 95% CI: 1.27–3.45, P = 0.004; and HR: 2.26, 95% CI: 1.19–4.27, P = 0.01, respectively). Among patients who underwent stent implantation, a sensitivity analysis additionally adjusted for stent diameter demonstrated similar findings. Stent diameter was not independently associated with repeat revascularization (HR: 0.82, 95% CI: 0.46–1.45, P = 0.49), whereas CRI-II remained independently associated with repeat revascularization (HR: 1.34, 95% CI: 1.11–1.61, P = 0.002). The multivariable model estimates are visually presented in Figure 2.

Maximally selected rank statistics identified an optimal CRI-II cutoff value of 3.44 for predicting repeat revascularization (Figure 3). Based on this data-derived threshold, patients were classified into high- and low-CRI-II groups. Repeat revascularization occurred in 38 of 180 patients (21.1%) in the high-CRI-II group and in 35 of 286 patients (12.2%) in the low-CRI-II group. Patients with elevated CRI-II levels experienced a significantly higher rate of repeat revascularization events throughout follow-up (log-rank P < 0.0001) (Figure 4).

A risk score model was constructed using the multivariable Cox regression model to estimate the likelihood of repeat revascularization. Patients were subsequently categorized into four risk groups based on quartiles of the calculated risk score: low-risk, intermediate-low-risk, intermediate-high-risk, and high-risk groups. Kaplan–Meier analysis revealed progressively lower event-free survival across increasing risk categories (log-rank P < 0.0001) (Figure 5).

Restricted cubic spline analysis demonstrated a significant overall association between CRI-II and repeat revascularization (P = 0.016), with no evidence of nonlinearity (p for nonlinearity=0.702), supporting an approximately linear relationship across the observed range of CRI-II values (Supplementary Figure 1A). Additionally, an adjusted partial effect plot was provided to visualize the continuous association between CRI-II and the risk of repeat revascularization after multivariable adjustment (Supplementary Figure 1B).

At 36 months, the time-dependent AUC of CRI-II for predicting repeat revascularization was 0.572. The optimal cutoff value was 3.44, with a sensitivity of 54.3% and a specificity of 59.7% (Supplementary Figure 2).

Harrell's C-index for the final model was 0.694, indicating moderate model discrimination.

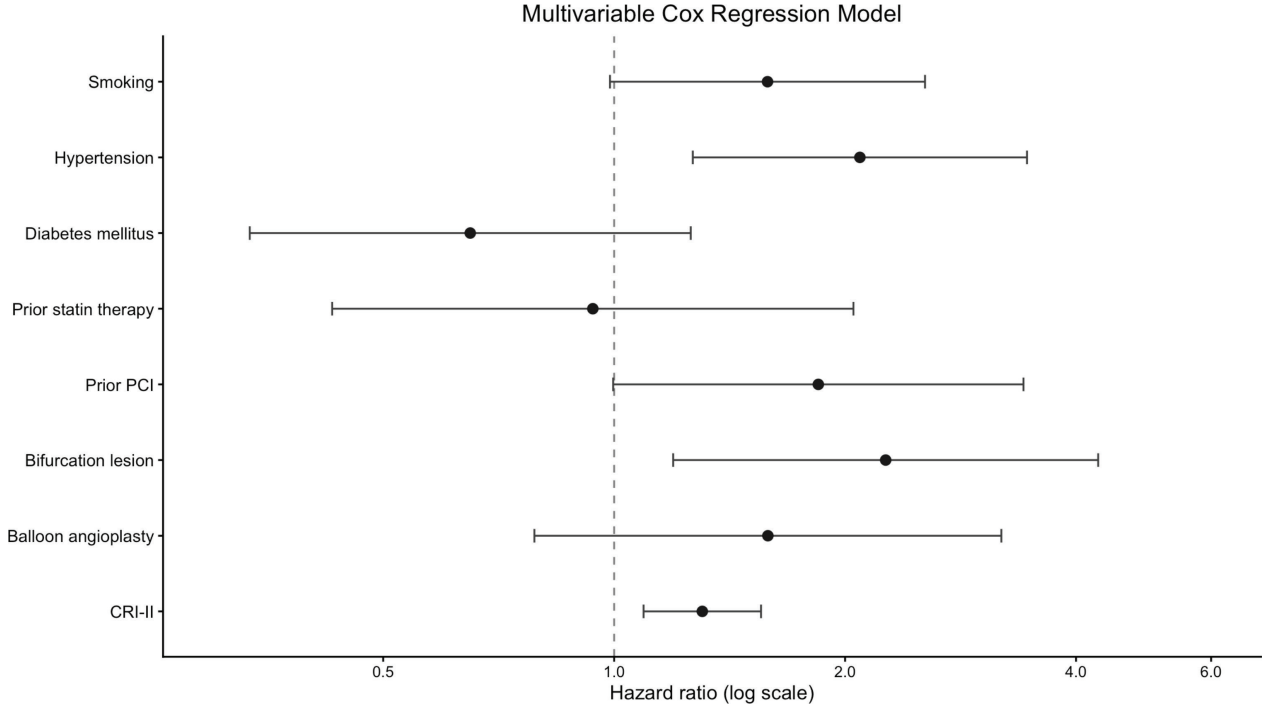



**Figure 2.** Forest plot showing hazard ratios and 95% confidence intervals for variables included in the multivariable Cox proportional hazards regression model.

Internal bootstrap validation using 1,000 resamples yielded an optimism-corrected C-index of 0.663 and an optimism-corrected calibration slope of 0.826, indicating some degree of model overfitting.

In endpoint-specific exploratory analyses, high CRI-II was strongly associated with non-TVR compared with low CRI-II (HR: 4.55, 95% CI: 2.13–10.00, P < 0.001). In contrast, no significant association was observed for TVR excluding TLR (HR: 0.88, 95% CI: 0.45–1.75, P = 0.73) or TLR (HR: 1.16, 95% CI: 0.57–2.33, P = 0.68) (Supplementary Table 3). Kaplan–Meier cumulative curves for endpoint-specific repeat revascularization according to CRI-II categories are shown in Supplementary Figure 3.

## Discussion

In this study, we investigated clinical and atherogenic factors associated with repeat revascularization in patients with premature NSTEMI treated with PCI. Our analyses revealed several key findings. First, 16% of young patients with NSTEMI underwent repeat revascularization during a median follow-up of 37.2 months, with non-TVR representing the predominant subtype. Second, CRI-II values were higher among patients requiring repeat revascularization and remained independently associated with repeat revascularization after multivariable adjustment. Third, HT and bifurcation lesions emerged as significant predictors of repeat revascularization; smoking and prior PCI were associated with repeat revascularization in the baseline model but did not retain independent significance after full adjustment. Fourth, higher predicted risk was associated with progressively lower event-free survival rates.

Although young patients with NSTEMI generally have lower short-term mortality rates, recurrent ischemic events and repeat revascularization remain clinically important because of their effects on long-term morbidity, recurrent hospitalizations, quality of life, and healthcare resource utilization. In our cohort, repeat revascularization occurred in 16% of patients, a rate comparable to those reported in previous observational studies.[17,18] Interestingly, non-TVR represented the predominant subtype of repeat revascularization. Although exploratory because of the limited number of endpoint-specific events, subgroup analyses demonstrated that the association between high CRI-II and repeat revascularization was primarily driven by non-TVR rather than TLR or TVR excluding TLR. These findings may suggest that progression of native coronary atherosclerosis, rather than lesion-related restenosis mechanisms alone, contributes more substantially to recurrent ischemic events in young patients with NSTEMI.

Lipid abnormalities contribute substantially to the pathogenesis and progression of ACS, including NSTEMI. Higher LDL-C and TG levels, along with lower HDL-C levels, have been associated with recurrent ischemic complications and adverse cardiovascular outcomes.[19,20] Beyond these conventional lipid parameters, several composite lipid-related indices have been proposed to improve atherogenic risk assessment.[14,15,21-24] However, in our study, only CRI-II remained independently associated with repeat revascularization after

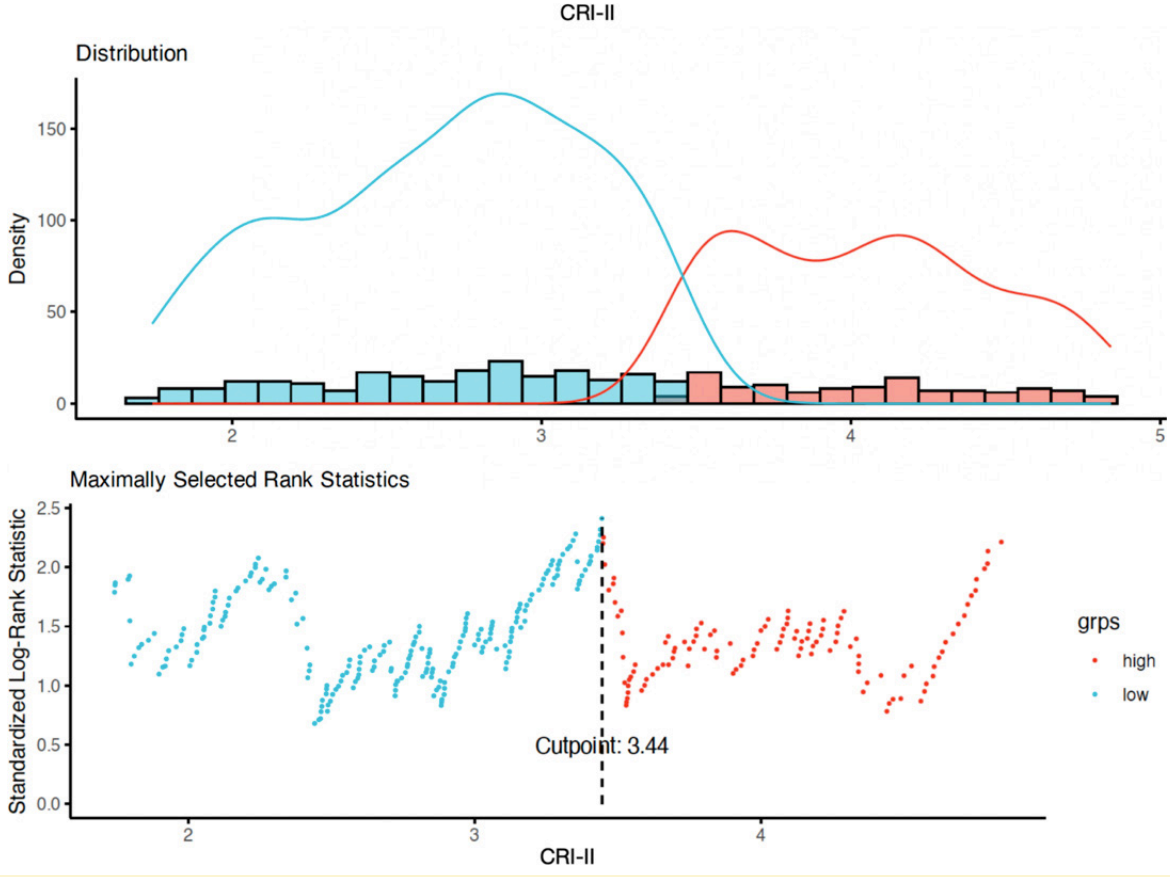



**Figure 3.** Distribution of CRI-II values and determination of the optimal cutoff value using maximally selected rank statistics. The dashed vertical line indicates the optimal cutoff value of 3.44 for stratification into low- and high-CRI-II groups.

multivariable adjustment, whereas AIP, RCII, the TyG index, and CRI-I showed no significant association with repeat revascularization. One possible explanation is that CRI-II reflects the balance between atherogenic and protective lipoproteins by integrating two complementary aspects of lipid metabolism that contribute to atherosclerotic plaque progression, which may help explain its association with recurrent coronary events in premature NSTEMI. Previous studies have also demonstrated that the LDL-C/HDL-C ratio is more closely associated with coronary atherosclerotic burden and adverse cardiovascular outcomes than isolated lipid parameters.[25,26] Because all indices were derived from a single fasting blood sample obtained during the acute phase of NSTEMI, they should not be interpreted as stable markers of long-term atherogenic risk.

In addition to lipid-related indices, several established clinical and procedural factors were associated with repeat revascularization in the present study. Patients who underwent repeat revascularization had a higher baseline burden of cardiovascular risk factors, prior CAD, and previous cardiovascular treatment. These findings suggest that the repeat revascularization group comprised patients with more advanced underlying coronary disease, which should be considered when interpreting the observed associations. Consistent with these baseline risk profiles, HT, smoking, and prior PCI have previously been associated with adverse cardiovascular outcomes and recurrent ischemic events.[27,28] In our cohort, HT remained independently associated with repeat revascularization after multivariable adjustment, whereas smoking and prior PCI were significant only in the baseline model and did not retain independent significance in the fully adjusted model. Lesion complexity may also contribute to recurrent coronary events following PCI. Oflar et al.[29] reported that angiographic lesion complexity, as quantified by the SYNTAX score, was associated with recurrent revascularization in young patients with ACS. In line with these findings, bifurcation lesions

**Table 4.** Nested multivariable Cox regression models and sensitivity analysis for repeat revascularization

| Variables | Model 1 HR (95% CI) | *P* | Model 2 HR (95% CI) | *P* | Sensitivity analysis HR (95% CI) | *P* |
|---|---|---|---|---|---|---|
| Smoking | 1.67 (1.04–2.67) | **0.03** | 1.58 (0.99–2.54) | 0.05 | 1.79 (1.07–3.00) | **0.02** |
| Hypertension | 1.99 (1.21–3.26) | **0.007** | 2.09 (1.27–3.45) | **0.004** | 1.81 (1.03–3.16) | **0.03** |
| Diabetes mellitus | 0.65 (0.34–1.26) | 0.20 | 0.65 (0.34–1.26) | 0.20 | 0.56 (0.26–1.18) | 0.12 |
| Prior statin therapy | 0.77 (0.36–1.66) | 0.50 | 0.94 (0.43–2.05) | 0.87 | 0.93 (0.37–2.33) | 0.87 |
| Prior PCI | 1.88 (1.01–3.49) | **0.04** | 1.85 (1.00–3.42) | 0.05 | 2.09 (1.07–4.06) | **0.03** |
| Bifurcation lesion | 2.13 (1.13–4.04) | **0.02** | 2.26 (1.19–4.27) | **0.01** | 1.99 (0.93–4.24) | 0.07 |
| Balloon angioplasty only | 1.63 (0.81–3.29) | 0.17 | 1.59 (0.79–3.20) | 0.19 | – | – |
| CRI-II (per 1-unit increase) | – | – | 1.30 (1.09–1.55) | **0.003** | 1.34 (1.11–1.61) | **0.002** |
| Stent diameter (per 1-mm increase) | – | – | – | – | 0.82 (0.46–1.45) | 0.49 |

Model 1 and Model 2 included all 466 patients and 73 repeat revascularization events. Model 1 included smoking, hypertension, diabetes mellitus, prior statin therapy, prior PCI, bifurcation lesion, and balloon angioplasty-only treatment. Model 2 additionally included CRI-II. The sensitivity analysis was restricted to patients who underwent stent implantation (n=431) and was additionally adjusted for stent diameter; therefore, balloon angioplasty-only treatment was not included in the sensitivity model. The proportional hazards assumption was satisfied (global Schoenfeld test, $P = 0.92$). CI, Confidence interval; CRI-II, Castelli risk index II; HR, Hazard ratio; PCI, Percutaneous coronary intervention.

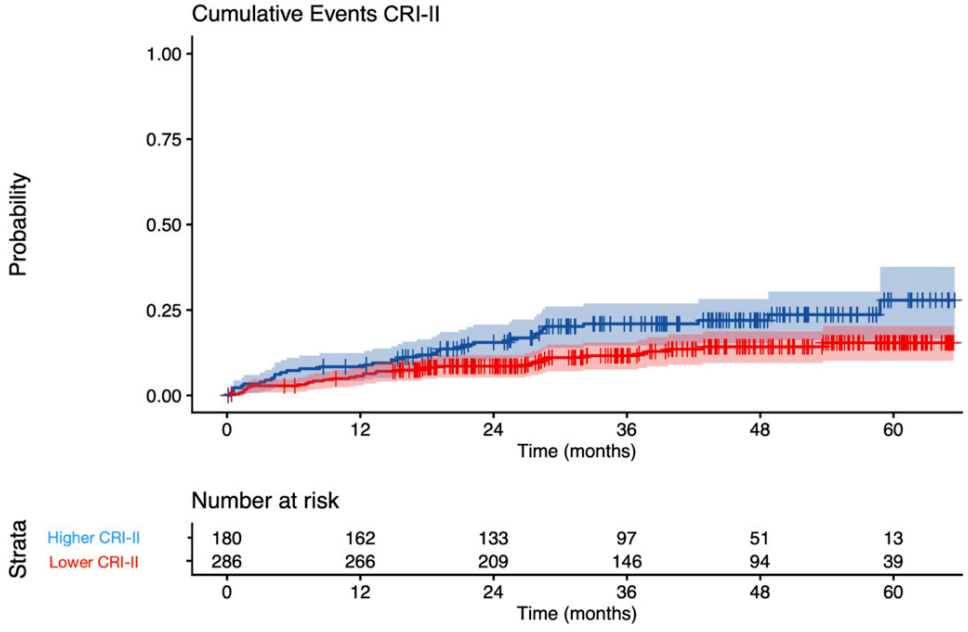



**Figure 4.** Kaplan–Meier cumulative event curves according to CRI-II groups stratified by the optimal cutoff value. Patients with higher CRI-II values demonstrated a significantly greater cumulative incidence of repeat revascularization than those with lower CRI-II values. Shaded areas represent 95% confidence intervals.

emerged as an independent predictor of repeat revascularization in our study. This association may be related to the greater procedural complexity, diffuse atherosclerotic burden, and challenging lesion anatomy frequently observed in bifurcation lesions.[30] To our knowledge, this is among the first studies to compare multiple lipid-derived indices for predicting repeat revascularization specifically in patients with premature NSTEMI. Our findings suggest that CRI-II was independently associated with repeat revascularization beyond established clinical and procedural predictors; however, its discriminatory performance was modest (C-index 0.694), and the identified CRI-II cutoff value of 3.44 was derived from the present cohort. Therefore, both the prediction model and the proposed cutoff should be considered exploratory and require external validation before clinical application. Accordingly, our findings should be interpreted within the context of the variables available in this retrospective dataset and should not be considered a comprehensive etiologic assessment of recurrent coronary risk in patients with premature NSTEMI.

### Limitations

This study has several limitations. The retrospective, single-center design, along with the relatively modest sample size and number of events, may have introduced selection bias, limited statistical power, and restricted the generalizability of our findings. The modest number of events relative to the number of variables included in the multivariable model may also have resulted in some degree of overfitting despite internal bootstrap validation. The low representation of women also precluded reliable sex-specific analyses. Repeat revascularization was identified from institutional records and was based on clinical indications rather than routine angiographic follow-up. Therefore, procedures performed at other institutions may not have been captured, and asymptomatic restenosis or disease progression may have been missed. Long-term mortality may also have been underascertained because it was based solely on institutional follow-up records. Because of the retrospective design, several clinically relevant variables were unavailable, including BMI, Lp(a), ApoB, detailed family history, lesion complexity scores (e.g., SYNTAX score), the use of intravascular imaging, and whether the index PCI was performed for in-stent restenosis. Longitudinal data regarding medication adherence, the intensity of lipid-lowering therapy, and treatment modifications were available only for patients who underwent repeat revascularization, precluding comparisons with patients without repeat revascularization. Serial lipid, glucose, and inflammatory marker measurements during follow-up were unavailable, precluding assessment of guideline-recommended lipid target attainment. Accordingly, the observed association should not be interpreted as solely reflecting residual atherogenic risk. Because lipid-derived indices were calculated from a single fasting blood sample obtained during the acute phase of NSTEMI, the potential effects of the acute-phase response on lipid and glucose measurements cannot be completely excluded. The absence of a composite hard clinical endpoint, such as MACCE, may limit interpretation of the clinical significance of our findings. Finally, the proposed risk stratification model was not externally validated.

### Conclusion

CRI-II was independently associated with repeat revascularization in patients with premature NSTEMI undergoing PCI; however, its discriminatory performance was limited, precluding its use as a stand-alone risk stratification tool. In addition, HT and bifurcation lesions were independently associated with repeat revascularization. These findings should be considered exploratory and require external validation before clinical application.

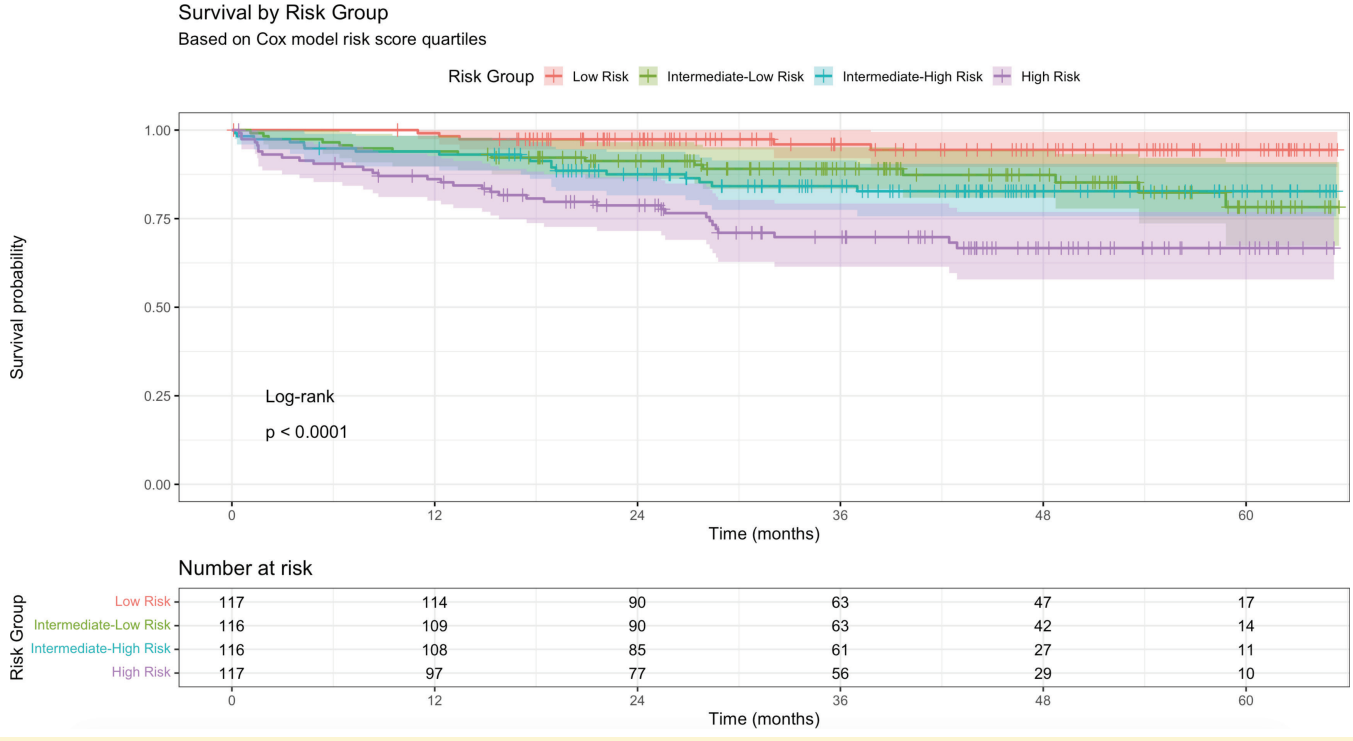



**Figure 5.** Kaplan–Meier survival curves according to Cox regression model-derived risk score quartiles. Patients were categorized into low-risk, intermediate-low-risk, intermediate-high-risk, and high-risk groups. Event-free survival progressively decreased across increasing risk categories (log-rank P < 0.0001).

**Supplementary Online File:** jag.journalagent.com/tkd/abs_files/TKDA-25252/TKDA-25252_(0)_xx.docx

**Ethics Committee Approval:** Ethics committee approval was obtained from Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2026/09/1466, Date: 05.05.2026).

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**Conflict of Interest:** The authors have no conflicts of interest to declare.

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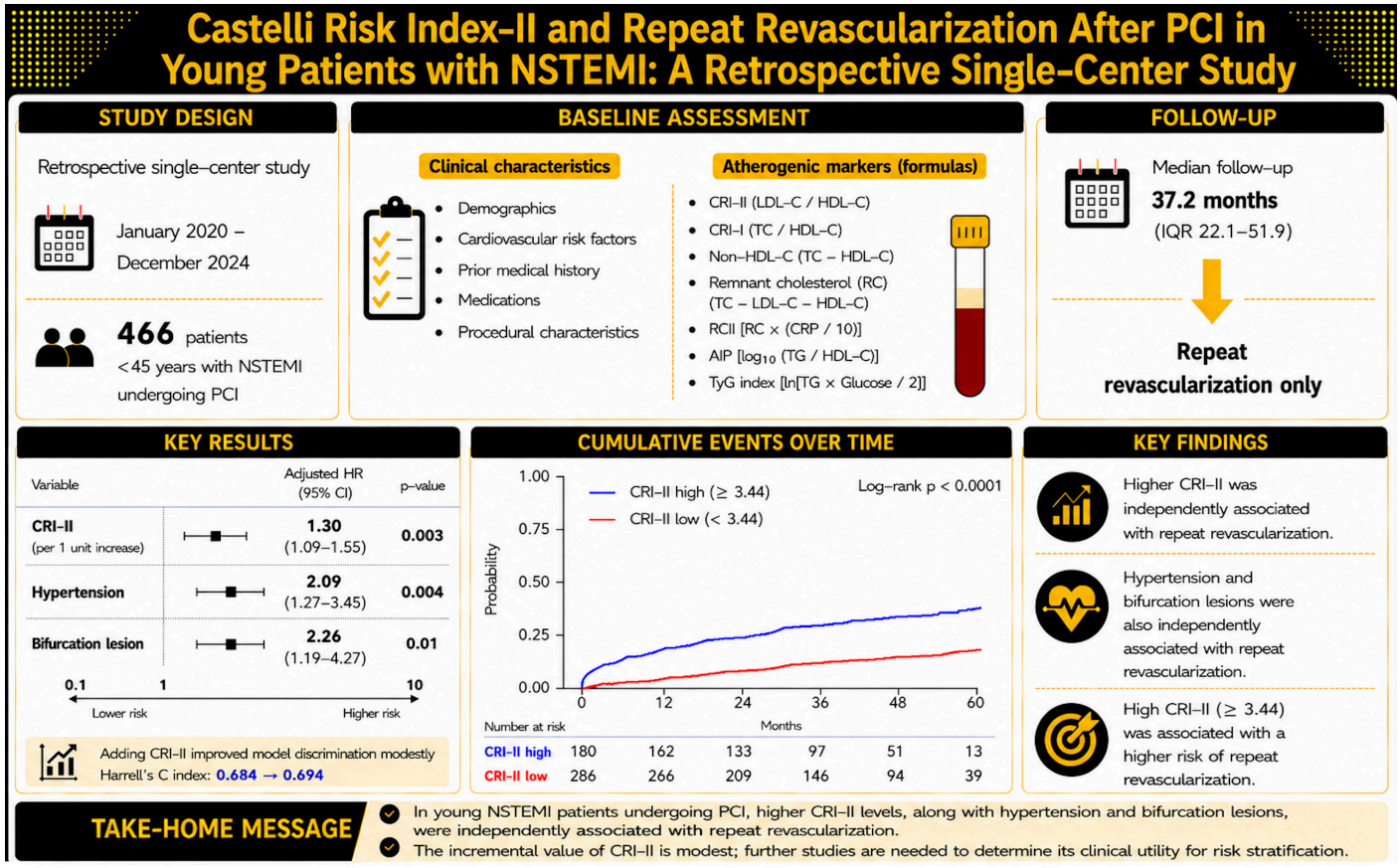
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**Abbreviations:** AIP, Atherogenic index of plasma; CRP, C-reactive protein; CRI-I, Castelli Risk Index-I; CRI-II, Castelli Risk Index-II; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; IQR, Interquartile range; Non-HDL-C, Non-high-density lipoprotein cholesterol; PCI, Percutaneous coronary intervention; RC, Remnant cholesterol; RCI, Remnant cholesterol inflammation index; TC, Total cholesterol; TG, Triglyceride; TyG, Triglyceride–glucose index; NSTEMI, Non-ST-segment elevation myocardial infarction.

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# Beyond the Culprit Lesion and Traditional Risk Factors: New Data on Residual Coronary Risk After Premature Myocardial Infarction

## Sorumlu Lezyon ve Geleneksel Risk Faktörlerinin Ötesinde: Erken Yaşta Miyokard Enfarktüsü Sonrası Rezidüel Koroner Riske İlişkin Yeni Veriler

**EDITORIAL COMMENT**
EDİTORYAL YORUM

Myocardial infarction (MI) occurring before the age of 45 years represents more than simply a premature acute coronary event. It identifies very-high-risk patients in whom coronary disease has developed after only a relatively short period of exposure to risk factors and may therefore have a major impact on life expectancy following this atherosclerotic cardiovascular disease (ASCVD) event. Although MI in young adults encompasses a heterogeneous spectrum of mechanisms, obstructive atherosclerotic coronary artery disease remains the predominant cause and poses major challenges for optimal lifelong secondary prevention strategies.[1]

In this issue of the Archives of the Turkish Society of Cardiology, Güvendi Şengör et al.[2] investigate repeat revascularization after percutaneous coronary intervention (PCI) in 466 patients younger than 45 years presenting with non-ST-segment elevation myocardial infarction (NSTEMI). During a median follow-up of 37.2 months, 73 patients (16%) underwent clinically indicated repeat revascularization. The Castelli Risk Index II (CRI-II), calculated as the ratio of low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C), was higher in patients who required repeat PCI and remained independently associated with repeat revascularization after multivariable adjustment. Hypertension and bifurcation lesions were also independently associated with this endpoint.[2]

Perhaps the most informative observation lies not in the overall number of repeat procedures but in their anatomical distribution. Only 12 of the 73 repeat procedures were target-lesion revascularizations, whereas 40 involved a different coronary artery.[2] Thus, more than half of the recurrent revascularizations reflected disease outside the initially treated vessel. The main findings and their implications for long-term secondary prevention are summarized in Figure 1. This observation is remarkably consistent with the landmark AFIJI prospective study of premature coronary artery disease, in which 880 patients aged 45 years or younger were followed for up to 20 years. Approximately one-third experienced an ischemic event, and recurrent MIs were more frequently related to newly developed coronary lesions than to the initial culprit site. Persistent smoking had the greatest adverse impact on recurrent outcomes.[3]

This distinction is particularly relevant in young patients. Successful PCI addresses an anatomically relevant stenosis, but it does not eliminate the biological conditions that allowed atherosclerosis to become clinically manifest at an unusually early age. The association between CRI-II and non-target-vessel revascularization may therefore identify a broader atherogenic phenotype that favors disease progression throughout the coronary tree rather than simply a propensity for restenosis.

At the same time, association should not be confused with clinically useful discrimination. CRI-II is appealing because it is simple, inexpensive, and available from routine lipid measurements. Nevertheless, the present data also support a global approach rather than the use of CRI-II as a stand-alone risk score. At 36 months, the area under the curve for CRI-II alone was 0.572. The exploratory threshold of 3.44 provided 54.3% sensitivity and 59.7% specificity, and adding CRI-II to the clinical model increased Harrell's C-index only from 0.684 to 0.694.[2] These findings reinforce an important

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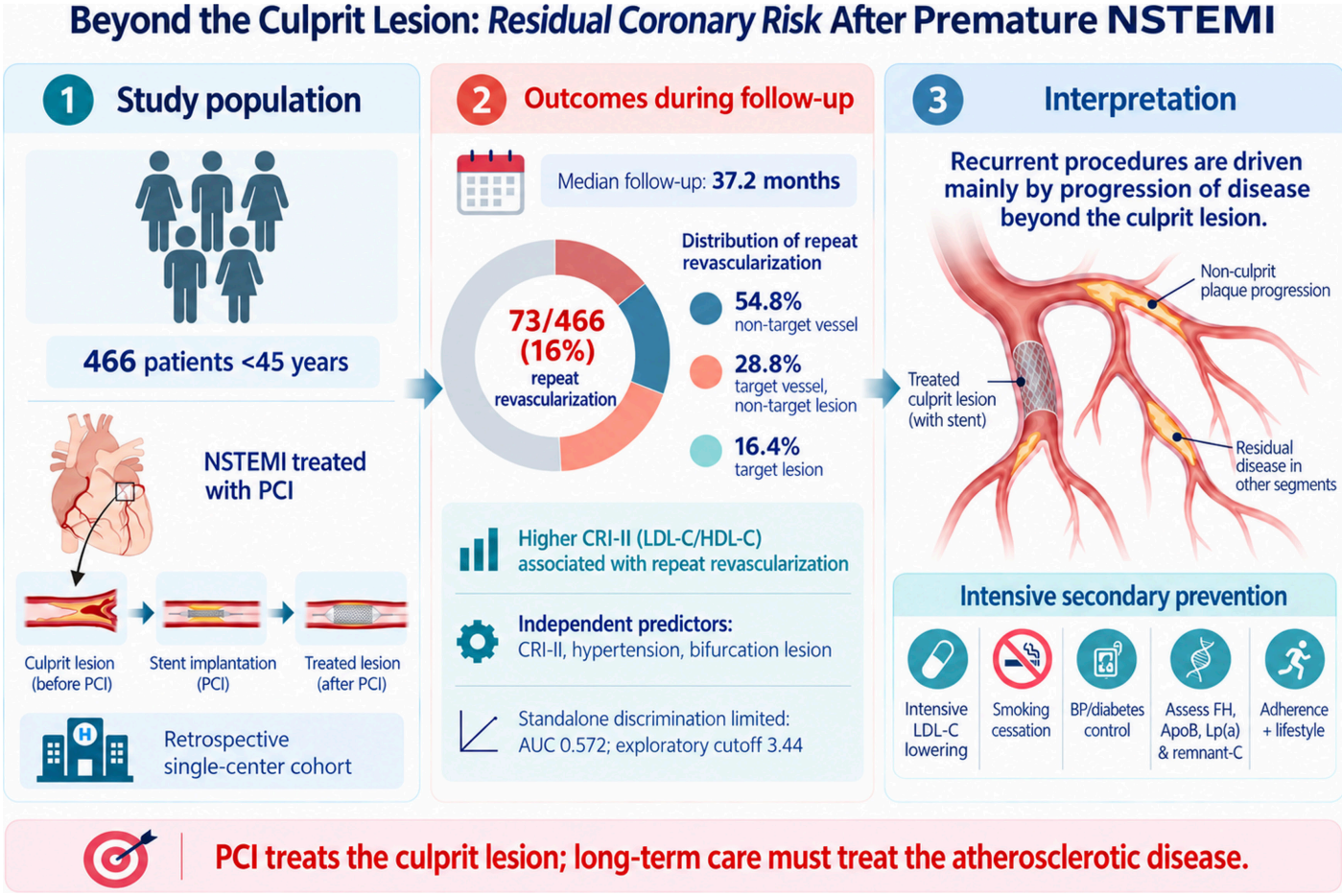



**Figure 1.** Beyond the culprit lesion: residual coronary risk after premature NSTEMI. Schematic summary of the study by Güvendi Şengör et al.[2] Among 466 patients younger than 45 years with NSTEMI treated with PCI, 16% underwent repeat revascularization during a median follow-up of 37.2 months. Most repeat procedures involved non-target vessels, supporting the concept that recurrent coronary events in young patients may reflect the progression of atherosclerotic disease beyond the initially treated culprit lesion. A higher CRI-II was associated with repeat revascularization, although its stand-alone discriminatory performance was limited. These findings reinforce the importance of intensive secondary prevention, including intensive LDL-C lowering, smoking cessation, blood pressure and diabetes control, and assessment of familial hypercholesterolemia, ApoB, Lp(a), and remnant cholesterol, together with long-term adherence to lifestyle and pharmacological interventions.

ApoB, apolipoprotein B; BP, blood pressure; CRI-II, Castelli Risk Index II; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; remnant-C, remnant cholesterol.

distinction: a statistically independent and promising predictor does not necessarily provide sufficient incremental information to alter individual patient management.

The study also raises a crucial question regarding residual lipid risk. LDL-C and non-HDL-C levels were not significantly different between patients with and without repeat revascularization, whereas CRI-II differed.[2] Growing evidence suggests that cholesterol carried in triglyceride-rich remnant particles may play a major role in recurrent ischemic events beyond the information provided by LDL-C alone. Indeed, in two large cohorts of patients with established ASCVD, higher remnant cholesterol levels were associated with recurrent events, whereas LDL-C was not associated with recurrence in the same analysis.[4] A 2026 meta-analysis including 21 studies and 114,592 patients with established ASCVD similarly found that higher remnant cholesterol levels were associated with major adverse cardiovascular events (MACE) and unplanned repeat revascularization.[5] Although these populations were not restricted to young adults, the signal is particularly relevant to premature MI, in which cumulative exposure to atherogenic particles begins earlier and extends over a longer lifetime.

Recent data further support looking beyond LDL-C alone. In the Copenhagen General Population Study, elevated apolipoprotein B (ApoB), driven predominantly by high remnant cholesterol levels, was associated with increased ASCVD risk even when LDL-C was comparatively low, whereas lipid-lowering therapy was initiated less frequently than in individuals with elevated LDL-C.[6] Recent research has also highlighted familial remnant hyperlipidemia (dysbetalipoproteinemia), an inherited remnant-rich phenotype associated with clinically relevant ASCVD risk.[7] The present study included the remnant cholesterol inflammation index among its exploratory lipid-related markers, but it was not designed to isolate the prognostic contribution of remnant cholesterol itself. Prospective studies specifically characterizing remnant cholesterol and ApoB may therefore help refine the biological interpretation of recurrent disease in premature coronary artery disease.

Another point worth noting is that lipoprotein(a) was not available in the present analysis, although it may also contribute to premature and recurrent atherosclerotic events. In a cohort this young, measurement of lipoprotein(a), together with careful assessment for familial hypercholesterolemia and family history, could provide a more complete picture of inherited and lifelong atherogenic risk.[8,9] This limitation should be interpreted in context: it does not detract from the observed association between CRI-II and repeat revascularization but rather identifies an opportunity for future prospective studies to provide more comprehensive lipid characterization.

Smoking also deserves emphasis. In the present cohort, current smoking was more frequent among patients who required repeat revascularization, although it did not remain independently associated with the endpoint in the final adjusted model.[2] This observation should not lead to an underestimation of the relevance of persistent smoking: in the larger AFIJI cohort with longer-term follow-up, persistent smoking was the strongest correlate of recurrent events.[3] For a patient experiencing coronary disease before the age of 45 years, sustained smoking cessation may therefore be one of the most important goals of secondary prevention.

The treatment landscape must also be considered. All patients were prescribed high-intensity statin therapy at discharge, but none received either ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor during the study period.[2] Current European guidance recommends intensive LDL-C lowering after acute coronary syndrome, targeting an LDL-C level below 55 mg/dL together with a reduction of at least 50% from baseline.[10] The 2025 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) focused update further emphasizes early treatment intensification and consideration of combination therapy during the index hospitalization when statin monotherapy is unlikely to achieve the required reduction.[9] In a patient experiencing NSTEMI before the age of 45 years, the potential benefit of maintaining optimal risk-factor control over several subsequent decades is particularly compelling.

CRI-II should therefore be viewed as a potentially informative marker rather than a therapeutic target. There is no established CRI-II treatment threshold, and secondary prevention should remain centered on reducing the burden of causal ApoB-containing lipoproteins, achieving guideline-recommended LDL-C goals, promoting smoking cessation, and rigorously controlling blood pressure, diabetes, lifestyle factors, and treatment adherence.[3,9,10]

Finally, repeat revascularization should be interpreted carefully as an endpoint. It is clinically relevant, but it is less robust than hard clinical endpoints such as MI, stroke, or cardiovascular death because it may be influenced by recurrent symptoms, access to angiography, physician decision-making, and local revascularization practices. The retrospective single-center design, relatively small number of events, potential undercapture of procedures performed elsewhere, absence of serial lipid measurements, and limited characterization of inherited lipid risk restrict causal interpretation.[2] Further prospective studies evaluating longitudinal lipid measurements, ApoB, remnant cholesterol, lipoprotein(a), familial hypercholesterolemia status, treatment adherence, coronary anatomy, and hard ischemic endpoints are needed to confirm these promising data.

The main message from this study is that premature NSTEMI identifies a distinct, very-high-risk group requiring holistic and intensive risk-factor management after the initial successful PCI. Treating the culprit lesion is only the beginning of the story; long-term prevention is essential.

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# No-Reflow in Young Acute Coronary Syndrome Patients: Association with the Inflammatory Prognostic Index

## Genç Akut Koroner Sendrom Hastalarında No-Reflow: İnflamatuvar Prognostik İndeks ile İlişkisi

**ABSTRACT**

**Objective:** The no-reflow phenomenon (NRP) is an important complication associated with adverse outcomes in patients undergoing PCI for acute coronary syndrome (ACS). Inflammation plays a central role in the pathophysiology of NRP. The inflammatory prognostic index (IPI), calculated using the neutrophil-to-lymphocyte ratio and C-reactive protein-to-albumin ratio, has recently emerged as a novel inflammatory marker. This study aimed to investigate the relationship between IPI and NRP in young patients with ACS undergoing PCI.

**Method:** In this single-center retrospective study, a total of 443 consecutive patients aged ≤45 years who underwent PCI for ACS between 2022 and 2025 were included. The study population comprised 305 patients with ST-segment elevation myocardial infarction (STEMI; 68.8%), 126 with non-ST-segment elevation myocardial infarction (NSTEMI; 28.4%), and 12 with unstable angina (2.7%). Laboratory parameters were obtained from the first venous blood sample collected before coronary angiography during the index hospitalization. NRP was defined as a final Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0–2 in the absence of mechanical obstruction or a final TIMI flow grade of 3 with a myocardial blush grade of 0–1. Clinical, laboratory, angiographic, and procedural characteristics were compared according to NRP status. Logistic regression and receiver operating characteristic (ROC) curve analyses were performed to identify independently associated factors and evaluate the discriminatory performance of inflammatory indices.

**Results:** NRP developed in 112 patients (25.3%), whereas 331 patients (74.7%) had normal flow. Patients with NRP had significantly higher IPI levels than those without NRP [6.88 (4.66–12.67) vs. 3.50 (2.03–7.41), P < 0.001]. The multivariable model included IPI modeled using a natural cubic spline with 4 degrees of freedom, STEMI presentation, left anterior descending (LAD) coronary artery as the culprit vessel, serum creatinine, and an initial TIMI flow grade of 0–1. IPI showed a significant nonlinear association with NRP in the multivariable analysis (p for overall association <0.001; p for nonlinearity <0.001). An initial TIMI flow grade of 0–1 and LAD involvement as the culprit vessel also remained independently associated with NRP. In the standalone ROC analysis, IPI demonstrated the highest discriminatory performance among the inflammatory indices evaluated for NRP [area under the curve (AUC): 0.725, 95% confidence interval (CI): 0.677–0.772], with a cutoff value of 3.45, providing 92.0% sensitivity and 49.8% specificity.

**Conclusion:** IPI showed a significant nonlinear association with NRP in young patients with ACS undergoing PCI and may provide additional information for identifying patients at increased risk of this procedural complication. However, its relatively low specificity limits its use as a standalone marker, and prospective validation is warranted.

**Keywords:** Acute coronary syndromes, inflammatory prognostic index, no-reflow.

**ÖZET**

**Amaç:** No-reflow fenomeni (NRP), akut koroner sendrom (AKS) nedeniyle perkütan koroner girişim (PKG) uygulanan hastalarda olumsuz sonuçlarla ilişkili önemli bir komplikasyondur. İnflamasyon, NRP'nin patofizyolojisinde merkezi bir rol oynamaktadır. Nötrofil-lenfosit oranı ile C-reaktif protein/albümin oranı kullanılarak hesaplanan inflamatuvar prognostik indeks (IPI), son dönemde yeni bir inflamatuvar belirteç olarak dikkat çekmektedir. Bu çalışmada, PKG uygulanan genç AKS hastalarında IPI ile NRP arasındaki ilişkinin araştırılması amaçlandı.

**Yöntem:** Bu tek merkezli retrospektif çalışmaya, 2022–2025 yılları arasında AKS nedeniyle PKG uygulanan ≤45 yaşındaki toplam 443 ardışık hasta dahil edildi. Çalışma popülasyonu 305 STEMI (%68,8), 126 NSTEMI (%28,4) ve 12 kararsız angina (%2,7) hastasından oluşmaktaydı. Laboratuvar parametreleri, indeks yatış sırasında koroner anjiyografi öncesinde alınan ilk venöz

**ORIGINAL ARTICLE**
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kan örneğinden elde edildi. NRP, mekanik obstrüksiyon yokluğunda işlem sonrası nihai TIMI akım derecesinin 0–2 olması veya nihai TIMI akım derecesi 3 iken miyokardiyal blush derecesinin 0–1 olması şeklinde tanımlandı. Klinik, laboratuvar, anjiyografik ve prosedürel özellikler NRP durumuna göre karşılaştırıldı. Bağımsız ilişkili faktörleri belirlemek ve inflamatuvar indekslerin ayırt edici performansını değerlendirmek amacıyla lojistik regresyon ve receiver operating characteristic (ROC) eğrisi analizleri yapıldı.

**Bulgular:** NRP 112 hastada (%25,3) gelişirken, 331 hastada (%74,7) normal akım izlendi. NRP gelişen hastalarda IPI düzeyleri, NRP gelişmeyen hastalara kıyasla anlamlı olarak daha yüksekti [6,88 (4,66–12,67) ve 3,50 (2,03–7,41), P < 0,001]. Multivaryant modelde IPI, doğal kübik spline (4 serbestlik derecesi) kullanılarak modellendi; model ayrıca STEMI başvurusu, LAD'nin suçlu damar olması, serum kreatinin düzeyi ve başlangıç TIMI akım derecesi 0–1 değişkenlerini içeriyordu. Multivaryant analizde IPI ile NRP arasında anlamlı ve doğrusal olmayan bir ilişki saptandı (genel ilişki için P < 0,001; doğrusal olmama için P < 0,001). Başlangıç TIMI akım derecesinin 0–1 olması ve LAD'nin suçlu damar olması da NRP ile bağımsız olarak ilişkili bulundu. Tek başına ROC analizinde IPI, değerlendirilen inflamatuvar belirteçler arasında NRP açısından en yüksek ayırt edici performansı gösterdi (AUC: 0,725, %95 GA: 0,677–0,772). IPI için 3,45 kesim değeri %92,0 duyarlılık ve %49,8 özgüllük sağladı; bu bulgu, yüksek duyarlılığa karşın özgüllüğün sınırlı olduğunu göstermektedir.

**Sonuç:** IPI, PKG uygulanan genç AKS hastalarında NRP ile anlamlı ve doğrusal olmayan bir ilişki göstermiştir ve bu prosedürel komplikasyon açısından artmış risk taşıyan hastaların belirlenmesinde ek bilgi sağlayabilir. Bununla birlikte, görece düşük özgüllüğü, tek başına bir belirteç olarak kullanımını sınırlamaktadır ve bulguların prospektif çalışmalarla doğrulanması gerekmektedir.

**Anahtar Kelimeler:** Akut koroner sendromlar, inflamatuvar prognostik indeks, no-reflow.

Acute coronary syndrome (ACS) is less common in young individuals and is generally considered a disease of older age.[1] However, the incidence of ACS in young adults has been increasing because of smoking, obesity, and unhealthy lifestyles.[2] In most studies, an age cutoff between 40 and 45 years is used to define young patients with ACS. The prevalence of myocardial infarction (MI) in young individuals varies according to the age threshold used to define young MI across studies and has generally been reported to range from 5% to 13%.[3] Following ACS, quality of life is significantly reduced in young patients, and this impact is considerably greater than that in older patients.[4] Percutaneous coronary intervention (PCI) is the main therapeutic approach for achieving myocardial reperfusion in patients with ACS. However, despite successful restoration of epicardial coronary artery patency, adequate microvascular tissue perfusion cannot be achieved in some patients. This condition, defined as the no-reflow phenomenon (NRP), has a complex pathophysiology involving multiple mechanisms, including distal embolization, increased thrombotic activity, microvascular spasm, endothelial dysfunction, inflammatory processes, oxidative stress, and ischemia-reperfusion injury.[5] The development of NRP is associated with larger infarct size, left ventricular dysfunction, arrhythmias, heart failure, and increased mortality. Therefore, preprocedural identification of patients at increased risk of NRP is clinically important for determining appropriate treatment strategies and implementing preventive measures.

Inflammation plays a central role in the pathophysiology of NRP through mechanisms such as endothelial dysfunction, distal microembolization, oxidative stress, platelet activation, and microvascular injury.[6] In recent years, inflammatory indices derived from complete blood count parameters have attracted attention for the diagnosis and prognosis of cardiovascular diseases. Previous studies have demonstrated an association between NRP and indices derived from various inflammatory parameters.[6,7] The inflammatory prognostic index (IPI) is a novel inflammatory marker reflecting the systemic inflammatory response and immunological activation and is calculated using the neutrophil-to-lymphocyte ratio (NLR) and the C-reactive protein (CRP)-to-albumin ratio (CAR).[8] A previous study demonstrated an association between IPI and NRP in patients

## ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| CAR | C-reactive protein -to-albumin ratio |
| CRP | C-reactive protein |
| IPI | Inflammatory prognostic index |
| LAD | Left anterior descending |
| LVEF | Left ventricular ejection fraction |
| MBG | Myocardial blush grade |
| MI | Myocardial infarction |
| MINOCA | Myocardial infarction with nonobstructive coronary arteries |
| NLR | Neutrophil-to-lymphocyte ratio |
| non-HDL | Non-high-density lipoprotein |
| NPV | Negative predictive value |
| NRP | No-reflow phenomenon |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| PLR | Platelet-to-lymphocyte ratio |
| PPV | Positive predictive value |
| SII | Systemic Immune-Inflammation Index |
| TIMI | Thrombolysis in Myocardial Infarction |
| WBC | White blood cell |

with ST-segment elevation myocardial infarction (STEMI).[9] However, data regarding the relationship between IPI and the development of NRP in young patients with ACS remain limited. Compared with older patients, young patients with ACS may exhibit distinct pathophysiological characteristics, including a higher thrombus burden, increased inflammatory activation, smoking-related endothelial dysfunction, and fewer chronic comorbidities. Young ACS has been defined using different age thresholds across previous studies, most commonly between 40 and 45 years. In the present study, an age cutoff of ≤45 years was selected because it is one of the most frequently used definitions in the literature and allows comparison with previous studies evaluating premature ACS.

Therefore, the present study aimed to investigate the relationship between preprocedural IPI levels and the development of NRP in young patients with ACS undergoing PCI. In addition, we aimed to evaluate the discriminatory performance of IPI for NRP in this specific patient population. An overview of the study design and main findings is provided in the Graphical Abstract.

## Materials and Methods

For this single-center retrospective study, a total of 1,154 consecutive patients aged ≤45 years who underwent coronary angiography for suspected ACS between 2022 and 2025 were screened. A total of 64 patients were excluded because of known hematologic disease, recent major surgery, an estimated glomerular filtration rate <50 mL/min/1.73 m², or active inflammatory or infectious disease. Following angiographic, clinical, and laboratory evaluation, an additional 647 patients were excluded, including 506 patients without an obstructive culprit lesion or with an alternative diagnosis [including myocardial infarction with nonobstructive coronary arteries (MINOCA), myocarditis, and Takotsubo syndrome], 113 patients with angiographic recordings unsuitable for reliable assessment of the NRP, 24 patients with spontaneous coronary artery dissection managed medically, and 4 patients for whom a valid preprocedural blood sample obtained before PCI could not be reliably confirmed from the available records. Consequently, 443 consecutive patients with ACS and an obstructive culprit coronary lesion who underwent PCI were included in the final analysis, comprising 305 patients with STEMI, 126 with non-ST-segment elevation myocardial infarction (NSTEMI), and 12 with unstable angina (Figure 1). The diagnosis and classification of ACS were established according to contemporary guideline criteria based on clinical presentation, electrocardiographic findings, and cardiac biomarker measurements.[10] All patients received 300 mg of aspirin and 180 mg of ticagrelor, an appropriate dose of clopidogrel (300 or 600 mg), or 60 mg of prasugrel in eligible patients. The study was approved by the Sakarya University Faculty of Medicine Health Sciences Scientific Research Ethics Committee (Approval Number: -43012747-050.04-590324/452, Date: 21.05.2026) and conducted in accordance with the Declaration of Helsinki.

Demographic characteristics, cardiovascular risk factors, and information regarding stent diameter and length were obtained from hospital records. Obesity was defined as a body mass index (BMI) ≥30 kg/m². Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg

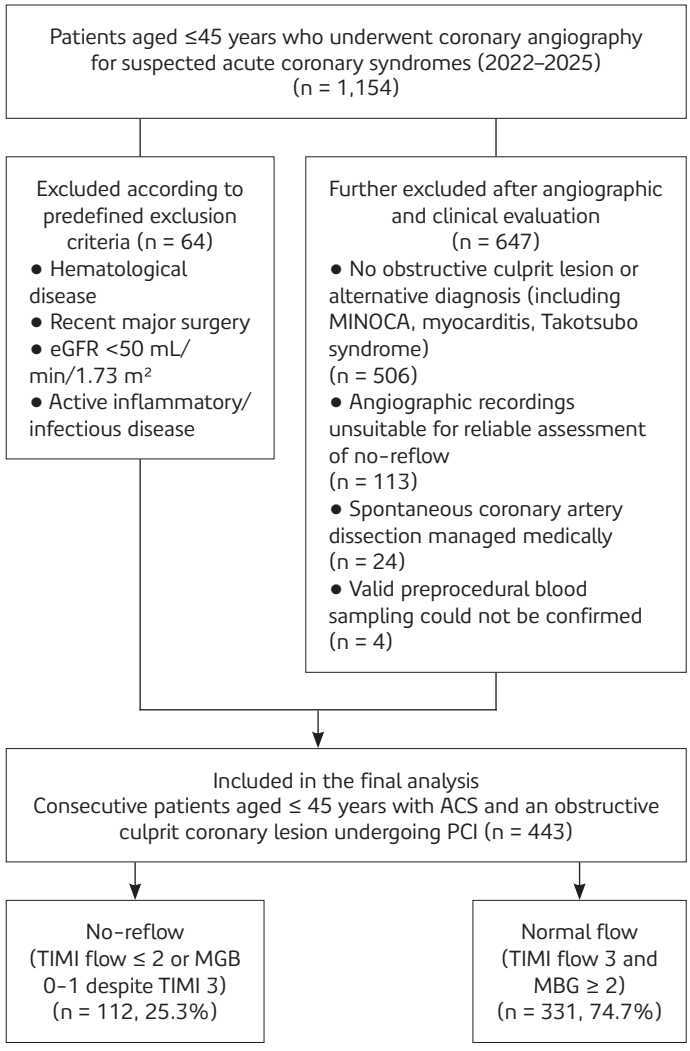



**Figure 1.** Study flowchart illustrating patient screening, exclusion criteria, selection of the study population, and classification of patients according to the no-reflow phenomenon (NRP).

eGFR, Estimated glomerular filtration rate; MBG, Myocardial blush grade; MINOCA, Myocardial infarction with nonobstructive coronary arteries; PCI, Percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

documented on at least two separate measurements or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting plasma glucose level ≥126 mg/dL, a random plasma glucose level ≥200 mg/dL, a glycated hemoglobin level ≥6.5%, or the use of antidiabetic therapy. Smoking was defined as the regular use of tobacco products within the previous 6 months.

Complete blood count, creatinine, serum lipid profile, albumin, and CRP results were obtained from the first venous blood sample collected before coronary angiography during the index hospitalization. The exact interval between symptom onset and blood sampling could not be reliably determined from the retrospective medical records. Only patients with available preprocedural laboratory results were included in the final analysis. Non-high-density lipoprotein (non-HDL) cholesterol was calculated as total cholesterol minus high-density lipoprotein (HDL) cholesterol. Because of the retrospective design, fasting status at the time of lipid measurement and information

regarding lipid-lowering therapy before admission could not be reliably determined from the medical records. Because of the lower detection limit of the laboratory assay used, CRP values below 3 mg/L were recorded as 3 mg/L. The NLR was calculated as the ratio of neutrophils to lymphocytes, and the platelet-to-lymphocyte ratio (PLR) was calculated as the ratio of platelets to lymphocytes. The systemic immune-inflammation index (SII) was calculated as the product of the neutrophil and platelet counts divided by the lymphocyte count.[11] The IPI was calculated by multiplying the NLR by the CRP-to-albumin ratio.[8] LVEF was calculated using the Simpson method on echocardiography performed within the first 24 hours after hospitalization.

All PCI procedures were performed using standard techniques with a 6-Fr guiding catheter via the left radial or right femoral approach. During the procedure, unfractionated heparin was administered at a dose of 50–70 U/kg. The use of mechanical thrombectomy, intracoronary glycoprotein IIb/IIIa receptor blockers, adrenaline, adenosine, or nitroglycerin was left to the operator's discretion. Coronary angiographic recordings were obtained using Toshiba Infinix 8000 V and Toshiba Infinix 8000 G5 systems (Toshiba Medical Systems, Nasushiobara, Japan). Angiographic images, including Thrombolysis in Myocardial Infarction (TIMI) flow and myocardial blush grade (MBG), were independently assessed by two experienced interventional cardiologists who were blinded to the inflammatory biomarker data. In cases of disagreement, the angiographic findings were reviewed by a third experienced interventional cardiologist, and the final classification was determined by consensus.

The angiographic slow-flow/no-reflow endpoint, hereafter referred to as NRP, was defined as inadequate myocardial tissue perfusion after a transient period of ischemia in the absence of signs of mechanical obstruction, such as dissection, spasm, or thrombus in the epicardial artery.[12] The TIMI angiographic grading scale, comprising grades 0, 1, 2, and 3, was used to determine epicardial coronary blood flow patterns before and after PCI.[13] Postprocedural myocardial perfusion was evaluated using the MBG method defined by van 't Hof et al.[14] According to this method, patients with no contrast density were classified as MBG 0, those with minimal contrast density as MBG 1, those with moderate but below-normal contrast density as MBG 2, and those with normal contrast density as MBG 3. NRP was classified as a final TIMI flow grade of 0–2 in the absence of mechanical obstruction or a final TIMI flow grade of 3 with an MBG of 0–1.[15]

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA), and Python version 3.13.5. Natural cubic spline modeling and logistic regression analyses involving spline terms were performed using statsmodels version 0.14.6, with spline basis construction implemented using Patsy version 1.0.2. Receiver operating characteristic (ROC) AUC calculations and nonparametric bootstrap validation were performed in Python using scikit-learn version 1.8.0, and paired AUCs were compared in Python using a custom implementation of DeLong's covariance-based method for correlated ROC curves. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were presented as mean±standard deviation or median [interquartile range (IQR)], according to data distribution, whereas categorical variables were expressed as numbers and percentages.

Comparisons between patients with and without the NRP were performed using the independent-samples t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Variables considered clinically relevant and those showing a significant association in descriptive analyses were evaluated using univariable logistic regression analysis to identify potential factors associated with NRP. Variables with clinical relevance, statistical significance in univariable analysis, and no evidence of substantial multicollinearity were subsequently entered into the multivariable logistic regression model. Multicollinearity was assessed using variance inflation factors (VIFs) and tolerance values; all VIFs were <1.5 and all tolerance values were >0.70, indicating no evidence of substantial multicollinearity. Linearity in the logit for continuous variables included in the multivariable model was assessed using the Box–Tidwell approach. Evidence of nonlinearity was observed for the IPI; therefore, IPI was modeled using a natural cubic spline with 4 degrees of freedom in the primary multivariable model. The spline basis was constructed using default quantile-based knot placement, with boundary knots at 0.7465 and 138.3504 and interior knots at 2.9606 and 6.7083. The overall association and nonlinear component of IPI were evaluated, and the spline model was compared with the linear specification using a likelihood-ratio test. Inflammatory indices derived from overlapping hematologic parameters were not included simultaneously in the same multivariable model to avoid multicollinearity. LVEF was not included in the multivariable model because it may represent a consequence rather than a baseline predictor of NRP. Predilatation was excluded from the final model because of the very small number of patients who underwent direct stenting without predilatation, which could adversely affect model stability. As a sensitivity analysis, predilatation was additionally included in the multivariable model to assess whether its inclusion materially affected the association between IPI and NRP. TIMI thrombus grade was not included in the primary multivariable model because of its close association with initial TIMI flow grade. As an additional sensitivity analysis, initial TIMI flow grade 0–1 was replaced by high thrombus burden (TIMI thrombus grade 4–5) in the multivariable model to assess whether adjustment for thrombus burden materially affected the association between IPI and NRP. Procedural treatments, including thrombus aspiration, glycoprotein IIb/IIIa inhibitor use, and intracoronary pharmacologic agents, were not entered into the multivariable model because their use was largely determined by intraprocedural findings and the occurrence or suspicion of NRP and, therefore, they were not considered baseline predictors. Postprocedural TIMI flow grade and MBG were not included because they constitute components of the definition of NRP. The final multivariable model included IPI modeled using a natural cubic spline with 4 degrees of freedom, STEMI presentation, left anterior descending (LAD) coronary artery as the culprit vessel, serum creatinine, and initial TIMI flow grade 0–1. With 112 NRP events and 8 model degrees of freedom, including 4 degrees of freedom allocated to spline-modeled IPI, the events-per-parameter ratio was 14.0.

Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for variables modeled linearly, whereas the spline-modeled IPI association was summarized using overall and nonlinearity tests.

To assess the robustness of the association between IPI and NRP, given the predominance of STEMI in the study population, a sensitivity analysis restricted to patients with STEMI was performed using multivariable logistic regression. In all sensitivity analyses, IPI was modeled using the same natural cubic spline specification with 4 degrees of freedom as in the primary multivariable model.

ROC curve analyses were performed to assess the discriminatory performance of inflammatory indices for NRP. The AUC with 95% CI, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+ and LR−), and optimal cutoff values determined using the Youden index were calculated. Pairwise comparisons between ROC curves were performed using the DeLong test.

To evaluate the incremental value of IPI while accounting for its nonlinear association with NRP, a clinical-angiographic model including STEMI presentation, LAD culprit vessel, serum creatinine, and initial TIMI flow grade 0–1 was compared with the same model after the addition of IPI modeled using a natural cubic spline with 4 degrees of freedom. Model discrimination was assessed using AUC, and paired AUCs were compared using the DeLong test. Model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Internal validation of the main multivariable model was performed using nonparametric bootstrapping with 1,000 resamples. Model optimism was estimated as the mean difference between bootstrap-sample and original-sample AUCs, and an optimism-corrected AUC was calculated. There were no missing data for the variables included in the analyses; therefore, all 443 patients were included in the complete-case analyses.

A two-sided p value <0.05 was considered statistically significant.

**Results**

A total of 443 patients aged ≤45 years with ACS and an obstructive culprit coronary lesion who underwent PCI were included in the study. The study population comprised 305 patients with ST-segment elevation myocardial infarction (STEMI; 68.8%), 126 patients with NSTEMI (28.4%), and 12 patients with unstable angina (2.7%). The NRP occurred in 112 patients (25.3%), whereas 331 patients (74.7%) had normal coronary flow after PCI. NRP occurred in 92 of 305 patients with STEMI (30.2%), 19 of 126 patients with NSTEMI (15.1%), and 1 of 12 patients with unstable angina (8.3%).

The clinical, demographic, and laboratory characteristics of the study population according to NRP status are presented in Table 1. There were no significant differences between the groups in terms of age, sex, hypertension, diabetes mellitus, smoking status, or history of coronary artery disease. STEMI presentation was significantly more frequent among patients with NRP (82.1% vs. 64.4%, P = 0.002).

Among the laboratory parameters, patients with NRP had significantly higher white blood cell (WBC) counts, neutrophil counts, creatinine, CRP, IPI, NLR, PLR, SII, and CRP-to-albumin ratio (CAR) values, whereas lymphocyte counts and left ventricular ejection fraction were significantly lower.

Angiographic and procedural characteristics are summarized in Table 2. Patients with NRP had significantly more impaired initial TIMI flow, higher TIMI thrombus grades, and more frequent use of thrombus aspiration, glycoprotein IIb/IIIa inhibitors, intracoronary adrenaline, intracoronary nitrates, and predilatation. No significant differences were observed between the groups in terms of postdilatation, number of stents, stent diameter, or stent length.

Regarding in-hospital clinical outcomes, ventricular tachycardia/ventricular fibrillation occurred in 17 patients (3.8%) (6.2% vs. 3.0%, P = 0.210). In-hospital reinfarction requiring repeat PCI occurred in 5 patients (1.1%), including 4 patients in the NRP group and 1 patient in the normal-flow group. No patient experienced stroke or major bleeding during hospitalization. The single in-hospital death occurred in the NRP group.

Variables demonstrating statistical significance in descriptive analyses were evaluated using univariable logistic regression analysis, and factors significantly associated with NRP in these analyses are presented in Table 3. STEMI presentation, LAD coronary artery as the culprit vessel, creatinine, WBC count, neutrophil count, lymphocyte count, CRP, IPI, NLR, SII, CAR, left ventricular ejection fraction, initial TIMI flow grade 0–1, high thrombus burden, and predilatation were significantly associated with NRP.

In multivariable analysis, IPI showed a significant nonlinear association with NRP (p for overall association <0.001; p for nonlinearity <0.001). A natural cubic spline model with 4 degrees of freedom provided a significantly better fit than the linear specification (likelihood-ratio $\chi^2$=40.84, df=3, P < 0.001). In the spline-based multivariable model, LAD culprit vessel (adjusted odds ratio [OR]: 2.15, 95% confidence interval [CI]: 1.31–3.51, P = 0.002) and initial TIMI flow grade 0–1 (adjusted OR: 3.21, 95% CI: 1.59–6.50, P = 0.001) remained independently associated with NRP, whereas STEMI presentation and serum creatinine were not independently associated with NRP (Table 4). The association was strongest across the lower-to-intermediate IPI range and became less clearly defined at higher IPI values, where the confidence intervals widened (Figure 2). In a sensitivity analysis additionally including predilatation in the multivariable model, IPI remained significantly associated with NRP when modeled using the same natural cubic spline specification as in the primary model (p for overall association <0.001; p for nonlinearity <0.001), whereas predilatation was not independently associated with NRP (adjusted OR: 5.67, 95% CI: 0.70–46.05, P = 0.105). In an additional sensitivity analysis addressing thrombus burden, initial TIMI flow grade 0–1 was replaced by high thrombus burden (TIMI thrombus grade 4–5) in the multivariable model. IPI remained significantly associated with NRP when modeled using the same natural cubic spline specification as in the primary model (p for overall association <0.001; p for nonlinearity <0.001). High thrombus burden was also independently associated with NRP (adjusted OR: 3.61, 95% CI: 1.63–7.97, P = 0.002), and LAD culprit vessel remained independently associated with NRP (adjusted OR: 2.16, 95% CI: 1.32–3.53, P = 0.002), whereas STEMI presentation and serum creatinine were not independently associated with NRP.

To evaluate the incremental value of IPI while accounting for its nonlinear association with NRP, a clinical-angiographic model including STEMI presentation, LAD culprit vessel, serum creatinine, and initial TIMI flow grade 0–1 was compared with the same model after the addition of IPI modeled using a natural cubic spline with 4 degrees of freedom. The AUC increased from 0.699 (95% CI: 0.646–0.752) for the clinical-angiographic model to 0.791 (95% CI: 0.747–0.835) after the addition of spline-modeled IPI. This improvement in discrimination was statistically significant (DeLong P < 0.001). Calibration was acceptable for both the clinical-angiographic model (Hosmer–Lemeshow P = 0.945) and the spline-extended model (Hosmer–Lemeshow P = 0.452). Internal validation using 1,000 bootstrap resamples yielded a mean optimism of 0.015 for the spline-extended model, resulting in an optimism-corrected AUC of 0.776.

In a sensitivity analysis restricted to patients with STEMI (n=305), NRP occurred in 92 patients (30.2%). IPI levels remained significantly higher in patients with NRP than in those without NRP [7.89 (5.34–13.20) vs. 4.64 (2.49–8.26), P < 0.001]. In multivariable logistic regression analysis restricted to patients with STEMI, IPI remained significantly associated with NRP when modeled using the same natural cubic spline specification as in the primary model (p for overall association <0.001; p for nonlinearity <0.001).

**Table 1.** Clinical, demographic, and laboratory characteristics according to NRP

| Variables | NRP (–) (n=331) | NRP (+) (n=112) | *P* |
|---|---|---|---|
| Age (years) | 41 (38–44) | 41.5 (39–43) | 0.779 |
| BMI (kg/m²) | 27.44 (25.98–28.73) | 27.77 (26.51–29.07) | 0.068 |
| Obesity, n (%) | 35 (10.6%) | 15 (13.4%) | 0.415 |
| Female sex, n (%) | 36 (10.9%) | 7 (6.2%) | 0.213 |
| Hypertension, n (%) | 68 (20.5%) | 29 (25.9%) | 0.293 |
| Diabetes mellitus, n (%) | 62 (18.7%) | 24 (21.4%) | 0.627 |
| Smoking, n (%) | 194 (58.6%) | 60 (53.6%) | 0.411 |
| History of coronary artery disease, n (%) | 50 (15.1%) | 13 (11.6%) | 0.448 |
| ACS type | | | **0.002** |
| STEMI | 213 (64.4%) | 92 (82.1%) | |
| NSTEMI | 107 (32.3%) | 19 (17.0%) | |
| Unstable angina | 11 (3.3%) | 1 (0.9%) | |
| Creatinine (mg/dL) | 0.81 (0.72–0.91) | 0.84 (0.76–0.93) | 0.029 |
| WBC (×10³/μL) | 11.37 (9.50–13.70) | 13.57 (11.58–16.32) | <0.001 |
| Hemoglobin (g/dL) | 14.70 (13.75–15.50) | 14.70 (13.98–15.50) | 0.564 |
| Platelet count (×10³/μL) | 264.00 (227.00–314.50) | 268.00 (226.25–318.25) | 0.784 |
| Neutrophil count (×10³/μL) | 8.06 (6.20–10.54) | 10.83 (8.59–13.17) | <0.001 |
| Lymphocyte count (×10³/μL) | 2.23 (1.73–3.01) | 2.01 (1.70–2.40) | 0.007 |
| Monocyte count (×10³/μL) | 0.60 (0.47–0.75) | 0.58 (0.48–0.72) | 0.911 |
| CRP (mg/L) | 3 (3–6) | 5.5 (3–8) | <0.001 |
| IPI | 3.50 (2.03–7.41) | 6.88 (4.66–12.67) | <0.001 |
| NLR | 3.55 (2.23–5.40) | 5.37 (4.14–6.96) | <0.001 |
| PLR | 117.97 (90.32–153.96) | 129.98 (105.62–159.29) | 0.007 |
| SII | 912.94 (605.37–1435.32) | 1381.86 (952.68–2040.47) | <0.001 |
| CAR | 0.79 (0.73–1.54) | 1.35 (0.88–2.01) | <0.001 |
| Total cholesterol (mg/dL) | 214.29±46.33 | 208.63±40.91 | 0.250 |
| Triglycerides (mg/dL) | 123.00 (75.00–197.50) | 116.50 (81.75–198.00) | 0.835 |
| HDL cholesterol (mg/dL) | 42 (38–48) | 41 (35–47) | 0.059 |
| LDL cholesterol (mg/dL) | 141.38±35.88 | 138.51±31.48 | 0.451 |
| Non-HDL-C (mg/dL) | 171.49±44.03 | 167.49±38.13 | 0.392 |
| Albumin (g/dL) | 4.00 (3.90–4.20) | 4.00 (3.90–4.20) | 0.720 |
| LVEF (%) | 49.00 (41.00–56.00) | 41.00 (33.00–49.00) | <0.001 |

Data are presented as mean±standard deviation, median (interquartile range), or number (percentage), as appropriate. Continuous variables were compared using the independent-samples t test or Mann–Whitney U test according to data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test. ACS, acute coronary syndrome; BMI, body mass index; CAR, C-reactive protein-to-albumin ratio; CRP, C-reactive protein; HDL, high-density lipoprotein; IPI, inflammatory prognostic index; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NLR, neutrophil-to-lymphocyte ratio; non-HDL-C, non-high-density lipoprotein cholesterol; NRP, no-reflow phenomenon; NSTEMI, non-ST-segment elevation myocardial infarction; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; STEMI, ST-segment elevation myocardial infarction; WBC, white blood cell count.

ROC curve analyses evaluating the discriminatory performance of inflammatory indices for NRP are shown in Table 5 and Figure 3. Among the inflammatory markers evaluated, IPI demonstrated the highest discriminatory performance, with an AUC of 0.725 (95% CI: 0.677–0.772), followed by NLR (AUC: 0.697, 95% CI: 0.646–0.748), SII (AUC: 0.676, 95% CI: 0.622–0.730), CAR (AUC: 0.652, 95% CI: 0.596–0.709), and PLR (AUC: 0.585, 95% CI: 0.528–0.642). The optimal cutoff value for IPI was 3.45, yielding 92.0% sensitivity, 49.8% specificity, a PPV of 38.3%, a NPV of 94.8%, a positive likelihood ratio (LR+) of 1.83, and a negative likelihood ratio (LR−) of 0.16.

Pairwise comparisons of ROC curves using the DeLong test demonstrated that the AUC of IPI was significantly higher than those of CAR (P = 0.001) and PLR (P < 0.001), whereas no statistically significant differences were observed between IPI and NLR (P = 0.236) or SII (P = 0.054).

## Discussion

In this study, the IPI showed a significant nonlinear association with the NRP in patients aged ≤45 years undergoing PCI for ACS.

Depending on the methods used to evaluate NRP, previous studies have demonstrated that NRP develops in 5% to 50% of patients undergoing PCI for ACS.[16] In a previous study conducted at our center among patients with STEMI, NRP occurred in 20% of patients.[6] In another study evaluating the outcomes of coronary angiography in young adults, NRP occurred in 18% of patients.[1] In our study, the rate of NRP was 25.3% among young patients undergoing PCI for ACS. This relatively high incidence should be interpreted in the context of the angiographic definition used in the present study. Consistent with previous studies, NRP was defined using both epicardial TIMI flow and MBG, thereby allowing impaired myocardial reperfusion to be identified even in patients with preserved TIMI 3 flow. Therefore, the observed event rate should not be interpreted

**Table 2.** Angiographic and procedural characteristics according to NRP

| Variables | NRP (−) (n=331) | NRP (+) (n=112) | *P* |
|---|---|---|---|
| Culprit vessel | | | **0.022** |
| LAD | 152 (45.9%) | 70 (62.5%) | |
| RCA | 88 (26.6%) | 22 (19.6%) | |
| CX | 78 (23.6%) | 16 (14.3%) | |
| Other | 13 (3.9%) | 4 (3.6%) | |
| Initial TIMI flow grade | | | **<0.001** |
| TIMI 0 | 152 (45.9%) | 89 (79.5%) | |
| TIMI 1 | 49 (14.8%) | 9 (8.0%) | |
| TIMI 2 | 87 (26.3%) | 11 (9.8%) | |
| TIMI 3 | 43 (13.0%) | 3 (2.7%) | |
| TIMI thrombus grade | | | **<0.001** |
| Grade 1 | 3 (0.9%) | 0 (0.0%) | |
| Grade 2 | 15 (4.5%) | 2 (1.8%) | |
| Grade 3 | 89 (26.9%) | 8 (7.1%) | |
| Grade 4 | 74 (22.4%) | 13 (11.6%) | |
| Grade 5 | 150 (45.3%) | 89 (79.5%) | |
| Bifurcation lesion, n (%) | 39 (11.8%) | 19 (17.0%) | 0.214 |
| Thrombus aspiration, n (%) | 8 (2.4%) | 9 (8.0%) | 0.017 |
| GP IIb/IIIa inhibitor use, n (%) | 22 (6.6%) | 32 (28.6%) | <0.001 |
| Intracoronary adenosine, n (%) | 2 (0.6%) | 4 (3.6%) | 0.061 |
| Intracoronary adrenaline, n (%) | 2 (0.6%) | 8 (7.1%) | <0.001 |
| Intracoronary nitrate, n (%) | 51 (15.4%) | 37 (33.0%) | <0.001 |
| Predilatation, n (%) | 307 (92.7%) | 111 (99.1%) | 0.022 |
| Postdilatation, n (%) | 177 (53.5%) | 60 (53.6%) | 1.000 |
| Number of stents | 1 (1–1) | 1 (1–1) | 0.713 |
| Stent diameter (mm) | 3.00 (2.75–3.50) | 3.00 (2.50–3.50) | 0.274 |
| Stent length (mm) | 28 (20–38) | 28 (19.75–38) | 0.437 |

Data are presented as median (interquartile range) or number (percentage), as appropriate. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. CX, circumflex artery; GP IIb/IIIa, glycoprotein IIb/IIIa; LAD, left anterior descending artery; NRP, no-reflow phenomenon; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

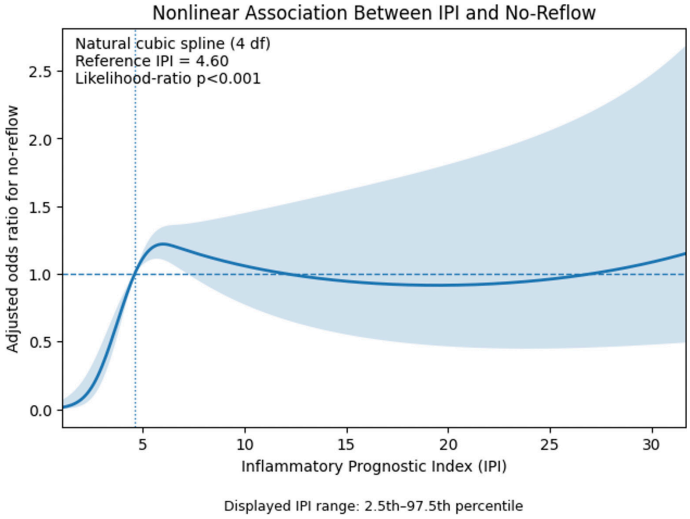



**Figure 2.** Nonlinear association between the inflammatory prognostic index (IPI) and the no-reflow phenomenon (NRP). Adjusted odds ratios for NRP according to IPI levels were estimated using a natural cubic spline with 4 degrees of freedom, with adjustment for ST-segment elevation myocardial infarction (STEMI) presentation, left anterior descending (LAD) coronary artery as the culprit vessel, serum creatinine, and initial Thrombolysis in Myocardial Infarction (TIMI) flow grade 0–1. The solid line represents the adjusted odds ratio, and the shaded area represents the 95% confidence interval. The median IPI value (4.60) was used as the reference. The displayed IPI range was restricted to the 2.5th–97.5th percentiles to reduce the influence of extreme values.

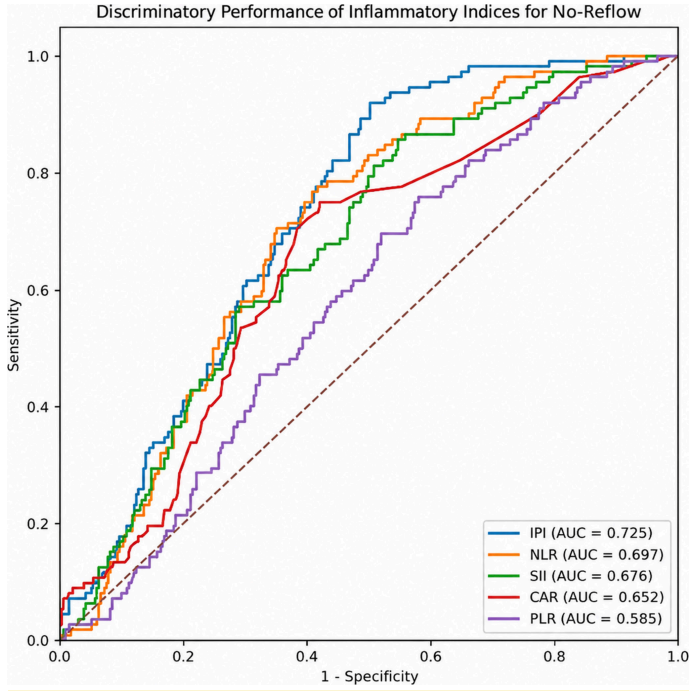



**Figure 3.** Receiver operating characteristic (ROC) curve analysis of the discriminatory performance of inflammatory indices for the no-reflow phenomenon (NRP) in patients aged ≤45 years presenting with acute coronary syndrome. The area under the curve (AUC) values were 0.725 (95% CI: 0.677–0.772) for the inflammatory prognostic index (IPI), 0.697 (95% CI: 0.646–0.748) for the neutrophil-to-lymphocyte ratio (NLR), 0.676 (95% CI: 0.622–0.730) for the systemic immune-inflammation index (SII), 0.652 (95% CI: 0.596–0.709) for the C-reactive protein-to-albumin ratio (CAR), and 0.585 (95% CI: 0.528–0.642) for the platelet-to-lymphocyte ratio (PLR). CI, confidence interval.

as representing classical no-reflow based solely on severely impaired epicardial flow. The observed NRP rate may also be related to the predominance of patients with STEMI, the high prevalence of impaired initial TIMI flow, and the high thrombus burden. Notably, the NRP rate was higher among patients presenting with STEMI than among those with NSTEMI (30.2% vs. 15.1%), which may partly explain the relatively high overall NRP rate in our predominantly STEMI population. Predilatation was more frequent among patients with NRP; however, only a small number of patients underwent direct stenting, limiting the stability of this estimate. In the sensitivity analysis that included predilatation in the multivariable model, predilatation was not independently associated with NRP, whereas the association between IPI and NRP remained significant.

Although IPI remained independently associated with NRP after adjustment for the clinical and angiographic variables included in the main multivariable model, independence from ischemic time cannot be established because reliable symptom-to-balloon and door-to-balloon times were unavailable. Importantly, the association between IPI and NRP remained significant in an additional sensitivity model in which initial TIMI flow grade was replaced by high thrombus burden, suggesting that the observed association was not solely attributable to thrombus burden. Nevertheless, residual confounding by unmeasured or incompletely measured factors cannot be excluded.

Inflammation is closely involved in the pathophysiology of NRP through interactions among leukocytes, platelets, and endothelial cells at the microcirculatory level.[16,17] Activated neutrophils may contribute to microvascular obstruction and endothelial dysfunction through adhesion to the endothelium, release of proinflammatory mediators, and interactions with platelets.[18,19] In our study, neutrophil counts were significantly higher in patients with NRP, supporting the potential contribution of systemic inflammatory activation to impaired microvascular reperfusion.

Lymphopenia may also reflect an enhanced systemic inflammatory and stress response in acute myocardial infarction and has been associated with adverse cardiovascular outcomes.[20–22] In our cohort, lymphocyte counts were significantly lower in patients with NRP, consistent with the concept that an imbalance between innate and adaptive immune responses may accompany impaired microvascular reperfusion.

Serum albumin and CRP reflect complementary aspects of systemic inflammation and oxidative stress and have previously been associated with coronary disease severity, impaired myocardial perfusion, and NRP after primary PCI.[23–30] The CRP-to-albumin ratio (CAR), which integrates CRP and albumin, has also been associated with NRP.[27] In our study, CRP and CAR were significantly higher in patients with NRP, whereas albumin levels did not differ between the groups. These findings suggest that the inflammatory component captured by CRP may have contributed more strongly to the observed differences in CAR in our cohort.

IPI is a novel inflammatory marker derived from the combined evaluation of the NLR and CAR, and its prognostic value has previously been demonstrated, particularly in oncology.[31,32] The combination of multiple inflammatory parameters is thought to reflect inflammatory burden and clinical risk more comprehensively than individual biomarkers. However,

IPI should be interpreted as a nonspecific composite marker of systemic inflammatory activity rather than as a specific measure of coronary microvascular inflammation. Previous studies evaluating IPI in patients with STEMI suggested that it may provide better overall discriminatory performance than conventional inflammatory indices.[9] In the present study, IPI showed moderate discriminatory performance (area under the curve [AUC]=0.725) and remained significantly associated with NRP after multivariable adjustment. Importantly, the association between IPI and NRP was nonlinear. Spline analysis suggested that the association was strongest across the lower-to-intermediate IPI range and became less clearly defined at higher IPI values, where confidence intervals widened. This finding indicates that the association between IPI and NRP varies across the observed IPI range and supports the use of a nonlinear rather than a single per-unit effect estimate. The association also remained significant in the sensitivity analysis restricted to patients with STEMI. Although its high sensitivity may facilitate the identification of patients at increased risk, its relatively low specificity suggests that IPI should be considered an adjunctive marker rather than a standalone tool for clinical decision-making. Accordingly, the receiver operating characteristic-derived IPI cutoff of 3.45 should be considered exploratory and hypothesis-generating rather than a clinically established decision threshold. However, despite having the numerically highest AUC among the inflammatory indices evaluated, IPI did not demonstrate statistically significant superiority over NLR or the SII in pairwise receiver operating characteristic comparisons. Therefore, the present findings do not establish a clear discriminatory advantage of IPI over these simpler inflammatory indices, particularly NLR. Moreover, when IPI was incorporated into the clinical-angiographic model using the same nonlinear spline specification, model discrimination improved from an AUC of 0.699 to 0.791, and this improvement persisted after bootstrap correction, supporting the incremental discriminatory information provided beyond the included clinical and angiographic variables. Given

**Table 3.** Univariable logistic regression analysis of factors associated with NRP

| Variables | OR | 95% CI | *P* |
|---|---|---|---|
| STEMI | 2.55 | 1.50–4.34 | <0.001 |
| Creatinine | 4.67 | 1.34–16.32 | 0.016 |
| WBC (per 1×10³/μL increase) | 1.17 | 1.10–1.24 | <0.001 |
| Neutrophil count (per 1×10³/μL increase) | 1.21 | 1.14–1.29 | <0.001 |
| Lymphocyte count (per 1×10³/μL increase) | 0.65 | 0.49–0.86 | 0.002 |
| CRP (per 1 mg/L increase) | 1.06 | 1.02–1.10 | 0.001 |
| IPI (per 1-unit increase) | 1.06 | 1.03–1.08 | <0.001 |
| NLR (per 1-unit increase) | 1.16 | 1.08–1.24 | <0.001 |
| SII (per 1-unit increase) | 1.0004 | 1.0002–1.0007 | <0.001 |
| CAR (per 1-unit increase) | 1.25 | 1.09–1.43 | 0.001 |
| LVEF (per 1% increase) | 0.93 | 0.91–0.95 | <0.001 |
| LAD culprit vessel | 1.96 | 1.26–3.05 | 0.003 |
| Initial TIMI flow grade 0–1 | 4.53 | 2.48–8.26 | <0.001 |
| High thrombus burden (TIMI grade 4–5) | 4.87 | 2.45–9.71 | <0.001 |
| Predilatation | 8.68 | 1.16–64.90 | 0.035 |

Univariable logistic regression analysis was performed to identify factors associated with NRP. CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; CRP, C-reactive protein; IPI, inflammatory prognostic index; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; NLR, neutrophil-to-lymphocyte ratio; NRP, no-reflow phenomenon; OR, odds ratio; SII, systemic immune-inflammation index; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell count.

**Table 4.** Multivariable logistic regression analysis of factors associated with NRP

| Variables | Adjusted OR | 95% CI | *P* |
|---|---|---|---|
| IPI, natural cubic spline (4 df) | – | – | <0.001* |
| LAD culprit vessel | 2.15 | 1.31–3.51 | 0.002 |
| Initial TIMI flow grade 0–1 | 3.21 | 1.59–6.50 | 0.001 |
| STEMI | 0.67 | 0.34–1.32 | 0.246 |
| Creatinine | 3.04 | 0.70–13.14 | 0.136 |

*For IPI, the p value represents the global test of association from the natural cubic spline model with 4 degrees of freedom. The nonlinear component was also statistically significant (P < 0.001). Because the association between IPI and NRP was nonlinear, a single per-unit adjusted OR is not reported for IPI in the primary model. TIMI thrombus grade was not included in the primary multivariable model because of its close association with initial TIMI flow grade. CI, confidence interval; df, degrees of freedom; IPI, inflammatory prognostic index; LAD, left anterior descending artery; NRP, no-reflow phenomenon; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

the use of a flexible spline specification and the single-center nature of the study, the observed improvement in discrimination should be interpreted cautiously and requires external validation. Accordingly, prospective multicenter studies are needed to validate these findings and determine whether IPI provides clinically meaningful incremental value before its potential use in clinical risk assessment can be considered.

However, the previous study evaluating the association between the IPI and the NRP was conducted exclusively in patients with STEMI, and the definition of NRP was based mainly on TIMI flow grades.[9] In contrast, our study was conducted in a specific population of young patients with ACS. Moreover, our evaluation of NRP did not rely solely on TIMI grading, which reflects epicardial flow, but also incorporated MBG assessment, which better reflects microvascular perfusion. The inclusion of MBG in addition to TIMI flow grade may partly explain the higher NRP rate observed in our study compared with previous studies. In addition, because young patients with ACS generally have a lower traditional atherosclerotic burden, inflammatory and thrombotic mechanisms may be more prominently associated with impaired microvascular reperfusion.

Patients who experience MI at a young age constitute a distinct patient group that differs from older patients with MI in terms of clinical characteristics and underlying pathophysiological mechanisms. In this patient population, in addition to conventional cardiovascular risk factors, nontraditional risk factors such as substance use, thrombophilic conditions, coronary artery anomalies, immunologic diseases, allergic mechanisms, and psychosocial stress may play a more prominent role.[3] Therefore, associations between inflammatory markers and impaired microvascular reperfusion may differ in young patients with ACS. The focus of our study on young patients with ACS is an important feature that distinguishes it from previous studies.

This study has several limitations. First, it was a single-center retrospective study. In addition, the relatively high proportion of excluded patients, particularly the exclusion of 113 patients because angiographic recordings were unsuitable for reliable NRP assessment, may have introduced selection bias and may limit the generalizability of our findings. Furthermore, the exclusion of patients with an estimated glomerular filtration rate <50 mL/min/1.73 $m^2$ may limit the generalizability of our findings to patients with reduced renal function. The present study was primarily designed to evaluate NRP as a procedural endpoint and was not designed to assess the prognostic utility of IPI or its association with long-term clinical outcomes. Long-term clinical follow-up was not available. In addition, several important clinical variables, including ischemic time (symptom-to-balloon or door-to-balloon time), Killip class, cardiogenic shock, and cardiac arrest before percutaneous coronary intervention (PCI), could not be reliably retrieved from the retrospective medical records and, therefore, could not be included in the multivariable analysis. Consequently, residual confounding cannot be completely excluded.

Information on several nontraditional risk factors and etiologic characteristics relevant to premature coronary artery disease, including family history of premature cardiovascular disease, history of dyslipidemia, lipoprotein(a), substance use, thrombophilic conditions, inflammatory or autoimmune diseases, and oral contraceptive or hormone use in women, was not consistently available and, therefore, could not be systematically evaluated.

The exact interval from symptom onset to blood sampling was not reliably available; therefore, the timing of laboratory sampling relative to ACS onset could not be standardized. This is particularly relevant because CRP and leukocyte subsets, and consequently the calculated IPI, may vary dynamically during the acute phase of ACS. Moreover, inflammatory biomarkers were assessed from a single preprocedural blood sample, and serial measurements were unavailable. These factors may have introduced variability in IPI values and should be considered when interpreting the observed association with NRP. In addition, fasting status at the time of lipid measurement and information regarding lipid-lowering therapy before admission could not be reliably determined because of the retrospective design.

Although TIMI thrombus grade was not included in the primary multivariable model because of its close association with initial TIMI flow grade, an additional sensitivity analysis replacing initial TIMI flow with high thrombus burden yielded consistent findings for IPI. The lower detection limit of the laboratory assay for CRP was 3 mg/L, and values below this threshold were reported as 3 mg/L by the institutional laboratory system. Consequently, discrimination among very low CRP concentrations was not possible, which may have influenced the calculation of the CARand IPI and should be considered when interpreting the proposed ROC-derived cutoff value. More advanced imaging modalities, such as myocardial contrast echocardiography or cardiac magnetic resonance imaging, were not used to evaluate NRP. Although angiographic assessments were independently performed by two experienced interventional cardiologists who were blinded to inflammatory biomarker data, with disagreements resolved by a third reviewer, formal interobserver agreement was not quantified. Furthermore, because STEMI constituted the majority of the study population, the generalizability of our findings to patients with NSTEMI or unstable angina may be

**Table 5.** ROC curve analysis of the discriminatory performance of inflammatory indices for NRP

| Variables | AUC (95% CI) | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | LR+ | LR− |
|---|---|---|---|---|---|---|---|---|
| IPI | 0.725 (0.677–0.772) | 3.45 | 92.0 | 49.8 | 38.3 | 94.8 | 1.83 | 0.16 |
| NLR | 0.697 (0.646–0.748) | 4.04 | 76.8 | 59.2 | 38.9 | 88.3 | 1.88 | 0.39 |
| SII | 0.676 (0.622–0.730) | 830.13 | 85.7 | 45.3 | 34.7 | 90.4 | 1.57 | 0.32 |
| CAR | 0.652 (0.596–0.709) | 0.91 | 75.0 | 58.0 | 37.7 | 87.3 | 1.79 | 0.43 |
| PLR | 0.585 (0.528–0.642) | 105.22 | 75.9 | 42.0 | 30.7 | 83.7 | 1.31 | 0.57 |

Optimal cutoff values were determined using the Youden index. AUC, area under the curve; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; IPI, inflammatory prognostic index; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; NRP, no-reflow phenomenon; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value; ROC, receiver operating characteristic; SII, systemic immune-inflammation index.

limited, despite the consistent findings observed in the STEMI-only sensitivity analysis. Finally, the same age cutoff (≤45 years) was applied to both men and women. Although this definition is widely used in studies of young ACS, sex-specific age thresholds may better identify women with clinically premature MI. Therefore, prospective multicenter studies including larger patient populations are needed to confirm our findings.

## Conclusion

In this study, IPI showed a significant nonlinear association with NRP in young patients with ACS undergoing PCI. IPI demonstrated the highest discriminatory performance among the inflammatory indices evaluated. Pairwise ROC comparisons showed significantly better performance than CAR and the PLR, whereas its performance did not differ significantly from that of the NLR or SII. In addition, initial TIMI flow grade 0–1 and the LAD coronary artery as the culprit vessel were independently associated with NRP. These findings support an association between systemic inflammatory activity and impaired microvascular reperfusion in young patients with ACS. However, the moderate discriminatory performance of IPI, the low specificity of the proposed cutoff, and the lack of external validation warrant cautious interpretation. Prospective multicenter studies with adjustment for established clinical and procedural determinants of NRP and assessment of clinical outcomes are needed to confirm these findings.

**Ethics Committee Approval:** Ethics committee approval was obtained from Sakarya University Faculty of Medicine Health Sciences Scientific Research Ethics Committee (Approval Number: -43012747-050.04-590324/452, Date: 21.05.2026).

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**Graphical Abstract. Overview of the study population, angiographic slow-flow/no-reflow endpoint, and main findings regarding the association between the inflammatory prognostic index and the no-reflow phenomenon (NRP).**

**No-Reflow in Young Acute Coronary Syndrome Patients**
**Association with the Inflammatory Prognostic Index**

| Study population | Inflammatory Prognostic Index (IPI) | Slow-flow/no-reflow endpoint (NRP) |
|---|---|---|
| 443 consecutive patients ≤45 years with acute coronary syndrome undergoing PCI (2022–2025)<br>STEMI: 305 (68.8%)<br>NSTEMI: 126 (28.4%)<br>Unstable Angina: 12 (2.7%) | Calculated as the neutrophil-to-lymphocyte ratio × the C-reactive protein-to-albumin ratio<br>IPI = NLR × (CRP / albumin) | Final TIMI flow grade 0–2 without mechanical obstruction, or final TIMI flow grade 3 with myocardial blush grade 0–1<br>NRP developed in 112 patients (25.3%) |

**Key findings**

| Association with NRP | Discriminatory performance | Incremental value | Multivariable findings |
|---|---|---|---|
| IPI showed a significant nonlinear association with NRP in multivariable analysis<br>p for overall association <0.001<br>p for nonlinearity <0.001 | IPI for predicting NRP<br>AUC 0.725 (95% CI: 0.677–0.772)<br>Cut-off value: 3.45<br>Sensitivity: 92.0%<br>Specificity: 49.8% | Adding IPI (spline terms) to a clinical-angiographic model increased the AUC from 0.699 to 0.791<br>P < 0.001 | IPI: significant nonlinear association (spline model)<br>Initial TIMI flow grade 0–1<br>OR 3.21 (95% CI: 1.59–6.50)<br>LAD culprit vessel<br>OR 2.15 (95% CI: 1.31–3.51) |

**Conclusion**

IPI was nonlinearly associated with angiographic slow-flow/no-reflow in young ACS patients undergoing PCI and provided incremental discriminatory information beyond clinical-angiographic variables. Its limited specificity warrants cautious interpretation and prospective validation.

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# No-Reflow in the Young: Does the Inflammatory Prognostic Index Add Anything?

## Gençlerde No-Reflow: İnflamatuvar Prognostik İndeks Ek Bir Katkı Sağlıyor mu?

**EDITORIAL COMMENT**
EDİTÖRYAL YORUM

Myocardial infarction (MI) occurring before the age of 45 is increasingly common and should not be regarded merely as the early onset of a disease affecting older adults. Young patients differ in their risk factor profiles, frequently present with a greater intracoronary thrombus burden, and experience a disproportionate loss of working years and quality of life.[1] Failure of myocardial reperfusion despite successful epicardial recanalization-the no-reflow phenomenon-complicates 2–44% of primary percutaneous coronary intervention (PCI) procedures, depending on the definition and imaging modality used, and independently predicts left ventricular dysfunction and death.[2] Accumulating evidence implicates systemic inflammation in its pathogenesis: admission high-sensitivity C-reactive protein, leukocyte and neutrophil counts, platelet-to-lymphocyte ratio, and red cell distribution width have each been associated with impaired myocardial reperfusion. Composite indices, including the systemic immune-inflammation index (SII) and pan-immune-inflammation value (PIV), have demonstrated promising predictive performance in large cohorts of patients with ST-segment elevation myocardial infarction (STEMI).[2,3] However, whether the determinants of no-reflow differ in patients with premature MI remains understudied.

In this issue, Çakmak et al.[4] examine this topic. Among 443 consecutive patients aged 45 years or younger who underwent PCI for acute coronary syndrome (ACS) at a single center between 2022 and 2025, angiographic slow-flow/no-reflow phenomenon (NRP) occurred in 112 patients (25.3%). The inflammatory prognostic index (IPI), calculated as the neutrophil-to-lymphocyte ratio (NLR) multiplied by the C-reactive protein (CRP)-to-albumin ratio, was approximately twice as high in patients who developed NRP (median, 6.88 versus 3.50). After adjustment, IPI showed a significant nonlinear association with the endpoint and an area under the curve (AUC) of 0.725. When incorporated as a spline term into a clinical-angiographic model, it improved discrimination from 0.699 to 0.791. Several aspects of this work merit recognition. The endpoint incorporated myocardial blush grade rather than relying solely on epicardial flow. This definition better reflects the underlying pathophysiology than Thrombolysis in Myocardial Infarction (TIMI) flow alone.[5,6] The statistical analyses were more rigorous than is typical in this literature: the authors tested rather than assumed linearity, modeled IPI using a spline, and respected the events-per-variable ratio. Sensitivity analyses examined predilatation, thrombus burden, and a STEMI-only subgroup, and the association remained consistent across all analyses. The authors also clearly acknowledged the limitations of their findings. Overall, this was a carefully conducted study; the concerns that follow relate to interpretation rather than execution.

The study did not include an older comparison group, which limits age-specific inference rather than the internal validity of the analysis. The study demonstrates that IPI is associated with NRP among patients aged 45 years or younger; however, it cannot establish whether this association is specific to young patients or differs from that observed among patients aged 65 years or older. Sex is another concern and the most consequential. An age threshold of 45 years is considerably more restrictive for women than for men, given that women develop coronary disease approximately a decade later. The study does not support conclusions regarding sex-specific determinants of microvascular reperfusion, and its findings should not be extrapolated to women. The authors acknowledge this limitation, and future studies should consider sex-specific age thresholds from the outset.

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Selection and spectrum bias also warrant emphasis. The cohort comprised young patients who underwent PCI at a single center, and only 443 of 1,154 screened patients were included in the analysis. Patients with myocardial infarction with nonobstructive coronary arteries (MINOCA), myocarditis, Takotsubo syndrome, or medically managed spontaneous coronary artery dissection were excluded, as were those with an estimated glomerular filtration rate below 50 mL/min/1.73 $m^2$ and 113 patients whose angiograms were unsuitable for assessing NRP; medically managed patients were absent by design, and vasospastic, embolic, or other nonatherosclerotic mechanisms may therefore be underrepresented. The findings thus apply to a selected, predominantly STEMI (69%) population with an obstructive culprit lesion. This is particularly relevant in young patients, in whom nontraditional and nonatherosclerotic mechanisms account for a proportionally larger share of events. The authors acknowledge some of these exclusions as potential sources of selection bias. The field's focus also warrants consideration. Mean low-density lipoprotein cholesterol levels were 141 mg/dL among patients without NRP and 139 mg/dL among those with NRP, at a median age of 41 years. Data on lipoprotein(a), family history of premature cardiovascular disease, and prior lipid-lowering therapy were unavailable, and familial hypercholesterolemia was not addressed.

Turning to the marker itself, IPI mathematically incorporates NLR (neutrophils/lymphocytes) together with the CRP-to-albumin ratio, so a substantial correlation with NLR is expected by construction. Such a composite inherits variability from both components and may add little information beyond either component alone. Any proposed composite measure should outperform its individual components. Its incremental value should therefore be demonstrated against NLR and the CRP-to-albumin ratio separately rather than inferred solely from the statistical significance of IPI. In this study, NLR largely accounted for the association between IPI and NRP. The authors compared a clinical-angiographic model with and without spline-modeled IPI, formally tested the change in AUC (DeLong $p<0.001$), assessed calibration using the Hosmer–Lemeshow test, and performed internal bootstrap validation (mean optimism, 0.015; optimism-corrected AUC, 0.776), which is commendable. However, as far as the methods describe, the same model was not repeated with NLR or the CRP-to-albumin ratio added separately, so the incremental value of IPI over its own components remains untested; in pairwise receiver operating characteristic (ROC) curve comparisons, IPI was not significantly better than NLR (AUC, 0.725 versus 0.697; $p=0.236$). Bootstrap optimism correction also addresses internal validity only: the increase in AUC from 0.699 to 0.791 (0.776 after correction) rests on a flexible spline in a single-center cohort and still requires external validation. Likewise, the 3.45 cutoff, selected using the Youden index in the same cohort in which it was evaluated, should be interpreted cautiously. The adjusted odds ratio rises steeply up to an IPI of approximately 5 and then plateaus. Thus, a low IPI was associated with a lower observed probability of NRP, but a high IPI was not associated with a progressively greater probability. As the authors themselves note, the score is useful for ruling out NRP but has limited capacity to rule it in. Measurement timing is another concern: the symptom-to-balloon, door-to-balloon, and symptom-to-sampling intervals were unavailable. CRP does not rise until approximately 6 hours after necrosis begins and peaks 1 day or more later. The CRP term may therefore reflect the timing of the patient's arrival as much as the patient's underlying characteristics. The concern extends beyond CRP: IPI also incorporates neutrophil, lymphocyte, and albumin values, all of which may be influenced by acute stress, infection, corticosteroid or immunosuppressive treatment, infarct severity, renal or hepatic dysfunction, nutritional status, and hydration. The authors used a single venous sample drawn before angiography and excluded patients with active infectious or inflammatory disease, hematologic disease, recent major surgery, or an estimated glomerular filtration rate below 50 mL/min/1.73 $m^2$. However, the interval from symptom onset to sampling was unavailable, so sampling could not be standardized, and corticosteroid or immunosuppressive treatment, hepatic dysfunction, nutritional status, and hydration were not described as having been addressed. A single, nonstandardized acute-phase measurement is therefore an additional limitation. Because CRP values below 3 mg/L were recorded as 3 mg/L, a floor effect may further influence IPI and its cutoff. At least three nonmutually exclusive explanations are compatible with these data: inflammation causally contributes to microvascular plugging; IPI marks delayed presentation; or IPI reflects a large, occluded infarct that was already evolving when the sample was obtained.

Two further issues concern the angiographic endpoint and residual confounding. Incorporating myocardial blush grade is a methodological strength, and the angiograms were assessed independently by two blinded interventional cardiologists, with adjudication by a third reader. Nevertheless, both TIMI flow and myocardial blush grade remain observer-dependent measures, and, as the authors acknowledge, formal interobserver agreement was not quantified. Because slow flow and no-reflow were combined into a single endpoint, it also remains unknown whether the association is similar when true no-reflow is examined separately; the 25.3% event rate should not be interpreted as classical no-reflow. Finally, the main multivariable model was adjusted for four covariates (STEMI presentation, left anterior descending [LAD] culprit vessel, serum creatinine, and initial TIMI flow grade 0–1), with sensitivity analyses for thrombus burden and predilatation. Total ischemic time, Killip class, cardiogenic shock, and cardiac arrest could not be retrieved, and infarct size, lesion complexity, glycemic status, and periprocedural pharmacotherapy were not included as adjustment variables, although all may influence both inflammatory indices and no-reflow. Residual confounding is therefore a substantial concern and warrants greater emphasis than the brief acknowledgment it receives.

A high thrombus burden is a well-established risk factor for adverse complications; however, no intervention has been shown to improve outcomes. Routine manual thrombus aspiration failed to reduce mortality in TASTE.[7] It also did not improve clinical outcomes in TOTAL.[8] Deferred stenting likewise did not improve outcomes in DANAMI-3-DEFER.[9] Interleukin-1 beta blockade in CANTOS reduced recurrent events in stable post-infarction patients but provides no evidence regarding periprocedural microvascular obstruction.[10] Intracoronary vasodilators and glycoprotein IIb/IIIa inhibitors remain reactive rather than preventive; in this cohort, their use followed the occurrence of the event.

This study demonstrates that systemic inflammatory activation, measured before PCI, is associated with impaired microvascular reperfusion in young patients with ACS and that this association was established with greater statistical rigor than in most previous studies. However, it does not establish that IPI provides additional value beyond NLR or the CRP-to-albumin ratio, that the relationship is graded rather than functioning as a low-value rule-out measure, that it is independent of the duration of arterial occlusion before blood sampling, or that it is reproducible and generalizable beyond a single-center cohort of young patients undergoing PCI. The authors acknowledge many of these limitations, and these caveats are among the paper's most noteworthy aspects. For the operator, the message is straightforward and largely familiar: a young patient with an occluded LAD, a substantial thrombus burden, and a markedly activated inflammatory profile is at high risk of inadequate tissue-level reperfusion. Neither IPI nor its cutoff of 3.45 should alter the subsequent course of action. Future cohorts should instead record the interval between symptom onset and blood sampling, as well as lipoprotein measurements that may help explain why a 41-year-old patient requires intervention. Any claimed incremental value of IPI should also be confirmed through internal and external validation.

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# Cluster-Based Analysis of Lipid-Derived Profiles and Clinical Presentation in Premature Acute Coronary Syndrome

## Prematür Akut Koroner Sendromda Lipid Türevi Profillerin ve Klinik Başvuru Özelliklerinin Kümeleme Analizi ile Değerlendirilmesi

**ABSTRACT**

**Objective:** Premature acute coronary syndrome (ACS) is clinically heterogeneous, and routine lipid parameters may not fully capture lipid-related risk profiles in young patients. We investigated whether lipid-derived indices could identify clusters associated with index ACS presentation and long-term outcomes.

**Method:** This retrospective, single-center observational cohort study included patients aged ≤50 years who presented with first documented angiographically obstructive premature ACS and had complete lipid data. Standardized non-HDL-C, remnant cholesterol, TG/HDL-C ratio, and atherogenic index of plasma were analyzed using k-means clustering. Associations with STEMI presentation and a composite cardiovascular/cerebrovascular endpoint were evaluated using logistic and Cox regression analyses.

**Results:** Of 1106 screened records, 195 were excluded because of incomplete lipid data or implausible lipid values, leaving 911 patients for analysis. At presentation, 152 patients (16.7%) had unstable angina, 224 (24.6%) had NSTEMI, and 535 (58.7%) had STEMI. Two clusters were identified: a lower atherogenic pattern (n=673, 73.9%) and a high atherogenic pattern (n=238, 26.1%). STEMI was less frequent in the high atherogenic pattern than in the lower atherogenic pattern (51.7% vs. 61.2%; P = 0.010) and remained independently associated after adjustment (OR, 0.69; 95% CI, 0.50–0.93; P = 0.016). In the MI-only sensitivity analysis, this association was attenuated and was no longer statistically significant. Sensitivity clustering yielded similar results. During a median clinical follow-up of 1370 days (IQR, 706–1991), 228 patients (25.0%) experienced the composite endpoint; the high atherogenic pattern was not independently associated with this outcome (HR, 1.11; 95% CI, 0.83–1.48; P = 0.496).

**Conclusion:** Lipid-derived clustering identified two phenotypic patterns associated with index ACS presentation but not with long-term composite outcomes. Prospective external validation is required.

**Keywords:** Atherogenic index of plasma, cluster analysis, lipid-derived phenotypic patterns, non-HDL cholesterol, premature acute coronary syndrome, remnant cholesterol, STEMI.

**ÖZET**

**Amaç:** Prematür akut koroner sendrom (AKS) klinik açıdan heterojen bir tablodur ve rutin lipid parametreleri genç hastalardaki lipid ilişkili riski tam olarak yansıtmayabilir. Bu çalışmada, lipid türevi indekslerin indeks AKS prezantasyonu ve uzun dönem sonuçlarla ilişkili paternleri belirleyip belirleyemeyeceğini araştırdık.

**Yöntem:** Bu retrospektif, tek merkezli gözlemsel kohort çalışmasına, 50 yaş ve altında ilk kez anjiyografik olarak doğrulanmış obstrüktif prematür AKS ile başvuran ve lipid verileri eksiksiz olan hastalar dahil edildi. Standardize edilmiş non-HDL-K, remnant kolesterol, TG/HDL-K oranı ve aterojenik plazma indeksi k-means kümeleme yöntemi ile analiz edildi. STEMI prezantasyonu ve kompozit kardiyovasküler/serebrovasküler sonlanım noktası ile ilişkiler lojistik ve Cox regresyon analizleri ile değerlendirildi.

**Bulgular:** Taranan 1106 kaydın 911'i analize dahil edildi. Başvuru sırasında 152 hastada (%16,7) kararsız anjina, 224 hastada (%24,6) NSTEMI ve 535 hastada (%58,7) STEMI mevcuttu. İki küme tanımlandı: düşük aterojenik patern (n=673, %73,9) ve yüksek aterojenik patern (n=238, %26,1). STEMI, yüksek aterojenik paternde düşük aterojenik paterne göre daha az sıktı (%51,7'ye karşı %61,2; P = 0,010) ve bu ilişki düzeltme sonrasında da devam etti (OR 0,69, %95 GA 0,50–0,93; P = 0,016). Yalnızca miyokard enfarktüslü hastaların değerlendirildiği duyarlılık analizinde bu ilişki zayıfladı ve istatistiksel anlamlılığını kaybetti. Duyarlılık kümeleme analizleri benzer sonuçlar verdi. Medyan 1370 günlük (ÇAA 706–1991) takipte 228 hastada (%25,0) kompozit sonlanım gelişti; yüksek aterojenik patern bu sonlanım ile bağımsız olarak ilişkili değildi (HR 1,11, %95 GA 0,83–1,48; P = 0,496).

**Sonuç:** Lipid türevi kümeleme, indeks AKS prezantasyonu ile ilişkili ancak uzun dönem kompozit sonuçlarla ilişkili olmayan iki keşifsel patern tanımladı. Prospektif dış doğrulama gereklidir.

**Anahtar Kelimeler:** Aterojenik plazma indeksi, kümeleme analizi, lipid türevi fenotipik paternler, non-HDL kolesterol, prematür akut koroner sendrom, remnant kolesterol, STEMI.

**ORIGINAL ARTICLE**
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Acute coronary syndrome (ACS) occurring at a young age represents a clinically important but heterogeneous condition. Although patients with premature ACS are often grouped together because of their early age at presentation, the underlying clinical and biological pathways may differ substantially among individuals.[1,2] This heterogeneity may be particularly relevant in patients aged ≤50 years, in whom traditional age-related risk accumulation is less pronounced and variations in metabolic, thrombotic, inflammatory, and lipid-related pathways may play comparatively larger roles.

Conventional lipid parameters, particularly LDL cholesterol, remain central to cardiovascular risk assessment and lipid-lowering treatment decisions. However, LDL-C alone may not fully capture the complexity of atherogenic lipid burden, especially in younger patients and those with triglyceride-rich lipoprotein abnormalities.[3] Several calculated lipid-derived indices, including remnant cholesterol, non-HDL cholesterol, the triglyceride-to-HDL cholesterol ratio (TG/HDL-C), and the atherogenic index of plasma (AIP), have been proposed to capture lipid-related risk beyond LDL-C alone. These markers reflect partially overlapping aspects of triglyceride-rich lipoprotein metabolism, insulin resistance, and residual atherogenic burden.[4-7]

Most previous studies evaluating these indices have focused on their associations as individual markers.[5,8] However, because these lipid-derived measures capture partially overlapping components of triglyceride-rich and atherogenic lipid metabolism, their joint assessment may provide an exploratory summary of correlated lipid-metabolic features in premature ACS. A cluster-based approach may therefore identify interpretable lipid-derived phenotypic patterns associated with index presentation, including STEMI versus non-ST-elevation presentations, while allowing their potential longitudinal associations to be evaluated separately.

Therefore, we aimed to identify lipid-derived phenotypic patterns in patients aged ≤50 years presenting with premature ACS using non-HDL-C, remnant cholesterol, TG/HDL-C ratio, and AIP. We then evaluated whether the resulting patterns were associated with index premature ACS presentation, with particular emphasis on STEMI, and with long-term composite cardiovascular/cerebrovascular outcomes. We hypothesized that joint clustering of these correlated lipid-derived indices would identify interpretable atherogenic patterns associated with clinical presentation, while their longitudinal association was evaluated as a separate exploratory objective.

## Methods

### Study Design and Population

This retrospective, single-center observational cohort study with an exploratory cluster-based analysis included consecutive patients aged ≤50 years who were hospitalized with first documented angiographically obstructive premature ACS between January 2018 and December 2024. ACS presentations were classified as unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI) according to the clinical diagnosis recorded at index admission, in line with contemporary universal definitions.[9,10] The diagnosis of myocardial infarction was based on serial high-sensitivity cardiac troponin I measurements interpreted according to sex-specific 99$^{th}$ percentile upper reference limits, together with ischemic symptoms and electrocardiographic findings. STEMI was defined according to standard ECG criteria.[10]

## ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| AIP | Atherogenic index of plasma |
| LVEF | Left ventricular ejection fraction |
| MINOCA | Myocardial infarction with non-obstructive coronary arteries |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| SCAD | Spontaneous coronary artery dissection |
| TG/HDL-C | Triglyceride-to-HDL cholesterol ratio |
| UA | Unstable angina |

All included patients underwent invasive coronary angiography. Patients with clinically documented myocardial infarction with non-obstructive coronary arteries (MINOCA), spontaneous coronary artery dissection (SCAD), type 2 myocardial infarction, myocarditis, Takotsubo syndrome, coronary embolism, vasospastic angina, or another identified non-atherosclerotic cause of ACS were excluded. Accordingly, the study cohort was restricted to patients with angiographically documented obstructive coronary artery disease presenting with premature ACS and without a clinically identified alternative non-atherosclerotic diagnosis. Patients with previously documented coronary artery disease, prior myocardial infarction, prior PCI/CABG, or chronic coronary syndrome were excluded. Therefore, the analytic cohort represented patients presenting with a first documented obstructive ACS event at age ≤50 years during the study period.

For the primary clustering analysis, patients were eligible if they had complete lipid measurements required for calculation of the prespecified lipid-derived indices, including total cholesterol, HDL cholesterol, triglycerides, and Sampson-estimated LDL cholesterol. Among 1106 screened records of patients with premature ACS, 195 were excluded because lipid-derived clustering variables were incomplete or unsuitable for analysis. Specifically, 189 records had incomplete lipid data, and 6 had implausible lipid values. The final analytic cohort therefore consisted of 911 patients with complete and plausible lipid measurements required for the derivation of lipid-based indices and clustering.

### Ethical Considerations

The study protocol was approved by İzmir Kâtip Çelebi University Health Research Ethics Committee (Approval Number: 0377, Date: 07.05.2026) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design of the study.

### Data Collection and Clinical Variables

Demographic, clinical, laboratory, echocardiographic, angiographic, and procedural data were obtained retrospectively from institutional medical records. Variables considered for descriptive and regression analyses included age, sex, diabetes mellitus, hypertension, prior hyperlipidemia history, smoking status, serum creatinine, left ventricular ejection fraction (LVEF), ACS presentation category, and revascularization strategy. For regression modeling, sex, diabetes mellitus, hypertension, smoking status, and prior hyperlipidemia history were coded as binary variables.

Diabetes mellitus, hypertension, and prior hyperlipidemia history were defined according to documented pre-existing diagnoses in the medical record or the use of corresponding glucose-lowering, antihypertensive, or lipid-lowering medications before

admission. Smoking status was defined as current or recent active smoking documented at index hospitalization. Recurrent myocardial infarction, recurrent cerebrovascular events, heart failure hospitalization, and recurrent revascularization were identified from the national electronic health record system and institutional electronic hospital databases using recorded clinical diagnoses, hospitalization records, and procedure codes.

**Calculation of Lipid-Derived Indices**

LDL-C was estimated using the Sampson equation, which provides reliable LDL-C estimation across a broad range of triglyceride concentrations.[11] Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol.[3] Remnant cholesterol was calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol.[3] The TG/HDL-C ratio was calculated as triglycerides divided by HDL cholesterol. AIP was calculated as log10(triglycerides/HDL cholesterol) after converting triglycerides and HDL cholesterol to mmol/L. For AIP calculation, triglycerides were converted from mg/dL to mmol/L by dividing by 88.57, and HDL cholesterol was converted from mg/dL to mmol/L by dividing by 38.67.[7]

Lipid measurements were obtained from fasting blood samples collected on the first morning following hospital admission.

**Outcomes and Follow-up**

The principal cross-sectional outcome was STEMI presentation at index admission. For this analysis, patients presenting with STEMI were coded as 1, whereas those presenting with NSTEMI or UA were coded as 0. The primary longitudinal outcome was a composite cardiovascular/cerebrovascular endpoint defined as the first occurrence of all-cause mortality, recurrent myocardial infarction, recurrent cerebrovascular event, heart failure hospitalization, or recurrent revascularization during follow-up.

For time-to-event analyses, follow-up time was calculated from the date of index hospitalization to the date of the first composite event or censoring, whichever occurred first. Outcome data were obtained through the national electronic health record system and institutional electronic hospital databases. Follow-up information was available for all patients included in the longitudinal analyses.

**Clustering and Sensitivity Analyses**

Lipid-derived clustering was performed using k-means clustering based on standardized values of non-HDL-C, remnant cholesterol, TG/HDL-C ratio, and AIP. Continuous clustering variables were scaled before clustering to ensure comparable weighting. Candidate solutions ranging from k=2 to k=10 were evaluated using the total within-cluster sum of squares, average silhouette width, Calinski–Harabasz index, and Davies–Bouldin index. Selection of the primary cluster number was based on the combined assessment of internal clustering metrics, parsimony, cluster size, and clinical interpretability rather than on a single statistical index. The two-cluster solution was selected as the primary classification after this assessment.

An exploratory three-cluster solution was additionally evaluated as an alternative k sensitivity analysis to determine whether further subdivision provided an additional clinically interpretable structure beyond the primary binary classification. Adjusted analyses of the exploratory three-cluster solution included age, sex, diabetes mellitus, hypertension, smoking status, and prior hyperlipidemia history.

Because several lipid-derived indices were mathematically related, inter-variable correlations were quantified using Spearman correlation coefficients. To evaluate the influence of this mathematical interdependence on the clustering solution, sensitivity clustering analyses were performed by excluding AIP and, separately, the TG/HDL-C ratio from the clustering variable set. Concordance between the primary and sensitivity clustering solutions was quantified using overall agreement and Cohen's kappa. Because cluster membership derived from unsupervised methods represents an estimated classification rather than an observed biological state, subsequent regression models treated cluster assignment as a fixed exposure and did not incorporate uncertainty in individual cluster assignment.

Associations between the sensitivity-defined clusters and STEMI presentation were then reassessed using Pearson's chi-square test and multivariable logistic regression adjusted for age, sex, diabetes mellitus, hypertension, smoking status, and prior hyperlipidemia history.

**Statistical Analysis**

Continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers and percentages. Distributional characteristics of continuous variables were assessed by examining skewness; because several variables showed substantial deviations from symmetry, a consistent non-parametric approach was used for descriptive reporting and group comparisons.

Comparisons across ACS presentation categories were performed using the Kruskal–Wallis test for continuous variables and Pearson's chi-square test for categorical variables. Kruskal–Wallis tests were interpreted as omnibus comparisons among the three ACS presentation groups. Because these analyses were intended for baseline descriptive characterization rather than pairwise hypothesis testing between individual ACS categories, post-hoc pairwise comparisons were not performed.

Comparisons between the two lipid-derived clusters were performed using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-square test for categorical variables. Expected cell frequencies were examined for categorical comparisons. Fisher's exact test was reserved for sparse contingency tables with an expected cell count <5; this criterion was not met in the categorical comparisons reported in the main analyses.

The association between lipid-derived cluster and STEMI presentation was examined using logistic regression. First, a crude model including cluster membership alone was fitted. Second, an adjusted model was constructed including cluster membership, age, sex, diabetes mellitus, hypertension, prior hyperlipidemia history, smoking status, and serum creatinine. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

As an additional sensitivity analysis addressing the inclusion of UA, the association between lipid-derived cluster and STEMI presentation was re-evaluated after restricting the cohort to patients with myocardial infarction only, defined as NSTEMI or STEMI.

Kaplan–Meier curves and Cox proportional hazards regression models were used to evaluate the association between lipid-derived clusters and the composite cardiovascular/cerebrovascular endpoint. Cox models were fitted as crude

models, multivariable models adjusted for age, sex, diabetes mellitus, hypertension, smoking, and prior hyperlipidemia history, and models additionally adjusted for STEMI presentation. Results are reported as hazard ratios with 95% confidence intervals. The proportional hazards assumption was assessed using Schoenfeld residuals.

All statistical analyses were conducted in the RStudio environment, version 2026.01.1 (Posit PBC, Boston, MA, USA), using standard packages for statistical analysis, clustering, regression modeling, and data visualization. A two-sided p-value <0.05 was considered statistically significant.

The manuscript was prepared in accordance with the STROBE reporting guideline, and the completed STROBE checklist is provided as a supplementary file.[12]

## Results

### Study Population

Of 1106 screened records of patients with premature ACS, 195 were excluded because lipid-derived clustering variables were incomplete or unsuitable for analysis, including 189 records with incomplete lipid data and 6 with implausible derived lipid values. Characteristics of included and excluded records are shown in Supplementary Table 7. The final analytic cohort consisted of 911 patients with complete and plausible lipid measurements (Figure 1 and Supplementary Table 1). The median age was 46.0 years (IQR, 42.0–48.7), and 773 patients (84.9%) were male. At index presentation, 152 patients (16.7%) had UA, 224 (24.6%) had NSTEMI, and 535 (58.7%) had STEMI (Table 1).

Across ACS presentation categories, lipid-derived indices showed only modest differences. Median remnant cholesterol levels were 35 mg/dL (IQR, 21–49) in UA, 32 mg/dL (IQR, 23–44) in NSTEMI, and 30 mg/dL (IQR, 22–42) in STEMI (P = 0.129). Median non-HDL-C levels were 154 mg/dL (IQR, 116–192), 157 mg/dL (IQR, 125–185), and 153 mg/dL (IQR, 125–183), respectively (P = 0.900). Median TG/HDL-C ratios were 4.5 (IQR, 2.6–7.1), 4.4 (IQR, 3.2–6.5), and 4.0 (IQR, 2.9–5.8), respectively (P = 0.144), whereas median AIP values were 0.29 (IQR, 0.06–0.49), 0.28 (IQR, 0.14–0.45), and 0.25 (IQR, 0.11–0.41), respectively (P = 0.144) (Table 1).

### Lipid-Derived Cluster Derivation and Internal Evaluation

Evaluation of candidate solutions from k=2 to k=10 favored the two-cluster classification when internal clustering metrics, parsimony, cluster size, and clinical interpretability were considered together (Supplementary Table 3 and Supplementary Figures 1 and 3). The k=2 solution had the highest average

**Table 1.** Baseline clinical, laboratory, lipid, and procedural characteristics according to index premature ACS presentation

| Characteristic | Overall (n=911) | UA (n=152) | NSTEMI (n=224) | STEMI (n=535) | *P* |
|---|---|---|---|---|---|
| Age, years | 46.0 (42.0–48.7) | 46.5 (43.0–48.1) | 46.0 (41.6–48.7) | 46.0 (42.0–48.7) | 0.739 |
| Sex, n (%) | | | | | 0.031 |
| Female | 138 (15%) | 29 (19%) | 42 (19%) | 67 (13%) | |
| Male | 773 (85%) | 123 (81%) | 182 (81%) | 468 (87%) | |
| Smoking, n (%) | 616 (68%) | 94 (62%) | 150 (67%) | 372 (70%) | 0.199 |
| Diabetes mellitus, n (%) | 157 (17%) | 38 (25%) | 41 (18%) | 78 (15%) | 0.010 |
| Hypertension, n (%) | 279 (31%) | 62 (41%) | 75 (33%) | 142 (27%) | 0.002 |
| Prior hyperlipidemia history, n (%) | 351 (39%) | 54 (36%) | 89 (40%) | 208 (39%) | 0.690 |
| LDL-C, mg/dL | 119 (94–146) | 115 (91–147) | 119 (94–146) | 120 (95–146) | 0.715 |
| HDL-C, mg/dL | 37 (32–43) | 37 (33–44) | 36 (31–43) | 37 (32–43) | 0.102 |
| Triglycerides, mg/dL | 156 (110–220) | 174 (107–249) | 161 (114–219) | 150 (109–213) | 0.130 |
| Total cholesterol, mg/dL | 191 (160–224) | 190 (154–233) | 195 (160–223) | 191 (161–223) | 0.966 |
| Non-HDL-C, mg/dL | 154 (123–185) | 154 (116–192) | 157 (125–185) | 153 (125–183) | 0.900 |
| Remnant-C, mg/dL | 31 (22–44) | 35 (21–49) | 32 (23–44) | 30 (22–42) | 0.129 |
| TG/HDL-C ratio | 4.1 (2.9–6.2) | 4.5 (2.6–7.1) | 4.4 (3.2–6.5) | 4.0 (2.9–5.8) | 0.144 |
| AIP | 0.26 (0.11–0.44) | 0.29 (0.06–0.49) | 0.28 (0.14–0.45) | 0.25 (0.11–0.41) | 0.144 |
| LVEF, % | 53 (45–60) | 60 (55–60) | 55 (45–60) | 50 (43–55) | <0.001 |
| CRP, mg/L | 3 (0–8) | 3 (0–6) | 3 (0–12) | 3 (1–8) | 0.082 |
| Creatinine, mg/dL | 0.90 (0.80–1.06) | 0.89 (0.77–1.04) | 0.85 (0.78–1.00) | 0.93 (0.82–1.08) | <0.001 |
| Hemoglobin, g/dL | 14.60 (13.60–15.60) | 14.50 (13.45–15.25) | 14.40 (13.30–15.50) | 14.80 (13.70–15.80) | 0.002 |
| Revascularization strategy, n (%) | | | | | <0.001 |
| PCI | 664 (73%) | 59 (39%) | 135 (60%) | 470 (88%) | |
| Surgery/CABG | 70 (7.7%) | 16 (11%) | 37 (17%) | 17 (3.2%) | |
| Medical | 177 (19%) | 77 (51%) | 52 (23%) | 48 (9.0%) | |

Values are presented as median (interquartile range) or n (%), as appropriate. Between-group comparisons were performed using the Kruskal–Wallis test for continuous variables and Pearson's chi-square test for categorical variables. Because AIP is a monotonic logarithmic transformation derived from the TG/HDL-C ratio, rank-based comparisons of AIP and TG/HDL-C yield identical p-values. ACS indicates acute coronary syndrome; AIP, atherogenic index of plasma; CABG, coronary artery bypass grafting; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; Remnant-C, remnant cholesterol; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides; TG/HDL-C, triglyceride-to-high-density lipoprotein cholesterol ratio; and UA, unstable angina.

silhouette width (0.463) and the highest Calinski–Harabasz index (695.1). Its Davies–Bouldin index was also low (0.912), although marginally lower values were observed in some more granular high-k solutions. As expected, the total within-cluster sum of squares decreased progressively with increasing k; however, this improvement was accompanied by lower silhouette and Calinski–Harabasz values and increasingly fragmented classifications. On this basis, k=2 was retained as the most parsimonious primary representation of the observed lipid-derived structure.

The primary two-cluster solution classified 673 patients (73.9%) into a lower atherogenic pattern and 238 patients (26.1%) into a high atherogenic pattern. By construction, the high atherogenic pattern was characterized by higher standardized values of non-HDL-C, remnant cholesterol, TG/HDL-C ratio, and AIP. It also showed higher observed LDL-C, triglyceride, and total cholesterol levels and lower HDL-C levels than the lower atherogenic pattern (Table 2 and Figure 2).

The exploratory k=3 sensitivity analysis separated the cohort into low (n=506), intermediate (n=359), and very high atherogenic groups (n=46) (Supplementary Table 5). The overall distribution of STEMI presentation did not differ significantly across the three clusters (Pearson's chi-square test, P = 0.100). Although the intermediate cluster showed a nominally lower adjusted odds of STEMI compared with the low atherogenic cluster (adjusted OR, 0.74; 95% CI, 0.55–0.99; P = 0.040), this subgroup comparison was exploratory, was not adjusted for multiple comparisons, and occurred in the absence of a significant overall cluster association. In addition, the smallest cluster included only 46 patients, and cross-tabulation showed that the k=3 solution mainly subdivided the primary high atherogenic pattern rather than identifying a clearly distinct additional pattern. The two-cluster solution was therefore retained as the primary classification.

### Clinical Characteristics According to Lipid-Derived Phenotypic Patterns

Compared with the lower atherogenic pattern, the high atherogenic pattern had higher frequencies of diabetes mellitus (22.7% vs. 15.3%; P = 0.010), hypertension (38.7% vs. 27.8%; P = 0.002), and prior hyperlipidemia history (50.4% vs. 34.3%; P < 0.001) (Table 2). Age, sex, smoking status, LVEF, C-reactive protein, and creatinine levels were broadly similar between the two patterns (Table 2). In the overall analytic cohort, TG ≥400 mg/dL and TG ≥500 mg/dL were present in 39 patients (4.3%) and 22 patients (2.4%), respectively; all patients with TG ≥400 mg/dL belonged to the high atherogenic pattern.

Index premature ACS presentation differed between the two lipid-derived patterns (P = 0.021) (Table 2 and Figure 3). STEMI was less frequent in the high atherogenic pattern than in the lower atherogenic pattern (51.7% vs. 61.2%), whereas UA and NSTEMI were numerically more frequent in the high atherogenic pattern (Table 2 and Figure 3). Revascularization strategy also differed between the two patterns (P = 0.013), with a higher proportion of surgical revascularization in the high atherogenic pattern (Table 2). Prior medication use and discharge medical therapy were broadly similar between the two lipid-derived

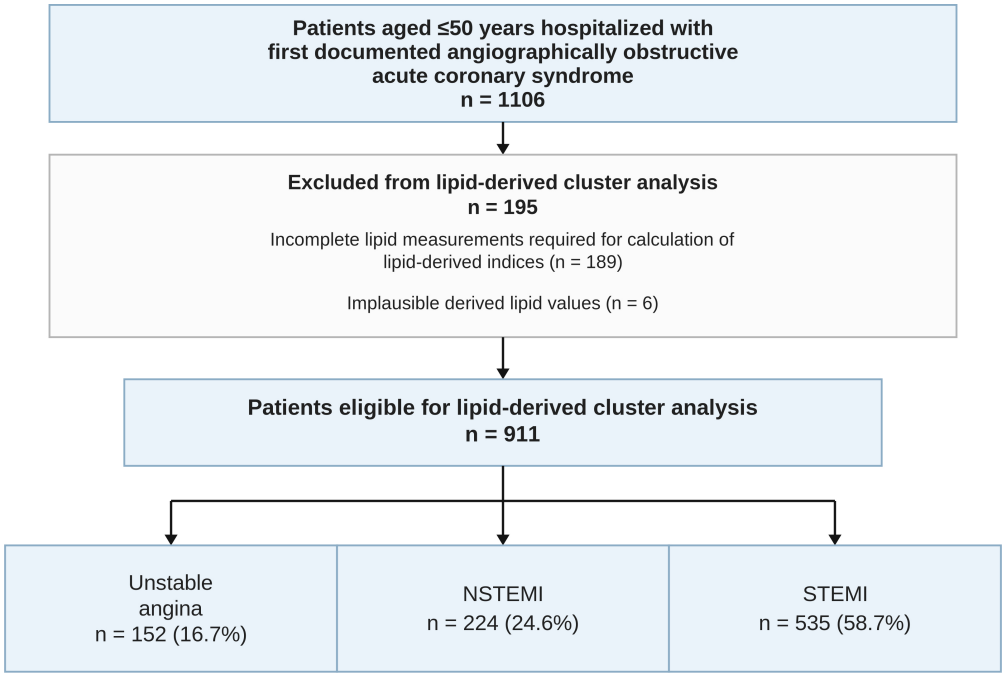



**Figure 1.** Study flow diagram.

Among 1106 screened records of patients aged ≤50 years hospitalized with first documented angiographically obstructive acute coronary syndrome, 195 were excluded because lipid measurements required for the calculation of lipid-derived indices were incomplete or because derived lipid values were implausible. The final analytic cohort included 911 patients eligible for lipid-derived cluster analysis. Patients with previously documented coronary artery disease, prior myocardial infarction, prior PCI or CABG, or chronic coronary syndrome were excluded. Patients with clinically identified MINOCA, spontaneous coronary artery dissection, type 2 myocardial infarction, myocarditis, Takotsubo syndrome, coronary embolism, vasospastic angina, or another non-atherosclerotic cause were also excluded from the obstructive premature ACS cohort.

phenotypic patterns, including prior statin use and discharge statin prescription (Supplementary Tables 8 and 9).

### Association with STEMI Presentation

STEMI presentation was less frequent in the high atherogenic pattern than in the lower atherogenic pattern (123/238 [51.7%] vs. 412/673 [61.2%]; Pearson's chi-square test, P = 0.010) (Figure 3). In logistic regression, membership in the high atherogenic pattern was associated with lower odds of STEMI presentation in the crude model (OR, 0.68; 95% CI, 0.50–0.91; P = 0.010) (Table 3). This association remained significant after adjustment for age, sex, diabetes mellitus, hypertension, smoking, prior hyperlipidemia history, and serum creatinine (adjusted OR, 0.69; 95% CI, 0.50–0.93; P = 0.016) (Table 3).

In a sensitivity analysis restricted to patients with myocardial infarction only after excluding UA, the direction of association was similar: STEMI presentation remained numerically less frequent in the high atherogenic pattern than in the lower atherogenic pattern (65.8% vs. 72.0%; Pearson's chi-square test, P = 0.104), although the adjusted association was attenuated and did not reach statistical significance (adjusted OR, 0.78; 95% CI, 0.54–1.13; P = 0.181) (Supplementary Table 10).

### Correlation and Sensitivity Analyses

Correlation analysis confirmed substantial interdependence among several lipid-derived clustering variables (Supplementary Table 2 and Supplementary Figure 2). The strongest correlation was observed between the TG/HDL-C ratio and AIP (Spearman rho=1.000), consistent with the derivation of AIP from the TG/HDL-C ratio (Supplementary Table 2 and Supplementary Figure 2). Remnant cholesterol was also strongly correlated with the TG/HDL-C ratio and AIP (rho=0.891 for both), whereas non-HDL-C showed moderate correlation with remnant cholesterol (rho=0.502) and weaker correlations with the TG/HDL-C ratio and AIP (rho=0.365 for both) (Supplementary Table 2 and Supplementary Figure 2).

Sensitivity clustering analyses supported the robustness of the primary classification after exclusion of mathematically related indices (Supplementary Table 4). After excluding AIP, 880 of 911 patients (96.6%) were assigned to the corresponding original lipid-derived pattern, with a Cohen's kappa of 0.911. Membership in the high atherogenic pattern remained associated with lower odds of STEMI presentation after multivariable adjustment (adjusted OR, 0.66; 95% CI, 0.48–0.91; P = 0.010). Similarly, after excluding the TG/HDL-C ratio, agreement with the original classification remained high (847/911 [93.0%]; Cohen's kappa=0.831), and the association with lower odds of STEMI presentation persisted (adjusted OR, 0.67; 95% CI, 0.50–0.91; P = 0.009) (Supplementary Table 4).

### Follow-up and Longitudinal Outcomes

During a median clinical follow-up of 1370 days (IQR, 706–1991), 228 patients (25.0%) experienced the composite cardiovascular/cerebrovascular endpoint (Supplementary Table 6). The individual components observed during follow-up were all-cause mortality in 28 patients (3.1%), recurrent myocardial infarction in 130 (14.3%), recurrent cerebrovascular events in 10 (1.1%), heart failure hospitalization in 7 (0.8%), and recurrent revascularization in 187 (20.5%) (Supplementary Table 6).

The composite endpoint occurred in 160 of 673 patients (23.8%) in the lower atherogenic pattern and in 68 of 238 patients (28.6%) in the high atherogenic pattern (Supplementary Table 6). This unadjusted difference was not statistically significant (Pearson's chi-square test, P = 0.142). Kaplan–Meier analysis showed no significant difference in event-free survival between the two lipid-derived patterns (log-rank P = 0.31) (Figure 4).

In Cox regression analyses, the high atherogenic pattern was not significantly associated with the composite endpoint in the crude model (HR, 1.16; 95% CI, 0.87–1.54; P = 0.313), the multivariable model adjusted for age, sex, diabetes mellitus, hypertension, smoking, and prior hyperlipidemia history (HR, 1.11; 95% CI, 0.83–1.48; P = 0.496), or the model additionally adjusted for STEMI presentation (HR, 1.09; 95% CI, 0.81–1.46; P = 0.566) (Table 3). The proportional hazards assumption was not violated globally in the Cox models, including the crude model (global Schoenfeld P = 0.759), the multivariable model (global Schoenfeld P = 0.509), and the STEMI-adjusted model (global Schoenfeld P = 0.505).

## Discussion

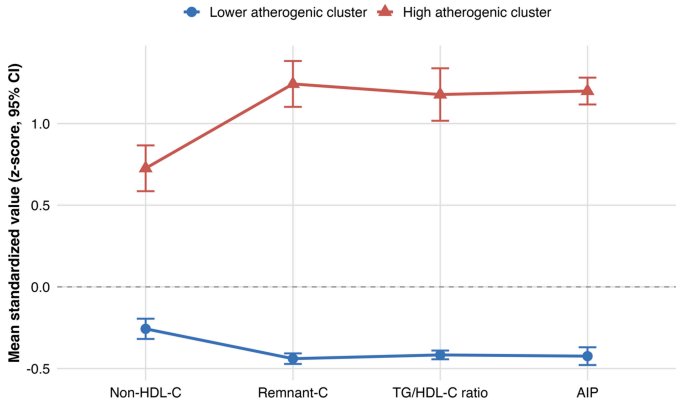



**Figure 2.** Standardized lipid-derived phenotypic patterns according to the primary two-cluster solution.

Mean z-scores with 95% confidence intervals are shown for the lipid-derived clustering variables in the lower and high atherogenic patterns. The high atherogenic pattern showed higher standardized values of non-HDL-C, remnant cholesterol, TG/HDL-C ratio, and AIP.

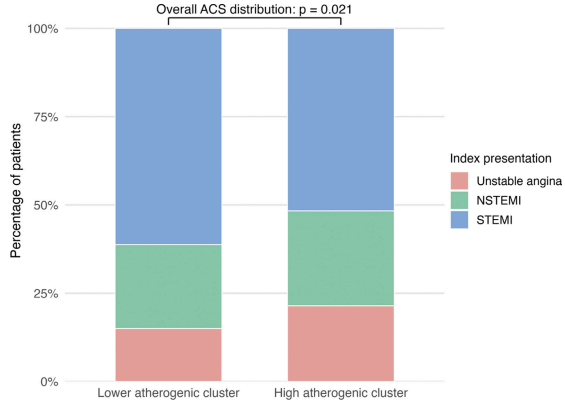



**Figure 3.** Index premature ACS presentation according to lipid-derived phenotypic patterns.

The distribution of unstable angina, NSTEMI, and STEMI differed between the lower and high atherogenic patterns (overall P = 0.021). STEMI presentation was less frequent in the high atherogenic pattern than in the lower atherogenic pattern (51.7% vs. 61.2%; Pearson's chi-square test, P = 0.010).

In this single-center cohort of patients with premature ACS, cluster-based analysis of routinely available lipid-derived indices identified two patterns with distinct measured lipid profiles. The high atherogenic pattern was characterized by higher LDL-C, triglycerides, total cholesterol, non-HDL-C, remnant cholesterol, TG/HDL-C ratio, and AIP values, together with lower HDL-C levels and a greater burden of conventional cardiovascular risk factors. Despite this more adverse lipid profile, STEMI presentation was 9.5 percentage points less frequent in the high atherogenic pattern than in the lower atherogenic pattern (51.7% vs. 61.2%), and this association remained significant after adjustment for age, sex, diabetes mellitus, hypertension, current/recent smoking, prior hyperlipidemia history, and serum creatinine. In contrast, the high atherogenic pattern was not independently associated with the composite cardiovascular/cerebrovascular endpoint during follow-up.

The demographic and clinical profile of our cohort was broadly consistent with previous young MI and ACS series. In the Partners YOUNG-MI Registry, which included 1,475 patients aged ≤50 years with a first MI who were not receiving statin therapy before the event, 57.4% presented with STEMI, 16.7% had diabetes, 44.0% had hypertension, and 52.3% were current smokers.[13] The corresponding proportions in our premature ACS cohort were 58.7%, 17.2%, 30.6%, and 67.7%, respectively. Similarly, among 1,182 patients aged ≤45 years in the ISACS-TC registry, 68.0% presented with STEMI, 61.2% were current smokers, 44.2% had hypertension, 38.6% had hypercholesterolemia, and 9.9% had diabetes.[14] Thus, the STEMI and diabetes frequencies in our cohort were similar to those reported in the YOUNG-MI Registry, whereas smoking was more prevalent and hypertension was less prevalent. These differences may reflect variations in age thresholds, geographic and population characteristics, inclusion of UA, and our restriction to first documented obstructive premature ACS.

The overall lipid profile of our cohort also closely resembled that reported in the Partners YOUNG-MI Registry. In that registry, mean total cholesterol, LDL-C, and HDL-C concentrations were 191.3, 118.4, and 37.0 mg/dL, respectively, and the median triglyceride concentration was 145 mg/dL.[13] In our cohort, the corresponding median values were 191, 119, 37, and 156 mg/dL.

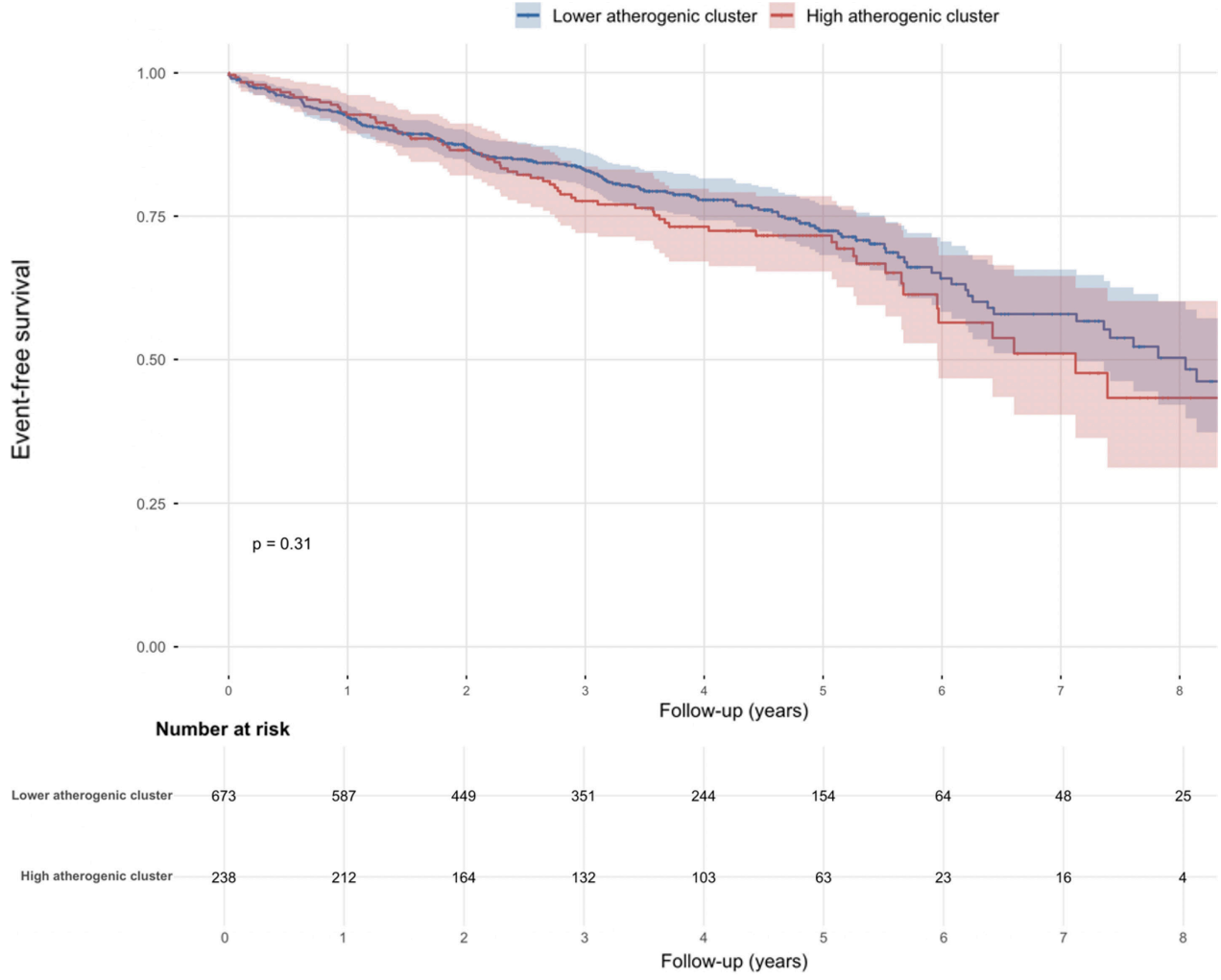



**Figure 4.** Kaplan–Meier curves for the composite cardiovascular/cerebrovascular endpoint according to lipid-derived phenotypic patterns.

Event-free survival did not differ significantly between the two lipid-derived patterns in unadjusted analysis (log-rank P = 0.31), and the high atherogenic pattern was not independently associated with the composite endpoint in multivariable Cox models.

This similarity supports the relevance of a triglyceride-rich, low-HDL lipid pattern in premature coronary disease rather than an exclusively LDL-C-dominant phenotype. Remnant cholesterol had a median value of 31 mg/dL in our cohort and reached 58 mg/dL in the high atherogenic pattern. For comparison, a study of 7,479 unselected patients admitted with ACS reported a median remnant cholesterol concentration of 28 mg/dL, with 45.9% of patients having concentrations ≥30 mg/dL.[15] In a multicenter case-control study of patients aged ≤40 years, mean remnant cholesterol was 61.1 mg/dL in premature MI survivors compared with 35.8 mg/dL in controls, and remnant cholesterol was independently associated with premature MI.[16] Although these values are not directly interchangeable because of differences in study design, age criteria, summary measures, and timing of lipid sampling, they place the high atherogenic pattern identified in our study within a clinically substantial triglyceride-rich remnant lipoprotein spectrum.

The present findings are also relevant to lipid and premature coronary disease patterns reported in Türkiye. In a multicenter study of 1,210 Turkish patients with STEMI, 80% of patients were male, and smoking was the most prevalent risk factor among younger patients.[17] The marked male predominance (84.9%) and high prevalence of current or recent smoking (67.7%) in our cohort are consistent with this national pattern. In the prospective Turkish Adult Risk Factor study, AIP was associated with non-HDL-C, apolipoprotein B, obesity, insulin-related metabolic abnormalities, and subsequent coronary events, supporting its interpretation as a marker of an integrated triglyceride-rich metabolic profile rather than an isolated lipid ratio.[6] Turkish studies published in the Archives of the Turkish Society of Cardiology have also highlighted the need for systematic identification of familial hypercholesterolemia and the substantial problem of undiagnosed or undertreated disease.[18,19] The national A-HIT registries subsequently demonstrated low awareness and poor LDL-C target attainment among Turkish patients with clinically diagnosed

**Table 2.** Baseline clinical, lipid, laboratory, and procedural characteristics according to lipid-derived phenotypic patterns

| Characteristic | Overall (n=911) | Lower atherogenic pattern (n=673) | High atherogenic pattern (n=238) | *P* |
|---|---|---|---|---|
| Age, years | 46.0 (42.0–48.7) | 46.0 (42.0–48.7) | 46.0 (42.0–48.1) | 0.587 |
| Sex, n (%) | | | | 0.394 |
| Female | 138 (15%) | 106 (16%) | 32 (13%) | |
| Male | 773 (85%) | 567 (84%) | 206 (87%) | |
| Smoking, n (%) | 616 (68%) | 447 (67%) | 169 (71%) | 0.203 |
| Diabetes mellitus, n (%) | 157 (17%) | 103 (15%) | 54 (23%) | 0.010 |
| Hypertension, n (%) | 279 (31%) | 187 (28%) | 92 (39%) | 0.002 |
| Prior hyperlipidemia history, n (%) | 351 (39%) | 231 (34%) | 120 (50%) | <0.001 |
| Index premature ACS presentation, n (%) | | | | 0.021 |
| Unstable angina | 152 (17%) | 101 (15%) | 51 (21%) | |
| NSTEMI | 224 (25%) | 160 (24%) | 64 (27%) | |
| STEMI | 535 (59%) | 412 (61%) | 123 (52%) | |
| LDL-C, mg/dL | 119 (94–146) | 116 (92–143) | 131 (101–154) | <0.001 |
| HDL-C, mg/dL | 37 (32–43) | 38 (33–44) | 33 (29–39) | <0.001 |
| Triglycerides, mg/dL | 156 (110–220) | 132 (100–165) | 291 (242–352) | <0.001 |
| Total cholesterol, mg/dL | 191 (160–224) | 181 (153–211) | 224 (194–247) | <0.001 |
| Non-HDL-C, mg/dL | 154 (123–185) | 143 (115–171) | 188 (162–213) | <0.001 |
| Remnant-C, mg/dL | 31 (22–44) | 26 (20–33) | 58 (48–68) | <0.001 |
| TG/HDL-C ratio | 4.1 (2.9–6.2) | 3.5 (2.5–4.6) | 8.3 (6.9–11.0) | <0.001 |
| AIP | 0.26 (0.11–0.44) | 0.19 (0.04–0.30) | 0.56 (0.48–0.68) | <0.001 |
| LVEF, % | 53 (45–60) | 53 (45–60) | 50 (45–60) | 0.660 |
| CRP, mg/L | 3 (0–8) | 3 (1–8) | 3 (0–8) | 0.333 |
| Creatinine, mg/dL | 0.90 (0.80–1.06) | 0.90 (0.80–1.06) | 0.89 (0.80–1.05) | 0.486 |
| Hemoglobin, g/dL | 14.60 (13.60–15.60) | 14.50 (13.50–15.60) | 14.75 (13.80–15.70) | 0.060 |
| Revascularization strategy, n (%) | | | | 0.013 |
| PCI | 664 (73%) | 489 (73%) | 175 (74%) | |
| Surgery/CABG | 70 (7.7%) | 43 (6.4%) | 27 (11%) | |
| Medical | 177 (19%) | 141 (21%) | 36 (15%) | |

Values are presented as median (interquartile range) or n (%), as appropriate. Between-group comparisons were performed using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-square test for categorical variables. The phenotypic pattern labels describe the relative lipid-derived profiles identified by the primary two-cluster solution and should not be interpreted as definitive biological entities. ACS indicates acute coronary syndrome; AIP, atherogenic index of plasma; CABG, coronary artery bypass grafting; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; Remnant-C, remnant cholesterol; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides; TG/HDL-C, triglyceride-to-high-density lipoprotein cholesterol ratio; and UA, unstable angina. In the overall analytic cohort, TG concentrations ≥400 mg/dL and ≥500 mg/dL were observed in 39 patients (4.3%) and 22 patients (2.4%), respectively. In the high atherogenic pattern, the corresponding proportions were 39/238 (16.4%) and 22/238 (9.2%), whereas no patient in the lower atherogenic pattern had a TG concentration ≥400 mg/dL.

familial hypercholesterolemia.[20] These observations reinforce that routine calculated lipid indices may help describe the metabolic burden of premature ACS but cannot replace standardized assessment of family history, familial hypercholesterolemia probability, lipoprotein(a), apolipoprotein B, and other inherited or secondary causes of premature coronary disease.

These comparative findings provide clinical context for the observed lipid profiles but do not establish discrete mechanistic subtypes. The present clustering framework was exploratory and was intended to summarize correlated lipid-derived features rather than determine causality or develop a clinical prediction tool.

The inverse association between the high atherogenic pattern and STEMI presentation should be interpreted cautiously. The first consideration is the timing of lipid measurement in relation to the acute ischemic event. Although fasting samples were obtained on the first morning after admission, the interval from symptom onset to blood sampling was not consistently available. Acute-phase changes following ACS may reduce measured total cholesterol, LDL-C, and HDL-C concentrations and may also alter triglyceride-related indices.[21] If these changes were more pronounced in patients with STEMI or a greater myocardial injury burden, some patients with a higher premorbid atherogenic lipid burden may have been assigned to the lower atherogenic pattern based on their post-event measurements. In the present cohort, median LVEF was 50% in patients with STEMI, compared with 55% in those with NSTEMI and 60% in those with UA, a pattern compatible with a greater functional impact of the index event, although infarct size and serial lipid measurements were not available. Accordingly, the lower proportion of STEMI in the high atherogenic pattern should not be interpreted as evidence that a more adverse lipid profile protects against STEMI.

Beyond potential acute-phase effects, the clinical manifestation of ACS is determined not only by chronic lipid burden but also by acute lesion biology and the thrombotic response. Plaque rupture, plaque erosion, thrombus burden, culprit lesion location, vasomotor tone, collateral circulation, inflammatory activation, and the timing of presentation may influence whether an event manifests as STEMI, NSTEMI, or UA.[1,22-24] In younger patients, smoking-related thrombosis, plaque erosion, or other acute non-lipid-dominant mechanisms may contribute to STEMI presentation even in the absence of an extreme measured atherogenic lipid profile. Conversely, the high atherogenic pattern in our cohort was associated with higher prevalences of diabetes mellitus (22.7% vs. 15.3%), hypertension (38.7% vs. 27.8%), and prior hyperlipidemia history (50.4% vs. 34.3%), together with a higher frequency of CABG (11.3% vs. 6.4%). This combination may be compatible with a more established metabolic and potentially diffuse coronary disease phenotype presenting more frequently with non-ST-elevation ACS. However, the extent and distribution of coronary atherosclerosis, plaque morphology, thrombus characteristics, and culprit lesion mechanisms were not systematically quantified; therefore, neither diffuse disease nor a specific plaque mechanism can be inferred from the present data.

The MI-only sensitivity analysis provides an additional reason for caution. After patients with UA were excluded, STEMI remained numerically less frequent in the high atherogenic pattern than in the lower atherogenic pattern (65.8% vs. 72.0%), but the association was attenuated and was no longer statistically significant after multivariable adjustment (adjusted OR, 0.78; 95% CI, 0.54–1.13; P = 0.181). This attenuation suggests that the inclusion and differential distribution of UA contributed, at least in part, to the association observed in the full premature ACS cohort. The primary finding should therefore be interpreted as a cross-sectional presentation pattern across the broader premature ACS spectrum rather than as a definitive MI-specific, mechanistic, or causal association. Prospective studies incorporating pre-event or very early serial lipid measurements, standardized symptom-to-sampling intervals, detailed angiographic characterization, and intracoronary plaque imaging are required to clarify this observation.

The mathematical interdependence of the lipid-derived indices is an important consideration when interpreting the clustering results. The TG/HDL-C ratio and AIP had identical rank ordering, as expected because AIP represents a logarithmic transformation of a ratio derived from the same underlying triglyceride and HDL-C measurements.[7] Remnant cholesterol was also strongly correlated with these indices. Therefore, we quantified the correlations explicitly and repeated the clustering after excluding AIP and, separately, the TG/HDL-C ratio. Agreement with the primary classification remained high, and the direction of the association with STEMI presentation was preserved. Together with the internal clustering metrics and the exploratory k=3 analysis, these findings support the use of k=2 as a concise representation of the observed lipid-metabolic spectrum. Nevertheless, the resulting groups should be interpreted as positions along a continuum of atherogenic lipid profiles rather than as independent biological entities. In addition, although clustering stability was assessed through internal metrics and sensitivity analyses, uncertainty related to individual cluster assignment was not propagated into downstream regression models.

**Table 3.** Association of the high atherogenic pattern with STEMI presentation and the longitudinal composite cardiovascular/cerebrovascular endpoint

| Outcome | Model | Effect estimate | *P* |
|---|---|---|---|
| STEMI presentation | Crude logistic regression | OR, 0.68 (95% CI, 0.50–0.91) | 0.010 |
| STEMI presentation | Multivariable logistic regression | OR, 0.69 (95% CI, 0.50–0.93) | 0.016 |
| Composite cardiovascular/cerebrovascular endpoint | Crude Cox regression | HR, 1.16 (95% CI, 0.87–1.54) | 0.313 |
| Composite cardiovascular/cerebrovascular endpoint | Multivariable Cox regression | HR, 1.11 (95% CI, 0.83–1.48) | 0.496 |
| Composite cardiovascular/cerebrovascular endpoint | Multivariable Cox regression additionally adjusted for STEMI presentation | HR, 1.09 (95% CI, 0.81–1.46) | 0.566 |

The lower atherogenic pattern was used as the reference group. Logistic regression was used to evaluate STEMI presentation, and Cox proportional hazards regression was used to evaluate the composite cardiovascular/cerebrovascular endpoint. The multivariable logistic regression model was adjusted for age, sex, diabetes mellitus, hypertension, current/recent smoking, prior hyperlipidemia history, and serum creatinine. The multivariable Cox regression model was adjusted for age, sex, diabetes mellitus, hypertension, current/recent smoking, and prior hyperlipidemia history. The additionally adjusted Cox regression model further included STEMI presentation. CI indicates confidence interval; HR, hazard ratio; OR, odds ratio; and STEMI, ST-segment elevation myocardial infarction.

The absence of an independent association between the high atherogenic pattern and the composite cardiovascular/cerebrovascular endpoint contrasts with some studies evaluating remnant cholesterol as an individual prognostic marker. In 7,479 patients with ACS, Cordero et al.[15] reported that remnant cholesterol concentrations >60 mg/dL were associated with higher long-term risks of mortality and heart failure hospitalization, although remnant cholesterol was not associated with in-hospital mortality. More recently, among 820 patients with premature ACS, a high remnant cholesterol group had a higher 3-year incidence of major adverse cardiovascular and cerebrovascular events than the low remnant cholesterol group (16.2% vs. 10.9%; adjusted HR, 1.68; 95% CI, 1.10–2.59).[25] In our study, the composite endpoint occurred in 28.6% of patients in the high atherogenic pattern and 23.8% of those in the lower atherogenic pattern, but the adjusted association was not statistically significant (HR, 1.11; 95% CI, 0.83–1.48). These findings are not necessarily contradictory. Previous studies evaluated remnant cholesterol directly or according to predefined thresholds, whereas our exposure was a multivariable cluster classification combining several mathematically related lipid-derived indices. Differences in age criteria, endpoint composition, acute-phase lipid sampling, follow-up treatment, and the high contribution of recurrent revascularization to our composite endpoint may also have influenced the results. The absence of statistical significance in the present cohort should therefore not be interpreted as evidence that triglyceride-rich or remnant-lipoprotein burden has no prognostic relevance. Rather, it indicates that this exploratory lipid-derived classification did not provide independent prognostic discrimination in our dataset.

From a clinical perspective, the present findings suggest that routinely calculated lipid-derived indices may complement, but should not replace, conventional lipid assessment in patients with premature ACS. Non-HDL-C, remnant cholesterol, TG/HDL-C ratio, and AIP may help describe a triglyceride-rich metabolic pattern that is not fully represented by LDL-C alone.[3,4,6] However, the binary pattern classification was neither developed nor externally validated as a diagnostic, therapeutic, or prognostic tool. It should not be interpreted as evidence of protection from STEMI and should not be used to determine lipid-lowering treatment intensity. Guideline-directed LDL-C reduction should remain central, whereas non-HDL-C, triglycerides, lipoprotein(a), apolipoprotein B, family history, familial hypercholesterolemia probability, and other inherited or secondary contributors may provide complementary etiologic information in premature ACS.[3,18–20] Accordingly, the present results support comprehensive lipid and etiologic assessment rather than direct clinical implementation of a cluster label. Future prospective, multicenter studies should determine whether reproducible lipid-based patterns provide information beyond established risk markers, advanced lipid measurements, plaque characterization, and longitudinal treatment data.

This study has several limitations. First, its retrospective, single-center design is subject to selection bias, residual confounding, and the limitations of routinely collected clinical data. The analysis was restricted to patients with complete and plausible lipid measurements required for clustering. Compared with included patients, excluded records differed in age, sex distribution, smoking status, ACS presentation, LVEF, serum creatinine, C-reactive protein, revascularization strategy, and all-cause mortality. Complete-case selection may therefore have resulted in underrepresentation of patients with different or potentially higher-risk clinical profiles.

Second, lipid measurements were obtained from fasting samples collected on the first morning after admission, but the exact interval between symptom onset, the acute ischemic event, and blood sampling was not consistently available. Acute-phase changes after ACS, particularly in patients with a greater myocardial injury burden, may have altered measured lipid concentrations and consequently influenced cluster assignment.[21] The inverse association between the high atherogenic pattern and STEMI presentation should therefore not be interpreted as evidence that a more adverse lipid profile protects against STEMI.

Third, although prior medication use and in-hospital or discharge treatment were reported, detailed information regarding the type, dose, intensity, duration, and adherence to pre-admission lipid-lowering therapy was not consistently available. Longitudinal information on statin intensification, ezetimibe or PCSK9 inhibitor use, treatment adherence, and achieved lipid concentrations during follow-up was also unavailable. These factors may have influenced both admission lipid profiles and subsequent clinical outcomes.

Fourth, several clinically relevant determinants of premature ACS were not systematically captured. These included lipoprotein(a), apolipoprotein B, body mass index and obesity measures, family history of premature coronary artery disease, clinical probability or genetic confirmation of familial hypercholesterolemia or familial combined hyperlipidemia, thrombophilia testing, immune-inflammatory disorders, substance use, and female-specific risk factors such as pregnancy-related complications, premature menopause, and hormonal exposures. Although patients with clinically identified MINOCA, SCAD, type 2 myocardial infarction, coronary embolism, vasospastic angina, myocarditis, Takotsubo syndrome, and other recognized non-atherosclerotic causes were not included, the study did not capture whether a standardized and comprehensive etiologic workup for premature ACS had been performed in every patient. Unrecognized inherited, thrombotic, inflammatory, toxic, or female-specific contributors therefore cannot be excluded.

Fifth, the clustering variables were calculated from a limited set of routine lipid measurements and were mathematically interdependent. Although this issue was addressed through correlation analyses and sensitivity clustering after removal of AIP or the TG/HDL-C ratio, the resulting groups should be regarded as lipid-derived phenotypic patterns along a shared atherogenic spectrum rather than independent biological entities. The study did not include apolipoprotein measurements, lipid particle characterization, genetic data, intracoronary plaque imaging, or external validation.

Finally, the longitudinal analysis may have been affected by unmeasured post-index determinants, including completeness of revascularization, serial left ventricular function, renal function, medication intensity and adherence, achieved lipid control, lifestyle modification, and subsequent clinical surveillance. Some of these variables may represent consequences of the index event or subsequent management decisions; including them indiscriminately in the primary models could also have introduced overadjustment.

Accordingly, the longitudinal findings should be interpreted as exploratory and should not be used to define prognostic risk strata.

## Conclusion

In patients with premature ACS, lipid-derived clustering identified two phenotypic patterns along an atherogenic lipid-metabolic spectrum. The high atherogenic pattern was associated with a lower likelihood of STEMI presentation, although this association was attenuated and no longer statistically significant in the MI-only sensitivity analysis. The lipid-derived classification was not independently associated with the composite cardiovascular/cerebrovascular endpoint during follow-up. These exploratory patterns should not be interpreted as definitive biological entities and require prospective external validation incorporating advanced lipid markers, familial or genetic dyslipidemia assessment, plaque characterization, and standardized longitudinal treatment data.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-70716/TKDA-70716_(0)_Supplementary_Materials.pdf

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**Informed Consent:** This retrospective study was conducted using de-identified data. Therefore, informed consent was waived by the institutional review board.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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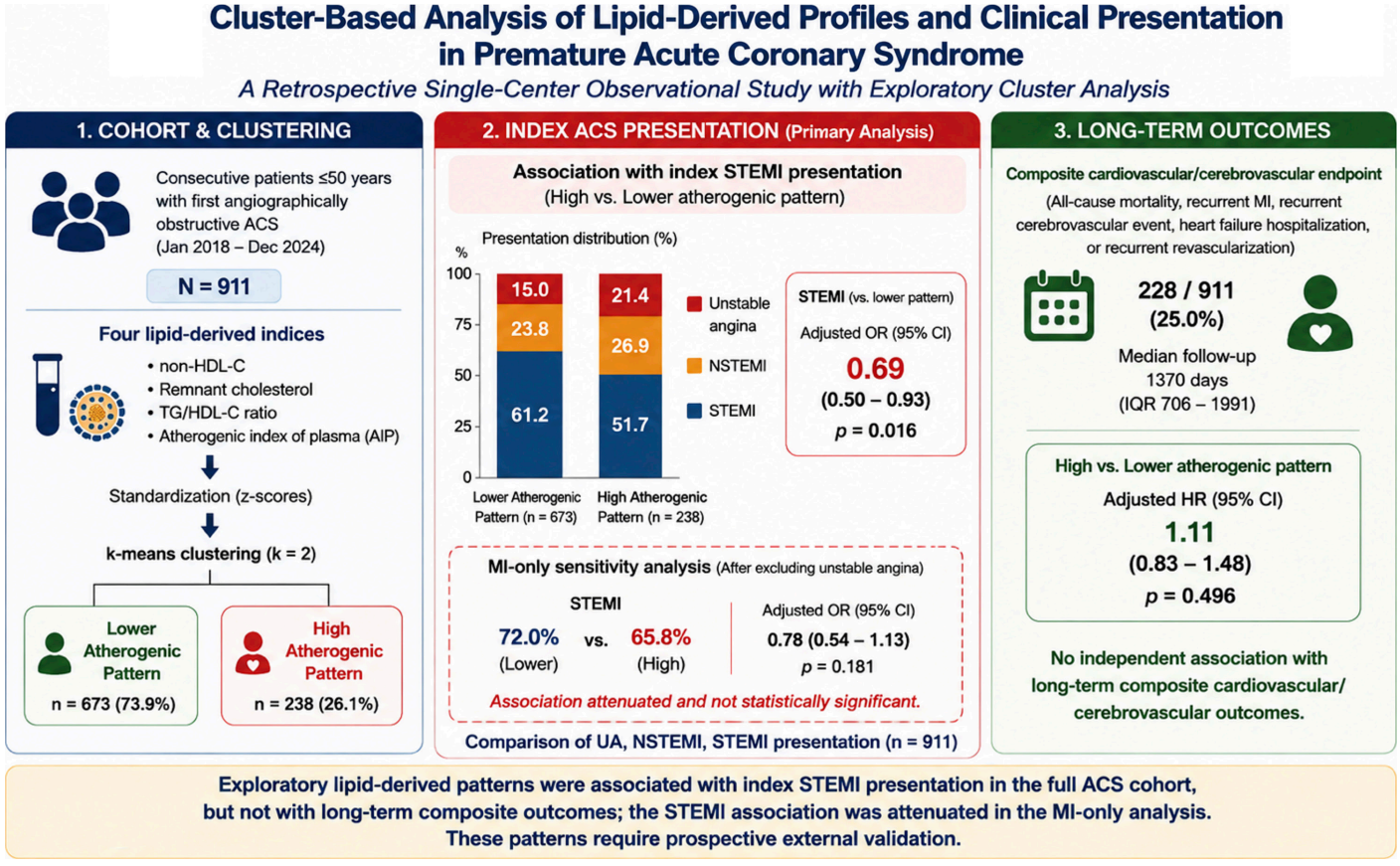
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Cluster-Based Analysis of Lipid-Derived Profiles and Clinical Presentation in Premature Acute Coronary Syndrome
A Retrospective Single-Center Observational Study with Exploratory Cluster Analysis
1. COHORT & CLUSTERING
Consecutive patients ≤50 years with first angiographically obstructive ACS (Jan 2018 – Dec 2024)
N = 911
Four lipid-derived indices
• non-HDL-C
• Remnant cholesterol
• TG/HDL-C ratio
• Atherogenic index of plasma (AIP)
Standardization (z-scores)
k-means clustering (k = 2)
Lower Atherogenic Pattern
n = 673 (73.9%)
High Atherogenic Pattern
n = 238 (26.1%)
2. INDEX ACS PRESENTATION (Primary Analysis)
Association with index STEMI presentation
(High vs. Lower atherogenic pattern)
Presentation distribution (%)
%
100
75
50
25
0
15.0
23.8
61.2
21.4
26.9
51.7
Unstable angina
NSTEMI
STEMI
Lower Atherogenic Pattern (n = 673)
High Atherogenic Pattern (n = 238)
STEMI (vs. lower pattern)
Adjusted OR (95% CI)
0.69
(0.50 – 0.93)
p = 0.016
MI-only sensitivity analysis (After excluding unstable angina)
STEMI
72.0% (Lower) vs. 65.8% (High)
Adjusted OR (95% CI)
0.78 (0.54 – 1.13)
p = 0.181
Association attenuated and not statistically significant.
Comparison of UA, NSTEMI, STEMI presentation (n = 911)
3. LONG-TERM OUTCOMES
Composite cardiovascular/cerebrovascular endpoint
(All-cause mortality, recurrent MI, recurrent cerebrovascular event, heart failure hospitalization, or recurrent revascularization)
228 / 911
(25.0%)
Median follow-up
1370 days
(IQR 706 – 1991)
High vs. Lower atherogenic pattern
Adjusted HR (95% CI)
1.11
(0.83 – 1.48)
p = 0.496
No independent association with long-term composite cardiovascular/cerebrovascular outcomes.
Exploratory lipid-derived patterns were associated with index STEMI presentation in the full ACS cohort, but not with long-term composite outcomes; the STEMI association was attenuated in the MI-only analysis. These patterns require prospective external validation.

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# Lipid-Derived Clusters in Premature Acute Coronary Syndrome: Feature Redundancy and the Choice of Comparator

## Erken Yaşta Görülen Akut Koroner Sendromda Lipid Temelli Kümeler: Değişken Tekrarlılığı ve Karşılaştırma Grubunun Seçimi

**LETTER TO THE EDITOR**
EDİTÖRE MEKTUP

To the Editor,

I read with interest the study by Çelik et al.,[1] which identified two lipid-derived clusters among 911 patients aged ≤50 years presenting with their first obstructive acute coronary syndrome (ACS). I would like to raise three points regarding the interpretation of these findings.

The first concerns the clustering variables, all four of which are derived from only three measured lipid parameters. Non-high-density lipoprotein cholesterol (non-HDL-C) is calculated by subtracting HDL-C from total cholesterol, while remnant cholesterol is calculated by additionally subtracting Sampson-estimated low-density lipoprotein cholesterol (LDL-C), which is itself derived from the same three lipid parameters. The atherogenic index of plasma (AIP) is the logarithm of the triglyceride/HDL-C ratio. The reported Spearman correlation was 1.000 between AIP and the triglyceride/HDL-C ratio and 0.891 between remnant cholesterol and each of these variables.[1] Thus, three of the four inputs largely reflect the same triglyceride-driven axis, and standardization does not eliminate the additional weight assigned to this axis in Euclidean k-means clustering.[2] The sensitivity analyses do not adequately address this issue because removing either AIP or the triglyceride/HDL-C ratio leaves the other variable in the model. In Table 2, the triglyceride interquartile ranges of the two clusters do not overlap (100–165 vs. 242–352 mg/dL), whereas the non-HDL-C ranges do (115–171 vs. 162–213 mg/dL). It would be useful to determine how closely cluster membership corresponds to a single triglyceride or triglyceride/HDL-C cutoff and whether clustering based on the three measured lipid parameters produces the same groups. Because the authors describe the clusters as positions along a continuum, a model incorporating continuous triglyceride and non-HDL-C values would be a natural comparator.

My second point concerns the dependence of the ST-segment elevation myocardial infarction (STEMI) association on the choice of comparator. For the high versus lower atherogenic cluster, I calculated an unadjusted odds ratio of 0.59 (95% confidence interval [CI], 0.40–0.88) for STEMI versus unstable angina using the counts in Table 2, compared with 0.75 (95% CI, 0.52–1.06) for STEMI versus non-ST-segment elevation myocardial infarction (NSTEMI). The latter is close to the myocardial infarction (MI)-only estimate reported by the authors (adjusted odds ratio, 0.78; 95% CI, 0.54–1.13).[1] The association therefore appears to be driven primarily by unstable angina, a diagnosis established without biomarker confirmation and included in this study only when obstructive coronary disease was demonstrated by angiography. An adjusted multinomial model would help identify which comparison accounts for the observed association.

Finally, the adjusted hazard ratio for the composite endpoint was 1.11 (95% CI, 0.83–1.48). This confidence interval is too wide to conclude that the two clusters have equivalent prognoses. Selection based on an index event can attenuate associations between risk factors and recurrent events.[3] In addition, recurrent revascularization occurred in 187 patients, whereas 228 patients experienced at least one component of the composite endpoint, and the article does not specify whether staged procedures were included. Cluster-specific results for death, myocardial infarction, and cerebrovascular events would be more informative.

Most of these analyses could be performed using the existing dataset and would help clarify whether lipid-derived clustering provides additional information beyond triglyceride levels alone.

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# Age Phenotypes, Angiographic Complexity, and Inflammatory–Metabolic Profiles in First-Presentation STEMI

## İlk Başvuru STEMI'de Yaş Fenotipleri, Anjiyografik Kompleksite ve İnflamatuvar–Metabolik Profiller

**ABSTRACT**

**Objective:** Age-based comparisons in ST-elevation myocardial infarction (STEMI) often use a binary young–older framework, which may obscure premature non-young disease. We evaluated age-group patterns in measured modifiable risk factors, angiographic complexity, inflammatory–metabolic indices, and in-hospital outcomes in patients presenting with first STEMI.

**Method:** This single-center retrospective study screened 421 STEMI records between January 2019 and May 2026. After exclusions, 150 patients were selected from an eligible pool of 229 using sex-stratified, equal-size quota sampling. The groups were defined as young STEMI (≤45 years), premature non-young STEMI (men 46–55 years, women 46–65 years), and older STEMI (men >55 years, women >65 years). Measured four-component standard modifiable cardiovascular risk factor (SMuRF) burden, angiographic findings, SYNTAX score, systemic immune-inflammation index (SII), hemoglobin–albumin–lymphocyte–platelet score (HALP), C-reactive protein/albumin ratio (CAR), mortality, and major adverse cardiovascular events (MACE) were analyzed. Two multivariable models were used to assess age group and SYNTAX score.

**Results:** Smoking prevalence decreased across groups, whereas diabetes, hypertension, hyperlipidemia, and measured four-component SMuRF burden increased with age. Thrombus was most frequently observed in young STEMI. SYNTAX score, multivessel disease, SYNTAX ≥23, SII, and CAR increased with age, whereas HALP decreased. Non-smoking SMuRF burden distinguished premature non-young STEMI and older STEMI from young STEMI; older STEMI was independently associated with a higher SYNTAX score. No significant differences in mortality or MACE were detected.

**Conclusion:** In this selected cohort, young STEMI was characterized by smoking predominance, a higher prevalence of angiographic thrombus, and lower coronary complexity, whereas older STEMI showed greater measured four-component SMuRF burden, increased coronary complexity, and less favorable inflammatory–metabolic indices. No differences were detected in in-hospital mortality or MACE.

**Keywords:** Age phenotypes, coronary angiography, inflammation, ST-elevation myocardial infarction, risk factors.

**ÖZET**

**Amaç:** ST-yükselmeli miyokard enfarktüsünde (STEMI) yaşa dayalı karşılaştırmalar sıklıkla ikili bir genç–yaşlı sınıflandırmasına dayanmakta ve prematür ancak genç olmayan hastalığı gözden kaçırabilmektedir. Bu çalışmada, ilk başvuru STEMI'de ölçülen değiştirilebilir risk faktörleri, anjiyografik kompleksite, trombüs varlığı, inflamatuvar–metabolik indeksler ve hastane içi sonuçların yaş gruplarına göre farklılıkları değerlendirildi.

**Yöntem:** Bu tek merkezli retrospektif çalışmada, Ocak 2019 ile Mayıs 2026 tarihleri arasındaki 421 STEMI kaydı tarandı. Dışlamalar sonrasında, uygun 229 hastadan oluşan kaynak havuzundan cinsiyete göre tabakalandırılmış eşit büyüklükte kota örneklemesi kullanılarak 150 hasta seçildi. Gruplar genç STEMI (≤45 yaş), prematür ancak genç olmayan STEMI (erkekler 46–55 yaş, kadınlar 46–65 yaş) ve ileri yaş STEMI (erkekler >55 yaş, kadınlar >65 yaş) olarak tanımlandı. Ölçülen dört bileşenli standart değiştirilebilir kardiyovasküler risk faktörü (SMuRF) yükü, anjiyografik bulgular, SYNTAX skoru, sistemik immün-inflamasyon indeksi (SII), hemoglobin–albümin–lenfosit–trombosit skoru (HALP), C-reaktif protein/albümin oranı (CAR), mortalite ve majör advers kardiyovasküler olaylar (MACE) analiz edildi. İki çok değişkenli model ile yaş grubu ve SYNTAX skoru değerlendirildi.

**ORIGINAL ARTICLE**
ARAŞTIRMA MAKALESİ

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**Bulgular:** Sigara kullanımı gruplar arasında azalırken diyabet, hipertansiyon, hiperlipidemi ve ölçülen dört bileşenli SMuRF yükü arttı. Trombüs varlığı en sık genç STEMI grubunda görüldü. SYNTAX skoru, çok damar hastalığı, SYNTAX ≥23, SII ve CAR yaşla birlikte artarken HALP skoru azaldı. Sigara dışı SMuRF yükü, prematür ancak genç olmayan ve ileri yaş STEMI gruplarını genç STEMI grubundan ayırırken, ileri yaş STEMI daha yüksek SYNTAX skoru ile bağımsız olarak ilişkiliydi. Mortalite veya MACE açısından anlamlı bir farklılık saptanmadı. Temel örüntüler, cinsiyetten bağımsız yaş eşikleri kullanıldığında da korundu.

**Sonuç:** Genç STEMI; sigara kullanımının baskınlığı, daha sık anjiyografik trombüs varlığı ve daha düşük koroner kompleksite ile karakterizeyken, ileri yaş STEMI daha yüksek ölçülen dört bileşenli SMuRF yükü, daha fazla koroner kompleksite ve daha olumsuz inflamatuvar–metabolik bulgular ile ilişkiliydi. Hastane içi mortalite veya MACE açısından farklılık saptanmadı.

**Anahtar Kelimeler:** Yaş fenotipleri, koroner anjiyografi, inflamasyon, ST yükselmeli miyokard enfarktüsü, risk faktörleri.

Acute myocardial infarction (AMI), one of the most serious manifestations of coronary artery disease, remains a major contributor to global cardiovascular morbidity and mortality. Despite advances in reperfusion therapy and secondary prevention, these benefits have not been equally extended to young adults. Contemporary data show that AMI-related hospitalizations have declined substantially among older adults, whereas the decrease has been more modest among younger adults, increasing their relative proportion within the AMI population.[1] AMI in early adulthood carries considerable individual and societal costs through mortality, morbidity, and loss of productive years.[2,3] Therefore, age-related differences in clinical and laboratory characteristics, particularly in first-presentation STEMI, require closer characterization.

Premature myocardial infarction is commonly defined as MI occurring at ≤55 years in men and ≤65 years in women.[4–6] In contrast, studies of "young MI" often use lower age thresholds,[3,7,8] creating substantial heterogeneity in age-based comparisons. Compared with older patients, young or premature AMI patients have a higher proportion of men and distinct cardiovascular risk profiles, as well as differences in angiographic features, including coronary anatomical complexity, culprit lesion morphology, and thrombotic characteristics.[2,3,6,7] However, most studies dichotomize patients as "young" or "older" using a single age cutoff, thereby obscuring a premature non-young intermediate group. Failure to examine this group separately limits the characterization of the clinical and angiographic transition from young to older STEMI.

Biomarkers of systemic inflammation, metabolic stress, thrombotic activity, and physiological reserve may provide an integrated view of STEMI. Routine laboratory-derived composite indices, including the systemic immune-inflammation index (SII), hemoglobin–albumin–lymphocyte–platelet (HALP) score, CRP/albumin ratio (CAR), and uric acid/HDL-C ratio, have been linked to risk stratification, coronary disease severity, and adverse outcomes in STEMI.[9–13] However, how these selected inflammatory–metabolic indices vary across STEMI age groups and their association with coronary anatomical complexity remain insufficiently defined.

Another relevant issue is the relationship between conventional risk-factor burden and coronary anatomical complexity across

## ABBREVIATIONS

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| AI | Artificial intelligence |
| AMI | Acute myocardial infarction |
| ARB | Angiotensin receptor blocker |
| CABG | Coronary artery bypass grafting |
| CAR | C-reactive protein/albumin ratio |
| CPR | Cardiopulmonary resuscitation |
| CRP | C-reactive protein |
| eGFR | Estimated glomerular filtration rate |
| HALP | Hemoglobin–albumin–lymphocyte–platelet score |
| HbA1c | Glycated hemoglobin |
| HDL-C | High-density lipoprotein cholesterol |
| hs-CRP | High-sensitivity C-reactive protein |
| IQR | Interquartile range |
| LAD | Left anterior descending coronary artery |
| LCx | Left circumflex coronary artery |
| LDL-C | Low-density lipoprotein cholesterol |
| LMCA | Left main coronary artery |
| Lp(a) | Lipoprotein(a) |
| LUCAS | Lund University Cardiopulmonary Assist System |
| LVEF | Left ventricular ejection fraction |
| MACE | Major adverse cardiovascular events |
| MI | Myocardial infarction |
| non-HDL-C | Non–high-density lipoprotein cholesterol |
| OCT | Optical coherence tomography |
| P2Y12 | Platelet P2Y12 receptor |
| PCI | Percutaneous coronary intervention |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| RCA | Right coronary artery |
| SGLT2 | Sodium–glucose cotransporter 2 |
| SII | Systemic immune-inflammation index |
| SMuRF | Standard modifiable cardiovascular risk factor |
| STEMI | ST-elevation myocardial infarction |
| SYNTAX | Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery |
| TIMI | Thrombolysis in Myocardial Infarction |
| VIRGO | Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients |

age groups. In this study, conventional risk-factor burden was assessed using the four-component standard modifiable cardiovascular risk factor (SMuRF) framework, comprising active smoking, hypertension, diabetes mellitus, and hyperlipidemia.[14–18] Because this framework does not include anthropometric measures, the resulting SMuRF burden represents measured four-component SMuRF burden and should not be interpreted as a comprehensive assessment of obesity-related or broader cardiometabolic risk. Heterogeneous findings in SMuRF-less STEMI, including early mortality despite low risk-factor burden, indicate that low conventional risk does not necessarily imply low STEMI risk.[14–18] Whereas SMuRF burden summarizes conventional risk factors, the SYNTAX score reflects the extent and complexity of coronary lesions. Therefore, an integrated assessment of these components across age groups may help characterize age-related differences in first-presentation STEMI.[7,10,12,13,19–23]

We therefore compared three prespecified groups-young STEMI, premature non-young STEMI, and older STEMI-to characterize age-related differences that may be obscured by conventional binary classification. The analysis focused on measured four-component SMuRF burden, angiographic characteristics, including thrombus presence and SYNTAX-defined anatomical complexity, selected inflammatory–metabolic indices, and in-hospital outcomes. We hypothesized that these clinical, angiographic, and laboratory characteristics would differ across the three age groups.

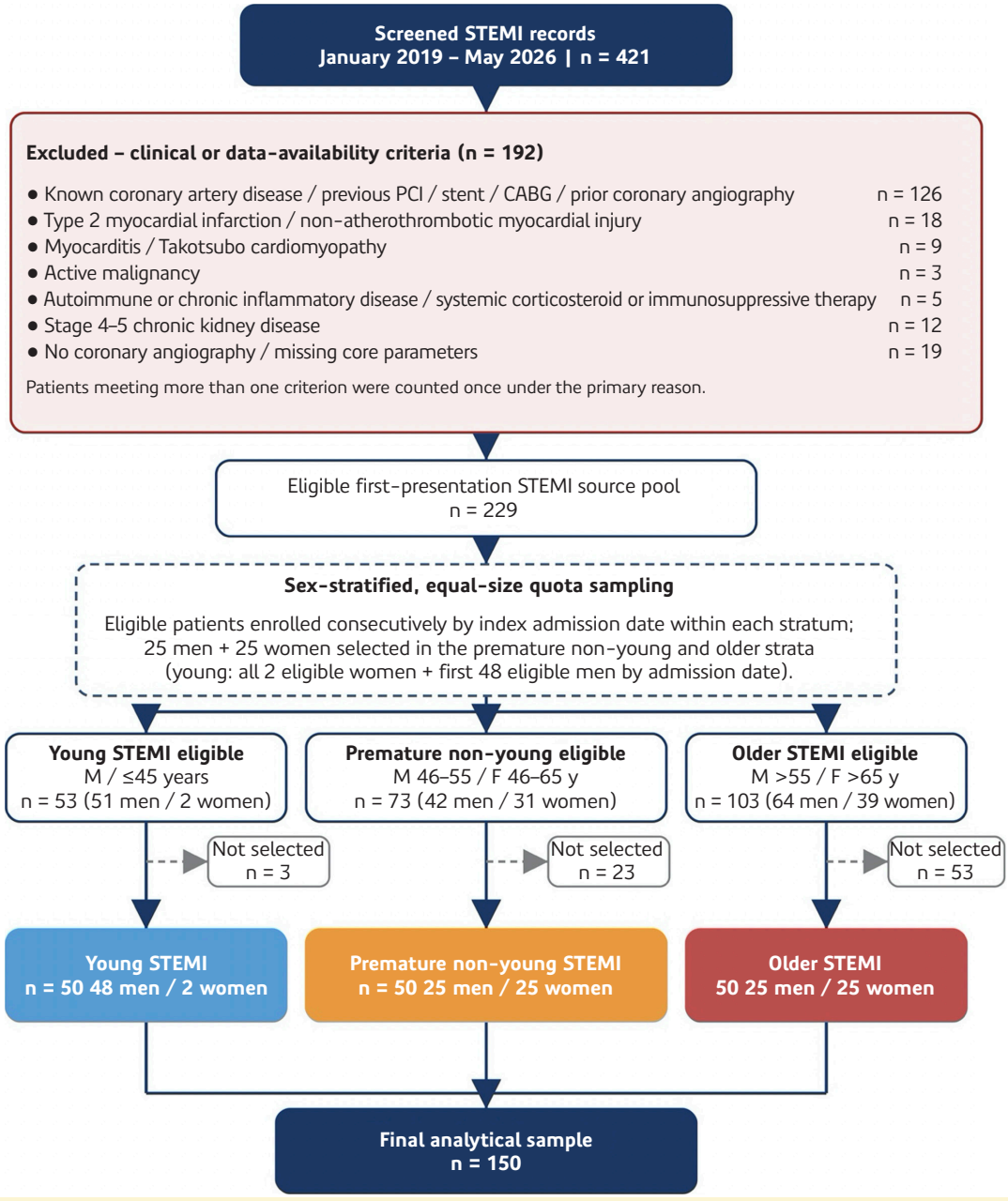



**Figure 1.** Study flow and age-phenotype classification.

CABG, Coronary artery bypass grafting; F, Female; M, Male; PCI, Percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

## Materials and Methods

### Study Design and Patient Population

This single-center, retrospective, observational study screened the medical records of patients evaluated for STEMI between January 1, 2019, and May 1, 2026. No formal sample size calculation was performed; the analytical cohort was derived from the available records according to prespecified eligibility and sampling criteria. Of the 421 STEMI records screened, 192 were excluded, yielding an eligible source pool of 229 patients with first-presentation STEMI. From this pool, 150 patients were selected for the final analysis using the prespecified age-phenotype and sex-stratified sampling procedure described below and illustrated in Figure 1.

Patients with known coronary artery disease or a history of percutaneous coronary intervention or coronary artery bypass grafting were excluded. The cohort therefore consisted of patients with first-presentation STEMI without known coronary anatomical disease. STEMI was diagnosed based on clinical, electrocardiographic, cardiac biomarker, and coronary angiographic findings. Myocardial infarction was classified according to the Fourth Universal Definition of Myocardial Infarction.[24] Additional exclusion criteria were type 2 myocardial infarction; non-atherothrombotic myocardial injury due to sepsis, severe anemia, hypoxia, tachyarrhythmia, or pulmonary embolism; myocarditis; Takotsubo cardiomyopathy; active infection; chronic inflammatory or autoimmune disease; active malignancy; stage 4–5 chronic kidney disease; systemic corticosteroid or immunosuppressive therapy; absence of coronary angiography; and unavailability of core study parameters. The number of patients excluded for each criterion is shown in Figure 1; patients meeting more than one criterion were counted once according to the primary reason for exclusion.

Given its retrospective, non-interventional design, no additional procedures or treatments were performed. Data were obtained from hospital records, laboratory results, and echocardiographic and coronary angiographic images. The study was reviewed and approved by the Bolu Abant İzzet Baysal University Non-Interventional Clinical Research Ethics Committee (Approval Number: 2026/241, Date: 20.05.2026) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was not obtained because the study was retrospective and non-interventional, used de-identified archival clinical data, and included deceased patients for whom consent could not reasonably be obtained.

### Definition of Age-Phenotype Groups

Patients were classified into three prespecified age groups using established definitions of young and premature myocardial infarction.[2–8]

1. Young STEMI: ≤45 years.
2. Premature non-young STEMI: Above the Young STEMI threshold but within premature myocardial infarction limits; men 46–55 years and women 46–65 years.
3. Older STEMI: Men >55 years and women >65 years.

This classification was used to compare clinical, angiographic, and laboratory characteristics across young, premature non-young, and older STEMI groups. After exclusions, the eligible source pool comprised 53 young, 73 premature non-young, and 103 older STEMI patients. Sex-stratified, equal-size quota sampling was applied to obtain 50 patients per group. Eligible patients were ordered by index admission date and selected consecutively within each sex stratum.

In the premature non-young and older groups, 25 men and 25 women were selected to better reflect the sex-specific premature myocardial infarction definition and allow sex-based comparisons. Because only two eligible women were available in the young group, both women and the first 48 eligible men were included (Figure 1). This imbalance was further assessed using male-only sensitivity and exploratory sex-based analyses (Supplementary Table 1). Because sex-specific thresholds may classify men and women of the same chronological age differently, we also performed a sensitivity analysis using sex-independent cutoffs of ≤45, 46–55, and >55 years (Supplementary Table 2). Accordingly, the final analytical sample was constructed to enable between-group comparisons within a selected analytical cohort; therefore, group-level frequencies should not be interpreted as population-representative prevalence estimates.

### Clinical Variables and Risk Factor Definitions

Demographic characteristics, cardiovascular risk factors, laboratory and echocardiographic findings, coronary angiographic features, treatments, and in-hospital outcomes were recorded.

Conventional risk-factor burden was assessed using the established four-component standard modifiable cardiovascular risk factor (SMuRF) framework, comprising active smoking, hypertension, diabetes mellitus, and hyperlipidemia, consistent with major contemporary SMuRF/SMuRF-less STEMI and AMI studies.[14–18]

Active smoking was defined as documented current tobacco use at the index STEMI admission. Hypertension was defined as a documented previous diagnosis, pre-admission antihypertensive treatment prescribed for hypertension, or a new diagnosis established during hospitalization based on persistently elevated blood pressure after clinical stabilization, with antihypertensive therapy initiated at discharge. Diabetes mellitus was defined as a documented previous diagnosis, pre-admission glucose-lowering therapy, or a new in-hospital diagnosis based on HbA1c ≥6.5% and/or repeated fasting plasma glucose measurements ≥126 mg/dL; admission glucose alone was not used because of the potential for stress hyperglycemia. Hyperlipidemia was defined as a documented previous diagnosis, pre-admission lipid-lowering therapy, or, in patients without either, LDL-C ≥130 mg/dL or total cholesterol ≥200 mg/dL in the earliest available fasting lipid profile obtained during hospitalization. Whether sampling preceded the first in-hospital statin dose could not be verified from the records. Triglycerides, HDL-C, and non-HDL-C were evaluated separately and were not used to define hyperlipidemia.

Anthropometric measures, including body mass index and waist circumference, were not systematically available; therefore, obesity could not be assessed separately. Accordingly, throughout this study, SMuRF burden refers to measured four-component SMuRF burden. Each SMuRF was assigned one point, yielding a total score of 0–4, categorized as 0, 1, or ≥2. Non-smoking

SMuRF burden was calculated as the sum of hypertension, diabetes mellitus, and hyperlipidemia.

**Coronary Angiographic Variables**

All patients underwent coronary angiography during the index STEMI admission. Index angiograms and procedural reports were reviewed by an experienced interventional cardiologist to record the culprit vessel, number of diseased vessels, presence of angiographic thrombus, SYNTAX score, and revascularization strategy. Infarct location was classified as anterior, inferior, or lateral. A diseased vessel was defined as a major epicardial coronary artery with ≥70% diameter stenosis; multivessel disease was defined as involvement of at least two major epicardial vessels.

Angiographic thrombus was defined as any culprit-lesion filling defect consistent with intracoronary thrombus, marked intraluminal opacity/haziness, thrombotic occlusion, contrast-retaining thrombus appearance, or procedural documentation supporting a thrombus or thrombotic lesion. Because TIMI thrombus grading was unavailable, angiographic thrombus was assessed as a binary present/absent variable rather than as a quantitative thrombus burden measure. High and low anatomical complexity were defined as SYNTAX scores ≥23 and ≤22, respectively.

**Laboratory Parameters**

Laboratory data obtained at presentation and during the index hospitalization included glucose, creatinine, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), albumin, uric acid, complete blood count parameters, total cholesterol, LDL-C, HDL-C, triglycerides, and admission and peak troponin levels. Lipid variables were obtained from the earliest available fasting lipid profile during hospitalization. Peak troponin was defined as the highest value recorded during hospitalization.

The following indices were calculated from admission laboratory values, except that lipid-based components were derived from the earliest available fasting lipid profile:

- SII = platelet count × neutrophil count / lymphocyte count
- HALP score = hemoglobin × albumin × lymphocyte count / platelet count
- CAR = CRP / albumin
- Uric acid/HDL-C ratio = serum uric acid / HDL-C
- Non-HDL-C = total cholesterol − HDL-C

**Echocardiographic Analysis and Clinical Outcomes**

Left ventricular ejection fraction was recorded from transthoracic echocardiography reports. LVEF <50% indicated impaired left ventricular systolic function, whereas LVEF ≤30% was separately assessed as marked systolic dysfunction. Clinical outcomes were assessed during the index hospitalization. In-hospital all-cause mortality and major adverse cardiovascular events (MACE) were prespecified secondary outcomes. In-hospital mortality was defined as all-cause death occurring during the index hospitalization.

MACE was defined as a per-patient composite outcome consisting of all-cause death, recurrent myocardial infarction, ischemic stroke, and recurrent (urgent, ischemia-driven target-vessel) revascularization. When more than one component occurred in the same patient, the patient was counted once in the composite outcome. Outcome data were abstracted from hospital records by the investigators. All potential MACE components were subsequently re-adjudicated by an experienced interventional cardiologist using the predefined study outcome criteria, with particular attention to distinguishing planned staged PCI from recurrent, urgent, ischemia-driven target-vessel revascularization. Planned staged PCI was excluded from the MACE composite. The adjudicator was not blinded to age-group assignment, and no independent second-adjudicator review was performed.

**Statistical Analysis**

Continuous variables are presented as mean ± standard deviation or median [interquartile range], as appropriate, and categorical variables are presented as counts and percentages. Three-group comparisons were performed using the Kruskal–Wallis test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Two-group comparisons were performed using the Mann–Whitney U test and chi-square/Fisher's exact tests.

To assess the influence of sex distribution and age-classification strategy, three additional analyses were performed: a male-only comparison across the primary age phenotypes, an exploratory comparison between women and men in the full cohort, and a sensitivity analysis using sex-independent age categories (≤45, 46–55, and >55 years). Two prespecified multivariable models were constructed:

- Model 1-Age phenotype:

Sex, active smoking, non-smoking SMuRF burden, thrombus presence, SYNTAX score, peak troponin, SII, HALP score, CRP/albumin, and uric acid/HDL were tested for associations with age phenotype. Although the groups were ordered, multinomial regression was used because the proportional odds assumption for ordinal regression was not met; Young STEMI was used as the reference category.

- Model 2-Anatomical complexity:

Age phenotype (categorical), sex, SMuRF count, peak troponin, SII, HALP score, CRP/albumin, and uric acid/HDL were tested for associations with SYNTAX score. Median quantile regression was selected because of the right-skewed distribution of the score; Young STEMI was used as the reference category, and coefficients represented estimated changes in median SYNTAX score.

Continuous variables were standardized in regression analyses, with effect sizes reported per 1-standard deviation increase. Right-skewed variables, including peak troponin, SII, and CRP/albumin ratio, were log-transformed before model entry. Multicollinearity was assessed using the variance inflation factor. All analyses used complete cases. Given the exploratory, phenotype-oriented design, no adjustment for multiple comparisons was applied. All tests were two-sided, with $P < 0.05$ indicating statistical significance. Statistical analyses were performed using Python version 3.13.5 (Python Software Foundation, Wilmington, Delaware, USA).

## Results

### Cohort Characteristics and Risk Factors

Of the 421 screened STEMI records, 192 were excluded, leaving an eligible source pool of 229 patients with first-presentation STEMI. From this pool, 150 patients were selected into three age-phenotype groups of 50 patients each (Figure 1). Mean age was 41.1 ± 4.3 years in Young STEMI, 55.0 ± 4.9 years in premature non-young STEMI, and 68.6 ± 7.5 years in older STEMI. The premature non-young and older groups each included 25 men and 25 women, whereas the Young STEMI group consisted almost entirely of men (48/50, 96%; P < 0.001). Overall, 52 patients (34.7%) were women.

Risk-factor profiles differed markedly across age groups. Smoking prevalence decreased from Young STEMI to premature non-young and older STEMI (70%, 54%, and 34%, respectively; P = 0.001), whereas diabetes mellitus (18%, 34%, and 60%), hypertension (20%, 50%, and 66%), and hyperlipidemia (8%, 28%, and 42%) increased across groups (all P < 0.001). The median measured four-component SMuRF count was 1.0, 2.0, and 2.0, respectively (P < 0.001), and the proportion of patients with SMuRF ≥2 was 22%, 60%, and 80%. Non-smoking SMuRF burden showed a similar gradient (median 0.0, 1.0, and 2.0; P <0.001) (Table 1; Figure 2).

Pre-admission and in-hospital/discharge medical therapies were generally similar across age groups, including aspirin (100%, 100%, and 96%; P = 0.13), P2Y12 inhibitors (98%, 100%, and 98%; P = 0.60), any statin therapy (100%, 96%, and 96%; P = 0.36), and high-intensity statin therapy (72%, 72%, and 84%; P = 0.27) (Table 1).

### Coronary Anatomical Complexity and Angiographic Thrombus Presence

MI location did not show a statistically significant difference across groups. Angiographic thrombus presence was highest in Young STEMI and decreased across premature non-young STEMI and older STEMI (66%, 42%, and 34%, respectively; P = 0.004). Diseased-vessel distribution also differed across age groups: single-vessel disease was present in 80% of Young STEMI, 74% of premature non-young STEMI, and 42% of older STEMI, whereas multivessel disease increased across groups (overall P < 0.001). Median SYNTAX score increased across groups (12.0, 13.0, and 18.0; P < 0.001), and high anatomical complexity (SYNTAX ≥23) was markedly more frequent in older STEMI (10%, 10%, and 42%; P < 0.001). LVEF did not show a statistically significant difference across groups (median 50% in all groups; P = 0.18), and the rates of LVEF <50% were similar (34%, 38%, and 48%; P = 0.34) (Table 2; Figure 3).

### Laboratory and Inflammatory–Metabolic Profiles

Laboratory and inflammatory–metabolic profiles also differed across groups (Table 1; Figure 4). Glucose, CRP, and peak troponin levels were higher, whereas albumin and eGFR were lower, in older STEMI. Among composite indices, SII increased progressively across groups (median 617, 854, and 1418; P < 0.001), as did CAR (0.08, 0.14, and 0.16; P = 0.005). HALP score decreased across groups (7.6, 5.7, and 3.6; P < 0.001), whereas the uric acid/HDL-C ratio did not differ between groups (0.15, 0.14, and 0.16; P = 0.70). Lipid profiles showed lower total cholesterol, triglyceride, and non-HDL-C levels in older STEMI. Median triglyceride levels were 166, 158, and 95 mg/dL (P < 0.001), and non-HDL-C levels were 166, 166, and 142 mg/dL (P = 0.005), whereas LDL-C and HDL-C levels did not differ significantly across groups.

### Clinical Outcomes: Mortality and MACE

In-hospital mortality occurred in 11 patients (7.3%), with no statistically significant difference detected across groups (6%, 8%, and 8%; P = 0.91; Table 2). Recurrent myocardial infarction (2%, 2%, and 0%; P = 0.60), recurrent urgent target-vessel revascularization (2%, 2%, and 4%; P = 0.77), and stroke (0%, 2%, and 0%; P = 0.36) were infrequent and similar across groups.

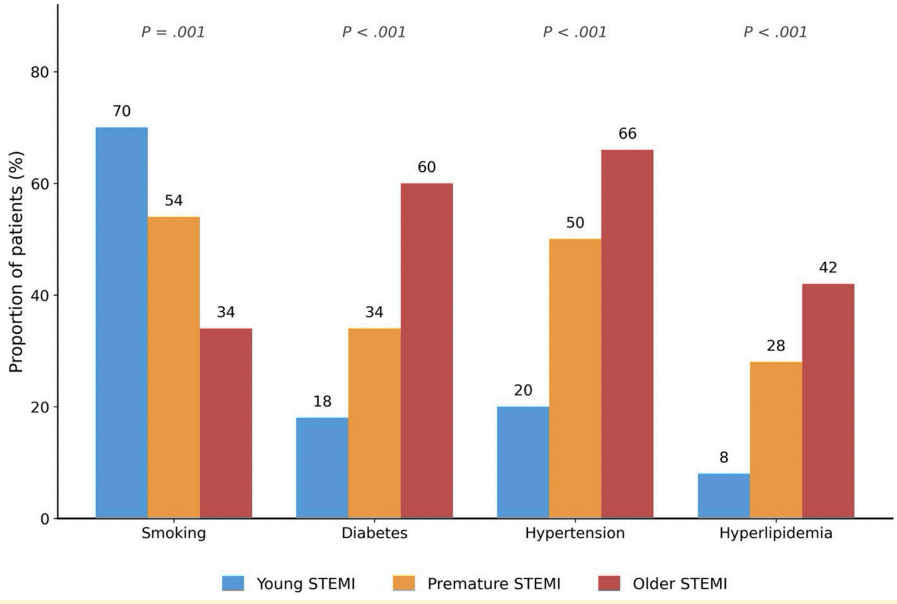



**Figure 2.** Distribution of measured conventional risk factors across age groups.

STEMI, ST-elevation myocardial infarction.

**Table 1.** Baseline characteristics by age phenotype

| Characteristic | Young STEMI (n = 50) | Premature non-young STEMI (n = 50) | Older STEMI (n = 50) | *P* |
|---|---|---|---|---|
| Demographics and risk factors | | | | |
| Age, mean ± SD, years | 41.1 ± 4.3 | 55.0 ± 4.9 | 68.6 ± 7.5 | < 0.001 |
| Male sex, n (%) | 48 (96) | 25 (50) | 25 (50) | < 0.001 |
| Smoking, n (%) | 35 (70) | 27 (54) | 17 (34) | 0.001 |
| Diabetes mellitus, n (%) | 9 (18) | 17 (34) | 30 (60) | < 0.001 |
| Hypertension, n (%) | 10 (20) | 25 (50) | 33 (66) | < 0.001 |
| Hyperlipidemia, n (%) | 4 (8) | 14 (28) | 21 (42) | < 0.001 |
| SMuRF count, median [IQR] | 1.0 [1.0–1.0] | 2.0 [1.0–2.0] | 2.0 [2.0–2.0] | < 0.001 |
| SMuRF 0, n (%) | 5 (10) | 3 (6) | 3 (6) | |
| SMuRF 1, n (%) | 34 (68) | 17 (34) | 7 (14) | |
| SMuRF ≥2, n (%) | 11 (22) | 30 (60) | 40 (80) | |
| SMuRF categories, overall P value | | | | < 0.001 |
| Non-smoking SMuRF burden, median [IQR] | 0.0 [0.0–1.0] | 1.0 [0.0–2.0] | 2.0 [1.0–2.0] | < 0.001 |
| Laboratory and inflammatory–metabolic indices | | | | |
| Glucose, mg/dL, median [IQR] | 119.0 [100.5–142.0] | 119.5 [102.2–143.8] | 146.5 [120.0–178.0] | 0.01 |
| Creatinine, mg/dL, median [IQR] | 0.9 [0.8–1.0] | 0.8 [0.7–1.0] | 0.9 [0.7–1.1] | 0.09 |
| eGFR, mL/min/1.73 m², median [IQR] | 107.0 [97.0–114.2] | 96.0 [81.0–101.0] | 80.0 [54.0–90.0] | < 0.001 |
| C-reactive protein, mg/L, median [IQR] | 3.1 [2.0–7.0] | 6.0 [2.3–8.8] | 7.0 [4.0–11.4] | 0.008 |
| Albumin, g/L, median [IQR] | 42.5 [41.2–46.3] | 42.0 [40.0–44.0] | 41.0 [40.0–44.0] | 0.049 |
| Admission troponin, ng/L, median [IQR] | 146 [26–809] | 178 [25–867] | 532 [53–2687] | 0.21 |
| Peak troponin, ng/L, median [IQR] | 16826 [5610–50000] | 27000 [8652–47403] | 49178 [26205–50000] | 0.005 |
| SII, median [IQR] | 617 [443–1030] | 854 [440–1365] | 1418 [778–1957] | < 0.001 |
| HALP score, median [IQR] | 7.6 [6.0–9.0] | 5.7 [3.9–8.0] | 3.6 [2.3–5.2] | < 0.001 |
| CRP/albumin ratio, median [IQR] | 0.08 [0.04–0.16] | 0.14 [0.05–0.22] | 0.16 [0.09–0.28] | 0.005 |
| Uric acid/HDL-C ratio, median [IQR] | 0.15 [0.13–0.18] | 0.14 [0.12–0.18] | 0.16 [0.12–0.20] | 0.70 |
| Lipid profile | | | | |
| Total cholesterol, mg/dL, median [IQR] | 204 [175–227] | 206 [179–232] | 182 [168–209] | 0.03 |
| LDL-C, mg/dL, median [IQR] | 126 [112–142] | 126 [98–158] | 114 [98–136] | 0.26 |
| HDL-C, mg/dL, median [IQR] | 38 [33–41] | 41 [34–47] | 40 [33–47] | 0.18 |
| Triglycerides, mg/dL, median [IQR] | 166 [104–226] | 158 [104–232] | 95 [64–140] | < 0.001 |
| Non-HDL-C, mg/dL, median [IQR] | 166 [137–192] | 166 [132–192] | 142 [122–164] | 0.005 |
| Pre-admission medical therapy | | | | |
| Prior statin therapy, n (%) | 4 (8) | 5 (10) | 11 (22) | 0.08 |
| Prior antiplatelet therapy, n (%) | 2 (4) | 2 (4) | 5 (10) | 0.34 |
| Prior beta-blocker therapy, n (%) | 2 (4) | 7 (14) | 6 (12) | 0.21 |
| Prior ACE inhibitor/ARB therapy, n (%) | 7 (14) | 14 (28) | 13 (26) | 0.20 |
| Prior antidiabetic therapy, n (%) | 2 (4) | 5 (10) | 12 (24) | 0.009 |
| Prior antihypertensive therapy, n (%) | 11 (22) | 21 (42) | 18 (36) | 0.09 |
| In-hospital/discharge medical therapy | | | | |
| Aspirin, n (%) | 50 (100) | 50 (100) | 48 (96) | 0.13 |
| P2Y12 inhibitor, n (%) | 49 (98) | 50 (100) | 49 (98) | 0.60 |
| Dual antiplatelet therapy, n (%) | 49 (98) | 50 (100) | 47 (94) | 0.17 |
| Oral anticoagulation, n (%) | 0 (0) | 0 (0) | 4 (8) | 0.02 |
| Any statin, n (%) | 50 (100) | 48 (96) | 48 (96) | 0.36 |
| High-intensity statin, n (%) | 36 (72) | 36 (72) | 42 (84) | 0.27 |
| Ezetimibe, n (%) | 0 (0) | 0 (0) | 0 (0) | – |
| PCSK9 inhibitor, n (%) | 0 (0) | 0 (0) | 0 (0) | – |
| Beta-blocker, n (%) | 36 (72) | 40 (80) | 40 (80) | 0.54 |
| ACE inhibitor/ARB, n (%) | 31 (62) | 34 (68) | 35 (70) | 0.68 |
| Mineralocorticoid receptor antagonist, n (%) | 6 (12) | 6 (12) | 9 (18) | 0.61 |
| Antihypertensive-class therapy, n (%) | 42 (84) | 48 (96) | 44 (88) | 0.14 |
| SGLT2 inhibitor, n (%) | 0 (0) | 0 (0) | 1 (2) | 0.36 |

Data are presented as n (%), mean ± SD, or median [IQR]. P < 0.05 is shown in bold. ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; HALP, Hemoglobin–albumin–lymphocyte–platelet; HDL-C, High-density lipoprotein cholesterol; IQR, Interquartile range; LDL-C, Low-density lipoprotein cholesterol; PCSK9, Proprotein convertase subtilisin/kexin type 9; SD, Standard deviation; SGLT2, Sodium–glucose cotransporter 2; SII, Systemic immune-inflammation index; SMuRF, Standard modifiable cardiovascular risk factor; STEMI, ST-elevation myocardial infarction.

Composite MACE occurred in 4, 6, and 6 patients, respectively (8%, 12%, and 12%; P = 0.76), with no statistically significant difference across age groups (Table 2).

In descriptive analyses, patients who died or experienced MACE generally had more severe clinical, ventricular, renal, and metabolic abnormalities (Supplementary Tables 3 and 4). Individual clinical characteristics of the 11 patients who died during hospitalization are summarized separately (Supplementary Table 5).

**Sex-Based and Sensitivity Analyses**

In sex-based analyses, women were older and had higher rates of diabetes mellitus, hypertension, hyperlipidemia, and measured four-component SMuRF burden but lower active smoking rates. Women also had higher SII and CAR and lower HALP scores and uric acid/HDL-C ratios. No statistically significant differences in SYNTAX score, LVEF, in-hospital mortality, or MACE were detected according to sex (Supplementary Table 1).

In the male-only sensitivity analysis, the main age-related patterns were directionally preserved: SMuRF category, peak troponin, and SYNTAX score increased across age groups, whereas angiographic thrombus presence and HALP score decreased (Table 3).

Using sex-independent age cutoffs (≤45, 46–55, and >55 years), the main age-related patterns were also generally retained, including differences in measured four-component

**Table 2.** Angiographic, procedural, and clinical outcomes by age phenotype

| Characteristic | Young STEMI (n = 50) | Premature non-young STEMI (n = 50) | Older STEMI (n = 50) | *P* |
|---|---|---|---|---|
| Angiographic and echocardiographic features | | | | |
| Anterior MI, n (%) | 31 (62) | 22 (44) | 24 (48) | |
| Inferior MI, n (%) | 16 (32) | 23 (46) | 21 (42) | |
| Lateral MI, n (%) | 3 (6) | 5 (10) | 5 (10) | |
| MI location, overall P value | | | | 0.46 |
| Culprit vessel-LAD, n (%) | 31 (62) | 22 (44) | 26 (52) | |
| Culprit vessel-RCA, n (%) | 15 (30) | 21 (42) | 16 (32) | |
| Culprit vessel-LCx, n (%) | 3 (6) | 6 (12) | 6 (12) | |
| Culprit vessel-LMCA/other, n (%) | 1 (2) | 1 (2) | 2 (4) | |
| Culprit vessel, overall P value | | | | 0.62 |
| 1-vessel disease, n (%) | 40 (80) | 37 (74) | 21 (42) | |
| 2-vessel disease, n (%) | 5 (10) | 10 (20) | 17 (34) | |
| 3-vessel disease, n (%) | 5 (10) | 3 (6) | 12 (24) | |
| Number of diseased vessels, overall P value | | | | < 0.001 |
| Angiographic thrombus presence, n (%) | 33 (66) | 21 (42) | 17 (34) | 0.004 |
| SYNTAX score, median [IQR] | 12.0 [11.0–16.0] | 13.0 [11.0–17.0] | 18.0 [13.0–26.0] | < 0.001 |
| High anatomical complexity (SYNTAX ≥23), n (%) | 5 (10) | 5 (10) | 21 (42) | < 0.001 |
| LVEF, %, median [IQR] | 50.0 [45.0–55.0] | 50.0 [45.0–55.0] | 50.0 [40.0–55.0] | 0.18 |
| LVEF <50%, n (%) | 17 (34) | 19 (38) | 24 (48) | 0.34 |
| LVEF ≤30%, n (%) | 5 (10) | 5 (10) | 5 (10) | > 0.99 |
| Revascularization strategy and procedural management | | | | |
| Primary PCI, n (%) | 50 (100) | 50 (100) | 50 (100) | – |
| Procedural success, n (%) | 50 (100) | 50 (100) | 50 (100) | – |
| Stent implantation, n (%) | 43 (86) | 46 (92) | 46 (92) | 0.51 |
| PCI without stent (balloon only), n (%) | 7 (14) | 4 (8) | 4 (8) | 0.51 |
| Thrombus aspiration, n (%) | 3 (6) | 2 (4) | 0 (0) | 0.23 |
| Culprit-only PCI at index, n (%) | 48 (96) | 50 (100) | 46 (92) | 0.12 |
| Multivessel PCI at index, n (%) | 2 (4) | 0 (0) | 4 (8) | 0.12 |
| Planned staged PCI, n (%) | 4 (8) | 8 (16) | 12 (24) | 0.09 |
| Planned/recommended CABG, n (%) | 2 (4) | 1 (2) | 5 (10) | 0.18 |
| Cardiogenic shock at presentation, n (%) | 3 (6) | 2 (4) | 3 (6) | 0.88 |
| Clinical outcomes | | | | |
| In-hospital mortality, n (%) | 3 (6) | 4 (8) | 4 (8) | 0.91 |
| Recurrent myocardial infarction, n (%) | 1 (2) | 1 (2) | 0 (0) | 0.60 |
| Recurrent (urgent target-vessel) revascularization, n (%) | 1 (2) | 1 (2) | 2 (4) | 0.77 |
| Stroke, n (%) | 0 (0) | 1 (2) | 0 (0) | 0.36 |
| MACE, n (%) | 4 (8) | 6 (12) | 6 (12) | 0.76 |

Data are presented as n (%) or median [IQR]. P < 0.05 is shown in bold. CABG, Coronary artery bypass grafting; LAD, Left anterior descending artery; LCx, Left circumflex artery; LMCA, Left main coronary artery; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiovascular events; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; RCA, Right coronary artery; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction.

SMuRF burden, angiographic thrombus presence, SYNTAX score, eGFR, SII, HALP, and CAR. Differences in peak troponin and non-HDL-C were attenuated under this alternative classification (Supplementary Table 2).

### Multivariable Models

In Model 1, with Young STEMI as the reference, higher non-smoking SMuRF burden was independently associated with both premature non-young STEMI (OR 2.29; 95% CI 1.14–4.58; P = 0.02) and older STEMI (OR 4.30; 95% CI 2.00–9.25; P < 0.001). Male sex was inversely associated with premature non-young STEMI (OR 0.04; P < 0.001); however, this estimate was considered strongly influenced by the prespecified sex-stratified sampling design and the marked male predominance in the Young STEMI group rather than representing a biological association. Lower HALP score was independently associated with older STEMI (OR 0.27; 95% CI 0.08–0.93; P = 0.04) (Table 4).

In Model 2, older STEMI was independently associated with a higher median SYNTAX score (β = 4.83; 95% CI 1.37–8.30; P = 0.007), whereas premature non-young STEMI did not differ from Young STEMI (β = -0.21; P = 0.90). Higher CAR (β = 1.71; P = 0.007) and uric acid/HDL-C ratio (β = 1.99; P = 0.003) were also associated with a higher median SYNTAX score. SII showed an inverse adjusted association with SYNTAX score (β = -2.08; P = 0.02), despite increasing across age groups in the unadjusted analysis. Because several correlated inflammatory–metabolic indices were included simultaneously in the model, this coefficient was interpreted cautiously and was not considered in isolation (Table 5).

## Discussion

In this study, we observed differences in measured risk-factor burden, coronary angiographic characteristics, and selected inflammatory–metabolic indices across the three age groups. The Young STEMI group, which was composed almost entirely of men, was characterized by smoking predominance, more frequent angiographic thrombus presence, and lower coronary anatomical complexity, whereas older STEMI showed greater measured four-component SMuRF burden, more multivessel disease, higher SYNTAX scores, and a less favorable inflammatory–metabolic profile. Premature non-young STEMI generally demonstrated intermediate patterns between the younger and older groups. No statistically significant differences in in-hospital mortality or MACE were detected across age groups. Overall, these findings suggest that first-presentation STEMI is associated with distinct measured clinical, angiographic, and laboratory characteristics across age groups in this selected analytical cohort.

A prominent difference across age groups was the distribution of measured conventional risk factors. Our findings are consistent with previous studies reporting a greater predominance of smoking and male sex in younger or premature myocardial infarction, along with higher frequencies of diabetes mellitus and hypertension at older ages.[2,5,25] In Model 1, non-smoking SMuRF burden was the main independent discriminator of both premature non-young STEMI (OR 2.29) and older STEMI (OR 4.30) compared with Young STEMI. These findings suggest a progressive accumulation of measured non-smoking conventional risk factors across age groups. The position of premature non-young STEMI between the smoking-dominant young group and the SMuRF burden–dominant older group indicates that a binary young–older classification may obscure a clinically meaningful intermediate stratum. The strong inverse association between male sex and the premature non-young group (OR 0.04; P < 0.001) is likely a consequence of the marked male predominance in Young STEMI and should not be interpreted as a biological protective effect. The principal age-related patterns were retained in the male-only analysis and after reclassification using sex-independent age cutoffs (Table 3; Supplementary Table 2). Accordingly, the relatively lower measured four-component SMuRF burden in Young STEMI should not be interpreted as indicating low acute coronary risk; because smoking is associated with poorer long-term survival, it remains an important target for secondary prevention in this group.[2,26]

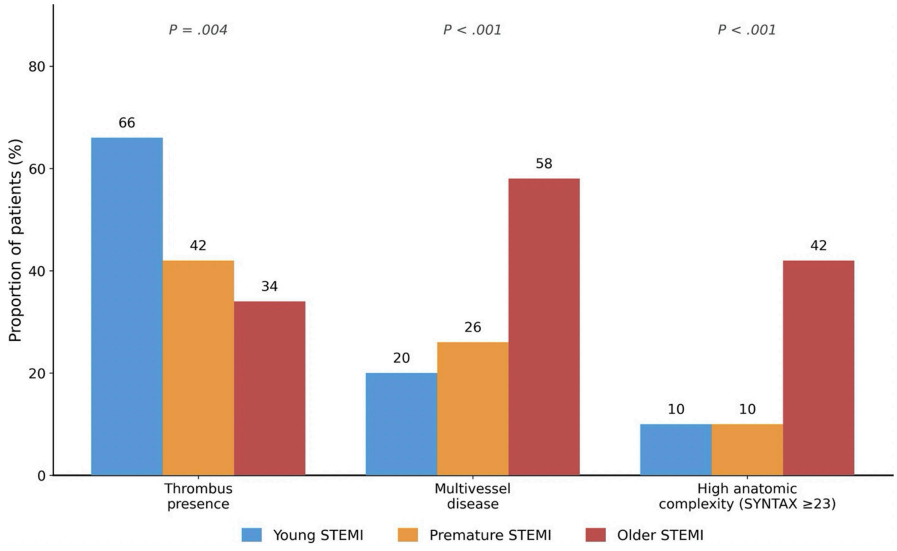



**Figure 3.** Angiographic characteristics and thrombus presence across age groups.

Multivessel disease was defined as ≥2 diseased vessels, and high anatomical complexity was defined as a SYNTAX score ≥23. STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

**Table 3.** Male-only sensitivity analysis by age phenotype

| Characteristic | Young STEMI (n = 48) | Premature non-young STEMI (n = 25) | Older STEMI (n = 25) | *P* |
|---|---|---|---|---|
| Demographics and risk factors | | | | |
| Age, mean ± SD, years | 41.0 ± 4.4 | 51.3 ± 2.2 | 65.0 ± 7.9 | < 0.001 |
| Smoking, n (%) | 34 (71) | 20 (80) | 15 (60) | 0.30 |
| Diabetes mellitus, n (%) | 9 (19) | 6 (24) | 13 (52) | 0.01 |
| Hypertension, n (%) | 8 (17) | 8 (32) | 13 (52) | 0.007 |
| Hyperlipidemia, n (%) | 3 (6) | 6 (24) | 11 (44) | 0.001 |
| SMuRF count, median [IQR] | 1.0 [1.0–1.0] | 2.0 [1.0–2.0] | 2.0 [2.0–3.0] | < 0.001 |
| SMuRF 0, n (%) | 5 (10) | 1 (4) | 1 (4) | |
| SMuRF 1, n (%) | 33 (69) | 11 (44) | 4 (16) | |
| SMuRF ≥2, n (%) | 10 (21) | 13 (52) | 20 (80) | |
| SMuRF categories, overall P value | | | | < 0.001 |
| Non-smoking SMuRF burden, median [IQR] | 0.0 [0.0–1.0] | 1.0 [0.0–1.0] | 2.0 [1.0–2.0] | < 0.001 |
| Laboratory and inflammatory–metabolic indices | | | | |
| Glucose, mg/dL, median [IQR] | 119.5 [101.5–143.5] | 116.0 [101.0–143.0] | 142.0 [109.0–159.0] | 0.44 |
| Creatinine, mg/dL, median [IQR] | 0.9 [0.8–1.0] | 0.9 [0.8–1.1] | 0.9 [0.9–1.0] | 0.60 |
| eGFR, mL/min/1.73 m², median [IQR] | 107.0 [97.2–114.8] | 94.0 [80.4–104.2] | 85.0 [74.0–91.0] | < 0.001 |
| C-reactive protein, mg/L, median [IQR] | 3.5 [2.0–7.2] | 5.8 [2.2–8.0] | 5.3 [2.5–8.0] | 0.26 |
| Albumin, g/L, median [IQR] | 42.0 [40.8–46.1] | 42.0 [40.0–44.0] | 43.0 [41.0–46.0] | 0.27 |
| Admission troponin, ng/L, median [IQR] | 172 [24–922] | 207 [26–858] | 98 [27–985] | 0.71 |
| Peak troponin, ng/L, median [IQR] | 20158 [5632–50000] | 24000 [2979–50000] | 50000 [30594–50000] | 0.03 |
| SII, median [IQR] | 617 [444–1123] | 755 [411–1242] | 1480 [674–1855] | 0.09 |
| HALP score, median [IQR] | 7.7 [6.0–9.0] | 7.2 [5.4–9.7] | 4.4 [3.5–6.3] | 0.003 |
| CRP/albumin ratio, median [IQR] | 0.1 [0.0–0.2] | 0.1 [0.1–0.2] | 0.1 [0.1–0.2] | 0.27 |
| Uric acid/HDL-C ratio, median [IQR] | 0.2 [0.1–0.2] | 0.2 [0.1–0.2] | 0.2 [0.2–0.2] | 0.09 |
| Lipid profile | | | | |
| Total cholesterol, mg/dL, median [IQR] | 206 [177–228] | 205 [179–215] | 182 [169–199] | 0.07 |
| LDL-C, mg/dL, median [IQR] | 127 [113–146] | 125 [97–149] | 125 [99–136] | 0.56 |
| HDL-C, mg/dL, median [IQR] | 38 [34–41] | 35 [33–45] | 35 [33–42] | 0.93 |
| Triglycerides, mg/dL, median [IQR] | 166 [107–223] | 189 [125–228] | 93 [66–131] | 0.001 |
| Non-HDL-C, mg/dL, median [IQR] | 166 [139–193] | 165 [131–176] | 147 [128–161] | 0.07 |
| Angiographic and echocardiographic features | | | | |
| Anterior MI, n (%) | 29 (60) | 10 (40) | 15 (60) | |
| Inferior MI, n (%) | 16 (33) | 13 (52) | 7 (28) | |
| Lateral MI, n (%) | 3 (6) | 2 (8) | 3 (12) | |
| MI location, overall P value | | | | 0.36 |
| 1-vessel disease, n (%) | 39 (81) | 21 (84) | 13 (52) | |
| 2-vessel disease, n (%) | 4 (8) | 3 (12) | 5 (20) | |
| 3-vessel disease, n (%) | 5 (10) | 1 (4) | 7 (28) | |
| Number of diseased vessels, overall P value | | | | 0.04 |
| Angiographic thrombus presence, n (%) | 32 (67) | 13 (52) | 7 (28) | 0.007 |
| SYNTAX score, median [IQR] | 12.0 [11.0–16.0] | 12.0 [11.0–17.0] | 19.0 [13.0–26.0] | 0.02 |
| High anatomical complexity (SYNTAX ≥23), n (%) | 5 (10) | 3 (12) | 12 (48) | < 0.001 |
| LVEF, %, median [IQR] | 50.0 [45.0–55.0] | 50.0 [40.0–55.0] | 50.0 [40.0–50.0] | 0.25 |
| LVEF <50%, n (%) | 17 (35) | 10 (40) | 12 (48) | 0.58 |
| LVEF ≤30%, n (%) | 5 (10) | 5 (20) | 4 (16) | 0.52 |
| Clinical outcomes | | | | |
| In-hospital mortality, n (%) | 3 (6) | 3 (12) | 1 (4) | 0.52 |
| Recurrent myocardial infarction, n (%) | 1 (2) | 0 (0) | 0 (0) | 0.59 |
| Recurrent (urgent target-vessel) revascularization, n (%) | 1 (2) | 0 (0) | 0 (0) | 0.59 |
| Stroke, n (%) | 0 (0) | 0 (0) | 0 (0) | – |
| MACE, n (%) | 4 (8) | 3 (12) | 1 (4) | 0.58 |

Data are presented as n (%), mean ± SD, or median [IQR]. P < 0.05 is shown in bold. The analysis was restricted to men (Young STEMI, n = 48; premature non-young STEMI, n = 25; older STEMI, n = 25). CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; HALP, Hemoglobin–albumin–lymphocyte–platelet; HDL-C, High-density lipoprotein cholesterol; IQR, Interquartile range; LDL-C, Low-density lipoprotein cholesterol; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiovascular events; MI, Myocardial infarction; SD, Standard deviation; SII, Systemic immune-inflammation index; SMuRF, Standard modifiable cardiovascular risk factor; STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

**Table 4.** Multinomial model of age phenotype

| Predictor | Premature vs young OR (95% CI) | *P* | Older vs young OR (95% CI) | *P* |
|---|---|---|---|---|
| Male sex | 0.04 (0.01–0.21) | < 0.001 | 0.19 (0.03–1.25) | 0.08 |
| Active smoking | 1.71 (0.53–5.56) | 0.37 | 0.57 (0.16–2.05) | 0.39 |
| Non-smoking SMuRF burden (per unit) | 2.29 (1.14–4.58) | 0.02 | 4.30 (2.00–9.25) | < 0.001 |
| Thrombus presence | 0.56 (0.21–1.50) | 0.25 | 0.35 (0.11–1.07) | 0.07 |
| SYNTAX score (per 1 SD) | 0.94 (0.51–1.74) | 0.85 | 1.90 (0.99–3.63) | 0.053 |
| Peak troponin (log, per 1 SD) | 0.90 (0.55–1.46) | 0.67 | 1.49 (0.80–2.78) | 0.21 |
| SII (log, per 1 SD) | 1.37 (0.61–3.09) | 0.44 | 0.93 (0.38–2.30) | 0.88 |
| HALP score (per 1 SD) | 1.29 (0.64–2.60) | 0.48 | 0.27 (0.08–0.93) | 0.04 |
| CRP/albumin ratio (log, per 1 SD) | 1.27 (0.64–2.52) | 0.49 | 1.36 (0.68–2.72) | 0.38 |
| Uric acid/HDL-C ratio (per 1 SD) | 1.33 (0.76–2.32) | 0.32 | 1.45 (0.76–2.79) | 0.26 |

Multinomial logistic regression with Young STEMI as the reference category. Odds ratios for continuous predictors are reported per 1-standard deviation increase, except for non-smoking SMuRF burden, which is reported per one-component increase. Peak troponin, SII, and CRP/albumin ratio were log-transformed before model entry. P < 0.05 is shown in bold. CAR, C-reactive protein/albumin ratio; CI, Confidence interval; HALP, Hemoglobin–albumin–lymphocyte–platelet score; HDL-C, High-density lipoprotein cholesterol; OR, Odds ratio; SD, Standard deviation; SII, Systemic immune-inflammation index; SMuRF, Standard modifiable cardiovascular risk factor; STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

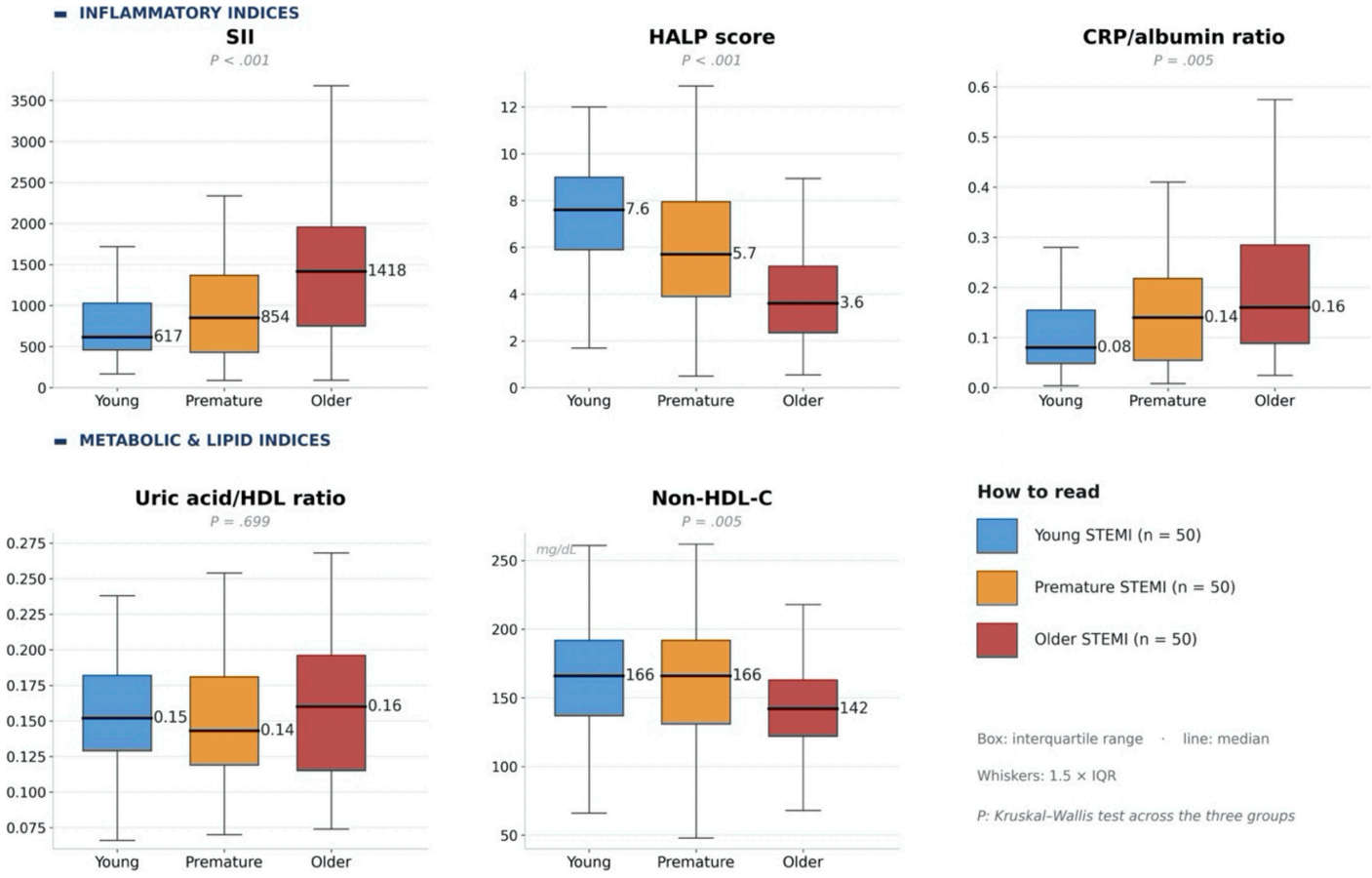



**Figure 4.** Inflammatory and metabolic indices across age groups.

Boxes represent the interquartile range, horizontal lines indicate medians, and whiskers extend to 1.5 × the interquartile range. CAR, C-reactive protein/albumin ratio; HALP, Hemoglobin–albumin–lymphocyte–platelet score; HDL-C, High-density lipoprotein cholesterol; SII, Systemic immune-inflammation index; STEMI, ST-elevation myocardial infarction.

A second prominent difference across age groups involved angiographic findings. Single-vessel disease predominated in Young STEMI, whereas multivessel disease and higher SYNTAX scores were more common in older STEMI. This finding is consistent with studies reporting less extensive atherosclerotic involvement and lower coronary disease burden in young MI.[2,7] In Model 2, older STEMI remained associated with a higher median SYNTAX score after adjustment (β = 4.83), whereas premature

non-young STEMI did not differ from Young STEMI. This finding suggests that age-related differences in coronary disease extent were not fully explained by measured risk factors. Because the SYNTAX score has been associated with adverse outcomes after STEMI and its prognostic value may vary with age,[21,27] assessment of anatomical complexity may provide information beyond conventional risk-factor burden. MI location, however, did not differ across age groups. The positive associations of CAR and the uric acid/HDL-C ratio with SYNTAX score are also consistent with previous studies linking inflammatory and metabolic markers to coronary disease severity.[10–12,28] Angiographic thrombus presence was more frequent in Young STEMI and decreased across the three age groups (66%, 42%, and 34%), a pattern also observed in the male-only sensitivity analysis. The higher thrombus frequency in younger patients may reflect differences in smoking exposure, coronary disease extent, and culprit lesion characteristics rather than an effect of age alone. This is consistent with studies reporting distinct plaque characteristics in younger patients with STEMI and an important role of smoking in coronary thrombosis.[2,7,29,30]

SII and CAR increased across age groups, whereas HALP decreased. These findings may reflect greater systemic inflammation and lower hematologic–nutritional reserve among older patients. Previous studies have associated SII and CAR with adverse outcomes, coronary disease severity, mortality, and angiographic thrombus in STEMI, whereas lower HALP has been linked to poorer nutritional–immune status and in-hospital mortality.[9,10,13,23,28] In our cohort, patients with MACE had higher SII and CAR and lower HALP; however, these unadjusted associations should not be interpreted as independent predictors. Notably, the adjusted association between SII and SYNTAX score was directionally discordant with the unadjusted group pattern: despite higher SII in older STEMI, SII was inversely associated with median SYNTAX score in Model 2. Given the simultaneous inclusion of correlated inflammatory–metabolic indices in a limited sample, this inverse coefficient should be interpreted cautiously and may reflect shared variance or statistical suppression.

**Table 5.** Median quantile regression for SYNTAX score

| Predictor | β coefficient (95% CI) | *P* |
|---|---|---|
| Premature non-young vs young STEMI | -0.21 (-3.40 to 2.99) | 0.90 |
| Older STEMI vs Young STEMI | 4.83 (1.37 to 8.30) | 0.007 |
| Male sex | -0.41 (-3.45 to 2.62) | 0.79 |
| SMuRF count (per 1 SD) | 0.41 (-0.87 to 1.70) | 0.53 |
| Peak troponin (log, per 1 SD) | 0.13 (-1.07 to 1.34) | 0.83 |
| SII (log, per 1 SD) | -2.08 (-3.81 to -0.35) | 0.02 |
| HALP score (per 1 SD) | -1.14 (-2.96 to 0.68) | 0.22 |
| CRP/albumin ratio (log, per 1 SD) | 1.71 (0.47 to 2.95) | 0.007 |
| Uric acid/HDL-C ratio (per 1 SD) | 1.99 (0.70 to 3.29) | 0.003 |

Median quantile regression for SYNTAX score. β coefficients represent estimated changes in median SYNTAX score. Young STEMI was the reference category; pseudo $R^2$ = 0.137. Continuous predictors were standardized; peak troponin, SII, and CRP/albumin ratio were log-transformed before model entry. P < 0.05 is shown in bold. CAR, C-reactive protein/albumin ratio; CI, Confidence interval; HALP, Hemoglobin–albumin–lymphocyte–platelet score; HDL-C, High-density lipoprotein cholesterol; SD, Standard deviation; SII, Systemic immune-inflammation index; SMuRF, Standard modifiable cardiovascular risk factor; STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Lipid profiles showed a pattern across age groups that was inverse to the risk-factor gradient. Triglyceride and non-HDL-C levels were higher in the two younger groups and lower in older STEMI, whereas no significant differences were observed in LDL-C or HDL-C. Our findings are consistent with data showing that non-HDL-C is the strongest lipid discriminator in young individuals experiencing a first MI.[31] Because non-HDL-C reflects cholesterol carried in major atherogenic apoB-containing lipoproteins,[32] the higher triglyceride and non-HDL-C levels observed in our younger groups may represent an atherogenic lipid pattern not fully captured by LDL-C alone. Conversely, our findings should not be interpreted as indicating a more favorable lipid profile in older STEMI. Pre-admission statin use was more frequent in this group (22% vs 8% and 10%; P = 0.08) and may have lowered lipid concentrations measured at the time of STEMI. Information regarding treatment duration, adherence, pretreatment lipid levels, and whether lipid sampling preceded the first in-hospital statin dose was unavailable. Although prospective acute coronary syndrome data suggest that mean lipid concentrations generally change only modestly during the first days after presentation, sampling during the acute event may still have influenced individual measurements.[33]

Restriction to first-presentation STEMI without previously recognized coronary disease, together with the constructed sampling design, may also have introduced survivor and selection effects. Individuals with a more adverse lifelong lipid phenotype may have experienced coronary events earlier and therefore been underrepresented among patients presenting with STEMI for the first time at older ages. The absence of anthropometric measurements, apoB, and Lp(a) also limits definitive characterization. Accordingly, these lipid differences should be regarded as hypothesis-generating observations potentially influenced by treatment exposure, sampling timing, and selection or survivorship effects rather than as intrinsic biological consequences of age.

In exploratory sex-based analyses, women were older than men and had higher rates of diabetes mellitus, hypertension, hyperlipidemia, and measured four-component SMuRF burden, but markedly lower active smoking rates. This pattern is consistent with findings from VIRGO and other studies of young AMI, in which women had a greater burden of diabetes and comorbid conditions.[34,35] Women also had higher SII and CAR and lower HALP scores and uric acid/HDL-C ratios. Previous studies have similarly reported sex-related differences in inflammatory markers in both healthy populations and after young AMI.[36,37] Despite these differences, no statistically significant differences in SYNTAX score, LVEF, mortality, or MACE were detected according to sex (Supplementary Table 1). The principal age-related patterns were also retained in the male-only sensitivity analysis, supporting that they were not solely driven by the sex composition of the Young STEMI group (Table 3). Nevertheless, these sex-based comparisons remain exploratory and should be interpreted cautiously because sex distribution was influenced by the sampling design.

No statistically significant difference in in-hospital mortality was detected across groups; however, this finding should not be interpreted as evidence of equivalent mortality risk because only 11 deaths occurred in the selected analytical cohort. The overall mortality rate of 7.3%, including 6% in Young STEMI, appeared to reflect clustering of severe index-event presentations. Patients who died were characterized by cardiogenic shock, cardiac arrest or resuscitation at admission, severe left ventricular dysfunction, renal impairment, and/or marked hyperglycemia. These patterns are consistent with previous STEMI studies linking ventricular dysfunction, renal impairment, and greater myocardial injury with adverse in-hospital outcomes.[38,39] Notably, all three deaths in the Young STEMI group occurred in patients presenting with cardiac arrest/CPR or profound hemodynamic compromise and reduced LVEF (20%–35%) (Supplementary Table 5). This indicates that the observed mortality rate was concentrated among critically ill presentations and should not be generalized to otherwise uncomplicated young STEMI patients. The single-center design and potential enrichment for critically ill or referred patients may also have contributed to the observed mortality.

Similarly, no statistically significant difference in MACE was detected across groups, and this comparison was likewise limited by the small number of events. In exploratory descriptive analyses, patients with MACE had greater angiographic complexity and less favorable inflammatory–metabolic indices, including higher SYNTAX scores, SII, and CAR and lower HALP scores (Supplementary Table 4), consistent with previous evidence linking anatomical complexity and inflammatory markers to adverse STEMI outcomes.[9,21]

### Limitations

This study has several limitations. Its retrospective, single-center design precludes causal inference and may involve residual confounding and selection bias. Sex-stratified quota sampling improved group comparability but did not reflect the natural sex distribution, limited the interpretation of group-level frequencies as population prevalence estimates, and influenced the sex coefficient in the multinomial model. The modest sample size and limited number of events reduced the precision of outcome and multivariable analyses. Because anthropometric data were unavailable, measured four-component SMuRF burden does not exclude obesity-related or broader cardiometabolic risk. Lp(a) and apolipoprotein B were also unavailable, and whether lipid sampling preceded the first in-hospital statin dose could not be verified. Potential etiologies of MI in younger patients, including familial/genetic, substance-related, thrombophilic/autoimmune, hormonal, and non-atherosclerotic coronary causes, were not systematically evaluated. SYNTAX score and thrombus presence were assessed by one interventional cardiologist without interobserver validation; thrombus was recorded only as a binary variable and may have influenced SYNTAX scoring. Key treatment-delay and procedural variables, including symptom-to-balloon and door-to-balloon times, TIMI flow, and detailed stent characteristics, were not systematically available. Laboratory indices were based on single measurements and may have been influenced by acute-phase and treatment-related factors. MACE was re-adjudicated by a single investigator who was not blinded to age group, without independent second review. Only in-hospital outcomes were available. Finally, no adjustment for multiple testing was applied; therefore, individual P values should be interpreted cautiously within the exploratory nature of the study.

### Conclusion

These exploratory data suggest that age groups in first-presentation STEMI may differ in measured four-component SMuRF burden, coronary anatomical complexity, angiographic thrombus presence, and selected inflammatory–metabolic indices. In this selected cohort, the Young STEMI group, composed almost entirely of men, was characterized by smoking predominance, lower measured SMuRF burden, lower coronary anatomical complexity, and more frequent angiographic thrombus, whereas older STEMI showed greater measured SMuRF burden, higher coronary complexity, and a more unfavorable inflammatory–metabolic profile. Premature non-young STEMI occupied an intermediate position between these two groups, and these patterns were largely retained when sex-independent age cutoffs were applied. No statistically significant differences in in-hospital mortality or MACE were detected; however, the limited number of events precludes inference of equivalent risk. These findings require confirmation in larger consecutive cohorts with more complete anthropometric, lipid, etiological, procedural, and long-term outcome data.

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# Association Between Eosinophil-to-Monocyte Ratio and ST-Segment Resolution in Young STEMI Patients Undergoing Primary Percutaneous Coronary Intervention

## Primer Perkütan Koroner Girişim Uygulanan Genç STEMI Hastalarında Eozinofil/Monosit Oranı ile ST-Segment Rezolüsyonu Arasındaki İlişki

**ABSTRACT**

**Objective:** Impaired myocardial reperfusion after primary percutaneous coronary intervention (pPCI) is associated with adverse outcomes in ST-segment elevation myocardial infarction (STEMI). This study investigated the relationship between the eosinophil-to-monocyte ratio (EMR) and ST-segment resolution in young patients with STEMI undergoing pPCI.

**Method:** This retrospective, single-center study included 492 consecutive patients with STEMI younger than 45 years who underwent pPCI between January 2022 and January 2026. The primary endpoint was incomplete ST-segment resolution (<70%), while no-reflow was evaluated as a secondary endpoint. Univariable and multivariable logistic regression, restricted cubic spline, and receiver operating characteristic (ROC) analyses were performed.

**Results:** Lower EMR was associated with greater thrombus burden, impaired postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow, increased glycoprotein IIb/IIIa inhibitor use, incomplete ST-segment resolution, and no-reflow (all P < 0.001). Incomplete ST-segment resolution occurred in 52 patients (10.6%), no-reflow in 25 (5.1%), and in-hospital death in 1 (0.2%). Lower EMR remained independently associated with incomplete ST-segment resolution (odds ratio [OR] 0.245, 95% confidence interval [CI] 0.127–0.475, P < 0.001). In a secondary analysis, lower EMR was associated with no-reflow (adjusted OR 0.079, 95% CI 0.021–0.238, P < 0.001). Restricted cubic spline analysis showed a nonlinear inverse association between EMR and impaired myocardial reperfusion. EMR demonstrated acceptable discriminatory performance for incomplete ST-segment resolution (area under the curve [AUC] 0.757) and no-reflow (AUC 0.827).

**Conclusion:** Lower admission EMR was associated with impaired myocardial reperfusion in young patients with STEMI undergoing pPCI. EMR may represent an admission reperfusion-associated marker, but its biological and clinical significance remains uncertain and requires prospective external validation.

**Keywords:** Eosinophil-to-monocyte ratio, no-reflow phenomenon, ST-segment resolution, Young myocardial infarction.

**ÖZET**

**Amaç:** Primer perkütan koroner girişim (PKG) sonrası bozulmuş miyokardiyal reperfüzyon, ST-segment elevasyonlu miyokard enfarktüsü (STEMI) hastalarında olumsuz klinik sonuçlarla ilişkilidir. Eozinofil/monosit oranı (EMR), tromboinflamatuvar aktiviteyi yansıtan bir biyobelirteç olarak öne çıkmaktadır. Bu çalışmada, primer PKG uygulanan genç STEMI hastalarında EMR ile ST-segment rezolüsyonu arasındaki ilişkinin araştırılması amaçlandı.

**Yöntem:** Bu retrospektif, tek merkezli çalışmaya Ocak 2022–Ocak 2026 tarihleri arasında STEMI nedeniyle primer PKG uygulanan ve 45 yaşın altında olan ardışık 492 hasta dahil edildi. Hastalar, başvuru sırasındaki EMR tertillerine göre sınıflandırıldı. Primer sonlanım noktası, primer PKG sonrası inkomplet ST-segment rezolüsyonu (<%70); ikincil sonlanım noktası ise no-reflow fenomeni olarak belirlendi. Klinik, laboratuvar, anjiyografik ve işlemsel özellikler EMR tertilleri arasında karşılaştırıldı. Tek değişkenli ve çok değişkenli lojistik regresyon, restricted cubic spline ve ROC analizleri gerçekleştirildi.

**Bulgular:** Düşük EMR değerleri; yüksek trombüs yükü, bozulmuş işlem sonrası TIMI akımı, artmış glikoprotein IIb/IIIa inhibitörü kullanımı, inkomplet ST-segment rezolüsyonu ve no-reflow fenomeni ile ilişkili bulundu (tümü P < 0,001). Çok değişkenli analizde düşük EMR, inkomplet ST-segment rezolüsyonu ile bağımsız olarak ilişkili bulundu (OR 0,245; %95 GA

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0,127–0,475; P < 0,001). İkincil analizde düşük EMR, no-reflow ile ilişkiliydi (düzeltilmiş OR 0,079; %95 GA 0,021–0,238; P < 0,001). ROC analizinde, EMR'nin inkomplet ST-segment rezolüsyonunu (AUC 0,757) ve no-reflow fenomenini (AUC 0,827) ayırt etmede kabul edilebilir düzeyde performans gösterdiği saptandı.

**Sonuç:** Düşük başvuru EMR değerleri, primer PKG uygulanan genç STEMI hastalarında bozulmuş miyokardiyal reperfüzyon ile ilişkili bulundu. EMR, başvuru sırasında reperfüzyonla ilişkili bir belirteç olarak değerlendirilebilir; ancak biyolojik ve klinik anlamı belirsizliğini korumakta olup ileriye dönük ve dış doğrulama içeren çalışmalarla doğrulanması gerekmektedir.

**Anahtar Kelimeler:** Eozinofil/monosit oranı, genç miyokard enfarktüsü, no-reflow fenomeni, ST-segment rezolüsyonu.

ST-segment elevation myocardial infarction (STEMI) remains a major cause of cardiovascular morbidity and mortality worldwide, with substantial short- and long-term adverse outcomes despite significant advances in reperfusion strategies and pharmacological therapy.[1,2]

The risk of myocardial infarction (MI) generally increases with age; however, the incidence of premature MI has been steadily increasing worldwide.[3] Young MI represents a distinct clinical entity and has become a significant contributor to premature mortality, morbidity, productivity loss, and healthcare burden among younger populations.[3–5] Consistent with these observations, recent data from Türkiye have highlighted the substantial burden of acute coronary syndrome hospitalizations among individuals younger than 45 years.[6] Previous studies have demonstrated that young patients with STEMI differ from older populations in terms of risk factor profiles, underlying pathophysiology, and clinical characteristics. Although this population frequently exhibits traditional cardiovascular risk factors such as smoking, dyslipidemia, hypertension, and diabetes mellitus, other mechanisms, including thrombosis, inflammatory activation, immune dysregulation, and hypercoagulability, may play a more prominent role in the development of premature STEMI.[4,7–9] Thrombo-inflammatory mechanisms also appear to influence the onset and clinical severity of coronary artery disease in young patients with STEMI.[10]

The recommended reperfusion strategy for STEMI is primary percutaneous coronary intervention (pPCI), which aims to rapidly restore myocardial perfusion and epicardial coronary flow. However, adequate microvascular and tissue-level reperfusion may not always follow successful reopening of the infarct-related artery. Impaired microvascular reperfusion after pPCI remains an important clinical problem and has been associated with increased infarct size, ventricular dysfunction, recurrent ischemic events, and higher mortality.[11–15] Angiographic Thrombolysis in Myocardial Infarction (TIMI) flow grade and electrocardiographic ST-segment resolution (STR) are commonly used to assess myocardial reperfusion. Incomplete STR after pPCI, typically defined as <70% ST-segment resolution, is considered a marker of impaired microvascular perfusion and adverse prognosis.[16–18] A large contemporary study involving 7,654 patients with STEMI treated with pPCI demonstrated that incomplete STR was independently associated with higher risks of heart failure, cardiogenic shock, recurrent MI, and cardiovascular death during follow-up.[15] Furthermore, increased thrombus burden, distal embolization, inadequate TIMI flow, and the development of the no-reflow phenomenon have all been associated with poor myocardial reperfusion.

## ABBREVIATIONS

| | |
|---|---|
| AHA/ACC | American Heart Association/American College of Cardiology |
| CRP | C-reactive protein |
| ECG | Electrocardiogram |
| EMR | Eosinophil-to-monocyte ratio |
| ESC | European Society of Cardiology |
| GFR | Glomerular filtration rate |
| HDL | High-density lipoprotein |
| ICC | Intraclass correlation coefficient |
| MI | Myocardial infarction |
| non-HDL | Non-high-density lipoprotein |
| pPCI | Primary percutaneous coronary intervention |
| STEMI | ST-segment elevation myocardial infarction |
| STR | ST-segment resolution |
| TIMI | Thrombolysis in myocardial ınfarction |

Inflammatory biomarkers derived from peripheral blood cell counts have recently gained attention as potential indicators of thrombotic and inflammatory activity in acute coronary syndromes. Among these parameters, the eosinophil-to-monocyte ratio (EMR) has emerged as a marker reflecting both inflammatory activity and thrombotic burden. Monocytes are known to contribute to plaque instability, thrombus formation, and endothelial dysfunction, whereas eosinophils may participate in platelet activation and thrombotic processes. According to Deng et al.,[19] lower EMR levels were independently associated with higher short- and long-term mortality rates among patients with STEMI undergoing pPCI. These findings suggest that EMR may reflect thrombo-inflammatory activity and impaired myocardial reperfusion in acute ischemic conditions.

Although previous studies have reported an association between EMR and mortality in patients with STEMI, evidence regarding its relationship with myocardial reperfusion markers, particularly ST-segment resolution, remains limited in young patients with STEMI undergoing pPCI. The purpose of this study was to investigate the relationship between EMR and ST-segment resolution in young patients with STEMI undergoing pPCI. Additionally, the associations of EMR with reperfusion-related parameters, such as postprocedural TIMI flow, glycoprotein IIb/IIIa inhibitor use, and the no-reflow phenomenon, were evaluated.

## Materials and Methods

### Study Design and Population

Consecutive young patients with STEMI who underwent pPCI at a tertiary referral center between January 2022 and January 2026 were included in this retrospective, observational, single-center cohort study.

Patients younger than 45 years who presented with STEMI and underwent pPCI were retrospectively identified using the hospital electronic medical records, digital archive system, and institutional cardiology database. The definition of "young" MI was based on previous literature, in which age thresholds ranging from 40 to 55 years have commonly been used, and a cutoff value of 45 years was selected to represent a relatively early-onset STEMI population.[3] Based on clinical presentation, electrocardiographic findings, and elevated cardiac biomarkers, the diagnosis of STEMI was established in accordance with current guidelines recommended by the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC).[17,18]

Patients were excluded if information required to determine eligibility, calculate the primary exposure, assess the primary endpoint, or perform essential angiographic/procedural evaluation was unavailable or uninterpretable. Missing covariate data that did not preclude eligibility or outcome assessment were retained and handled using multiple imputation. Furthermore, because these conditions may affect eosinophil and monocyte counts, patients with active infections, autoimmune diseases, cancer, hematologic disorders, severe hepatic failure, advanced renal failure, or systemic corticosteroid use were excluded. Among 2,236 patients with STEMI who underwent pPCI during the study period, 1,624 were excluded because they were 45 years of age or older, leaving 612 patients younger than 45 years for eligibility assessment. Of these, 120 patients were excluded (28 with missing admission eosinophil or monocyte counts, 31 with missing or uninterpretable electrocardiographic data for ST-segment resolution assessment, 17 with missing angiographic or procedural data, 12 with active infection, 9 with autoimmune disease or systemic corticosteroid use, 8 with malignancy or a hematologic disorder, 6 with severe hepatic or advanced renal failure, and 9 for other predefined exclusion criteria), resulting in a final study population of 492 patients (Supplementary Figure 1). No cases of spontaneous coronary artery dissection or other clearly documented nonatherosclerotic STEMI etiologies were identified during the study period.

Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee approved the study protocol (Approval Number: 2026/09/1462, Date: 05.05.2026). The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived by the institutional ethics committee.

ChatGPT (OpenAI) was used exclusively for English-language editing and grammatical correction during the preparation of this manuscript. The authors assumed full responsibility for the final version of the manuscript.

### Data Collection

The hospital information system and electronic patient records were used to retrospectively collect patient demographics, cardiovascular risk factors, laboratory results, electrocardiographic findings, echocardiographic measurements, angiographic characteristics, and procedural data.

Baseline clinical variables included age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking history, prior coronary artery disease, and family history of coronary artery disease.

Hypertension was defined as a documented history of hypertension or current antihypertensive treatment. Diabetes mellitus was defined as a documented diagnosis of diabetes or current glucose-lowering treatment. Hyperlipidemia was defined as a documented previous diagnosis or current lipid-lowering therapy; the relatively low prevalence of hyperlipidemia in this cohort likely reflects this diagnosis- and treatment-based definition rather than systematic lipid-threshold screening. Current smoking was defined as active cigarette smoking at the time of admission. A family history of premature coronary artery disease was defined as coronary artery disease occurring before 55 years of age in a first-degree male relative or before 65 years of age in a first-degree female relative. Previous coronary artery disease was defined as a documented history of MI, previous percutaneous coronary intervention, or coronary artery bypass graft surgery. Non-high-density lipoprotein (non-HDL) cholesterol was calculated as total cholesterol minus high-density lipoprotein (HDL) cholesterol. Body mass index and obesity status were not consistently available in the retrospective records and therefore could not be reliably included in the present analysis.

As part of the institutional STEMI protocol, blood samples for admission laboratory analyses were routinely obtained immediately upon presentation to the emergency department, before coronary angiography and pPCI.

Admission laboratory analyses included white blood cell, eosinophil, monocyte, hemoglobin, and platelet counts, as well as serum creatinine, estimated glomerular filtration rate (GFR), C-reactive protein (CRP), lipid parameters, and routine biochemical measurements.

The admission EMR was calculated by dividing the absolute eosinophil count by the absolute monocyte count.

### Angiographic and Procedural Evaluation

All coronary angiographic procedures were performed via radial or femoral artery access in accordance with conventional clinical practice. Angiographic assessments included identification of the infarct-related artery, preprocedural and postprocedural TIMI flow grades, thrombus grade, stent-related procedural characteristics, and glycoprotein IIb/IIIa inhibitor use.

Thrombus burden was classified according to the TIMI thrombus grading system, and a TIMI thrombus grade of ≥4 was considered indicative of high thrombus burden.

The administration of glycoprotein IIb/IIIa inhibitors, primarily tirofiban infusion, was determined by the interventional cardiologist based on thrombus burden, the risk of distal embolization, and angiographic/procedural findings.

The no-reflow phenomenon was defined as persistent postprocedural TIMI flow grade ≤1 despite successful epicardial coronary recanalization and the absence of identifiable mechanical causes of impaired coronary flow, including significant residual stenosis, coronary dissection, epicardial spasm, and distal vessel

occlusion. No-reflow was independently adjudicated by two experienced interventional cardiologists who were blinded to clinical and laboratory data, including EMR values. In cases of disagreement, the final classification was established by consensus.[20]

**Electrocardiographic Assessment**

Twelve-lead electrocardiograms (ECGs) were routinely recorded at admission, immediately after pPCI, and again 60–90 minutes after the procedure. For the primary analysis, STR was assessed using the 12-lead ECG obtained 60–90 minutes after pPCI. ST-segment elevation was measured using a digital caliper at the J point+60 ms in all infarct-related leads, and STR was calculated as the percentage reduction in summed ST-segment elevation compared with the admission ECG. Resolution of ≥70% was considered complete STR, whereas a reduction of <70% in summed ST-segment elevation was classified as incomplete STR.[17,18,21] STR measurements were independently assessed by two experienced cardiologists who were blinded to clinical, laboratory, and angiographic data. In cases of disagreement, the final classification was established by consensus. Interobserver and intraobserver reproducibility of STR measurements was evaluated in a randomly selected subset of 50 patients. One observer repeated all measurements after a 2-week interval. Interobserver and intraobserver agreement was excellent, with intraclass correlation coefficients (ICCs) of 0.95 (95% confidence interval [CI], 0.91–0.97) and 0.97 (95% CI, 0.94–0.98), respectively.

**Study Endpoints**

The primary endpoint was incomplete ST-segment resolution after pPCI. The no-reflow analysis was secondary and hypothesis-generating.

**Statistical Analysis**

Continuous variables were assessed for distributional characteristics and are presented as mean±standard deviation or median (interquartile range), as appropriate. Categorical variables are presented as counts and percentages. Between-group comparisons were performed using Student's t test or the Mann–Whitney U test for continuous variables and the $\chi^2$ test or Fisher's exact test for categorical variables, as appropriate. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

The EMR was calculated as the absolute eosinophil count divided by the absolute monocyte count. Because EMR had a skewed distribution, analyses were performed using both its continuous form and an interquartile range (IQR) increment. Associations between candidate variables and incomplete ST-segment resolution or no-reflow were initially assessed using univariable logistic regression.

Candidate variables were considered within four conceptual categories: admission clinical and laboratory characteristics, angiographic characteristics, procedural treatments, and postprocedural findings. Multivariable models were restricted to variables available before assessment of the reperfusion outcome. Accordingly, procedural treatments (e.g., glycoprotein IIb/IIIa inhibitor use) and postprocedural findings (e.g., no-reflow and final TIMI flow) were considered post-baseline variables associated with the reperfusion outcome and were therefore excluded from the primary multivariable models. Multivariable logistic regression was used to identify independent factors associated with incomplete ST-segment resolution. For the no-reflow endpoint, Firth penalized logistic regression was used because of the limited number of events. Candidate variables for multivariable analysis were selected based on univariable associations ($P < 0.10$) and clinical relevance.

The functional form of the association between EMR and the study outcomes was further evaluated using restricted cubic spline analysis. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory performance of EMR, and the optimal threshold was determined using the Youden index. The discriminatory performance of EMR was compared with that of its individual components using DeLong's test for correlated ROC curves. The ROC-derived threshold was considered provisional and requires external validation.

Missing covariate data were handled using multiple imputation with predictive mean matching (10 imputations), and estimates were pooled across imputed datasets using Rubin's rules. A complete-case sensitivity analysis of the primary multivariable model was additionally performed to evaluate whether the association between EMR and incomplete ST-segment resolution was materially affected by the imputation approach. Internal validation of the multivariable models was performed using bootstrap resampling with optimism correction, including assessments of discrimination and calibration. Sensitivity analyses examined the consistency of the association between EMR and reperfusion outcomes across sex strata, with formal tests for interaction.

All statistical analyses were performed using R statistical software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria).

**Results**

A total of 492 consecutive patients younger than 45 years who presented with STEMI and were treated with pPCI were included in the study. Patients were stratified into tertiles according to admission EMR values: low EMR (T1, EMR<0.174, n=164), intermediate EMR (T2, EMR 0.174–0.341, n=164), and high EMR (T3, EMR>0.341, n=164).

**Baseline Clinical, Laboratory, and Procedural Characteristics**

Table 1 summarizes the baseline clinical, laboratory, angiographic, and procedural characteristics according to EMR tertiles. Age, sex, hypertension, smoking, family history of coronary artery disease, and other major demographic characteristics were broadly comparable across the three groups. However, diabetes mellitus, hyperlipidemia, and prior percutaneous coronary intervention (PCI) differed significantly across EMR tertiles, with diabetes and hyperlipidemia being more frequent in the intermediate and high EMR groups, whereas prior PCI was less frequent in the low EMR group.

As expected, marked differences were observed in hematologic parameters. Patients in the lowest EMR tertile had higher white blood cell and monocyte counts and substantially lower eosinophil counts than those in the higher EMR tertiles. In contrast, CRP and serum albumin levels were similar across groups. Renal indices also differed, with higher creatinine levels and lower GFR observed among patients with higher EMR values. Lipid profiles showed modest between-group differences, with total cholesterol, low-density lipoprotein (LDL) cholesterol, non-HDL cholesterol, and triglyceride levels varying significantly across EMR tertiles, whereas HDL cholesterol did not differ significantly.

**Table 1.** Baseline clinical, laboratory, angiographic, and procedural characteristics according to EMR tertiles

| Variables | T1: Low EMR <0.174 (n=164) | T2: Intermediate EMR 0.174–0.341 (n=164) | T3: High EMR >0.341 (n=164) | *P* |
|---|---|---|---|---|
| Demographics and history | | | | |
| Age, years | 41.00 (39.00–43.00) | 42.00 (39.00–43.00) | 42.00 (40.00–43.00) | 0.344 |
| Male sex, n (%) | 149 (90.9%) | 146 (89.0%) | 141 (86.0%) | 0.373 |
| Hypertension, n (%) | 43 (26.2%) | 52 (31.7%) | 47 (28.7%) | 0.547 |
| Diabetes mellitus, n (%) | 29 (17.7%) | 46 (28.0%) | 27 (16.5%) | 0.018 |
| Hyperlipidemia, n (%) | 13 (7.9%) | 36 (22.0%) | 29 (17.7%) | 0.002 |
| Smoking, n (%) | 81 (49.4%) | 67 (40.9%) | 69 (42.1%) | 0.242 |
| Prior PCI, n (%) | 19 (11.6%) | 36 (22.0%) | 34 (20.7%) | 0.029 |
| Family history of CAD, n (%) | 40 (24.4%) | 31 (18.9%) | 34 (20.7%) | 0.466 |
| Previous cerebrovascular disease, n (%) | 0 (0.0%) | 1 (0.6%) | 2 (1.2%) | 0.776 |
| Peripheral arterial disease, n (%) | 1 (0.6%) | 1 (0.6%) | 2 (1.2%) | 1.000 |
| COPD, n (%) | 1 (0.6%) | 6 (3.7%) | 5 (3.0%) | 0.171 |
| Admission laboratory data | | | | |
| White blood cell count, $\times10^3/\mu L$ | 10.90 (9.50–12.71) | 9.55 (8.12–11.43) | 9.57 (8.19–11.10) | <0.001 |
| Hemoglobin, g/dL | 14.80 (13.9–15.6) | 15.00 (13.8–16.0) | 15.10 (13.8–15.8) | 0.164 |
| Platelet count, $\times10^3/\mu L$ | 258 (224–302) | 259 (223–294) | 260 (222–310) | 0.668 |
| Eosinophil count, $\times10^3/\mu L$ | 0.07 (0.04–0.10) | 0.16 (0.13–0.21) | 0.30 (0.23–0.40) | <0.001 |
| Monocyte count, $\times10^3/\mu L$ | 0.74 (0.59–0.91) | 0.68 (0.54–0.83) | 0.60 (0.48–0.75) | <0.001 |
| Eosinophil-to-monocyte ratio | 0.095 (0.054–0.135) | 0.250 (0.208–0.289) | 0.487 (0.399–0.659) | <0.001 |
| C-reactive protein, mg/L | 3.52 (1.94–6.51) | 3.70 (1.90–7.65) | 3.52 (1.89–7.60) | 0.962 |
| Serum albumin, g/L | 45.0 (43.0–48.0) | 45.5 (42.0–47.8) | 45.0 (40.8–48.0) | 0.965 |
| Creatinine, mg/dL | 0.81 (0.71–0.89) | 0.83 (0.72–0.95) | 0.87 (0.75–0.97) | 0.008 |
| GFR, mL/min/1.73 $m^2$ | 110.0 (104–115) | 107.0 (97–113) | 106.0 (95–112) | <0.001 |
| Admission glucose, mg/dL | 110 (97–128) | 106 (95–147) | 103 (92–133) | 0.076 |
| Total cholesterol, mg/dL | 190 (165–218) | 189 (166–221) | 208 (166–232) | 0.035 |
| LDL cholesterol, mg/dL | 117 (95–141) | 109 (87–133) | 117 (89–146) | 0.030 |
| HDL cholesterol, mg/dL | 36 (32–44) | 35 (31–41) | 36 (31–43) | 0.250 |
| Non-HDL cholesterol, mg/dL | 151 (129–179) | 154 (128–183) | 170 (129–194) | 0.032 |
| Triglycerides, mg/dL | 154 (103–221) | 181 (119–275) | 167 (122–260) | 0.008 |
| Clinical presentation | | | | |
| Infarct location, n (%) | | | | 0.171 |
| Anterior | 74 (45.1%) | 64 (39.0%) | 82 (50.0%) | |
| Inferior | 61 (37.2%) | 67 (40.9%) | 45 (27.4%) | |
| Lateral | 10 (6.1%) | 16 (9.8%) | 14 (8.5%) | |
| Posterior | 19 (11.6%) | 17 (10.4%) | 23 (14.0%) | |
| Anterior MI, n (%) | 74 (45.1%) | 64 (39.0%) | 82 (50.0%) | 0.135 |
| Killip class ≥2, n (%) | 13 (7.9%) | 9 (5.5%) | 14 (8.5%) | 0.533 |
| Cardiogenic shock, n (%) | 1 (0.6%) | 0 (0.0%) | 2 (1.2%) | 0.776 |
| Echocardiography | | | | |
| LVEF, % | 60.0 (45.0–65.0) | 65.0 (53.7–65.0) | 65.0 (55.0–65.0) | <0.001 |
| >Mild mitral regurgitation, n (%) | 56 (34.1%) | 51 (31.1%) | 54 (32.9%) | 0.363 |
| Angiographic Data | | | | |
| Initial TIMI flow grade, n (%) | | | | 0.941 |
| Grade 0 | 110 (67.1%) | 109 (66.5%) | 103 (62.8%) | |
| Grade 1 | 44 (26.8%) | 45 (27.4%) | 50 (30.5%) | |
| Grade 2 | 10 (6.1%) | 10 (6.1%) | 11 (6.7%) | |

**Table 1 (cont).** Baseline clinical, laboratory, angiographic, and procedural characteristics according to EMR tertiles

| Variables | T1: Low EMR <0.174 (n=164) | T2: Intermediate EMR 0.174–0.341 (n=164) | T3: High EMR >0.341 (n=164) | *P* |
|---|---|---|---|---|
| Left anterior descending artery, n (%) | 100 (61.0%) | 77 (47.0%) | 100 (61.0%) | 0.013 |
| Right coronary artery, n (%) | 64 (39.0%) | 63 (38.4%) | 43 (26.2%) | 0.023 |
| Circumflex artery, n (%) | 37 (22.6%) | 40 (24.4%) | 44 (26.8%) | 0.667 |
| Diagonal branch, n (%) | 9 (5.5%) | 14 (8.5%) | 15 (9.1%) | 0.413 |
| Obtuse marginal branch, n (%) | 17 (10.4%) | 19 (11.6%) | 12 (7.3%) | 0.406 |
| Intermediate branch, n (%) | 9 (5.5%) | 10 (6.1%) | 5 (3.0%) | 0.399 |
| Saphenous vein graft, n (%) | 2 (1.2%) | 3 (1.8%) | 3 (1.8%) | 1.000 |
| Multivessel disease, n (%) | 49 (29.9%) | 43 (26.2%) | 38 (23.2%) | 0.386 |
| Lesion length, mm | 21 (16–28) | 20 (15–26) | 21 (16–29) | 0.047 |
| Reference vessel diameter, mm | 2.95 ± 0.46 | 2.91 ± 0.45 | 2.90 ± 0.46 | 0.605 |
| High TIMI thrombus grade (≥4), n (%) | 94 (57.3%) | 85 (51.8%) | 60 (36.6%) | 0.004 |
| Procedural data | | | | |
| Door-to-balloon time, min | 23 (21–26) | 24 (21–26) | 23 (20–25) | 0.182 |
| Ticagrelor, n (%) | 80 (48.8%) | 116 (70.7%) | 114 (69.5%) | <0.001 |
| Prasugrel, n (%) | 72 (43.9%) | 40 (24.4%) | 47 (28.7%) | <0.001 |
| Clopidogrel, n (%) | 12 (7.3%) | 8 (4.9%) | 3 (1.8%) | 0.062 |
| Balloon predilatation, n (%) | 147 (89.6%) | 144 (87.8%) | 153 (93.3%) | 0.234 |
| Stent implantation, n (%) | 162 (98.8%) | 148 (90.2%) | 158 (96.3%) | 0.001 |
| Balloon-only angioplasty, n (%) | 3 (1.8%) | 16 (9.8%) | 6 (3.7%) | 0.003 |
| Stent diameter, mm | 2.97±0.38 | 2.95±0.39 | 2.96±0.38 | 0.830 |
| Stent length, mm | 24 (19–32) | 24 (18–29) | 24 (20–32) | 0.025 |
| Postdilatation, n (%) | 98 (59.8%) | 86 (52.4%) | 99 (60.4%) | 0.271 |
| Intracoronary nitrate use, n (%) | 13 (7.9%) | 22 (13.4%) | 15 (9.1%) | 0.225 |
| Thrombus aspiration, n (%) | 7 (4.3%) | 2 (1.2%) | 1 (0.6%) | 0.089 |
| GP IIb/IIIa inhibitor use, n (%) | 60 (36.6%) | 19 (11.6%) | 22 (13.4%) | <0.001 |
| Final TIMI flow <3, n (%) | 36 (22.0%) | 16 (9.8%) | 12 (7.3%) | <0.001 |
| Clinical outcomes | | | | |
| Incomplete ST-segment resolution (<70%), n (%) | 38 (23.2%) | 8 (4.9%) | 6 (3.7%) | <0.001 |
| No-reflow phenomenon, n (%) | 22 (13.4%) | 0 (0.0%) | 3 (1.8%) | <0.001 |
| In-hospital mortality, n (%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0.367 |

Continuous variables are presented as median (interquartile range [IQR]) or mean±standard deviation (SD), as appropriate. Categorical variables are presented as n (%). CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; EMR, eosinophil-to-monocyte ratio; GFR, glomerular filtration rate; GP IIb/IIIa, glycoprotein IIb/IIIa; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction.

Regarding clinical presentation, the distribution of infarct location, Killip class ≥2, and cardiogenic shock was similar across EMR tertiles. Left ventricular ejection fraction, however, was significantly lower in the low EMR group than in the intermediate and high EMR groups (60.0% vs. 65.0% vs. 65.0%, respectively; P < 0.001).

Angiographic characteristics also differed across EMR tertiles. The distribution of initial TIMI flow grade was comparable among groups; however, the culprit vessel distribution differed, with a higher frequency of left anterior descending artery involvement in the low and high EMR groups and a higher frequency of right coronary artery involvement in the low EMR group. Lesion length was modestly greater in the high EMR group, whereas reference vessel diameter and multivessel disease did not differ significantly. Importantly, a high TIMI thrombus grade (≥4) was significantly more frequent among patients with low EMR values (57.3% vs. 51.8% vs. 36.6%; P = 0.004).

Several procedural characteristics differed significantly across EMR tertiles. Ticagrelor use was more frequent in the intermediate and high EMR groups, whereas prasugrel use was more common in the low EMR group; clopidogrel use did not differ significantly among groups. Stent implantation was most frequent in the low EMR group, whereas balloon-only angioplasty was more common in the intermediate EMR group. Stent length also differed modestly across tertiles, whereas door-to-balloon time, balloon predilatation, stent diameter, postdilatation, intracoronary nitrate use, and thrombus aspiration did not differ significantly.

The lowest EMR tertile was also associated with markedly higher rates of glycoprotein IIb/IIIa inhibitor use, impaired final epicardial flow, incomplete ST-segment resolution, and the no-reflow phenomenon. Glycoprotein IIb/IIIa inhibitor use was significantly more common in patients with low EMR values (36.6% vs. 11.6% vs. 13.4%; P < 0.001). Final TIMI flow <3 occurred more

frequently in the low EMR group (22.0% vs. 9.8% vs. 7.3%; P < 0.001). Similarly, incomplete ST-segment resolution was observed in 23.2%, 4.9%, and 3.7% of patients in the low, intermediate, and high EMR groups, respectively (P < 0.001). No-reflow was predominantly observed in the low EMR tertile (13.4% vs. 0.0% vs. 1.8%; P < 0.001). In-hospital mortality was rare, with only one death (0.2%) in the entire cohort, and did not differ significantly across EMR tertiles (P = 0.367).

**Factors Associated With Incomplete ST-Segment Resolution**

Supplementary Table 1 summarizes the univariable logistic regression analyses assessing factors associated with incomplete ST-segment resolution. Both the standard EMR model (odds ratio [OR] 0.003, 95% confidence interval [CI] <0.001–0.032, P < 0.001) and the interquartile range (IQR)-based EMR model (OR 0.22, 95% CI 0.12–0.42, P < 0.001) showed a strong inverse association between EMR and incomplete ST-segment resolution.

Several other variables, including younger age, higher white blood cell count, lower serum albumin levels, TIMI thrombus grade 5, the no-reflow phenomenon, and glycoprotein IIb/IIIa inhibitor use, were significantly associated with incomplete ST-segment resolution. The no-reflow phenomenon (OR 54.38, 95% CI 20.50–172.0, P < 0.001) and glycoprotein IIb/IIIa inhibitor use (OR 18.30, 95% CI 9.47–37.50, P < 0.001) showed the strongest associations among these variables.

After multivariable adjustment, EMR remained independently associated with incomplete ST-segment resolution, with each IQR increase in EMR associated with lower odds of incomplete ST-segment resolution (OR 0.245, 95% CI 0.127–0.475, P < 0.001). Higher TIMI thrombus grade, younger age, and lower serum albumin levels also remained significantly associated with incomplete ST-segment resolution after adjustment, whereas inferior infarct location did not reach statistical significance. Additionally, within this exclusively young STEMI population, younger age was independently associated with incomplete ST-segment resolution (Table 2).

Forest plot visualization of the multivariable regression model further demonstrated the strong inverse association between EMR and incomplete ST-segment resolution (Figure 1). Internal validation of the multivariable model showed an optimism-corrected area under the curve (AUC) of 0.779, with a calibration slope of 0.898 and a calibration intercept of −0.153 (Supplementary Table 2).

**Restricted Cubic Spline Analysis**

Restricted cubic spline analysis further demonstrated a nonlinear inverse association between EMR levels and the probability of incomplete ST-segment resolution (Figure 2). The predicted probability of incomplete ST-segment resolution increased more steeply at lower EMR values, particularly below approximately 0.20, whereas the curve tended to plateau at higher EMR values. However, the confidence intervals widened at the extremes of the EMR distribution, and these findings should therefore be interpreted with caution. The ROC-derived EMR cutoff value was 0.183, which was close to the lower boundary of the lowest EMR tertile. This data-derived threshold should be considered provisional rather than a validated clinical decision threshold and requires external validation before any potential clinical application. Importantly, its proximity to the tertile boundary should not be interpreted as evidence of a biological threshold or as indicating that progressively higher EMR values are uniformly protective. Overall, the spline analysis supports a nonlinear association between EMR and incomplete ST-segment resolution, with greater uncertainty at the extreme ends of the EMR distribution.

**Factors Associated With the No-Reflow Phenomenon**

Supplementary Table 3 presents univariable logistic regression analyses assessing factors associated with the no-reflow phenomenon. Lower EMR levels were significantly associated with no-reflow in both the conventional EMR model and the interquartile range (IQR)-based model (odds ratio [OR] 0.07, 95% confidence interval [CI] 0.02–0.23, P < 0.001). Increased white blood cell count, elevated CRP levels, hyperlipidemia, TIMI thrombus grade 5, and glycoprotein IIb/IIIa inhibitor use were also significantly associated with no-reflow.

Given the limited number of no-reflow events, multivariable analysis was performed using Firth penalized logistic regression. Lower admission EMR remained independently associated with the occurrence of no-reflow (adjusted OR 0.079, 95% CI 0.021–0.238, P < 0.001), whereas the associations of TIMI thrombus grade and age were no longer statistically significant after adjustment (Table 3). Internal validation showed successful model convergence, no evidence of undue influence from individual observations, and an optimism-corrected area under the curve (AUC) of 0.811 with a calibration slope of 0.919 (Supplementary Table 4). Given the limited number of no-reflow events, these findings should be interpreted cautiously and require confirmation in larger cohorts. No-reflow events were predominantly concentrated in the lower EMR deciles, with 22 of 25 events (88.0%) occurring within the lowest four deciles (EMR≤0.202) (Supplementary Table 5).

**Table 2.** Multivariable logistic regression analysis of factors associated with incomplete ST-segment resolution

| Variables | OR | 95% CI | *P* |
|---|---|---|---|
| Eosinophil-to-monocyte ratio, per interquartile range increment (0.135→0.398) | 0.245 | 0.127–0.475 | <0.001 |
| TIMI thrombus grade, per grade | 1.982 | 1.141–3.442 | 0.015 |
| Age, per year | 0.842 | 0.761–0.933 | <0.001 |
| Serum albumin, per g/L | 0.895 | 0.810–0.988 | 0.028 |
| Inferior infarct location | 1.816 | 0.968–3.405 | 0.063 |

The model included all 492 patients (52 events; 10.4 events per variable). Variables were selected based on univariable associations (P < 0.10) and clinical relevance. Only variables available before assessment of the reperfusion outcome were considered eligible for inclusion; therefore, glycoprotein IIb/IIIa inhibitor use, thrombus aspiration, final TIMI flow grade, and the no-reflow phenomenon were excluded from the multivariable model. Serum albumin was unavailable in 187 patients (38.0%) and was handled using multiple imputation (m=10, predictive mean matching), with estimates pooled using Rubin's rules. EMR, eosinophil-to-monocyte ratio; OR, odds ratio; CI, confidence interval; TIMI, thrombolysis in myocardial infarction.

**Table 3.** Multivariable Firth penalized logistic regression analysis of factors associated with no-reflow

| Variables | aOR | 95% CI | *P* |
|---|---|---|---|
| Eosinophil-to-monocyte ratio, per interquartile range increment (0.135→0.398) | 0.079 | 0.021–0.238 | <0.001 |
| TIMI thrombus grade, per grade | 1.209 | 0.651–2.392 | 0.557 |
| Age, per year | 0.905 | 0.802–1.031 | 0.127 |

No-reflow occurred in 25 of 492 patients (5.1%). The model included three covariates, yielding 8.3 events per variable. Because of the small number of events, the model was estimated using Firth's penalized maximum likelihood method with profile penalized likelihood confidence intervals and penalized likelihood-ratio p values. An analysis by EMR tertiles was not performed because no events occurred in the intermediate tertile (22, 0, and 3 events across ascending tertiles), precluding estimation. As in the incomplete ST-segment resolution model, only variables available before assessment of the reperfusion outcome were eligible for inclusion; therefore, procedural treatments (glycoprotein IIb/IIIa inhibitor use) and other postprocedural findings were not entered as candidate predictors in this model. Accordingly, all findings for this endpoint should be considered exploratory. aOR, adjusted odds ratio; CI, confidence interval; EMR, eosinophil-to-monocyte ratio; TIMI, thrombolysis in myocardial infarction.

### Discriminative Performance of EMR

With an AUC of 0.757 (95% CI, 0.684–0.831), ROC analysis demonstrated that EMR provided acceptable discriminatory performance for identifying incomplete ST-segment resolution (Figure 3). Based on the Youden index, the ROC-derived EMR threshold for discriminating patients with incomplete ST-segment resolution was 0.183. Operating characteristics for this threshold, including sensitivity, specificity, predictive values, and bootstrap-based internal validation, are presented in Supplementary Table 6. To further evaluate whether EMR provided greater discriminatory performance than its individual components, ROC curves for EMR, absolute eosinophil count, and absolute monocyte count were compared. EMR demonstrated significantly better discriminatory performance than eosinophil count alone (AUC 0.654, 95% CI, 0.566–0.742; ΔAUC +0.104, P = 0.041) and monocyte count (AUC 0.533, 95% CI, 0.444–0.621; ΔAUC +0.225, P < 0.001) according to formal DeLong comparisons (Figure 3).

Similarly, EMR showed acceptable discriminatory performance for the no-reflow phenomenon, with an AUC of 0.827 (95% CI, 0.728–0.926) (Figure 4). The ROC-derived EMR cutoff value for discriminating patients with no-reflow was 0.13, with corresponding operating characteristics and bootstrap-based internal validation presented in Supplementary Table 6. For the secondary no-reflow endpoint, EMR significantly outperformed monocyte count (ΔAUC +0.273, P < 0.001), whereas the difference compared with eosinophil count did not reach statistical significance (ΔAUC +0.164, P = 0.063) (Supplementary Table 7).

EMR distributions were comparable between women and men (P = 0.083), and no significant interaction between sex and EMR was observed for either incomplete ST-segment resolution (likelihood-ratio test for interaction, P = 0.190) or no-reflow (likelihood-ratio test for interaction, P = 0.796) (Supplementary Table 8).

### Sensitivity Analyses

Sensitivity analyses demonstrated that the association between EMR and incomplete ST-segment resolution was robust across different adjustment strategies. In the model including admission clinical and laboratory variables without angiographic thrombus burden, the association remained significant (OR 0.221, 95% CI 0.115–0.424, P < 0.001). Further adjustment for the P2Y12 inhibitor agent did not materially alter the EMR estimate (OR 0.251, 95% CI 0.129–0.486, P < 0.001). In the complete-case analysis without multiple imputation, the association remained significant and directionally consistent (OR 0.176, 95% CI 0.089–0.341, P < 0.001). These sensitivity analyses are presented in Supplementary Table 9.

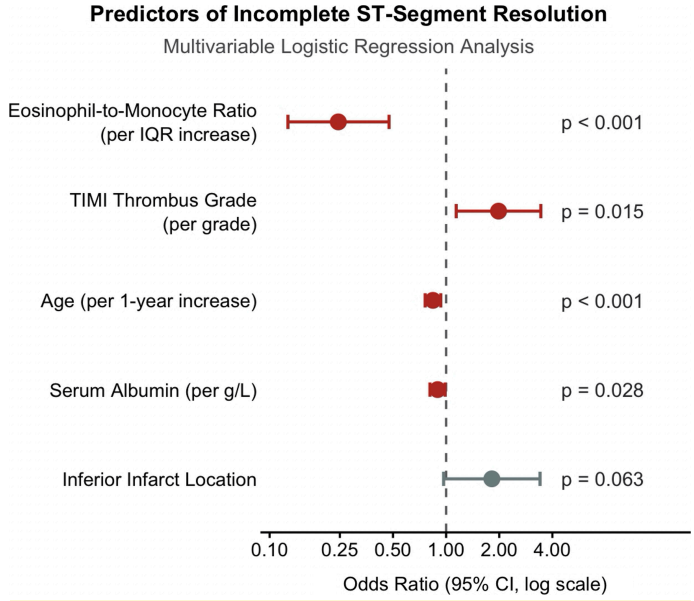



**Figure 1.** Forest plot of the multivariable logistic regression analysis of factors associated with incomplete ST-segment resolution. Odds ratios are shown on a logarithmic scale with 95% confidence intervals. Red markers indicate statistically significant model covariates (P < 0.05), whereas gray markers indicate nonsignificant covariates. The eosinophil-to-monocyte ratio (EMR) was modeled per interquartile range increase.

CI, confidence interval; EMR, eosinophil-to-monocyte ratio.

## Discussion

The current investigation demonstrated a strong association between lower admission EMR values and impaired myocardial reperfusion across electrocardiographic, angiographic, and procedural reperfusion parameters among young patients with STEMI undergoing pPCI. The main findings of our study were as follows: (1) lower EMR was independently associated with impaired ST-segment resolution after pPCI; (2) lower EMR values were associated with greater thrombus burden, more frequent impairment of postprocedural TIMI flow, and higher rates of glycoprotein IIb/IIIa inhibitor administration; (3) lower EMR remained independently associated with no-reflow; and (4) the association between EMR and impaired myocardial reperfusion was nonlinear, with a steeper increase in the probability of impaired reperfusion at lower EMR levels rather than evidence of a fixed biological threshold. To the best of our knowledge, this study is among the first to comprehensively investigate the association between EMR and myocardial reperfusion markers, including ST-segment resolution and the no-reflow phenomenon, specifically in a young STEMI cohort treated with pPCI.

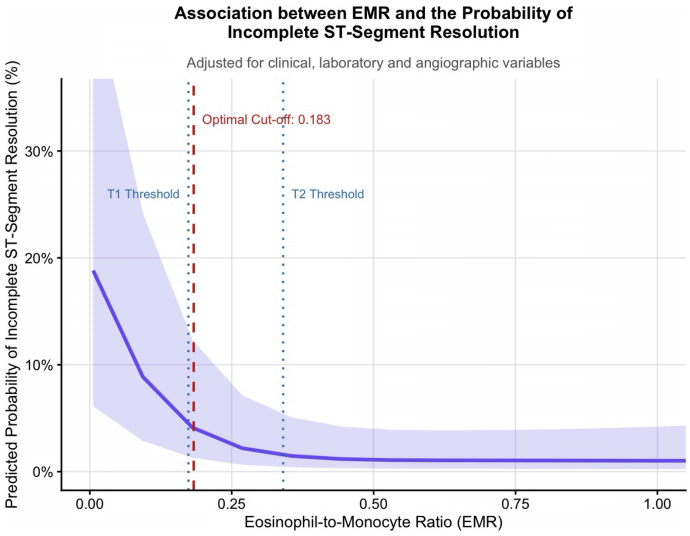



**Figure 2.** Restricted cubic spline showing the association between the eosinophil-to-monocyte ratio (EMR) and the predicted probability of incomplete ST-segment resolution. The model was adjusted for age, serum albumin, Thrombolysis in Myocardial Infarction (TIMI) thrombus grade, and inferior infarct location. The solid line represents the adjusted predicted probability, and the shaded area indicates the 95% confidence interval. The red dashed line denotes the receiver operating characteristic (ROC)-derived EMR cutoff (0.183), presented as a provisional threshold, whereas the blue dotted lines indicate the thresholds defining the EMR tertiles.

CI, confidence interval; EMR, eosinophil-to-monocyte ratio; ROC, receiver operating characteristic; TIMI, Thrombolysis in Myocardial Infarction.

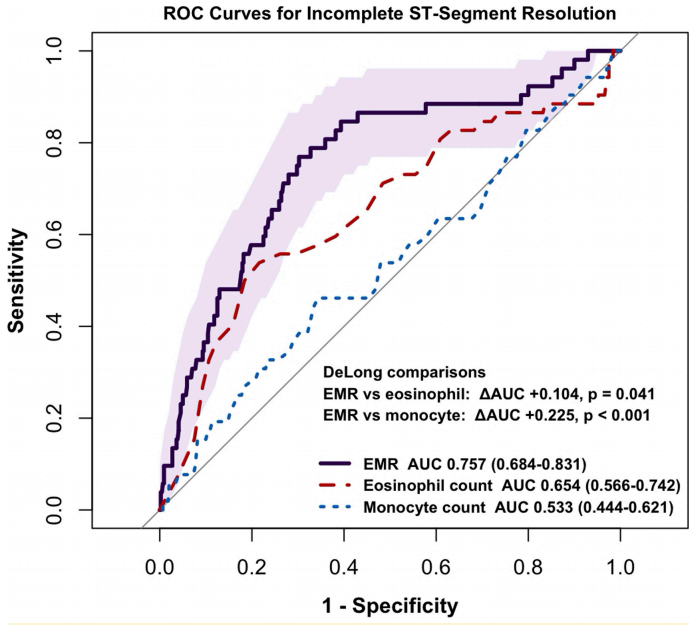



**Figure 3.** Receiver operating characteristic (ROC) curves comparing the discriminatory performance of the eosinophil-to-monocyte ratio (EMR), eosinophil count, and monocyte count for identifying incomplete ST-segment resolution after primary percutaneous coronary intervention. The shaded area represents the 95% confidence interval of the ROC curve for EMR. Pairwise comparisons between correlated ROC curves were performed using DeLong's test.

AUC, area under the receiver operating characteristic curve; EMR, eosinophil-to-monocyte ratio; ROC, receiver operating characteristic.

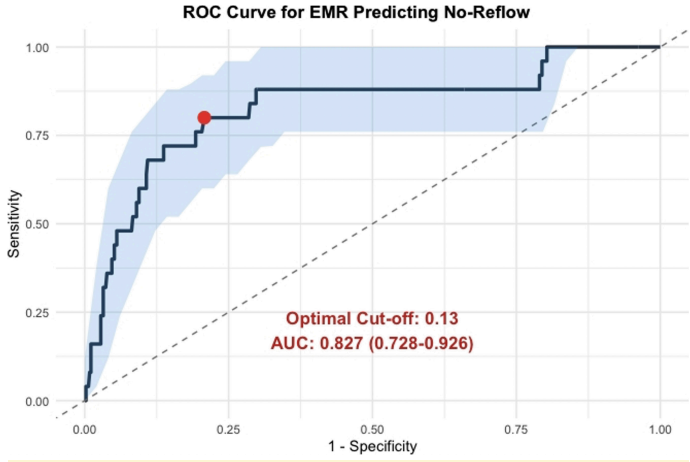



**Figure 4.** Receiver operating characteristic (ROC) curve demonstrating the discriminatory performance of the eosinophil-to-monocyte ratio (EMR) for identifying the no-reflow phenomenon after primary percutaneous coronary intervention. The shaded area represents the 95% confidence interval of the ROC curve. The red dot indicates the ROC-derived cutoff value determined using the Youden index and presented as a provisional threshold.

AUC, area under the receiver operating characteristic curve; EMR, eosinophil-to-monocyte ratio; ROC, receiver operating characteristic.

Although pPCI successfully restores epicardial coronary patency in most patients with STEMI, adequate tissue-level myocardial reperfusion cannot always be achieved. Persistent microvascular dysfunction despite successful reperfusion continues to play a major role in determining infarct size, ventricular dysfunction, heart failure, and mortality.[11–15] Electrocardiographic STR is considered a practical and reliable indicator of myocardial tissue-level reperfusion. Previous studies have demonstrated that, even after successful epicardial coronary recanalization, incomplete ST-segment resolution is strongly associated with poor microvascular perfusion and adverse cardiovascular outcomes.[22–24] In addition, STR is considered a simple, inexpensive, and readily available bedside tool that can be used repeatedly during follow-up to assess myocardial reperfusion, complementing angiographic assessment of TIMI flow. In the current study, patients with lower EMR values exhibited markedly higher rates of incomplete ST-segment resolution, suggesting a potential association between EMR and impaired microvascular reperfusion.

The exact mechanisms underlying the relationship between low EMR and impaired myocardial reperfusion are likely multifactorial. Inflammatory activation and thrombosis play central roles in STEMI pathophysiology, particularly in younger patients, in whom thrombo-inflammatory mechanisms may contribute more prominently to plaque instability and coronary thrombosis.[7–10] Premature STEMI is often characterized by a predominantly thrombotic and inflammatory phenotype rather than advanced chronic atherosclerosis. Previous studies have provided substantial evidence regarding the role of monocytes in STEMI pathogenesis. Monocytes are among the key inflammatory cells involved in endothelial dysfunction, atherosclerotic plaque progression, inflammatory cytokine release, and thrombus propagation.[25] In patients with STEMI, increased monocyte activity has also been associated with worse angiographic outcomes and greater thrombus burden.[26] In contrast, eosinophils may exert modulatory effects on both thrombosis and inflammation through the release of various mediators and have been shown to infiltrate coronary thrombi and infarct-related myocardial tissue, which

may partially explain the reduction in circulating eosinophil levels observed during acute STEMI.[27–30] Thus, EMR may capture the balance between eosinophil- and monocyte-related processes associated with thrombo-inflammatory activity rather than representing a specific pathophysiological mechanism.

An important consideration, however, is that admission EMR may reflect not only a pre-existing thrombo-inflammatory phenotype but also the acute biological response to STEMI. Acute physiological stress and endogenous glucocorticoid responses may contribute to transient eosinopenia through redistribution of circulating eosinophils and changes in tissue trafficking. Accordingly, a low EMR at presentation may partly represent an acute severity-related response rather than an antecedent biological phenotype. This distinction is particularly relevant because the observed associations in the present study appear to be driven predominantly by the eosinophil component, whereas monocyte count alone showed limited discriminatory performance for the study endpoints. Therefore, the biological significance of a low admission EMR remains uncertain, and the present findings should be interpreted as an association between admission EMR and reperfusion rather than as evidence that EMR identifies an established pre-existing risk phenotype.

Although absolute eosinophil count was also associated with impaired myocardial reperfusion, the relative discriminatory advantage of EMR should be interpreted cautiously. For incomplete ST-segment resolution, EMR demonstrated statistically greater discrimination than eosinophil count alone, although the difference was modest. In contrast, for the secondary no-reflow endpoint, EMR did not demonstrate statistically superior discrimination compared with eosinophil count alone, suggesting that the eosinophil component may account for an important part of the observed association. Thus, the present findings do not establish EMR as a fundamentally superior biomarker to its individual components. Whether combining eosinophil and monocyte information provides clinically meaningful incremental value beyond established clinical and procedural variables remains uncertain and requires prospective external validation.

It should also be noted that eosinophil counts may be elevated by conditions other than STEMI-related thrombo-inflammatory activity, including allergic or atopic disease, parasitic infection, recent drug hypersensitivity reactions, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndromes, and Kounis syndrome. Patients with known autoimmune disease or systemic corticosteroid use were excluded, but these conditions were not systematically or uniformly screened for in this retrospective cohort and could not be reliably identified or excluded beyond the information available in the medical records. Patients with higher EMR values may therefore represent a biologically heterogeneous group rather than a uniformly low-risk population, and the present findings should be interpreted as an association rather than as evidence that progressively higher EMR values are uniformly protective.

Findings from previous studies of thrombotic disorders also support the association between low EMR levels and thrombus burden. In patients with acute pulmonary embolism, reduced EMR values were reported to correlate with higher Qanadli scores, indicating greater thrombus burden.[31] Likewise, earlier studies reported that, in patients with acute ischemic stroke undergoing thrombolytic therapy, lower EMR levels were associated with worse clinical outcomes.[32] Deng et al.[19] also showed that, in patients with STEMI undergoing pPCI, lower EMR levels at hospital admission were independently associated with higher short- and long-term mortality (adjusted hazard ratio [HR] 0.10, 95% confidence interval [CI] 0.01–0.90 for 1-month mortality; HR 0.18, 95% CI 0.05–0.69 for long-term mortality), with an area under the curve (AUC) of 0.79 for 1-month mortality prediction, comparable in magnitude to the discriminatory performance of EMR for incomplete ST-segment resolution (AUC 0.757) observed in the present study. Taken together, these observations from diverse acute ischemic conditions suggest that lower EMR values may reflect enhanced thrombo-inflammatory activity, consistent with the impaired reperfusion observed in the present study.

Consistent with these mechanisms, patients in the lowest EMR tertile had significantly higher rates of high TIMI thrombus grade, impaired final TIMI flow, increased glycoprotein IIb/IIIa inhibitor use, incomplete ST-segment resolution, and no-reflow. Angiographic thrombus burden and distal embolization are among the principal mechanisms contributing to microvascular obstruction and impaired tissue-level reperfusion after pPCI. Previous meta-analyses investigating no-reflow in patients with STEMI demonstrated that high thrombus burden represents one of the strongest predictors of no-reflow and adverse clinical outcomes.[20] In this context, the more frequent use of glycoprotein IIb/IIIa inhibitors in patients with lower EMR values may indirectly reflect greater procedural thrombus burden rather than an independent mechanistic pathway. Furthermore, Parsova et al.[33] demonstrated that elevated systemic inflammatory indices were associated with increased tirofiban use due to high thrombus burden in patients with STEMI. Accordingly, the association between lower EMR and impaired myocardial reperfusion may be mediated, at least in part, by greater angiographic thrombus burden and the consequent need for intensified antithrombotic therapy.

The association between EMR and incomplete ST-segment resolution also persisted in a model without adjustment for angiographic thrombus burden, suggesting that the observed association was not fully explained by thrombus burden. Nevertheless, because thrombus burden may lie on the biological pathway between inflammatory status and impaired reperfusion, adjustment for thrombus grade may attenuate part of the total association.

Differences in P2Y12 inhibitor therapy represented another potential source of confounding because treatment selection differed across EMR tertiles. However, adjustment for P2Y12 inhibitor agent did not materially alter the association between EMR and incomplete ST-segment resolution, supporting the robustness of this finding.

In patients with STEMI undergoing pPCI, the no-reflow phenomenon-defined as insufficient myocardial perfusion despite successful epicardial coronary recanalization-remains a significant predictor of adverse clinical outcomes. Distal embolization, endothelial dysfunction, inflammatory activation, platelet aggregation, and ischemia-reperfusion injury all contribute to the pathogenesis of no-reflow.[20] Recently, Taşolar et al.[34] demonstrated that advanced machine learning models achieved high predictive performance for no-reflow in patients with STEMI, further supporting the multifactorial nature of no-reflow pathophysiology. In the present study, lower EMR values were associated with

no-reflow in both univariable and Firth-penalized multivariable analyses. Nevertheless, given the limited number of no-reflow events and the lack of statistically significant superiority of EMR over eosinophil count alone, this finding should be interpreted as hypothesis-generating and requires confirmation in larger cohorts.

As a secondary observation, younger age within this exclusively young STEMI cohort was independently associated with incomplete ST-segment resolution. One possible explanation for this observation may be the relatively limited collateral coronary circulation in younger patients compared with older individuals with more chronic and progressive coronary artery disease. Previous studies have demonstrated that older patients with longstanding coronary atherosclerosis may develop more extensive collateral circulation, potentially attenuating ischemic injury and improving tissue-level reperfusion during acute coronary occlusion.[35] In contrast, younger patients with STEMI may exhibit a more abrupt, thrombosis-driven presentation with less chronic ischemic preconditioning and insufficient collateral development, potentially increasing susceptibility to impaired microvascular reperfusion. However, given the narrow age range of the study population and the exploratory nature of this analysis, this result should be interpreted with caution.

Restricted cubic spline analysis further demonstrated a nonlinear association between EMR and incomplete ST-segment resolution, with a steeper increase in the predicted probability of impaired reperfusion at lower EMR values. Given the wider confidence intervals at the extremes of the EMR distribution, the ROC-derived cutoff should be regarded as provisional rather than as evidence of a biological threshold.

Overall, our findings support EMR as an admission marker associated with impaired myocardial reperfusion in young patients with STEMI rather than as an established clinical risk biomarker. The observed association may reflect a combination of thrombo-inflammatory activity, angiographic thrombus burden, and acute stress-related changes in circulating eosinophils. Whether EMR provides incremental clinical information beyond its individual components and established clinical and procedural variables, or whether EMR-guided risk stratification could play any role in individualized management, remains uncertain and requires prospective, multicenter external validation. In particular, the ROC-derived EMR thresholds identified in this study are hypothesis-generating rather than validated decision points and should not be used to guide procedural decision-making in real-world practice until externally validated.

**Limitations**

This study has several limitations that should be considered. First, the retrospective, observational, single-center design carries an inherent risk of selection bias, which may limit the generalizability of our findings. In addition, the exclusion of patients with missing data required for eligibility determination, EMR calculation, ST-segment resolution assessment, or essential angiographic/procedural evaluation may have introduced selection bias and limited the representativeness of the study population. Second, EMR was derived from a single admission blood sample obtained upon presentation to the emergency department, while serial inflammatory marker measurements were unavailable. Moreover, because of the retrospective design, the interval between symptom onset and blood sampling was not standardized and could not be incorporated into the analyses. Consequently, lower admission EMR may partly reflect acute stress-related eosinopenia occurring during STEMI rather than a pre-existing biological predisposition, and the possibility of reverse causation cannot be excluded. Conditions that may influence eosinophil counts, such as allergic or atopic diseases, parasitic infections, drug hypersensitivity reactions, Kounis syndrome, or other eosinophilic disorders, were not systematically assessed. Although patients with autoimmune diseases and systemic corticosteroid use were excluded, unrecognized eosinophil-associated conditions could not be reliably evaluated. A systematic etiologic workup for young MI, including thrombophilia testing, substance exposure, lipoprotein(a), and other nonatherosclerotic causes, was not routinely available in this retrospective cohort. Body mass index and obesity status were also not consistently available in the retrospective records and therefore could not be incorporated into the baseline characterization or regression analyses. Third, because advanced imaging modalities such as cardiac magnetic resonance imaging were not routinely available, myocardial reperfusion was assessed primarily using electrocardiographic and angiographic measures. Fourth, glycoprotein IIb/IIIa inhibitor use was at the operator's discretion and may have varied according to procedural findings and operator preference. Fifth, although the multivariable model underwent internal validation using bootstrap optimism correction and calibration analyses, external validation in an independent cohort was not available. In addition, the relatively small number of no-reflow events may have limited the statistical stability of the secondary no-reflow analyses. Furthermore, although sex-specific analyses and formal interaction testing were performed (Supplementary Table 8), only 56 women (11.4%) were included, and the small number of events in this subgroup limited statistical power; no significant interaction between sex and EMR was observed, but these findings should be interpreted as exploratory, and potential sex-related differences in the association between EMR and myocardial reperfusion warrant further investigation in larger cohorts. In women, potentially relevant factors associated with premature MI, such as oral contraceptive exposure, pregnancy-related complications, and hormonal status, were not consistently available and could not be evaluated. Symptom-to-door time, total ischemic time, and collateral circulation were also not consistently available in this retrospective cohort and therefore could not be incorporated into the multivariable analyses. Moreover, the observational nature of this study precludes causal inference, and the association between EMR and impaired myocardial reperfusion should not be interpreted as causal. Despite adjustment for measured confounders, residual confounding cannot be completely excluded. Finally, because follow-up data were unavailable, the prognostic value of EMR beyond the index hospitalization could not be assessed.

**Conclusion**

Lower admission EMR was associated with incomplete ST-segment resolution and no-reflow in this retrospective cohort of young patients with STEMI undergoing pPCI. Lower EMR levels were also associated with greater thrombus burden, impaired postprocedural TIMI flow, and more frequent glycoprotein IIb/IIIa inhibitor use. Whether EMR provides incremental clinical information beyond its individual components and established clinical and procedural variables requires prospective external validation.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-80962/TKDA-80962_(0)_Supplementary_Materials.pdf

**Ethics Committee Approval:** Ethics committee approval was obtained from Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2026/09/1462, Date: 05.05.2026).

**Informed Consent:** Due to the retrospective nature of the study, the requirement for informed consent was waived by the institutional ethics committee.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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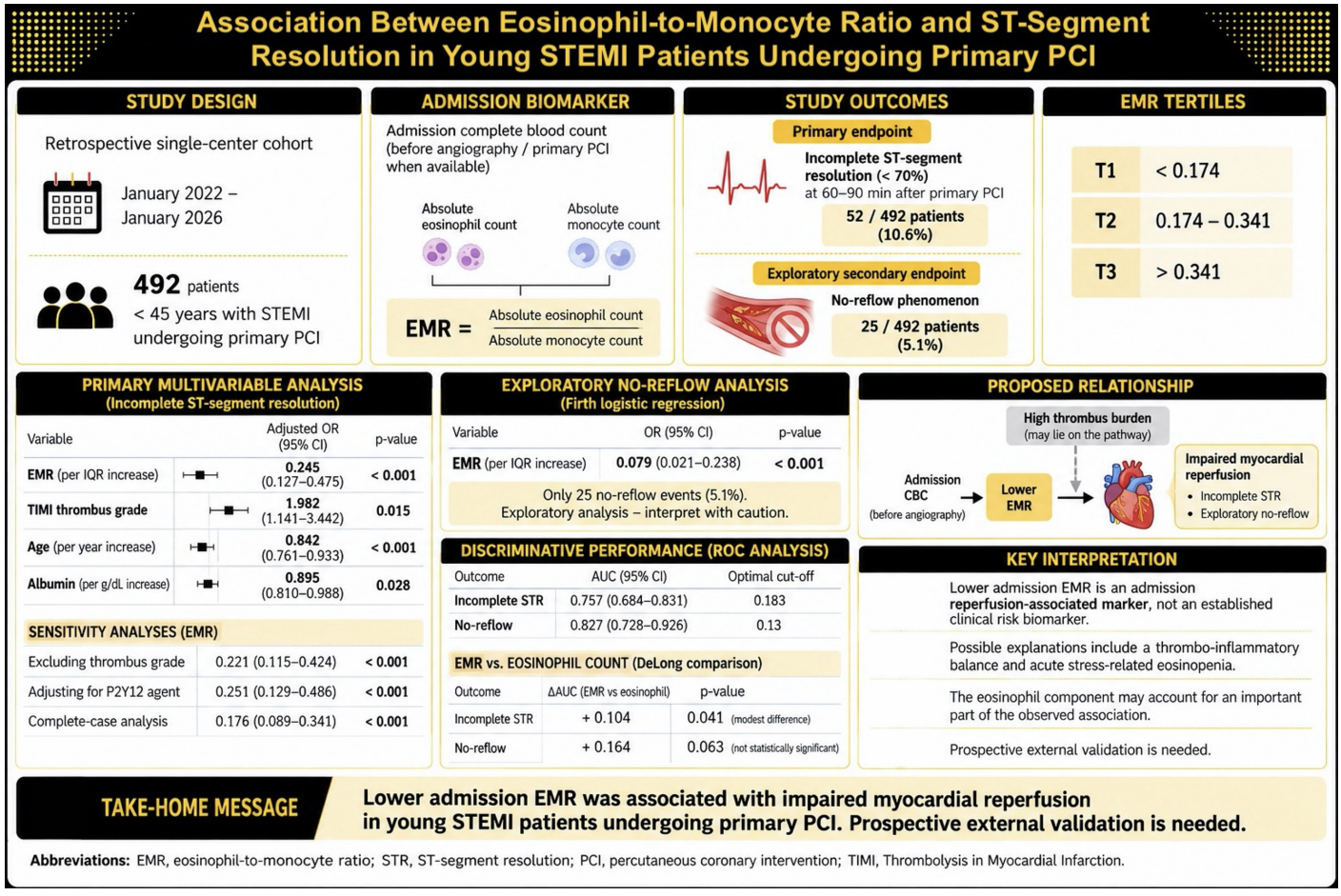
**Use of AI for Writing Assistance:** Authors declare that ChatGPT (OpenAI, GPT 5.5) was only used for English language editing and grammatical correction.

**Author Contributions:** Concept – İ.B.; Design – İ.B., B.K.; Supervision – K.B., Ç.K.; Data Collection and/or Processing – S.E., A.N.K.; Analysis and/or Interpretation – İ.B., B.K., K.B.; Literature Review – İ.B., S.E., A.N.K.; Writing – İ.B., K.B.; Critical Review – Ç.K.

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Association Between Eosinophil-to-Monocyte Ratio and ST-Segment Resolution in Young STEMI Patients Undergoing Primary PCI
STUDY DESIGN
Retrospective single-center cohort
January 2022 – January 2026
492 patients
< 45 years with STEMI undergoing primary PCI
ADMISSION BIOMARKER
Admission complete blood count (before angiography / primary PCI when available)
Absolute eosinophil count
Absolute monocyte count
EMR = Absolute eosinophil count / Absolute monocyte count
STUDY OUTCOMES
Primary endpoint
Incomplete ST-segment resolution (< 70%) at 60–90 min after primary PCI
52 / 492 patients (10.6%)
Exploratory secondary endpoint
No-reflow phenomenon
25 / 492 patients (5.1%)
EMR TERTILES
T1 < 0.174
T2 0.174 – 0.341
T3 > 0.341
PRIMARY MULTIVARIABLE ANALYSIS (Incomplete ST-segment resolution)
Variable | Adjusted OR (95% CI) | p-value
EMR (per IQR increase) | 0.245 (0.127–0.475) | < 0.001
TIMI thrombus grade | 1.982 (1.141–3.442) | 0.015
Age (per year increase) | 0.842 (0.761–0.933) | < 0.001
Albumin (per g/dL increase) | 0.895 (0.810–0.988) | 0.028
SENSITIVITY ANALYSES (EMR)
Excluding thrombus grade | 0.221 (0.115–0.424) | < 0.001
Adjusting for P2Y12 agent | 0.251 (0.129–0.486) | < 0.001
Complete-case analysis | 0.176 (0.089–0.341) | < 0.001
EXPLORATORY NO-REFLOW ANALYSIS (Firth logistic regression)
Variable | OR (95% CI) | p-value
EMR (per IQR increase) | 0.079 (0.021–0.238) | < 0.001
Only 25 no-reflow events (5.1%). Exploratory analysis – interpret with caution.
DISCRIMINATIVE PERFORMANCE (ROC ANALYSIS)
Outcome | AUC (95% CI) | Optimal cut-off
Incomplete STR | 0.757 (0.684–0.831) | 0.183
No-reflow | 0.827 (0.728–0.926) | 0.13
EMR vs. EOSINOPHIL COUNT (DeLong comparison)
Outcome | ΔAUC (EMR vs eosinophil) | p-value
Incomplete STR | + 0.104 | 0.041 (modest difference)
No-reflow | + 0.164 | 0.063 (not statistically significant)
PROPOSED RELATIONSHIP
High thrombus burden (may lie on the pathway)
Admission CBC (before angiography)
Lower EMR
Impaired myocardial reperfusion
Incomplete STR
Exploratory no-reflow
KEY INTERPRETATION
Lower admission EMR is an admission reperfusion-associated marker, not an established clinical risk biomarker.
Possible explanations include a thrombo-inflammatory balance and acute stress-related eosinopenia.
The eosinophil component may account for an important part of the observed association.
Prospective external validation is needed.
TAKE-HOME MESSAGE
Lower admission EMR was associated with impaired myocardial reperfusion in young STEMI patients undergoing primary PCI. Prospective external validation is needed.
Abbreviations: EMR, eosinophil-to-monocyte ratio; STR, ST-segment resolution; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

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# Risk Factors, Ischemic Delay, and In-Hospital Outcomes by Sex in Adults Aged 18–50 Years with STEMI Undergoing Primary Percutaneous Coronary Intervention: An Exploratory Single-Center Cohort

## Primer Perkütan Koroner Girişim Uygulanan 18–50 Yaş STEMI Hastalarında Cinsiyete Göre Risk Faktörleri, İskemik Gecikme ve Hastane İçi Sonuçlar: Keşifsel Tek Merkezli Kohort

**ABSTRACT**

**Objective:** To describe sex differences in cardiovascular risk factors and reperfusion delays and explore in-hospital outcomes in adults aged 18–50 years with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

**Method:** This retrospective single-center cohort included 497 consecutive patients (71 [14.3%] women) treated during 2023–2024. Hard major adverse cardiac and cerebrovascular events (MACCE) comprised all-cause death, recurrent myocardial infarction, or stroke. A nonstandard expanded clinical deterioration composite additionally included incident cardiogenic shock and, among patients admitted in Killip class I, incident heart failure. Sex comparisons and Firth penalized logistic models were exploratory.

**Results:** Mean age was 40.7 ± 5.3 years. Current smoking was more frequent in men (69.0% vs 39.4%; P < 0.001), whereas obesity was more frequent in women (54.9% vs 26.8%; P < 0.001). Age-adjusted median symptom-to-first-medical-contact, first-medical-contact-to-device, and total ischemic times were 46, 10, and 48 minutes longer in women, respectively (all P < 0.001). Hard MACCE occurred in 21 patients (4.2%), incident heart failure occurred in 13 of 390 eligible patients (3.3%), and the expanded composite occurred in 46 patients (9.3%). The expanded composite occurred in 12 of 71 women and 34 of 426 men (16.9% vs 8.0%; unadjusted P = 0.025), and incident cardiogenic shock occurred in 7 women and 13 men (9.9% vs 3.1%; unadjusted P = 0.015). In the parsimonious baseline model, the adjusted odds ratio (OR) for female sex was 2.61 (95% confidence interval [CI], 1.21–5.42), attenuating to 1.90 (95% CI, 0.83–4.18) after adding admission Killip class ≥II.

**Conclusion:** Women had a different risk-factor distribution and longer documented ischemic delays. The association between sex and the expanded composite was sensitive to adjustment for baseline clinical severity. Sex-specific outcome estimates are hypothesis-generating given the small female subgroup and event counts. The retrospective single-center design, absence of post-discharge follow-up, and unavailable care- and referral-pathway variables limit causal interpretation.

**Keywords:** Cardiovascular risk factors, ischemic delay, sex differences, ST-segment elevation myocardial infarction, young myocardial infarction.

**ÖZET**

**Amaç:** Primer perkütan koroner girişim (PKG) uygulanan 18–50 yaş arasındaki ST-segment yükselmeli miyokart enfarktüsü (STEMI) hastalarında kardiyovasküler risk faktörleri ve reperfüzyon gecikmesindeki cinsiyet farklılıklarını tanımlamak ve hastane içi sonuçları keşifsel olarak incelemek.

**Yöntem:** Bu retrospektif tek merkezli kohorta 2023–2024 döneminde tedavi edilen ardışık 497 hasta (71'i [%14,3] kadın) alındı. Sert majör advers kardiyak ve serebrovasküler olaylar (MACCE), tüm nedenlere bağlı ölüm, tekrarlayan miyokart enfarktüsü veya inme olarak tanımlandı. Standart olmayan genişletilmiş klinik kötüleşme bileşiğine başvuru sonrası gelişen kardiyojenik şok ve kalp yetersizliği (ikincisi yalnızca başvuruda Killip sınıf I olan hastalarda) eklendi. Cinsiyet karşılaştırmaları ve Firth penalize lojistik modeller keşifseldi.

**Bulgular:** Ortalama yaş 40,7 ± 5,3 yıldı. Güncel sigara kullanımı erkeklerde (%69,0'a karşı %39,4; P < 0,001), obezite ise kadınlarda (%54,9'a karşı %26,8; P < 0,001) daha sıktı. Yaşa göre düzeltilmiş medyan semptom-ilk tıbbi temas, ilk tıbbi temas-cihaz ve toplam iskemik

**ORIGINAL ARTICLE**
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süreleri kadınlarda sırasıyla 46, 10 ve 48 dakika daha uzundu (tümü P < 0,001). Sert MACCE 21 hastada (%4,2), başvuru sonrası gelişen kalp yetersizliği uygun olan 390 hastanın 13'ünde (%3,3) ve genişletilmiş bileşik 46 hastada (%9,3) görüldü. Genişletilmiş bileşik 71 kadının 12'sinde ve 426 erkeğin 34'ünde (%16,9'a karşı %8,0; düzeltilmemiş P = 0,025), başvuru sonrası kardiyojenik şok 7 kadın ve 13 erkekte (%9,9'a karşı %3,1; düzeltilmemiş P = 0,015) görüldü. Yalın başlangıç modelinde kadın cinsiyeti için düzeltilmiş olasılık oranı (OR) 2,61 (%95 güven aralığı [GA], 1,21–5,42) iken, başvurudaki Killip sınıfı ≥II eklendiğinde 1,90'a (%95 GA, 0,83–4,18) geriledi.

**Sonuç:** Kadınlarda risk faktörü dağılımı farklı ve kaydedilen iskemik gecikmeler daha uzundu. Genişletilmiş bileşik ile cinsiyet arasındaki ilişki, başlangıçtaki klinik şiddet için düzeltmeye duyarlıydı. Kadın alt grubunun ve olay sayılarının azlığı nedeniyle cinsiyete özgü sonuç tahminleri hipotez oluşturucudur. Retrospektif tek merkezli tasarım, taburculuk sonrası izlemin olmaması ve bakım ve sevk sürecine ilişkin değişkenlerin bulunmaması nedensel yorumu sınırlar.

**Anahtar Kelimeler:** Kardiyovasküler risk faktörleri, iskemik gecikme, cinsiyet farkları, st-segment yükselmeli miyokart enfarktüsü, genç miyokart enfarktüsü.

Premature myocardial infarction (MI) carries lifelong consequences, yet no single age threshold defines a young patient. Reported cutoffs range from approximately 40 to 55 years: patients younger than 40 years are often labeled very young, whereas many registries adopt 40 to 45 years or a broader limit near 50 years.[1-3] For the present cohort, we set a uniform age range of 18 to 50 years before analysis to capture premature obstructive ST-segment elevation myocardial infarction (STEMI) in both sexes and retain enough women for descriptive comparison. This threshold is operational and is not proposed as a universal definition.

Young adults with MI carry a substantial burden of smoking, dyslipidemia, obesity, and family history, and the distribution of these factors differs between women and men.[1,4-7] Women are underrepresented in STEMI cohorts and may reach reperfusion later, partly because symptom recognition and care-seeking take longer.[8,9] Nontraditional contributors can coexist with the usual risk factors, including inherited lipid disorders, elevated lipoprotein(a), inflammatory disease, substance use, thrombophilia, and pregnancy-related conditions.[1]

Contemporary Turkish data on angiographically obstructive Type 1 STEMI treated with primary PCI remain limited. National secondary prevention studies have shown a relatively young coronary population with persistent gaps in risk-factor control, and a recent single-center series described young coronary care admissions, but neither study characterizes acute sex differences along a primary PCI pathway.[10,11] A well-described single-center benchmark can therefore add value, provided that descriptive comparisons, sparse outcomes, and unavailable confounders are presented with appropriate restraint.

We hypothesized that women would have a different conventional risk-factor profile and longer documented ischemic delays than men. Comparisons of no-reflow and in-hospital outcomes were prespecified as exploratory because a marked sex imbalance and few events were expected. Hard MACCE and a broader, nonstandard clinical deterioration composite are reported separately.

## ABBREVIATIONS

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| AMI | Acute myocardial infarction |
| BMI | Body mass index |
| CABG | Coronary artery bypass grafting |
| FMC | First medical contact |
| HDL | High-density lipoprotein |
| LDL | Low-density lipoprotein |
| LVEF | Left ventricular ejection fraction |
| MACCE | Major adverse cardiac and cerebrovascular events |
| MI | Myocardial infarction |
| MINOCA | Myocardial infarction with nonobstructive coronary arteries |
| PCI | Percutaneous coronary intervention |
| RCA | Right coronary artery |
| SCAD | Spontaneous coronary artery dissection |
| STEMI | ST-segment elevation myocardial infarction |
| TIMI | Thrombolysis in Myocardial Infarction |

## Materials And Methods

### Study Design and Setting

This retrospective observational cohort study was conducted at a tertiary cardiovascular center in Türkiye and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) framework. Consecutive patients aged 18 to 50 years who were admitted with STEMI between January 2023 and December 2024 and treated with primary PCI were identified from the catheterization laboratory log and electronic hospital records.

The protocol was approved by Van Training and Research Hospital Clinic Research Ethics Committee (Approval Number: 2026/04-04, Date: 21.05.2026) and followed the Declaration of Helsinki and national regulations. The requirement for individual informed consent was waived because the study used routinely collected clinical data in a retrospective design.

### Participants

Eligible patients were 18 to 50 years old at admission, met electrocardiographic and biomarker criteria for STEMI, and

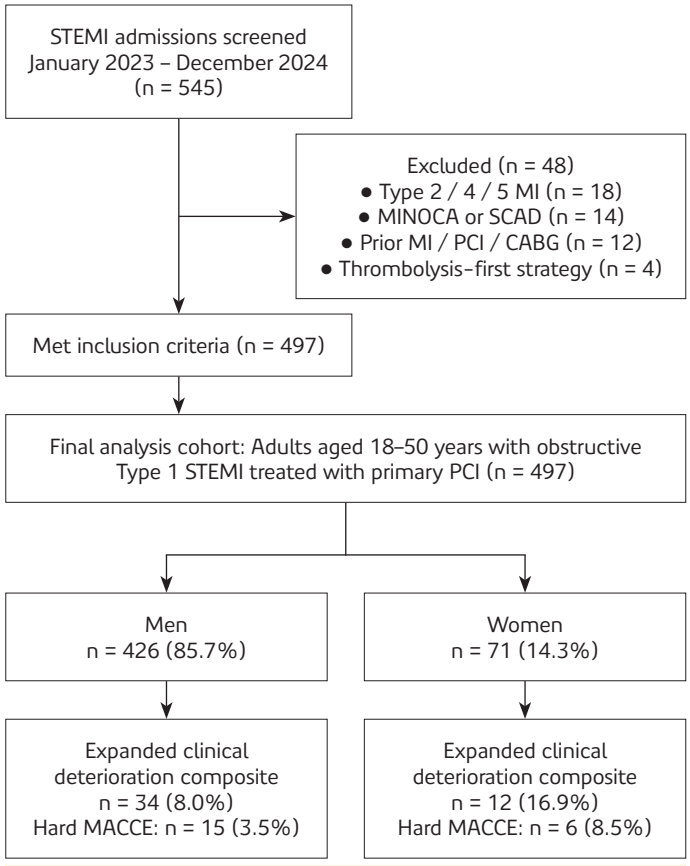



**Figure 1.** Patient selection and study flow. Of 545 screened STEMI admissions, 497 met the inclusion criteria. Hard MACCE comprised death, recurrent MI, or stroke; the reconstructed expanded clinical deterioration composite additionally included incident cardiogenic shock and incident heart failure restricted to patients in Killip class I at admission.

underwent primary PCI for an angiographically identified obstructive culprit lesion judged to be consistent with Type 1 MI.[12] Intravascular ultrasound and optical coherence tomography were not routinely used; therefore, plaque rupture, plaque erosion, embolism, and other culprit mechanisms were not centrally adjudicated.

Exclusion criteria were Type 2, 4a, 4b, 4c, or 5 MI; MI with nonobstructive coronary arteries (MINOCA); angiographically confirmed or clinically suspected spontaneous coronary artery dissection (SCAD); previous MI, PCI, or coronary artery bypass grafting (CABG); and a thrombolysis-first strategy followed by rescue or delayed PCI. Of 545 screened admissions, 48 were excluded: Type 2/4/5 MI (n=18), MINOCA or SCAD (n=14), previous MI, PCI, or CABG (n=12), and thrombolysis-first treatment (n=4) (Figure 1).

**PCI Procedure and Medical Therapy**

Primary PCI followed contemporary acute coronary syndrome recommendations.[13] Vascular access, thrombus aspiration, glycoprotein IIb/IIIa inhibitor use, and adjunctive treatment were left to the operator's discretion. Aspirin, a P2Y12 inhibitor, and unfractionated heparin were administered before or during PCI unless contraindicated. Drug-eluting stents were the default platform. Recorded procedural variables included access site, drug-eluting stent use, glycoprotein IIb/IIIa inhibitor use, manual thrombus aspiration, total stent length, contrast volume, and fluoroscopy time. Several variables were not available as structured fields: transfer status, arrival mode, off-hours presentation, culprit-only versus multivessel PCI, staged PCI, stent number and diameter, balloon-only PCI, reasons for not using a drug-eluting stent, intracoronary imaging, mechanical circulatory support, the specific antiplatelet agent, the anticoagulant strategy, and the statin agent or dose.

**Variables and Operational Definitions**

Biological sex was obtained from the admission record and coded as female or male. Current smoking denoted active smoking at presentation; former smoking was recorded separately. Obesity was defined as a body mass index (BMI) of 30 kg/m$^2$ or higher, using admission height and weight. Hypertension was based on a documented pre-existing diagnosis or antihypertensive treatment. Diabetes mellitus was based on a documented diagnosis, glucose-lowering treatment, or a glycated hemoglobin (HbA1c) level of 6.5% or higher during the admission. Documented dyslipidemia reflected a previous diagnosis or lipid-lowering treatment and was kept separate from admission lipid values. Because chronicity could not be established from a single admission measurement, the former chronic kidney disease variable was relabeled as an admission estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m$^2$. Family history of premature coronary artery disease was obtained from the structured admission history; the degree of relationship and age threshold were not recorded.

Total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, HbA1c, admission glucose, creatinine, eGFR, hemoglobin, white blood cell count, platelet count, and peak troponin I were obtained from routine in-hospital laboratory records. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Details regarding whether the lipid panel was obtained from the first blood sample, the exact sampling time, fasting status, timing relative to initiation of high-intensity statin therapy, and whether LDL cholesterol was measured directly or calculated (and, if so, by which formula) were not available. Lipid measurements were therefore treated as descriptive values reflecting the acute hospitalization period.

Killip class was recorded at admission. The first left ventricular ejection fraction (LVEF) documented by routine transthoracic echocardiography within 24 hours was available for all 497 patients. The exact time from admission or PCI, the method of LVEF measurement, and the temporal order relative to each later endpoint component were not recorded consistently; therefore, LVEF was summarized descriptively and excluded from the main multivariable models.

Symptom onset was defined as the earliest clearly documented start of persistent or recurrent ischemic symptoms that led the patient to seek care. First medical contact (FMC) was defined as the first assessment by emergency medical services or a physician; for patients who presented directly, emergency department triage was used. Symptom-to-FMC and FMC-to-device times were abstracted from charted times, and total ischemic time was calculated as their sum. Transfer status, arrival mode, intermittent or atypical symptoms, off-hours presentation, and a separate door-to-device interval were not recorded as distinct fields.

No-reflow was defined as a final post-PCI Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or less in the absence of residual mechanical obstruction or significant culprit-vessel stenosis. This flow-based definition does not incorporate myocardial blush grade or corrected TIMI frame count.

**Outcomes and Ascertainment**

Hard MACCE was defined as all-cause in-hospital death, recurrent MI, or stroke. Recurrent MI required new ischemic symptoms or electrocardiographic changes together with a new biomarker rise after a prior fall, consistent with the Fourth Universal Definition.[12] Isolated postprocedural biomarker elevation did not count. Stroke required a new focal or global neurologic deficit supported by neurologic assessment or brain imaging.

A secondary, nonstandard expanded clinical deterioration composite comprised hard MACCE, incident cardiogenic shock after admission, or incident heart failure during the index hospitalization. Cardiogenic shock was defined as a sustained systolic blood pressure below 90 mm Hg for at least 30 minutes or vasopressor support to maintain blood pressure, together with clinical evidence of hypoperfusion and a cardiac cause. Shock present at admission was treated as a baseline severity variable and was not counted as an incident component. Baseline heart failure was operationalized as Killip class II–IV at admission. Only patients in Killip class I at admission were eligible for incident heart failure, which required new pulmonary or systemic congestion after admission that prompted intravenous diuretic therapy or respiratory support. Source heart failure flags in patients with Killip class II–IV were not counted as incident heart failure; these patients remained eligible for all other components. Shock and heart failure were recorded as separate components when both criteria were met. A patient with several components contributed only once to a composite endpoint.

Events were identified from coronary care unit and hospital electronic records, discharge summaries, catheterization reports, echocardiography and other imaging reports, and neurologic documentation when relevant. There was no independent blinded adjudication committee, and the retrospective assessors were not blinded to sex or the recorded ischemic times.

Other outcomes were the individual components, any in-hospital cardiogenic shock, no-reflow, final TIMI 3 flow, hospital length of stay, and discharge prescriptions for dual antiplatelet therapy, high-intensity statins, beta-blockers, and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker among survivors.

**Statistical Analysis**

Continuous variables are presented as median (interquartile range, IQR) unless otherwise stated, and categorical variables as number (percentage). Sex comparisons used the Mann-Whitney U test, Pearson chi-square test, or Fisher exact test, as appropriate. The full four-level Killip distribution was compared using a global chi-square test. All sex-stratified comparisons were exploratory, and no correction for multiple testing was applied.

Age-adjusted differences in median symptom-to-FMC, FMC-to-device, and total ischemic times were estimated using median quantile regression that included female sex and age per 5-year increase. Sensitivity analyses used age categories of <40, 40–45, and 46–50 years; a uniform cutoff of ≤45 years; and a post hoc sex-specific cutoff of ≤45 years for men and ≤50 years for women. The last of these differentially truncates the male sample and was interpreted only as a sensitivity analysis.

The reconstructed expanded composite had 46 events. To limit overfitting and avoid adjustment for possible downstream severity markers, the main exploratory parsimonious baseline model focused on sex and ischemic time and included age per 5 years, female sex, anterior STEMI, and total ischemic time per hour. Because Killip class was available at presentation but might also reflect infarct severity along the pathway from delay to deterioration, a sensitivity model added admission Killip class ≥II. A separate four-variable procedural model included age, female sex, anterior STEMI, and no-reflow. LVEF was not included in these models. Minimal four-variable models for hard MACCE and incident cardiogenic shock are reported as supplementary analyses because they contained only 21 and 20 events, respectively. All estimates describe adjusted associations rather than independent effects, causal effects, or prediction-model performance.

Firth estimates were produced using a custom Python implementation of bias-reduced logistic regression that maximized the Jeffreys-prior penalized log likelihood, $l^*(\beta)=l(\beta)+0.5\ \log|X'WX|$.[14,15] The primary fit used numerical maximization with the analytic Firth modified score. Confidence intervals were derived from profile penalized likelihood, and P values were obtained from penalized likelihood-ratio tests. Statsmodels does not provide Firth logistic regression and was not used for these models. A separately coded adjusted-score Newton-Raphson algorithm with step halving was used as a numerical cross-check; the maximum absolute coefficient difference across all reported models was 3.3×10–8 log-odds units. The complete analysis script is provided as Supplementary File S1. No C statistic was reported. A detectable-effect analysis used a 2-sided $\alpha$ of 0.05 and 80% power for 2 independent proportions, conditional on the observed male event rate and the fixed group sizes of 426 men and 71 women.

All primary analytic variables were complete; discharge medications were not applicable to the 15 patients who died, and no imputation was undertaken. Analyses were performed in Python 3.13.5 with NumPy 2.3.5, SciPy 1.17.0, and statsmodels 0.14.6. Statsmodels was used for median quantile regression and detectable-effect calculations. A 2-sided $P < 0.05$ was used as a descriptive threshold.

**Results**

**Cohort Composition and Baseline Characteristics**

Of 545 screened admissions, 497 patients met the inclusion criteria (Figure 1). Mean age was 40.7 ± 5.3 years, and median age was 42 years (IQR, 37–45). The cohort comprised 426 men (85.7%) and 71 women (14.3%). Women were older than men (median, 44 vs 41 years; $P < 0.001$). The age strata contained 190 patients younger than 40 years, 213 aged 40–45 years, and 94 aged 46–50 years.

Current smoking was present in 322 patients (64.8%) and was more frequent in men than women (69.0% vs 39.4%;

**Table 1.** Baseline demographics, risk factors, and laboratory values

| Variables | Overall | Men | Women | *P* |
|---|---|---|---|---|
| Age, years | 42 (37–45) | 41 (37–44) | 44 (41–46) | <0.001 |
| BMI, kg/m² | 27.9 (25.0–30.6) | 27.4 (24.9–30.2) | 30.4 (28.5–32.1) | <0.001 |
| Obesity (BMI ≥30 kg/m²) | 153 (30.8) | 114 (26.8) | 39 (54.9) | <0.001 |
| Current smoking | 322 (64.8) | 294 (69.0) | 28 (39.4) | <0.001 |
| Former smoking | 22 (4.4) | 18 (4.2) | 4 (5.6) | 0.538 |
| Hypertension | 144 (29.0) | 126 (29.6) | 18 (25.4) | 0.467 |
| Diabetes mellitus | 126 (25.4) | 107 (25.1) | 19 (26.8) | 0.768 |
| Documented dyslipidemia | 226 (45.5) | 192 (45.1) | 34 (47.9) | 0.659 |
| Prior statin use | 94 (18.9) | 77 (18.1) | 17 (23.9) | 0.242 |
| Family history of premature CAD | 100 (20.1) | 83 (19.5) | 17 (23.9) | 0.385 |
| Admission eGFR <60 mL/min/1.73 m² | 27 (5.4) | 24 (5.6) | 3 (4.2) | 0.783 |
| Total cholesterol, mg/dL | 205.0 (177.0–234.0) | 205.0 (177.2–233.8) | 207.0 (174.0–237.0) | 0.983 |
| LDL cholesterol, mg/dL | 125.0 (101.0–152.0) | 126.0 (101.0–154.0) | 124.0 (96.5–141.5) | 0.223 |
| HDL cholesterol, mg/dL | 42.0 (36.0–48.0) | 41.0 (35.0–48.0) | 46.0 (40.5–53.0) | <0.001 |
| Non-HDL cholesterol, mg/dL | 163.0 (137.0–190.0) | 163.0 (137.2–190.0) | 162.0 (127.0–185.0) | 0.249 |
| Triglycerides, mg/dL | 171.0 (119.0–239.0) | 170.0 (118.2–242.8) | 171.0 (125.5–229.0) | 0.792 |
| HbA1c, % | 5.6 (5.3–6.1) | 5.6 (5.3–6.1) | 5.5 (5.2–6.0) | 0.369 |
| Admission glucose, mg/dL | 147.0 (124.0–175.0) | 146.0 (124.0–173.8) | 158.0 (133.0–177.0) | 0.186 |
| Creatinine, mg/dL | 0.96 (0.81–1.12) | 0.99 (0.84–1.14) | 0.78 (0.67–0.93) | <0.001 |
| eGFR, mL/min/1.73 m² | 99.0 (83.0–112.0) | 99.0 (84.0–112.0) | 97.0 (81.5–110.0) | 0.154 |
| Hemoglobin, g/dL | 14.3 (13.2–15.3) | 14.5 (13.5–15.5) | 12.7 (11.9–13.6) | <0.001 |
| WBC, ×10³/μL | 11.0 (9.1–13.2) | 11.0 (8.8–13.0) | 11.9 (10.4–13.9) | 0.005 |
| Platelets, ×10³/μL | 255.0 (214.0–295.0) | 254.0 (213.0–295.0) | 259.0 (231.0–303.5) | 0.146 |

Values are median (IQR) or n (%). P values are unadjusted exploratory comparisons between men and women. Documented dyslipidemia reflects a pre-existing diagnosis or prior lipid-lowering therapy. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; WBC, white blood cell count.

P < 0.001). Obesity was more frequent in women (54.9% vs 26.8%; P < 0.001), and median BMI was higher (30.4 vs 27.4 kg/m²; P < 0.001). Documented dyslipidemia was present in 45.5% of patients. Admission total cholesterol and non-HDL cholesterol did not differ by sex, whereas HDL cholesterol was higher in women. Baseline characteristics are shown in Table 1 and Figure 2.

### Presentation, Ischemic Delay, and PCI

Anterior STEMI occurred in 265 patients (53.3%). The Killip distribution was class I in 390 patients (78.5%), class II in 57 (11.5%), class III in 38 (7.6%), and class IV in 12 (2.4%); the global distribution did not differ significantly by sex (P = 0.104). The proportion with Killip class II or higher was greater in women (31.0% vs 20.0%; exploratory P = 0.036). LVEF was available for all patients and had the same median value in women and men.

Unadjusted intervals were longer in women: symptom-to-FMC, 155 vs 110 minutes; FMC-to-device, 75 vs 65 minutes; and total ischemic time, 218 vs 180 minutes (all P < 0.001). In age-adjusted median regression, female sex was associated with differences of 46.1 minutes (95% CI, 20.2–72.0), 10.0 minutes (95% CI, 4.7–15.3), and 48.0 minutes (95% CI, 21.8–74.2), respectively (all P < 0.001) (Figure 3 and Supplementary Table S1).

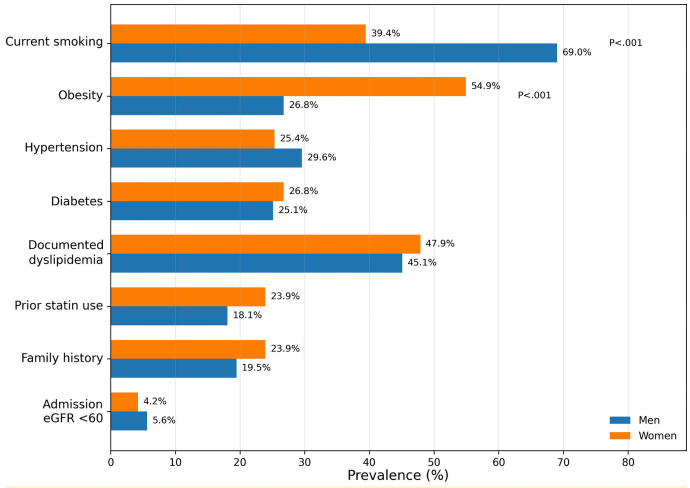



**Figure 2.** Cardiovascular risk-factor prevalence by sex. Current smoking was more frequent in men, whereas obesity was more frequent in women. All comparisons are unadjusted and exploratory. Documented dyslipidemia reflects a pre-existing diagnosis or prior lipid-lowering therapy; reduced renal function is shown as an admission eGFR below 60 mL/min/1.73 m².

Post-PCI TIMI 3 flow was achieved in 441 patients (88.7%), and no-reflow occurred in 56 (11.3%). Neither no-reflow nor final TIMI 3 flow differed by sex. Drug-eluting stents were used in

475 patients (95.6%); the unadjusted rate was lower in women (90.1% vs 96.5%; P = 0.026), and total stent length was slightly greater (median, 32.0 vs 28.5 mm; P = 0.049). These comparisons were not corrected for multiple testing, and reasons for not using a drug-eluting stent were unavailable (Table 2).

**In-Hospital Outcomes**

In-hospital death occurred in 15 patients (3.0%), recurrent MI in 7 (1.4%), and stroke in 5 (1.0%); hard MACCE occurred in 21 (4.2%). The source in-hospital heart failure field was positive in 35 patients: 13 were in Killip class I, 8 in class II, 12 in class III, and 2 in class IV at admission. After applying the baseline eligibility rule, only the 13 events among 390 patients in Killip class I were classified as incident heart failure (3.3%). Incident cardiogenic shock occurred in 20 patients (4.0%), and any in-hospital shock in 32 (6.4%). The reconstructed expanded clinical deterioration composite occurred in 46 unique patients (9.3%). Eleven patients had 2 or more component events, including 1 who met both the incident shock and incident heart failure criteria; each patient was counted once in the composite (Table 3 and Supplementary Table S6).

Hard MACCE occurred in 6 of 71 women and 15 of 426 men (8.5% vs 3.5%; P = 0.100). The reconstructed expanded composite occurred in 12 women and 34 men (16.9% vs 8.0%; unadjusted P = 0.025). Incident shock occurred in 7 women and 13 men (9.9% vs 3.1%; unadjusted P = 0.015). Among patients in Killip class I at admission, incident heart failure occurred in 3 of 49 women and 10 of 341 men (6.1% vs 2.9%; P = 0.216). These comparisons involved few events and were not corrected for multiple testing (Table 3 and Figure 4).

Among the 482 survivors, discharge prescription rates were 99.0% for dual antiplatelet therapy, 94.0% for high-intensity statins, 84.6% for beta-blockers, and 87.1% for an ACE inhibitor or angiotensin receptor blocker. The 15 in-hospital deaths were the only patients excluded from this denominator. Prescription rates did not differ significantly by sex.

**Table 2.** Clinical presentation, ischemic time, angiographic, and procedural characteristics

| Variables | Overall | Men | Women | *P* |
|---|---|---|---|---|
| Anterior STEMI | 265 (53.3) | 230 (54.0) | 35 (49.3) | 0.463 |
| Killip class I | 390 (78.5) | 341 (80.0) | 49 (69.0) | 0.104 |
| Killip class II | 57 (11.5) | 45 (10.6) | 12 (16.9) | – |
| Killip class III | 38 (7.6) | 29 (6.8) | 9 (12.7) | – |
| Killip class IV | 12 (2.4) | 11 (2.6) | 1 (1.4) | – |
| Killip class ≥II | 107 (21.5) | 85 (20.0) | 22 (31.0) | 0.036 |
| Cardiogenic shock at admission | 12 (2.4) | 11 (2.6) | 1 (1.4) | 1.000 |
| LVEF within 24 hours, % | 45.0 (40.0–50.0) | 45.0 (40.0–50.0) | 45.0 (40.0–50.0) | 0.377 |
| Peak troponin I, ng/mL | 52.8 (28.1–103.8) | 53.4 (28.9–103.1) | 50.6 (19.7–106.8) | 0.421 |
| Symptom-to-FMC, min | 120.0 (75.0–187.0) | 110.0 (71.0–177.0) | 155.0 (99.0–242.0) | <0.001 |
| FMC-to-device, min | 67.0 (55.0–77.0) | 65.0 (54.2–75.8) | 75.0 (64.5–86.5) | <0.001 |
| Total ischemic time, min | 188.0 (142.0–249.0) | 180.0 (137.0–242.8) | 218.0 (176.0–303.0) | <0.001 |
| Culprit vessel: LAD | 269 (54.1) | 234 (54.9) | 35 (49.3) | 0.819 |
| Culprit vessel: RCA | 133 (26.8) | 111 (26.1) | 22 (31.0) | – |
| Culprit vessel: LCx | 88 (17.7) | 75 (17.6) | 13 (18.3) | – |
| Culprit vessel: LM | 7 (1.4) | 6 (1.4) | 1 (1.4) | – |
| Multivessel disease (≥2 vessels) | 216 (43.5) | 180 (42.3) | 36 (50.7) | 0.184 |
| Pre-PCI TIMI flow 0/1 | 400 (80.5) | 345 (81.0) | 55 (77.5) | 0.488 |
| Post-PCI TIMI flow 3 | 441 (88.7) | 379 (89.0) | 62 (87.3) | 0.685 |
| No-reflow | 56 (11.3) | 47 (11.0) | 9 (12.7) | 0.685 |
| Drug-eluting stent used | 475 (95.6) | 411 (96.5) | 64 (90.1) | 0.026 |
| Radial access | 124 (24.9) | 112 (26.3) | 12 (16.9) | 0.090 |
| GP IIb/IIIa inhibitor | 72 (14.5) | 63 (14.8) | 9 (12.7) | 0.640 |
| Manual thrombus aspiration | 102 (20.5) | 85 (20.0) | 17 (23.9) | 0.441 |
| Total stent length, mm | 29.0 (21.0–37.0) | 28.5 (21.0–36.0) | 32.0 (23.5–41.0) | 0.049 |
| Contrast volume, mL | 201.0 (183.0–222.0) | 201.5 (183.0–220.0) | 198.0 (177.0–228.5) | 0.939 |
| Fluoroscopy time, min | 12.5 (10.4–15.2) | 12.4 (10.5–15.4) | 13.3 (10.2–15.1) | 0.769 |

Values are median (IQR) or n (%). The P value for the 4-level Killip distribution is a global chi-square test and is shown on the class I row. Other P values are unadjusted exploratory comparisons. Total ischemic time was calculated as symptom-to-FMC plus FMC-to-device time. FMC, first medical contact; GP, glycoprotein; IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

### Exploratory Multivariable and Sensitivity Analyses

In the parsimonious baseline model for the reconstructed expanded composite, the estimated OR was 2.61 for female sex (95% CI, 1.21–5.42; P = 0.016) and 3.07 for anterior STEMI (95% CI, 1.58–6.40; P < 0.001); age and total ischemic time were not associated with the endpoint. In the sensitivity model adding admission Killip class ≥II, the estimate for female sex attenuated to an OR of 1.90 (95% CI, 0.83–4.18; P = 0.125), whereas Killip class ≥II had an OR of 6.76 (95% CI, 3.55–13.16; P < 0.001). In the separate procedural model, the estimated ORs were 2.58 for female sex (95% CI, 1.18–5.38; P = 0.018), 2.26 for anterior STEMI (95% CI, 1.12–4.86; P = 0.023), and 4.12 for no-reflow (95% CI, 1.99–8.39; P < 0.001) (Table 4 and Figure 5).

Exploratory models for hard MACCE and incident shock are provided in Supplementary Table S2. For hard MACCE, the estimate for female sex was an OR of 2.77 (95% CI, 0.96–7.36; P = 0.060). For incident shock, it was an OR of 3.03 (95% CI, 1.11–7.79; P = 0.032).

The direction of the delay difference was generally preserved across age strata, although individual comparisons were underpowered; symptom-to-FMC and total ischemic time did not reach statistical significance in the 46–50-year stratum (Supplementary Table S3). Delay differences were also present under both alternative age definitions (Supplementary Table S4). Outcome estimates varied across strata because the numbers of women and events were small. With 71 women, 80% power

**Table 3.** In-hospital outcomes and discharge medical therapy

| Variables | Overall | Men | Women | *P* |
|---|---|---|---|---|
| All-cause death | 15 (3.0) | 12 (2.8) | 3 (4.2) | 0.460 |
| Recurrent MI | 7 (1.4) | 4 (0.9) | 3 (4.2) | 0.064 |
| Stroke | 5 (1.0) | 4 (0.9) | 1 (1.4) | 0.539 |
| Hard MACCE (death/recurrent MI/stroke) | 21 (4.2) | 15 (3.5) | 6 (8.5) | 0.100 |
| Cardiogenic shock at admission | 12 (2.4) | 11 (2.6) | 1 (1.4) | 1.000 |
| Incident cardiogenic shock | 20 (4.0) | 13 (3.1) | 7 (9.9) | 0.015 |
| Any in-hospital cardiogenic shock | 32 (6.4) | 24 (5.6) | 8 (11.3) | 0.111 |
| Incident heart failure among admission Killip I patients | 13/390 (3.3) | 10/341 (2.9) | 3/49 (6.1) | 0.216 |
| Reconstructed expanded clinical deterioration composite | 46 (9.3) | 34 (8.0) | 12 (16.9) | 0.025 |
| Length of stay, days | 4.0 (3.0–4.0) | 4.0 (3.0–4.0) | 4.0 (3.0–5.0) | 0.095 |
| Dual antiplatelet therapy | 477 (99.0) | 410 (99.0) | 67 (98.5) | 0.534 |
| High-intensity statin | 453 (94.0) | 389 (94.0) | 64 (94.1) | 1.000 |
| Beta-blocker | 408 (84.6) | 353 (85.3) | 55 (80.9) | 0.353 |
| ACE inhibitor/ARB | 420 (87.1) | 365 (88.2) | 55 (80.9) | 0.096 |

Values are median (IQR) or n (%), except that incident heart failure is reported as n/N (%) among patients in Killip class I at admission, who were the only eligible patients. Hard MACCE comprises all-cause death, recurrent MI, or stroke. The nonstandard expanded clinical deterioration composite includes incident cardiogenic shock after admission and incident heart failure. Eleven of 46 patients had more than 1 component; each patient was counted once in the composite. Discharge medications are reported among 482 survivors; the 15 in-hospital deaths were the only exclusions. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

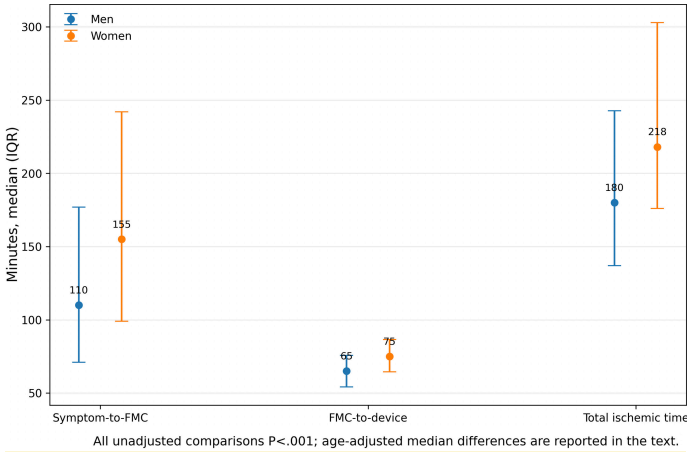



**Figure 3.** Ischemic time intervals by sex. Points show median values, and error bars show interquartile ranges. All 3 unadjusted comparisons had P < 0.001. In age-adjusted median regression, female sex was associated with differences of 46.1 minutes for symptom-to-FMC, 10.0 minutes for FMC-to-device, and 48.0 minutes for total ischemic time.

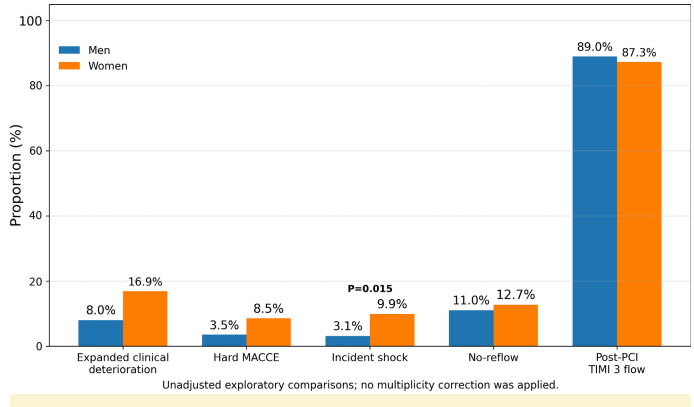



**Figure 4.** Selected in-hospital outcomes and procedural endpoints by sex. The reconstructed expanded clinical deterioration composite occurred in 34 men and 12 women. The difference in incident cardiogenic shock was based on 13 events among men and 7 among women. Comparisons are unadjusted and exploratory, with no correction for multiple testing.

MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

**Table 4.** Exploratory Firth penalized logistic regression models for the reconstructed expanded clinical deterioration composite

| Variables | Odds ratio | 95% CI lower | 95% CI upper | *P* |
|---|---|---|---|---|
| Panel A. Parsimonious baseline model focused on sex and ischemic time (46 events) | | | | |
| Age (per 5 years) | 0.95 | 0.71 | 1.29 | 0.739 |
| Female sex | 2.61 | 1.21 | 5.42 | 0.016 |
| Anterior STEMI | 3.07 | 1.58 | 6.40 | <0.001 |
| Total ischemic time (per hour) | 1.00 | 0.84 | 1.17 | 0.950 |
| Panel B. Sensitivity model adding admission Killip class ≥II (46 events) | | | | |
| Age (per 5 years) | 0.98 | 0.72 | 1.33 | 0.876 |
| Female sex | 1.90 | 0.83 | 4.18 | 0.125 |
| Anterior STEMI | 3.46 | 1.73 | 7.41 | <0.001 |
| Total ischemic time (per hour) | 0.99 | 0.83 | 1.16 | 0.912 |
| Killip class ≥II at admission | 6.76 | 3.55 | 13.16 | <0.001 |
| Panel C. Procedural model including no-reflow (46 events) | | | | |
| Age (per 5 years) | 0.99 | 0.73 | 1.35 | 0.922 |
| Female sex | 2.58 | 1.18 | 5.38 | 0.018 |
| Anterior STEMI | 2.26 | 1.12 | 4.86 | 0.023 |
| No-reflow | 4.12 | 1.99 | 8.39 | <0.001 |

Confidence intervals are profile penalized-likelihood intervals; P values are penalized likelihood-ratio tests. Panel A is the parsimonious baseline model focused on sex and ischemic time. Panel B adds admission Killip class ≥II as a sensitivity analysis. Panel C separately evaluates post-PCI no-reflow. These are adjusted association models, not causal, mediation, or prediction models. CI, confidence interval; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

for the reconstructed expanded composite required a female event rate of 20.2% (OR, 2.92) if the male rate remained at 8.0%; the observed female rate was 16.9%. Detectable female event rates were 13.0% for hard MACCE and 12.1% for incident shock, corresponding to odds ratios of approximately 4.1 and 4.4, respectively (Supplementary Table S5).

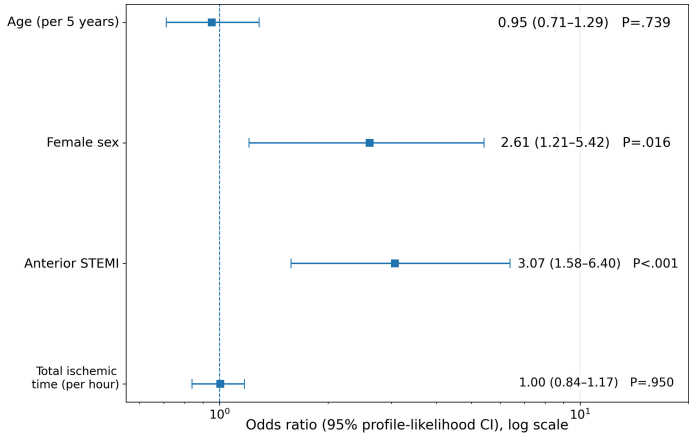



**Figure 5.** Exploratory parsimonious baseline associations with the reconstructed expanded clinical deterioration composite. Forest plot from a 4-variable Firth penalized logistic model based on 46 events and profile penalized-likelihood 95% confidence intervals. The model included age, female sex, anterior STEMI, and total ischemic time. A sensitivity model adding admission Killip class ≥II is reported in Table 4. Estimates should not be interpreted as independent or causal effects or as validated prediction performance.

## Discussion

In this consecutive single-center cohort of adults aged 18 to 50 years treated with primary PCI for obstructive Type 1 STEMI, current smoking was more frequent in men and obesity in women. Women had longer symptom-to-FMC, FMC-to-device, and total ischemic intervals, including after age adjustment. No-reflow occurred with similar frequency in both sexes. After restricting incident heart failure to patients without heart failure at admission, the reconstructed expanded composite occurred in 46 patients. Its estimated association with female sex was present in the parsimonious baseline model but attenuated after admission Killip class was added. Given the 71 women, low event counts, and sensitivity of the estimate to model specification, all outcome findings remain exploratory and hypothesis-generating.

The observed risk-factor distribution is broadly consistent with the young MI literature, in which smoking, dyslipidemia, and obesity are common and their prevalence differs between women and men.[1,4-6,16] The overall smoking prevalence and male excess resemble those reported in earlier young-STEMI series, whereas the higher prevalence of obesity and greater median BMI among women are consistent with prior reports in young women with infarction. Contemporary Turkish single-center data in patients admitted with acute coronary syndrome before age 45 years also describe a high burden of conventional risk factors.[11] Documented dyslipidemia (45.5%) likely reflects prior recognition or treatment rather than the full prevalence of lipid abnormalities. Admission total and non-HDL cholesterol did not differ by sex; however, because lipid sampling was not standardized with respect to timing, fasting status, treatment exposure, or LDL measurement method, these acute-hospitalization values are descriptive and cannot identify mechanisms underlying the observed sex differences.

The delay findings are consistent with previous reports. In the VIRGO study, young women were more likely than men to exceed guideline-recommended reperfusion times, and

symptom attribution and care-seeking behavior contributed to longer delays before treatment.[8,9] In the present cohort, both the symptom-to-FMC and FMC-to-device intervals were longer in women, and the difference in total ischemic time remained after adjustment for age. Neither interval can be attributed exclusively to patient- or system-related factors based on these data. Transfer status, mode of arrival, off-hours presentation, atypical symptoms, and a separate door-to-device interval were unavailable, so the observed differences cannot be apportioned among symptom recognition, referral logistics, transport, and in-hospital processes.

The in-hospital mortality, overall cardiogenic shock rate, and proportion of patients presenting in Killip class II or higher indicate a relatively severe case mix for such young patients. Reported outcomes in young-STEMI and young-AMI cohorts vary widely according to whether enrollment is restricted to STEMI, how shock at presentation is handled, and the duration of follow-up; some recent single-center series have described cardiogenic shock rates close to that observed here, whereas nationwide young-AMI registries generally report lower rates of acute heart failure and shock than in older patients.[2,3,17] A tertiary referral role, the inclusion of patients already in cardiogenic shock at admission, and the prolonged documented ischemic times may all have contributed. Because transfer status was not recorded, these explanations cannot be quantified, and a single-center referral cohort may not represent the general population.

In contrast to some previous reports, no-reflow did not differ by sex, and final TIMI 3 flow was similar in women and men, whereas a previous analysis linked female sex to suboptimal post-PCI coronary flow.[18] Several factors may account for this difference. MINOCA and spontaneous coronary artery dissection, which are overrepresented among young women and associated with distinct microvascular behavior, were excluded; the cohort was young and narrowly defined; and, with only 71 women, the power to detect a moderate difference was limited.[19,20] The overall no-reflow rate (11.3%) lies at the lower end of the range reported across primary PCI series, partly because the flow-based definition applied here is more restrictive than definitions incorporating myocardial blush grade or corrected TIMI frame count.[21,22]

Women had higher unadjusted rates of the reconstructed expanded composite and incident cardiogenic shock, whereas the hard-MACCE comparison remained imprecise. The parsimonious baseline estimate for female sex was also imprecise despite its confidence interval excluding unity, and it attenuated when admission Killip class ≥II was added. This pattern is compatible with an important contribution from baseline clinical severity, but the data cannot distinguish confounding from mediation or other case-mix differences. The incident shock estimate was derived from only 20 events, and the hard-MACCE confidence interval crossed unity. Prior studies in young patients with acute MI have reported heterogeneous sex differences after accounting for case mix and sample size.[23] The detectable-effect analysis further shows that only large differences could be identified with adequate power. These data therefore do not support a definitive or independent effect of female sex on in-hospital outcomes.

The main model was designed as a parsimonious baseline association model focused on sex and ischemic time rather than as a complete prognostic model. It excluded LVEF and no-reflow because they may be downstream of ischemic injury and overlap physiologically with the shock and heart-failure components. Although Killip class was available at presentation, it was included in a sensitivity model rather than the main model because it can reflect both baseline case mix and early infarct severity. Adding Killip class markedly attenuated the female-sex estimate, demonstrating the model dependence of that result. No-reflow was assessed separately in a procedural model. These analyses should not be interpreted as causal effects, mediation analyses, independent effects, or validated predictive performance.

Because no universally accepted age threshold defines young MI, the uniform range of 18 to 50 years was adopted as an operational enrollment criterion. The direction of the delay difference was generally preserved across age strata, although individual comparisons were underpowered, and alternative age definitions yielded a similar descriptive pattern. A sex-specific age threshold was examined only as a sensitivity analysis because applying different age limits by sex after cohort selection excludes older men and does not yield directly comparable groups.[1]

Several nontraditional and sex-specific contributors to premature infarction were not captured, including lipoprotein(a), assessment for familial hypercholesterolemia, thrombophilia, use of cocaine, amphetamines, cannabis, anabolic steroids, or energy drinks, autoimmune and inflammatory disease, hormonal therapy, contraceptive use, and pregnancy-related conditions such as preeclampsia and gestational diabetes, as well as menopausal status. These omissions are particularly relevant in a young cohort and among women and limit any etiologic interpretation of the findings. Exclusion of MINOCA and spontaneous coronary artery dissection improves homogeneity for obstructive Type 1 STEMI but does not eliminate these other contributors.

The study has several strengths, including consecutive enrollment, a contemporary drug-eluting stent era, a homogeneous obstructive Type 1 STEMI population with explicit exclusion of MINOCA and spontaneous coronary artery dissection, and separation of hard MACCE from the nonstandard expanded composite. Its limitations bear directly on interpretation. The retrospective single-center design limits generalizability and permits referral and selection bias. Outcome assessment was not independently or blindly adjudicated. The incident heart failure endpoint was reconstructed from the recorded admission Killip class and the source in-hospital heart failure field; although this prevents prevalent heart failure from being counted as incident, residual retrospective misclassification remains possible. With only 71 women and few events, sex-specific outcome estimates were underpowered and sensitive to model specification. Follow-up ended at hospital discharge, so late events, medication adherence, and longitudinal secondary prevention were not assessed. Transfer status, mode of arrival, several procedural details, and echocardiography timing and method were unavailable. Lipid sampling was not standardized with respect to fasting status, timing during hospitalization, relation to statin initiation, or LDL measurement method. Numerous descriptive comparisons were not corrected for multiplicity. Residual confounding is likely, and all associations are confined to the index admission.

## Conclusion

Among adults aged 18 to 50 years treated with primary PCI for obstructive Type 1 STEMI, smoking was more frequent in men, obesity was more frequent in women, and women had longer documented ischemic delays. After excluding prevalent heart failure from the incident heart failure component, the estimated association between female sex and the reconstructed expanded composite attenuated when baseline Killip class was included. Sex-specific clinical outcome estimates remain imprecise and exploratory. Larger multicenter studies with standardized endpoint adjudication and detailed care-pathway, etiologic, and longitudinal data are needed.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-76537/TKDA-76537_(0)_Supplementary_Materials.pdf

**Ethics Committee Approval:** Ethics committee approval was obtained from Van Training and Research Hospital Clinic Research Ethics Committee (Approval Number: 2026/04-04, Date: 21.05.2026).

**Informed Consent:** The requirement for individual informed consent was waived because the study used routinely collected clinical data in a retrospective design.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Use of AI for Writing Assistance:** Generative artificial intelligence tools were used during revision to assist with language editing, statistical code review, and preparation of revision documents. They were not used to create or alter source data. All analyses, numerical results, interpretations, and final text were independently reviewed and approved by the authors, who take full responsibility for the work.

**Author Contributions:** Concept – Ö.B., Ö.K.; Design – Ö.B., R.D., İ.P.; Supervision – Ö.B., Ö.K.; Resource – Ö.B., R.D., İ.P.; Materials – Ö.K.; Data Collection and/or Processing – Ö.K.; Analysis and/or Interpretation – Ö.B., R.D.; Literature Review – R.D., İ.P.; Writing – Ö.B.; Critical Review – Ö.K., R.D., İ.P.

**Peer-review:** Externally peer-reviewed.

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## Sex differences in risk factors, ischemic delay, and in-hospital outcomes among adults aged 18–50 years with STEMI undergoing primary PCI

Retrospective single-center cohort, 2023–2024

Women
Men

### Study population

**497**
consecutive patients
type 1 STEMI · primary PCI



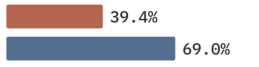
*≈ 1 in 7 patients was a woman*



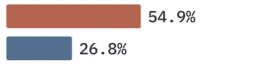
| | |
|---|---|
| Men | 426 (85.7%) |
| Women | 71 (14.3%) |
| Mean age | **40.7 ± 5.3 y** |
| Median age, W / M | **44 / 41 y** |
| Killip ≥II, W / M | **31.0 / 20.0%** |

### Risk-factor profile

**Current smoking** P < .001




**Obesity (BMI ≥30)** P < .001



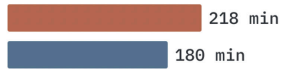

| Similar in both sexes | W | M |
|---|---|---|
| Hypertension | 25.4% | 29.6% |
| Diabetes | 26.8% | 25.1% |
| Dyslipidemia | 47.9% | 45.1% |
| Family history | 23.9% | 19.5% |

### Ischemic delay




| | Symptom onset → FMC | FMC → Device |
|---|---|---|
| W | 155 min | 75 min |
| M | 110 min | 65 min |
| Δ | +46 min | +10 min |
| | 95% CI 20–72 | 95% CI 5–15 |

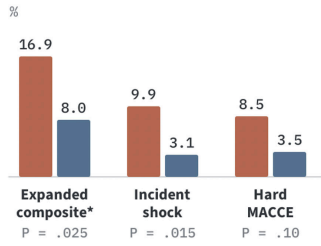
**Total ischemic time (median)**



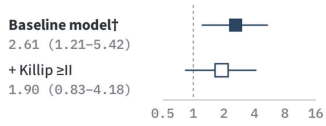

Age-adjusted difference **+48 min**
95% CI 22–74

*Women vs men; all differences P < .001*

### In-hospital outcomes




**Adjusted OR for female sex**
Expanded composite endpoint




**Women had a different risk-factor distribution and longer documented ischemic delays.**
The association between female sex and the expanded clinical deterioration composite attenuated after adjustment for admission Killip class; therefore, sex-specific outcome findings should be considered exploratory and hypothesis-generating.

*Expanded composite comprises hard MACCE (death, recurrent MI, or stroke), incident cardiogenic shock, and incident heart failure among patients in Killip class I at admission.
†Firth penalized logistic regression adjusted for age, anterior STEMI and total ischemic time.
CI, confidence interval; FMC, first medical contact; M, men; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI; W, women.

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# Premature Myocardial Infarction: Clinical Risk Profiles and Angiographic Insights

## Prematür Miyokard Enfarktüsü: Klinik Risk Profilleri ve Anjiyografik Bulgular

**EDITORIAL COMMENT**
EDİTORYAL YORUM

Acute myocardial infarction (MI) in young adults poses a significant clinical challenge, not only because of its immediate clinical consequences but also because of the long-term cardiovascular burden that may persist for decades.[1,2] MI in younger individuals raises important questions about the interplay among conventional cardiovascular risk factors, coronary plaque characteristics, and acute thrombotic events.[3] Whether premature MI merely represents an earlier manifestation of the atherosclerotic process observed in older patients or has distinct clinical and angiographic features remains an important question.[4]

The study published in this issue of the Archives of the Turkish Society of Cardiology provides valuable insights into age-related differences in MI presentation.[5] In this retrospective, single-center observational study, the authors evaluated 905 consecutive patients with acute MI who underwent coronary angiography and stratified them into three age groups: <45 years (n = 96), 45–54 years (n = 226), and ≥55 years (n = 583). The findings highlight age-related differences in cardiovascular risk profiles and angiographic characteristics, particularly the greater thrombus burden observed in younger patients despite the absence of a statistically significant difference in overall coronary anatomical complexity, as assessed by the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score.[5,6] The study also highlights the substantial burden of modifiable cardiovascular risk factors among younger patients presenting with acute MI. A history of smoking was reported in 81.3% of young patients and 80.1% of middle-aged patients, compared with 58.8% of older patients. Young patients also had higher admission low-density lipoprotein cholesterol (LDL-C) levels, non-high-density lipoprotein cholesterol (non-HDL-C) levels, and non-HDL-C/high-density lipoprotein cholesterol (HDL-C) ratios than older patients. In contrast, hypertension and diabetes mellitus were more prevalent among older patients.[5]

These findings support the importance of identifying cardiovascular risk factors before the clinical manifestation of coronary artery disease.[7] Nevertheless, the observed differences do not establish the relative contributions of smoking and dyslipidemia to premature MI because of the retrospective study design and the absence of a comparison group without MI. Furthermore, admission lipid measurements may be influenced by the acute-phase response and prior lipid-lowering therapy.[8,9] From a clinical perspective, these observations reinforce the importance of early cardiovascular risk assessment, smoking prevention and cessation, and appropriate lipid management in younger adults.[7,10] The occurrence of MI at a young age also underscores the need for sustained secondary prevention, as the consequences of premature coronary artery disease may persist for several decades.[11]

From an interventional perspective, a notable finding is the greater angiographic thrombus burden in younger patients despite the absence of a significant difference in overall coronary anatomical complexity.[12] In the current study, ST-segment elevation myocardial infarction (STEMI) accounted for 59.4% of presentations among young patients, while a high Thrombolysis in Myocardial Infarction (TIMI) thrombus burden (grades 3–5) was observed in 61.5% of young patients and 61.1% of middle-aged patients, compared with 45.6% of older patients (P < 0.001).[5] Bifurcation lesions were also more frequent in younger patients (25.0% vs. 19.0% vs. 10.3%, respectively; P < 0.001), whereas SYNTAX scores did not differ significantly across age groups (11.8 ±

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9.0, 12.9 ± 8.2, and 12.0 ± 8.3, respectively; P = 0.060). These findings suggest that similar levels of anatomical complexity may coexist with different thrombotic and lesion-level angiographic profiles. However, whether these differences reflect variations in plaque morphology or thrombotic mechanisms remains uncertain without intravascular imaging.[13]

Procedural characteristics also varied by age. Balloon predilatation was more frequent in young patients (89.6% vs. 79.9% in older patients), whereas vascular tortuosity (28.1% vs. 16.7%) and repeated balloon dilatation (26.4% vs. 9.4%) were more common in older patients. These differences may have implications for procedural planning, although the optimal interventional or antithrombotic strategies for different age groups cannot be determined from this study.

Inflammatory and immunonutritional profiles also differed across age groups. Hemoglobin, albumin, lymphocyte, and platelet (HALP) scores and lymphocyte-to-monocyte ratios (LMRs) were higher in young patients, whereas systemic inflammation response indices (SIRIs), platelet-to-lymphocyte ratios (PLRs), and Naples prognostic scores (NPSs) were higher in older patients, with the C-reactive protein–albumin–lymphocyte (CALLY) index being lowest in the older group.[5] Whether these indices provide additional information about coronary thrombus burden, plaque characteristics, or procedural outcomes warrants further investigation.[14]

Older patients experienced higher rates of in-hospital complications, including pulmonary edema (9.3% vs. 2.1% in young patients), acute kidney injury (10.6% vs. 2.1%), and new-onset atrial fibrillation (8.1% vs. 5.2%), as well as longer hospital stays (2.6 ± 1.5 vs. 2.3 ± 1.3 days).[5] Although in-hospital mortality did not differ significantly across age groups, this finding should be interpreted cautiously given the limited number of deaths and the relatively small cohort of young patients. Importantly, the absence of a significant difference in short-term mortality does not imply comparable long-term cardiovascular risk. Without longitudinal follow-up, the prognostic implications of the observed clinical and angiographic differences remain uncertain. These findings reinforce the importance of sustained secondary prevention and highlight the need for studies evaluating long-term outcomes in younger patients with MI.

In conclusion, this study highlights important age-related differences in the clinical and angiographic characteristics of acute MI, with younger patients exhibiting a higher prevalence of smoking history, less favorable lipid profiles, and greater angiographic thrombus burden despite the absence of a significant difference in overall coronary anatomical complexity. These findings emphasize the importance of integrating early cardiovascular risk identification and prevention with individualized interventional management and sustained secondary prevention. Further studies incorporating intracoronary imaging and long-term follow-up are needed to clarify the underlying mechanisms and prognostic implications of premature MI.

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# Long-Term Follow-up of Spontaneous Coronary Artery Dissection in Young Women: A Single-Center Tertiary Referral Cohort

## Genç Kadınlarda Spontan Koroner Arter Diseksiyonunun Uzun Dönem Takibi: Tek Merkezli Tersiyer Referans Merkezi Kohortu

**ABSTRACT**

**Objective:** Spontaneous coronary artery dissection (SCAD) is an uncommon but important cause of acute coronary syndrome (ACS) and sudden cardiac death, particularly in women aged 50 years or younger, including those without typical atherosclerotic coronary lesions. This study aimed to evaluate the clinical presentation, angiographic features, management strategies, and outcomes of patients with SCAD.

**Method:** This retrospective, single-center study included female patients aged 50 years or younger who underwent coronary angiography for ACS between January 2019 and January 2025. Patients presenting with chest pain, ST-T segment changes, and/or elevated high-sensitivity cardiac troponin levels were evaluated. The diagnosis of SCAD was established according to angiographic criteria and categorized using the Yip–Saw classification system.

**Results:** Among 352 women screened, 40 patients were diagnosed with SCAD, including 18 with ST-segment elevation myocardial infarction and 22 with non-ST-segment elevation myocardial infarction. According to the Yip–Saw classification, Type 3 SCAD was the most frequently observed angiographic pattern. The left anterior descending artery was the most commonly involved vessel. Most patients (n=35) underwent percutaneous coronary intervention, whereas 3 patients were managed conservatively and 2 underwent coronary artery bypass grafting. During follow-up, repeat revascularization was required in only one patient. Two patients died: one from cardiogenic shock during the index event and the other from complications of heart failure.

**Conclusion:** SCAD is an important but underdiagnosed cause of ACS in young women. The mortality rate in the study population was 5%. These findings provide real-world observational data and should be confirmed in larger, multicenter, prospective studies.

**Keywords:** Acute coronary syndromes, myocardial infarction, spontaneous coronary artery dissection, women.

**ÖZET**

**Amaç:** Spontan koroner arter diseksiyonu (SCAD), özellikle tipik aterosklerotik koroner lezyonları bulunmayan 50 yaş ve altındaki kadınlarda akut koroner sendromun (AKS) ve ani kardiyak ölümün nadir ancak önemli nedenlerinden biridir. Bu çalışmanın amacı, SCAD tanısı alan hastaların klinik başvuru özelliklerini, anjiyografik özelliklerini, tedavi stratejilerini ve klinik sonuçlarını değerlendirmektir.

**Yöntem:** Bu retrospektif, tek merkezli çalışmaya, Ocak 2019 ile Ocak 2025 tarihleri arasında şüpheli AKS nedeniyle koroner anjiyografi yapılan 50 yaş ve altındaki kadın hastalar dahil edildi. Göğüs ağrısı, ST-T segment değişiklikleri ve/veya yüksek duyarlılıklı kardiyak troponin düzeylerinde yükselme ile başvuran hastalar değerlendirildi. SCAD tanısı anjiyografik kriterlere göre konuldu ve Yip–Saw sınıflama sistemine göre sınıflandırıldı.

**Bulgular:** Taranan 352 kadın hastanın 40'ına SCAD tanısı konuldu (ST-segment yükselmeli miyokard enfarktüsü, n=18; ST-segment yükselmesiz miyokard enfarktüsü, n=22). Yip–Saw sınıflamasına göre en sık gözlenen anjiyografik patern Tip 3 SCAD idi. En sık etkilenen damar sol ön inen arterdi. Hastaların büyük çoğunluğuna (n=35) perkütan koroner girişim uygulanırken, 3 hasta konservatif olarak tedavi edildi ve 2 hastaya koroner arter baypas greftleme uygulandı. Takip süresince yalnızca 1 hastada tekrar revaskülarizasyon gerekti. İki hasta yaşamını yitirdi: biri indeks olay sırasında gelişen kardiyojenik şok, diğeri ise kalp yetersizliği komplikasyonları nedeniyle.

**Sonuç:** SCAD, genç kadınlarda AKS'nin önemli ancak yeterince tanınmayan nedenlerinden biridir. Çalışma popülasyonundaki mortalite oranı %5'tir. Bu bulgular gerçek yaşamdan elde edilen gözlemsel veriler sunmakta olup daha geniş, çok merkezli ve prospektif çalışmalarla doğrulanmalıdır.

**Anahtar Kelimeler:** Akut koroner sendrom, miyokard enfarktüsü; spontan koroner arter diseksiyonu, kadın.

**ORIGINAL ARTICLE**
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Spontaneous coronary artery dissection (SCAD) is defined as a nontraumatic and noniatrogenic separation of the coronary arterial wall caused by either an intimal tear or spontaneous intramural hematoma, resulting in compression of the true lumen and subsequent myocardial ischemia.[1] It is characterized by disruption of the coronary arterial wall, leading to the formation of an intramural hematoma and false lumen that can propagate along the length of the artery, compress the true lumen, and cause myocardial ischemia.

SCAD should be considered in young women with acute coronary syndrome (ACS), including those without typical atherosclerotic coronary lesions.[2–5] Although most cases of SCAD heal spontaneously and conservative treatment is sufficient for uncomplicated cases, SCAD remains underdiagnosed in women, likely because of sex- and age-related biases.[1–3] Its potential to cause sudden cardiac death and its risk of recurrence highlight the importance of accurate diagnosis and appropriate management. Although its etiopathogenesis remains unclear, associations between SCAD and fibromuscular dysplasia (FMD), pregnancy and the postpartum period, connective tissue disorders, systemic inflammatory diseases, hormonal influences (female sex hormones), emotional and physical stressors, and other predisposing conditions have been extensively documented in the literature.[6] The lack of consensus regarding the optimal investigation and treatment of SCAD emphasizes the need for further research.

This study aimed to characterize the clinical presentation, angiographic characteristics, management strategies, and long-term clinical outcomes of young women with SCAD treated at our tertiary referral center, thereby contributing to greater clinical awareness of this frequently underdiagnosed condition.

## Methods

In this single-center study, we retrospectively analyzed female patients aged 50 years or younger who underwent coronary angiography for suspected ACS at a tertiary referral hospital between January 2019 and January 2025. Three experienced interventional cardiologists independently reviewed the patients' coronary angiograms. The inclusion criteria were female sex, age 50 years or younger, coronary angiography performed for suspected ACS, and a diagnosis of SCAD based on angiographic criteria. SCAD lesions were classified according to the Yip–Saw angiographic classification system.[7] Intravascular imaging using optical coherence tomography (OCT) or intravascular ultrasound (IVUS) was not routinely performed and was reserved for selected cases at the operator's discretion. The exclusion criteria were normal coronary arteries, atherosclerotic coronary artery disease, intracoronary thrombus, coronary vasospasm, coronary aneurysm associated with vasculitis, anomalous pulmonary venous return, anomalous origin of the coronary arteries, and iatrogenic coronary artery dissection. Regarding pregnancy and postpartum status, none of the patients were pregnant or in the postpartum period at presentation, and no other embolic causes of myocardial infarction (MI) were identified. Alternative causes of myocardial injury, including myocarditis and Takotsubo syndrome, were excluded when clinically suspected based on the available clinical, laboratory, imaging, and angiographic findings.

## ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| CABG | Coronary artery bypass grafting |
| DAPT | Dual antiplatelet therapy |
| FMD | Fibromuscular dysplasia |
| IVUS | Intravascular ultrasound |
| LAD | Left anterior descending artery |
| LVEF | Left ventricular ejection fraction |
| MACE | Major adverse cardiovascular events |
| MI | Myocardial infarction |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| OCT | Optical coherence tomography |
| PCI | Percutaneous coronary intervention |
| RCA | Right coronary artery |
| SCAD | Spontaneous coronary artery dissection |
| STEMI | ST-segment elevation myocardial infarction |
| TIMI | Thrombolysis in myocardial infarction |

Treatment decisions were individualized according to the patients' clinical presentation, hemodynamic status, and angiographic findings. Stable patients were treated conservatively, whereas percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was performed in patients with ongoing ischemia and/or high-risk features. Follow-up data were obtained through a comprehensive review of hospital medical records, outpatient clinic visits, and the national registry. Follow-up data were available for all patients, and no patients were lost to follow-up. For patients whose national registry data were unavailable or inaccessible, follow-up information was obtained by telephone contact. This approach allowed us to ascertain long-term clinical outcomes for the entire study cohort.

Major adverse cardiovascular events (MACE) were defined as a composite of all-cause mortality, recurrent MI, and unplanned repeat coronary revascularization with PCI or CABG. The research protocol was approved by Ankara Bilkent City Hospital Medical Research Scientific and Ethics Committee (Approval Number: TABED 2-25-1522, Date: 17.09.2025) and was conducted in accordance with the principles of the Declaration of Helsinki. In addition, informed consent was obtained from all patients upon hospital admission.

### Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies (n) and percentages (%), whereas normally distributed continuous variables were presented as mean±standard deviation (SD). Given the descriptive nature of the study, comparative statistical analyses were not performed.

## Results

Among 352 women screened during the study period, 40 patients were diagnosed with SCAD. The mean follow-up duration was 49.5±10.1 months. In the SCAD population, the mean age was 44.2±5.1 years, and Type 3 SCAD was the most commonly observed angiographic subtype (Figures 1 and 2). Twenty-two patients presented with non-ST-segment elevation myocardial infarction (NSTEMI), whereas the remaining 18 presented

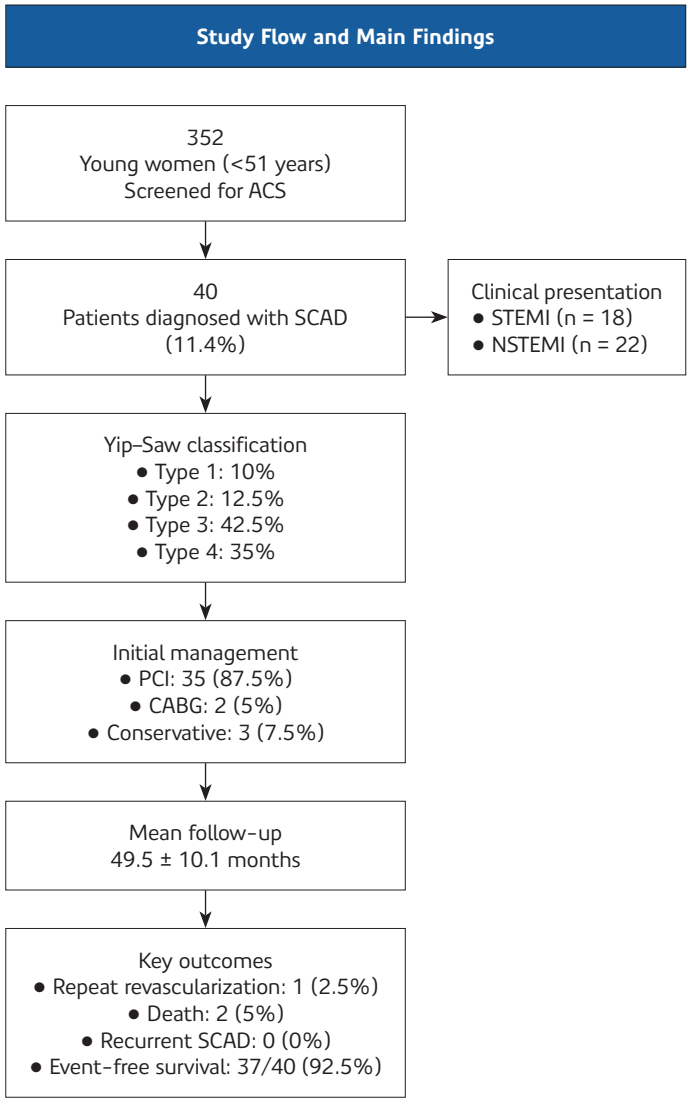



**Figure 1.** Flowchart of the study.

ACS, Acute coronary syndrome; SCAD, Spontaneous coronary artery dissection; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

with ST-segment elevation myocardial infarction (STEMI). The left anterior descending artery (LAD) was the most frequently involved vessel (n=25).

Regarding preexisting conditions, 7 patients had hypertension, 5 had type 2 diabetes mellitus, 4 had systemic inflammatory diseases [Sjögren syndrome (n=1), Churg–Strauss syndrome (n=1), ankylosing spondylitis (n=1), and psoriasis (n=1)], 2 had asthma, 2 had migraine, 2 had hypothyroidism, 1 had a previous history of subarachnoid hemorrhage, 1 had an adrenal medulla tumor, 1 had epilepsy, 1 had cervical cancer, 1 had fibromyalgia, and 15 had a body mass index >25 kg/m$^2$ (Table 1). Although systematic vascular screening for FMD was not performed, no clinically documented FMD was identified. Emotional stress was identified in 12 patients (30%), 2 of whom had been diagnosed with anxiety before the index event. None of the patients were pregnant or postpartum at the time of presentation. The mean



**Figure 2.** Angiographic image showing Type 3 spontaneous coronary artery dissection (SCAD) in a 48-year-old woman who developed symptoms following an emotional trigger and had a preexisting diagnosis of anxiety. No angiographic evidence of atherosclerotic plaque was observed in the remaining coronary segments.

left ventricular ejection fraction (LVEF) was 49.6±10.1%; 10 patients had reduced LVEF, 6 had mid-range LVEF, and 24 had preserved LVEF.

Most patients (n=35) underwent PCI of the SCAD-involved vessel because of persistent ischemia, proximal vessel involvement (n=26, 65%), or impaired coronary flow. The culprit vessel was the LAD in 25 patients (62.5%), the circumflex artery (CX) in 2 (5%), and the right coronary artery (RCA) in 8 (20%). One patient underwent PCI of two SCAD-involved vessels (48 years old, Type 3 SCAD, CX and RCA). Only 3 patients who were considered clinically stable were managed conservatively. CABG was required in 2 patients with extensive coronary involvement who were unsuitable for PCI. The distribution of SCAD types was as follows: Type 1, n=4 (10%); Type 2, n=5 (12.5%); Type 3, n=17 (42.5%); and Type 4, n=14 (35%). Thrombolysis in myocardial infarction (TIMI) flow grades before intervention were as follows: grade 0, n=15 (37.5%); grade 1, n=2 (5%); grade 2, n=11 (27.5%); and grade 3, n=12 (30%). After intervention, TIMI flow grade 3 was achieved in most patients (n=31). Among patients with Type 3 SCAD, 1 underwent CABG, 1 was treated conservatively, and the remaining patients underwent PCI.

Patients were followed in outpatient clinics. Although patients were enrolled over a 6-year period, not all participants completed a full 5-year follow-up because follow-up duration depended on the timing of recruitment relative to the index event. During follow-up, no bleeding events were recorded, and no recurrent MI was documented. Only 1 patient underwent repeat revascularization because of stent restenosis. Coronary computed tomography angiography was not routinely

**Table 1.** Baseline patient characteristics

| Variables | Values |
|---|---|
| Number of patients | 40 |
| Mean age, years | 44.2±5.1 |
| ACS presentation | |
| STEMI, n (%) | 18 (45%) |
| NSTEMI, n (%) | 22 (55%) |
| Risk factors | |
| Hypertension, n (%) | 7 (17.5%) |
| Diabetes mellitus, n (%) | 5 (12.5%) |
| Smoking, n (%) | 27 (67.5%) |
| Overweight, n (%) | 15 (37.5%) |
| Systemic inflammatory disease, n (%) | 4 (10%) |
| Sjögren syndrome | 1 |
| Churg–Strauss syndrome | 1 |
| Ankylosing spondylitis | 1 |
| Psoriasis | 1 |
| Menopause, n (%) | 0 (0.0%) |
| Laboratory parameters | |
| Mean total cholesterol, mg/dL | 173.1±38.1 |
| Mean fasting LDL-C, mg/dL | 109.5±30 |
| Mean HDL-C, mg/dL | 41.5±15.7 |
| Median triglycerides (IQR), mg/dL | 113 (67–148) |
| Mean non-HDL-C, mg/dL | 132.7±40.3 |
| Mean creatinine, mg/dL | 0.65±0.16 |
| Mean eGFR, mL/min/1.73 m² | 108.1±15 |
| Mean fasting glucose, mg/dL | 126.5±82.1 |
| Mean HbA1c, % | 5.9±1.2 |
| Median CRP (IQR), mg/L | 2 (0–11) |
| Mean ejection fraction, % | 49.6±10.1 |
| SCAD angiographic features | |
| Type 1 SCAD, n (%) | 4 (10%) |
| Type 2 SCAD, n (%) | 5 (12.5%) |
| Type 3 SCAD, n (%) | 17 (42.5%) |
| Type 4 SCAD, n (%) | 14 (35%) |
| Percutaneous coronary intervention | |
| LAD PCI, n (%) | 25/40 (62.5%) |
| CX PCI, n (%) | 2/40 (5%) |
| RCA PCI, n (%) | 8/40 (20%) |
| Major adverse cardiovascular events*, n (%) | 3 (7.5%) |
| Mortality, n (%) | 2 (5%) |
| Repeat revascularization, n (%) | 1 (2.5%) |

ACS, acute coronary syndrome; CRP, C-reactive protein; CX, circumflex artery; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LAD, left anterior descending artery; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SCAD, spontaneous coronary artery dissection; STEMI, ST-segment elevation myocardial infarction. *Major adverse cardiovascular events were defined as the composite of all-cause mortality, recurrent myocardial infarction, and unplanned repeat coronary revascularization.

performed. Of the 2 patients who died, 1 died during the index hospitalization because of cardiogenic shock. This 46-year-old patient presented with cardiac arrest secondary to anterior STEMI, with the LAD identified as the culprit vessel and classified as Type 4 SCAD. The patient underwent stenting of the LAD extending into the left main coronary artery, achieving TIMI flow grade 2. However, the patient died on the operating table before mechanical circulatory support could be initiated. The second patient, a 29-year-old woman with Type 4 SCAD who underwent LAD stent implantation, died 8 months after the index event because of progressive heart failure with a severely reduced LVEF of 20%. This death was classified as cardiovascular based on hospital records. Apart from multiple hospitalizations for worsening heart failure symptoms, no recurrent SCAD event was documented before death. Event-free survival was observed in 37 patients.

Follow-up medications included aspirin, statins, angiotensin-converting enzyme inhibitors, beta-blockers, and clopidogrel or ticagrelor when indicated. Patients with reduced ejection fraction received guideline-directed heart failure therapy. Among patients who survived the index hospitalization, dual antiplatelet therapy (DAPT) was prescribed according to the revascularization strategy. In patients undergoing coronary stenting, the intended duration of DAPT was 12 months, followed by aspirin monotherapy when clinically appropriate. Given the limited evidence supporting prolonged DAPT in SCAD, particularly in patients without stent implantation, treatment duration was determined according to clinical presentation, bleeding risk, and follow-up assessment. Among medically managed patients, antiplatelet therapy was prescribed based on the overall treatment strategy and the operator's discretion. Of these patients, 2 received DAPT for 6 months, followed by aspirin monotherapy. The remaining patient was switched to oral anticoagulation with a vitamin K antagonist after 3 months of DAPT because of left ventricular thrombus formation. Treatment adherence was assessed through outpatient visits and prescription records.

## Discussion

In the current study, we retrospectively evaluated the clinical features, angiographic findings, management strategies, and long-term outcomes of young female patients diagnosed with SCAD in a contemporary single-center cohort. Our findings showed that SCAD remains an important and likely underrecognized cause of ACS in women aged 50 years or younger, including those without typical atherosclerotic coronary lesions. Similar to previous studies, all patients in our cohort presented with NSTEMI or STEMI, despite the absence of a significant atherosclerotic burden in the other coronary artery branches. Despite its relatively rare occurrence compared with atherosclerotic coronary artery disease, SCAD should always be considered in the differential diagnosis of MI, particularly in younger women presenting with otherwise unexplained ACS.

Because SCAD can closely mimic plaque rupture–related ACS in both clinical presentation and angiographic appearance, accurate diagnosis remains challenging, and misclassification may occur.[1,8] Careful angiographic assessment is therefore essential. Recognition of typical angiographic patterns, including long diffuse stenosis, abrupt changes in vessel caliber,

and radiolucent intimal flaps, may help clinicians establish the diagnosis more accurately.[9] Particularly in women aged 50 years or younger presenting with ACS, SCAD should be strongly suspected and thoroughly evaluated, as it may account for up to 35% of ACS cases in this population.[10–12] Regarding the angiographic distribution observed in our study, the LAD was the most frequently involved vessel, which was also consistent with the current literature.[6,8] In contrast to the Serbian SCAD Registry, in which Type 2A was the most frequently observed angiographic subtype, Type 3 SCAD was the predominant subtype in our cohort.[8] Because Type 3 SCAD may mimic atherosclerotic stenosis, OCT or IVUS may provide additional diagnostic value in selected angiographically uncertain cases.[7] However, the use of intracoronary imaging in SCAD should be individualized because, in some cases, advancing an OCT or IVUS catheter after guidewire placement into the dissection plane may cause propagation of the dissection or extension of the intramural hematoma.

The optimal treatment strategy for SCAD remains controversial and is still largely based on observational evidence rather than randomized trials. Current evidence generally supports conservative management in clinically stable patients because spontaneous healing of the vessel wall occurs in most cases.[3,5,13–15] Nevertheless, in real-world practice, invasive treatment is often unavoidable in patients with ongoing ischemia, hemodynamic compromise, left main coronary artery involvement, or impaired distal coronary flow. In the Serbian SCAD Registry, PCI was performed in 41.5% of patients, whereas in our cohort, PCI was performed in most patients (87.5%). The higher PCI rate in our cohort may reflect the high prevalence of persistent ischemia or high-risk angiographic features, as well as tertiary referral bias, whereby patients with more complex or unstable presentations may have been preferentially referred to our center.

PCI may be technically challenging and potentially harmful in SCAD because of false-lumen wiring, propagation of the dissection, and extension of the intramural hematoma; therefore, invasive treatment should be reserved for appropriate high-risk cases.

The long-term prognosis after SCAD is generally favorable in terms of survival, although recurrent cardiovascular events may still occur.[1–6,8] In the CanSCAD study, recurrence rates of MI and *de novo* SCAD were 9.9% and 2.4%, respectively.[16] During the available follow-up period, repeat revascularization was required in 1 patient, and 2 cardiovascular deaths occurred. In the Serbian SCAD Registry, 10 patients died, while MACE occurred in 18.1% of patients.[8] These findings suggest that although many patients with SCAD may remain clinically stable, severe outcomes can still occur in selected high-risk patients.

FMD, pregnancy-related hormonal changes, connective tissue disorders, emotional stress, and intense physical exertion have all been associated with SCAD in previous reports.[6,17] Although pregnancy- and postpartum-associated SCAD are well-recognized clinical entities, none of the patients in our cohort were pregnant or in the postpartum period at presentation, suggesting that other mechanisms may have contributed to SCAD in this population. Heritable connective tissue disorders and systemic arteriopathies are recognized, although relatively uncommon, predisposing conditions for SCAD.[17] In our study population, 4 patients had previously been diagnosed with systemic inflammatory diseases, including Sjögren syndrome, Churg–Strauss syndrome, ankylosing spondylitis, and psoriasis. Although no patient in our cohort was diagnosed with FMD, systematic vascular screening was not routinely performed; therefore, the presence of asymptomatic FMD or other vasculopathies cannot be completely excluded.

**Limitations**

The present study has several limitations. First, this was a retrospective, single-center observational study with a relatively small sample size and was designed as a descriptive analysis rather than a comparative or hypothesis-testing study. Second, intracoronary imaging was not systematically performed in all patients, which may have affected classification accuracy in some angiographically ambiguous lesions. Third, treatment decisions were not randomized and were individualized according to clinical status and operator preference. Therefore, direct comparisons between conservative and invasive treatment strategies cannot be reliably performed.

The relatively high rate of PCI in our cohort should be interpreted with caution and should not be considered representative of the overall SCAD population. Our institution serves as a tertiary referral center, and many patients were referred because of ongoing ischemia, impaired coronary flow, or high-risk clinical features requiring urgent revascularization. In addition, the predominance of Type 3 SCAD may have contributed to the higher PCI rate because these lesions frequently resemble focal atherosclerotic stenoses and are among the most difficult SCAD subtypes to recognize angiographically. Although IVUS was selectively used in 2 patients with equivocal findings, intracoronary imaging was not routinely performed. Therefore, the possibility that some focal atherosclerotic lesions, particularly those with an angiographic appearance suggestive of Type 3 SCAD, were misclassified as SCAD cannot be completely excluded. In addition, because of the retrospective study design, IVUS images could not be retrieved because they were not routinely archived in our institutional imaging system. Therefore, the IVUS findings could not be retrospectively reviewed or included as figures in the manuscript. As a result, referral bias, lesion complexity, and the selective use of intracoronary imaging may all have influenced the angiographic distribution observed in our study.

Because data on stent length and the number of stents were not systematically recorded in this retrospective registry, our findings should not be interpreted as supporting routine PCI for SCAD, and conservative treatment remains the preferred strategy in clinically stable patients whenever feasible. In addition, complete information on long-term medication adjustments and treatment adherence was not available for all patients. Regarding antiplatelet therapy, the duration of DAPT was not protocol-driven and was determined according to clinical judgment; therefore, the reported DAPT duration should not be interpreted as evidence-based standard care for patients with SCAD.

Finally, because of the retrospective design of our study, the impact of different etiologic factors was not systematically evaluated. In addition, systematic vascular screening was not performed

in all patients. The absence of pregnancy- or postpartum-associated SCAD in this cohort may reflect the relatively older age profile of the study population, the small sample size, and the tertiary referral pattern. Moreover, only pregnancy and postpartum status at presentation were recorded; detailed obstetric history, lactation status, oral contraceptive or hormone therapy use, and pregnancy-related vascular complications were not systematically collected. Therefore, pregnancy-related mechanisms cannot be completely excluded, and this should be acknowledged as a limitation. Despite these limitations, our study reflects real-world clinical practice and provides additional data on the presentation and long-term outcomes of patients with SCAD treated at a contemporary tertiary referral center.

## Conclusion

SCAD is an increasingly recognized but often underdiagnosed nonatherosclerotic cause of ACS, predominantly affecting young women. Early recognition, careful angiographic assessment, and individualized management strategies are essential for improving clinical outcomes. The mortality rate in the study population was 5%. These findings suggest that morbidity, mortality, and procedural challenges remain clinically relevant in selected high-risk patients with SCAD.

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# Spontaneous Coronary Artery Dissection in Young Women: Looking Beyond the Lumen

## Genç Kadınlarda Spontan Koroner Arter Diseksiyonu: Lümenin Ötesine Bakmak

**EDITORIAL COMMENT**
EDİTORYAL YORUM

For decades, spontaneous coronary artery dissection (SCAD) was regarded as a curiosity of the catheterization laboratory, recognized primarily at autopsy or in peripartum women. Contemporary studies have changed this perception. SCAD is now recognized as a distinct, nonatherosclerotic cause of acute coronary syndrome (ACS) that predominantly affects middle-aged women, accounts for a substantial proportion of myocardial infarctions in women aged 50 years or younger, and has a natural history, treatment approach, and recurrence risk that differ fundamentally from those of plaque rupture–related infarction.[1–3] The central clinical challenge is that SCAD is easily overlooked: coronary angiography provides a two-dimensional image of the vessel lumen, and an intramural hematoma compressing the true lumen can closely resemble an atherosclerotic stenosis.

In this issue of the Archives of the Turkish Society of Cardiology, I read with great interest the article by Balcı et al.[4] on the long-term follow-up of SCAD in young women. Their study makes a valuable contribution to the literature and addresses an important knowledge gap. They report 40 women aged 50 years or younger with angiographically diagnosed SCAD among 352 women who underwent coronary angiography for ACS at a tertiary center in Ankara between 2019 and 2025, with a mean follow-up period of nearly 50 months. The cohort presented with ST-segment elevation myocardial infarction (STEMI) in 45% of cases and non-ST-segment elevation myocardial infarction (NSTEMI) in 55%; type 3 SCAD was the most common angiographic pattern (42.5%), 87.5% of patients underwent percutaneous coronary intervention (PCI), and two patients (5%) died. Follow-up was complete, representing a notable strength of this retrospective study, and the findings provide valuable long-term data from a population in which SCAD has been inadequately characterized. The authors also openly acknowledge the limitations of their study. However, their findings raise important questions about how SCAD is diagnosed and managed in routine clinical practice, warranting further discussion.

### Is It Really SCAD? The Type 3 Problem

The angiographic profile of this cohort is unusual. In large North American and European studies, type 2 SCAD (diffuse, smooth narrowing caused by an intramural hematoma) is by far the most common pattern, whereas type 3, characterized by focal or tubular stenosis that mimics atherosclerosis, is the least common and most difficult type to recognize.[2,3] Balcı et al.[4] report the opposite pattern: type 3 in 42.5%, type 4 (total occlusion) in 35%, and type 2 in only 12.5% of patients. Together, types 3 and 4 account for more than three-quarters of the cohort, and these are precisely the two patterns in which angiography alone is least reliable for distinguishing SCAD from an atherothrombotic lesion. A completely occluded vessel obscures its underlying pathology until blood flow is restored, and once a guidewire and balloon have crossed the lesion, its original appearance is lost.

The cardiovascular risk factor profile raises additional concerns. Patients with SCAD generally have a relatively low burden of conventional atherosclerotic risk factors. In this cohort, 67.5% were smokers, 12.5% had diabetes, the mean fasting glucose level was 126.5 mg/dL, and 37.5% were overweight.[4] Although these findings do not exclude SCAD, and smoking is common among young women in Türkiye, they increase the pretest probability of early atherosclerotic disease or plaque erosion in lesions

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that are particularly difficult to classify. Intracoronary imaging was performed in only two patients.[4] Direct visualization of an intramural hematoma requires optical coherence tomography (OCT) or intravascular ultrasound (IVUS), and the authors appropriately acknowledge that some focal atherosclerotic lesions may have been misclassified.

This distinction has important clinical implications. A misclassified patient may not receive appropriate long-term secondary prevention for atherosclerotic cardiovascular disease or, conversely, may undergo unnecessary stenting and prolonged dual antiplatelet therapy (DAPT), which SCAD does not routinely require. Misclassification can also distort estimates of incidence and potentially recurrence: both the 11.4% SCAD rate among the women screened and the absence of recurrence may reflect a heterogeneous population rather than patients with SCAD alone.

The practical implication is not that every young woman with ACS requires OCT. Intracoronary imaging in SCAD carries a genuine risk of propagating the dissection or extending the hematoma, and both the American Heart Association (AHA) scientific statement and the European Society of Cardiology (ESC) position paper recommend its selective use when angiographic findings are equivocal.[2,3] Nevertheless, a type 3 or recanalized type 4 lesion in a young woman, particularly when PCI is already planned and the vessel has been wired, represents precisely the clinical scenario in which selective intracoronary imaging may be appropriate.

**The PCI Paradox**

The most striking finding in the study is the revascularization rate: 87.5% of patients underwent PCI, 5% underwent coronary artery bypass surgery, and only 7.5% were managed conservatively.[4] In the Canadian SCAD cohort, most patients were managed conservatively, whereas PCI was performed in 41.5% of patients in the Serbian registry cited by the authors.[4,5] A conservative-first strategy is generally preferred, particularly in clinically stable patients. This approach is based on the observation that most dissected coronary segments heal spontaneously over weeks to months and on consistent evidence that PCI in SCAD is associated with procedural complications: the guidewire may enter the false lumen, balloon inflation and stent deployment may propagate the hematoma proximally or distally, and long stents are often required to cover segments that might otherwise heal spontaneously, creating a risk of late stent malapposition after hematoma resorption.[3,6]

However, the difference between these revascularization rates should not be interpreted simply as a deviation from best practice. Several factors likely contributed. First, referral bias: as a high-volume tertiary center, the authors' institution receives a selected patient population in which unstable patients, those with ongoing ischemia, and those transferred for urgent revascularization are overrepresented.[4] Second, disease severity: 45% of patients presented with STEMI, 42.5% had Thrombolysis in Myocardial Infarction (TIMI) grade 0–1 flow, 65% had proximal coronary involvement, one-quarter had reduced ejection fraction, and one patient presented with cardiac arrest and left main coronary artery extension.[4] These are clinical features for which both the AHA scientific statement and the ESC position paper consider revascularization appropriate.[2,3] Third, institutional and healthcare system factors: within a primary PCI network, clinical decisions must be made within minutes, often before SCAD is recognized, and once a guidewire has crossed an occluded or flow-limiting lesion, completing the procedure may appear to be the safer option. Operator experience with SCAD, the availability of intracoronary imaging, and local treatment protocols also influence clinical practice, and these factors vary across institutions and countries.

Notably, the outcomes associated with this invasive strategy were acceptable: postprocedural TIMI grade 3 flow was achieved in 31 patients, and only one patient required repeat revascularization.[4] However, data on technical failure, stent length, number of stents, and procedural complications, including hematoma propagation, were not systematically recorded, preventing a comprehensive assessment of PCI safety in this cohort. The authors appropriately caution that their findings should not be interpreted as supporting routine PCI in patients with SCAD.

**Outcomes and What Happens After Discharge**

The mortality rate of 5% (two deaths among 40 patients) was higher than the in-hospital and midterm mortality rates typically reported in SCAD; however, both deaths occurred in patients with type 4 left anterior descending coronary artery dissection and extensive anterior myocardial infarction, including one patient who experienced cardiac arrest and left main coronary artery extension.[4] These cases underscore that SCAD is not uniformly benign: when it occludes a large proximal coronary artery, its clinical consequences resemble those of any other extensive anterior STEMI, and access to mechanical circulatory support is essential.

The absence of recurrent SCAD or myocardial infarction over a mean follow-up period of 49.5 months is difficult to interpret. In the Canadian cohort, recurrent myocardial infarction and de novo SCAD occurred in 9.9% and 2.4% of patients, respectively, over three years.[5] The absence of recurrence in this cohort may reflect the small sample size, reliance on medical records for outcome ascertainment, or the inclusion of some atherosclerotic lesions that do not share the recurrence characteristics of SCAD. Recurrence is more than a clinical endpoint: it influences counseling regarding pregnancy, contraception, physical exertion, and blood pressure management in young women who may live with this diagnosis for decades.

Three aspects of secondary prevention deserve emphasis. First, beta-blockers: in an observational analysis of the Vancouver cohort, hypertension was associated with a higher risk of recurrence, whereas beta-blocker therapy was associated with a lower risk.[7] The BA-SCAD trial (Randomized Study of Beta-Blockers and Antiplatelets in Patients With Spontaneous Coronary Artery Dissection), which evaluates beta-blockers and short versus prolonged antiplatelet therapy using a 2 × 2 factorial design, aims to provide the first randomized evidence.[8] Second, antiplatelet therapy: among conservatively managed patients in the DISCO registry, DAPT was associated with more adverse events at one year than single antiplatelet therapy, potentially due to hematoma expansion.[9] The individualized DAPT durations in this cohort are reasonable, but the authors appropriately acknowledge that they should not be considered a standard approach. Third, extracoronary vascular screening: fibromuscular dysplasia (FMD) is the most common associated arteriopathy in

SCAD and is identified in a substantial proportion of systematically screened patients, along with aneurysms and dissections in other vascular territories.[1] As the authors note, the absence of documented FMD in this cohort reflects a lack of screening rather than an absence of disease. Expert consensus statements recommend imaging from the brain to the pelvis using computed tomography angiography or magnetic resonance angiography at least once after a SCAD event.[2,3] However, this recommendation is based primarily on the prevalence of vascular abnormalities rather than evidence that screening improves clinical outcomes and should therefore be implemented following an individualized assessment.

The absence of pregnancy-associated SCAD is also noteworthy, given the mean age of 44 years and the absence of postmenopausal women.[4] As the authors acknowledge, data on oral contraceptive and hormone therapy use, parity, and detailed obstetric history were not collected, leaving potential hormonal mechanisms unexplored. Similarly, emotional stress was documented in 30% of patients, but physical triggers were not systematically investigated.

**Looking Beyond the Lumen**

Balcı et al.[4] have provided clinically relevant observational data on SCAD in young women in Türkiye and, more importantly, have highlighted persistent gaps in its recognition and management. Several practical lessons emerge for clinicians evaluating young women with ACS:

1. Consider SCAD before advancing the guidewire, particularly in women without conventional cardiovascular risk factors, during the peripartum period, following emotional or physical stress, or in those with known FMD or systemic arteriopathy.
2. In ambiguous type 3 or recanalized type 4 lesions, use intracoronary imaging selectively and cautiously when the findings may influence management, rather than classifying lesions based on angiographic appearance alone.
3. In clinically stable patients with preserved coronary flow, conservative management remains the preferred initial strategy, consistent with current ESC ACS guidelines and expert consensus.[3,10] When PCI is unavoidable, a minimalist approach involving careful guidewire manipulation and close attention to hematoma propagation is advisable.
4. Following the index event, screen for extracoronary arteriopathy, optimize blood pressure control, consider beta-blocker therapy, avoid unnecessarily prolonged DAPT, and provide structured counseling regarding pregnancy, contraception, and exercise.

Finally, single-center experience, regardless of how carefully the data are collected, cannot fully address the questions raised by this study. It is important to recognize that recommendations in dedicated SCAD papers and consensus documents are derived predominantly from observational studies and expert opinion, reflecting the limited randomized evidence available in this field.[2,3] A prospective, multicenter national SCAD registry incorporating core laboratory angiographic adjudication, protocolized intracoronary imaging when indicated, systematic vascular screening, and standardized follow-up would provide a more accurate estimate of the SCAD burden in Türkiye, clarify whether the predominance of type 3 lesions and high PCI utilization reported here reflect underlying disease characteristics or variations in clinical practice, and enable patients in Türkiye to contribute to the prospective controlled evidence that is beginning to emerge. The Turkish Society of Cardiology is well positioned to lead such an initiative.

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# High Thrombus Burden in Premature Type 1 Myocardial Infarction: Cross-Sectional Associations with STEMI Presentation, Coronary Flow, and Systemic Inflammation

## Prematür Tip 1 Miyokard Enfarktüsnde Yüksek Trombüs Yükü: STEMI ile Başvuru, Koroner Akım ve Sistemik İnflamasyon Arasındaki Kesitsel İlişkiler

**ABSTRACT**

**Objective:** We evaluated whether admission complete blood count-derived inflammatory indices were associated with angiographic high thrombus burden (HTB) in premature myocardial infarction (MI).

**Method:** Consecutive patients aged <45 years with type 1 MI and an identifiable culprit lesion who underwent coronary angiography between 2020 and 2024 were included in this single-center, retrospective, cross-sectional analysis. Thrombus burden was assessed using the Thrombolysis in Myocardial Infarction (TIMI) thrombus grading scale, with occluded vessels reclassified after restoration of coronary flow; HTB was defined as grades 4–5. The neutrophil-to-lymphocyte ratio (NLR) and systemic inflammatory response index (SIRI) were evaluated using clinically defined multivariable logistic regression models, with and without adjustment for ST-elevation myocardial infarction (STEMI) presentation.

**Results:** Among 137 patients (77 with STEMI and 60 with non-ST-elevation myocardial infarction [NSTEMI]), 81 had an occluded culprit vessel; after restoration of coronary flow, only two lesions remained classified as grade 5. HTB was identified in 79 patients (57.7%) and was associated with STEMI presentation (67.1% vs. 41.4%, P = 0.003) and culprit vessel occlusion (69.6% vs. 44.8%, P = 0.004). Neither NLR (P = 0.54) nor SIRI (P = 0.20) differed significantly between thrombus burden categories, and neither was associated with HTB after adjustment for pre-event characteristics (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.94–1.17 and OR 1.13, 95% CI 0.95–1.35, respectively) or additional adjustment for STEMI presentation (OR 1.03, 95% CI 0.92–1.14 and OR 1.08, 95% CI 0.90–1.30, respectively), whereas STEMI presentation remained significantly associated with HTB (OR 2.75, 95% CI 1.33–5.68, P = 0.006). The findings were consistent across all sensitivity analyses, and discriminatory performance was negligible (areas under the curve of 0.531 and 0.564). No significant differences in in-hospital outcomes were detected; however, these comparisons were underpowered.

**Conclusion:** In young patients with angiographically confirmed type 1 MI, HTB was associated with STEMI presentation and initial coronary occlusion but not with admission inflammatory indices.

**Keywords:** Coronary angiography, coronary thrombosis, inflammation, myocardial infarction, ST-elevation myocardial infarction.

**ÖZET**

**Amaç:** Prematür miyokard enfarktüsü (Mİ) geçiren hastalarda, başvuru sırasında hemogramdan elde edilen inflamatuvar indekslerin anjiyografik olarak belirlenen yüksek trombüs yükü (YTY) ile ilişkisi değerlendirildi.

**Yöntem:** 2020–2024 yılları arasında koroner anjiyografi uygulanan, 45 yaşından önce tip 1 Mİ geçirmiş ve sorumlu koroner lezyonu belirlenmiş ardışık hastalar, tek merkezli, retrospektif ve kesitsel bir çalışma kapsamında incelendi. Trombüs yükü, Thrombolysis in Myocardial Infarction (TIMI) trombüs derecelendirme skalası kullanılarak değerlendirildi; sorumlu damarı tıkalı olan hastalarda antegrad akım sağlandıktan sonra yeniden sınıflandırma yapıldı. YTY, derece 4–5 olarak tanımlandı. Nötrofil/lenfosit oranı (NLO) ve sistemik inflamatuvar yanıt indeksi (SIRI), klinik gerekçelerle oluşturulan ve ST yükselmeli miyokard enfarktüsü (STEMI) ile başvurunun dahil edildiği ve edilmediği çok değişkenli lojistik regresyon modellerinde incelendi.

**ORIGINAL ARTICLE**
ARAŞTIRMA MAKALESİ

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**Bulgular:** Toplam 137 hastanın (77 STEMI, 60 ST yükselmesiz miyokard enfarktüsü [NSTEMI]) 81'inde sorumlu damar başlangıçta tıkalıydı; antegrad akım sağlandıktan sonra yalnızca iki lezyon derece 5 olarak sınıflandırılmaya devam edildi. YTY, 79 hastada (%57,7) saptandı ve STEMI ile başvuru (%67,1'e karşı %41,4; P = 0,003) ve sorumlu damarın tıkalı olması (%69,6'ya karşı %44,8; P = 0,004) ile ilişkili bulundu. NLO (P = 0,54) ve SIRI (P = 0,20) değerleri trombüs yükü kategorileri arasında anlamlı farklılık göstermedi ve ne olay öncesi özelliklere göre düzeltme yapıldığında (sırasıyla olasılık oranı [OR] 1,05; %95 güven aralığı [GA] 0,94–1,17 ve OR 1,13; %95 GA 0,95–1,35) ne de STEMI ile başvuru için ek düzeltme uygulandığında (sırasıyla OR 1,03; %95 GA 0,92–1,14 ve OR 1,08; %95 GA 0,90–1,30) YTY ile ilişkili bulundu; buna karşılık STEMI ile başvuru, YTY ile anlamlı düzeyde ilişkiliydi (OR 2,75; %95 GA 1,33–5,68; P = 0,006). Bulgular tüm duyarlılık analizlerinde tutarlılık gösterirken ayırt edici performans ihmal edilebilir düzeydeydi (eğri altında kalan alan değerleri 0,531 ve 0,564). Hastane içi klinik sonlanımlar açısından anlamlı farklılık saptanmadı; ancak bu karşılaştırmaların istatistiksel gücü yetersizdi.

**Sonuç:** Anjiyografik olarak doğrulanmış tip 1 Mİ geçiren genç hastalarda YTY, STEMI ile başvuru ve başlangıçtaki koroner oklüzyon ile ilişkili bulunurken başvuru sırasında ölçülen inflamatuvar indekslerle ilişkili değildi.

**Anahtar Kelimeler:** Koroner anjiyografi, koroner tromboz, inflamasyon, miyokard enfarktüsü, ST yükselmeli miyokard enfarktüsü.

Myocardial infarction (MI) at a young age represents a major cardiovascular concern because it affects individuals during their working, family, and social lives and can have lasting medical and psychosocial consequences. The diagnosis of MI relies on acute myocardial injury accompanied by clinical evidence of ischemia, while current acute coronary syndrome (ACS) guidelines emphasize prompt risk assessment and timely reperfusion or revascularization when appropriate.[1,2] Population-based studies indicate that young adults still account for a substantial subgroup of MI hospitalizations, with variations according to sex and baseline risk factors,[3] and a recent single-center study from Türkiye has documented the burden of ACS in patients younger than 45 years.[4] Compared with older patients, young adults with MI more commonly have a history of smoking, dyslipidemia, a family history of premature coronary artery disease, and, in selected cases, prothrombotic or nonatherosclerotic mechanisms.[5,6]

Thrombus formation within the culprit coronary artery is a central step in acute MI. On angiography, a higher thrombus grade usually reflects a greater amount of intraluminal clot and is often accompanied by coronary occlusion, impaired perfusion, and more challenging percutaneous coronary intervention (PCI).[7,8] Substantial thrombotic material can embolize into the distal circulation, contribute to slow-flow or no-reflow phenomena, enlarge the infarcted territory, and adversely affect outcomes after reperfusion.[9–12] Thus, early recognition of high thrombus burden (HTB) can be useful for anticipating procedural complexity and selecting an appropriate lesion-management strategy.

Inflammation contributes to both plaque destabilization and thrombosis after plaque disruption.[13,14] Its clinical importance is reinforced by trials in which selected anti-inflammatory treatments reduced recurrent cardiovascular events.[15] During acute MI, inflammatory pathways also influence myocardial injury, tissue repair, and ventricular remodeling.[16] For this reason, inexpensive indices derived from routine complete blood counts, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-high-density lipoprotein cholesterol ratio (MHR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI), have attracted interest as practical measures of immune activation, thromboinflammation, and prognosis in ACS.[17–21]

Despite this background, the association between these blood count-derived indices and angiographic thrombus burden remains unclear in premature MI, a population in which acute thrombosis may be relatively prominent and chronic atherosclerosis less dominant.[5] In this study, premature MI was defined as MI occurring before 45 years of age, with the same threshold applied to both sexes; this threshold is among the most widely used in studies of young patients with MI, including studies from our region,[4,5] and sex-specific thresholds were avoided because they derive from family history-based risk criteria

## ABBREVIATIONS

| | |
|---|---|
| ACC/AHA | American College of Cardiology/American Heart Association |
| ACS | Acute coronary syndrome |
| HTB | High thrombus burden |
| LVEF | Left ventricular ejection fraction |
| MHR | Monocyte-to-high-density lipoprotein cholesterol ratio |
| MI | Myocardial infarction |
| NLR | Neutrophil-to-lymphocyte ratio |
| NSTEMI | Non-ST-elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| PLR | Platelet-to-lymphocyte ratio |
| SII | Systemic Immune-Inflammation Index |
| SIRI | Systemic Inflammatory Response Index |
| STEMI | ST-elevation myocardial infarction |
| SYNTAX | Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery |
| TIMI | Thrombolysis in Myocardial Infarction |
| VF | Ventricular fibrillation |
| VT | Ventricular tachycardia |

rather than from the classification of affected patients. We did not hypothesize a priori that any single index would outperform the others; all routinely available complete blood count–derived indices were examined on an explicitly exploratory basis. We therefore examined whether inflammatory indices derived from admission complete blood counts were associated with HTB in young patients undergoing coronary angiography for type 1 MI, after accounting for clinical and angiographic characteristics.

## Materials and Methods

### Study Population

At a single tertiary care center, we retrospectively reviewed consecutive patients who underwent coronary angiography for ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) between January 2020 and December 2024 and who met the age criterion for premature MI. MI was adjudicated according to the Fourth Universal Definition of Myocardial Infarction.[1] Eligibility was restricted to patients with type 1 MI and an identifiable culprit coronary lesion on angiography. Patients without an identifiable culprit lesion (including those with type 2 MI, MI with nonobstructive coronary arteries, spontaneous coronary artery dissection, or coronary embolism) were not included in the screening list, so their number could not be reported; the cohort therefore represents angiographically confirmed atherothrombotic MI rather than the full spectrum of premature MI. Presentation type (STEMI or NSTEMI) was determined from the diagnosis recorded by the treating physicians in the discharge summary or angiography report; this diagnosis was made during routine care with knowledge of both the electrocardiographic and angiographic findings, and the admission electrocardiograms were not adjudicated by independent blinded reviewers. Premature MI was defined as an event occurring before 45 years of age.[5]

Patients were excluded if their medical records indicated an active infection, chronic inflammatory disease, malignancy, hematologic disorder, severe liver dysfunction, end-stage renal disease, or missing angiographic or laboratory data. Of 185 consecutive records meeting the initial eligibility criteria, 37 were excluded (active infection, n=9; chronic inflammatory disease, n=3; malignancy, n=0; hematologic disorder, n=2; severe liver dysfunction, n=1; end-stage renal disease, n=9; missing laboratory data, n=8; inadequate angiographic image quality, n=5; patients meeting more than one criterion were counted only once, under the first applicable criterion). An audit of the analysis file against the source records identified 11 duplicate entries involving 9 patients (the same index admission had been entered more than once); these duplicates were removed, and only one record per patient was retained. After these problems were identified, the entire final dataset of 137 patients, maintained as a single consolidated analysis file, was re-audited patient by patient against the source records (hospital information system, catheterization laboratory reports, and admission electrocardiograms) to verify unique identifiers, index admissions, laboratory results, angiographic variables, and in-hospital outcomes; no further discrepancies were identified during that audit. One final Thrombolysis in Myocardial Infarction (TIMI) flow value was subsequently corrected, and no-reflow

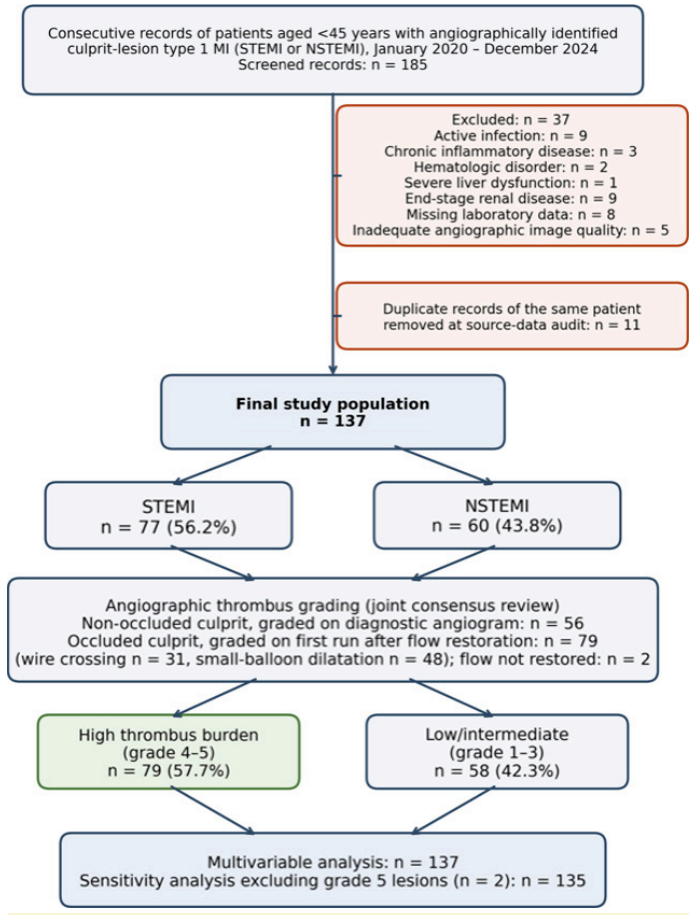



**Figure 1.** Study flowchart. Screening was restricted to patients with type 1 myocardial infarction (MI) and an identifiable culprit lesion; patients without an identifiable culprit lesion (including those with MI with nonobstructive coronary arteries, type 2 MI, spontaneous coronary artery dissection, or coronary embolism) were not included in the screening list.

HTB, high thrombus burden; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

status was recalculated from final TIMI flow according to the definition provided below. The final study population comprised 137 patients (Figure 1). No patient received fibrinolytic therapy before angiography. Demographic information, conventional cardiovascular risk factors, laboratory results, echocardiographic measurements, and coronary angiographic findings were extracted from the electronic hospital database. Family history of premature coronary artery disease, known dyslipidemia, previous coronary artery disease, and cerebrovascular disease were recorded as documented in the admission history and are reported as documented medical histories rather than systematically ascertained prevalence estimates. Body mass index, familial hypercholesterolemia, antiphospholipid antibodies, homocysteine levels, thrombophilia testing, substance use, hormonal or oral contraceptive exposure, autoimmune disease, and previous or concurrent coronavirus disease 2019 (COVID-19) infection could not be reliably ascertained from the records and are not reported; lipoprotein(a) was measured only in selected patients at the treating physician's discretion. The study protocol was approved by Kayseri City Hospital Non-interventional Clinical Research Ethics Committee (Approval Number: 1044, Date:

14.07.2026), and the study was conducted in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived because the analysis was retrospective and used anonymized patient data.

**Coronary Angiography and Thrombus Burden Assessment**

Coronary angiography was performed routinely via femoral access. TIMI flow grade was documented before intervention and at the end of the procedure using the standard TIMI classification.[22] No-reflow was defined, in patients treated with PCI, as a final TIMI flow grade ≤2 in the absence of a mechanical cause (persistent occlusion after failed PCI, dissection, residual stenosis, distal embolic occlusion, or spasm).[9]

All angiograms were jointly reviewed by two experienced interventional cardiologists who were blinded to laboratory data and previously recorded thrombus grades, and a single consensus grade was assigned to each culprit lesion; because grading was performed by consensus, interobserver agreement could not be quantified. Thrombus burden was graded using the TIMI thrombus scale.[7] In nonoccluded culprit vessels, the grade was assigned based on the diagnostic angiogram before guidewire passage. In culprit vessels with thrombotic total occlusion (initial grade 5), the lesion was reclassified according to the residual thrombus visualized on the first angiographic run obtained after antegrade flow had been restored by guidewire crossing or small-diameter balloon dilation, as described by Sianos et al.;[8] images obtained after stent implantation were not used. A final grade of 5 was retained only when antegrade flow could not be restored. The procedural stage at which the grade was assigned (diagnostic angiogram, after guidewire crossing, after small-balloon dilation, or failure to restore flow) was recorded for every patient. Presentation type was also reassessed using the admission electrocardiogram during the same session. This reassessment was not blinded to the angiographic findings, and in some patients with hyperacute T waves and an angiographically occluded culprit vessel, the reviewers classified the presentation as STEMI although the ST-elevation criterion was not met. Because this classification was neither blinded nor strictly criterion-based and was performed together with thrombus grading, it was not used in the analysis; all analyses used the presentation type recorded in the clinical records.

For statistical comparisons, grades 1–3 were classified as low/intermediate thrombus burden and grades 4–5 as HTB. An occluded culprit vessel was defined as preprocedural TIMI flow grade 0. Multivessel disease, culprit vessel, American College of Cardiology/American Heart Association (ACC/AHA) lesion classification, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score, chronic total occlusion, and glycoprotein IIb/IIIa inhibitor (tirofiban) use were recorded as previously described.

**In-Hospital Outcomes**

In-hospital adverse events were retrieved from hospital records and included all-cause in-hospital mortality, cardiogenic shock, ventricular fibrillation (VF) or sustained ventricular tachycardia (VT), stroke, acute stent thrombosis, contrast-induced nephropathy, bleeding, access-site hematoma, and length of hospital stay. A composite outcome was defined as the occurrence of in-hospital death, cardiogenic shock, stroke, acute stent thrombosis, or VF/sustained VT during the index hospitalization. Acute stent thrombosis was defined as angiographically confirmed thrombotic occlusion or flow-limiting thrombus within the implanted stent during the index hospitalization. Contrast-induced nephropathy was defined as an increase in serum creatinine of at least 0.5 mg/dL or at least 25% above baseline within 48–72 hours after contrast exposure. Bleeding was classified according to the TIMI criteria and recorded when major or minor bleeding occurred; access-site hematoma was recorded separately.

**Laboratory Measurements and Inflammatory Markers**

Venous blood samples obtained at admission were processed using routine laboratory techniques. The NLR was calculated as the neutrophil count divided by the lymphocyte count; the PLR as the platelet count divided by the lymphocyte count; the MHR as the monocyte count ($\times 10^3/\mu L$) divided by high-density lipoprotein (HDL) cholesterol (mg/dL); the SII as the platelet count multiplied by the neutrophil count and divided by the lymphocyte count; and the SIRI as the neutrophil count multiplied by the monocyte count and divided by the lymphocyte count, with all cell counts expressed as $\times 10^3/\mu L$. Low-density lipoprotein (LDL) cholesterol was measured directly using an automated enzymatic assay, and non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Samples were obtained in the emergency department at initial presentation, before coronary angiography, as part of the initial routine evaluation and were therefore nonfasting. The exact sampling time and interval from symptom onset were not recorded and could not be verified at the individual patient level; in patients with STEMI, sampling immediately preceded emergency angiography, whereas in patients with NSTEMI, the interval between sampling and angiography was longer and more variable. Admission high-sensitivity troponin T levels were recorded (Table 1) and included in a sensitivity analysis as an exploratory covariate reflecting the degree of myocardial injury at presentation.

Left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiography using the modified Simpson method, in accordance with contemporary recommendations for cardiac chamber quantification.[23]

**Statistical Analysis**

Continuous variables are expressed as mean±standard deviation or median (interquartile range), depending on their distribution, as assessed using the Kolmogorov–Smirnov test, and were compared using the independent-samples t-test or Mann–Whitney U test. Categorical variables are expressed as frequencies and percentages and were compared using the chi-square test or Fisher's exact test.

The association between each inflammatory index and HTB was examined using clinically defined multivariable logistic regression models. The adjustment covariates were selected on clinical grounds rather than through p value–based selection. The selection of indices, by contrast, was data-driven: NLR and SIRI were included in subsequent analyses because they were the only indices that differed between thrombus burden categories in the initial univariable analysis performed using the originally recorded grades; this selection was made before consensus regrading and

**Table 1.** Patient characteristics, laboratory results, and angiographic findings by thrombus burden category (n=137)

| Variables | Low/intermediate TB (n=58) | High TB (n=79) | *P* |
|---|---|---|---|
| Demographics and cardiovascular risk factors | | | |
| Age, years | 40.9±3.5 | 40.9±3.5 | 0.95 |
| Male sex, n (%) | 54 (93.1) | 74 (93.7) | >0.99 |
| Hypertension, n (%) | 11 (19.0) | 14 (17.7) | 0.85 |
| Diabetes mellitus, n (%) | 13 (22.4) | 11 (13.9) | 0.20 |
| Current smoking, n (%) | 50 (86.2) | 73 (92.4) | 0.24 |
| Documented family history of premature CAD, n (%) | 6 (10.3) | 8 (10.1) | 0.97 |
| Documented dyslipidemia, n (%) | 0 (0.0) | 3 (3.8) | 0.26 |
| Previous coronary artery disease, n (%) | 7 (12.1) | 10 (12.7) | 0.92 |
| Cerebrovascular disease, n (%) | 0 (0.0) | 1 (1.3) | >0.99 |
| Clinical presentation and left ventricular function | | | |
| STEMI presentation, n (%) | 24 (41.4) | 53 (67.1) | 0.003 |
| LVEF, % | 50.6±5.5 | 46.8±7.9 | 0.001 |
| Hematologic and biochemical measurements | | | |
| WBC count, $\times10^3$/μL | 10.9 (9.1–12.5) | 12.3 (10.3–14.3) | 0.01 |
| Neutrophil count, $\times10^3$/μL | 6.8 (5.3–8.6) | 8.4 (6.1–10.2) | 0.02 |
| Lymphocyte count, $\times10^3$/μL | 2.55 (2.06–3.25) | 2.88 (1.98–4.03) | 0.47 |
| Monocyte count, $\times10^3$/μL | 0.73 (0.53–0.88) | 0.77 (0.59–0.96) | 0.33 |
| Platelet count, $\times10^3$/μL | 254 (230–298) | 260 (210–306) | 0.81 |
| MPV, fL | 9.8 (9.0–10.6) | 9.7 (9.0–10.4) | 0.69 |
| CRP, mg/L | 2.6 (1.5–5.4) | 4.1 (2.0–7.2) | 0.06 |
| Admission hs-troponin T, ng/L | 94 (40–176) | 104 (38–304) | 0.46 |
| LDL-C, mg/dL | 126 (114–154) | 125 (109–156) | 0.83 |
| HDL-C, mg/dL | 35 (30–41) | 33 (29–38) | 0.29 |
| Total cholesterol, mg/dL | 189 (159–216) | 185 (161–218) | 0.93 |
| Triglycerides, mg/dL | 151 (121–250) | 129 (98–210) | 0.050 |
| Non-HDL-C, mg/dL | 152 (128–179) | 151 (128–184) | 0.87 |
| Inflammatory indices | | | |
| NLR | 2.46 (1.71–3.72) | 2.51 (1.61–5.93) | 0.54 |
| PLR | 102.3 (80.2–130.9) | 90.4 (65.2–129.9) | 0.31 |
| MHR | 0.021 (0.015–0.028) | 0.023 (0.018–0.034) | 0.14 |
| SII | 644.5 (469.2–949.2) | 732.7 (439.0–1212.2) | 0.43 |
| SIRI | 1.72 (1.24–2.91) | 2.02 (1.43–3.65) | 0.20 |
| Angiographic findings | | | |
| Occluded culprit vessel (preprocedural TIMI flow grade 0), n (%) | 26 (44.8) | 55 (69.6) | 0.004 |
| Final TIMI flow grade 3, n (%) | 55 (94.8) | 73 (92.4) | 0.73 |
| No-reflow, n (%) | 1 (1.7) | 1 (1.3) | >0.99 |
| Culprit vessel: LAD, n (%) | 24 (41.4) | 46 (58.2) | 0.03 |
| Culprit vessel: RCA, n (%) | 15 (25.9) | 23 (29.1) | – |
| Culprit vessel: LCx, n (%) | 16 (27.6) | 9 (11.4) | – |
| Multivessel disease, n (%) | 18 (31.6) | 30 (38.0) | 0.44 |
| ACC/AHA type C lesion, n (%) | 34 (58.6) | 58 (73.4) | 0.07 |
| SYNTAX score | 10.2 (8.0–16.5) | 15.0 (10.0–21.0) | 0.001 |
| Chronic total occlusion, n (%) | 1 (1.8) | 5 (6.4) | 0.40 |
| Glycoprotein IIb/IIIa inhibitor (tirofiban) use, n (%) | 8 (13.8) | 21 (26.6) | 0.07 |
| Underwent PCI, n (%) | 57 (98.3) | 78 (98.7) | >0.99 |

High thrombus burden was defined as a final TIMI thrombus grade of 4 or 5 following joint consensus re-review. Continuous variables are presented as mean±SD or median (IQR), and categorical variables as n (%). Family history and dyslipidemia are reported as documented in the admission history. The culprit vessel was an artery other than the LAD, RCA, or LCx in four patients (three in the low/intermediate TB category and one in the high TB category); the p value refers to the overall LAD/RCA/LCx distribution. Data on MPV, CRP, troponin, LDL-C, and triglycerides were available for 78 patients in the high TB category; multivessel disease data were available for 57 patients in the low/intermediate TB category; and chronic total occlusion data were available for 57 and 78 patients, respectively. The two patients who did not undergo PCI received surgical revascularization (one in each category). ACC/AHA, American College of Cardiology/American Heart Association; CAD, coronary artery disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; hs-troponin T, high-sensitivity troponin T; IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MHR, monocyte-to-high-density lipoprotein cholesterol ratio; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PCI, percutaneous coronary intervention; PLR, platelet-to-lymphocyte ratio; RCA, right coronary artery; SD, standard deviation; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TB, thrombus burden; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.

was retained afterward. PLR, MHR, and SII, which did not differ between categories in either analysis and were not associated with HTB in the univariable analysis (Supplementary Table 1), were not included in the multivariable models. NLR and SIRI were modeled separately because they share cellular components. Three nested models were fitted for each index. Model 1 was adjusted for pre-event patient characteristics selected on clinical grounds as potential confounders (age, sex, diabetes mellitus, current smoking, and non-HDL cholesterol). Model 2 additionally included STEMI presentation to test whether the index provided information beyond the presentation phenotype. Model 3 additionally included an occluded culprit vessel (preprocedural TIMI flow grade 0) and is presented as a sensitivity analysis because initial occlusion and thrombus grade partially reflect the same occlusive process. Variables that are themselves manifestations of the angiographic outcome ACC/AHA lesion type and SYNTAX score, both of which incorporate thrombus and occlusion into their definitions) or consequences of the infarction (LVEF) were not included as covariates; complete univariable results for all candidate variables are provided in Supplementary Table 1 for transparency. Additional sensitivity analyses repeated Model 2 (a) with the addition of log-transformed admission troponin, (b) with the addition of MHR, and (c) after excluding the two lesions with a final thrombus grade of 5. Inflammatory indices were also compared between thrombus burden categories within the STEMI and NSTEMI strata, and effect modification was assessed using STEMI-by-index interaction terms. Spearman's correlation analysis was used to examine the relationships between the indices and admission troponin levels. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Multicollinearity was assessed using variance inflation factors, discrimination using the c-statistic, and calibration using the Hosmer–Lemeshow test and Nagelkerke $R^2$. Receiver operating characteristic (ROC) analysis was retained as an exploratory assessment of discrimination; areas under the curve (AUCs) are reported with asymptotic 95% CIs, and Youden-derived cutoffs are reported for descriptive purposes only. Comparisons of baseline, laboratory, and angiographic characteristics and in-hospital outcomes were exploratory and were not adjusted for multiple testing; in-hospital outcomes were compared using Fisher's exact test and are presented descriptively. A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

## Results

### Study Population and Thrombus Grading

The final study population comprised 137 patients (128 men; 77 with STEMI [56.2%] and 60 with NSTEMI [43.8%]) (Figure 1). On angiographic re-review, the culprit vessel was totally occluded in 81 patients (59.1%). Antegrade flow was restored by guidewire crossing in 31 patients and by small-balloon dilation in 48; on the first angiographic run after flow restoration, these 79 lesions were reclassified as grade 4 in 53 patients, grade 3 in 18, grade 2 in 7, and grade 1 in 1. In two patients, flow could not be restored (final TIMI flow grade 0), and grade 5 was retained. The 56 nonoccluded culprit vessels were graded on the diagnostic angiogram (grade 1, n=6; grade 2, n=6; grade 3, n=20; grade 4, n=24) (Table 2). The final distribution of thrombus grades was grade 1 in 7 patients (5.1%), grade 2 in 13 (9.5%), grade 3 in 38 (27.7%), grade 4 in 77 (56.2%), and grade 5 in 2 (1.5%); no patient had grade 0. Accordingly, 79 patients (57.7%) were classified as having HTB and 58 (42.3%) as having low/intermediate thrombus burden. HTB was present in 53 of 77 patients with STEMI (68.8%) and 26 of 60 patients with NSTEMI (43.3%), and in 55 of 81 initially occluded vessels (67.9%) compared with 24 of 56 nonoccluded vessels (42.9%). For comparison, based on the grades originally recorded before consensus review, 99 patients (72.3%) had been classified as having HTB.

### Baseline Clinical, Laboratory, and Angiographic Characteristics

Baseline characteristics by thrombus burden category are presented in Table 1; these comparisons were exploratory and were not adjusted for multiple testing. The two categories were similar in terms of age, sex, cardiovascular risk factors, documented family history, previous coronary artery disease, and lipid parameters. LVEF was lower in the HTB category (46.8±7.9% vs. 50.6±5.5%, P = 0.001). White blood cell and neutrophil counts were higher in the HTB category (P = 0.01 and P = 0.02, respectively), whereas NLR (2.51 [1.61–5.93] vs. 2.46 [1.71–3.72], P = 0.54), SIRI (2.02 [1.43–3.65] vs. 1.72 [1.24–2.91], P = 0.20), PLR, MHR, SII, and C-reactive protein levels did not differ significantly. Admission troponin levels did not differ between categories (P = 0.46). STEMI presentation (67.1% vs. 41.4%, P = 0.003) and an occluded culprit vessel (69.6% vs. 44.8%, P = 0.004) were more frequent in the HTB category, as were a higher SYNTAX score (15.0 vs. 10.2, P = 0.001) and the left anterior descending artery as the culprit vessel (58.2% vs. 41.4%; overall culprit vessel distribution, P = 0.03).

**Table 2.** Final thrombus grade according to the procedural stage at which grading was performed (n=137)

| Stage of grading | n | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | HTB, n (%) |
|---|---|---|---|---|---|---|---|
| Nonoccluded culprit vessel: diagnostic angiogram | 56 | 6 | 6 | 20 | 24 | – | 24 (42.9) |
| Occluded culprit vessel: first angiographic run after guidewire crossing | 31 | 1 | 3 | 3 | 24 | – | 24 (77.4) |
| Occluded culprit vessel: first angiographic run after small-balloon dilation | 48 | – | 4 | 15 | 29 | – | 29 (60.4) |
| Occluded culprit vessel: antegrade flow not restored | 2 | – | – | – | – | 2 | 2 (100) |
| Total | 137 | 7 (5.1%) | 13 (9.5%) | 38 (27.7%) | 77 (56.2%) | 2 (1.5%) | 79 (57.7) |

Occluded culprit vessels (preprocedural TIMI flow grade 0, initial thrombus grade 5) were reclassified according to the residual thrombus observed on the first angiographic run after restoration of antegrade flow, as described by Sianos et al.[8] HTB, high thrombus burden (grades 4–5); TIMI, Thrombolysis in Myocardial Infarction.

ACC/AHA type C lesions (73.4% vs. 58.6%, P = 0.07) and tirofiban use (26.6% vs. 13.8%, P = 0.07) were numerically more frequent, although the differences were not statistically significant. Final TIMI flow grade 3 (92.4% vs. 94.8%, P = 0.73) and no-reflow (1.3% vs. 1.7%, P > 0.99) did not differ significantly. Final TIMI flow grade ≤2 occurred in six patients with HTB and three with low/intermediate thrombus burden; apart from the two patients with no-reflow, this was attributable to surgical referral without PCI (n=2), persistent occlusion after failed PCI (n=2), or another mechanical cause (n=3).

**Multivariable Analysis**

The results of the multivariable models are presented in Table 3. Neither index was associated with HTB after adjustment for pre-event characteristics (Model 1: NLR, odds ratio [OR] 1.05, 95% confidence interval [CI] 0.94–1.17, P = 0.37; SIRI, OR 1.13, 95% CI 0.95–1.35, P = 0.17). Adding STEMI presentation (Model 2) further attenuated the point estimates (NLR, OR 1.03, 95% CI 0.92–1.14, P = 0.64; SIRI, OR 1.08, 95% CI 0.90–1.30, P = 0.39), whereas STEMI presentation was independently associated with HTB (OR 2.75, 95% CI 1.33–5.68, P = 0.006 in the NLR model; OR 2.65, 95% CI 1.28–5.49, P = 0.009 in the SIRI model). In Model 3, an occluded culprit vessel was associated with HTB (OR 2.32, 95% CI 1.08–5.00, P = 0.03, and OR 2.28, 95% CI 1.06–4.92, P = 0.04), the association between STEMI and HTB was attenuated to borderline significance (OR 2.12, 95% CI 0.98–4.57, P = 0.056, and OR 2.07, 95% CI 0.95–4.47, P = 0.065), and the indices remained unassociated with HTB. Model discrimination was modest (c-statistic 0.60–0.61 for Model 1, 0.66–0.67 for Model 2, and 0.69 for Model 3; Nagelkerke $R^2$ 0.04–0.16), calibration was adequate in all models (Hosmer–Lemeshow P = 0.33–0.83), and no multicollinearity was detected (all variance inflation factors <2).

**Sensitivity Analyses**

The conclusions remained unchanged in all sensitivity analyses. Adding admission troponin to Model 2 did not alter the estimates for NLR (OR 1.02, 95% CI 0.91–1.13, P = 0.75) or SIRI (OR 1.05, 95% CI 0.88–1.26, P = 0.57), and troponin itself was not associated with HTB (OR per log-unit increase 1.17, 95% CI 0.89–1.55, P = 0.26). Adding MHR (OR per 0.01-unit increase 1.21, 95% CI 0.86–1.71, P = 0.28) likewise did not change the results. After excluding the two lesions with a final thrombus grade of 5 (n=135), the results remained unchanged (NLR, OR 1.03, P = 0.58; SIRI, OR 1.08, P = 0.43; STEMI, OR 2.92 and 2.83, p≤0.006). Within the presentation strata, neither index differed between thrombus burden categories: in patients with NSTEMI (26 with HTB vs. 34 with low/intermediate thrombus burden), NLR was 2.30 (1.87–3.01) versus 2.45 (1.84–3.04) (P = 0.57), and SIRI was 1.88 (1.51–2.75) versus 1.56 (1.12–2.30) (P = 0.22); in patients with STEMI (53 vs. 24), NLR was 3.41 (1.50–6.30) versus 2.83 (1.44–4.36) (P = 0.48), and SIRI was 2.32 (1.39–4.08) versus 2.16 (1.52–3.72) (P = 0.83). No STEMI-by-index

**Table 3.** Clinically defined multivariable logistic regression models for high thrombus burden (n=137)

| Model | Odds ratio (95% CI) | *P* |
|---|---|---|
| NLR (per unit increase) | | |
| Model 1: Pre-event characteristics (c=0.601; Nagelkerke $R^2$=0.04; Hosmer–Lemeshow P = 0.33) | | |
| NLR | 1.05 (0.94–1.17) | 0.37 |
| Model 2: Model 1 + STEMI presentation (c=0.665; Nagelkerke $R^2$=0.11; Hosmer–Lemeshow P = 0.75) | | |
| NLR | 1.03 (0.92–1.14) | 0.64 |
| STEMI | 2.75 (1.33–5.68) | 0.006 |
| Model 3 (sensitivity analysis): Model 2 + occluded culprit vessel (c=0.692; Nagelkerke $R^2$=0.15; Hosmer–Lemeshow P = 0.41) | | |
| NLR | 1.02 (0.92–1.15) | 0.67 |
| STEMI | 2.12 (0.98–4.57) | 0.056 |
| Occluded culprit vessel (TIMI flow grade 0) | 2.32 (1.08–5.00) | 0.03 |
| SIRI (per unit increase) | | |
| Model 1: Pre-event characteristics (c=0.610; Nagelkerke $R^2$=0.05; Hosmer–Lemeshow P = 0.76) | | |
| SIRI | 1.13 (0.95–1.35) | 0.17 |
| Model 2: Model 1 + STEMI presentation (c=0.664; Nagelkerke $R^2$=0.12; Hosmer–Lemeshow P = 0.83) | | |
| SIRI | 1.08 (0.90–1.30) | 0.39 |
| STEMI | 2.65 (1.28–5.49) | 0.009 |
| Model 3 (sensitivity analysis): Model 2 + occluded culprit vessel (c=0.694; Nagelkerke $R^2$=0.16; Hosmer–Lemeshow P = 0.78) | | |
| SIRI | 1.07 (0.89–1.29) | 0.47 |
| STEMI | 2.07 (0.95–4.47) | 0.065 |
| Occluded culprit vessel (TIMI flow grade 0) | 2.28 (1.06–4.92) | 0.04 |

Model 1 was adjusted for age, sex, diabetes mellitus, current smoking, and non-HDL cholesterol, with covariates selected on clinical grounds. Model 2 additionally included STEMI presentation, as documented in the clinical records. Model 3 additionally included an occluded culprit vessel (preprocedural TIMI flow grade 0) and was considered a sensitivity analysis because initial occlusion and thrombus grade partially reflect the same occlusive process. NLR and SIRI were modeled separately. Odds ratios for the adjustment covariates are available on request; none was statistically significant in any model. CI, confidence interval; HDL, high-density lipoprotein; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammatory response index; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

interaction was detected (P = 0.16 for NLR and P = 0.73 for SIRI). Both indices correlated with admission troponin levels in the overall cohort (Spearman's ρ=0.21, P = 0.01 for NLR; ρ=0.24, P = 0.005 for SIRI), and this correlation was most evident in patients with NSTEMI (ρ=0.40, P = 0.002, and ρ=0.35, P = 0.006), which may reflect, among other factors, the longer and more variable interval between symptom onset and sampling in NSTEMI.

### ROC Analysis

The discriminatory ability of the indices for HTB was negligible: the area under the receiver operating characteristic curve (AUC) was 0.531 (95% CI 0.434–0.628) for NLR and 0.564 (95% CI 0.467–0.661) for SIRI, with confidence intervals that included 0.5 for both indices (Figure 2); given the lack of discrimination, the two areas were not formally compared. The Youden-derived cutoffs (NLR, 5.83, sensitivity 27.8%, specificity 87.9%; SIRI, 3.08, sensitivity 34.2%, specificity 79.3%) are reported for descriptive purposes only; they were derived and evaluated in the same dataset and have no established clinical predictive value.

### In-Hospital Outcomes

In-hospital events were infrequent (Table 4). In-hospital death occurred in three patients (3.8%) in the HTB category and four (6.9%) in the low/intermediate thrombus burden category (P = 0.46), and the composite outcome of in-hospital death, cardiogenic shock, stroke, acute stent thrombosis, or VF/sustained VT occurred in 12 (15.2%) and 5 (8.6%), respectively (P = 0.30). No statistically significant differences in in-hospital outcomes were detected; the number of events was small, and these comparisons were underpowered.

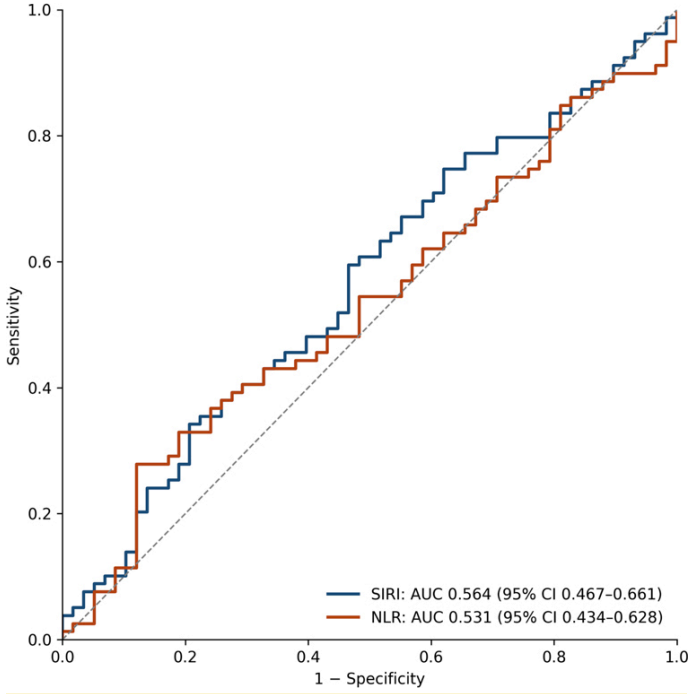



**Figure 2.** Receiver operating characteristic (ROC) curves for the systemic inflammatory response index (SIRI) and neutrophil-to-lymphocyte ratio (NLR) in relation to high thrombus burden (n=137). The area under the curve was 0.564 (95% confidence interval [CI] 0.467–0.661) for SIRI and 0.531 (95% CI 0.434–0.628) for NLR. Both confidence intervals included 0.5. The curves are presented solely as an exploratory assessment of discriminatory ability.

## Discussion

In this selected cohort of young patients with angiographically confirmed type 1 MI, HTB was present in more than half of the patients and was associated, in exploratory comparisons, with STEMI presentation, an initially occluded culprit vessel, and a lower LVEF. Inflammatory indices derived from admission complete blood counts were not associated with HTB in unadjusted or adjusted analyses, and their discriminatory ability for HTB was negligible. The contribution of the present study is primarily methodological: it shows that the apparent association between complete blood count–derived indices and thrombus burden depends on how thrombus burden is graded and that, with standardized consensus grading, these indices provide no information on thrombus burden in young patients with type 1 MI.

Thrombus grade 5 denotes a thrombotic total occlusion in which the amount of thrombus cannot be assessed, and Sianos et al.[8] therefore recommend reclassifying such lesions after antegrade flow has been restored. When, in a post hoc comparison, the same 137 patients were instead classified using the grades originally recorded before consensus review, in which initially occluded vessels had generally not been reclassified, the prevalence of HTB was 72.3% rather than 57.7%, the unadjusted odds ratio for the association between STEMI and HTB was 17.6 rather than 2.9, and both the (NLR; P = 0.03) and (SIRI P = 0.002) appeared to differ between thrombus burden categories. With standardized consensus grading and reclassification after flow restoration, these apparent differences disappeared. The inflammatory signal observed with the original grades thus reflected their close association with STEMI presentation rather than a relationship between systemic inflammation and the amount of thrombus. How thrombus burden was graded in previous studies reporting such associations, including whether initially occluded vessels were reclassified, is often not stated.[18–20] We cannot determine whether their findings were affected, but the present data suggest that the grading method should be explicitly reported in future thrombus burden studies. Differences in age range, presentation characteristics, and adjustment strategies may also contribute to the discrepancies with earlier reports.

The associations of STEMI presentation and initial occlusion with HTB are consistent with the pathophysiology of acute coronary occlusion.[7,22] Because these two variables are concurrent manifestations of the same occlusive process, and because occlusion partly determines how the grade is assigned, their associations should be interpreted as descriptive correlates rather than independent predictors; the association between STEMI and HTB was attenuated to borderline significance when occlusion was included alongside it. Nevertheless, HTB was not confined to STEMI, being present in 43% of patients with NSTEMI, and approximately one-third of initially occluded vessels were assigned a grade below 4 once flow was restored. Among the exploratory secondary findings, the higher SYNTAX score and the greater frequency of the left anterior descending artery as the culprit vessel in the HTB category should be interpreted similarly. The SYNTAX algorithm assigns additional points for thrombus and total occlusion, so part of the difference is inherent to the score, which is why the SYNTAX score and lesion classification were not used as covariates. Multivessel disease did not differ between categories.

The absence of an association between inflammatory indices and thrombus burden, together with their correlation with admission troponin levels, is consistent with two nonexclusive explanations. First, leukocyte subpopulations change within hours of coronary occlusion, so an admission complete blood count obtained at an unrecorded and variable interval after symptom onset may reflect a consequence of infarction rather than a determinant of thrombus formation; the data cannot distinguish cause from consequence, and reverse causation is plausible. The indices should therefore be interpreted as a snapshot of the leukocyte response at presentation rather than as a measure of pre-event inflammatory status. Second, thrombus burden is a lesion-level phenomenon governed largely by local factors, whereas complete blood count-derived indices are crude systemic measures. The higher white blood cell and neutrophil counts observed in patients with HTB in exploratory comparisons did not translate into differences in the composite indices and, as isolated unadjusted differences, should not be considered biologically meaningful. In either case, the present data do not support a role for these indices in characterizing thrombus burden: they were not associated with HTB in any model, their areas under the curve (AUCs) did not differ significantly from 0.5, and no incremental value beyond clinical variables was demonstrated or should be inferred.

HTB has been associated with in-hospital mortality in young adults in previous studies,[24] but in the present cohort, in-hospital events were infrequent (7 deaths and 17 composite events), the comparisons were underpowered, and no prognostic conclusions can be drawn in the absence of postdischarge follow-up.

Premature MI is etiologically heterogeneous, and a structured etiologic evaluation is recommended in this age group.[5] Because our cohort was restricted to patients with type 1 MI and an identifiable culprit lesion and was not systematically evaluated for nonatherosclerotic mechanisms, the frequency of HTB should be regarded as a descriptive characteristic of this cohort.

**Limitations**

Several limitations should be acknowledged. This was a retrospective, single-center analysis of a relatively small cohort without a formal sample size calculation; therefore, a type II error cannot be excluded, and although the confidence intervals do not support a large association per unit increase in the NLR or SIRI, modest effects cannot be entirely ruled out. The retrospective database was susceptible to duplicate records and misclassification of thrombus grade: both errors were identified only during re-auditing against the source records, and their correction materially altered the principal findings. Although the final dataset was verified individually for each patient, this issue should be considered when interpreting the results. Thrombus burden was jointly assessed by two interventional cardiologists who assigned a single consensus grade; independent grading was not performed, interobserver agreement could not be quantified, and independent reassessment is no longer feasible. Therefore, the reproducibility of the outcome classification remains undetermined. Presentation type was obtained from the clinical records, in which it had been assigned with knowledge of the angiographic findings; an unblinded reassessment by the investigators, performed during the same session as thrombus grading and without strict application of diagnostic criteria, resulted in the reclassification of 42 patients (30.7%) and was not used in the analyses. Independent adjudication by blinded reviewers was unavailable; therefore, the reliability of the STEMI/NSTEMI classification remains uncertain, and its association with HTB may have been influenced by knowledge of the angiographic findings. Only patients with an identifiable culprit lesion were screened; therefore, the cohort represents angiographically confirmed atherothrombotic premature MI rather than the full spectrum of MI in young adults, and the low documented frequencies of dyslipidemia and family history likely reflect incomplete ascertainment rather than their true prevalence. Inflammatory indices were calculated from a single admission blood sample, with no recorded information on the interval between symptom onset and sampling; consequently, sampling

**Table 4.** In-hospital outcomes by thrombus burden category

| Outcome | Low/intermediate TB (n=58) | HTB (n=79) | *P* |
|---|---|---|---|
| In-hospital death | 4 (6.9) | 3 (3.8) | 0.46 |
| Cardiogenic shock | 0 (0.0) | 3 (3.8) | 0.26 |
| VF or sustained VT | 1 (1.7) | 5 (6.3) | 0.40 |
| Stroke | 0 (0.0) | 2 (2.5) | 0.51 |
| Acute stent thrombosis | 3 (5.2) | 3 (3.8) | 0.70 |
| Contrast-induced nephropathy | 4 (6.9) | 2 (2.5) | 0.40 |
| Major or minor bleeding (TIMI criteria) | 1 (1.7) | 0 (0.0) | 0.42 |
| Access-site hematoma | 1 (1.7) | 0 (0.0) | 0.43 |
| Composite outcome | 5 (8.6) | 12 (15.2) | 0.30 |
| Length of hospital stay, days | 3 (2–3) | 3 (2–3) | 0.64 |

Values are presented as n (%) or median (IQR). The composite outcome included in-hospital death, cardiogenic shock, stroke, acute stent thrombosis, or VF/sustained VT. Data on access-site hematoma were available for 78 patients in the HTB category. p values were calculated using Fisher's exact test, except for length of hospital stay, which was compared using the Mann–Whitney U test. No statistically significant differences were detected; however, the number of events was small, and these comparisons were underpowered. HTB, high thrombus burden; IQR, interquartile range; TB, thrombus burden; TIMI, Thrombolysis in Myocardial Infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

conditions differed systematically between patients with STEMI and NSTEMI, exposure misclassification cannot be excluded, and because blood sampling necessarily occurred after infarction onset, these indices cannot distinguish cause from consequence. Admission troponin was included only as an exploratory marker of myocardial injury and cannot substitute for direct information on sampling time. No adjustment was made for multiple comparisons; therefore, all secondary findings, including differences in leukocyte counts, LVEF, culprit vessel, and SYNTAX score, should be considered exploratory. The study period overlapped with the coronavirus disease 2019 (COVID-19) pandemic, which has been associated with a prothrombotic state and changes in hospital admission patterns for ACS among young patients in Türkiye.[4] COVID-19 status could not be reliably determined, and undetected recent infection represents a potential unmeasured confounder that may have influenced both thrombus burden and inflammatory indices. Only patients who underwent coronary angiography were included, 13 of 185 eligible records (7.0%) were excluded because of missing laboratory data or inadequate angiographic image quality, and only 9 patients (6.6%) were women; therefore, the findings are primarily generalizable to young men. Definitions of premature coronary artery disease vary across studies and sometimes differ by sex, which should be considered when comparing our findings with those of cohorts using different definitions. Information on preadmission medications, periprocedural antithrombotic regimens, thrombus aspiration, stent characteristics, intracoronary imaging, and distal protection was unavailable; because the procedure used to restore coronary flow may itself affect the residual thrombus on which grading is based, the procedural stage of thrombus assessment was recorded for each patient (Table 2), but the effects of other procedural decisions on the final thrombus grade could not be evaluated. Tirofiban was used numerically more frequently in the HTB category, a difference likely reflecting confounding by indication. Etiologic variables relevant to premature MI, including familial hypercholesterolemia, lipoprotein(a), thrombophilia, antiphospholipid antibodies, homocysteine levels, substance use, hormonal exposure, autoimmune disease, and a structured evaluation for spontaneous coronary artery dissection and other nonatherosclerotic mechanisms, were also unavailable; statin therapy may reduce both lipid concentrations and inflammatory indices, previous antithrombotic treatment may decrease angiographically visible thrombus, and lipid measurements obtained during the acute phase may underestimate baseline levels. Because previous coronary artery disease was uncommon and similarly distributed between categories, substantial differences in exposure to secondary prevention therapies appear unlikely; nevertheless, residual confounding cannot be excluded. Finally, the number of in-hospital adverse events was small, and the lack of postdischarge follow-up prevented assessment of longer-term prognostic implications.

## Conclusion

Among young patients with angiographically confirmed type 1 MI, HTB was present in more than half of the cohort when thrombus burden was consistently graded after restoration of coronary flow and was associated with STEMI presentation and an initially occluded culprit vessel. Inflammatory indices derived from admission complete blood counts were not associated with HTB in either unadjusted or adjusted analyses, demonstrated negligible discriminatory ability, and provided no additional information on thrombus burden beyond the clinical presentation phenotype. These findings reflect cross-sectional angiographic associations at presentation, have no established prognostic implications, and do not support the use of these indices to characterize thrombus burden in young patients with MI.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-94455/TKDA-94455_(0)_Supplementary_Materials.pdf

**Ethics Committee Approval:** Ethics committee approval was obtained from Kayseri City Hospital Non-interventional Clinical Research Ethics Committee (Approval Number: 1044, Date: 14.07.2026).

**Informed Consent:** The requirement for written informed consent was waived because the analysis was retrospective and used anonymized patient data.

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# Coronary Thrombosis in Young Patients with Myocardial Infarction

## Miyokard Enfarktüsü Geçiren Genç Hastalarda Koroner Tromboz

**EDITORIAL COMMENT**
EDİTÖRYAL YORUM

Although myocardial infarction (MI) is more common in middle-aged and older individuals, it is not uncommon among young adults younger than 45 years.[1] Understanding the underlying causes and factors that trigger acute coronary events at a young age is important for preventing MI in young adults. Therefore, studies on premature MI are particularly valuable. Investigating factors associated with coronary thrombus burden may also provide useful insights into the underlying mechanisms and their potential clinical significance.

The present study examines the association between inflammatory indices at admission and angiographic thrombus burden in 137 patients younger than 45 years with type 1 MI. High thrombus burden was observed in 57.7% of patients and was associated with ST-elevation MI (STEMI) and initial coronary occlusion. However, neither the neutrophil-to-lymphocyte ratio (NLR) nor the systemic inflammatory response index (SIRI) was associated with thrombus burden. These findings provide insights into a selected group of young patients. However, their biological and clinical implications require careful interpretation.

The inclusion of patients with both non-ST-elevation MI (NSTEMI) and STEMI complicates the interpretation of these findings. STEMI is often associated with a larger myocardial infarct and, in this study, was also associated with greater thrombus burden.[2] Higher inflammatory indices may therefore reflect more extensive myocardial injury rather than a direct association with thrombus burden.[3] Adjustment for STEMI presentation cannot fully distinguish these effects. The timing of blood sampling represents another limitation. Acute MI triggers an inflammatory response that evolves over time, but the interval between symptom onset and blood sampling was not recorded.[3] A single blood sample obtained at admission cannot distinguish preexisting inflammation from the inflammatory response to infarction. Adjustment for admission troponin levels does not resolve this issue because this measurement cannot reliably establish the timing or total extent of myocardial injury.[4] Therefore, the absence of an association between NLR or SIRI and thrombus burden does not exclude a role for inflammation in coronary thrombosis; likewise, a positive association would not establish causality. Thrombus assessment also has limitations. Reclassification of an initially occluded artery after restoration of antegrade flow through guidewire crossing or passage or dilation of a small balloon follows the approach described by Sianos et al.[5] However, these procedures may alter the amount of thrombus visualized on angiography and consequently affect its grading. The lack of information on several procedural and antithrombotic treatment variables introduces additional uncertainty because these factors may influence the thrombus burden observed on angiography. Furthermore, the absence of long-term clinical follow-up limits conclusions regarding the prognostic significance of high thrombus burden in this cohort.

The determinants of high angiographic thrombus burden have been investigated in several studies. Small observational studies have reported associations with elevated C-reactive protein (CRP) levels, a higher CRP-to-albumin ratio, increased red cell distribution width, higher monocyte counts, and elevated lipoprotein(a) [Lp(a)] levels.[6-9] However, these findings do not establish causality. Other associated findings, such as STEMI presentation, distal embolization, and no-reflow, primarily reflect the clinical presentation or consequences of extensive thrombosis rather than explain why some patients develop a greater thrombus burden.[9] Hypertension has also been identified as an independent predictor of high thrombus burden in young men with STEMI.[10]

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Beyond thrombus burden, the inclusion of patients with premature MI highlights the importance of discussing the underlying etiology of MI in this age group. Although atherosclerosis is the most common underlying cause of MI in young adults, understanding premature MI requires consideration of factors that both accelerate atherosclerosis and promote thrombosis at an earlier age.[1] Coronary thrombosis does not always result from plaque rupture or erosion. Other causes of MI in young patients, including coronary embolism, spontaneous coronary artery dissection, and coronary vasospasm, should also be considered. Although the Fifth Universal Definition includes these mechanisms within the broader category of primary MI, identifying the underlying pathology remains important for guiding further investigations and treatment.[11] Causes other than atherothrombosis, as well as a possible thrombophilic predisposition, should also be considered during the diagnostic evaluation of premature MI.[12]

The etiological assessment of premature MI should begin with a detailed cardiovascular and family history and a thorough evaluation of conventional risk factors.[13] In addition to routine biochemical testing and a lipid profile, including Lp(a), further laboratory investigations should be guided by the clinical history and coronary findings. These investigations may include inflammatory markers and tests for acquired thrombophilia when the clinical history or findings suggest an underlying inflammatory, autoimmune, or thrombotic disorder, particularly testing for antiphospholipid antibodies when conventional risk factors and the extent of atherosclerosis do not adequately explain the event. Antiphospholipid syndrome is particularly important in premature MI because it is a well-established cause of arterial thrombosis, and its identification may influence treatment decisions.[14] Extensive coronary thrombosis has been reported in young patients with antiphospholipid syndrome.[15,16] Antiphospholipid antibody testing should be performed when the clinical history or findings suggest antiphospholipid syndrome.

The role of inherited thrombophilia in arterial events is less well established than its role in venous thromboembolism.[17] Some studies and meta-analyses have reported associations between factor V Leiden and the prothrombin G20210A variant and MI, particularly in younger patients.[18,19] Routine screening for inherited thrombophilia is not recommended for every young patient with MI; however, it should be considered when the personal or family history suggests an inherited thrombotic disorder and the results could influence management.[17] In addition to these thrombophilic factors, hyperhomocysteinemia, which may be associated with methylenetetrahydrofolate reductase (MTHFR) gene variants or deficiencies in vitamin B12 or folate, has been linked to increased cardiovascular risk.[20] A higher prevalence of the MTHFR C677T TT genotype has been reported in young men with MI compared with controls.[21]

In the present study, information on antiphospholipid antibodies, homocysteine levels, and thrombophilia testing was unavailable, whereas Lp(a) was measured only in selected patients. These gaps limit a comprehensive assessment of the underlying etiology of premature MI in this cohort.

Although etiological assessment may help clarify the underlying causes of premature MI, identifying the determinants of high thrombus burden is a separate question that requires specific investigation. The findings of this study provide limited insight into these determinants. Further studies incorporating standardized thrombus assessment and longitudinal follow-up are needed to clarify the determinants and clinical significance of high thrombus burden. Additional research on premature MI is also needed to better understand its underlying etiology and prognostic factors.

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# Clinical, Inflammatory, and Angiographic Characteristics of Young, Middle-Aged, and Older Patients with Myocardial Infarction: A Single-Center Retrospective Study

## Genç, Orta Yaşlı ve Yaşlı Miyokard Enfarktüsü Hastalarının Klinik, Enflamatuvar ve Anjiyografik Özellikleri: Tek Merkezli Retrospektif Bir Çalışma

**ABSTRACT**

**Objective:** This study aimed to evaluate age-related differences in the clinical, inflammatory, and angiographic characteristics of patients with myocardial infarction (MI).

**Method:** This retrospective, single-center observational study analyzed 905 consecutive patients with acute MI who underwent coronary angiography between February 2024 and April 2026. Patients were divided into three age groups: <45 years (n=96), 45–54 years (n=226), and ≥55 years (n=583). Demographic characteristics, cardiovascular risk factors, inflammatory indices, laboratory findings, and angiographic features were retrospectively analyzed.

**Results:** The mean age was 61.0±13 years, and 71.2% of the patients were male. ST-segment elevation myocardial infarction was present in 59.4% of young patients. Young patients had a higher prevalence of ever smoking, higher admission low-density lipoprotein cholesterol levels, a higher prevalence of high TIMI thrombus burden, and more frequent bifurcation lesions. In contrast, hypertension, diabetes mellitus, chronic kidney disease, and previous coronary artery disease were less common among young patients. Exploratory multinomial logistic regression analyses identified fewer statistically significant adjusted associations when comparing patients aged 45–54 years with those aged <45 years than when comparing patients aged ≥55 years with those aged <45 years.

**Conclusion:** Age-related differences were observed in the clinical, inflammatory, and angiographic characteristics of patients with MI, with fewer between-group differences between young and middle-aged patients than between young and older patients. These findings represent descriptive associations derived from a retrospective, single-center observational study and should not be interpreted as causal.

**Keywords:** Acute coronary syndrome, age groups, coronary angiography, myocardial infarction, young adult.

**ÖZET**

**Amaç:** Bu çalışmada, miyokard enfarktüsü (MI) hastalarında yaşa bağlı klinik, enflamatuvar ve anjiyografik özelliklerin değerlendirilmesi amaçlandı.

**Yöntem:** Bu retrospektif, tek merkezli gözlemsel çalışmada, Şubat 2024 ile Nisan 2026 tarihleri arasında akut MI tanısıyla koroner anjiyografi uygulanan ardışık 905 hastadan oluşan bir kohort analiz edildi. Hastalar <45 yaş (n=96), 45–54 yaş (n=226) ve ≥55 yaş (n=583) olmak üzere üç yaş grubuna ayrıldı. Demografik özellikler, kardiyovasküler risk faktörleri, enflamatuvar indeksler, laboratuvar bulguları ve anjiyografik özellikler retrospektif olarak analiz edildi.

**Bulgular:** Hastaların ortalama yaşı 61,0±13 yıl olup %71,2'si erkekti. ST-segment elevasyonlu miyokard enfarktüsü genç hastaların %59,4'ünde mevcuttu. Genç hastalarda sigara kullanım öyküsü daha yaygın, başvuru sırasındaki düşük yoğunluklu lipoprotein kolesterol düzeyleri daha yüksek, yüksek TIMI trombüs yükü daha sık ve bifurkasyon lezyonları daha fazlaydı. Buna karşılık hipertansiyon, diabetes mellitus, kronik böbrek hastalığı ve geçirilmiş koroner arter hastalığı genç hastalarda daha az sıktı. Keşifsel multinomiyal lojistik regresyon analizlerinde, 45–54 yaş grubu ile <45 yaş grubu arasındaki karşılaştırmada, ≥55 yaş grubu ile <45 yaş grubu arasındaki karşılaştırmaya göre daha az sayıda istatistiksel olarak anlamlı düzeltilmiş ilişki saptandı.

**Sonuç:** MI hastalarında klinik, enflamatuvar ve anjiyografik özellikler açısından yaşa bağlı farklılıklar gözlendi; genç ve orta yaşlı hastalar arasında, genç ve ileri yaştaki hastalar arasındaki karşılaştırmaya kıyasla daha az sayıda gruplar arası farklılık saptandı. Bu bulgular, retrospektif, tek merkezli gözlemsel bir çalışmadan elde edilen tanımlayıcı ilişkileri temsil etmektedir ve nedensel olarak yorumlanmamalıdır.

**Anahtar Kelimeler:** Akut koroner sendrom, yaş grupları, koroner anjiyografi, miyokard enfarktüsü, genç erişkin.

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Cardiovascular diseases remain the leading cause of mortality worldwide. Although advances in revascularization strategies and contemporary medical therapies have reduced mortality associated with acute myocardial infarction (MI), the increasing prevalence of MI among young patients has emerged as an important clinical and epidemiological concern.[1]

There is currently no universally accepted age definition for young patients with MI. Previous studies have used different age cutoffs, most commonly <40 or <45 years, while some definitions have also incorporated sex-specific thresholds.[2,3]

The Atherosclerosis Risk in Communities (ARIC) study reported that approximately 30% of patients hospitalized with acute MI were between 35 and 54 years of age.[4] In Türkiye, patients with MI tend to present at younger ages than those reported in many Western populations, and young patients constitute a considerable proportion of all MI cases.[5]

Although previous studies have mainly focused on traditional cardiovascular risk factors in young patients with MI, data comparing inflammatory markers and coronary angiographic characteristics across different age groups remain limited. In particular, comparative data specifically addressing patients aged 45–54 years are scarce.

Therefore, the present study aimed to describe the proportion of patients aged <45 years in this MI cohort. We also compared clinical, inflammatory, laboratory, and angiographic characteristics across predefined age groups among patients presenting to the only primary PCI center in central Hatay during the post-earthquake period.

## Methods

### Study Design

This retrospective, single-center observational study analyzed consecutive patients with acute MI who underwent coronary angiography and met the predefined eligibility criteria. Patients admitted between February 2024 and April 2026 were screened for inclusion. The study was conducted at our center, which served as the only primary percutaneous coronary intervention (PCI) facility in central Hatay during the study period.

The diagnoses of STEMI and NSTEMI were based on current guideline recommendations. STEMI was defined as symptoms suggestive of myocardial ischemia accompanied by new ST-segment elevation in at least two contiguous leads. NSTEMI was defined as symptoms suggestive of myocardial ischemia with elevated cardiac biomarkers in the absence of ST-segment elevation.[6]

Coronary angiography and PCI data were retrospectively reviewed. No formal sample size calculation was performed, and all consecutive eligible patients were included.

Clinical characteristics, medical history, medication use, and lifestyle-related variables, including smoking and alcohol consumption, were obtained from hospital electronic medical records and, when necessary, confirmed through telephone contact with patients or their relatives.

Medication data were classified as preadmission medication use or in-hospital medical treatment. Preadmission use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and statins was recorded. Following hospital admission, patients received antiplatelet, anticoagulant, and high-intensity statin therapies according to current guideline recommendations.

For the present analysis, P2Y12 inhibitor data represented loading doses administered in the emergency department before coronary angiography and did not represent overall P2Y12 inhibitor administration later during hospitalization or treatment prescribed at discharge. Clopidogrel and ticagrelor

## ABBREVIATIONS

| | |
|---|---|
| ACEI | Angiotensin-converting enzyme inhibitor |
| AI | Artificial intelligence |
| ARB | Angiotensin receptor blocker |
| ARIC | Atherosclerosis Risk in Communities |
| BMI | Body mass index |
| CABG | Coronary artery bypass grafting |
| CALLY | C-reactive protein–albumin–lymphocyte index |
| $CHA_2DS_2$-VASc | Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, and sex category |
| CRP | C-reactive protein |
| EBR | Eosinophil-to-basophil ratio |
| eGFR | Estimated glomerular filtration rate |
| EUROASPIRE-IV | European Action on Secondary and Primary Prevention by Intervention to Reduce Events IV |
| GRACE | Global Registry of Acute Coronary Events |
| HALP | Hemoglobin–albumin–lymphocyte–platelet score |
| HbA1c | Hemoglobin A1c |
| HDL-C | High-density lipoprotein cholesterol |
| LDL-C | Low-density lipoprotein cholesterol |
| LMR | Lymphocyte-to-monocyte ratio |
| LMWH | Low-molecular-weight heparin |
| LVEF | Left ventricular ejection fraction |
| MBR | Monocyte-to-basophil ratio |
| MI | Myocardial infarction |
| NLR | Neutrophil-to-lymphocyte ratio |
| non-HDL-C | Non-high-density lipoprotein cholesterol |
| non-HDL/HDL | Non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio |
| NPS | Naples prognostic score |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| P2Y12 | Platelet P2Y12 receptor |
| PCI | Percutaneous coronary intervention |
| PLR | Platelet-to-lymphocyte ratio |
| PMI | Prognostic metabolic index |
| POT | Proximal optimization technique |
| SGLT2 | Sodium–glucose cotransporter 2 |
| SII | Systemic immune-inflammation index |
| SIRI | Systemic inflammation response index |
| STEMI | ST-segment elevation myocardial infarction |
| SYNTAX | Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery |
| TG/BMI | Triglyceride-to-body mass index ratio |
| TIMI | Thrombolysis in Myocardial Infarction |
| TURKMI | Turkish Acute Myocardial Infarction Registry |
| UFH | Unfractionated heparin |

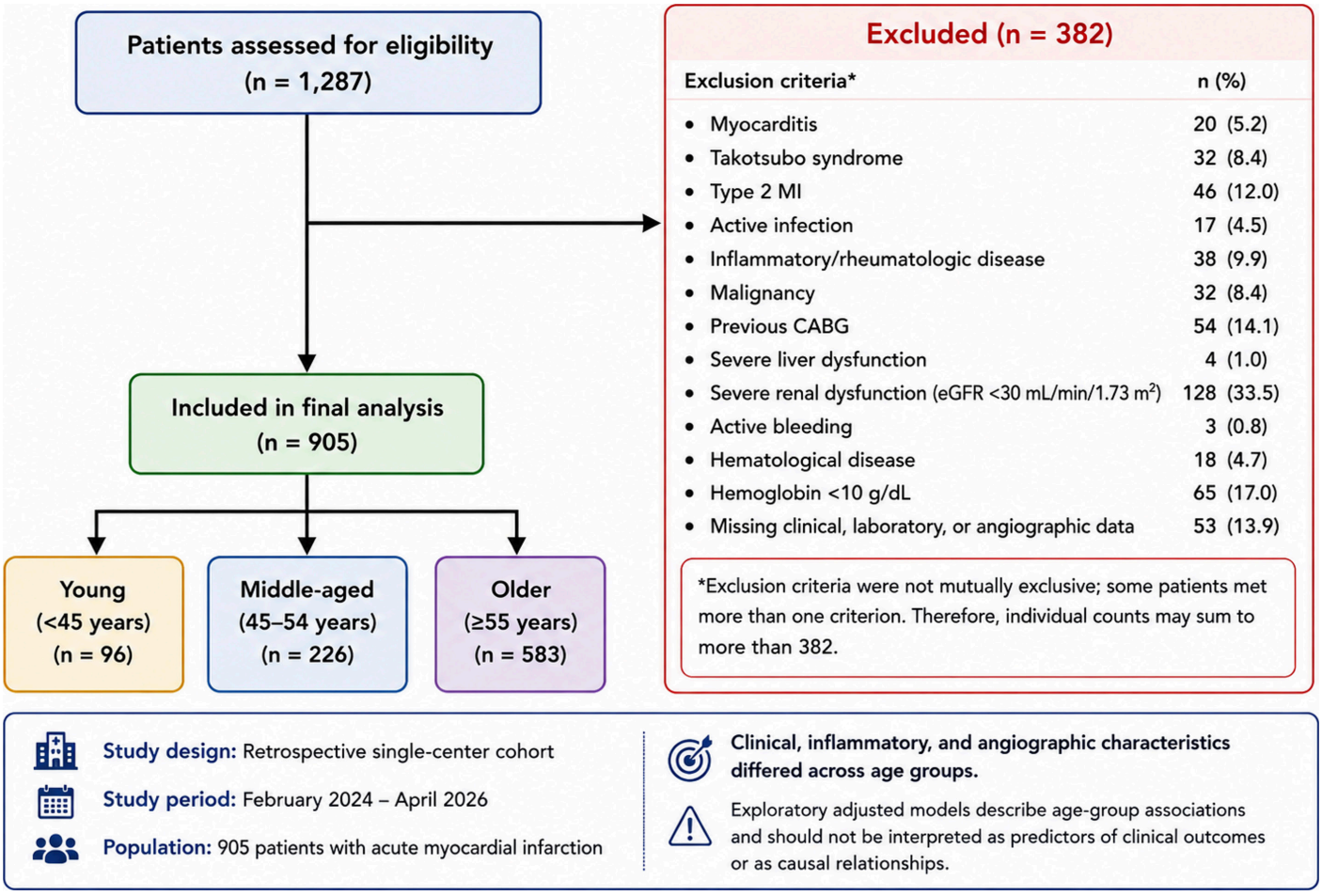



**Figure 1.** Flow diagram of patient selection and age-group classification.

CABG, Coronary artery bypass grafting; eGFR, Estimated glomerular filtration rate; MI, Myocardial infarction.

were available during the study period, whereas prasugrel was not available in the region.

### Study Population

Patients were categorized into three age groups: young patients aged <45 years (n=96), middle-aged patients aged 45–54 years (n=226), and older patients aged ≥55 years (n=583).

Eligible patients were required to be 18 years of age or older, have a diagnosis of STEMI or NSTEMI, and undergo coronary angiography. Patients with myocarditis, Takotsubo syndrome, type 2 MI, active infection, chronic inflammatory or rheumatologic disorders, malignancy, severe renal dysfunction (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²), severe liver dysfunction, active bleeding, hematological disease, hemoglobin levels below 10 g/dL, previous coronary artery bypass grafting (CABG), or missing clinical, laboratory, or angiographic data were excluded from the analysis.

Information regarding demographic characteristics, comorbid conditions, medication use, laboratory measurements, inflammatory indices, echocardiographic findings, and coronary angiographic characteristics was retrospectively obtained from the hospital electronic medical record database. When necessary, clinical history and lifestyle-related variables were confirmed through telephone contact with patients or their relatives. Smoking and alcohol consumption were recorded as dichotomous ever/never variables.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee (Approval Number: 67, Date: 06.05.2026). During the study period, 1,287 patients with suspected or confirmed MI were screened. After application of the predefined eligibility criteria, 382 patients were excluded. The exclusion criteria were not mutually exclusive, and some patients met more than one criterion. The recorded exclusion criteria included myocarditis (n=20), Takotsubo syndrome (n=32), type 2 MI (n=46), active infection (n=17), chronic inflammatory or rheumatologic disease (n=38), malignancy (n=32), previous CABG (n=54), severe liver dysfunction (n=4), severe renal dysfunction defined as eGFR <30 mL/min/1.73 m² (n=128), active bleeding (n=3), hematological disease (n=18), hemoglobin below 10 g/dL (n=65), and missing clinical, laboratory, or angiographic data (n=53). Because individual patients could meet more than one exclusion criterion, the numbers for the individual criteria do not sum to the total number of excluded patients. Finally, 905 patients were included in the analysis (Figure 1).

**Coronary Angiography and PCI**

Coronary angiography and PCI were performed by experienced interventional cardiologists in accordance with current international guidelines.[6] The extent and anatomical complexity of coronary artery disease were assessed using the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score.[7]

Coronary flow was evaluated before and after PCI according to the Thrombolysis in Myocardial Infarction (TIMI) classification. TIMI grade 0 indicated absent flow, grade 1 minimal distal penetration, grade 2 delayed distal perfusion, and grade 3 normal coronary perfusion.[8]

Intracoronary thrombus burden was assessed using the TIMI thrombus grading system. Grade 0 indicated no thrombus, grade 1 possible thrombus, grade 2 thrombus occupying less than one-half of the vessel diameter, grade 3 thrombus occupying between one-half and two vessel diameters, grade 4 thrombus occupying more than two vessel diameters, and grade 5 total thrombotic occlusion.[9] For statistical analyses, thrombus burden was categorized as low (grades 0–2) or high (grades 3–5), consistent with previous reports defining TIMI thrombus grade ≥3 as high thrombus burden.

The culprit lesion location, involved vessel, bifurcation lesions, total occlusion, and procedural characteristics were recorded. All angiograms were independently reviewed by two experienced interventional cardiologists. In cases of disagreement, a final decision was made after review by a third interventional cardiologist.

**Laboratory and Clinical Data Collection**

Laboratory data were retrospectively retrieved from the hospital electronic medical record system. Blood samples obtained at hospital admission were used for hematological and biochemical analyses. Complete blood count parameters, biochemical measurements, lipid profiles, renal and liver function tests, and inflammatory markers were recorded. Left ventricular ejection fraction (LVEF) values were obtained from transthoracic echocardiographic examinations performed during the index hospitalization.

Lipid parameters included low-density lipoprotein cholesterol (LDL-C), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, non–high-density lipoprotein cholesterol (non-HDL-C), the non-HDL/HDL ratio, and the triglyceride-to-body mass index (TG/BMI) ratio. Non-HDL-C was calculated as total cholesterol minus HDL-C. The non-HDL/HDL ratio was calculated by dividing non-HDL-C by HDL-C, and the TG/BMI ratio was calculated by dividing the triglyceride level by body mass index (BMI). Based on previously published criteria used in a Turkish acute coronary syndrome follow-up study, LDL-C ≥100 mg/dL was defined as elevated LDL-C, and total cholesterol ≥174 mg/dL was defined as high total cholesterol.[10] These thresholds were used for descriptive age-group comparisons and were not intended to represent treatment targets in this acute MI cohort.

The Global Registry of Acute Coronary Events (GRACE) score and Killip classification were calculated using clinical and admission data available at presentation. According to the GRACE score, patients were categorized as low risk (<109), intermediate risk (109–140), or high risk (>140).[11,12] The $CHA_2DS_2$-VASc score was calculated using the available clinical variables.

**Inflammatory Indices**

Inflammatory assessment included the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), hemoglobin–albumin–lymphocyte–platelet (HALP) score, Naples prognostic score (NPS), and C-reactive protein–albumin–lymphocyte (CALLY) index.

The NLR and PLR were calculated as the ratios of neutrophils and platelets to lymphocytes, respectively, whereas the LMR was calculated as the ratio of lymphocytes to monocytes. The SII was calculated as platelet count × neutrophil count / lymphocyte count, whereas the SIRI was calculated as neutrophil count × monocyte count / lymphocyte count. The HALP score was calculated using the formula hemoglobin × albumin × lymphocyte count / platelet count. The NPS was determined according to albumin level, total cholesterol level, NLR, and lymphocyte-to-monocyte ratio. The CALLY index was calculated as albumin × lymphocyte count / C-reactive protein.[13–16]

**Outcomes**

The study primarily evaluated age-related differences in clinical characteristics, cardiovascular risk factors, inflammatory indices, laboratory findings, and coronary angiographic features among patients with MI. Only in-hospital clinical outcomes were assessed.

In-hospital outcomes included pulmonary edema, acute kidney injury, atrial fibrillation, ventricular arrhythmias, cardiogenic shock, in-hospital mortality, and length of hospital stay. Pulmonary edema was defined as acute heart failure with clinical and/or radiographic evidence of pulmonary congestion requiring intravenous diuretic therapy or ventilatory support. Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥1.5 times the baseline value during hospitalization.[17] Atrial fibrillation was defined as new-onset atrial fibrillation documented by electrocardiography during hospitalization. Ventricular arrhythmias included sustained ventricular tachycardia lasting >30 seconds or requiring intervention because of hemodynamic instability, as well as ventricular fibrillation. Cardiogenic shock was defined as persistent systolic blood pressure <90 mmHg for at least 30 minutes or the need for vasopressor/inotropic support to maintain systolic blood pressure ≥90 mmHg, accompanied by clinical signs of end-organ hypoperfusion.[6] In-hospital mortality was defined as death from any cause during the index hospitalization. Length of hospital stay was calculated as the number of days from admission to discharge or in-hospital death.

All outcomes were retrospectively ascertained from hospital electronic medical records, physician notes, laboratory results, electrocardiographic records, echocardiography reports, and discharge summaries.

**Statistical Analysis**

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was assessed using visual methods (histograms and probability plots) together with analytical tests. Continuous

variables were expressed as the mean±standard deviation (SD) or median with interquartile range (IQR), as appropriate.

Differences among the three age groups were assessed using the Kruskal–Wallis test for continuous variables. When a statistically significant overall difference was identified, pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni correction.

Categorical variables were presented as percentages and compared using the chi-square test or Fisher's exact test, as appropriate. For pairwise analyses of categorical variables, Bonferroni-adjusted chi-square or Fisher's exact tests were applied.

Exploratory multivariable multinomial logistic regression analyses were performed with age group as the dependent variable. The <45-year group was specified as the reference outcome category, and the models estimated the adjusted odds of membership in the 45–54-year and ≥55-year groups relative to the <45-year group. These analyses were intended to evaluate variables associated with age-group membership rather than to identify predictors of clinical outcomes or angiographic findings. The models included sex, smoking status, diabetes mellitus, hypertension, eGFR, STEMI presentation, preadmission ACEI, ARB, beta-blocker, and SGLT2 inhibitor use, bifurcation lesion status, length of hospital stay, TIMI thrombus burden, and one inflammatory index. To reduce multicollinearity among inflammatory indices, two separate models were constructed: one including the CALLY and the other including the HALP score. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

All statistical tests were two-sided. Statistical significance was defined as $P < 0.05$ for overall group comparisons and regression analyses and $P < 0.017$ for pairwise post hoc analyses after Bonferroni correction.

## Results

A total of 905 patients were included in the study. The mean age of the study population was 61.0±13 years, and 644 patients (71.2%) were male. ST-segment elevation myocardial infarction (STEMI) was present in 461 patients (50.9%), whereas non-ST-segment elevation myocardial infarction (NSTEMI) was present in 444 patients (49.1%). Patients were classified into three age groups: <45 years (n=96), 45–54 years (n=226), and ≥55 years (n=583). The demographic and clinical characteristics of the study groups are summarized in Table 1.

### Baseline Characteristics of Young Patients with MI

In the young patient group (<45 years), 77.1% of patients were male, and the mean age was 36.6±4.5 years; the youngest patient was 27 years old. STEMI was present in 59.4% of young patients. Ever smoking was reported in 81% of young patients (Table 1). Women constituted 22.9% of the young group, 12.8% of the middle-aged group, and 36.0% of the older group. Thus, although the proportion of women was numerically higher in the young group than in the middle-aged group, the young MI group remained predominantly male.

The prevalence of hypertension, diabetes mellitus, chronic kidney disease, and previous coronary artery disease differed across age groups (all $P < 0.05$). Pairwise analyses showed that hypertension and diabetes mellitus were less frequent in young patients than in older patients (both $P < 0.001$).

Smoking was more common in young patients than in older patients ($P < 0.001$). Mean BMI was lower in the young group. BMI did not differ significantly between young and middle-aged patients after Bonferroni correction ($P = 0.029$), whereas BMI was lower in young patients than in older patients ($P < 0.001$).

### Laboratory Findings and Inflammatory Parameters

Laboratory and lipid parameters are presented in Table 2, and inflammatory indices are presented in Table 3.

LDL-C levels differed significantly across age groups and were highest in young patients (143±38 mg/dL vs. 135±43 mg/dL vs. 129±39 mg/dL, $P = 0.008$). Non-HDL-C levels also differed significantly across age groups and were highest in young patients (165.9±51.5 mg/dL vs. 153.5±42.4 mg/dL vs. 149.3±47.0 mg/dL, $P = 0.014$).

**Table 1.** Baseline demographic characteristics and cardiovascular risk factors

| Variables | Age <45 years (n=96) | Age 45–54 years (n=226) | Age ≥55 years (n=583) | *P* |
|---|---|---|---|---|
| Age (years) | 36.6±4.5 | 49.9±2.8 | 68.8±8.5 | – |
| Male sex, n (%) | 74 (77.1) | 197 (87.2) | 373 (64.0) | <0.001 |
| Female sex, n (%) | 22 (22.9) | 29 (12.8) | 210 (36.0) | <0.001 |
| STEMI presentation, n (%) | 57 (59.4) | 121 (53.5) | 283 (48.5) | 0.096 |
| NSTEMI presentation, n (%) | 39 (40.6) | 105 (46.5) | 300 (51.5) | 0.096 |
| Body mass index (kg/m²) | 22.8±2.3 | 23.6±2.9 | 24.1±2.9 | <0.001 |
| Hypertension, n (%) | 23 (24.0) | 52 (23.0) | 337 (57.8) | <0.001 |
| Diabetes mellitus, n (%) | 26 (27.1) | 53 (23.5) | 273 (46.8) | <0.001 |
| Previous coronary artery disease, n (%) | 9 (9.4) | 21 (9.3) | 88 (15.1) | 0.047 |
| Chronic kidney disease, n (%) | 6 (6.3) | 4 (1.8) | 70 (12.0) | <0.001 |
| Ever smoking, n (%) | 78 (81.3) | 181 (80.1) | 343 (58.8) | <0.001 |
| Ever alcohol consumption, n (%) | 56 (58.3) | 123 (54.4) | 203 (34.8) | <0.001 |

Data are presented as mean±standard deviation or n (%). Smoking and alcohol consumption were recorded as ever/never variables based on patient self-report documented in the medical records and, when necessary, confirmed by telephone contact. No p value was calculated for age because age was used to define the study groups. SD, Standard deviation; STEMI, ST-Segment elevation myocardial infarction; NSTEMI, Non-ST-segment elevation myocardial infarction.

The TG/BMI ratio (P = 0.033) and non-HDL/HDL ratio (P = 0.021) did not differ significantly between young and middle-aged patients after Bonferroni correction. However, both parameters differed significantly between young and older patients (P = 0.002 and P < 0.001, respectively).

Inflammatory indices also varied across age groups. The HALP score and LMR were higher in young patients, whereas SIRI, PLR, and the NPS were higher in older patients (all P < 0.05). The CALLY index differed significantly among age groups and was lowest in older patients. No significant differences were identified among age groups for SII, EBR, PMI, or MBR (Table 3).

**Angiographic Characteristics and Interventional Procedures**

Angiographic and procedural findings are presented in Table 4. The distribution of TIMI thrombus grades differed significantly across age groups (P < 0.001). High TIMI thrombus burden was observed in 61.5% of young patients, 61.1% of middle-aged patients, and 45.6% of older patients. Pairwise analysis showed no significant difference between young and middle-aged patients (P = 0.950), whereas high TIMI thrombus burden was significantly more frequent in young patients than in older patients (P = 0.004), and this difference remained significant after Bonferroni correction.

The frequencies of vascular tortuosity and bifurcation lesions differed significantly across age groups (overall P = 0.024 and P < 0.001, respectively). Vascular tortuosity was most frequent in older patients (28.1%), whereas bifurcation lesions were most frequent in young patients (25.0%).

Pairwise analyses showed no significant differences between young and middle-aged patients in vascular tortuosity (P = 0.290) or bifurcation lesions (P = 0.230). In the comparison between young and older patients, bifurcation lesions differed significantly (P < 0.001), whereas the difference in coronary tortuosity did not meet the Bonferroni-adjusted significance threshold (P = 0.018).

**Table 2.** Laboratory and lipid parameters

| Variables | Age <45 years (n=96) | Age 45–54 years (n=226) | Age ≥55 years (n=583) | *P* |
|---|---|---|---|---|
| eGFR (mL/min/1.73 m²) | 100.5 (87.5–112.5) | 98 (86–104) | 78 (59.9–95) | <0.001 |
| Triglycerides (mg/dL) | 202±190 | 152±91 | 148±89 | 0.050 |
| Total cholesterol (mg/dL) | 201±53 | 190±44 | 187±49 | 0.070 |
| High total cholesterol, n (%) | 73 (76.0) | 145 (64.2) | 348 (59.7) | 0.008 |
| Elevated LDL-C, n (%) | 81 (84.4) | 186 (82.3) | 448 (76.8) | 0.091 |
| LDL-C (mg/dL) | 143±38 | 135±43 | 129±39 | 0.008 |
| HDL-C (mg/dL) | 35±10 | 36±9 | 37±12 | <0.001 |
| Non-HDL-C (mg/dL) | 165.9±51.5 | 153.5±42.4 | 149.3±47.0 | 0.014 |
| HbA1c (%) | 6.8±2.2 | 6.3±1.5 | 6.7±1.6 | <0.001 |
| TG/BMI ratio | 8.9±8.3 | 6.6±4.1 | 6.2±3.8 | 0.007 |
| Non-HDL/HDL ratio | 5.0±2.0 | 4.5±1.6 | 4.3±4.4 | <0.001 |

Data are presented as mean±standard deviation or median (interquartile range), as appropriate. Elevated LDL-C was defined as LDL-C ≥100 mg/dL, and high total cholesterol was defined as total cholesterol ≥174 mg/dL. These cutoffs were used only for descriptive age-group comparisons and should not be interpreted as treatment targets in this acute MI cohort. Non-HDL-C was calculated as total cholesterol minus HDL-C. The triglyceride-to-body mass index ratio was calculated as the triglyceride level divided by body mass index. BMI, Body mass index; eGFR, Estimated glomerular filtration rate; HbA1c, Hemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; IQR, Interquartile range; LDL-C, Low-density lipoprotein cholesterol; MI, Myocardial infarction; non-HDL-C, Non–high-density lipoprotein cholesterol; non-HDL/HDL, Non–high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio; SD, Standard deviation; TG, Triglycerides.

**Table 3.** Inflammatory and calculated indices according to age groups

| Variables | Age <45 years (n=96) | Age 45–54 years (n=226) | Age ≥55 years (n=583) | *P* |
|---|---|---|---|---|
| HALP score | 4.8 (2.8–6.9) | 4.5 (2.9–6.3) | 3.6 (2.4–5.3) | <0.001 |
| CALLY index | 21.1 (9.9–49.2) | 27.1 (11.0–62.0) | 14.1 (6.2–40.4) | <0.001 |
| SII | 730 (448–1182) | 807 (497–1445) | 867 (551–1544) | 0.110 |
| SIRI | 1.4 (0.9–2.4) | 1.7 (1.0–3.3) | 1.9 (1.2–3.4) | 0.002 |
| EBR | 2.0 (0.5–6.0) | 3.0 (1.0–6.7) | 3.0 (1.0–6.7) | 0.310 |
| MBR | 18.5 (7.0–28.8) | 16.7 (8.0–29.5) | 19.7 (10.6–34.0) | 0.050 |
| PMI | 2604 (2290–3025) | 2555 (2121–3030) | 2557 (2163–2922) | 0.110 |
| PLR | 114 (83–158) | 118 (91–182) | 139 (100–191) | 0.002 |
| LMR | 4.5 (2.9–6.4) | 3.9 (2.7–5.1) | 3.2 (2.2–4.6) | <0.001 |
| NPS | 2 (1–3) | 2 (1–3) | 3 (2–3) | <0.001 |

Data are presented as median (interquartile range). CALLY, C-reactive protein–albumin–lymphocyte index; EBR, Eosinophil-to-basophil ratio; HALP, Hemoglobin–albumin–lymphocyte–platelet score; IQR, Interquartile range; LMR, Lymphocyte-to-monocyte ratio; MBR, Monocyte-to-basophil ratio; NPS, Naples prognostic score; PLR, Platelet-to-lymphocyte ratio; PMI, Prognostic metabolic index; SII, Systemic immune-inflammation index; SIRI, Systemic inflammation response index.

Balloon predilatation differed significantly across age groups and was most frequent in young patients (90%) and least frequent in older patients (80%; overall P = 0.004). Repeated balloon dilatation also differed across age groups, increasing from 9.4% in young patients to 26.4% in older patients (overall P < 0.001).

Stent diameter differed across age groups (overall P = 0.040), with mean diameters of 3.26±0.47 mm, 3.13±0.53 mm, and 3.16±0.47 mm in the young, middle-aged, and older groups, respectively. SYNTAX scores were comparable among age groups, and TIMI flow grades and total occlusion rates did not differ significantly among the groups (Table 4).

**Clinical Course, Complications, and Risk Scoring**

Clinical risk scores, LVEF, and in-hospital outcomes are summarized in Table 5. GRACE score, GRACE risk category, Killip classification, and $CHA_2DS_2$-VASc score differed significantly across age groups (all P < 0.05).

Although the overall comparison demonstrated a statistically significant difference in LVEF among age groups (P = 0.027), pairwise comparisons between young and middle-aged patients (P = 0.026) and between young and older patients (P = 0.045) did not remain significant after Bonferroni correction.

Among in-hospital outcomes, the frequencies of pulmonary edema, acute kidney injury, and atrial fibrillation differed significantly across age groups and were highest in older patients (all P < 0.05). In-hospital mortality, cardiogenic shock, ventricular tachycardia, and ventricular fibrillation were comparable across age groups. Length of hospital stay differed significantly across age groups (P < 0.001) and was longest in older patients (2.6 days vs. 2.3 days in both young and middle-aged patients).

**Table 4.** Angiographic and procedural findings

| Variables | Age <45 years (n=96) | Age 45–54 years (n=226) | Age ≥55 years (n=583) | *P* |
|---|---|---|---|---|
| Pre-PCI TIMI flow grade, n (%) | | | | 0.209 |
| 0 | 45 (46.9) | 106 (46.9) | 256 (43.9) | |
| 1 | 2 (2.1) | 7 (3.1) | 14 (2.4) | |
| 2 | 22 (22.9) | 27 (11.9) | 105 (18.0) | |
| 3 | 27 (28.1) | 86 (38.1) | 208 (35.7) | |
| TIMI thrombus burden, n (%) | | | | **<0.001** |
| 0 | 1 (1.0) | 3 (1.3) | 10 (1.7) | |
| 1 | 16 (16.7) | 39 (17.3) | 85 (14.6) | |
| 2 | 20 (20.8) | 46 (20.4) | 222 (38.1) | |
| 3 | 30 (31.3) | 69 (30.5) | 128 (22.0) | |
| 4 | 20 (20.8) | 43 (19.0) | 97 (16.6) | |
| 5 | 9 (9.4) | 26 (11.5) | 41 (7.0) | |
| TIMI thrombus burden category, n (%) | | | | **<0.001** |
| Low thrombus burden (grades 0–2) | 37 (38.5) | 88 (38.9) | 317 (54.4) | |
| High thrombus burden (grades 3–5) | 59 (61.5) | 138 (61.1) | 266 (45.6) | |
| Total occlusion, n (%) | 41 (42.7) | 105 (46.5) | 252 (43.2) | 0.683 |
| Subtotal occlusion, n (%) | 52 (54.2) | 121 (53.5) | 331 (56.8) | 0.673 |
| Tortuous coronary arteries, n (%) | 16 (16.7) | 50 (22.1) | 164 (28.1) | **0.024** |
| Coronary calcification, n (%) | 32 (33.3) | 75 (33.2) | 203 (34.8) | 0.890 |
| Bifurcation lesion, n (%) | 24 (25.0) | 43 (19.0) | 60 (10.3) | **<0.001** |
| Lesion length >20 mm, n (%) | 70 (72.9) | 150 (66.4) | 381 (65.4) | 0.347 |
| SYNTAX score | 11.8±9.0 | 12.9±8.2 | 12.0±8.3 | 0.060 |
| Balloon predilatation, n (%) | 86 (89.6) | 199 (88.1) | 466 (79.9) | **0.004** |
| Repeated balloon dilatation, n (%) | 9 (9.4) | 43 (19.0) | 154 (26.4) | **<0.001** |
| Stent diameter (mm) | 3.26±0.47 | 3.13±0.53 | 3.16±0.47 | **0.040** |
| Stent length (mm) | 25.83±20.10 | 24.61±7.66 | 24.55±7.79 | 0.440 |
| Post-PCI TIMI flow grade, n (%) | | | | 0.069 |
| 0 | 4 (4.2) | 3 (1.3) | 16 (2.7) | |
| 1 | 0 (0.0) | 0 (0.0) | 6 (1.0) | |
| 2 | 5 (5.2) | 33 (14.6) | 62 (10.6) | |
| 3 | 87 (90.6) | 190 (84.1) | 499 (85.6) | |

Data are presented as mean±standard deviation or n (%), as appropriate. p values represent overall comparisons across the three age groups. PCI, percutaneous coronary intervention; SD, standard deviation; SYNTAX, Synergy between percutaneous coronary intervention with taxus and cardiac surgery; TIMI, Thrombolysis in myocardial infarction.

Admission vital signs, medication use, and additional procedural characteristics are summarized in Supplementary Table S1, whereas additional laboratory and inflammatory parameters are presented in Supplementary Table S2. Preadmission statin use did not differ significantly across age groups and was documented in 15 (15.6%) young patients, 20 (8.8%) middle-aged patients, and 65 (11.1%) older patients (P = 0.210; Supplementary Table S1).

**Multivariable Analysis**

Exploratory multivariable multinomial logistic regression analyses were performed with age group as the dependent variable. The <45-year group was specified as the reference outcome category. Accordingly, the models estimated the adjusted odds of membership in the 45–54-year and ≥55-year groups relative to the <45-year group. These models were designed to evaluate variables associated with age-group membership rather than to identify predictors of clinical outcomes or angiographic findings. Two separate models were constructed to reduce multicollinearity among the inflammatory indices. Table 6 presents the model that included the CALLY index.

In the CALLY model, male sex showed a statistically significant adjusted association in the comparison between the 45–54-year and <45-year groups. Smoking status, eGFR rate, hypertension status, bifurcation lesion status, and TIMI thrombus burden showed statistically significant adjusted associations in the comparison between the ≥55-year and <45-year groups.

In the second model, which included the HALP score instead of the CALLY index, a similar pattern of associations was observed; therefore, the full results are not shown. Male sex showed a statistically significant adjusted association in the comparison between the 45–54-year and <45-year groups (OR=2.544, 95% CI 1.257–5.147; P = 0.009). In the comparison between the ≥55-year and <45-year groups, eGFR rate (OR=0.962, 95% CI 0.954–0.971; P < 0.001), ever smoking (OR=0.380, 95% CI 0.198–0.728; P = 0.004), and hypertension (OR=2.392, 95% CI 1.175–4.878; P = 0.016) showed statistically significant adjusted associations. The presence of bifurcation lesions (OR=0.427, 95% CI 0.234–0.776; P = 0.005) and high TIMI thrombus burden (OR=0.473, 95% CI 0.283–0.790; P = 0.004) also showed statistically significant adjusted associations in this comparison.

**Discussion**

In this single-center cohort from central Hatay, young patients had a higher prevalence of smoking, higher admission

**Table 5.** In-hospital outcomes

| Variables | Age <45 years (n=96) | Age 45–54 years (n=226) | Age ≥55 years (n=583) | *P* |
|---|---|---|---|---|
| In-hospital acute stent thrombosis, n (%) | 0 (0.0) | 0 (0.0) | 4 (0.7) | 0.330 |
| In-stent restenosis at index angiography, n (%) | 6 (6.3) | 10 (4.4) | 35 (6.0) | 0.657 |
| $CHA_2DS_2$-VASc score, median (IQR) | 0 (0–1) | 0 (0–2) | 2 (1–4) | **<0.001** |
| In-hospital mortality, n (%) | 2 (2.1) | 6 (2.7) | 22 (3.8) | 0.564 |
| Pulmonary edema, n (%) | 2 (2.1) | 16 (7.1) | 54 (9.3) | **0.047** |
| Cardiogenic shock, n (%) | 2 (2.1) | 4 (1.8) | 22 (3.8) | 0.280 |
| Ventricular tachycardia, n (%) | 4 (4.2) | 4 (1.8) | 20 (3.4) | 0.385 |
| Ventricular fibrillation, n (%) | 4 (4.2) | 9 (4.0) | 31 (5.3) | 0.691 |
| Atrial fibrillation, n (%) | 5 (5.2) | 2 (0.9) | 47 (8.1) | **<0.001** |
| Killip class, n (%) | | | | **<0.001** |
| I | 91 (94.8) | 208 (92.0) | 485 (83.2) | |
| II | 3 (3.1) | 4 (1.8) | 52 (8.9) | |
| III | 0 (0.0) | 10 (4.4) | 26 (4.5) | |
| IV | 2 (2.1) | 4 (1.8) | 20 (3.4) | |
| GRACE score | 78.4±24.5 | 86.8±25.6 | 109.4±37.7 | **<0.001** |
| GRACE risk category, n (%) | | | | **<0.001** |
| Low | 87 (90.6) | 195 (86.3) | 326 (55.9) | |
| Intermediate | 7 (7.3) | 25 (11.1) | 155 (26.6) | |
| High | 2 (2.1) | 6 (2.7) | 102 (17.5) | |
| LVEF (%) | 47.2±9.3 | 46.8±8.5 | 45.5±8.8 | **0.027** |
| Acute kidney injury, n (%) | 2 (2.1) | 4 (1.8) | 62 (10.6) | **<0.001** |
| Endotracheal intubation, n (%) | 2 (2.1) | 4 (1.8) | 26 (4.5) | 0.128 |
| Mechanical complications, n (%) | 0 (0.0) | 2 (0.9) | 6 (1.0) | 0.608 |
| Length of hospital stay (days) | 2.3±1.3 | 2.3±1.1 | 2.6±1.5 | **<0.001** |

Data are presented as mean±standard deviation, median (interquartile range), or n (%), as appropriate. p values represent overall comparisons across the three age groups. In-hospital acute stent thrombosis refers to acute stent thrombosis occurring after the index PCI during the same hospitalization. In-stent restenosis refers to restenosis involving a previously implanted coronary stent identified as the culprit lesion at index angiography in patients presenting with acute coronary syndrome. $CHA_2DS_2$-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, and sex category; GRACE, Global Registry of Acute Coronary Events; IQR, Interquartile range; LVEF, Left ventricular ejection fraction; PCI, Percutaneous coronary intervention; SD, Standard deviation.

LDL-C levels and non-HDL/HDL ratios, greater thrombus burden, and more frequent bifurcation lesions. Older patients had higher prevalences of hypertension, diabetes mellitus, chronic kidney disease, previous coronary artery disease, and vascular tortuosity, along with higher values for selected inflammatory indices. Fewer statistically significant differences were observed between young and middle-aged patients than between young and older patients. These findings were broadly consistent with our study hypothesis that young patients with MI would differ from older patients in several clinical, inflammatory, laboratory, and angiographic characteristics, while the 45–54-year group provided an additional age stratum for descriptive comparison.

There is no universally accepted age threshold for defining young patients with MI, and different cutoffs have been used across studies and populations.[2,3,18] In the present study, the <45-year cutoff was used to define young MI, while patients aged 45–54 years were evaluated separately to characterize age-related variation within the cohort. The ARIC study reported that nearly one-third of MI hospitalizations occurred in patients aged 35–54 years.[4] Similarly, patients younger than 55 years constituted 35.6% of our cohort, indicating that a substantial proportion of MI cases in this cohort occurred before the age of 55 years.

The age distribution observed in our cohort should be interpreted within the regional context of Hatay. As a border province, Hatay has demographic and healthcare characteristics shaped by regional migration and, during the study period, by the post-earthquake setting. In the Turkish Acute Myocardial Infarction (TURKMI) registry, the mean age of patients with acute MI was 62 years, and STEMI accounted for approximately 38% of cases, whereas STEMI was present in 51% of our cohort.[5] Previous Turkish data have also suggested a substantial burden of premature coronary disease; in EUROASPIRE-IV Türkiye, 19.3% of patients were younger than 50 years at the index coronary event, and the study population was younger than the EUROASPIRE-IV European cohort.[19] Similarly, Iranian registry data reported a mean age at MI of approximately 61 years, close to that observed in our cohort.[20] These comparisons place our findings within a broader Turkish and regional context rather than indicating a pattern unique to Hatay. The higher prevalence of STEMI in our cohort should be interpreted cautiously and cannot be attributed to earthquake-related effects because no pre-earthquake comparison cohort was available. Potential effects of healthcare disruption, psychosocial stress, population displacement, and altered health-seeking behavior should therefore be considered only as contextual factors.[21,22]

Regarding sex distribution, women constituted 22.9% of the young group, compared with 12.8% of the middle-aged group and 36.0% of the older group. Thus, although the proportion of women was numerically higher in the young group than in the middle-aged group, the young MI group remained predominantly male (77.1%), and the proportion of women was highest in the older group. Previous studies have similarly reported a clear male predominance among young patients with MI.[18] Given the single-center design, differences in age definitions and case mix across studies, and the lack of data

**Table 6.** Multivariable multinomial logistic regression analysis with age group as the dependent variable and <45 years as the reference category

| Variables | 45–54 years vs. <45 years OR (95% CI) | *P* | ≥55 years vs. <45 years OR (95% CI) | *P* |
|---|---|---|---|---|
| Male sex (reference: female) | 2.500 (1.240–5.041) | 0.010 | 1.067 (0.566–2.015) | 0.840 |
| Ever smoking (reference: never) | 0.613 (0.306–1.230) | 0.170 | 0.374 (0.195–0.719) | **0.003** |
| Diabetes mellitus present (reference: absent) | 1.400 (0.668–2.937) | 0.370 | 0.703 (0.358–1.379) | 0.310 |
| Hypertension present (reference: absent) | 1.292 (0.585–2.849) | 0.530 | 2.387 (1.167–4.878) | **0.017** |
| eGFR, per 1 mL/min/1.73 m² increase | 1.000 (0.997–1.004) | 0.830 | 0.962 (0.954–0.971) | **<0.001** |
| STEMI (reference: NSTEMI) | 1.273 (0.749–2.161) | 0.370 | 1.090 (0.655–1.812) | 0.740 |
| Preadmission ACEI use (reference: no use) | 1.343 (0.576–3.136) | 0.500 | 0.750 (0.353–1.594) | 0.460 |
| Preadmission ARB use (reference: no use) | 1.648 (0.405–6.708) | 0.490 | 1.050 (0.325–3.395) | 0.940 |
| Preadmission beta-blocker use (reference: no use) | 0.932 (0.321–2.707) | 0.900 | 0.858 (0.331–2.222) | 0.750 |
| Preadmission SGLT2 inhibitor use (reference: no use) | 0.785 (0.305–2.019) | 0.620 | 1.393 (0.593–3.274) | 0.450 |
| Bifurcation lesion present (reference: absent) | 0.724 (0.402–1.304) | 0.280 | 0.421 (0.232–0.764) | 0.004 |
| CALLY index, per 1-unit increase | 1.002 (0.998–1.007) | 0.290 | 1.000 (0.996–1.005) | 0.840 |
| Length of hospital stay, per 1-day increase | 1.057 (0.863–1.294) | 0.590 | 1.037 (0.853–1.260) | 0.720 |
| High TIMI thrombus burden, grades 3–5 (reference: low thrombus burden, grades 0–2) | 1.020 (0.596–1.743) | 0.940 | 0.478 (0.286–0.798) | 0.005 |

Age group was the dependent variable, with the <45-year group as the reference category. Odds ratios compare the adjusted odds of membership in each older age group with those in the <45-year group; they are neither crude prevalence ratios nor predictors of clinical outcomes. For ever smoking, hypertension, and bifurcation lesion status, ORs and 95% CIs were reciprocally re-expressed to correspond to the first-listed category relative to the parenthetical reference category; p values were unchanged. ORs for continuous predictors are expressed per 1-unit increase. The model was exploratory; given the 96 patients in the reference group and the number of included covariates, model overfitting and instability of the estimates are possible. The findings should therefore be interpreted cautiously. This table presents the CALLY model; the alternative HALP model is reported in the text. ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CALLY, C-reactive protein–albumin–lymphocyte index; CI, Confidence interval; eGFR, Estimated glomerular filtration rate; HALP, Hemoglobin–albumin–lymphocyte–platelet score; NSTEMI, Non-ST-segment elevation myocardial infarction; OR, Odds ratio; SGLT2, Sodium–glucose cotransporter 2; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction.

on women-specific risk factors, the observed sex distribution should be interpreted descriptively and should not be used to infer sex-specific determinants of MI.

Preadmission statin use did not differ significantly across age groups despite the higher prevalence of previous coronary artery disease in older patients. Age-group comparisons of admission lipid parameters were not adjusted for preadmission statin use or previous coronary artery disease. Nevertheless, admission lipid levels may have been influenced by prior lipid-lowering therapy and the acute-phase setting. Accordingly, the observed age-group differences in LDL-C and related lipid parameters should be interpreted cautiously and should not be considered representative of untreated baseline lipid status.

Rather than focusing on a single biomarker, our study evaluated several composite inflammatory and immunonutritional indices across age groups. Young patients had higher HALP and LMR values, whereas older patients had higher SIRI, PLR, and NPS values. The CALLY index also differed across age groups and was lowest in older patients. These findings indicate that the distribution of composite inflammatory and immunonutritional indices differed across age groups. Aging is known to be accompanied by changes in systemic inflammatory and immune responses, which may provide a broader context for the differences observed in our cohort.[23-25] However, because these indices are influenced by multiple hematologic, inflammatory, nutritional, and comorbidity-related factors, the observed differences should be interpreted as descriptive associations rather than evidence of specific pathophysiological mechanisms.

Despite similar SYNTAX scores across age groups, lesion-level angiographic characteristics differed. Young patients had a higher observed thrombus burden and more frequent bifurcation lesions, whereas coronary tortuosity was more frequent in older patients. These findings indicate differences in angiographic characteristics despite similar overall anatomical complexity; however, the underlying mechanisms cannot be determined from the present observational data.

Young patients had lower GRACE scores and lower observed rates of in-hospital complications, including pulmonary edema, acute kidney injury, and atrial fibrillation, along with a shorter observed hospital stay. In-hospital mortality was numerically 2%, 3%, and 4% in the young, middle-aged, and older groups, respectively, but this difference was not statistically significant. The absence of a significant mortality difference should be interpreted cautiously given the low number of deaths and the modest size of the young group. Accordingly, similar in-hospital mortality rates should not be interpreted as indicating an absence of subsequent cardiac risk, particularly among younger patients.[26]

In the exploratory multinomial models, male sex showed a statistically significant adjusted association in the comparison between the 45–54-year and <45-year groups. Smoking status, eGFR rate, hypertension status, bifurcation lesion status, and TIMI thrombus burden showed statistically significant adjusted associations in the comparison between the ≥55-year and <45-year groups. Because age group was the dependent variable, these estimates describe conditional associations with age-group membership rather than predictors of clinical outcomes or angiographic findings. Some adjusted effect directions differed from the corresponding unadjusted group frequencies; therefore, these findings should be interpreted cautiously.

**Study Limitations**

Several limitations should be considered when interpreting the findings of this study. First, the retrospective, single-center observational design may limit generalizability and introduce selection bias. Although the overall cohort was relatively large, the young MI group was modest in size compared with the older group, which may have limited the statistical power of pairwise comparisons, particularly for infrequent in-hospital outcomes such as mortality and cardiogenic shock. The exploratory multinomial regression models also included a relatively large number of covariates in relation to the size of the <45-year reference group (n=96), which may have increased the risk of model overfitting and instability of the adjusted estimates. Accordingly, the regression findings should be considered exploratory and hypothesis-generating rather than confirmatory. No a priori sample size calculation was performed because of the retrospective observational design and the consecutive inclusion of eligible patients.

Second, long-term follow-up data were unavailable; therefore, postdischarge mortality, recurrent MI, stroke, repeat revascularization, treatment adherence, and major adverse cardiovascular or cerebrovascular events could not be assessed. Third, a detailed etiologic evaluation of premature MI was not possible because data regarding family history of premature atherosclerotic cardiovascular disease, thrombophilia, substance abuse, oral contraceptive use, pregnancy-related factors, immune-mediated diseases, vasculitis, spontaneous coronary artery dissection, myocardial bridging, coronary anomalies, vasospasm, recent infection, and thromboembolic history were not systematically available. In addition, Lp(a), ApoB, and systematic assessment for familial hypercholesterolemia were not routinely available. Therefore, the present study should be interpreted as a descriptive age-group comparison rather than an etiologic investigation of premature MI.

Admission lipid measurements may have been influenced by the acute-phase response and prior lipid-lowering therapy and therefore may not fully reflect pre-event lipid status. Although preadmission statin use was available, information regarding ezetimibe use, PCSK9 inhibitor therapy, lipid-lowering treatment at discharge, and long-term treatment adherence was not consistently available. Residual confounding related to lipid-lowering therapy therefore cannot be excluded when interpreting age-group differences in admission lipid parameters.

Intravascular imaging was not routinely available; therefore, detailed plaque characterization could not be performed. Residual confounding from unmeasured variables cannot be excluded. Smoking and alcohol consumption were recorded only as dichotomous ever/never variables based on self-report; detailed information on quantity, frequency, duration, and timing was unavailable, precluding assessment of dose–response relationships. Finally, no pre-earthquake comparison cohort was available; therefore, despite the post-earthquake study setting, the observed findings cannot be attributed to earthquake-related effects.

## Conclusion

Age-related differences were observed in the clinical, inflammatory, and angiographic characteristics of patients with MI. Fewer between-group differences were observed between young and middle-aged patients than between young and older patients. These findings represent descriptive associations derived from a retrospective, single-center observational study and should not be interpreted as causal.

Patients younger than 55 years accounted for 35.6% of MI cases in our cohort, underscoring the clinical relevance of cardiovascular risk assessment in younger individuals. More broadly, attention to established modifiable cardiovascular risk factors, particularly smoking and dyslipidemia, remains important in preventive strategies for premature MI.

Supplementary Online File: https://jag.journalagent.com/tkd/abs_files/TKDA-07150/TKDA-07150_(0)_Supplementary_Tables.docx

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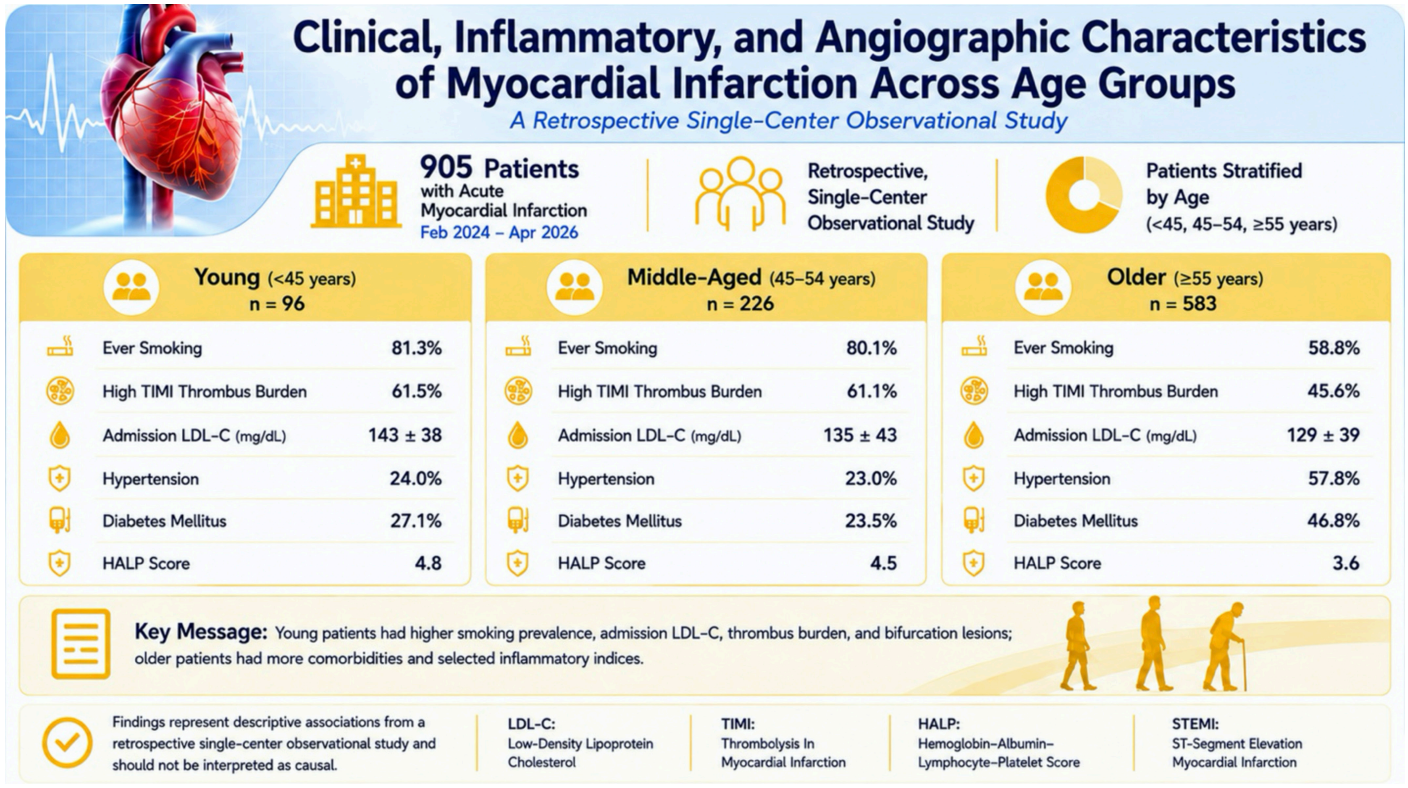
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Clinical, Inflammatory, and Angiographic Characteristics of Myocardial Infarction Across Age Groups
A Retrospective Single-Center Observational Study
905 Patients with Acute Myocardial Infarction
Feb 2024 – Apr 2026
Retrospective, Single-Center Observational Study
Patients Stratified by Age (<45, 45–54, ≥55 years)
Young (<45 years) n = 96
Ever Smoking 81.3%
High TIMI Thrombus Burden 61.5%
Admission LDL-C (mg/dL) 143 ± 38
Hypertension 24.0%
Diabetes Mellitus 27.1%
HALP Score 4.8
Middle-Aged (45–54 years) n = 226
Ever Smoking 80.1%
High TIMI Thrombus Burden 61.1%
Admission LDL-C (mg/dL) 135 ± 43
Hypertension 23.0%
Diabetes Mellitus 23.5%
HALP Score 4.5
Older (≥55 years) n = 583
Ever Smoking 58.8%
High TIMI Thrombus Burden 45.6%
Admission LDL-C (mg/dL) 129 ± 39
Hypertension 57.8%
Diabetes Mellitus 46.8%
HALP Score 3.6
Key Message: Young patients had higher smoking prevalence, admission LDL-C, thrombus burden, and bifurcation lesions; older patients had more comorbidities and selected inflammatory indices.
Findings represent descriptive associations from a retrospective single-center observational study and should not be interpreted as causal.
LDL-C: Low-Density Lipoprotein Cholesterol
TIMI: Thrombolysis In Myocardial Infarction
HALP: Hemoglobin–Albumin–Lymphocyte–Platelet Score
STEMI: ST-Segment Elevation Myocardial Infarction

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# Inflammatory, Lipid, and Angiographic Differences in Young Versus Middle-Aged Hospital Survivors of Myocardial Infarction with Obstructive, Revascularization-Requiring Coronary Artery Disease

## Obstrüktif, Revaskülarizasyon Gerektiren Koroner Arter Hastalığı Olan Genç ve Orta Yaşlı Miyokard Enfarktüsü Sağkalanlarında İnflamatuvar İndeksler, Lipid Profili ve Anjiyografik Farklılıklar

**ABSTRACT**

**Objective:** To compare composite inflammatory indices, the Atherogenic Index of Plasma (AIP), and angiographic findings between patients with acute myocardial infarction (MI) aged <55 years and those aged 55–65 years.

**Method:** Patients with acute coronary syndrome were retrospectively screened (n=205). Forty patients who died during hospitalization were excluded post hoc, along with 10 patients with normal coronary arteries and 10 with noncritical stenosis not requiring revascularization, leaving 145 patients: Group 1 (<55 years, n=72) and Group 2 (55–65 years, n=73). The Systemic Inflammatory Response Index (SIRI), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), AIP, and C-reactive protein were compared between groups, together with lipid, angiographic, and left ventricular ejection fraction (LVEF) parameters.

**Results:** Younger patients had significantly higher SIRI (1.63 vs. 1.11, P < 0.001), NLR (2.65 vs. 2.26, P = 0.004), MLR (0.261 vs. 0.200, P < 0.001), and AIP (0.440 vs. 0.298, P = 0.039). Because SIRI and MLR were collinear, each index was modeled separately with AIP and ST-segment elevation myocardial infarction (STEMI)/non-ST-segment elevation myocardial infarction (NSTEMI) status; when modeled separately, each was independently associated with younger age after adjustment for MI type (all P ≤ 0.009). LVEF was better preserved (P < 0.001), and among patients with a single identifiable culprit vessel, the right coronary artery was more frequently implicated in younger patients (47.3% vs. 22.2%, P = 0.006).

**Conclusion:** Young patients with MI and obstructive coronary disease showed higher inflammatory indices and a more atherogenic lipid profile than middle-aged patients. SIRI, NLR, MLR, and AIP were each independently associated with younger age in the primary multivariable models; however, across exploratory sensitivity analyses using stricter age thresholds, a continuous age model, and a death-inclusive cohort, complete blood count (CBC)-derived inflammatory indices—particularly SIRI and MLR-showed relatively consistent age-associated differences, whereas the association with AIP was more dependent on how age was defined and modeled. These findings support further investigation of CBC-derived inflammatory indices, particularly SIRI and MLR, as candidate markers of age-associated inflammatory and lipid differences among MI survivors rather than as biomarkers of premature MI or as a basis for clinical recommendations.

**Keywords:** Acute myocardial infarction, atherogenic index of plasma, inflammatory indices, premature coronary artery disease, Systemic Inflammatory Response Index.

**ÖZET**

**Amaç:** Akut miyokard enfarktüsü (Mİ) geçiren 55 yaş altındaki hastalar ile 55–65 yaş arasındaki hastaları kompozit inflamatuvar indeksler, Plazmanın Aterojenik İndeksi (AİP) ve anjiyografik bulgular açısından karşılaştırmaktır.

**Yöntem:** Akut koroner sendromlu hastalar retrospektif olarak tarandı (n=205). Hastanede yatış sırasında yaşamını yitiren 40 hasta post hoc olarak, normal koroner arterleri olan 10 hasta ve revaskülarizasyon gerektirmeyen nonkritik koroner darlığı bulunan 10 hasta çalışma dışı bırakıldı ve 145 hasta analize dahil edildi: Grup 1 (<55 yaş, n=72) ve Grup 2 (55–65 yaş, n=73). Sistemik İnflamatuvar Yanıt İndeksi (SİYİ), nötrofil-lenfosit oranı (NLO), monosit-lenfosit oranı (MLO), AİP ve C-reaktif protein; lipid, anjiyografik ve sol ventrikül ejeksiyon fraksiyonu (LVEF) parametreleriyle birlikte gruplar arasında karşılaştırıldı.

**Bulgular:** Genç hastalarda SİYİ (1,63 vs. 1,11; P < 0,001), NLO (2,65 vs. 2,26; P = 0,004), MLO (0,261 vs. 0,200; P < 0,001) ve AİP (0,440 vs. 0,298; P = 0,039) anlamlı düzeyde daha

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yüksekti. SİYİ ve MLO kollineer olduğundan, her bir indeks AİP ve STEMI/NSTEMI durumu ile birlikte ayrı ayrı modellendi; ayrı ayrı modellendiğinde her biri, Mİ tipine göre düzeltme sonrasında genç yaşla bağımsız olarak ilişkili bulundu (tümü p≤0,009). LVEF genç hastalarda daha iyi korunmuştu (P < 0,001) ve tek bir sorumlu damarın tanımlanabildiği hastalar arasında sağ koroner arter genç hastalarda sorumlu damar olarak daha sık saptandı (%47,3 vs. %22,2; P = 0,006).

**Sonuç:** Obstrüktif koroner arter hastalığı olan genç Mİ hastaları, orta yaşlı hastalara kıyasla daha yüksek inflamatuvar indeksler ve daha aterojenik bir lipid paterni göstermektedir. SİYİ, NLO, MLO ve AİP, birincil çok değişkenli modellerde genç yaşla bağımsız olarak ilişkiliydi. Bununla birlikte, daha katı yaş eşiklerinin, yaşın sürekli değişken olarak modellendiği bir analizin ve ölümleri de içeren bir kohortun kullanıldığı keşifsel duyarlılık analizlerinde, tam kan sayımı (TKS) kaynaklı inflamatuvar indeksler–özellikle SİYİ ve MLO–yaşla ilişkili farklılıklar açısından görece tutarlı sonuçlar gösterirken, AİP ile olan ilişki yaşın nasıl tanımlandığına ve modellendiğine daha bağımlıydı. Bu bulgular, TKS kaynaklı inflamatuvar indekslerin, özellikle SİYİ ve MLO'nun, Mİ sağkalanlarında yaşla ilişkili inflamatuvar ve lipid farklılıklarının aday belirteçleri olarak daha ileri araştırılmasını desteklemektedir; ancak bunların prematür Mİ biyobelirteçleri olarak değerlendirilmesini veya bu bulgulara dayanarak klinik bir öneride bulunulmasını desteklememektedir.

**Anahtar Kelimeler:** Akut miyokard enfarktüsü, plazmanın aterojenik indeksi, inflamatuvar indeksler, prematür koroner arter hastalığı, sistemik inflamatuvar yanıt indeksi.

Acute myocardial infarction (MI) in young adults is a growing public health concern. Although the overall incidence of MI has declined in older age groups, the rate among individuals aged <55 years has remained stable or increased, occurring alongside a substantial burden of metabolic and traditional cardiovascular risk factors; smoking and psychosocial factors may also contribute to risk in younger individuals.[1,2] Young patients with MI have a distinct cardiovascular risk-factor profile compared with older patients, including a higher prevalence of smoking and a family history of premature coronary heart disease, while nontraditional risk factors may also contribute to premature coronary artery disease.[3]

Systemic inflammation plays a central role in the development and destabilization of atherosclerotic plaques.[4] Composite inflammatory indices derived from routine complete blood count (CBC) parameters-including the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and Systemic Inflammatory Response Index (SIRI; neutrophil × monocyte/lymphocyte)-have gained considerable attention as inexpensive, widely available surrogate markers of systemic inflammatory activity.[5,6] These indices reflect the balance between proinflammatory cellular components (neutrophils and monocytes) and anti-inflammatory cellular components (lymphocytes) and have been shown to have prognostic value in acute coronary syndromes.[7–9]

The Atherogenic Index of Plasma (AIP), defined as $\log_{10}$(triglyceride/HDL-C), integrates lipid metabolism with cardiovascular risk and has been independently associated with coronary artery disease severity and adverse outcomes.[10,11] Despite increasing interest in premature MI and its distinct clinical characteristics, data evaluating inflammatory and lipid indices together with angiographic findings in young versus middle-aged populations with MI remain limited.[6,12–15]

There is no universally accepted age threshold for defining premature or young MI; published studies have used cutoffs ranging from approximately 40 to 55 years, and some have proposed sex-specific definitions.[16] In the present study, <55 years was selected a priori as a pragmatic threshold intended to balance sample size with the biological rationale for an earlier, more atherogenic phenotype; the robustness of this choice was subsequently assessed using sensitivity analyses with stricter thresholds (<45 and <50 years; see Statistical Analysis and Results).

The present study aimed to comprehensively compare inflammatory indices, lipid markers, and angiographic characteristics-including culprit artery distribution, extent of coronary artery disease, and left ventricular function-between patients aged <55 years and those aged 55–65 years with obstructive, revascularization-requiring coronary artery disease. The cohort was restricted to hospital survivors with an obstructive, revascularization-requiring culprit lesion to avoid confounding of

## ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| AIP | Atherogenic Index of Plasma |
| CABG | Coronary artery bypass grafting |
| CBC | Complete blood count |
| CRP | C-reactive protein |
| CX | Circumflex artery |
| HDL-C | High-density lipoprotein cholesterol |
| LAD | Left anterior descending |
| LDL-C | Low-density lipoprotein cholesterol |
| LVEF | Left ventricular ejection fraction |
| MI | Myocardial infarction |
| MLR | Monocyte-to-lymphocyte ratio |
| NLR | Neutrophil-to-lymphocyte ratio |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| RCA | Right coronary artery |
| SIRI | Systemic Inflammatory Response Index |
| STEMI | ST-segment elevation myocardial infarction |

inflammatory biomarkers by perimortem physiological changes or nonobstructive coronary presentations. We hypothesized that among patients with obstructive, revascularization-requiring coronary artery disease, younger patients (<55 years) would have higher composite inflammatory indices and AIP than middle-aged patients (55–65 years); the primary endpoint was the between-group difference in these indices, with their independent association with younger age in multivariable analysis as a secondary endpoint.

## Methods

### Study Design and Population

This single-center, retrospective, observational study was conducted at a tertiary referral center. Patients were enrolled between December 2020 and December 2025. Ethical approval was obtained from İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (Approval Number: 2801, Date: 25.02.2026). All procedures were conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

The retrospective screening dataset comprised 205 eligible records of patients aged 18–65 years who were admitted to the coronary intensive care unit with suspected ACS/MI and identified in the source database after application of its clinical and laboratory eligibility criteria. Sequential enrollment at the time of hospital admission could not be independently verified beyond what was captured by these source-database criteria; therefore, consecutive enrollment cannot be assumed. Cases were classified as ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) according to the treating cardiology team's final hospital diagnosis. The individual diagnostic components could not be independently reconstructed for every record, and plaque rupture, erosion, or thrombosis was not centrally adjudicated according to the Universal Definition of MI.

Exclusion criteria were active infection, inflammatory or autoimmune disease, hematologic malignancy, missing laboratory or angiographic data, use of corticosteroids, immunosuppressants, or chemotherapy at admission, death during the index hospitalization, angiographically normal coronary arteries, and noncritical coronary stenosis not requiring revascularization. Obstructive, revascularization-requiring coronary artery disease was defined as visually assessed severe stenosis (≥80% diameter stenosis in the source database) of a major epicardial vessel treated with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). This ≥80% threshold reflects the categorical stenosis cutoff used for revascularization decisions in the source database and is higher than the ≥70% threshold conventionally cited for non-left-main lesions; therefore, the findings should not be extrapolated to patients with 70%–79% stenosis. Noncritical stenosis was defined as stenosis below this source-database threshold that was not treated with revascularization. Angiographic severity was assessed visually by the treating interventional cardiologist; formal quantitative coronary angiography and independent core laboratory adjudication were not performed.

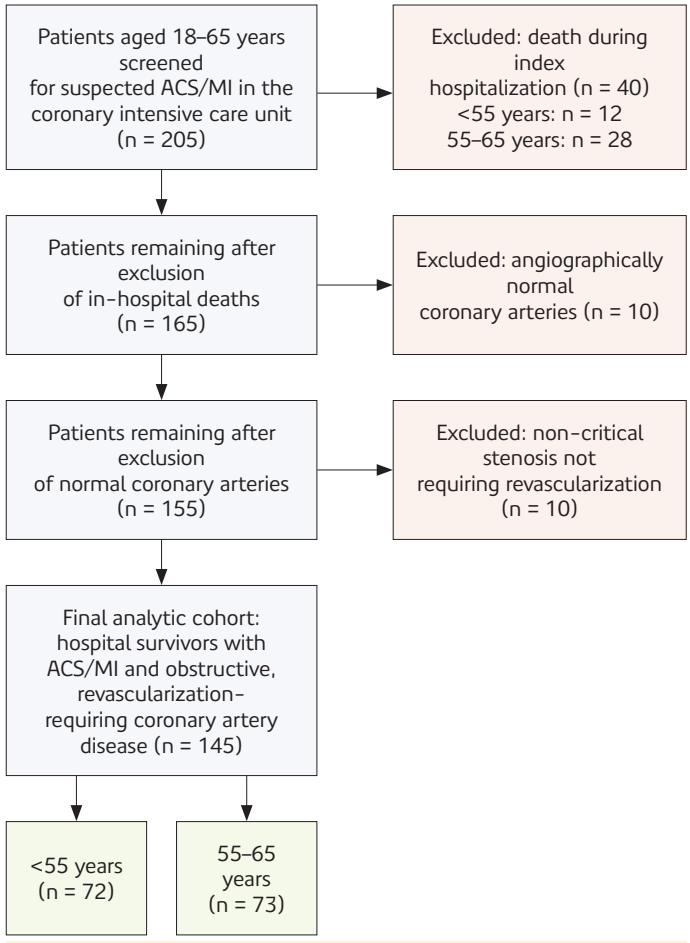



**Figure 1.** Patient flow diagram showing sequential screening and exclusions.

For the primary analysis, patients who died during the index hospitalization were excluded because event-level data required to distinguish admission biology from arrest-, resuscitation-, shock-, and perimortem physiology were incomplete. This post hoc restriction changed the analytic target to hospital survivors and necessarily introduced selection and survivorship bias. Patients with angiographically normal coronary arteries and noncritical stenosis not requiring revascularization were also excluded, restricting the cohort to patients with obstructive coronary disease treated with PCI or CABG. Because the plaque mechanism was not independently adjudicated, the term "type 1 MI" is not used. After application of these criteria, 40 patients were excluded because of in-hospital death, 10 because of angiographically normal coronary arteries, and 10 because of noncritical stenosis, yielding 145 patients: Group 1 (<55 years, n=72) and Group 2 (55–65 years, n=73). The resulting analysis cannot estimate in-hospital mortality or the frequency of nonobstructive presentations. Patient flow is summarized in Figure 1.

### Data Collection

Demographic data, cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking, and family history), MI type (STEMI/NSTEMI), echocardiographic left ventricular ejection fraction (LVEF), and coronary angiographic findings (culprit artery and number of diseased vessels) were collected from electronic medical records. LVEF was assessed by

transthoracic echocardiography after revascularization during the index hospitalization using visual qualitative estimation rather than formal quantitative methods, such as the Simpson biplane method; this is noted as a limitation below.

Admission blood samples were obtained at presentation to the coronary intensive care unit. The precise timing relative to the initiation of pharmacologic treatment could not be consistently verified from the retrospective records. Pre-admission medication data were recorded when available; however, complete data were unavailable for a substantial proportion of patients, representing an acknowledged limitation.

Cardiovascular risk factors were coded as recorded in the source database. Hypertension, diabetes mellitus, and hyperlipidemia reflected a pre-existing diagnosis and/or current pharmacologic treatment for the condition rather than a specific biochemical or blood pressure threshold measured at admission. Smoking reflected current or recent use as documented at admission, and family history reflected a documented history of premature coronary artery disease in a first-degree relative. The historical source-database definitions did not specify a numerical age cutoff for "premature" family history or a time window for "recent" smoking; therefore, further specification of these variables was not possible. Because these definitions were based on diagnosis and/or treatment rather than biochemical criteria, they may not capture undiagnosed disease, and this limitation was considered when interpreting the hyperlipidemia findings below.

**Calculation of Inflammatory Indices**

The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The MLR was calculated as the absolute monocyte count divided by the absolute lymphocyte count. SIRI was calculated as (neutrophil × monocyte)/lymphocyte. Because absolute leukocyte counts were expressed as $\times 10^3/\mu L$, SIRI is reported in $\times 10^3/\mu L$. The AIP was calculated as $\log_{10}$(triglyceride/HDL-C), with lipid concentrations expressed in mmol/L. Source laboratory values recorded in mg/dL were converted using standard conversion factors (triglycerides: mg/dL ÷ 88.5=mmol/L; HDL-C: mg/dL ÷ 38.67=mmol/L). Non-high-density lipoprotein cholesterol was calculated as total cholesterol minus HDL-C, with both values expressed in mg/dL. Lipid parameters, CBC, and C-reactive protein (CRP) were measured in the central clinical laboratory using standard analyzers in routine clinical use; CRP was measured by nephelometry and reported in mg/L. Peak troponin was measured as high-sensitivity cardiac troponin T (hs-cTnT; Roche Elecsys assay) and reported in ng/L, with a 99th-percentile upper reference limit of 14 ng/L according to the manufacturer. Troponin measurements were repeated according to routine clinical practice rather than a prespecified study protocol; therefore, sampling frequency varied among patients. Peak hs-cTnT was defined retrospectively as the highest hs-cTnT value recorded during the index hospitalization.

**Statistical Analysis and Software**

Statistical analyses were performed using Python (version 3.11; Python Software Foundation, Wilmington, DE, USA) with the SciPy (version 1.11), statsmodels (version 0.14), and scikit-learn (version 1.8) libraries. Normality was assessed using the Shapiro-Wilk test for n<50 and the D'Agostino-Pearson test for n≥50. Age was approximately normally distributed and was compared using Student's t-test; all other continuous variables were nonnormally distributed and were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test with Yates continuity correction for 2×2 tables; Fisher's exact test was used where appropriate. Results are presented as mean ± standard deviation, median (interquartile range [IQR]), or frequency (%), with exact p values reported except when $P < 0.001$. A two-tailed $P < 0.05$ was considered statistically significant.

Multivariable binary logistic regression analysis was performed to identify factors independently associated with younger age (<55 years) at the time of MI. Variables were selected based on clinical relevance and univariable significance. Each primary multivariable model included one inflammatory index (SIRI, NLR, or MLR), together with AIP, STEMI/NSTEMI classification, sex, hypertension, diabetes mellitus, hyperlipidemia, and smoking. STEMI/NSTEMI classification was included because STEMI was significantly more frequent among younger patients (Table 1), and the inflammatory indices were measured during the acute phase of MI, making MI type a plausible confounder of the biomarker–age association. Preliminary variance inflation factor (VIF) analysis identified substantial collinearity between SIRI and MLR (VIF≈10) when modeled jointly. Given this instability, a combined model was not pursued; instead, each inflammatory index (SIRI, NLR, or MLR) was entered into a separate multivariable model together with AIP, STEMI/NSTEMI classification, sex, and the same risk factors to isolate the association of each index without collinearity from the others. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported for all models.

As a sensitivity analysis, univariable comparisons of SIRI, NLR, MLR, and AIP were repeated using stricter age thresholds (<45 years vs. 45–65 years and <50 years vs. 50–65 years) within the same 145-patient cohort. These were unadjusted comparisons only because the small number of patients aged <45 years (n=22) would make multivariable modeling at this threshold unstable and underpowered. Two additional post hoc exploratory sensitivity analyses, neither of which was prespecified in the original protocol, were performed. First, the association between age and each biomarker was reassessed with age modeled as a continuous variable using Spearman's rank correlation within the same 145-patient survivor cohort, in which no age or biomarker values were missing. Second, univariable comparisons of SIRI, NLR, MLR, AIP, and LVEF were repeated in a broader, clinically heterogeneous cohort of 185 patients formed by reincluding the 40 patients excluded because of in-hospital death alongside the 145-patient survivor cohort, while retaining the exclusion of the 10 patients with angiographically normal coronary arteries and 10 with noncritical stenosis. Patients were stratified according to the age group (<55 or 55–65 years) to which they would have been assigned, using admission-recorded values for the reincluded deaths and the Mann-Whitney U test. Any patient with a missing value for a given biomarker was excluded only from that specific comparison. No correction for multiplicity was applied, and no internal validation, such as bootstrap or split-sample validation, was performed.

## Results

**Baseline Clinical and Demographic Characteristics**

Of the 205 patients initially screened, 40 (19.5%) died during hospitalization, 10 had angiographically normal coronary

arteries, and 10 had noncritical coronary stenosis not requiring revascularization; all were excluded from the primary analysis (see Methods). The final cohort comprised 72 patients in Group 1 (<55 years; mean age, 46.9±6.2 years) and 73 patients in Group 2 (55–65 years; mean age, 58.9±3.0 years). Male sex predominated in both groups, with no significant difference (88.9% vs. 90.4%, P = 0.978). STEMI was significantly more frequent among younger patients (44.4% vs. 26.0%, P = 0.032). The older group had significantly higher rates of hypertension (36.1% vs. 60.3%, P = 0.006) and hyperlipidemia (63.9% vs. 87.7%, P = 0.002); diabetes mellitus showed a nonsignificant trend in the same direction (34.7% vs. 52.1%, P = 0.053). Smoking rates (76.4% vs. 86.1%, P = 0.200) and family history (30.6% vs. 33.8%, P = 0.813) did not differ significantly. Baseline characteristics are presented in Table 1.

Among the 40 excluded patients who died during hospitalization, the median age was 58.0 years (interquartile range [IQR], 53.0–63.0; range, 34–64 years); 12 (30.0%) were aged <55 years, and 28 (70.0%) were aged 55–65 years at death. Among the 185 patients for whom age-stratum assignment was available for this comparison (i.e., excluding the 20 patients with normal or noncritical coronary disease whose individual ages were not retained in the extracted analysis dataset), exclusion because of in-hospital death occurred in 28/101 patients in the 55–65-year stratum and 12/84 patients in the <55-year stratum (27.7% vs. 14.3%; Fisher's exact P = 0.032), indicating that death-related exclusion removed a disproportionately larger proportion of the older stratum. Because 101+84=185 rather than 205, these percentages should not be interpreted as mortality rates for the entire screened cohort. STEMI was the presenting diagnosis in 32 (80.0%) of the excluded deaths, whereas NSTEMI was present in 8 (20.0%), representing a substantially higher STEMI proportion than that observed among survivors (35.2%, 51/145). Arrest location was available for all 40 patients: 35 (87.5%) experienced out-of-hospital cardiac arrest, and 5 (12.5%) experienced in-hospital cardiac arrest. Compared with the analytic survivor cohort, this excluded group had lower LVEF and higher peak troponin, creatinine, neutrophil count, SIRI, and NLR values (all P < 0.05). Because arrest status was not recorded among hospital survivors and other severity variables were incomplete, these findings are reported only as clinical characterization and not as comparative incidence or mortality estimates.

**Angiographic Findings and Left Ventricular Function**

LVEF was significantly better preserved in younger patients (median, 55.0% vs. 50.0%; P < 0.001). Reduced LVEF (<50%) was present in 22.2% of younger patients compared with 46.6% of older patients (P = 0.004), whereas severely reduced LVEF (<40%) did not differ significantly between groups (6.9% vs. 16.4%, P = 0.129). Among patients with NSTEMI, median LVEF was 55.0% in Group 1 versus 50.0% in Group 2 (P < 0.001); among patients with STEMI, the difference did not reach statistical significance (50.0% vs. 45.0%, P = 0.088). A formal age × MI-type interaction test was not performed; therefore, these subgroup observations should not be interpreted as demonstrating a statistically significant difference between the subgroups.

The overall distribution of culprit arteries differed significantly between groups (P = 0.016). The frequencies of left anterior descending (LAD) and circumflex (CX) artery involvement did not differ significantly between groups (LAD, 32.7% vs. 46.0%, Fisher's exact P = 0.187; CX, 20.0% vs. 31.7%, Fisher's exact P = 0.208; both calculated among the n=55 and n=63 patients with a single identifiable culprit vessel, respectively), whereas the right coronary artery (RCA) was significantly more frequently implicated in younger patients (47.3% vs. 22.2%, Fisher's exact P = 0.006). A substantial proportion of patients (55 in Group 1 and 63 in Group 2) had a single identifiable culprit vessel recorded; the remainder underwent CABG, for which a single culprit vessel was not applicable. Regarding treatment modality, PCI was performed in 55/72 (76.4%) younger patients versus 63/73 (86.3%) older patients, whereas CABG was performed in 17/72 (23.6%) versus 10/73 (13.7%), respectively; this difference was not statistically significant (Fisher's exact P = 0.140).

**Table 1.** Baseline clinical and demographic characteristics

| Variables | <55 years (n=72) | 55–65 years (n=73) | *P* |
|---|---|---|---|
| Age (years), mean±SD | 46.9±6.2 | 58.9±3.0 | **<0.001** |
| Male sex, n (%) | 64 (88.9%) | 66 (90.4%) | 0.978 |
| STEMI, n (%) | 32 (44.4%) | 19 (26.0%) | **0.032** |
| Hypertension, n (%) | 26 (36.1%) | 44 (60.3%) | **0.006** |
| Diabetes mellitus, n (%) | 25 (34.7%) | 38 (52.1%) | 0.053 |
| Hyperlipidemia, n (%) | 46 (63.9%) | 64 (87.7%) | **0.002** |
| Smoking, n (%) | 55 (76.4%) | 62 (86.1%) | 0.200 |
| Family history, n (%) | 22 (30.6%) | 24 (33.8%) | 0.813 |
| LVEF (%), median (IQR) | 55.0 (50.0–60.0) | 50.0 (40.0–55.0) | **<0.001** |
| Creatinine (mg/dL), median (IQR) | 0.97 (0.84–1.06) | 0.92 (0.80–1.10) | 0.975 |
| Peak hs-cTnT (ng/L), median (IQR) | 152.5 (40.5–1181.0) | 187.0 (39.0–1145.0) | 0.729 |

Bold indicates P < 0.05. Patients who died during hospitalization (n=40), those with angiographically normal coronary arteries (n=10), and those with noncritical coronary stenosis (n=10) were excluded from this cohort (see Methods). All variables were available for the full n=72 in Group 1 and n=73 in Group 2, except for smoking (n=72 in Group 1; n=72 in Group 2) and family history (n=72 in Group 1; n=71 in Group 2), reflecting isolated missing values in the source records. hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; LVEF, left ventricular ejection fraction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction

The overall extent of coronary artery disease did not differ significantly between groups (P = 0.412). Single-vessel disease was the most common pattern in both groups (58.3% vs. 63.0%), and the frequency of multivessel disease (≥2 vessels) did not differ significantly (41.7% vs. 37.0%, P = 0.684). One record in the older group that was originally coded as normal-vessel disease had an LAD culprit lesion treated with PCI and was therefore classified as single-vessel disease. Because patients with genuinely normal coronary angiograms, noncritical coronary stenosis, and in-hospital death were excluded by design, these subgroups were not compared between age groups. Detailed results are presented in Table 2.

### Lipid Profile and Atherogenic Index

Total cholesterol (207.0 vs. 196.0 mg/dL, P = 0.039) and low-density lipoprotein cholesterol (LDL-C; 125.5 vs. 103.0 mg/dL, P = 0.018) were higher in younger patients, whereas HDL-C was lower (33.0 vs. 36.0 mg/dL, P = 0.040). Triglyceride levels showed a nonsignificant difference (214.5 vs. 171.0 mg/dL, P = 0.085). Non-HDL cholesterol was higher in younger patients (170.0 vs. 153.0 mg/dL, P = 0.004). The AIP, calculated from triglyceride and HDL-C concentrations expressed in mmol/L, was also higher in the younger group (0.440 vs. 0.298, P = 0.039; Table 3).

### Inflammatory Indices

The SIRI (SIRI; 1.63 vs. 1.11, P < 0.001), monocyte-to-lymphocyte ratio (MLR; 0.261 vs. 0.200, P < 0.001), and neutrophil-to-lymphocyte ratio (NLR; 2.65 vs. 2.26, P = 0.004) were all significantly higher in younger patients. Absolute neutrophil, lymphocyte, monocyte, and total white blood cell counts did not differ significantly between groups. CRP levels were similar in both groups (3.5 vs. 4.0 mg/L, P = 0.547), suggesting that CBC-derived ratios and CRP may capture distinct aspects of the inflammatory response. Detailed results are presented in Table 4.

### Multivariable Logistic Regression Analysis

Because SIRI and MLR were collinear when modeled jointly (variance inflation factor [VIF]≈10), each inflammatory index was entered into a separate multivariable model together with AIP and adjusted for sex, cardiovascular risk factors, and STEMI/NSTEMI classification. This approach was used to isolate the association of each index without collinearity from the others and to account for the higher proportion of STEMI among younger patients. In these models, SIRI (odds ratio [OR], 1.988; 95% confidence interval [CI], 1.289–3.066; P = 0.002), NLR (OR, 1.206; 95% CI, 1.048–1.387; P = 0.009), and MLR per 0.1-unit increase (OR, 1.630; 95% CI, 1.152–2.307; P = 0.006) were each independently associated with younger age. AIP per 0.1-unit increase also remained independently associated with younger age in all three models (OR range, 1.255–1.301; all P ≤ 0.003). STEMI/NSTEMI classification itself was not independently associated with younger age in any model (OR range, 1.762–2.290; all P ≥ 0.05); therefore, the associations of SIRI, NLR, and MLR persisted after adjustment for STEMI/NSTEMI classification. These index-specific models were considered the primary multivariable analyses; complete results, including all covariates, are presented in Table 5.

**Table 2.** Angiographic findings and left ventricular function

| Variables | <55 years (n=72) | 55–65 years (n=73) | *P* |
|---|---|---|---|
| Myocardial infarction type | | | |
| STEMI, n (%) | 32 (44.4%) | 19 (26.0%) | **0.032** |
| NSTEMI, n (%) | 40 (55.6%) | 54 (74.0%) | **0.032** |
| Left ventricular function | | | |
| LVEF (%), median (IQR) | 55.0 (50.0–60.0) | 50.0 (40.0–55.0) | **<0.001** |
| LVEF <50%, n (%) | 16 (22.2%) | 34 (46.6%) | **0.004** |
| LVEF <40%, n (%) | 5 (6.9%) | 12 (16.4%) | 0.129 |
| LVEF in STEMI, median (IQR) | 50.0 (45.0–56.3) | 45.0 (40.0–55.0) | 0.088 |
| LVEF in NSTEMI, median (IQR) | 55.0 (50.0–60.0) | 50.0 (41.3–55.0) | **<0.001** |
| Culprit artery† | | | |
| Overall distribution | – | – | **0.016** |
| LAD, n (%) | 18 (32.7%) | 29 (46.0%) | 0.187 |
| CX, n (%) | 11 (20.0%) | 20 (31.7%) | 0.208 |
| RCA, n (%) | 26 (47.3%) | 14 (22.2%) | **0.006** |
| Extent of coronary artery disease‡ | | | |
| Overall distribution | – | – | 0.412 |
| Single-vessel disease, n (%) | 42 (58.3%) | 46 (63.0%) | N/A |
| Two-vessel disease, n (%) | 13 (18.1%) | 16 (21.9%) | N/A |
| Three-vessel disease, n (%) | 17 (23.6%) | 11 (15.1%) | N/A |
| Multivessel disease (≥2 vessels), n (%) | 30 (41.7%) | 27 (37.0%) | 0.684 |

Bold indicates P < 0.05. Patients with angiographically normal coronary arteries and noncritical coronary stenosis were excluded from this cohort by design (see Methods); all remaining patients had obstructive, revascularization-requiring coronary artery disease. Patients who died during hospitalization were also excluded; therefore, in-hospital mortality is not reported. †Percentages for LAD, CX, and RCA and their p values were calculated among patients with a single identifiable culprit vessel recorded (n=55 in Group 1; n=63 in Group 2) using Fisher's exact test; the remaining patients underwent coronary artery bypass grafting, for which a single culprit vessel was not applicable. ‡Vessel-disease percentages were calculated in the full analytic cohort (n=72 in Group 1; n=73 in Group 2); one LAD-PCI record in the older group that was initially coded as normal was classified as single-vessel disease for this summary. CX, circumflex artery; IQR, interquartile range; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; N/A, not applicable; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction.

Hyperlipidemia was inversely associated with younger age in all three models (see Discussion).

**Sensitivity Analyses**

Within the same 145-patient cohort, age subgroup counts were as follows: <40 years, n=13; <45 years, n=22; <50 years, n=38; and <55 years (Group 1, as defined above), n=72. Unadjusted comparisons of the four biomarkers were repeated using two stricter age thresholds, each compared with all remaining patients aged up to 65 years in the cohort. At the <45-year threshold (n=22 vs. n=123 aged 45–65 years), SIRI (median, 2.014 vs. 1.351; P = 0.005), NLR (2.773 vs. 2.259, P = 0.033), and MLR (0.288 vs. 0.210, P = 0.022) remained significantly elevated in the younger subgroup, whereas AIP did not differ significantly (0.322 vs. 0.352, P = 0.628). At the <50-year threshold (n=38 vs. n=107 aged 50–65 years), SIRI (1.556 vs. 1.233, P = 0.006), NLR (2.751 vs. 2.270, P = 0.022), and MLR (0.265 vs. 0.210, P = 0.030) again remained significantly elevated, whereas AIP did not differ significantly (0.440 vs. 0.339, P = 0.480). Detailed results are presented in Table 6. These sensitivity analyses were not adjusted for covariates, and the <45-year subgroup in particular (n=22) was underpowered for stable multivariable modeling; therefore, adjusted analyses at these stricter thresholds were not attempted.

As a post hoc exploratory sensitivity analysis, the association between age and each biomarker was also assessed with age modeled as a continuous variable using Spearman's rank correlation within the same 145-patient survivor cohort, in which no age or biomarker values were missing. SIRI ($\rho$=−.326, P < 0.001), NLR ($\rho$=−.229, P = 0.006), and MLR ($\rho$=−.236, P = 0.004) each correlated significantly with age, consistent with the group-based comparisons above, whereas AIP did not ($\rho$=−.081, P = 0.333). This finding indicates that the AIP–age association was sensitive to how age was modeled and should therefore be regarded as less robust than the inflammatory-index associations, which were consistent whether age was treated as a dichotomous or continuous variable.

As a further post hoc exploratory sensitivity analysis, the primary comparisons were repeated in a broader, clinically heterogeneous cohort of 185 patients formed by reincluding the 40 patients who died during hospitalization alongside the 145-patient survivor cohort. This cohort comprised 84 patients who would have been assigned to the <55-year stratum and 101 who would have been assigned to the 55–65-year stratum. Admission-recorded values available for the reincluded deaths were used, while acknowledging that the timing of blood sampling relative to cardiac arrest or resuscitation could not be verified for this subgroup (see Methods). Unlike the primary 145-patient cohort, this broader cohort was not restricted to patients with angiographically confirmed, obstructive, revascularization-requiring coronary disease. Whether the 40 reincluded patients otherwise met these angiographic and revascularization criteria, and whether complete admission biomarker data were available for all 40, could not be reconstructed from the available records. These patients had been excluded from the primary analytic dataset at the time of data extraction because of in-hospital death, and their angiographic, revascularization, and biomarker-completeness details were therefore not extracted for this analysis. This analysis is consequently reported exclusively as an exploratory robustness analysis of a broader, less clinically defined population rather than of the primary target population and is not considered confirmatory evidence or validation of the primary findings.

**Table 3.** Lipid profile and atherogenic index of plasma

| Parameters | <55 years (n=72), median (IQR) | 55–65 years (n=73), median (IQR) | *P* |
|---|---|---|---|
| Total cholesterol (mg/dL) | 207.0 (174.0–248.5) | 196.0 (152.0–214.0) | **0.039** |
| LDL-C (mg/dL) | 125.5 (102.5–160.3) | 103.0 (87.0–133.0) | **0.018** |
| HDL-C (mg/dL) | 33.0 (29.8–39.3) | 36.0 (31.0–43.0) | **0.040** |
| Triglycerides (mg/dL) | 214.5 (133.5–279.3) | 171.0 (112.0–235.0) | 0.085 |
| Non-HDL cholesterol (mg/dL) | 170.0 (144.8–214.5) | 153.0 (109.0–181.0) | **0.004** |
| AIP [$\log_{10}$(TG/HDL-C)] | 0.440 (0.200–0.578) | 0.298 (0.158–0.487) | **0.039** |

Bold indicates P < 0.05. Non-HDL cholesterol was calculated as total cholesterol minus HDL-C. AIP, Atherogenic Index of Plasma; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

**Table 4.** Inflammatory indices and complete blood count parameters

| Parameters | <55 years, median (IQR) | 55–65 years, median (IQR) | Test | *P* |
|---|---|---|---|---|
| SIRI (×10³/μL) | 1.63 (1.16–2.66) | 1.11 (0.85–1.77) | MWU | **<0.001** |
| NLR | 2.65 (1.85–3.79) | 2.26 (1.37–2.70) | MWU | **0.004** |
| MLR | 0.261 (0.200–0.368) | 0.200 (0.162–0.286) | MWU | **<0.001** |
| CRP (mg/L) | 3.5 (2.0–8.0) | 4.0 (2.0–9.0) | MWU | 0.547 |
| Neutrophils (10³/μL) | 6.45 (5.58–7.58) | 5.90 (4.00–8.10) | MWU | 0.094 |
| Lymphocytes (10³/μL) | 2.25 (1.88–3.40) | 2.70 (2.00–3.70) | MWU | 0.104 |
| Monocytes (10³/μL) | 0.70 (0.50–0.90) | 0.60 (0.50–0.80) | MWU | 0.067 |
| WBC (10³/μL) | 9.95 (8.68–11.40) | 9.80 (7.30–12.30) | MWU | 0.645 |

Bold indicates P < 0.05. CRP, C-reactive protein; IQR, interquartile range; MLR, monocyte-to-lymphocyte ratio; MWU, Mann-Whitney U test; NLR, neutrophil-to-lymphocyte ratio; SIRI, Systemic Inflammatory Response Index (neutrophil × monocyte/lymphocyte); WBC, white blood cell count.

Within this broader cohort, SIRI (median, 1.575 vs. 1.357; P = 0.045), MLR (0.250 vs. 0.203, P = 0.015), and AIP (0.432 vs. 0.292, P = 0.021) remained significantly higher in the younger stratum, whereas LVEF remained significantly lower in the older stratum (P < 0.001); NLR no longer reached statistical significance (2.577 vs. 2.348, P = 0.212). Because LVEF among the reincluded deaths, when recorded, reflected an admission or peri-arrest measurement rather than the standardized post-revascularization assessment used in the survivor cohort (see Methods), the LVEF comparison in this analysis was less directly comparable across strata than the biomarker comparisons and is reported for completeness rather than as confirmatory evidence. These results should be interpreted with caution because the admission-recorded values for the death subgroup may have been influenced by perimortem physiology in ways that cannot be excluded. The direction of the SIRI, MLR, AIP, and LVEF findings was retained in this exploratory death-inclusive analysis, whereas the NLR difference was not statistically significant.

## Discussion

This study provides a comprehensive comparison of inflammatory indices, lipid markers, and angiographic findings between young (<55 years) and middle-aged (55–65 years) patients with obstructive, revascularization-requiring coronary artery disease, restricted to hospital survivors with an obstructive, revascularization-requiring culprit lesion. The principal findings were as follows: (1) younger patients had significantly elevated composite inflammatory indices, including the SIRI, NLR, and MLR; (2) younger patients had higher AIP, non-HDL-C, and low-density lipoprotein cholesterol (LDL-C) levels, consistent with a more atherogenic lipid pattern; (3) in models adjusted for sex, cardiovascular risk factors, and MI type, with each inflammatory index entered separately to avoid SIRI/MLR collinearity, all three indices remained independently associated with younger age after adjustment for STEMI/NSTEMI classification, along with AIP (odds ratio [OR] range, 1.255–1.301), whereas STEMI/NSTEMI classification itself was not independently associated with younger age in any model; and (4) younger patients showed differences in angiographic characteristics, including more frequent RCA involvement, together with better-preserved LVEF.

Three exclusions defined the analytic cohort: 40 in-hospital deaths, 10 angiographically normal coronary arteries, and 10 cases of noncritical stenosis not requiring revascularization.

**Table 5.** Separate multivariable models for each inflammatory index (adjusted for sex, cardiovascular risk factors, and MI type)

| Model | Variables | OR | 95% CI | *P* |
|---|---|---|---|---|
| Model 1 (SIRI) | SIRI, per 1-unit increase | 1.988 | 1.289–3.066 | **0.002** |
| | AIP, per 0.1-unit increase | 1.255 | 1.078–1.462 | **0.003** |
| | STEMI (vs. NSTEMI) | 1.762 | 0.760–4.085 | 0.186 |
| | Female sex | 2.877 | 0.763–10.847 | 0.119 |
| | Hypertension | 0.663 | 0.279–1.573 | 0.351 |
| | Diabetes mellitus | 0.688 | 0.293–1.617 | 0.392 |
| | Hyperlipidemia | 0.255 | 0.088–0.737 | **0.012** |
| | Smoking | 0.766 | 0.270–2.169 | 0.615 |
| Model 2 (NLR) | NLR, per 1-unit increase | 1.206 | 1.048–1.387 | **0.009** |
| | AIP, per 0.1-unit increase | 1.301 | 1.114–1.519 | **<0.001** |
| | STEMI (vs. NSTEMI) | 2.185 | 0.983–4.854 | 0.055 |
| | Female sex | 2.435 | 0.645–9.196 | 0.189 |
| | Hypertension | 0.560 | 0.242–1.299 | 0.177 |
| | Diabetes mellitus | 0.715 | 0.311–1.645 | 0.431 |
| | Hyperlipidemia | 0.227 | 0.080–0.646 | **0.005** |
| | Smoking | 0.772 | 0.276–2.162 | 0.623 |
| Model 3 (MLR) | MLR, per 0.1-unit increase | 1.630 | 1.152–2.307 | **0.006** |
| | AIP, per 0.1-unit increase | 1.265 | 1.086–1.474 | **0.003** |
| | STEMI (vs. NSTEMI) | 2.290 | 0.988–5.309 | 0.053 |
| | Female sex | 2.512 | 0.668–9.450 | 0.173 |
| | Hypertension | 0.712 | 0.303–1.672 | 0.435 |
| | Diabetes mellitus | 0.675 | 0.290–1.570 | 0.362 |
| | Hyperlipidemia | 0.255 | 0.088–0.739 | **0.012** |
| | Smoking | 0.725 | 0.255–2.064 | 0.547 |

Bold indicates P < 0.05. Each model (n=144) includes one inflammatory index (SIRI, NLR, or MLR) together with AIP, STEMI (vs. NSTEMI) classification, female sex, hypertension, diabetes mellitus, hyperlipidemia, and smoking as covariates; complete covariate estimates are presented for each model. STEMI/NSTEMI classification was included because STEMI was significantly more frequent among younger patients (Table 1), and the inflammatory indices were measured during the acute phase of myocardial infarction, making MI type a plausible confounder. All three inflammatory indices and AIP remained independently associated with younger age after this adjustment, whereas STEMI/NSTEMI classification itself was not independently associated with younger age in any model (all P ≥ 0.05). Modeling each inflammatory index separately avoided the SIRI/MLR collinearity described in the Methods. AIP and MLR are reported per 0.1-unit increase, whereas SIRI and NLR are reported per 1-unit increase, reflecting the native numeric range of each marker. AIP, Atherogenic Index of Plasma; CI, confidence interval; MI, myocardial infarction; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NSTEMI, non-ST-segment elevation myocardial infarction; OR, odds ratio; SIRI, Systemic Inflammatory Response Index; STEMI, ST-segment elevation myocardial infarction.

The exclusion of patients who died during hospitalization was introduced post hoc because the available event-level data could not adequately distinguish admission biomarker patterns from those associated with cardiac arrest, resuscitation, shock, and perimortem physiology. This decision changed the target population to hospital survivors and introduced selection and survivorship bias. Because exclusion due to in-hospital death represented a larger proportion of the older age stratum among the 185 patients included in this comparison (27.7% vs. 14.3%, Fisher's exact P = 0.032), this exclusion removed a disproportionate proportion of older, more severely ill patients and should be considered when interpreting the between-group comparisons. The other exclusions restricted the cohort to patients with obstructive coronary disease treated with PCI or CABG. Because the plaque mechanism was not independently adjudicated, the analysis does not classify these events as type 1 MI. Mortality and the frequency of nonobstructive presentations cannot be evaluated from this cohort.

The relatively high crude proportion of in-hospital deaths in the initially screened population (40/205, 19.5%) should be interpreted in the context of the institutional admission pathway. At our center, patients resuscitated after out-of-hospital cardiac arrest are routinely admitted directly to the coronary intensive care unit because a separate anesthesiology/reanimation intensive care pathway for these cardiac patients is not available. Consistent with this practice, 35 of the 40 excluded deaths (87.5%) occurred after out-of-hospital cardiac arrest. This institutional pathway enriches the coronary care population with critically ill postresuscitation patients and likely contributed to the high crude proportion of deaths observed in the screened cohort. Accordingly, this proportion should not be compared directly with mortality rates reported in conventional unselected MI cohorts. Importantly, this institutional explanation does not eliminate the selection and survivorship bias introduced by excluding these patients from the primary analysis.

The predominance of the RCA as the culprit artery in younger patients (47.3% vs. 22.2%, Fisher's exact P = 0.006) is a noteworthy angiographic distinction in this obstructive coronary artery disease cohort; LAD and CX artery involvement did not differ significantly between groups. This RCA finding applies only to patients with a single identifiable culprit vessel (55/72 younger patients and 63/73 older patients) and does not extend to the CABG subgroup or to the cohort as a whole. The mechanistic explanation for this distribution remains speculative and cannot be established from the present data. The better preservation of LVEF in younger patients, most evident among NSTEMI presentations, is consistent with either less cumulative myocardial damage or a shorter total ischemic time; however, symptom-to-treatment and ischemic times were not systematically available in this retrospective dataset, so this explanation remains a plausible hypothesis rather than a finding supported by the available data. The absence of a significant difference within the STEMI subgroup is reported as an observation rather than evidence of a mechanistic interaction between MI type and age.

All three composite CBC-derived inflammatory indices (SIRI, NLR, and MLR) were significantly elevated in younger patients, and each remained independently associated with younger age when entered separately into multivariable models that included AIP, STEMI/NSTEMI classification, sex, and cardiovascular risk factors. Thus, these associations persisted after adjustment for MI type, although residual confounding by unmeasured markers of acute MI severity cannot be excluded. Absolute neutrophil, lymphocyte, monocyte, and total white blood cell counts did not differ significantly between groups, consistent with the possibility that the elevated composite ratios reflect a shifted balance among leukocyte subpopulations rather than a single dominant absolute change. However, the nonsignificance of these individual components does not itself establish such a shift, because several modest, individually nonsignificant differences can combine mathematically to produce a significant ratio. The observation that CRP levels did not differ significantly between groups, whereas CBC-derived ratios did, suggests a possible mechanistic distinction. The discordance between CRP and CBC-derived indices may reflect differences in their temporal and biological responses during acute MI; however, sampling time, fasting status, treatment timing, and resuscitation status were not standardized, and this single-time-point analysis cannot distinguish acute from chronic inflammatory activity or directly test a plaque-instability mechanism.[4,5,17]

The elevated AIP, non-HDL-C, and LDL-C levels in younger patients indicate a more atherogenic lipid pattern within this selected cohort of survivors with obstructive coronary artery

**Table 6.** Sensitivity analyses using stricter age thresholds (unadjusted)

| Marker | <45 years (n=22), median | 45–65 years (n=123), median | Test | *P* |
|---|---|---|---|---|
| SIRI | 2.014 | 1.351 | MWU | **0.005** |
| NLR | 2.773 | 2.259 | MWU | **0.033** |
| MLR | 0.288 | 0.210 | MWU | **0.022** |
| AIP | 0.322 | 0.352 | MWU | 0.628 |
| **Marker** | **<50 years (n=38), median** | **50–65 years (n=107), median** | **Test** | ***P*** |
| SIRI | 1.556 | 1.233 | MWU | **0.006** |
| NLR | 2.751 | 2.270 | MWU | **0.022** |
| MLR | 0.265 | 0.210 | MWU | **0.030** |
| AIP | 0.440 | 0.339 | MWU | 0.480 |

Bold indicates p<0.05. All comparisons were performed within the same 145-patient analytic cohort. For the <45-year threshold, the comparator group comprised all patients aged 45–65 years in the cohort (n=123); for the <50-year threshold, the comparator group comprised all patients aged 50–65 years (n=107). These were unadjusted (univariable) Mann–Whitney U comparisons. Multivariable models were not fitted at these thresholds because of the limited sample size, particularly in the <45-year subgroup (n=22). AIP, Atherogenic Index of Plasma; MLR, monocyte-to-lymphocyte ratio; MWU, Mann–Whitney U test; NLR, neutrophil-to-lymphocyte ratio; SIRI, Systemic Inflammatory Response Index.

disease (CAD). AIP reflects the balance between triglyceride-rich and HDL-related lipoprotein metabolism and is closely associated with smaller LDL particle size and coronary atherosclerotic burden.[10–13] The independent associations of AIP alongside the SIRI, NLR, and MLR suggest that lipid and inflammatory measures may provide complementary correlates of younger age among patients who already have MI; however, they do not establish contributors to MI occurrence or identify treatment targets. The threshold sensitivity of AIP and incomplete medication data further limit its clinical interpretation. Notably, despite higher LDL-C, non-HDL-C, and AIP levels in younger patients, hyperlipidemia as coded in the source database (reflecting a pre-existing diagnosis and/or treatment rather than a biochemical threshold; see Methods) was more common in the older group and was inversely associated with younger age in covariate-adjusted models. This apparent paradox may reflect differences in prior diagnosis and treatment exposure between age groups rather than a protective biological effect of hyperlipidemia; however, because prehospital statin use and the duration of diagnosed dyslipidemia were incompletely recorded, this explanation cannot be established from the available data, and the regression finding is presented descriptively only. These observations support prospective evaluation of lipid measures beyond LDL-C rather than a clinical assessment recommendation based on the present dataset.[18,19]

Notably, sensitivity analyses using stricter age thresholds (<45 and <50 years; Table 6) showed that statistically significant differences in SIRI, NLR, and MLR between age groups persisted at both stricter thresholds in these unadjusted exploratory comparisons, whereas the association with AIP was no longer statistically significant at either the <45-year or <50-year threshold despite remaining significant at the primary <55-year threshold. This finding indicates that the AIP association is threshold-sensitive and should not be generalized beyond the <55-year comparison reported here. In contrast, the inflammatory indices showed a more consistent unadjusted association with younger age across the age thresholds examined; however, these sensitivity analyses were not adjusted for covariates and should be interpreted as exploratory. Two additional post hoc exploratory sensitivity analyses are reported in the Results: modeling age as a continuous variable yielded materially consistent conclusions for SIRI, NLR, and MLR but not for AIP, whereas an exploratory robustness analysis in a broader, clinically heterogeneous 185-patient cohort formed by reincluding the 40 patients who died during hospitalization retained the direction of the SIRI, MLR, AIP, and LVEF differences, while the NLR difference was not statistically significant. Both analyses should be interpreted with the same exploratory caution as the primary analyses, and the death-inclusive analysis in particular cannot exclude an influence of perimortem physiology on the admission values used or establish that the reincluded patients who died otherwise met the angiographic eligibility criteria of the primary cohort. Taken together, CBC-derived inflammatory indices, particularly SIRI and MLR, showed relatively consistent age-associated differences across these exploratory sensitivity analyses, whereas the association with AIP was more dependent on how age was defined and modeled.

**Limitations**

Several limitations merit consideration. First, the retrospective, single-center, tertiary-referral design limits causal inference and generalizability and introduces referral bias. The 205-patient screening dataset was available only after application of the source database's clinical and laboratory eligibility criteria; a more granular reconstruction of earlier screening exclusions was not possible. Second, no a priori sample size calculation was performed, and subgroup analyses may have been underpowered. Third, biomarkers were measured once at admission; symptom-to-sampling time, fasting status, treatment timing, and resuscitation status were not consistently available. Fourth, incomplete pre-admission medication data introduce unmeasured treatment-related confounding, particularly for lipid and AIP comparisons. Fifth, body mass index (BMI), metabolic syndrome, and relevant etiologies of MI in younger patients-including lipoprotein(a), thrombophilia, antiphospholipid antibodies, autoimmune conditions, hormonal and substance exposure, and spontaneous coronary artery dissection (SCAD)-related factors-were not systematically recorded; a history of known coronary artery disease, previous PCI or CABG, peripheral artery disease, and cerebrovascular disease was also not systematically recorded and could not be reported. Sixth, LVEF was visually estimated after revascularization rather than measured quantitatively at a standardized baseline. Seventh, the cohort was approximately 90% male, precluding reliable sex-stratified analysis. Eighth, STEMI/NSTEMI classification relied on the treating team's final diagnosis; the individual diagnostic components and plaque mechanism could not be independently reconstructed or centrally adjudicated. Ninth, the post hoc exclusion of 40 in-hospital deaths and 20 nonobstructive/noncritical presentations introduces selection and survivorship bias and restricts inference to hospital survivors with obstructive disease treated with PCI or CABG. The excluded-death cohort was clinically more severe and older on average (median, 58.0 years) than the survivor cohort, and exclusion due to in-hospital death represented a larger proportion of the older age stratum among the 185 patients included in this comparison (27.7% vs. 14.3%, P = 0.032). The age distribution of the 20 excluded patients with nonobstructive or noncritical disease was not available for this analysis; age was applied as an eligibility filter at the source-database level for all 205 screened patients, but individual age values for these 20 patients were not retained in the dataset extracted for the present stratified analysis, so their distribution across the <55- and 55–65-year strata cannot be reported. Incomplete shock and treatment data precluded outcome analysis. Tenth, SIRI and MLR were collinear (variance inflation factor [VIF]≈10); separate index-specific models reduced this instability but were not externally validated. Eleventh, AIP was not significant at the <45- and <50-year thresholds, making the primary <55-year association threshold-sensitive and exploratory. Finally, no correction for multiplicity or internal validation, such as bootstrap or split-sample validation, was performed for any of the analyses above.

**Conclusion**

Young hospital survivors with MI and obstructive, revascularization-requiring coronary artery disease differed from middle-aged patients across several inflammatory, lipid, and angiographic measures

in this cohort. They exhibited elevated composite inflammatory indices and a more atherogenic admission lipid profile. In models adjusted for sex, cardiovascular risk factors, and MI type, the SIRI, NLR, and MLR were each independently associated with younger age when modeled separately, along with the AIP (odds ratio [OR] range, 1.255–1.301). However, across exploratory sensitivity analyses-including stricter <45- and <50-year thresholds, age modeled as a continuous variable, and a broader death-inclusive cohort-CBC-derived inflammatory indices, particularly SIRI and MLR, showed relatively consistent age-associated differences, whereas the association with AIP was more dependent on how age was defined and modeled, losing statistical significance at both stricter thresholds and when age was modeled continuously. Younger patients also demonstrated more frequent RCA culprit involvement and better-preserved LVEF.

Because patients who died during hospitalization and those with nonobstructive coronary presentations were excluded from the primary cohort by design, no inferences regarding in-hospital mortality or the frequency of these presentations can be drawn from these findings, and the observed associations are exploratory and specific to this survivor cohort with obstructive coronary disease. CBC-derived inflammatory indices, particularly SIRI and MLR, warrant further investigation as candidate markers of age-associated inflammatory and lipid differences among MI survivors rather than as biomarkers of premature MI; these findings do not, on their own, support a specific clinical assessment or monitoring recommendation. Prospective, adequately powered, sex-balanced studies with serial biomarker measurements, complete enrollment documentation, and outcome-focused designs are needed to clarify the mechanistic roles of these pathways.

**Ethics Committee Approval:** Ethics committee approval was obtained from İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (Approval Number: 2801, Date: 25.02.2026)

**Informed Consent:** The requirement for informed consent was waived by the ethics committee because of the retrospective nature of the study.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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# Early Creatinine-Defined Acute Kidney Injury and 1-Year Mortality in Critically Ill AMI-Coded Patients Meeting Premature-Age Criteria: A MIMIC-IV Retrospective Cohort Study

## Prematür Yaş Ölçütlerini Karşılayan, Yoğun Bakımda İzlenen Akut Miyokard Enfarktüsü Kodlu Hastalarda Erken Kreatinin-Tanımlı Akut Böbrek Hasarı ve 1 Yıllık Mortalite: MIMIC-IV Retrospektif Kohort Çalışması

**ABSTRACT**

**Objective:** Acute kidney injury may complicate acute myocardial infarction and has prognostic significance in broad acute coronary syndrome cohorts. However, the timing of early kidney injury and the prognostic differentiation among acute kidney injury phenotypes remain insufficiently characterized in critically ill patients with acute myocardial infarction who meet premature-age criteria and require intensive care.

**Method:** This retrospective cohort study used MIMIC-IV, a deidentified, single-center critical care database from an academic health system in the United States. The study cohort should be interpreted as ICU-admitted patients with AMI codes who met prespecified sex-specific premature-age criteria rather than as a general young or angiographically adjudicated premature myocardial infarction population. Premature myocardial infarction was prespecified as age younger than 55 years in men and younger than 65 years in women. The primary exposure was early creatinine-defined acute kidney injury reconstructed according to the KDIGO serum creatinine relative and absolute change criteria, with the first qualifying creatinine-based onset occurring within 0–48 hours after ICU admission. Urine-output and renal-replacement-therapy variables were derived separately for phenotype analyses and were not incorporated into the primary exposure. The primary outcome was 1-year all-cause mortality. The main analysis used a time-dependent Cox model, with landmark phenotype analyses performed as supportive analyses.

**Results:** The cohort included 1261 patients, of whom 363 (28.8%) developed early creatinine-defined acute kidney injury. Within 1 year, 275 patients died (21.8%), including 151 deaths during the index hospitalization (12.0%). Early creatinine-defined acute kidney injury was associated with higher mortality in the primary time-dependent Cox model (hazard ratio 1.37, 95% confidence interval 1.06–1.79; P=0.018). The association was also maintained in the supportive parsimonious multivariable Cox model (hazard ratio 1.63, 95% confidence interval 1.23–2.16; P<0.001). The expanded complete-case model and prespecified multiple-imputation sensitivity analysis also supported an association in the same direction. In the 24-hour landmark analysis, the urine-output-only acute kidney injury phenotype did not retain an independent association with mortality, whereas the creatinine- or renal-replacement-therapy-positive phenotype remained directionally associated with higher risk.

**Conclusion:** Early creatinine-defined acute kidney injury may serve as a marker of increased risk among ICU-admitted, AMI-coded patients who meet sex-specific premature-age criteria. The findings should not be generalized to all young or premature myocardial infarction patients and should be interpreted cautiously in view of ICU-only selection, coding-based disease definitions, incomplete etiologic profiling, and residual confounding.

**Keywords:** Acute kidney injury, critical care, MIMIC-IV, mortality, premature-age myocardial infarction.

**ÖZET**

**Amaç:** Akut böbrek hasarı, akut miyokard enfarktüsüne eşlik edebilir ve geniş akut koroner sendrom kohortlarında prognostik önem taşır. Prematür yaş ölçütlerini karşılayan ve yoğun bakımda izlenen kritik akut miyokard enfarktüsü hastalarında erken böbrek hasarının zamanlaması ve akut böbrek hasarı fenotipleri arasındaki prognostik ayrışma yeterince tanımlanmamıştır.

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**Yöntem:** Bu retrospektif kohort çalışması, Amerika Birleşik Devletleri'nde tek merkezli bir akademik sağlık sisteminden elde edilen, kimlikten arındırılmış bir yoğun bakım veri tabanı olan MIMIC-IV kullanılarak yürütüldü. Çalışma kohortu, genel prematür miyokard enfarktüsü popülasyonunu değil, yoğun bakım yatışı olan ve akut miyokard enfarktüsü kodu taşıyan, prematür yaş ölçütlerini karşılayan hastaları yansıtmaktadır. Prematür miyokard enfarktüsü, erkeklerde 55 yaş altı ve kadınlarda 65 yaş altı olarak önceden tanımlandı. Primer maruziyet, yoğun bakım yatışından sonraki ilk 48 saat içinde gelişen kreatinin-tanımlı akut böbrek hasarıydı. Primer sonlanım, 1 yıllık tüm nedenlere bağlı mortaliteydi. Ana analiz zaman-bağımlı Cox modeli kullanılarak gerçekleştirildi; landmark fenotip analizleri ise destekleyici analizler olarak değerlendirildi.

**Bulgular:** Kohort 1261 hastadan oluştu ve 363 hastada (%28.8) erken kreatinin-tanımlı akut böbrek hasarı gelişti. Bir yıl içinde 275 ölüm (%21.8), indeks hastanede ise 151 ölüm (%12.0) gerçekleşti. Erken kreatinin-tanımlı akut böbrek hasarı, primer zaman-bağımlı Cox modelinde daha yüksek mortalite ile ilişkiliydi (HR 1.37, %95 GA 1.06–1.79; P=0.018). Bu ilişki, destekleyici sadeleştirilmiş çok değişkenli Cox modelinde de korundu (HR 1.63, %95 GA 1.23–2.16; P<0.001). Genişletilmiş tam-olgu modeli ve önceden belirlenmiş çoklu imputasyon duyarlılık analizi de ilişkinin aynı yönde olduğunu destekledi. Yirmi dört saatlik landmark analizinde, yalnızca idrar çıkışıyla tanımlanan akut böbrek hasarı fenotipi mortalite ile bağımsız bir ilişki göstermedi.

**Sonuç:** Erken kreatinin-tanımlı akut böbrek hasarı, yoğun bakımda izlenen ve akut miyokard enfarktüsü kodu taşıyan, prematür yaş ölçütlerini karşılayan hastalarda artmış riskin bir belirteci olabilir. Bulgular, genel genç veya prematür miyokard enfarktüsü popülasyonuna genellenmemeli; yoğun bakım hastalarıyla sınırlı seçilim, kod-temelli hastalık tanımları, eksik etiyolojik profilleme ve kalıntı karıştırıcılık dikkate alınarak yorumlanmalıdır.

**Anahtar Kelimeler:** Akut böbrek hasarı, yoğun bakım, MIMIC-IV, mortalite, prematür miyokard enfarktüsü.

Premature myocardial infarction exposes patients to decades of recurrent ischemic risk, heart failure, chronic kidney disease (CKD) progression, and early mortality.[1,2] The clinical profile of premature myocardial infarction differs from that observed in older infarction cohorts, yet the disease burden remains substantial among young and middle-aged adults.[3,4]

Most studies of premature myocardial infarction have focused on risk factors, recurrent events, and outpatient prognosis rather than on the subgroup of patients who deteriorate sufficiently to require intensive care.[5,6] Methodological guidance for research in this field also emphasizes that premature myocardial infarction should not be regarded simply as a younger-age counterpart of infarction in older adults because exposure patterns, competing risks, and long-term implications differ.[7] This distinction is particularly important in ICU-selected cohorts, which should not be interpreted as representative of all young or premature myocardial infarction presentations.

Acute kidney injury (AKI) following acute coronary syndromes has been associated with increased short- and long-term mortality.[8,9] This association has also been observed in cardiac intensive care and infarction-related cardiogenic shock populations, in which renal injury is closely associated with hemodynamic compromise and multiorgan failure.[10,11]

Two clinically relevant gaps remain. First, many analyses combine kidney injury occurring at any point during hospitalization, thereby weakening the definition of time zero and blurring the distinction between early cardiorenal injury and later treatment-related events.[12,13] Second, urine-output and creatinine criteria identify overlapping but nonidentical phenotypes, and their prognostic implications may differ among critically ill cardiovascular patients.[14,15] The present study therefore examined whether early creatinine-defined AKI occurring within the first 48 hours after intensive care unit (ICU) admission was associated with 1-year mortality in a patient-level cohort meeting premature myocardial infarction age criteria and whether urine-output-only AKI carried a weaker prognostic signal than creatinine- or renal-replacement-therapy-positive (RRT) injury.

## ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| AKI | Acute kidney injury |
| AMI | Acute myocardial infarction |
| CABG | Coronary artery bypass grafting |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CRRT | Continuous renal-replacement therapy |
| ESC | European Society of Cardiology |
| HR | Hazard ratio |
| ICU | Intensive care unit |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| MICE | Multiple imputation by chained equations |
| MIMIC-IV | Medical Information Mart for Intensive Care IV |
| NSTEMI | Non–ST-segment elevation myocardial infarction |
| RRT | Renal-replacement therapy |
| SOFA | Sequential Organ Failure Assessment |
| STEMI | ST-segment elevation myocardial infarction |

## Methods

### Study Design and Data Source

This retrospective cohort study used the Medical Information Mart for Intensive Care IV (MIMIC-IV), version 3.1, a deidentified, single-center U.S. critical care database derived from patients treated within the Beth Israel Deaconess Medical Center system and distributed through PhysioNet to credentialed users under a data use agreement.[16] MIMIC-IV was developed through a collaboration between Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. The database consists of routinely collected clinical data that were transformed, deidentified, and released as a research resource following review by the Beth Israel Deaconess Medical Center Institutional Review Board, which approved the data-sharing initiative and granted a waiver of individual informed consent. Access to MIMIC-IV is restricted to credentialed PhysioNet users who complete the required human research and data training and sign the PhysioNet data use agreement; the author responsible for data extraction completed this process before querying the database. Structured data were extracted using SQL queries executed within the MIMIC BigQuery environment. MIMIC-IV contains structured hospital and ICU data, including demographics, diagnoses, procedures, medications, laboratory tests, vital signs, ICU support variables, and mortality data available within the database framework. The study was reported in accordance with the STROBE and RECORD principles for observational studies using routinely collected health data. The present secondary analysis was reviewed and approved by the relevant institutional academic board (Meeting Number: 5, Approval Number: 1, Date: 31.03.2026). Individual informed consent was waived because the study used deidentified MIMIC-IV data. The study was conducted in accordance with the Declaration of Helsinki. Cohort assembly followed a sequential process of screening AMI-coded hospitalizations, applying the ICU-stay requirement, applying sex-specific premature-age criteria, and selecting the first eligible hospitalization.

### Cohort Definition

Hospitalizations with diagnostic codes for acute myocardial infarction (AMI) were screened and restricted to admissions linked to at least one ICU stay. AMI coding was aligned with the Fourth Universal Definition of Myocardial Infarction and contemporary ACS guidelines.[17,18]

Current major ACS guidelines do not specify a universal age threshold for premature myocardial infarction. The cohort definition was therefore prespecified on the basis of contemporary literature on premature myocardial infarction and methodological recommendations in this field rather than selected post hoc for this dataset.[2,7] Premature myocardial infarction was defined as age younger than 55 years in men and younger than 65 years in women at admission. The analytic unit was the patient rather than the ICU stay. Only the first eligible hospitalization per patient and the first ICU stay within that hospitalization were retained.

Standardized, severity-resolved echocardiographic fields capable of reliably identifying severe valvular disease, mitral or aortic annular calcification, left ventricular assist device support, or constrictive pericardial disease were not available in a harmonized form across the full database. These structural conditions therefore could not be excluded with confidence during primary cohort construction and were addressed as an a priori limitation rather than through unverifiable retrospective adjudication. This represented a structural limitation of the database rather than a convenience-based decision.

### Exposure and Outcomes

The primary exposure was early creatinine-defined AKI within 48 hours after ICU admission. Serum creatinine staging was reconstructed according to Kidney Disease: Improving Global Outcomes (KDIGO) relative and absolute change criteria, and only events with a first qualifying creatinine-based onset within the 0- to 48-hour ICU window were counted as primary exposure events.[19] Patients were not assumed to have AKI at ICU admission unless the creatinine-based KDIGO threshold was first met within the 0- to 48-hour ICU window.

Urine-output and RRT flags were also derived from the same early window. These variables were not incorporated into the primary exposure because the primary prognostic exposure focused on creatinine-positive injury. Instead, they were reserved for phenotype analyses.

The primary outcome was all-cause mortality within 365 days. Survival analyses measured follow-up from ICU admission in the primary model and from the 24- or 48-hour landmark in secondary landmark analyses. In-hospital mortality was retained as a descriptive secondary outcome. All-cause mortality was determined using the mortality fields available in MIMIC-IV, which integrate in-hospital death information with linked postdischarge death records available within the database structure.

### Covariates

Prespecified baseline covariates included age, sex, myocardial infarction subtype coding, diabetes mellitus, CKD, heart failure, cardiogenic shock, and renal dysfunction at admission. Early dynamic critical care covariates measured within the first 24 hours included hemoglobin, bicarbonate, mean arterial pressure, peak lactate, blood urea nitrogen, glucose, vasopressor exposure, invasive mechanical ventilation, and continuous renal replacement therapy. Procedure and support variables included coronary angiography, percutaneous coronary intervention, coronary artery bypass grafting, intra-aortic balloon pump use, Impella support, and extracorporeal membrane oxygenation. Additional treatment, lipid, and premature-myocardial-infarction profile variables were extracted for descriptive context only. These variables included antiplatelet, anticoagulant, beta-blocker, renin-angiotensin-system inhibitor, statin, diuretic, nephrotoxic-drug, and procedure-timing indicators; early lipid measurements; and coding-based markers such as dyslipidemia, family history of ischemic heart disease, stimulant use, thrombophilia, and autoimmune or inflammatory disease. These fields were not treated as adjudicated etiologic classifications or causal treatment variables. Traditional lipid fractions were available for only a minority of patients, and apolipoprotein B and lipoprotein(a) were unavailable.

Rhythm status, contrast volume, and cumulative fluid balance were not incorporated into the primary adjusted model set because no harmonized, low-missingness early variable layer

was available across the full cohort. Composite severity scores such as APSIII and SOFA were also not included in the primary prognostic exposure models. Both scores incorporate renal, hemodynamic, and ventilatory components that overlap with the exposure itself and with early treatment mediators. Their inclusion could therefore have resulted in overadjustment, mechanical collinearity, and attenuation of the renal signal that the study was designed to evaluate. This choice reflected the exposure-focused prognostic aim of the analysis rather than omission of available data.

**Missing Data**

Missingness was quantified before model fitting. Variables with low levels of missingness were entered directly into parsimonious models. Variables with greater levels of missingness were not forced into the primary adjusted model set. Multiple imputation by chained equations was prespecified as a sensitivity analysis for the expanded model. Lactate and body mass index had substantial missingness, troponin T was missing in nearly one-third of patients, and troponin I was entirely unavailable; therefore, these variables did not drive the primary adjusted inference. Detailed flow counts are presented in Figure 1 and Supplementary Table S1. Missingness for candidate variables is summarized in Supplementary Table S2. Because only five imputed datasets were generated and missingness was substantial for some candidate variables, the MICE analysis was interpreted as supportive sensitivity evidence rather than as the primary estimator.

**Statistical Analysis**

Continuous variables were summarized as the mean with standard deviation or median with interquartile range, according to their distribution. Categorical variables were summarized as counts and percentages. Group comparisons were performed using the Mann–Whitney U test, Kruskal–Wallis test, chi-square test, or Fisher exact test, as appropriate.

The primary analysis used a time-dependent Cox proportional hazards model in which creatinine-defined AKI exposure status changed at the observed onset time. This model was selected to avoid immortal-time bias. A parsimonious multivariable Cox model served as the principal supporting adjusted analysis. An expanded complete-case model and a multiple-imputation model were prespecified as sensitivity analyses. The 24-hour landmark phenotype model was prespecified as a secondary analysis and was not interpreted as co-primary evidence.

Model diagnostics included assessment of variance inflation factors, Schoenfeld residual testing for the prespecified primary exposure term, and restricted cubic spline analyses for selected continuous covariates. Discrimination was summarized using the concordance index. Prespecified subgroup analyses included interaction terms for sex, ICD-based STEMI-like coding, diabetes mellitus, cardiogenic shock, and admission renal dysfunction. Two-sided P values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA), and R software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Admission renal dysfunction was retained as a binary adjustment covariate in the primary models, whereas admission creatinine and blood urea nitrogen were evaluated using restricted cubic splines in supporting analyses because formal tests suggested nonlinearity.

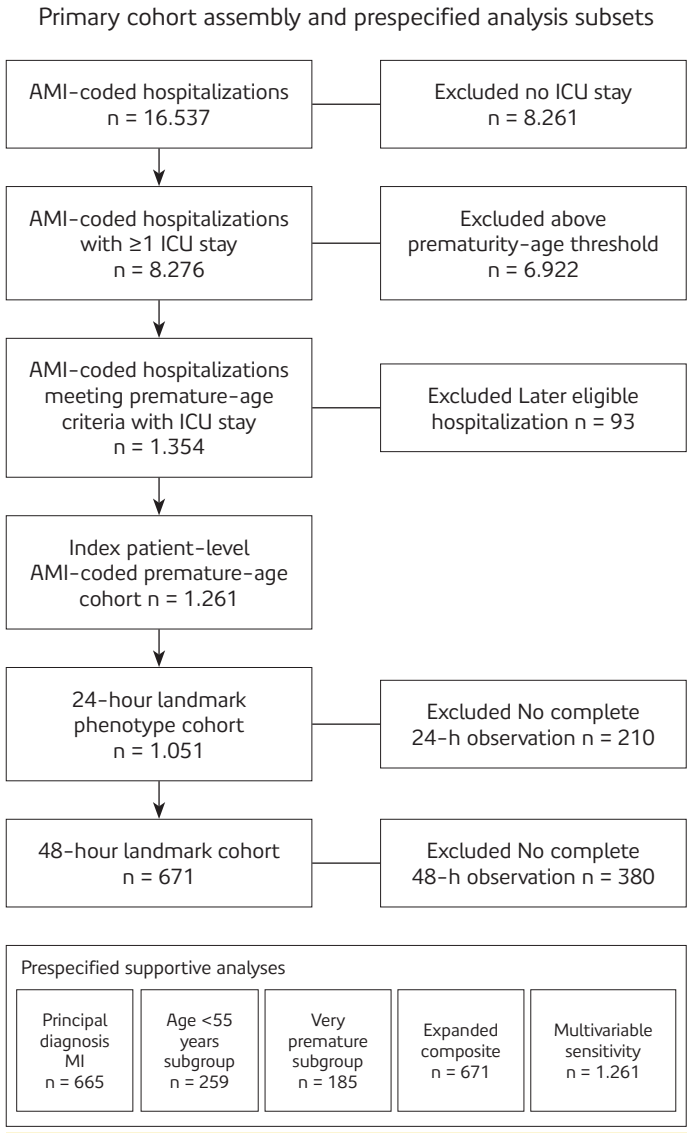



**Figure 1.** Cohort flow diagram with explicit exclusion reasons.

Right-sided arrows indicate excluded hospitalizations or patients at each transition, and separate branch boxes identify the prespecified principal-diagnosis MI sensitivity cohort and age-based subgroup cohorts. The figure is intended to emphasize the ICU-selection framework and the secondary nature of the landmark and subgroup analyses. AMI, Acute myocardial infarction; ICU, Intensive care unit; MI, Myocardial infarction; Cox, Cox proportional hazards model.

## Results

**Cohort Assembly**

A total of 16,537 AMI-coded hospitalizations were identified. Of these, 8,276 included at least one ICU stay, whereas 8,261 were excluded because no ICU stay occurred during the index admission. Application of the sex-specific premature myocardial infarction age thresholds further restricted the ICU cohort to 1,354 hospitalizations, with 6,922 hospitalizations excluded because age exceeded the prespecified definition of premature myocardial infarction. Patient-level index selection yielded a final cohort of 1,261 patients after exclusion of 93 subsequent eligible hospitalizations occurring in

the same patients. AKI ascertainment was available for all 1,261 patients. The 24-hour landmark cohort included 1,051 patients, whereas 210 were excluded because death occurred or complete observation through 24 hours was unavailable. The 48-hour landmark cohort included 671 patients, with an additional 380 excluded because death occurred or complete observation between 24 and 48 hours was unavailable. The principal-diagnosis MI sensitivity cohort included 656 patients, the subgroup younger than 45 years included 259 patients, and the very-premature subgroup included 185 patients (Figure 1; Supplementary Table S1).

**Table 1.** Baseline characteristics according to early creatinine-defined acute kidney injury

| Characteristic | Overall (N=1261) | No early creatinine-defined AKI (n=898) | Early creatinine-defined AKI (n=363) | *P* |
|---|---|---|---|---|
| Demographics | | | | |
| Age, y | 50.9 (8.9) | 51.0 (8.9) | 50.8 (8.9) | 0.777 |
| Weight, kg | 84.0 [69.8–99.8] | 84.0 [70.0–100.0] | 83.7 [68.9–99.4] | 0.640 |
| Body mass index, kg/m² | 29.4 [25.2–34.2] | 29.3 [25.1–33.6] | 29.7 [25.5–35.4] | 0.341 |
| Female sex | 632 (50.1%) | 448 (49.9%) | 184 (50.7%) | 0.845 |
| Myocardial infarction variables | | | | |
| ICD-based STEMI-like MI coding | 620 (49.2%) | 452 (50.3%) | 168 (46.3%) | 0.214 |
| PCI during hospitalization | 342 (27.1%) | 286 (31.8%) | 56 (15.4%) | <0.001 |
| CABG during hospitalization | 268 (21.3%) | 180 (20.0%) | 88 (24.2%) | 0.116 |
| Cardiovascular risk factors | | | | |
| Diabetes mellitus | 497 (39.4%) | 305 (34.0%) | 192 (52.9%) | <0.001 |
| Hypertension | 776 (61.5%) | 522 (58.1%) | 254 (70.0%) | <0.001 |
| Smoking-related diagnosis coding | 608 (48.2%) | 450 (50.1%) | 158 (43.5%) | 0.040 |
| Obesity | 236 (18.7%) | 158 (17.6%) | 78 (21.5%) | 0.127 |
| Previous cardiovascular disease | | | | |
| Heart failure | 492 (39.0%) | 320 (35.6%) | 172 (47.4%) | <0.001 |
| Peripheral artery disease | 68 (5.4%) | 34 (3.8%) | 34 (9.4%) | <0.001 |
| Stroke/TIA | 106 (8.4%) | 65 (7.2%) | 41 (11.3%) | 0.025 |
| Renal status and hemodynamic severity | | | | |
| Chronic kidney disease | 250 (19.8%) | 103 (11.5%) | 147 (40.5%) | <0.001 |
| ESRD or chronic dialysis | 103 (8.2%) | 25 (2.8%) | 78 (21.5%) | <0.001 |
| Admission renal dysfunction | 367 (29.1%) | 149 (16.6%) | 218 (60.1%) | <0.001 |
| Cardiogenic shock | 166 (13.2%) | 94 (10.5%) | 72 (19.8%) | <0.001 |
| Laboratory parameters | | | | |
| Admission creatinine, mg/dL | 1.0 [0.7–1.7] | 0.9 [0.7–1.2] | 1.8 [1.0–3.7] | <0.001 |
| Hemoglobin, g/dL | 11.4 [9.2–13.3] | 11.9 [9.8–13.5] | 10.0 [8.3–11.9] | <0.001 |
| White blood cell count, ×10⁹/L | 12.1 [8.8–16.6] | 12.0 [9.1–16.2] | 12.3 [7.8–17.3] | 0.479 |
| Platelet count, ×10⁹/L | 214.0 [158.0–270.5] | 220.0 [170.0–273.0] | 184.0 [131.5–257.0] | <0.001 |
| Peak lactate within the first 24 h, mmol/L | 2.3 [1.6–3.6] | 2.2 [1.5–3.2] | 2.6 [1.7–4.8] | <0.001 |
| Bicarbonate, mmol/L | 22.0 [20.0–25.0] | 23.0 [20.0–25.0] | 21.0 [18.0–24.0] | <0.001 |
| Mean arterial pressure, mmHg | 86.0 [75.0–99.0] | 86.0 [75.5–98.5] | 85.0 [73.0–100.5] | 0.999 |
| Glucose, mg/dL | 136.0 [110.0–190.0] | 133.0 [110.0–180.5] | 150.0 [111.5–214.0] | 0.002 |
| Blood urea nitrogen, mg/dL | 17.0 [12.0–30.8] | 15.0 [12.0–23.0] | 28.0 [16.5–48.0] | <0.001 |
| ICU support or treatment-intensity variables | | | | |
| Vasopressor use within the first 24 h | 432 (34.3%) | 276 (30.7%) | 156 (43.0%) | <0.001 |
| Invasive ventilation within the first 24 h | 592 (46.9%) | 371 (41.3%) | 221 (60.9%) | <0.001 |
| CRRT within the first 24 h | 31 (2.5%) | 15 (1.7%) | 16 (4.4%) | 0.008 |

Values are presented as mean (SD), median [IQR], or n (%), as appropriate. Characteristics are grouped into demographics, myocardial infarction variables, cardiovascular risk factors, previous cardiovascular disease, renal status and hemodynamic severity, laboratory parameters, and ICU support or treatment-intensity variables. P values were derived using the Mann–Whitney U test, chi-square test, or Fisher exact test, as appropriate for the variable type. Additional descriptive treatment, procedural, lipid, and coding-based risk-profile variables are summarized in Supplementary Tables S7–S9. AKI, Acute kidney injury; CABG, Coronary artery bypass grafting; CRRT, Continuous renal replacement therapy; ESRD, End-stage renal disease; ICU, Intensive care unit; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; TIA, Transient ischemic attack.

### Baseline Characteristics

Early creatinine-defined AKI occurred in 363 of 1,261 patients (28.8%). Baseline age was similar between the exposure groups, at approximately 51 years, and the proportion of female patients was comparable. Diabetes mellitus, hypertension, heart failure, CKD, end-stage renal disease or chronic dialysis, cardiogenic shock, peripheral artery disease, stroke or transient ischemic attack, and admission renal dysfunction were more common in the AKI group. Admission creatinine, blood urea nitrogen, glucose, and lactate levels were higher, whereas hemoglobin, platelet count, and bicarbonate levels were lower. Early vasopressor use, invasive mechanical ventilation, and continuous renal replacement therapy were also more frequent in the AKI group. Descriptive coding-based variables showed frequent coding for dyslipidemia and less frequent coding for family history of ischemic heart disease, stimulant use, thrombophilia, and autoimmune or inflammatory disease. Aspirin, anticoagulant, beta-blocker, and statin use were common during hospitalization. Early lipid measurements were available for only a minority of patients, and apolipoprotein B and lipoprotein(a) were unavailable. Baseline comparisons are summarized in Table 1, and descriptive treatment, lipid-availability, and coding-based risk-profile variables are summarized in Supplementary Tables S7–S9.

### Primary Outcome

A total of 275 deaths occurred within 1 year, corresponding to a 1-year mortality rate of 21.8%, and 151 patients died during the index hospitalization, corresponding to an in-hospital mortality rate of 12.0%. Figure 2 shows descriptive unadjusted Kaplan–Meier separation according to creatinine-defined AKI status, whereas the primary inferential framework was the prespecified time-dependent Cox model. The primary and supporting hazard models are summarized in Table 2. In univariable analysis, early creatinine-defined AKI was associated with higher mortality [hazard ratio (HR), 2.52; 95% CI, 1.98–3.19; P<0.001]. The primary time-dependent Cox model and the parsimonious fixed-time multivariable Cox model both included 1,232 patients and 265 deaths after complete-case restriction for hemoglobin, bicarbonate, and mean arterial pressure; accordingly, 29 patients and 10 deaths within 1 year were excluded from adjusted complete-case analyses. In the prespecified primary time-dependent Cox model, early creatinine-defined AKI remained associated with 1-year mortality (HR, 1.37; 95% CI, 1.06–1.79; P=0.018). The supporting parsimonious multivariable Cox model showed a similar direction of association with a larger effect estimate (HR, 1.63; 95% CI, 1.23–2.16; P<0.001).

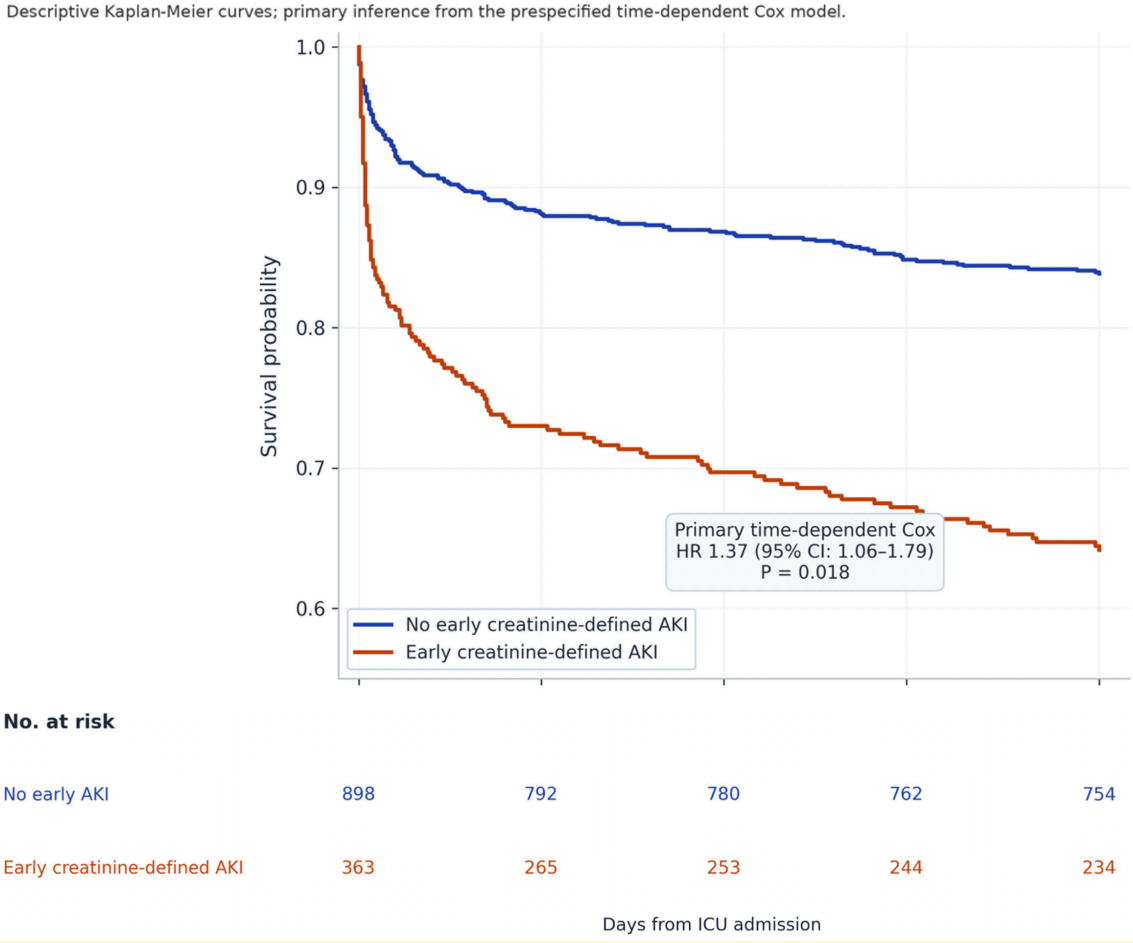



**Figure 2.** Descriptive Kaplan–Meier estimates for 1-year mortality according to early creatinine-defined AKI status.

Curves are labeled as no early creatinine-defined AKI and early creatinine-defined AKI. The number-at-risk table is displayed beneath the panel. Kaplan–Meier curves are descriptive; the hazard ratio shown in the legend refers to the prespecified time-dependent Cox model. No log-rank p value is presented. AKI, Acute kidney injury; CI, Confidence interval; HR, Hazard ratio; ICU, Intensive care unit.

### Sensitivity Analyses

The expanded complete-case model retained the association (HR, 1.41; 95% CI, 1.03–1.93; P=0.033), and the prespecified multiple-imputation sensitivity model provided additional supportive evidence in the same direction (HR, 1.51; 95% CI, 1.15–1.98; P=0.003). The association remained directionally consistent in the principal-diagnosis myocardial infarction cohort, the sensitivity analysis excluding patients with end-stage renal disease, and the 48-hour landmark analysis. Exploratory models among patients younger than 45 years and those in the very-premature subgroup were imprecise because of the lower numbers of events. Detailed sensitivity results are provided in Supplementary Table S3.

### Secondary Phenotype Analysis

Across the full cohort of 1,261 patients, 131 had no AKI, 752 had urine-output-only AKI, and 378 had creatinine- or RRT-positive AKI. The analytic 24-hour landmark cohort included 1,051 patients, of whom 80 had no AKI, 647 had urine-output-only AKI, and 324 had creatinine- or RRT-positive AKI. One-year mortality rates across the full-cohort phenotype groups were 16.0%, 14.8%, and 36.8%, respectively, and in-hospital mortality rates were 4.0%, 7.7%, and 22.6%, respectively. Supplementary Figure S1 shows descriptive Kaplan–Meier estimates from the 24-hour landmark analysis. In the unadjusted 24-hour landmark model, the creatinine- or RRT-positive phenotype was associated with a higher risk of mortality than the no-acute-kidney-injury reference group (HR, 2.22; 95% CI, 1.27–3.87; P=0.005). After adjustment, urine-output-only AKI was not independently associated with mortality (HR, 0.85; 95% CI, 0.46–1.56; P=0.589), whereas the creatinine- or RRT-positive phenotype remained directionally associated with higher mortality, although with wider CIs (HR, 1.58; 95% CI, 0.85–2.93; P=0.150). Full-cohort and landmark-specific phenotype summaries are provided in Supplementary Table S4.

### Subgroup Analyses and Model Performance

Prespecified subgroup estimates are reported in Table 3 and illustrated in Figure 3. The association between early creatinine-defined AKI and 1-year mortality was stronger in patients with ICD-based STEMI-like infarction coding than in those with ICD-based NSTEMI-like infarction coding (P for interaction=0.008). A stronger association was also observed in patients without admission renal dysfunction than in those with admission renal dysfunction (P for interaction=0.009). No statistically significant interactions were observed for sex, diabetes mellitus, or cardiogenic shock, and these findings should not be overinterpreted. Model discrimination increased from a concordance index of 0.606 in the univariable model to 0.638 in the primary time-dependent model and 0.728 in the parsimonious multivariable model; the expanded complete-case and secondary multiple-imputation sensitivity models yielded concordance indices of 0.750 and 0.749, respectively.

### Model Diagnostics, Nonlinearity, and Missingness

Variance inflation factors remained low, with a maximum value of 1.86, indicating no important multicollinearity in the primary adjusted model. The proportional hazards assessment showed no evidence of violation for the prespecified primary creatinine-defined AKI exposure term, although several adjustment covariates exhibited time-varying behavior on Schoenfeld residual testing

**Table 2.** Association of early creatinine-defined acute kidney injury with 1-year mortality

| Model | Description | Exposure term | HR (95% CI) | *P* | n | Events | C-index |
|---|---|---|---|---|---|---|---|
| Model 0 | Univariable Cox model | Early creatinine-defined AKI | 2.52 (1.98–3.19) | <0.001 | 1261 | 275 | 0.606 |
| Model 1 | Primary time-dependent Cox model | Time-updated early creatinine-defined AKI | 1.37 (1.06–1.79) | 0.018 | 1232 | 265 | 0.638 |
| Model 2 | Parsimonious multivariable Cox model | Early creatinine-defined AKI | 1.63 (1.23–2.16) | <0.001 | 1232 | 265 | 0.728 |
| Model 3 | Expanded multivariable Cox model (complete case) | Early creatinine-defined AKI | 1.41 (1.03–1.93) | 0.033 | 786 | 208 | 0.750 |
| Model 4 | Expanded multivariable Cox model (MICE sensitivity analysis) | Early creatinine-defined AKI | 1.51 (1.15–1.98) | 0.003 | 1261 | 275 | 0.749 |

Model 1 was the prespecified primary analysis. C-index values represent discrimination metrics for the locked models. Model 0 was unadjusted. Model 1 was the prespecified time-dependent Cox model adjusted for age, sex, ICD-based infarction subtype, diabetes mellitus, chronic kidney disease, heart failure, cardiogenic shock, admission renal dysfunction, first hemoglobin, first bicarbonate, and mean arterial pressure. Model 2 used the same covariate set with fixed early creatinine-defined AKI. Model 3 additionally included peak lactate, first blood urea nitrogen, first glucose, vasopressor use, invasive ventilation, and continuous renal replacement therapy in a complete-case expanded model. Model 4 used the Model 3 covariate set after multiple imputation by chained equations. AKI, Acute kidney injury; CI, Confidence interval; Cox, Cox proportional hazards model; HR, Hazard ratio; MICE, Multiple imputation by chained equations.

(Supplementary Table S5). The adjusted Cox framework was therefore interpreted primarily as an exposure-focused association model rather than as an etiologic model for each individual covariate coefficient. Restricted cubic spline test results are presented in Supplementary Table S6. Restricted cubic spline testing showed no evidence of nonlinearity for age or mean arterial pressure, whereas admission creatinine showed strong evidence of nonlinearity (P<0.001) and blood urea nitrogen also showed evidence of nonlinearity (P=0.021). The admission creatinine spline is shown in Figure 4. The age spline is shown in Supplementary Figure S2. The blood urea nitrogen spline is shown in Supplementary Figure S3. Because admission creatinine and blood urea nitrogen showed nonlinear associations, these variables were interpreted using spline-based analyses rather than a simplistic linear-risk assumption. Missingness was modest for most clinical covariates, but lactate was missing in 36.5% of patients, body mass index in 35.1%, troponin T in 29.8%, and troponin I in 100.0% (Supplementary Table S2; Supplementary Figure S4).

**Table 3.** Prespecified subgroup analyses of the primary association

| Subgroup | n | Events | Adjusted HR (95% CI) | *P* | *P* for interaction |
|---|---|---|---|---|---|
| Male | 615 | 113 | 2.15 (1.38–3.37) | <0.001 | 0.084 |
| Female | 617 | 152 | 1.28 (0.89–1.85) | 0.178 | 0.084 |
| STEMI-like: No | 627 | 134 | 1.24 (0.83–1.83) | 0.292 | 0.008 |
| STEMI-like: Yes | 605 | 131 | 2.21 (1.47–3.32) | <0.001 | 0.008 |
| Diabetes: No | 743 | 150 | 1.65 (1.13–2.42) | 0.010 | 0.998 |
| Diabetes: Yes | 489 | 115 | 1.52 (1.00–2.33) | 0.050 | 0.998 |
| Cardiogenic shock: No | 1072 | 205 | 1.56 (1.14–2.15) | 0.006 | 0.871 |
| Cardiogenic shock: Yes | 160 | 60 | 1.67 (0.89–3.15) | 0.110 | 0.871 |
| Admission renal dysfunction: No | 871 | 121 | 2.01 (1.35–3.00) | <0.001 | 0.009 |
| Admission renal dysfunction: Yes | 361 | 144 | 1.35 (0.94–1.93) | 0.102 | 0.009 |

Subgroup-specific adjusted hazard ratios were estimated using reduced multivariable Cox models. Subgroup n and event counts reflect the complete-case population used in the reduced subgroup models. Interaction p values were derived from formal interaction-term testing. AKI, Acute kidney injury; CI, Confidence interval; HR, Hazard ratio; NSTEMI, Non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

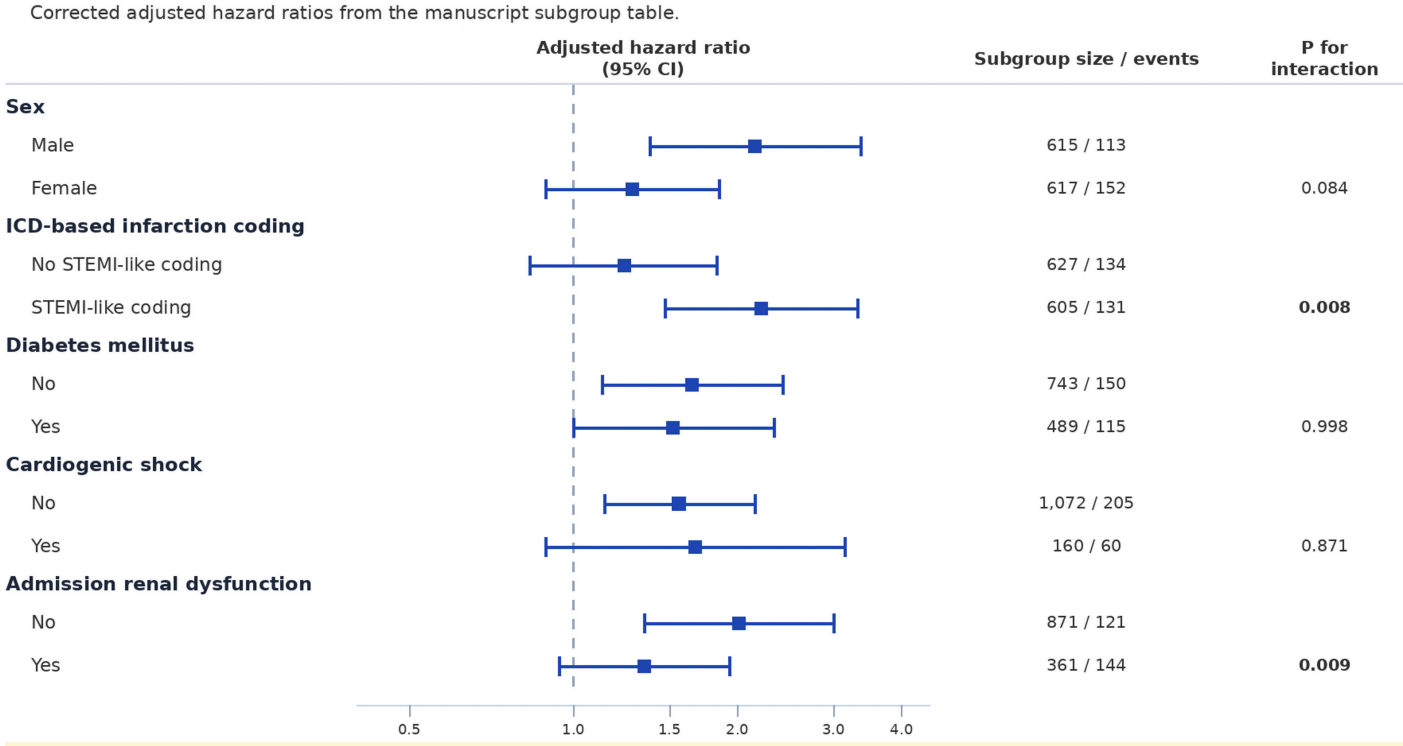



**Figure 3.** Forest plot of prespecified subgroup analyses of the association between early creatinine-defined AKI and 1-year mortality.

Subgroup-specific adjusted hazard ratios are presented with subgroup size, event count, and one interaction p value for each subgroup pair. Sex-specific subgroup estimates are shown for completeness, but the interaction test was not statistically significant. Point estimates and 95% confidence intervals were derived from reduced adjusted Cox models within subgroup strata. AKI, Acute kidney injury; CI, Confidence interval; HR, Hazard ratio; NSTEMI, Non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

## Discussion

The present ICU-admitted, AMI-coded cohort meeting premature-age criteria included 1,261 patients, 363 cases of early creatinine-defined AKI, 275 deaths within 1 year, and 151 in-hospital deaths. Early creatinine-defined AKI remained associated with 1-year mortality in the primary time-dependent Cox model (HR, 1.37; 95% CI, 1.06–1.79; P=0.018) and in supporting sensitivity analyses. In this study, the term premature-age myocardial infarction refers to AMI-coded ICU admissions meeting prespecified sex-specific premature-age criteria; it does not denote an angiographically adjudicated registry of young patients with type 1 myocardial infarction.

The 21.8% 1-year mortality and 12.0% in-hospital mortality rates should be interpreted in the context of ICU selection. The cohort was enriched for cardiogenic shock, CKD, end-stage renal disease or chronic dialysis, admission renal dysfunction, vasopressor exposure, invasive ventilation, and continuous renal replacement therapy. The higher prevalence of CKD, admission renal dysfunction, cardiogenic shock, vasopressor use, invasive ventilation, and continuous renal replacement therapy among patients with early creatinine-defined AKI suggests that the AKI group represented a more clinically vulnerable critical care phenotype rather than an isolated renal injury category. These mortality rates distinguish the present cohort from population-based or registry-based studies of premature myocardial infarction and support interpreting the findings as evidence from a selected ICU population rather than the broader premature myocardial infarction population.[3,10]

The low procedure rates further support this interpretation. PCI during hospitalization was recorded in 342 patients (27.1%), PCI on days 0–1 in 289 patients (22.9%), and coronary angiography during hospitalization in 281 patients (22.3%). These rates are low for a typical young population with type 1 myocardial infarction and are compatible with an AMI-code-based ICU cohort that may include type 2 myocardial infarction, myocardial injury associated with critical illness, hemodynamic instability, competing organ failure, and treatment-selection effects.

The association between early creatinine-defined AKI and mortality should be interpreted as a marker of risk rather than as a causal estimate. AKI may reflect hemodynamic instability, renal vulnerability, multiorgan dysfunction, treatment intensity, and severity of critical illness. Kim et al.[20] analyzed 855 STEMI survivors discharged from the hospital and reported AKI in 74 patients (8.7%), whereas early creatinine-defined AKI occurred in 363 patients (28.8%) in the present ICU-admitted, AMI-coded cohort meeting premature-age criteria. Parikh et al.[21] studied 147,007 elderly Medicare patients with AMI and reported AKI in 19.4%; 10-year crude mortality was 68.3% among patients without AKI and 93.5% among those with severe AKI, whereas the present analysis observed 21.8% 1-year mortality in a much younger but ICU-selected cohort. Bjørn et al.[22] reported AKI in 44% and RRT in 25% of 1,473 patients with AMI-related cardiogenic shock, whereas Guo et al.[23] analyzed 5,715 patients with AMI and reported an association between

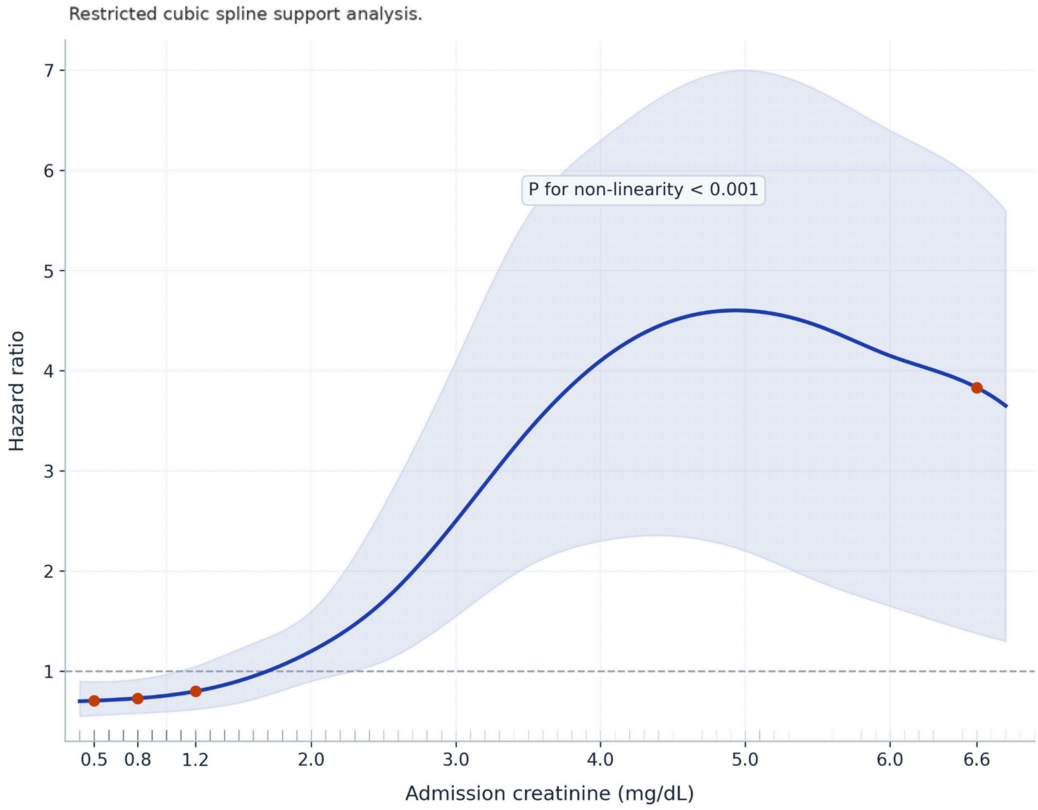



**Figure 4.** Restricted cubic spline of admission creatinine and 1-year mortality.

The curve is centered at the cohort median admission creatinine, displays the four-knot placement used for spline construction, includes a rug plot to indicate data support, and reports the p value for nonlinearity. The figure is intended as a supportive visualization of nonlinearity rather than as a stand-alone inferential result. CI, Confidence interval.

moderate-to-severe AKI and 1-year mortality (HR, 1.22; 95% CI, 1.07–1.38); the primary time-dependent estimate in the present study was a HR of 1.37 (95% CI, 1.06–1.79). These comparisons support interpreting the present findings in the context of critical care risk stratification rather than as evidence from an unselected premature myocardial infarction population. The time-dependent Cox model reduced immortal-time bias, but residual confounding remains inherent to the retrospective ICU database design.

The phenotype analysis further clarified the prognostic role of creatinine-positive injury. Urine-output-only AKI was common, but its adjusted association with mortality was weak. Creatinine- or RRT-positive AKI identified the highest-risk phenotype. In ICU practice, isolated oliguria may reflect transient vasoconstriction, diuretic exposure, effects of mechanical ventilation, or hemodynamic changes during resuscitation, whereas creatinine-positive injury more often reflects sustained renal dysfunction and cumulative cardiorenal stress.[14,24] Reviews of AKI in cardiogenic shock also support interpreting creatinine-positive injury as a marker of sustained cardiorenal stress rather than isolated fluctuations in urine output.[25] The urine-output-only phenotype should therefore remain descriptive.

The premature-MI label and risk-profile data also warrant caution. The study used a broad sex-specific definition, particularly for women younger than 65 years; therefore, the cohort should not be interpreted as representing a strictly young MI population. SCAD, coronary anomalies, pregnancy-related or hormonal factors, detailed family history, familial hypercholesterolemia phenotype, thrombophilia work-up, autoimmune characteristics, and substance-use history beyond diagnostic coding were not reliably available. Early lipid measurements were sparse, with total cholesterol available in 24.4%, HDL-C in 23.7%, LDL-C in 23.6%, triglycerides in 29.3%, and non-HDL-C in 23.7% of patients; ApoB and Lp(a) were unavailable. Therefore, the cohort cannot be interpreted as having undergone comprehensive lipid or inherited-risk phenotyping for premature MI.

This study has important limitations. The database was derived from a single U.S. academic health system and included only ICU-admitted patients. Diagnostic code-identified AMI in the critical care setting may include type 1 MI, type 2 MI, and myocardial injury associated with critical illness; subtype classification was based on diagnostic coding rather than adjudication using ECG or angiographic findings. Structural cardiac conditions could not be uniformly adjudicated. Treatment and procedure variables were susceptible to indication bias and were therefore used descriptively. Troponin I was unavailable, troponin T was frequently missing, and cardiovascular death, recurrent myocardial infarction, stroke, repeat revascularization, and heart failure hospitalization were not available as adjudicated longitudinal outcomes. Early creatinine-defined AKI may serve as a marker of increased risk, but external validation should use multicenter data with adjudicated MI type, angiographic information, standardized treatment timing, and comprehensive lipid and premature-MI etiologic profiling.

## Conclusion

In this ICU-admitted, AMI-coded cohort meeting sex-specific premature-age criteria, early creatinine-defined AKI was associated with higher 1-year mortality in the primary time-dependent Cox model. This finding should be interpreted as evidence of a risk marker in a selected critical care population rather than as proof of a causal renal pathway or as evidence generalizable to all patients with premature myocardial infarction.

**Supplementary Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-95875/TKDA-95875_(0)_supp.docx

**Ethics Committee Approval:** The creation and sharing of MIMIC-IV were reviewed by the Beth Israel Deaconess Medical Center Institutional Review Board, which approved the data-sharing initiative and granted a waiver of individual informed consent. Access to MIMIC-IV was obtained through PhysioNet credentialing and a data-use agreement. The present secondary analysis was reviewed and approved by the Academic Board of the Department of Cardiology (Meeting Number: 5, Approval Number: 1, Date: 31.03.2026).

**Informed Consent:** Individual informed consent for the present analysis was waived because the study used deidentified data.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Use of AI for Writing Assistance:** Structured Query Language (SQL), the standard language for querying structured databases, was used only for data extraction from the MIMIC BigQuery environment in this study. LLM was used solely to assist with drafting these SQL queries. It was not used for analysis, interpretation, or manuscript writing. All authors reviewed and approved this use, verified the extracted data, and take full responsibility for the accuracy of the data and the content of the manuscript.

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**Data Availability Statement:** Source data are available through MIMIC-IV version 3.1 to credentialed users who complete the required PhysioNet training and data-use agreement (Johnson A, Bulgarelli L, Pollard T, et al. MIMIC-IV. Version 3.1. PhysioNet, 2024. Accessed August 11, 2026. https://physionet.org/content/mimiciv/3.1/). The analytic code, variable definitions, and summary outputs can be made available from the corresponding author on reasonable request within database-use constraints.

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# Substance Abuse as a Trigger for Myocardial Infarction in Young Adults: An Underrecognized Major Risk

## Genç Erişkinlerde Miyokard Enfarktüsünün Tetikleyicisi Olarak Madde Kötüye Kullanımı: Yeterince Tanınmayan Önemli Bir Risk

**ABSTRACT**

Myocardial infarction (MI) remains a major public health problem worldwide. The use of illicit substances is increasing. These substances may be associated with an increased incidence of MI through various mechanisms, regardless of the presence of pre-existing risk factors. Although data on this subject are limited, it is important to highlight this issue. The aim of this review is to establish the association between substance misuse and MI, particularly in young adults, and to evaluate the underlying mechanisms based on the current literature. This review was prepared using publications identified through searches of the PubMed/MEDLINE, Scopus, and Web of Science databases using the names of the relevant substances in combination with terms associated with MI. The most commonly misused substances are classified as stimulants, depressants, and performance-enhancing hormones. Stimulants (cocaine, amphetamines, etc.) cause an imbalance between myocardial oxygen supply and demand through effects such as tachycardia, coronary vasospasm, and thrombosis resulting from increased sympathetic activity. Opioids, which belong to the depressant class, cause an imbalance between myocardial oxygen supply and demand by altering coronary hemodynamics secondary to complications such as hypotension, hypoxemia due to respiratory depression, and infection. In the case of cannabis and synthetic cannabinoids, coronary vasospasm, thrombosis, and plaque rupture are important effects. Anabolic-androgenic steroids (AAS) adversely affect the lipid profile. Furthermore, effects associated with AAS use include atherosclerosis, thrombosis, and erythrocytosis. These effects resulting from substance use are recognized as mechanisms underlying the development of MI.

**Keywords:** Myocardial infarction, substance abuse, young adults.

**ÖZET**

Miyokard enfarktüsü (ME), dünya genelinde önemli bir halk sağlığı sorunu olmaya devam etmektedir. Yasa dışı madde kullanımı giderek artmaktadır. Bu maddeler, önceden var olan risk faktörlerinin bulunup bulunmamasından bağımsız olarak, çeşitli mekanizmalar aracılığıyla ME insidansında artışla ilişkili olabilir. Bu konudaki veriler sınırlı olmakla birlikte, sorunun vurgulanması önem taşımaktadır. Bu derlemenin amacı, özellikle genç erişkinlerde madde kötüye kullanımı ile ME arasındaki ilişkiyi ortaya koymak ve altta yatan mekanizmaları güncel literatür doğrultusunda değerlendirmektir. Bu derleme, PubMed/MEDLINE, Scopus ve Web of Science veri tabanlarında ilgili maddelerin adları ile ME ile ilişkili terimlerin birlikte kullanıldığı aramalar sonucunda belirlenen yayınlar temel alınarak hazırlanmıştır. En sık kötüye kullanılan maddeler uyarıcılar, depresanlar ve performans artırıcı hormonlar olarak sınıflandırılmaktadır. Uyarıcılar (kokain, amfetaminler vb.), artmış sempatik aktivite sonucunda gelişen taşikardi, koroner vazospazm ve tromboz gibi etkiler yoluyla miyokardiyal oksijen sunumu ile gereksinimi arasında dengesizliğe neden olur. Depresan sınıfında yer alan opioidler ise hipotansiyon, solunum depresyonuna bağlı hipoksemi ve enfeksiyon gibi komplikasyonlara ikincil olarak koroner hemodinamiği değiştirerek miyokardiyal oksijen sunumu ile gereksinimi arasında dengesizliğe yol açar. Cannabis ve sentetik kannabinoidlerde koroner vazospazm, tromboz ve plak rüptürü önemli etkiler arasındadır. Anabolik-androjenik steroidler (AAS) lipid profilini olumsuz etkiler. Ayrıca AAS kullanımıyla ilişkili etkiler arasında ateroskleroz, tromboz ve eritrositoz yer almaktadır. Madde kullanımına bağlı ortaya çıkan bu etkiler, ME gelişiminin altında yatan mekanizmalar olarak kabul edilmektedir.

**Anahtar Kelimeler:** Miyokard enfarktüsü, madde kötüye kullanımı, genç erişkinler.

**INVITED REVIEW**
DAVETLİ DERLEME

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The World Health Organization estimates that cannabis, the most commonly abused substance worldwide, was used by more than 180 million people in 2013.[1] According to data published in 2024 by the United Nations Office on Drugs and Crime (UNODC) on substance use worldwide, cannabis ranked first, with 256 million people reported to have used it.[2] According to data published by the Turkish Monitoring Centre for Drugs and Drug Addiction, 427 drug-related deaths were recorded in Türkiye in 2024. The risk of death increases further with polysubstance use. Of the 427 deaths, 242 were attributed to the use of multiple substances. Among individuals younger than 40 years, deaths accounted for a substantial proportion of 70.8%.[3]

The increasing prevalence and availability of substance use worldwide also pose various risks.[2] Substances that exert numerous effects on cells, tissues, and organ systems through various mechanisms of action can cause significant cardiovascular complications.[4] The relationship between these substances and myocardial infarction (MI), a serious health problem, remains under investigation. Substance use disorder should be considered a potential cause of MI, particularly in young adults and adolescents without traditional cardiovascular risk factors. Factors such as the inability to determine the dose consumed and frequency of use, the inability to perform diagnostic tests in some cases, reliance on patient self-reports, and polysubstance use make it difficult to establish this relationship. Accordingly, research on this topic consists primarily of case reports and observational studies.

Substance-induced MI refers to MI resulting from the use of illicit or recreational substances, either in the absence of underlying atherosclerotic disease (direct effect) or as a result of triggering pre-existing cardiovascular pathologies (indirect effect).[5] The various pathophysiological mechanisms leading to MI, as shown in Figure 1, include coronary artery spasm, thrombotic changes, endothelial dysfunction, an imbalance between myocardial oxygen supply and demand, plaque rupture, and direct cardiac toxicity.[5] Substances that may lead to cardiovascular disorders include stimulants (cocaine, amphetamine-type stimulants, and fenetylline), depressants (opioids and cannabinoids), and performance-enhancing hormones (anabolic-androgenic steroids). Stimulants such as cocaine and amphetamines activate the sympathetic nervous system and, because of the pathophysiological mechanisms associated with this activation, are among the substances most frequently associated with MI.[6] Coronary vasospasm is particularly strongly associated with smoking and cocaine use.[6]

## Methods

A literature review was conducted to assess the association between substance use and MI, including studies published in the PubMed/MEDLINE, Scopus, and Web of Science databases through July 30, 2026. For substance use, search terms included "illicit drug," "substance abuse," "substance use," "recreational drug," "drug abuse," and the specific names of substances; for cardiovascular pathologies, keywords included "myocardial infarction," "acute myocardial infarction," "coronary syndrome," "acute coronary syndrome," "coronary artery disease," and "cardiovascular."

Meta-analyses, systematic reviews, observational studies, case series, and case reports were included in the review. The reference lists of relevant studies were examined, and pertinent sources not identified during the initial screening were also included. Pharmacological and experimental studies were used in certain circumstances when research on the subject was insufficient.

## ABBREVIATIONS

| | |
|---|---|
| AAS | Anabolic-androgenic steroids |
| ADHD | Attention-deficit/hyperactivity disorder |
| CARDIA | The Coronary Artery Risk Development in Young Adults |
| CB1&CB2 | Cannabinoid receptors 1&2 |
| MDMA | 3,4-methylenedioxymethamphetamine |
| MI | Myocardial infarction |
| THC | Tetrahydrocannabinol |
| UNODC | United Nations Office on Drugs and Crime |

## Stimulants

### Cocaine

Cocaine is a plant-derived (Erythroxylum coca) substance with sympathomimetic effects that can be administered intravenously or by inhalation and has a high potential for addiction. It primarily exerts two distinct effects in the body. First, cocaine acts as a local anesthetic by inhibiting voltage-gated sodium channels. Second, it blocks the presynaptic reuptake of monoamines, including norepinephrine, serotonin, and dopamine. This mechanism contributes to cocaine's addictive and pleasurable effects.[7,8]

The increase in catecholamine levels following cocaine use leads to an increase in heart rate and systemic arterial pressure, thereby increasing myocardial oxygen demand; at the same time, it causes coronary vasoconstriction, reducing myocardial oxygen supply.[9] This imbalance predisposes to ischemia and contributes to cardiovascular complications in both the acute and chronic phases. In the acute phase, conditions such as MI, coronary vasospasm, hypertension, and arrhythmias may occur, whereas chronic use may lead to conditions such as atherosclerosis and cardiomyopathy.[7]

Mittleman et al.[10] reported that the risk of MI increased significantly, by 24-fold, within the first hour after cocaine use and declined during the subsequent hours. The group of patients who used cocaine in their study consisted predominantly of young male smokers.[10] These findings highlight the need to consider cocaine use in the differential diagnosis of MI, particularly in young adults without traditional cardiovascular risk factors.

The pharmacological properties of the substances and their effects contributing to the development of MI are presented in Table 1.

### Amphetamine-Type Stimulants

According to the literature, the class of amphetamine-type stimulants includes amphetamine, methamphetamine, ecstasy (methylenedioxymethamphetamine), and other amphetamine derivatives.[11] These substances increase catecholamine, dopamine, and serotonin levels, resulting in stimulation of the sympathetic nervous system. As a result of this stimulation, acute effects such as increased blood pressure and heart rate, mydriasis, insomnia, decreased appetite, and euphoria may occur.[12] Amphetamine has been approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) and narcolepsy.[13] Long-term use of amphetamines and their derivatives is associated with cognitive impairment, seizures, psychosis, dependence, and hyperthermia.[11]

The sympathetic stimulation caused by amphetamine and its derivatives increases cardiac workload. As a result, myocardial oxygen demand increases. When increased oxygen demand is combined with drug-induced vasoconstriction and increased sympathetic activity, myocardial ischemia may occur.[5] At the same time, these compounds can induce oxidative stress and mitochondrial damage through the generation of reactive oxygen species.[14] In individuals at risk for ischemia and in the presence of coronary vasospasm, the course of MI may progress more rapidly.

A study conducted in Texas included more than 3 million individuals aged 18–44 years and identified 11,011 cases of MI. In an analysis adjusted for other risk factors and cocaine use, a significant association was found between amphetamine use and the incidence of MI (adjusted odds ratio=1.61; 95% confidence interval=1.24–2.04; P = 0.0004).[15] The inclusion of young individuals in this study, together with adjustment for other risk factors, suggests that amphetamine use may significantly increase the risk of MI in patients without conventional risk factors.

Curran et al.[14] examined the association between methamphetamine use and cardiovascular disease among patients treated at hospitals in California between 2005 and 2011. In this retrospective study, methamphetamine use was

**Table 1.** Pharmacological properties of substances of abuse and mechanisms contributing to myocardial infarction

| Substance | Mechanism of action | Half-life | Effects contributing to MI development | Coronary effects | Cardiac effects |
|---|---|---|---|---|---|
| Cocaine | Voltage-gated $Na^+$ channel blockade; inhibition of presynaptic reuptake of monoamines; increased levels of catecholamines, serotonin, and dopamine | 1 hour | Coronary vasospasm, increased myocardial oxygen demand, reduced myocardial oxygen supply, atherosclerosis, endothelial dysfunction, and thrombosis | Coronary vasospasm, endothelial dysfunction, thrombosis | Hypertension, tachycardia, arrhythmias, myocarditis |
| Amphetamine-Type Stimulants | Increased levels of catecholamines, serotonin, and dopamine | Amphetamine: 10–14 hours; methamphetamine: IV and oral forms: 9 hours; smoking: 12 hours; intranasal: 11 hours; MDMA: 4–9 hours | Coronary vasospasm, increased myocardial oxygen demand, reduced myocardial oxygen supply, endothelial dysfunction, thrombosis | Coronary vasospasm, endothelial dysfunction, thrombosis | Tachycardia, hypertension, arrhythmias, cardiomyopathy, myocarditis, sudden cardiac death |
| Fenetylline | Metabolized to amphetamine and theophylline; combined sympathomimetic and xanthine-related stimulant effects | 1.3 hours | Coronary vasospasm, increased myocardial oxygen demand, thrombotic effects | Coronary vasospasm, thrombosis | Tachycardia, hypertension, arrhythmias |
| Opioids | Effects are exerted through specific opioid receptors | Morphine: 2–4 hours; heroin: 3–8 minutes | Increased myocardial oxygen demand, thrombosis, hypoxemia, reduced coronary perfusion, hemodynamic changes resulting from infection and systemic inflammation | Reduced coronary perfusion secondary to hypoxia/hypotension | Hypotension, bradycardia, arrhythmias, infective endocarditis |
| Cannabis | Effects are exerted through CB1 and CB2 receptors | THC: 1–3 days; occasional users: 1–3 days; chronic users: 5–13 days; CBD: 18–32 hours | Coronary vasospasm, increased myocardial oxygen demand, thrombosis, endothelial dysfunction, plaque rupture | Coronary vasospasm, thrombosis, endothelial dysfunction | Cardiomyopathy, arrhythmias, sudden death |
| Synthetic Cannabinoids | Effects are exerted through CB1 and CB2 receptors | JWH-018: 1–3 hours; JWH-073: 40 minutes | Coronary vasospasm, increased myocardial oxygen demand, thrombosis, endothelial dysfunction, plaque rupture | Coronary vasospasm, thrombosis, endothelial dysfunction | Cardiomyopathy, ventricular tachycardia, hypotension, hypertension, sudden death |
| Anabolic-Androgenic Steroids | Effects mediated through androgen receptors in the body; similar to those of natural androgens | Nandrolone decanoate: 7–12 days; testosterone propionate: 4–5 days; testosterone enanthate: 7–9 days; testosterone cypionate: 8 days | Dyslipidemia, atherosclerosis, thrombosis, plaque rupture, erythrocytosis, hypercoagulability | Accelerated atherosclerosis, endothelial dysfunction, arterial thrombosis | Thrombosis, hypertension, left ventricular hypertrophy, ventricular dysfunction, sudden cardiac death |

MI, myocardial infarction; IV, intravenous; MDMA, 3,4-methylenedioxymethamphetamine; THC, tetrahydrocannabinol; CBD, cannabidiol; LV, left ventricle; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2.

associated with an increased risk of MI. The hazard ratio (HR) calculated in the study was 1.19 (95% CI, 1.08–1.31). In addition to MI, the term "methamphetamine-induced heart failure" has gained increasing recognition in the literature in recent years.

Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is a member of the amphetamine class and, like other members of this group, is associated with increases in blood pressure and heart rate.[16] In addition, MDMA use may result in intracranial hemorrhage, vascular rupture, bleeding, and heart failure.[17]

**Fenetylline**

Fenetylline is a synthetic stimulant composed of theophylline and amphetamine that, following hydrolysis in the body, is metabolized into these components. Theophylline exerts its effects by modulating adenosine receptors. Amphetamine exerts its effects by increasing dopamine release and norepinephrine activity, modulating serotonergic activity, and activating the sympathetic nervous system. These mechanisms result in physiological and psychological effects such as tachycardia, bronchodilation, hypertension, euphoria, increased alertness, increased physical endurance, decreased appetite, and pupillary dilation.[18]

Fenetylline was originally developed to treat conditions such as ADHD and narcolepsy. Illicit products subsequently marketed on the street became known as "Captagon."[18] Captagon use is widespread in Southern Europe, Türkiye, and countries in the Middle East, including Saudi Arabia, Syria, Jordan, and Iraq. In Syria, where prolonged conflict and instability have persisted, its use and production have steadily increased.[19–21]

Data on the cardiovascular effects of Captagon use, particularly its association with the development of MI, are limited. Available information on Captagon consists primarily of case reports. Amphetamine, which may be present in illicit Captagon products, may facilitate the development of MI by increasing platelet activation and promoting thrombus formation, in addition to the effects resulting from enhanced sympathetic activity. Several case reports from Türkiye have described MI associated with Captagon use. These reports involved male patients aged 23 and 21 years.[22,23]

**Depressants**

**Opioids**

Opioid is a general term for substances and medications classified as natural, semisynthetic, or synthetic. The opium poppy, also known as Papaver somniferum, is a plant that has been cultivated for many centuries, dating back to approximately 3000 BC, and is the source of opioids.[24,25] Opioids act as agonists, partial agonists, or antagonists at mu, delta, and kappa receptors, which are G-protein-coupled receptors.[26] Despite their potential for abuse, opioids, which have been used as analgesics for many years, are also used in anesthetic induction and in the treatment of cough and diarrhea.[27]

The acute cardiovascular effects of opioids include hypotension, vasodilation, bradycardia, and syncope. These effects are mediated through opioid receptors.[28] Hypotension and vasodilation may contribute to impaired coronary perfusion and, particularly in individuals with risk factors, to myocardial ischemia. Respiratory depression resulting from high doses of opioids, however, may lead to hypoxemia and exacerbate the imbalance between myocardial oxygen supply and demand.[5] In addition to these mechanisms that may cause MI, another controversial issue concerns the delayed gastrointestinal absorption of medications associated with opioid use. Opioid medications are thought to be beneficial in the treatment of MI because of their analgesic effects and ability to reduce sympathetic activity; on the other

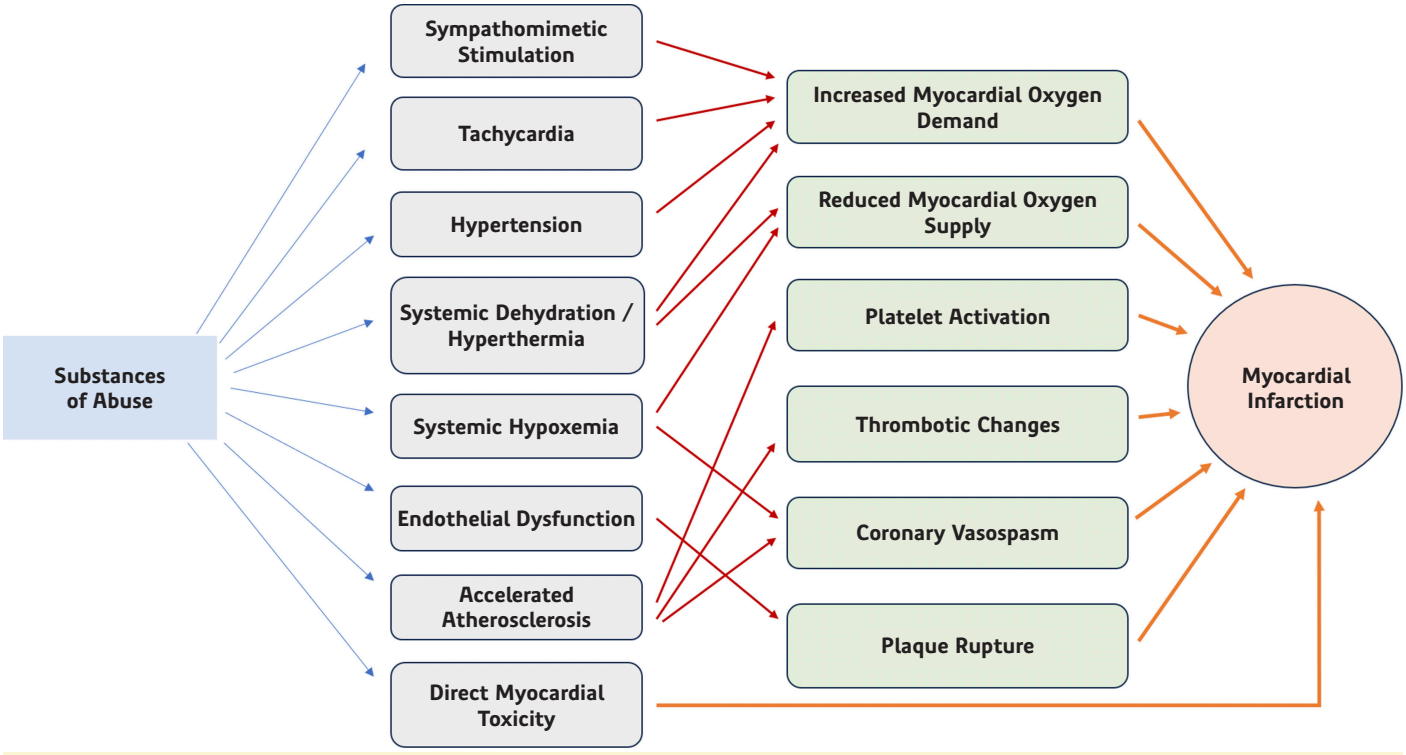



**Figure 1.** Proposed pathophysiological mechanisms underlying substance-induced myocardial infarction.

hand, they may have adverse effects because of their tendency to delay the absorption of antithrombotic agents.[29] Because opioids reduce gastrointestinal transit, illicit opioid use in patients receiving antithrombotic therapy may delay the onset of the drugs' effects. This may be particularly important in patients with a history of MI or other ischemic conditions.

A meta-analysis conducted in an Iranian population examined the association between morphine dependence and MI and concluded that opioid dependence was closely associated with MI.[30] In another retrospective observational study, patients diagnosed with ST-elevation MI were divided into two groups: those with opioid dependence and those without. The study found no significant difference in in-hospital mortality rates between patients with and without opioid dependence. However, opioid-dependent patients had a longer duration of hospitalization.[31]

According to a study by Pavlidis et al.,[32] in which 113 intravenous heroin users were followed for more than 3 years, one case of MI was identified. The study does not adequately demonstrate an association between heroin use and MI. Furthermore, the limited number of detailed studies examining the association between heroin use and MI means that knowledge on this subject remains limited.

Opioids may also cause cardiac arrhythmias and infective endocarditis to varying degrees.[28] Methadone, a potent opioid agonist, can cause QT interval prolongation and torsades de pointes at high doses, whereas oxycodone and tramadol, the latter of which is not a typical opioid agonist but belongs to the class of centrally acting analgesics, may cause these effects to a lesser extent.[33] Opioid abuse, particularly involving injectable formulations, can lead to valvular endocarditis caused by bacterial and fungal infections.[28] Cardioembolic stroke associated with endocarditis has also been reported in intravenous heroin users.[28]

**Cannabis and Synthetic Cannabinoids**

Cannabis, derived from the plant Cannabis sativa, and synthetic cannabinoids exert their effects in the body through cannabinoid receptors 1 and 2 (CB1 and CB2).[34,35] CB1 receptors are widely distributed throughout the central nervous system and modulate the release of several neurotransmitters, including norepinephrine, dopamine, GABA, and serotonin. CB2 receptors, meanwhile, are widely distributed throughout the immune system and exert regulatory effects on immune and inflammatory responses.[36]

The three cannabis-derived drugs approved for use by the FDA are cannabidiol, dronabinol, and nabilone. Cannabidiol has been approved for the treatment of seizures associated with certain childhood-onset syndromes, including Dravet syndrome, tuberous sclerosis complex, and Lennox-Gastaut syndrome. Dronabinol is used in the treatment of HIV-associated anorexia and chemotherapy-induced nausea and vomiting, for which nabilone is also approved.[36]

The legal status of cannabis varies by country. Uruguay, Canada, the United States, and Thailand are among the countries that have legalized the recreational use of cannabis.[37] This legalization has led to increased cannabis use, and research on its cardiovascular effects has become more widespread.[1]

Synthetic cannabinoids are compounds found in products marketed as "Spice" and "K2" and include substances such as JWH-018, JWH-073, AM-2201, and HU-210.[38] Compared with tetrahydrocannabinol (THC), the active component of cannabis, synthetic cannabinoids exert a stronger agonist effect on CB1 receptors. Consequently, these substances may be more likely than cannabis to cause myocardial ischemia and other cardiovascular conditions.[39]

When considering the cumulative effects associated with long-term use of cannabis and its derivatives, metabolic effects related to appetite stimulation and inflammatory effects mediated primarily through the CB2 receptor appear to be more prominent than cardiovascular effects.[40] Cardiovascular effects generally include changes in heart rate and coronary perfusion associated with acute use, leading to increased myocardial oxygen demand and potentially resulting in myocardial ischemia.[5,40] Furthermore, the risk of MI has been reported to increase fivefold within the first hour after cannabis use.[40]

Two systematic reviews and meta-analyses published in recent years have yielded inconsistent findings regarding statistical significance. Theerasuwipakorn et al.[41] found no significant association between cannabis use and acute MI among the 20 studies included in their analysis (pooled odds ratio [OR], 1.29; 95% CI, 0.80–2.08). In a more recent meta-analysis that included 24 studies, a significant association was found between cannabis use and acute coronary syndrome (RR, 1.29; 95% CI, 1.05–1.59).[42] The differences between the findings of these two studies may be attributable to differences in the cardiovascular outcomes assessed, the measures of effect used (RR and OR), and the study designs included.

The Coronary Artery Risk Development in Young Adults (CARDIA) study found that more than 80% of participants had used cannabis at some point in their lives, whereas only a very small proportion continued to use it into middle age. In this study, cannabis use was associated with behaviors such as polyphagia and smoking; however, no increased risk of cardiovascular events was observed compared with nonusers.[43] In this study, cannabis use was assessed based on self-reports, and the effect of cannabis on acute coronary heart disease was not investigated.

According to the current literature, more than 50 case reports have described MI associated with the use of cannabis and synthetic cannabinoids.[1] This number appears to be higher than the number of reported cases of MI associated with the use of other illicit substances. Although this does not clearly establish an association between cannabis and synthetic cannabinoids and MI, it provides some insight from a clinical practice perspective.

**Performance-Enhancing Hormones (Anabolic-Androgenic Steroids)**

With the isolation of testosterone and the synthesis of new androgenic compounds in the 1930s, anabolic-androgenic steroids (AAS) began to be used by athletes.[44] Initially used primarily by athletes, these hormones have become increasingly common among nonprofessional individuals for bodybuilding purposes over the years.[44,45] However, their widespread use has been accompanied by undesirable adverse effects and complications.

The effects of AAS on the cardiovascular system have been investigated in both in vitro and clinical studies. According to these studies, adverse cardiovascular effects include atherosclerosis,

thromboembolism, hypertension, coronary spasm, vascular calcification, cardiac hypertrophy, cardiomyopathy, dyslipidemia, and arrhythmias.[46,47]

A cohort study conducted at fitness centers in Denmark evaluated men who used AAS. The study included 1,189 AAS users and 59,450 control subjects, who were followed for an average of 11 years. The incidence of MI among AAS users was found to be three times higher than that in the control group.[48]

A study comparing cardiac function in young adult weightlifters who used AAS with those who did not showed that left ventricular systolic and diastolic function was significantly lower among athletes using AAS. In addition, coronary artery plaque volume, which is considered an indicator of coronary atherosclerosis, was significantly higher in AAS users. The severity of atherosclerosis was also reported to be associated with the duration of use and cumulative dose.[49] Taken together, these findings suggest that AAS use may contribute to the progression of atherosclerosis and, consequently, the occurrence of MI. Furthermore, coronary artery plaque volume may increase depending on the dose and duration of AAS use.

### Medical Treatment Approaches in Acute Coronary Syndromes Associated with Substance Abuse

#### Beta-Blocker Use and Controversial Mechanisms

The use of beta-blockers in the treatment of MI caused by substances that increase sympathetic activity, particularly cocaine, remains controversial. This controversy primarily arises from the concern that beta-blockade without concurrent alpha-receptor blockade may lead to vasoconstriction and increased blood pressure.[50] Ultimately, impaired coronary perfusion may further exacerbate ischemia. However, the 2014 AHA/ACC guidelines recommend that beta-blockers not be administered to patients using cocaine or methamphetamine who show signs of acute toxicity.[51] Furthermore, labetalol and carvedilol, which also have alpha-blocking activity, may be considered in the treatment of this condition.[50] Nevertheless, there are no clear guidelines regarding their use. A meta-analysis examining beta-blocker use in patients with cocaine-related chest pain divided patients into two groups, those who received beta-blockers and those who did not, and found no significant difference between the groups.[52] Another meta-analysis evaluated patients with cocaine-related chest pain and a history of cocaine use, dividing them into groups according to beta-blocker use, and similarly found no significant difference between the groups.[53] The limitations of these studies include the inclusion of patients presenting with chest pain, uncertainty regarding the specific beta-blocker subgroups used, and the unknown doses of cocaine consumed. More comprehensive studies may help clarify this controversy.

#### The Role of Benzodiazepines in Treatment

Benzodiazepines may be considered in the treatment of chest pain associated with cocaine use because of their potential to reduce sympathetic activity and provide anxiolytic effects. In a prospective study of patients presenting with cocaine-induced chest pain, nitroglycerin alone was compared with the combination of nitroglycerin and lorazepam, and a significant reduction in chest pain was observed in patients who received lorazepam in addition to nitroglycerin.[54] Another prospective study evaluated diazepam, nitroglycerin, and the combination of these agents and found no significant difference among the groups.[55] The AHA guidelines published in 2020 state that benzodiazepines may be beneficial in cases of cocaine-induced chest discomfort, hypertension, and tachycardia.[56] The differences between the findings of these two studies may be attributable to their small sample sizes, differences in the drugs being compared, and variations in the duration and dosage of substance use among the participating patients.

## Conclusion

MI remains one of the leading causes of morbidity and mortality worldwide. The incidence of MI not only increases with advancing age but is also steadily rising among young adults.[6] In young adults, excluding genetic factors, dyslipidemia, obesity, diabetes, smoking, and substance use are common risk factors for MI.[57] MI phenotypes in young adults include plaque rupture, embolism, hypercoagulability, coronary vasospasm, drug- and substance-induced coronary artery dissection, and spontaneous coronary artery dissection. Although substances of abuse contribute to the development of MI through different mechanisms, they may lead to common pathophysiological outcomes. These common outcomes include an imbalance between myocardial oxygen supply and demand, endothelial dysfunction, and thrombosis. Furthermore, these effects may vary depending on the pharmacological properties of the substances, route of administration, dose, and frequency of use.

For example, cocaine and cannabis use are associated with a marked increase in the risk of MI during the first few hours after use.[10,40] In contrast, AAS use may lead to a greater increase in MI risk depending on the dose and duration of use.[49] These findings also indicate that there may be no safe dose of these substances with respect to the risk of MI and that their effects may occur not only with long-term use but also acutely.

Limitations in clearly establishing the relationship between substance use and MI include inaccurate or incomplete patient reporting of substance use, inability to determine the exact dose and frequency of use, polysubstance use, confounding by other cardiovascular risk factors, regional variations in substance composition, inadequate diagnostic testing and toxicological confirmation, and selection bias in study populations. In light of these factors, data on certain substances, such as Captagon and synthetic cannabinoids, are largely derived from case reports. Further research in this field and the generation of evidence-based data would be beneficial from a public health perspective.

Consequently, substance use should be considered a potential trigger or etiological factor in the development of MI, particularly in young adults and adolescents without traditional cardiovascular risk factors or known genetic predispositions.

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**Peer-review:** Externally peer-reviewed.

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# Energy Drink Consumption and Premature Coronary Events: Two Case Reports and a Systematic Patient-Level Review of 31 Published and Newly Reported Patients

## Enerji İçeceği Tüketimi ve Prematür Koroner Olaylar: İki Olgu Sunumu ile Yayımlanmış ve Yeni Bildirilen Toplam 31 Hastanın Hasta Düzeyinde Sistematik Derlemesi

**ABSTRACT**

Energy drink (ED) consumption has been temporally associated with acute coronary events, particularly in young individuals; however, causality remains uncertain. We aimed to characterize coronary events reported following ED consumption and evaluate their clinical features, underlying mechanisms, and causal plausibility. Two new cases of premature myocardial infarction (MI) were combined with cases identified through a systematic review of the literature published through September 2026. Patient-level data on ED exposure, cardiovascular risk factors, coronary mechanisms, and clinical outcomes were analyzed. Causality was assessed using an adapted World Health Organization–Uppsala Monitoring Centre (WHO-UMC) framework. The cohort comprised 31 male patients (29 previously published cases and two new cases; mean age, 25.6 ± 5.4 years). Twenty-eight patients (90.3%) met strict criteria for MI or acute coronary syndrome (ACS), and 25 (80.6%) presented with ST-segment elevation myocardial infarction (STEMI). Coronary thrombosis was documented in 13 patients (41.9%), coronary vasospasm in eight (25.8%), and spontaneous coronary artery dissection in three (9.7%). Additional exposures or physiological stressors were identified in 22 patients (71.0%). The initial left ventricular ejection fraction was below 50% in 10 of the 19 evaluable patients (52.6%). Cardiac arrest occurred in six patients (19.4%), and two patients died (6.5%). Causality was classified as probable/likely in five patients (16.1%), possible in 23 (74.2%), and unlikely in three (9.7%). Coronary events temporally associated with ED consumption predominantly affected young men, involved heterogeneous mechanisms, and were associated with potentially severe outcomes. The frequent presence of coexisting risk factors and limited causal evidence preclude definitive attribution of these events to ED consumption. Prospective controlled studies are needed to clarify the independent cardiovascular risks associated with ED consumption.

**Keywords:** Caffeine, case report, coronary thrombosis, energy drinks, myocardial infarction, thrombophilia.

**ÖZET**

Enerji içeceği tüketimi, özellikle genç bireylerde akut koroner olaylarla zamansal olarak ilişkilendirilmiştir; ancak nedensellik ilişkisi belirsizliğini korumaktadır. Bu çalışmada, enerji içeceği tüketimi sonrasında bildirilen koroner olayların klinik özelliklerinin, altta yatan mekanizmalarının ve nedensellik ilişkisinin değerlendirilmesi amaçlandı. Prematür miyokard enfarktüsü (ME) gelişen iki yeni olgu, Eylül 2026'ya kadar yayımlanan olguların sistematik derlemesine dahil edildi. Enerji içeceği maruziyeti, kardiyovasküler risk faktörleri, koroner mekanizmalar ve klinik sonuçlara ilişkin veriler hasta düzeyinde analiz edildi. Nedensellik ilişkisi, uyarlanmış Dünya Sağlık Örgütü–Uppsala İzleme Merkezi (WHO-UMC) sınıflandırması kullanılarak değerlendirildi. Toplam 31 erkek hasta (daha önce yayımlanmış 29 olgu ve iki yeni olgu; ortalama yaş 25,6±5,4 yıl) değerlendirildi. Hastaların 28'i (%90,3) kesin ME/akut koroner sendrom tanı kriterlerini karşılarken, 25'inde (%80,6) ST segment elevasyonlu ME saptandı. Koroner tromboz 13 hastada (%41,9), koroner vazospazm sekiz hastada (%25,8) ve spontan koroner arter diseksiyonu üç hastada (%9,7) bildirildi. Yirmi iki hastada (%71,0) ek maruziyet veya fizyolojik stres faktörü saptandı. Başlangıç sol ventrikül ejeksiyon fraksiyonu, değerlendirilebilen 19 hastanın 10'unda (%52,6) %50'nin altındaydı. Altı hastada (%19,4) kardiyak arrest gelişti ve iki hasta (%6,5) hayatını kaybetti. Nedensellik ilişkisi beş hastada (%16,1) kuvvetle muhtemel, 23 hastada (%74,2) olası ve üç hastada (%9,7) düşük olasılıklı olarak sınıflandırıldı. Enerji içeceği tüketimiyle zamansal olarak ilişkili koroner olaylar ağırlıklı olarak genç erkeklerde bildirilmiş olup farklı koroner mekanizmalar ve potansiyel olarak ciddi klinik sonuçlarla karakterizedir. Eşlik eden risk faktörlerinin sık görülmesi ve nedenselliğe ilişkin kanıtların sınırlı olması, bu olayların doğrudan enerji içeceği tüketimine bağlanmasını engellemektedir. Enerji içeceği tüketiminin bağımsız kardiyovasküler riskinin belirlenmesi için prospektif kontrollü çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Kafein, olgu sunumu, koroner tromboz, enerji içecekleri, miyokard enfarktüsü, trombofili.

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Energy drinks (EDs) are widely consumed, particularly among adolescents and young adults, and typically contain caffeine, taurine, guarana, sugars, glucuronolactone, and other bioactive compounds.[1–3] Acute or excessive ED consumption has been associated with elevated blood pressure, increased sympathetic activity, endothelial dysfunction, platelet activation, and cardiac arrhythmias.[1–3] These physiological effects provide plausible mechanisms for coronary vasospasm, thrombosis, and myocardial ischemia. However, a causal relationship between ED consumption and acute coronary syndromes (ACS) has not been established.[1–5]

Controlled human studies have demonstrated acute hemodynamic and electrophysiological effects following ED consumption. In a randomized, placebo-controlled crossover trial, Svatikova et al.[6] reported significant increases in systolic and diastolic blood pressure, accompanied by a marked increase in plasma norepinephrine concentrations. Similarly, a randomized crossover trial demonstrated that high-volume ED consumption resulted in greater corrected QT interval (QTc) prolongation and a more sustained increase in systolic blood pressure than consumption of a caffeine-matched control beverage.[7] These findings suggest that the cardiovascular effects of EDs may extend beyond those attributable to caffeine alone.

Case reports have described myocardial ischemia and myocardial infarction (MI) temporally associated with ED consumption, predominantly in young individuals.[5,8–35] In 2016, Lippi et al.[5] identified eight such cases but emphasized that the available evidence was insufficient to establish causality. Although additional cases have since been reported, a comprehensive patient-level synthesis examining exposure characteristics, concurrent risk factors, individual susceptibility, underlying coronary mechanisms, and clinical outcomes is still lacking. Furthermore, the quality of reporting and the strength of evidence supporting a causal association have not been systematically evaluated.

The present study aimed to systematically characterize published cases of MI and other acute coronary ischemic events temporally associated with ED consumption, with a focus on exposure patterns, coexisting cardiovascular risk factors, potential coronary mechanisms, and clinical outcomes. We also report two cases involving detailed etiological investigations and longitudinal follow-up. As a secondary objective, we explored the feasibility of using a structured causality assessment to evaluate the strength of the reported associations while explicitly acknowledging the methodological limitations inherent in case-report evidence.

## Methods

### Study Design and Index Cases

This study comprised two components: (1) two original case reports of young men presenting with premature MI temporally associated with energy drink (ED) consumption and (2) a systematic review and patient-level analysis of previously published cases. The systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[36] The review protocol was not prospectively registered.

Both index patients were evaluated at the Department of Cardiology, Ege University. Clinical records were comprehensively reviewed to obtain information on demographic characteristics, cardiovascular risk factors, family history, ED consumption patterns, concomitant use of caffeine, alcohol, and other substances, and potential precipitating factors. The diagnostic evaluation included biochemical, thrombophilia, and autoimmune investigations; electrocardiography, echocardiography, and cardiac magnetic resonance imaging (MRI); and coronary angiographic findings. Revascularization strategies, treatments, and longitudinal clinical outcomes were also assessed.

Written informed consent for the publication of clinical information and images was obtained from both patients. The reporting completeness of the index cases was assessed using the CAse REport (CARE) checklist (Supplementary Table 1).[37]

### Literature Search Strategy

A systematic literature search was conducted in PubMed/MEDLINE, Web of Science Core Collection, Scopus, and TR Dizin (ULAKBİM) from database inception through September 2026. The search aimed to identify case reports and case series describing MI, acute coronary syndrome (ACS), myocardial ischemia, coronary thrombosis, coronary vasospasm, spontaneous coronary artery dissection (SCAD), or severe myocardial injury temporally associated with ED consumption.

Database-specific search strategies incorporating Medical Subject Headings (MeSH), where applicable, and free-text terms are provided in the Supplementary Material. The reference lists of eligible publications and relevant narrative and systematic reviews were manually screened. Forward and backward citation tracking was also performed to identify potentially eligible letters, brief reports, conference abstracts, and case series that were not retrieved through database searches. No restrictions were imposed on publication date or language.

## ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| CARE | CAse REport |
| ECG | Electrocardiogram |
| ED | Energy drink |
| FH | Familial hypercholesterolemia |
| LAD | Left anterior descending artery |
| LDL-C | Low-density lipoprotein cholesterol |
| LGE | Late gadolinium enhancement |
| LV | Left ventricular |
| LVEF | Left ventricular ejection fraction |
| MeSH | Medical Subject Headings |
| MI | Myocardial infarction |
| MINOCA | Myocardial infarction with nonobstructive coronary arteries |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| NT-proBNP | N terminal pro brain natriuretic peptide |
| PAI-1 | Plasminogen activator inhibitor-1 |
| PCI | Percutaneous coronary intervention |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QTc | QT interval |
| STEMI | ST-segment elevation myocardial infarction |
| WHO-UMC | World Health Organization–Uppsala Monitoring Centre |

Two reviewers (MK and ZK) independently screened titles, abstracts, and full-text articles for eligibility. Disagreements were resolved through consensus. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

**Eligibility Criteria and Case Selection**

Reports were eligible for inclusion if they described an individual patient or a case series with extractable patient-level data in which ED consumption preceded a clinically documented coronary ischemic event or severe myocardial injury. Eligible clinical presentations included MI, ACS, myocardial ischemia, coronary thrombosis, coronary vasospasm, SCAD, and severe myocardial injury supported by objective clinical findings.

No maximum interval between ED exposure and symptom onset was prespecified. Instead, the temporal plausibility of the association was evaluated during the structured causality assessment. Reports describing exclusively noncardiovascular toxicity or nonischemic cardiovascular manifestations without evidence of myocardial ischemia or injury were excluded.

For analytical purposes, eligible events were categorized as either strict MI/ACS events or broader myocardial ischemia/severe myocardial injury events according to the diagnostic criteria described below. Each patient described in a multipatient publication was included as an individual observation. When multiple publications described the same patient, duplicate records were identified and reconciled, and the most comprehensive primary report was retained.

**Data Extraction**

Patient-level data were extracted by two reviewers (MK and ZK) using a standardized data collection framework and cross-checked for accuracy. The following variables were collected when available:

- Publication characteristics: First author, year of publication, and country.
- Patient characteristics: Age, sex, smoking status, conventional cardiovascular risk factors, comorbidities, and family history of premature coronary artery disease (CAD).
- ED exposure: Beverage brand, quantity consumed, estimated caffeine content, consumption pattern (acute, repeated/chronic, or repeated/chronic with acute binge consumption), and interval between exposure and symptom onset.
- Concomitant exposures and potential triggers: Coffee or other caffeine sources, alcohol, recreational drugs, prescription stimulants, performance-enhancing substances, physical exertion, and other physiological stressors.
- Laboratory and clinical findings: Thrombophilia and homocysteine test results, presenting symptoms, electrocardiographic findings, cardiac troponin measurements, and MI phenotype.

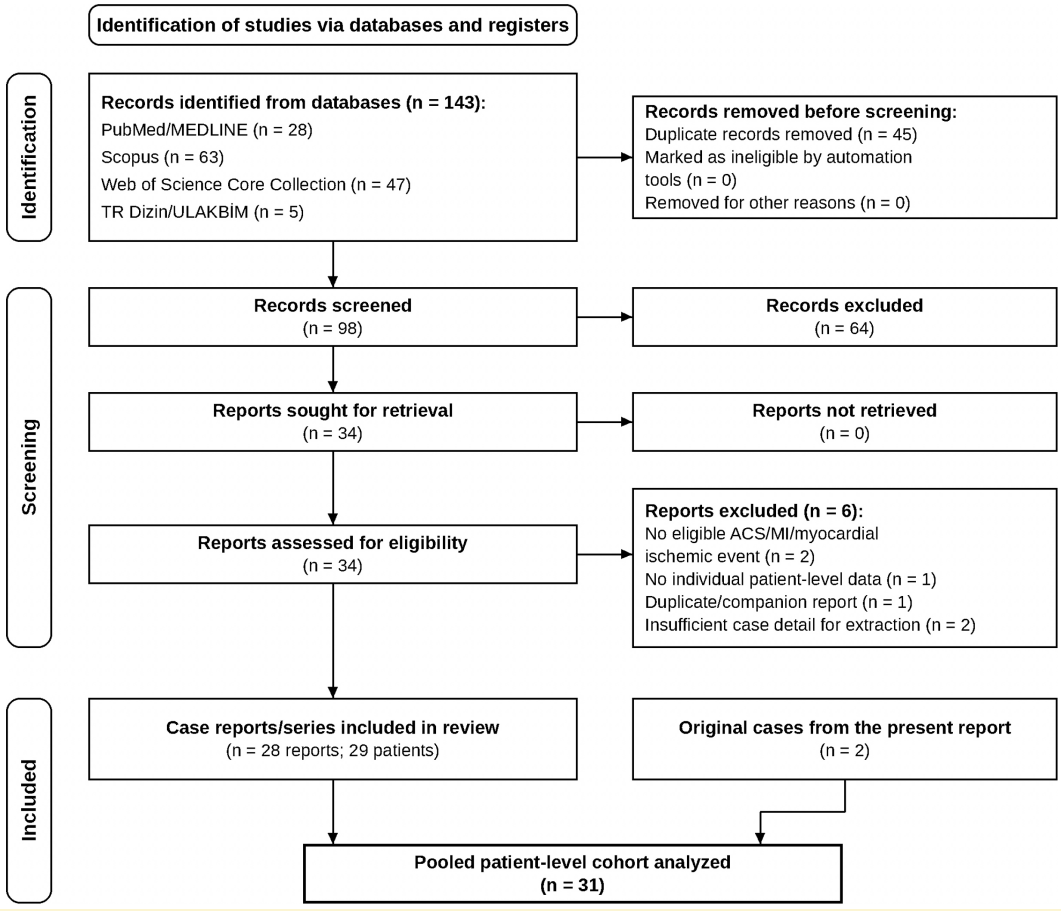



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram illustrating study identification, screening, eligibility assessment, and inclusion. Twenty-nine previously published cases and the two index cases were included (n=31).

TR Dizin, Turkish Academic Network and Information Center National Citation Index.

- Cardiac imaging and coronary findings: Initial and follow-up left ventricular ejection fraction (LVEF), coronary angiographic findings, and proposed coronary mechanisms, including thrombosis, vasospasm, SCAD, or atherosclerotic plaque-related disease.
- Management and outcomes: Pharmacological treatment, revascularization, in-hospital complications, and follow-up outcomes.

Caffeine exposure was recorded as reported in the original publication or, when sufficient product information was available, estimated using the reported beverage volume and manufacturer-specified caffeine concentration. Caffeine exposure was expressed as a daily amount for chronic consumption and as an amount per episode for acute consumption.

When a numerical range was reported for caffeine exposure or LVEF, the midpoint of the range was used. For reported ranges of container counts, the lower bound was retained. The first available quantitative LVEF measurement was designated as the initial LVEF.

Coronary thrombosis was recorded only when thrombus formation was explicitly described in the original report. Potential modifying factors included tobacco use, alcohol consumption, additional caffeine sources, psychoactive or performance-enhancing substances, physical exertion, and physiological stressors, such as severe vomiting, dehydration, trauma, sleep deprivation, or psychological stress.

Variables that could not be reliably determined from the original publication were classified as not reported rather than inferred. The complete patient-level dataset is provided in Supplementary Table 2.

**Causality Assessment**

The association between ED exposure and the reported cardiovascular event was evaluated using an adapted version of the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) system for standardized causality assessment.[38] Two reviewers (MK and ZK) independently evaluated each case, and disagreements were resolved through consensus.

The assessment considered the temporal relationship between ED exposure and symptom onset, the presence of alternative etiologies, concurrent exposures, and available information on the clinical course following ED cessation. Cases were classified as Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified, or Unassessable/Unclassifiable.

The principal operational criteria were as follows:

- Probable/Likely: A clinically plausible temporal relationship between ED exposure and the event, with no major competing etiology. The absence of recurrence following ED cessation was considered supportive when documented.
- Possible: A plausible temporal relationship accompanied by one or more credible alternative explanations, including established atherosclerotic disease, inherited or acquired thrombophilia, concomitant alcohol or stimulant exposure, another major physiological trigger, or an alternative nonischemic diagnosis that had not been adequately excluded.
- Unlikely: A weak temporal association combined with a substantially more compelling alternative etiology.
- Conditional/Unclassified: An event for which additional information was required to allow a more definitive causality assessment.
- Unassessable/Unclassifiable: A report containing insufficient or contradictory information that precluded reliable assessment.

No case was classified as Certain because of the nonspecific nature of the clinical events, the limitations of the available evidence, and the absence of sufficiently definitive evidence of causality. Individual causality classifications and their supporting rationales are presented in Supplementary Table 3.

**Definition of Outcomes**

The overall cohort comprised patients with MI, ACS, other coronary ischemic events, or severe myocardial injury temporally associated with ED exposure. The strict MI/ACS category included cases diagnosed by the original authors as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), myocardial infarction with nonobstructive coronary arteries (MINOCA), or unstable angina. The broader myocardial ischemia/severe myocardial injury category additionally included patients with objective evidence of myocardial ischemia or injury, such as electrocardiographic abnormalities, elevated cardiac biomarkers, ventricular dysfunction, or hemodynamic compromise, for whom MI had not been clearly diagnosed by the original authors.

Clinical outcomes of interest included survival to hospital discharge, cardiac arrest, all-cause mortality, recurrent cardiovascular events, and recovery or persistence of left ventricular (LV) systolic dysfunction during follow-up.

**Methodological Quality Assessment**

The methodological and reporting quality of eligible published case reports was independently assessed by two reviewers (MK and ZK) using the JBI Critical Appraisal Checklist for Case Reports.[39]

The checklist evaluates eight domains: (1) patient demographic characteristics, (2) clinical history and timeline, (3) clinical condition at presentation, (4) diagnostic assessment, (5) therapeutic interventions, (6) clinical condition following intervention, (7) adverse or unanticipated events, and (8) key clinical lessons.

Each domain was rated as Yes, No, Unclear, or Not applicable. The Unclear designation was used when the available information was insufficient to determine whether a criterion had been met. Disagreements between reviewers were resolved through consensus.

The appraisal was conducted to characterize the completeness and methodological quality of reporting rather than to determine study eligibility. Accordingly, no report was excluded solely on the basis of its JBI appraisal results. Individual assessments are presented in Supplementary Table 4.

**Statistical Analysis**

Statistical analyses were primarily descriptive and were performed using patient-level data. Continuous variables are

presented as the mean±standard deviation or median with IQR, calculated using Tukey's hinges, depending on the data distribution. Categorical variables are summarized as absolute frequencies and percentages, with denominators reflecting the number of patients for whom data were available for each variable. Patients with and without cardiac arrest and those with reduced LVEF(<50%) and preserved (LVEF ≥50%) initial LV systolic function were compared descriptively; no inferential statistical tests were performed because of the small, selected, and heterogeneous sample of case reports. A sensitivity analysis restricted to patients meeting the strict MI/ACS definition was conducted to assess the robustness of the descriptive findings after excluding broader presentations of myocardial ischemia or severe myocardial injury.

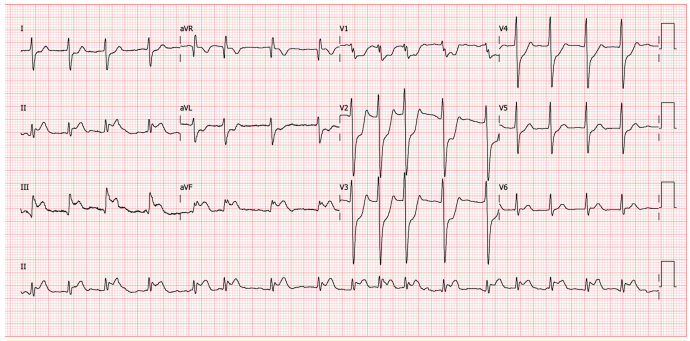



**Figure 2.** Admission electrocardiogram (ECG) of Case 1. Sinus rhythm with ST-segment elevation in leads II, III, and aVF and reciprocal ST-segment depression in leads I and aVL, consistent with acute inferior ST-segment elevation myocardial infarction (STEMI).

## Results

The clinical, laboratory, and etiological characteristics of the two index cases are summarized in Table 1, whereas the characteristics of the pooled cohort are presented in Table 2.

### Case Presentations

#### *Case 1*

A 30-year-old man presented with sudden-onset retrosternal chest pressure and diaphoresis that awakened him from sleep. Approximately 2–3 hours before symptom onset, he had consumed one large can of an ED and one large cup of filtered coffee in rapid succession to remain awake while driving. He reported occasional ED consumption and habitual daily coffee intake. Although the exact ED container size could not be confirmed, manufacturer-reported compositions of commercially available 355–473-mL formulations suggested an estimated intake of 114–151 mg of caffeine, 1,420–1,890 mg of taurine, and 39–52 g of sugar. The additional caffeine exposure from coffee could not be quantified. He denied alcohol and recreational drug use; however, toxicological screening was not performed.

The admission electrocardiogram (ECG) demonstrated ST-segment elevation in the inferior leads with reciprocal ST-segment depression in the anterolateral leads, consistent with acute inferior STEMI (Figure 2). Peak hs-cTnT (hs-cTnT) was 6,120 ng/L. Emergency coronary angiography revealed a long, thrombus-containing lesion causing total occlusion of the proximal dominant left circumflex artery (LCx) (Figure 3A). Following multiple balloon dilatations using a 2.5 × 20-mm balloon, a 3.5 × 24-mm drug-eluting stent was implanted, achieving Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow (Figure 3B). The patient received intravenous tirofiban and dual antiplatelet therapy with aspirin and ticagrelor. Manual thrombus aspiration was not performed, consistent with current recommendations against its routine use during primary percutaneous coronary intervention (PCI).[40] The left anterior descending artery (LAD) was patent with TIMI grade 3 flow; however, its distal segment was incompletely visualized in the projection selected to demonstrate the LCx occlusion (Figure 3). Initial transthoracic echocardiography demonstrated a LVEF of 50%, with inferior, inferoseptal, and posterior wall hypokinesia.

A comprehensive etiological evaluation was undertaken because of the patient's young age (Table 1). Cardiovascular risk factors included active smoking (15 pack-years), obesity (body mass index [BMI], 32.7 kg/m$^2$), and prediabetes. There was no history of hypertension or previously diagnosed dyslipidemia. Low-density lipoprotein cholesterol (LDL-C) was 60 mg/dL, and lipoprotein(a) was 15.3 mg/dL. His mother had hypertension, his father had diabetes mellitus, and his grandfather had experienced a MI at 67 years of age. No family history of premature CAD or familial hypercholesterolemia (FH) was identified.

Thrombophilia testing revealed heterozygosity for the *MTHFR* A1298C variant and homozygosity for the factor XIII V34L variant. The *factor V* Leiden, *prothrombin* G20210A, and *MTHFR* C677T variants were absent, and the plasminogen activator inhibitor-1 (PAI-1) genotype was 5G/5G. Protein C, protein S, and antithrombin activities were within reference ranges. Autoimmune investigations, including tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, anticardiolipin antibodies, and other antiphospholipid antibodies, were negative. Plasma homocysteine was mildly elevated at 14.6 µmol/L.

Cardiac MRI performed one year after the index event demonstrated myocardial thinning and hypokinesia of the LV lateral wall on cine steady-state free precession sequences (Figure 3). Late gadolinium enhancement (LGE) imaging revealed subendocardial enhancement involving the basal-to-mid and apical inferolateral walls, the inferoseptal region, and the inferior papillary muscle, consistent with an ischemic infarction pattern. LVEF on cardiac MRI was 35%. LGE images supported the presence of post-infarction remodeling.

During 26 months of follow-up, the patient remained clinically stable without recurrent cardiovascular events. His weight decreased from 100 to 88 kg, glycated hemoglobin (HbA1c) improved to 5.4%, and N terminal pro brain natriuretic peptide (NT-proBNP) decreased from 623 to 115 ng/L. Nevertheless, he developed post-infarction LV systolic dysfunction, with an LVEF of 30–32% on echocardiography at 12 months. Repeat coronary angiography at 12 months confirmed patency of the proximal LCx stent, with no significant abnormalities in the left main, LAD, or right coronary arteries (Figure 3C). The patient reported complete abstinence from ED consumption following the index event. Nonischemic causes of LV dysfunction were excluded. He was started on optimal guideline-directed medical therapy for reduced LVEF and cardiovascular prevention and remained in New York Heart Association (NYHA) functional class I.

**Table 1.** Clinical, laboratory, and etiological characteristics of the patients

| Characteristic | Case 1 | Case 2 |
|---|---|---|
| Age, sex | 30-year-old man | 28-year-old man |
| Previous cardiovascular disease | None documented | None documented |
| Energy drink-related characteristics | | |
| Energy drink exposure | 1 large can of ED | 1 regular-sized can of ED |
| Additional caffeinated beverage | 1 large cup of filtered coffee | 1 can of caffeinated cold coffee |
| Concomitant exposure to other substances | None | None |
| Alcohol/recreational drug use around the event | None | None |
| Relevant preceding circumstances | Acute ED and coffee consumption during a long drive | Sleepless and highly stressful night preceding ED and cold coffee consumption |
| Interval between ED/caffeine exposure and symptom onset | Approximately 2–3 h | Approximately 2 h |
| Cardiovascular risk factors | | |
| Smoking | Active smoker, 15 pack-years | Active smoker, 10 pack-years |
| Obesity | Present (BMI, 32.7 kg/m$^2$) | Absent (BMI, 22.5 kg/m$^2$) |
| Diabetes mellitus | Absent; prediabetes present | Absent |
| Hypertension | Absent | Absent |
| Dyslipidemia | Normal lipid profile and Lp(a) level | Present (hypercholesterolemia) |
| Lp(a) (mg/dL) | 15.3 | 22 |
| Family history of premature CAD | Family history of CAD in the seventh decade, but no documented premature CAD or FH | Strong family history of premature CAD |
| Acute coronary syndrome-related characteristics | | |
| Index diagnosis | Acute inferior STEMI | Acute anterior STEMI with inferior involvement |
| Peak hs-TnT | 6,120 ng/L | >2,000 ng/L |
| Initial LVEF | 50% | 50% |
| Culprit vessel/angiographic findings | Long thrombotic lesion causing acute total occlusion of the proximal LCx | Approximately 95%–99% thrombotic culprit stenosis in the LAD territory, distal to D1 |
| Other coronary arteries | LMCA, LAD, and RCA normal on follow-up angiography | Approximately 30% proximal LAD stenosis and vasospasm of the nondominant RCA |
| Revascularization | Balloon dilatation followed by implantation of a 3.5 × 24-mm DES in the proximal LCx; TIMI grade 3 flow achieved | PCI with LAD stenting; TIMI grade 3 flow achieved; nitroglycerin administered for RCA vasospasm |
| Adjunctive acute therapy | IV tirofiban; DAPT with aspirin and ticagrelor | DAPT and intensive preventive medical therapy |
| Comorbidities and etiological investigations | | |
| Thrombophilia/prothrombotic findings | Mild hyperhomocysteinemia; heterozygous *MTHFR* A1298C variant; homozygous factor XIII V34L variant | Hyperhomocysteinemia and low folate levels; heterozygous factor V Leiden |
| Homocysteine (μmol/L) | 14.6 | 25.55 |
| Autoimmune evaluation | Negative for ANA, ANCA, and aPL antibodies | Negative for ANA, ANCA, and aPL antibodies |
| Follow-up | | |
| Outcome | Survived | Survived |
| Follow-up ventricular function | Persistent LV systolic dysfunction; LVEF 30%–32% | Long-term LVEF remained at 50% |
| Follow-up coronary imaging | Patent LCx stent; normal LMCA, LAD, and RCA | Patent LAD stents on CCTA; 30%–40% proximal LAD stenosis associated with noncalcified plaque |
| Clinical follow-up | Clinically stable, with no recurrent MI or cardiovascular events at approximately 26 months; complete avoidance of ED consumption | Clinically stable for 4 years; complete avoidance of ED consumption |

ACS, acute coronary syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; aPL, antiphospholipid; BMI, body mass index; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; D1, first diagonal branch; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ED, energy drink; FH, familial hypercholesterolemia; h, hour; hs-TnT, high-sensitivity troponin T; IV, intravenous; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LMCA, left main coronary artery; Lp(a), lipoprotein(a); LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; *MTHFR*, methylenetetrahydrofolate reductase; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

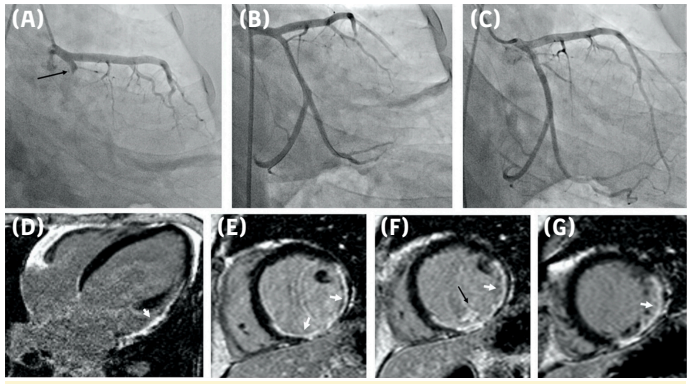



**Figure 3.** Coronary angiographic and cardiac magnetic resonance imaging findings in Case 1. (A) Emergency coronary angiography showing thrombotic total occlusion of the proximal left circumflex artery (arrow). (B) Final angiographic result following percutaneous coronary intervention (PCI), demonstrating Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. (C) Follow-up coronary angiography at 12 months showing a patent stent without restenosis or new lesions. (D–G) Late gadolinium enhancement images in the four-chamber (D) and short-axis (E–G) views, demonstrating subendocardial enhancement involving the basal-to-mid and apical inferolateral walls and inferoseptal region (white arrows), as well as the inferior papillary muscle (black arrow).

### *Case 2*

A 28-year-old man without previously documented cardiovascular disease presented with acute MI following ED consumption (Table 1). After a sleepless night accompanied by substantial psychological stress, he consumed one regular-sized can of the same ED brand as in Case 1, together with one can of a caffeinated ready-to-drink coffee beverage. Approximately two hours later, he developed severe retrosternal chest pain radiating to the left arm, accompanied by diaphoresis. He denied concurrent alcohol, recreational drug, or other stimulant use; however, toxicological screening was not performed.

His cardiovascular risk profile included active smoking (10 pack-years), dyslipidemia (LDL-C, 120 mg/dL), and a strong family history of premature CAD affecting both paternal and maternal relatives. His father had died of MI at 40 years of age. Lipoprotein(a) was 22 mg/dL. The Dutch Lipid Clinic Network score was 3 (possible FH), driven by the personal and family history of premature CAD rather than the LDL-C level; an untreated LDL-C level of 120 mg/dL (3.1 mmol/L) made heterozygous FH clinically unlikely.[41] Genetic testing for FH was not performed. There was no history of diabetes mellitus, hypertension, or obesity (BMI, 22.5 kg/m$^2$).

The admission ECG demonstrated slight ST-segment elevation in leads III and aVF, with more pronounced elevation in leads V3–V6 and reciprocal changes in leads I and aVL, consistent with anterior STEMI with inferior involvement (Figures 4A–B). Peak hs-cTnT exceeded 2,000 ng/L, and initial LVEF was 50%. Coronary angiography demonstrated approximately 30% proximal LAD stenosis and a severe (95%–99%) thrombotic culprit lesion immediately distal to the first diagonal branch (D1) (Figure 5A). PCI involving balloon angioplasty and implantation of two drug-eluting stents (3.0 × 12 mm and 3.0 × 15 mm) restored TIMI grade 3 flow. The D1 ostium exhibited approximately 20% luminal narrowing. The nondominant right coronary artery exhibited angiographic vasoconstriction that resolved following intracoronary nitroglycerin administration. Figure 4C shows the ECG following revascularization.

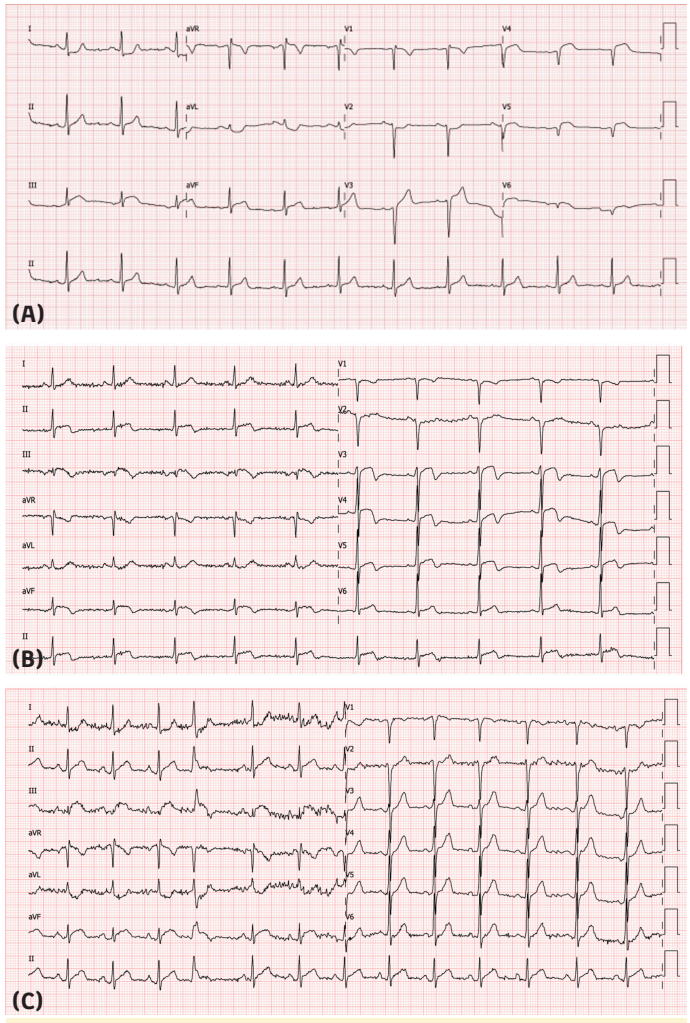



**Figure 4.** Serial ECGs of Case 2. (A) Initial 12-lead ECG obtained in the emergency department, showing slight ST-segment elevation in leads III and aVF, more pronounced elevation in leads V3–V6, and reciprocal changes in leads I and aVL. (B) ECG obtained immediately before PCI, demonstrating persistent ST-segment elevation in leads III, aVF, and V3–V6. (C) ECG obtained after PCI, showing resolution of ST-segment elevation.

Given the premature thrombotic coronary presentation, an extensive etiological evaluation was performed. Heterozygous factor V Leiden was identified, whereas protein C, protein S, and antithrombin activities were within reference ranges. Testing for lupus anticoagulant, anticardiolipin and other antiphospholipid antibodies, antineutrophil cytoplasmic antibodies, and an extended autoimmune panel yielded negative results (Table 1). Plasma homocysteine was elevated at 25.55 µmol/L in association with folate deficiency and subsequently normalized following folate supplementation. Medical therapy included dual antiplatelet therapy, rosuvastatin 40 mg/day, and ezetimibe.

At two years, coronary computed tomography angiography demonstrated an Agatston calcium score of 0, patent LAD stents, and 30%–40% proximal LAD stenosis attributable to noncalcified plaque (Figures 5B–C). During four years of follow-up, the patient experienced no recurrent MI or other major cardiovascular events, and LVEF remained stable at 50%. He reported complete avoidance of ED consumption following the index event.

**Table 2.** Clinical characteristics, energy drink exposure, co-exposures, angiographic findings, and outcomes of the pooled cohort

| Characteristic | Overall cohort | Denominator/definition |
|---|---|---|
| Demographics | | |
| Patients, n | 31 | Entire pooled cohort |
| Age, years, mean±SD (range) | 25.6±5.4 (13–37) | n=31 |
| Age, years, median (IQR) | 26 (24–28) | n=31 |
| Age ≤30 years | 27/31 (87.1%) | Entire cohort |
| Male sex | 31/31 (100%) | Entire cohort |
| Clinical presentation | | |
| ACS type | | |
| STEMI | 25/31 (80.6%) | 25/28 (89.3%) of strict MI/ACS cases |
| NSTEMI | 2/31 (6.5%) | Entire cohort |
| Unstable angina | 1/31 (3.2%) | Entire cohort |
| Broader severe myocardial ischemia/injury only | 3/31 (9.7%) | Included in the broader cohort but not in the strict MI/ACS subgroup |
| Cardiac arrest | 6/31 (19.4%) | Entire cohort |
| Death | 2/31 (6.5%) | 33.3% of patients with cardiac arrest |
| Energy drink exposure patterns | | |
| Predominantly acute exposure | 15/31 (48.4%) | Acute exposure or acute binge consumption |
| Repeated or chronic consumption | 11/31 (35.5%) | Without a separately documented acute binge |
| Repeated/chronic consumption with superimposed acute binge | 5/31 (16.1%) | Chronic or repeated exposure with superimposed acute binge consumption |
| Exposure intensity | Ranged from a single drink to consumption of multiple cans | Reported patterns included several cans consumed within hours and habitual consumption of 4–10 cans/day; exact caffeine doses were inconsistently reported |
| Exposure timing and dose–severity analysis | | |
| Quantifiable interval following discrete acute ED exposure | 11/31 (35.5%) | Entire cohort |
| Interval between ED exposure and symptom onset, h, median (IQR) | 3.0 (2.3–4.8) | Patients with a quantifiable interval (n=11) |
| Interval between ED exposure and symptom onset, h, range | 1–8 | Patients with a quantifiable interval (n=11) |
| Symptoms occurring during or immediately after ED consumption | 2/31 (6.5%) | Additional cases without a quantifiable interval |
| Estimated caffeine exposure in patients with cardiac arrest, mg, median (IQR) | 960 (600–1,600) | Patients with cardiac arrest and estimable caffeine exposure (n=5) |
| Estimated caffeine exposure in patients without cardiac arrest, mg, median (IQR) | 360 (133–680) | Patients without cardiac arrest and with estimable caffeine exposure (n=10) |
| Consumption of ≥5 ED cans/bottles per episode or day among patients with cardiac arrest | 4/5 (80.0%) | Patients with cardiac arrest and classifiable container counts |
| Consumption of ≥5 ED cans/bottles per episode or day among patients without cardiac arrest | 7/21 (33.3%) | Patients without cardiac arrest and with classifiable container counts |
| Co-exposures and modifying factors | | |
| Tobacco exposure | 14/24 (58.3%) | Patients with reported smoking status (n=24) |
| Concomitant alcohol consumption | 8/31 (25.8%) | Entire cohort; documented concomitant consumption |
| Exposure to other psychoactive or performance-enhancing substances | 4/31 (12.9%) | Included cannabis, MDMA, or anabolic-androgenic steroids |
| Acute physical exertion temporally associated with the event | 4/31 (12.9%) | Exertion immediately preceding or coinciding with symptom onset |
| Any recent strenuous physical exertion (broader definition) | 6/31 (19.4%) | Also included recent weightlifting or strenuous drills performed earlier on the same day |
| Severe vomiting, dehydration, trauma, sleep deprivation, or psychological stress | 5/31 (16.1%) | Entire cohort |

**Table 2 (cont).** Clinical characteristics, energy drink exposure, co-exposures, angiographic findings, and outcomes of the pooled cohort

| Characteristic | Overall cohort | Denominator/definition |
|---|---|---|
| Additional coffee/caffeine exposure | 2/31 (6.5%) | Index Cases 1 and 2 |
| ≥1 potential modifying factor | 22/31 (71.0%) | Tobacco, alcohol, other substances, additional coffee, physical exertion, or physiological stressors |
| ≥2 potential modifying factors | 9/31 (29.0%) | Entire cohort |
| ≥3 potential modifying factors | 6/31 (19.4%) | Entire cohort |
| Baseline Cardiovascular Risk Factors and Prothrombotic Conditions | | |
| Conventional cardiovascular risk factors other than smoking (hypertension, diabetes/prediabetes, dyslipidemia, or obesity) | 5/31 (16.1%) | Entire cohort |
| Any baseline comorbidity or cardiovascular/metabolic condition | 13/31 (41.9%) | Included conventional cardiovascular risk factors and other cardiac or noncardiac conditions, thrombophilia, or hyperhomocysteinemia |
| Inherited thrombophilia | 3/11 (27.3%) | Patients who underwent a documented thrombophilia evaluation (n=11) |
| Any thrombophilia-related genetic or laboratory abnormality | 5/11 (45.5%) | Patients who underwent a documented thrombophilia evaluation (n=11) |
| Potential prothrombotic condition, including hypereosinophilic syndrome | 6/12 (50.0%) | Patients evaluated for thrombophilia, including the patient with hypereosinophilic syndrome |
| Hyperhomocysteinemia | 3/31 (9.7%) | Minimum observed prevalence; homocysteine levels were reported in only five patients |
| Coronary angiography, mechanisms, and revascularization | | |
| Documented coronary thrombus | 13/31 (41.9%) | Entire cohort; two acute occlusions without thrombus characterization were excluded from this count |
| Spontaneous coronary artery dissection | 3/31 (9.7%) | Entire cohort |
| Suspected or demonstrated coronary vasospasm | 8/31 (25.8%) | Entire cohort; mechanisms were not mutually exclusive |
| Catheter-based coronary intervention/revascularization | 15/31 (48.4%) | Entire cohort |
| Coronary stent implantation | 10/31 (32.3%) | Entire cohort |
| Coronary artery bypass grafting | 1/31 (3.2%) | Entire cohort |
| Left Ventricular Systolic Function | | |
| Quantitative initial LVEF available | 19/31 (61.3%) | First reported quantitative LVEF measurement |
| Initial LVEF, %, mean±SD (range) | 44.6±11.4 (25–62) | n=19 |
| Initial LVEF, %, median (IQR) | 46 (35.0–52.0) | n=19 |
| Initial LVEF <50% | 10/19 (52.6%) | Patients with quantitative initial LVEF data |
| Initial LVEF ≤35% | 6/19 (31.6%) | Patients with quantitative initial LVEF data |
| LVEF <50% at any documented time point | 11/19 (57.9%) | Patients with quantitative LVEF data available at baseline and/or follow-up |
| LVEF ≤35% at any documented time point | 8/19 (42.1%) | Patients with quantitative LVEF data available at baseline and/or follow-up |
| Quantitative follow-up LVEF available | 8/31 (25.8%) | Patients with reported quantitative follow-up LVEF measurements |
| Follow-up LVEF, %, median (IQR; range) | 48.5 (33.8–56.0; 31–62) | n=8 |

Data are presented as n/N (%) unless otherwise indicated. Denominators vary because reporting of smoking status, co-exposures, thrombophilia testing, and LVEF was incomplete across case reports. Medians and interquartile ranges were calculated using Tukey's hinges. When a numerical range was reported (e.g., LVEF 30%–35% or caffeine exposure 480–640 mg), the midpoint was used; for container counts, the lower bound of the reported range was retained. Strict MI/ACS cases included STEMI, NSTEMI, and unstable angina (n=28). ACS, acute coronary syndrome; CV, cardiovascular; ED, energy drink; h, hour; IQR, interquartile range; LVEF, left ventricular ejection fraction; MDMA, 3,4-methylenedioxymethamphetamine; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; SCAD, spontaneous coronary artery dissection; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

**Table 3.** Distribution of World Health Organization–Uppsala Monitoring Centre (WHO–UMC) causality categories in the pooled cohort

| WHO–UMC category | All patients (n=31), n (%) | Strict MI/ACS cases (n=28), n (%) | Case numbers* |
|---|---|---|---|
| Certain | 0 (0.0) | 0 (0.0) | – |
| Probable/likely | 5 (16.1) | 5 (17.9) | 2, 7, 12, 16, 26 |
| Possible | 23 (74.2) | 20 (71.4) | 1, 3, 4, 5, 6, 8, 9, 10, 11, 13, 14, 15, 17, 18†, 19†, 20, 21, 22†, 23, 25, 27, 30, 31 |
| Unlikely | 3 (9.7) | 3 (10.7) | 24, 28, 29 |
| Conditional/unclassified | 0 (0.0) | 0 (0.0) | – |
| Unassessable/unclassifiable | 0 (0.0) | 0 (0.0) | – |

Case numbers correspond to the patient-level numbering in Supplementary Tables 2–4; Cases 30 and 31 are the two index cases reported in the present study. † Cases included in the broader myocardial ischemia/severe myocardial injury category and excluded from the strict MI/ACS analysis. No case was classified as Certain because myocardial infarction is not a specific pharmacological reaction to ED exposure, and no case involved rechallenge. Category definitions and case-level rationales are provided in Supplementary Table 2. ACS, acute coronary syndrome; ED, energy drink; MI, myocardial infarction; WHO–UMC, World Health Organization–Uppsala Monitoring Centre causality assessment system.

No procedure- or treatment-related adverse events were documented during follow-up in either index patient.

### Clinical Characteristics and Exposure Patterns of the Pooled Cohort

The pooled cohort comprised 31 patients, including 29 previously published cases and the two index cases.[8–35] The literature search and study selection process are summarized in the PRISMA flow diagram (Figure 1). Aggregate cohort characteristics are presented in Table 2, and individual patient-level data are provided in Supplementary Table 2.

All 31 patients were male. The mean age was 25.6±5.4 years, and the median age was 26 years (QR], 24–28 years; range, 13–37 years). Twenty-seven patients (87.1%) were aged ≤30 years. Twenty-eight patients (90.3%) met the strict MI/ACS/coronary-event definition, whereas three (9.7%) were included in the broader myocardial ischemia/severe myocardial injury category. STEMI was the predominant presentation, occurring in 25 patients (80.6% of the overall cohort; 89.3% of the strict subgroup). NSTEMI was reported in two patients (6.5%), and unstable angina was reported in one (3.2%).

ED consumption was classified as acute in 15 patients (48.4%), repeated or chronic in 11 (35.5%), and repeated or chronic with superimposed acute binge consumption in five (16.1%). Exposure intensity varied considerably, ranging from consumption of a single ED to multiple containers within several hours or habitual consumption of 4–10 containers daily.

The interval between ED consumption and symptom onset was inconsistently documented. A quantifiable interval following a discrete acute exposure was available for 11 patients (35.5%), with a median of 3.0 hours (IQR, 2.3–4.8 hours; range, 1–8 hours). In two additional patients (6.5%), symptoms developed during or immediately after consumption. The remaining reports described events following repeated or chronic exposure without sufficient information to determine the precise interval since the most recent ED consumption.

### Cardiovascular Risk Factors, Co-Exposures, and Potential Modifying Factors

Conventional cardiovascular risk factors and preexisting conditions were variably documented. Five patients (16.1%) had at least one conventional cardiovascular risk factor other than smoking, including hypertension, diabetes or prediabetes, dyslipidemia, or obesity. When additional cardiac and noncardiac conditions, thrombophilia, and hyperhomocysteinemia were considered, 13 patients (41.9%) had at least one documented baseline comorbidity or cardiovascular or metabolic condition.

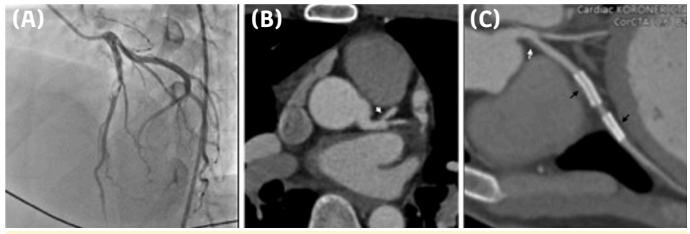



**Figure 5.** Coronary imaging findings in Case 2. (A) Invasive coronary angiography showing a thrombotic lesion in the left anterior descending artery (LAD) adjacent to the first diagonal branch, with preserved distal flow. (B) Axial and (C) curved multiplanar coronary computed tomography angiographic images obtained at two years, demonstrating noncalcified proximal LAD plaque (asterisk in B; white arrow in C) causing 30%–40% stenosis and patent LAD stents (black arrows).

Smoking status was reported in 24 patients, of whom 14 (58.3%) were smokers. Concomitant alcohol consumption was documented in eight patients (25.8%). Four patients (12.9%) reported concomitant exposure to another psychoactive or performance-enhancing substance, including cannabis, 3,4-methylenedioxymethamphetamine (MDMA), or anabolic-androgenic steroids.

At least one potential exposure-related modifying factor, including tobacco use, alcohol consumption, another psychoactive substance, additional coffee consumption, physical exertion, or physiological stress, was identified in 22 patients (71.0%). Nine patients (29.0%) had at least two such factors, and six (19.4%) had three or more.

Acute physical exertion immediately preceding or coinciding with symptom onset was documented in four patients (12.9%). This number increased to six (19.4%) when recent weightlifting or strenuous physical drills performed earlier on the same

day were included. Severe vomiting, dehydration, trauma, sleep deprivation, or psychological stress was reported in five patients (16.1%). Additional caffeine exposure from coffee was documented in both index cases (2/31, 6.5%).

**Thrombophilia and Prothrombotic Conditions**

Thrombophilia investigations were reported in 11 patients. An established inherited thrombophilia was identified in three patients (27.3% of those investigated), including heterozygous factor V Leiden, heterozygous prothrombin G20210A, and protein C deficiency.

When genetic polymorphisms of uncertain clinical significance *MTHFR*, PAI-1, and factor XIII variants) and hyperhomocysteinemia were also considered, five of the 11 investigated patients (45.5%) had at least one abnormal finding. When hypereosinophilic syndrome was included as an acquired prothrombotic condition, a potentially prothrombotic substrate was documented in six of 12 evaluable patients (50.0%).

Hyperhomocysteinemia was identified in three patients (9.7% of the overall cohort), although homocysteine measurements were reported for only five patients. Because thrombophilia and homocysteine testing were neither uniformly performed nor consistently reported, these findings reflect abnormalities observed among selectively evaluated patients and cannot be interpreted as reliable estimates of prevalence within the cohort.

**Coronary Angiographic Findings and Management**

Angiographically documented coronary thrombus was reported in 13 patients (41.9%). In two additional patients, acute coronary occlusion was reported without sufficient characterization of the underlying mechanism. SCAD was identified in three patients (9.7%), whereas coronary vasospasm was suspected or demonstrated in eight (25.8%). The proposed coronary mechanisms were not mutually exclusive. Catheter-based coronary intervention was performed in 15 patients (48.4%), including coronary stent implantation in 10 (32.3%). One patient (3.2%) underwent coronary artery bypass grafting.

**Left Ventricular Function and Clinical Outcomes**

Quantitative initial LVEF data were available for 19 patients (61.3%). The mean initial LVEF was 44.6±11.4%, and the median LVEF was 46% (IQR, 35.0–52.0%; range, 25–62%). Ten of these 19 patients (52.6%) had an initial LVEF <50%, and six (31.6%) had an LVEF ≤35%. Considering both initial and follow-up assessments, 11 of 19 patients (57.9%) had an LVEF <50% at some point, whereas eight (42.1%) had an LVEF ≤35%.

Quantitative follow-up LVEF data were reported for only eight patients (25.8% of the overall cohort). The median follow-up LVEF was 48.5% (IQR, 33.8–56.0%; range, 31–62%), indicating substantial variability in reported ventricular function. Notably, one of the index patients had an initial LVEF of 50% but subsequently developed post-infarction LV systolic dysfunction, with an LVEF of 30–32%.

Cardiac arrest occurred in six patients (19.4%), and two patients died (6.5% of the overall cohort). The mortality rate among patients who experienced cardiac arrest was 33.3%.

**Characteristics of Patients with Cardiac Arrest**

Among the six patients who experienced cardiac arrest, five (83.3%) had at least one additional exposure or physiological stressor. Tobacco exposure was documented in four patients, acute physical exertion in two, concomitant alcohol consumption in one, and MDMA exposure in one. One patient had an established inherited thrombophilia (prothrombin G20210A), and coronary thrombus was documented in two. Quantitative LVEF data were available for only two patients with cardiac arrest, both of whom had an LVEF ≤35%. An additional fatal case was characterized by severe biventricular dysfunction without a reported numerical LVEF.

The median estimated caffeine exposure was 960 mg (iIQR, 600–1,600 mg; n=5) among patients with cardiac arrest and 360 mg (IQR, 133–680 mg; n=10) among those without cardiac arrest. Among patients with classifiable ED container counts, consumption of ≥5 cans or bottles per episode or per day was reported in four of five patients with cardiac arrest (80.0%), compared with seven of 21 patients without cardiac arrest (33.3%). Thus, higher estimated caffeine exposure and greater ED consumption were numerically more frequent among patients who experienced cardiac arrest; however, given the very small sample sizes, these differences are descriptive only and do not support inferential conclusions. These exploratory findings were based on small samples with substantial heterogeneity in beverage composition, exposure duration, concurrent exposures, and reporting completeness.

**Characteristics According to Initial Left Ventricular Ejection Fraction**

Among the 10 patients with an initial LVEF <50%, coronary thrombus was documented in five (50.0%), and six (60.0%) underwent catheter-based coronary intervention. Tobacco exposure was reported in four of the eight patients with available smoking data (50.0%). Concomitant alcohol consumption was documented in four patients (40.0%), and exposure to another psychoactive or performance-enhancing substance was documented in two (20.0%). Six patients (60.0%) had at least one additional exposure or physiological stressor, and two (20.0%) experienced cardiac arrest.

Among the nine patients with preserved initial LVEF (≥50%), coronary thrombus was documented in five (55.6%), tobacco exposure in two of the six patients with available smoking data (33.3%), and at least one additional modifying factor in five (55.6%). No concomitant alcohol consumption or cardiac arrest was reported in this subgroup.

**Sensitivity Analysis Restricted to Strict MI/ACS/Coronary Events**

The sensitivity analysis restricted to the 28 patients meeting the strict MI/ACS/coronary-event definition yielded a mean age of 25.9±5.2 years. Cardiac arrest occurred in four patients (14.3%), and one patient died (3.6%). Quantitative initial LVEF data were available for 17 patients, of whom eight (47.1%) had an LVEF <50% and four (23.5%) had an LVEF ≤35%.

**Causality Assessment**

Using the adapted WHO-UMC framework, five of the 31 patients (16.1%) were classified as Probable/Likely, 23 (74.2%) as Possible, and three (9.7%) as Unlikely. No patient fulfilled the study-

specific criteria for a Certain association, and none was classified as Conditional/Unclassified or Unassessable/Unclassifiable.

Among the 28 patients meeting the strict MI/ACS/coronary-event definition, five (17.9%) were classified as Probable/Likely, 20 (71.4%) as Possible, and three (10.7%) as Unlikely. Both index cases were classified as Possible. Although ED exposure occurred shortly before symptom onset in both cases, each patient had additional cardiovascular risk factors or potentially prothrombotic conditions that provided plausible competing explanations. Individual causality classifications and their supporting rationales are presented in Supplementary Table 3, and the overall distribution of causality categories is summarized in Table 3.

**Discussion**

In this systematic patient-level review, we identified 29 previously published cases of coronary ischemic events or severe myocardial injury temporally associated with ED consumption and added two new cases of premature MI, yielding a pooled cohort of 31 patients.[8–35] The principal findings included a predominance of young men, frequent coexisting cardiovascular risk factors and additional exposures, heterogeneous coronary mechanisms, and clinically significant complications, including cardiac arrest and LV dysfunction. The mean age was 25.6±5.4 years, 87.1% of patients were aged ≤30 years, and all patients were male. Twenty-eight patients (90.3%) met the strict MI/ACS/coronary-event definition, with STEMI accounting for 25 of the 31 cases (80.6%). Coronary thrombus was documented in 13 patients (41.9%), SCAD in three (9.7%), and suspected or demonstrated coronary vasospasm in eight (25.8%). Six patients (19.4%) experienced cardiac arrest, and two (6.5%) died. Among patients with quantitative initial LVEF measurements, 52.6% had an LVEF <50%. Although estimated caffeine exposure was numerically higher among patients who experienced cardiac arrest, the sample size was too small to support statistical inference. Collectively, these observations highlight the heterogeneity of coronary events reported following ED consumption and suggest that ED exposure may interact with individual susceptibility and additional physiological stressors rather than produce a single characteristic pattern of coronary injury.

The two index cases further illustrate the potential importance of underlying cardiovascular susceptibility. Both patients were young male smokers who developed thrombotic STEMI approximately 2–3 hours after consuming a single ED together with a caffeinated coffee beverage. Neither reported excessive ED consumption, indicating that the temporal association was not limited to extreme ED intake. However, both had clinically relevant competing risk factors. The first patient had obesity, prediabetes, and mildly elevated homocysteine concentrations, whereas the second had dyslipidemia, a strong family history of premature CAD, noncalcified coronary plaque, heterozygous factor V Leiden, and hyperhomocysteinemia. The first patient subsequently developed substantial post-infarction LV systolic dysfunction despite angiographically confirmed stent patency. Both cases were classified as Possible according to the adapted WHO-UMC causality framework. Although the close temporal relationship is noteworthy, it does not establish that ED consumption precipitated the events. Indeed, the conventional and prothrombotic risk factors present in both patients could independently explain these events, and ED consumption, with a caffeine content comparable to that of one or two cups of coffee, can at most be considered a possible contributing trigger. ED consumption, potentially combined with additional caffeine intake, sleep deprivation, or psychological stress, may have contributed to an acute physiological response in patients with preexisting cardiovascular vulnerability.

This distinction is fundamental to interpreting the available literature. Of the 31 patients, only five (16.1%) were classified as Probable/Likely, whereas 23 (74.2%) were classified as Possible and three (9.7%) as Unlikely. These classifications reflect the frequent presence of plausible alternative etiologies and the limited information available for causal attribution. ED consumption patterns were also highly heterogeneous: 15 patients (48.4%) had predominantly acute exposure, 11 (35.5%) reported repeated or chronic consumption, and five (16.1%) had chronic consumption with superimposed acute binge exposure. Reported quantities ranged from a single beverage to several containers consumed within hours or habitual consumption of 4–10 containers daily. Consequently, the available evidence does not support the identification of a specific ED dose or caffeine threshold associated with coronary complications.

Among patients with available quantitative exposure data, the median estimated caffeine intake was numerically higher in those who experienced cardiac arrest than in those who did not (960 vs. 360 mg), and consumption of ≥5 ED containers per episode or per day was more frequent (80.0% vs. 33.3%). These descriptive differences were based on only five patients with cardiac arrest and were insufficient to support statistical inference. Moreover, acute and chronic consumption were not directly comparable, and the small sample sizes, variability in beverage formulations, incomplete exposure quantification, and potential publication bias preclude conclusions regarding dose–response relationships or prognostic effects.

Co-exposures and physiological stressors were prominent features of the reported cases. At least one potential modifying factor was documented in 22 patients (71.0%), two or more in nine (29.0%), and three or more in six (19.4%). Smoking was reported in 14 of the 24 patients with available data, concomitant alcohol consumption in eight, and exposure to another psychoactive or performance-enhancing substance in four. Physical exertion, vomiting, dehydration, trauma, sleep deprivation, and psychological stress were also reported. Five of the six patients who experienced cardiac arrest had at least one additional exposure or physiological stressor. These observations raise the hypothesis that the cardiovascular consequences of ED consumption may depend on cumulative stimulant exposure, concurrent physiological demands, and preexisting susceptibility rather than ED quantity alone (Figure 6). Nevertheless, modifying factors were also common among patients with both reduced and preserved initial LVEF, and the available data do not allow estimation of their independent contributions to clinical severity.

Several biological mechanisms could plausibly link ED consumption to acute coronary ischemia. Caffeine, the principal stimulant component of most EDs, antagonizes

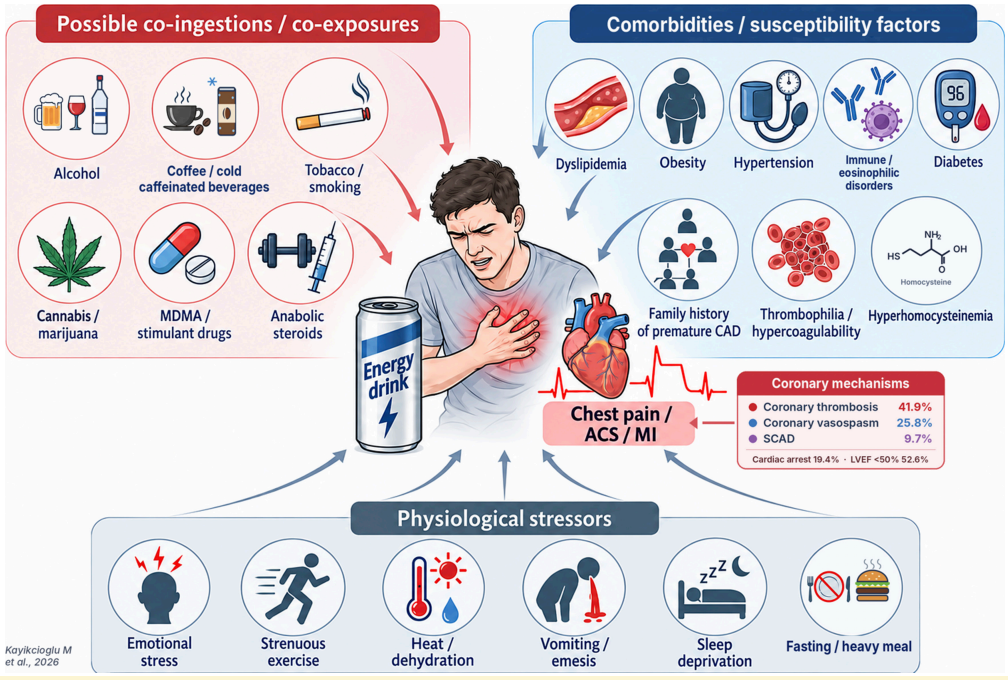



**Figure 6.** Potential modifying factors associated with acute coronary events following energy drink (ED) consumption, including co-exposures, comorbidities, susceptibility factors, and physiological stressors. These factors may accompany coronary events temporally associated with ED consumption but do not establish causality.

CAD, coronary artery disease; MDMA, 3,4-methylenedioxymethamphetamine.

adenosine receptors and can increase sympathetic activity and catecholamine release, potentially increasing arterial pressure, myocardial contractility, and myocardial oxygen demand.[1-2] Alterations in vascular tone, including enhanced vasoconstrictor responses, may contribute to an imbalance between myocardial oxygen supply and demand or facilitate coronary vasospasm in susceptible individuals. Experimental evidence also suggests potential effects on endothelial function and platelet activity. Worthley et al.[3] demonstrated increased platelet aggregation and impaired endothelial function following acute ED consumption in healthy young adults. Such responses could theoretically promote coronary thrombosis, particularly in the presence of endothelial injury, coronary plaque, or an underlying prothrombotic condition.

The cardiovascular effects of EDs may not be entirely attributable to caffeine. Commercial formulations frequently contain taurine, guarana, glucuronolactone, sugars, and other additives, although their concentrations vary substantially among products. Guarana may provide additional caffeine, whereas interactions among beverage constituents could influence acute hemodynamic and electrophysiological responses.[1-3] Controlled studies have demonstrated increased blood pressure and sympathetic activation following ED consumption, as well as greater QTc prolongation and more sustained systolic blood pressure elevation compared with caffeine-matched control beverages.[6,7] Nevertheless, the clinical relevance of these short-term physiological changes to coronary thrombosis or MI remains uncertain. The available evidence supports biological plausibility but does not establish that these mechanisms mediate the coronary events described in individual case reports.

Previous reviews identified substantially fewer coronary events associated with ED exposure. Lippi et al.[5] highlighted the potential association between ED consumption and myocardial ischemia while emphasizing the limitations of case-report evidence in establishing causality. Zacher et al.[18] described presentations involving coronary thrombosis and SCAD, including cases complicated by alcohol consumption and prolonged vomiting. Chami and Di Primio subsequently summarized a broader spectrum of cardiovascular complications, including MI and cardiac arrest.[25] The present study extends these observations through a systematic patient-level synthesis of exposure characteristics, coronary anatomy, coexisting cardiovascular risk factors, potential modifying exposures, ventricular function, clinical outcomes, reporting quality, and structured causality assessments.

The diversity of coronary angiographic findings is particularly relevant to understanding the potential mechanisms underlying these events. Several patients presented with extensive coronary thrombosis despite limited or previously unrecognized underlying atherosclerosis. Benjo et al.[12] reported a large left main coronary artery thrombus following consumption of an ED mixed with vodka. In contrast, Ünal et al.[14] described severe left main coronary artery thrombosis and complete proximal LAD occlusion after consumption of five EDs in a previously healthy 32-year-old man. Other reports, however, documented an identifiable atherosclerotic substrate. Ramcharan et al.[31] described cardiac arrest following acute ED binge consumption in a 24-year-old man, with coronary angiography revealing proximal LAD plaque rupture and superimposed thrombosis. Demir et al.[20] reported coronary vasospasm in the presence of severe fixed LAD stenosis.

At the other end of the spectrum, MI has been reported despite angiographically normal or nonobstructive coronary arteries. Gharacholou et al.[17] described STEMI with normal coronary angiographic findings and subsequent cardiac MRI evidence of

infarction. In contrast, Gordeeva et al.[32] reported MI attributed to diagonal branch vasospasm in an 18-year-old patient with prolonged heavy ED consumption. Reports from Türkiye similarly encompass SCAD, proximal LAD thrombosis, and extensive multivessel coronary thrombosis, sometimes accompanied by alcohol or other substance exposure.[13,14,20–22,26,28,33] Importantly, normal coronary angiographic findings do not establish vasospasm or transient thrombosis as the underlying mechanism without additional supporting evidence. Collectively, these reports suggest that temporally associated coronary events may arise through distinct mechanisms, including plaque-related thrombosis, coronary vasospasm, spontaneous dissection, or thrombosis without clearly documented plaque disruption. Whether ED exposure contributes to the initiation of these events remains unresolved.

The potential contribution of inherited or acquired prothrombotic conditions also warrants consideration. Thrombophilia testing was reported in only 11 patients, of whom three had an established inherited thrombophilia: heterozygous factor V Leiden, heterozygous prothrombin G20210A, or protein C deficiency. When genetic variants of uncertain clinical significance and hyperhomocysteinemia were also considered, five of these 11 patients had at least one reported abnormality. When hypereosinophilic syndrome was included as an acquired prothrombotic condition, a potentially relevant prothrombotic substrate was identified in six of 12 evaluable patients. However, because testing was performed selectively and findings were incompletely reported, these results cannot be interpreted as prevalence estimates or evidence of an increased frequency of these conditions compared with the general population.

Doğan et al.[26] described extensive coronary thrombosis without evidence of plaque rupture or erosion on intravascular ultrasound in a patient with elevated homocysteine levels, homozygous *MTHFR* C677T, and heterozygous PAI-1 4G/5G variants. In our series, the second index patient had heterozygous factor V Leiden and hyperhomocysteinemia, whereas the first had mildly elevated homocysteine levels and *MTHFR* A1298C and factor XIII V34L polymorphisms. These findings require cautious interpretation. Common *MTHFR* polymorphisms are not considered established inherited thrombophilias, and the factor XIII V34L variant has been associated with neutral or potentially protective effects in certain thrombotic settings.[42] Furthermore, factor V Leiden and prothrombin G20210A are more strongly associated with venous thromboembolism than with arterial coronary thrombosis. Hyperhomocysteinemia may also reflect acquired or nutritional factors rather than an independent causal mechanism.

Accordingly, these abnormalities cannot be considered evidence that ED consumption interacted with an inherited thrombophilia to cause coronary thrombosis. A possible interaction among transient sympathetic activation, endothelial dysfunction, platelet reactivity, and individual prothrombotic susceptibility remains a hypothesis requiring investigation in controlled studies. In clinical practice, the evaluation of premature MI should prioritize established cardiovascular risk factors, coronary anatomy, family history, and potential nonatherosclerotic mechanisms, with additional investigations guided by the individual clinical presentation rather than performed indiscriminately.[4]

Another notable observation was the exclusive representation of male patients. This finding may reflect several overlapping factors rather than a sex-specific biological effect of ED consumption. ED use is common among adolescent and young adult males and may coexist with smoking, alcohol consumption, and exposure to other stimulants.[1–4,43] Premature MI also predominantly affects men, particularly in younger age groups.[4] Potential biological differences in caffeine responses have been reported, including sex-related variations in blood pressure and heart rate responses that may be influenced by hormonal status.[44] Caffeine metabolism also varies according to smoking status, hormonal factors, and cytochrome P450 1A2 (*CYP1A2*) activity.[45]

Genetic variations in *CYP1A2*, *AHR*, and *ADORA2A* have been associated with differences in caffeine metabolism, consumption patterns, or physiological sensitivity, although evidence linking these variants to clinical cardiovascular outcomes remains inconsistent.[46] Importantly, publication practices and selective recognition of ED exposure may also contribute to the observed sex distribution. Therefore, the exclusively male composition of the present cohort should not be interpreted as evidence that women are protected against cardiovascular complications potentially associated with ED consumption. Future studies should include participants of both sexes and investigate whether individual differences in caffeine metabolism, adenosine signaling, and cardiovascular susceptibility modify responses to ED consumption.[47]

**Study Limitations**

Several limitations warrant emphasis. First, the evidence was derived predominantly from case reports and small case series, including two reports available only as conference or supplement abstracts. These data correspond to level 4 evidence according to the Oxford Centre for Evidence-Based Medicine classification.[48] Such reports are inherently susceptible to publication, selection, and reporting biases, particularly when an unusual exposure is perceived as potentially associated with a serious clinical event. In the absence of an unexposed comparison group or a defined source population, the present findings cannot establish incidence, relative risk, attributable risk, or a causal relationship between ED consumption and coronary events.

Second, the structured causality assessment was based on an adaptation of the WHO-UMC system, originally developed for adverse drug reactions. This approach has not been validated for complex cardiovascular events following ED consumption and necessarily involves subjective assessments of temporal relationships and competing etiologies. Therefore, the resulting classifications should be interpreted as exploratory judgments regarding the plausibility of the reported associations rather than definitive estimates of causality.

Third, exposure assessment was heterogeneous and predominantly based on retrospective self-reporting. ED brand, container size, caffeine concentration, consumption rate, habitual use, and the interval between exposure and symptom onset were often incompletely documented. In the JBI appraisal, the interval between exposure and symptom onset was unclear in 11 of the 29 published reports. Additional caffeine sources, alcohol, recreational drugs, prescription stimulants, dietary supplements, physical activity, hydration status, and sleep deprivation were

inconsistently reported. Consequently, cumulative stimulant exposure could not be reliably quantified in many cases.

Fourth, clinical investigations and follow-up assessments were not standardized. Smoking status was unavailable for seven patients, thrombophilia testing was not reported for 20, and quantitative LVEF data were unavailable for 12. Coronary angiographic descriptions varied in detail, and intracoronary imaging was performed in only a minority of cases, limiting the ability to differentiate among plaque rupture, plaque erosion, coronary embolism, vasospasm, and other nonatherosclerotic mechanisms. Follow-up duration and assessments of ventricular recovery were also inconsistent. Furthermore, the small sample size, incomplete data, and heterogeneity of reported exposures limit the reliability of exploratory subgroup comparisons, including those examining cardiac arrest and estimated caffeine consumption.

The two index cases also have specific limitations. In Case 1, the exact ED container size could not be confirmed, and both patients consumed additional caffeinated beverages. Toxicological screening and intracoronary imaging were not performed in either case. Consequently, the underlying coronary mechanism, whether plaque rupture, plaque erosion, or thrombus formation on a nonobstructive substrate, could not be determined, and genetic testing for FH was not performed in Case 2. Both patients also had clinically relevant conventional or familial cardiovascular risk factors, making it inappropriate to attribute their coronary events solely to ED consumption. In addition, the more extensive metabolic, genetic, and thrombophilia investigations performed in the index cases, compared with most published cases, may have increased the detection of potentially relevant abnormalities and introduced ascertainment bias.

Finally, publication bias and incomplete exposure ascertainment may substantially distort the apparent clinical spectrum. Reports are more likely to be published when severe or unusual cardiovascular events occur following a recognizable exposure, whereas ED consumption may remain undocumented in routine clinical practice. Therefore, the frequency of recent ED consumption among unselected patients presenting with premature MI, as well as its prevalence relative to comparable individuals without coronary events, remains unknown.

### Clinical Implications and Future Directions

Despite these limitations, the findings support increased attention to ED consumption during the clinical evaluation of adolescents and young adults presenting with ACS or otherwise unexplained myocardial ischemia. Exposure history should include the type and quantity of EDs consumed, timing relative to symptom onset, habitual consumption patterns, additional caffeine sources, and concurrent use of alcohol, recreational drugs, stimulants, or performance-enhancing substances. Recent physical exertion, sleep deprivation, dehydration, and psychological stress should also be considered.

Importantly, identification of ED exposure should not divert attention from established diagnostic pathways or the systematic evaluation of conventional cardiovascular risk factors, atherosclerotic disease, familial predisposition, and nonatherosclerotic coronary mechanisms. In selected patients with premature coronary thrombosis, unexpectedly low atherosclerotic burden, recurrent thrombotic events, or suggestive personal or family histories, targeted investigations for established acquired or inherited prothrombotic conditions may be appropriate.

Future research should move beyond isolated case reports toward prospective studies with standardized assessments of ED exposure, concurrent substance use, cardiovascular risk factors, and coronary imaging findings. Comparative study designs are needed to determine whether ED consumption independently increases the risk of acute coronary events, whether this risk varies by dose or product formulation, and whether identifiable patient characteristics modify individual susceptibility. Mechanistic investigations integrating endothelial function, platelet reactivity, coronary vasomotor responses, and caffeine pharmacogenetics may further clarify the biological relevance of these observations.

## Conclusion

In this systematic patient-level review of 31 patients, coronary ischemic events temporally associated with ED consumption predominantly affected young men and involved heterogeneous mechanisms, including coronary thrombosis, vasospasm, and SCAD. Cardiac arrest, death, and persistent LV dysfunction were reported, although the selected nature of the evidence precludes estimation of their frequency among ED consumers. Conventional cardiovascular risk factors, concurrent stimulant exposure, and physiological stressors were common, and most cases were classified as having only a possible causal association. Within the limitations of level 4 evidence, ED consumption may represent a potential acute trigger in susceptible individuals; however, causality and dose-dependent risk have not been established. Systematic assessment of ED consumption and co-exposure history may be useful in young patients presenting with ACS, while controlled prospective studies are needed to determine whether ED consumption independently contributes to coronary risk.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-44773/TKDA-44773_(0)_Supplementary_Materials.pdf

**Informed Consent:** Written informed consent for the publication of clinical information and accompanying images was obtained from both patients.

**Conflict of Interest:** MK has received honoraria for lectures and consultancy from Abbott, Abdi Ibrahim, Amgen, AstraZeneca, Chiesi, Bayer Schering, Humanis, MSD, Novartis, Pfizer, and Ultragenyx and has participated in clinical trials with Amgen, Ionis, Lilly, MSD, Novartis, Novo Nordisk, and Medpace over the past three years. UC has served as a proctor for Biotronik, Boston Scientific, Medtronic, and Philips. All other authors declare no conflicts of interest.

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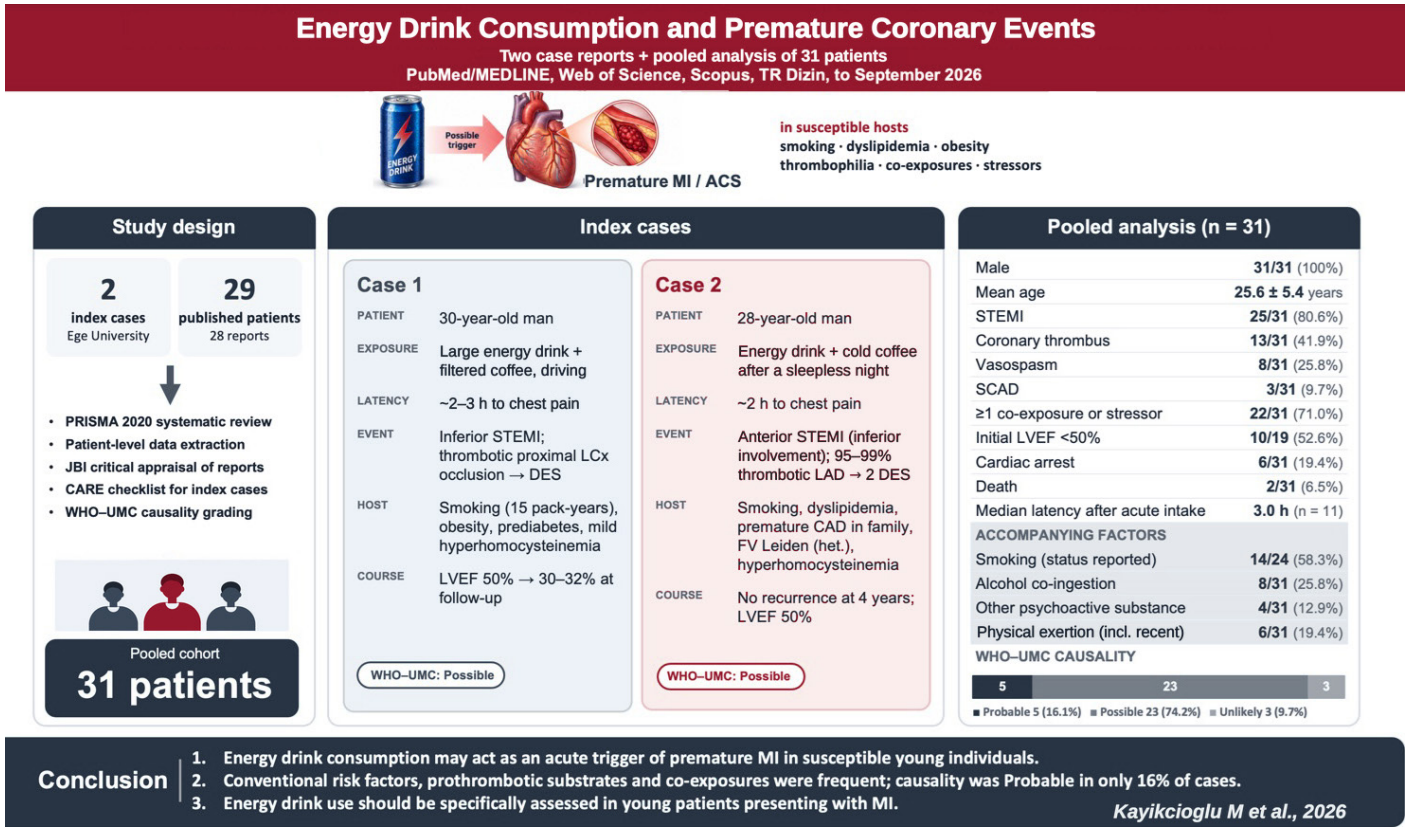
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Energy Drink Consumption and Premature Coronary Events
Two case reports + pooled analysis of 31 patients
PubMed/MEDLINE, Web of Science, Scopus, TR Dizin, to September 2026
Possible trigger
Premature MI / ACS
in susceptible hosts
smoking · dyslipidemia · obesity
thrombophilia · co-exposures · stressors
Study design
2
index cases
Ege University
29
published patients
28 reports
PRISMA 2020 systematic review
Patient-level data extraction
JBI critical appraisal of reports
CARE checklist for index cases
WHO–UMC causality grading
Pooled cohort
31 patients
Index cases
Case 1
PATIENT 30-year-old man
EXPOSURE Large energy drink + filtered coffee, driving
LATENCY ~2–3 h to chest pain
EVENT Inferior STEMI; thrombotic proximal LCx occlusion → DES
HOST Smoking (15 pack-years), obesity, prediabetes, mild hyperhomocysteinemia
COURSE LVEF 50% → 30–32% at follow-up
WHO–UMC: Possible
Case 2
PATIENT 28-year-old man
EXPOSURE Energy drink + cold coffee after a sleepless night
LATENCY ~2 h to chest pain
EVENT Anterior STEMI (inferior involvement); 95–99% thrombotic LAD → 2 DES
HOST Smoking, dyslipidemia, premature CAD in family, FV Leiden (het.), hyperhomocysteinemia
COURSE No recurrence at 4 years; LVEF 50%
WHO–UMC: Possible
Pooled analysis (n = 31)
Male 31/31 (100%)
Mean age 25.6 ± 5.4 years
STEMI 25/31 (80.6%)
Coronary thrombus 13/31 (41.9%)
Vasospasm 8/31 (25.8%)
SCAD 3/31 (9.7%)
≥1 co-exposure or stressor 22/31 (71.0%)
Initial LVEF <50% 10/19 (52.6%)
Cardiac arrest 6/31 (19.4%)
Death 2/31 (6.5%)
Median latency after acute intake 3.0 h (n = 11)
ACCOMPANYING FACTORS
Smoking (status reported) 14/24 (58.3%)
Alcohol co-ingestion 8/31 (25.8%)
Other psychoactive substance 4/31 (12.9%)
Physical exertion (incl. recent) 6/31 (19.4%)
WHO–UMC CAUSALITY
5
23
3
Probable 5 (16.1%) Possible 23 (74.2%) Unlikely 3 (9.7%)
Conclusion
1. Energy drink consumption may act as an acute trigger of premature MI in susceptible young individuals.
2. Conventional risk factors, prothrombotic substrates and co-exposures were frequent; causality was Probable in only 16% of cases.
3. Energy drink use should be specifically assessed in young patients presenting with MI.
Kayikcioglu M et al., 2026

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# Bee Sting–Associated Kounis Syndrome Presenting as Myocardial Infarction: A Case Report and Systematic Review with Age-Based Analysis

## Miyokard Enfarktüsü ile Başvuran Arı Sokmasıyla İlişkili Kounis Sendromu: Olgu Sunumu ve Yaşa Dayalı Analiz İçeren Sistematik Derleme

**ABSTRACT**

Kounis syndrome (KS) is an uncommon acute coronary syndrome triggered by allergic or hypersensitivity reactions. Bee stings are a recognized precipitant, although the available evidence is largely limited to case reports and small case series. We present a 44-year-old man with probable bee sting–associated KS and systematically review published cases, including an exploratory age-based comparison using ≤45 years as the cutoff for myocardial infarction in younger individuals. PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE) and Scopus were searched in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 recommendations. A total of 47 patients were included, comprising 46 previously reported cases and our index case. The mean age was 55.7±13.0 years, and 39/47 patients (83.0%) were male. Symptoms developed within 30 minutes in 29/47 patients (61.7%), and chest pain occurred in 41/47 (87.2%). Type II KS predominated (29/43, 67.4%), while ST-segment elevation myocardial infarction (STEMI) occurred in 37/47 patients (78.7%), and revascularization was performed in 27/47 (57.4%). Cardiogenic shock, cardiac arrest, and rhythm or conduction disturbances occurred in 11/46 (23.9%), 5/46 (10.9%), and 7/46 patients (15.2%), respectively. Recovery at the last reported assessment was documented in 45/46 patients (97.8%), with no reported deaths. No follow-up data were available after the index patient left the hospital against medical advice approximately five hours after presentation. Thirteen patients (27.7%) were aged ≤45 years; age-stratified descriptive analyses did not reveal clear differences in most clinical characteristics; however, interpretation was limited by the small number of younger patients. Bee sting–associated KS may cause severe acute coronary presentations, including in younger individuals. Given the case-based and heterogeneous nature of the evidence, these findings should be interpreted cautiously and confirmed in systematically collected cohorts.

**Keywords:** Bee sting, Kounis syndrome, myocardial infarction.

**ÖZET**

Kounis sendromu (KS), alerjik veya aşırı duyarlılık reaksiyonlarıyla tetiklenen nadir bir akut koroner sendrom tablosudur. Arı sokmaları, KS'nin bilinen tetikleyicileri arasında yer almakla birlikte, mevcut kanıtlar büyük ölçüde olgu sunumları ve küçük olgu serileriyle sınırlıdır. Bu çalışmada, arı sokmasıyla ilişkili olası KS tanısı alan 44 yaşındaki bir erkek hasta sunulmuş ve yayımlanmış literatür sistematik olarak gözden geçirilmiştir. Genç yaşta miyokard enfarktüsünün literatürde yaygın olarak kullanılan tanımına dayanılarak, ≤45 yaş sınırı kullanılarak keşifsel bir yaş grubu karşılaştırması yapılmıştır. PubMed/MEDLINE ve Scopus veri tabanları, PRISMA 2020 önerileri doğrultusunda sistematik olarak taranmıştır. Demografik özellikler, klinik bulgular, tanısal yöntemler, tedavi yaklaşımları ve klinik sonuçlara ilişkin veriler değerlendirilmiştir. Toplam 47 hasta analize dahil edilmiş olup bunların 46'sı daha önce yayımlanmış olgular, biri ise indeks olgumuzdur. Hastaların ortalama yaşı 55,7±13,0 yıl olup 39/47'si (%83,0) erkekti. Semptomlar, 29/47 (%61,7) hastada arı sokmasını izleyen ilk 30 dakika içinde ortaya çıkmış ve en sık başvuru semptomu göğüs ağrısı (41/47, %87,2) olmuştur. KS alt tipi bildirilen hastalar arasında Tip II KS en sık görülen alt tipti (29/43, %67,4); STEMI ise 37/47 (%78,7) hastada bildirilmiştir. Revaskülarizasyon 27/47 (%57,4) hastaya uygulanmıştır. Verileri mevcut olan hastalar arasında kardiyojenik şok, kardiyak arrest ve kardiyak ritim veya ileti bozuklukları sırasıyla 11/46 (%23,9), 5/46 (%10,9) ve 7/46 (%15,2) hastada bildirilmiştir. Klinik sonuç verisi bulunan 46 hastanın 45'inde (%97,8) iyileşme, birinde (%2,2) ise persistan semptomlar bildirilmiş; mortalite gözlenmemiştir. İndeks hasta, başvurudan yaklaşık beş saat sonra kendi isteğiyle hastaneden ayrıldığından, sonraki takip verilerine ulaşılamamıştır. Hastaların 13'ü (%27,7) ≤45 yaşındaydı. Yaşa göre yapılan tanımlayıcı analizlerde çoğu klinik özellik açısından belirgin bir farklılık gözlenmemiştir; ancak sonuçların yorumlanması, genç hasta sayısının az olması nedeniyle sınırlıdır. Arı sokmasına bağlı Kounis sendromu, genç bireyler de dahil olmak üzere ciddi akut koroner tablolara yol açabilir. Mevcut kanıtların olgu bildirimlerine dayanması ve heterojen bir yapıya sahip olması nedeniyle, bu bulgular dikkatle yorumlanmalı ve sistematik olarak oluşturulmuş daha geniş hasta kohortlarında doğrulanmalıdır.

**Anahtar Kelimeler:** Arı sokması, Kounis sendromu, miyokard enfarktüsü.

**REVIEW**
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Kounis syndrome (KS) is defined as the concurrence of acute coronary syndromes, including coronary spasm, acute myocardial infarction (MI), and stent thrombosis, with conditions associated with mast cell and platelet activation involving interrelated inflammatory cells, such as macrophages and T lymphocytes, in the setting of allergic, hypersensitivity, anaphylactic, or anaphylactoid reactions.[1,2] These mediators may induce coronary vasospasm, endothelial dysfunction, plaque erosion or rupture, and coronary thrombosis, ultimately leading to myocardial ischemia or infarction.[3] Accordingly, KS has been classified into three variants: Type I, which occurs in patients with angiographically normal coronary arteries; Type II, which involves hypersensitivity-mediated coronary vasospasm in patients with pre-existing coronary atherosclerosis, with or without plaque erosion or rupture; and Type III, which is characterized by coronary stent thrombosis or restenosis associated with allergic reactions.[4] Bee stings represent one of the most common environmental triggers of KS. Bee venom contains numerous biologically active substances capable of inducing both systemic allergic reactions and direct cardiovascular effects. Consequently, bee sting–associated KS may manifest as acute MI, even in individuals without established coronary artery disease or traditional cardiovascular risk factors.[5]

Although premature atherosclerosis remains the leading cause of MI in young adults, nonatherosclerotic mechanisms account for a greater proportion of cases than in older populations. Coronary vasospasm, spontaneous coronary artery dissection, hypercoagulable states, inflammatory disorders, and MI with nonobstructive coronary arteries (MINOCA) are well-recognized causes of MI in younger individuals.[6] Therefore, identifying uncommon etiologies is particularly important in younger patients presenting with acute coronary syndromes.

Despite the increasing recognition of bee sting–associated KS, the available evidence consists almost exclusively of isolated case reports and small case series. As a result, current knowledge regarding patient characteristics, clinical presentation, diagnostic findings, management strategies, and outcomes remains fragmented. Moreover, data on age-related differences in the clinical manifestations and prognosis of bee sting–associated KS are lacking. In this report, we present a 44-year-old man with acute MI and probable bee sting–associated KS. We therefore performed a systematic review of published cases of bee sting–associated KS, focusing on demographic characteristics, clinical presentation, diagnostic findings, treatment strategies, and outcomes. In addition, we compared younger (≤45 years) and older (>45 years) patients to explore potential age-related differences and better define the role of bee sting–associated KS as a cause of MI in younger individuals.

## Methods

A comprehensive literature search was conducted in the PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE) and Scopus databases using combinations of the following keywords: "bee sting," "Kounis syndrome," "coronary artery disease," "acute coronary syndrome," and "myocardial infarction." The search covered the period from database inception through August 5, 2026. The complete Boolean search strategies used for PubMed/MEDLINE and Scopus are provided in the Supplementary Material. All retrieved records were imported into EndNote, and duplicate records were identified and removed before screening. Two investigators (AY and ÖFY) independently screened the retrieved records and assessed potentially eligible publications according to the predefined eligibility criteria. To minimize duplicate patient inclusion across publications, potentially overlapping reports were cross-checked using available patient characteristics, including age, sex, country and institution, publication timing, clinical presentation, and other case-specific details. When reports were considered to describe the same patient, only the most complete report was retained for patient-level data extraction. Data extraction was also performed independently by the two investigators. Any disagreements regarding study eligibility or data extraction were resolved through consultation with a third investigator (YZS). The study selection process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] The PRISMA flow diagram is presented in Figure 1. The review protocol was not prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) or another systematic review registry.

Studies were considered eligible if they reported individual adult cases (aged ≥18 years) of KS occurring in temporal association with a bee sting and provided sufficient patient-level clinical information to characterize the presentation, diagnostic evaluation, management, and/or clinical outcome. Eligible publication types included case reports, case series, and other original reports containing extractable individual case data. Only articles published in English were included. Pediatric cases (aged <18 years), animal studies, narrative reviews, and systematic reviews without an original, identifiable individual case presentation were excluded. Cases in which KS was triggered by causes other than a bee sting were also excluded. In particular, cases associated with other Hymenoptera species, including wasps and hornets, were excluded because of interspecies differences in venom composition and allergenic profiles. Reports in which the offending insect could not be reliably identified as a bee were also

## ABBREVIATIONS

| | |
|---|---|
| ApoB | Apolipoprotein B |
| CMR | Cardiac magnetic resonance |
| ECG | Electrocardiogram |
| HbA1c | Glycated hemoglobin |
| HDL-C | High-density lipoprotein cholesterol |
| hs-TnT | High-sensitivity troponin T |
| IgE | Immunoglobulin E |
| KS | Kounis syndrome |
| LDL-C | Low-density lipoprotein cholesterol |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| MI | Myocardial infarction |
| MINOCA | Myocardial infarction with nonobstructive coronary arteries |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PROSPERO | International Prospective Register of Systematic Reviews |
| STEMI | ST-segment elevation myocardial infarction |

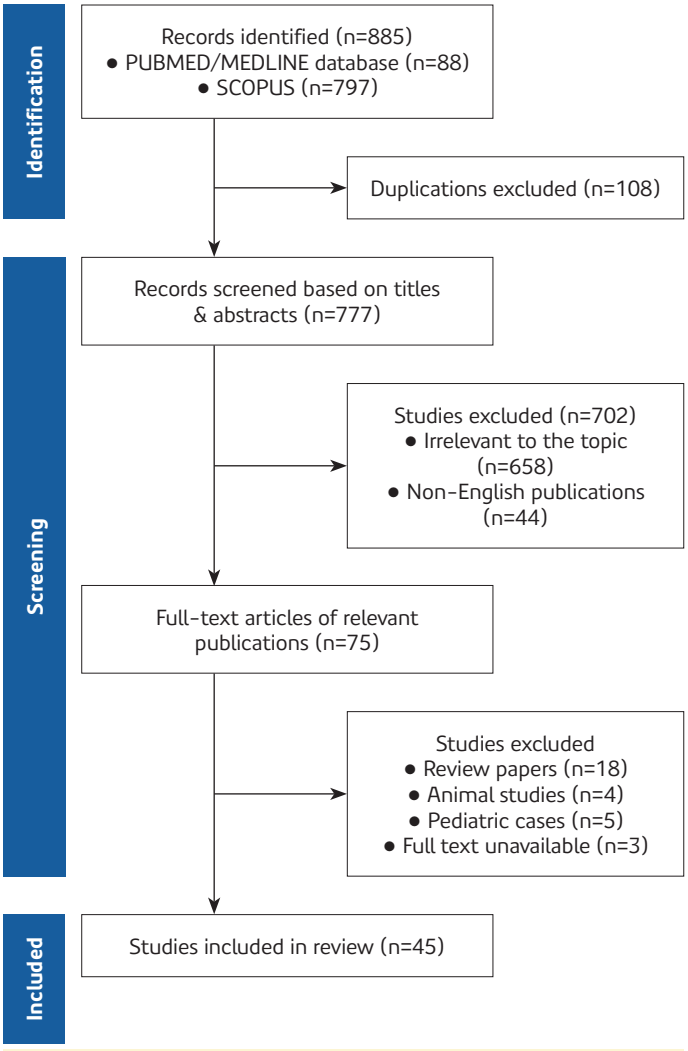



**Figure 1.** PRISMA flow diagram illustrating study identification, screening, eligibility assessment, and inclusion in the systematic review of bee sting–associated Kounis syndrome.

excluded. In addition, the reference lists of relevant articles and existing reviews were manually screened to identify potentially eligible reports that may have been missed during the database search. Overall, 45 publications comprising 46 individual cases of bee sting–associated KS were identified and included in the systematic review in addition to our index case. Written informed consent was obtained from the patient for publication of the clinical information and all accompanying images, including electrocardiographic and coronary angiographic images.

Methodological quality was independently assessed by two reviewers (AY and ÖFY) using the Joanna Briggs Institute (JBI) critical appraisal tools appropriate for each study design. Publications reporting a single patient were evaluated using the JBI Critical Appraisal Checklist for Case Reports, whereas the publication reporting two patients was assessed using the JBI Critical Appraisal Checklist for Case Series, with the results presented in Supplementary Material 2 and 3.[8] Each domain was rated as Yes, No, Unclear, or Not applicable in accordance with JBI guidance. Disagreements between reviewers were resolved through discussion and consensus, with consultation of a third reviewer (AB) when necessary. No publication was excluded solely on the basis of the critical appraisal findings; rather, these assessments were used to contextualize the descriptive synthesis and identify limitations in the available evidence. No aggregate numerical quality score or cutoff was applied.

The following variables were extracted from each case: age, sex, comorbidities, history of allergy, number and site of bee stings, time from bee sting to symptom onset, presenting symptoms, presence of anaphylaxis, type of KS, type of MI, electrocardiographic findings, cardiac biomarkers, echocardiographic findings, coronary angiographic findings, medical treatment, revascularization strategy, clinical outcomes, and length of hospital stay. For data extraction, complications were recorded as reported in the source publications. Anaphylaxis was considered present when explicitly diagnosed by the original authors or when the reported clinical findings fulfilled accepted World Allergy Organization diagnostic criteria.[9] For the index case, the diagnosis of anaphylaxis was assessed according to the same criteria. For exploratory descriptive analyses, patients were categorized according to sting-to-symptom onset as early (≤30 minutes) or delayed (>30 minutes), based on the commonly used 30-minute threshold for distinguishing early- from delayed-onset systemic allergic reactions in the allergy literature.[10] Cardiac rhythm or conduction disturbances included newly reported atrial or ventricular arrhythmias and atrioventricular or intraventricular conduction abnormalities during the acute presentation. Clinical outcomes were categorized according to the last available status reported in each source. "Reported recovery" was defined as resolution of the acute clinical presentation with discharge or documented clinical stabilization without persistent cardiovascular symptoms or complications at the last reported assessment. "Persistent symptoms or complications" was assigned when ongoing symptoms or unresolved cardiovascular abnormalities were reported at the last available assessment. Death was recorded when mortality occurred during hospitalization or the reported follow-up period.

Continuous variables were expressed as mean±standard deviation (SD) when normally distributed and as median (interquartile range [IQR]) when non-normally distributed, with ranges reported where appropriate. Categorical variables were presented as frequencies and percentages. Patients were stratified into younger (≤45 years) and older (>45 years) age groups. Given the small number of younger patients and the heterogeneous availability of patient-level data, age-stratified analyses were considered exploratory and were presented descriptively without formal hypothesis testing. Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

## Case Report

A 44-year-old man with a history of hypertension and dyslipidemia presented with acute chest pain that developed within minutes after sustaining multiple bee stings (approximately 6–7) to the face while gardening. He had been receiving atorvastatin 20 mg daily for approximately one year, although adherence was irregular; his pretreatment (statin-naive) low-density lipoprotein cholesterol (LDL-C) level had been 133 mg/dL. He had no known history of allergy or atopic

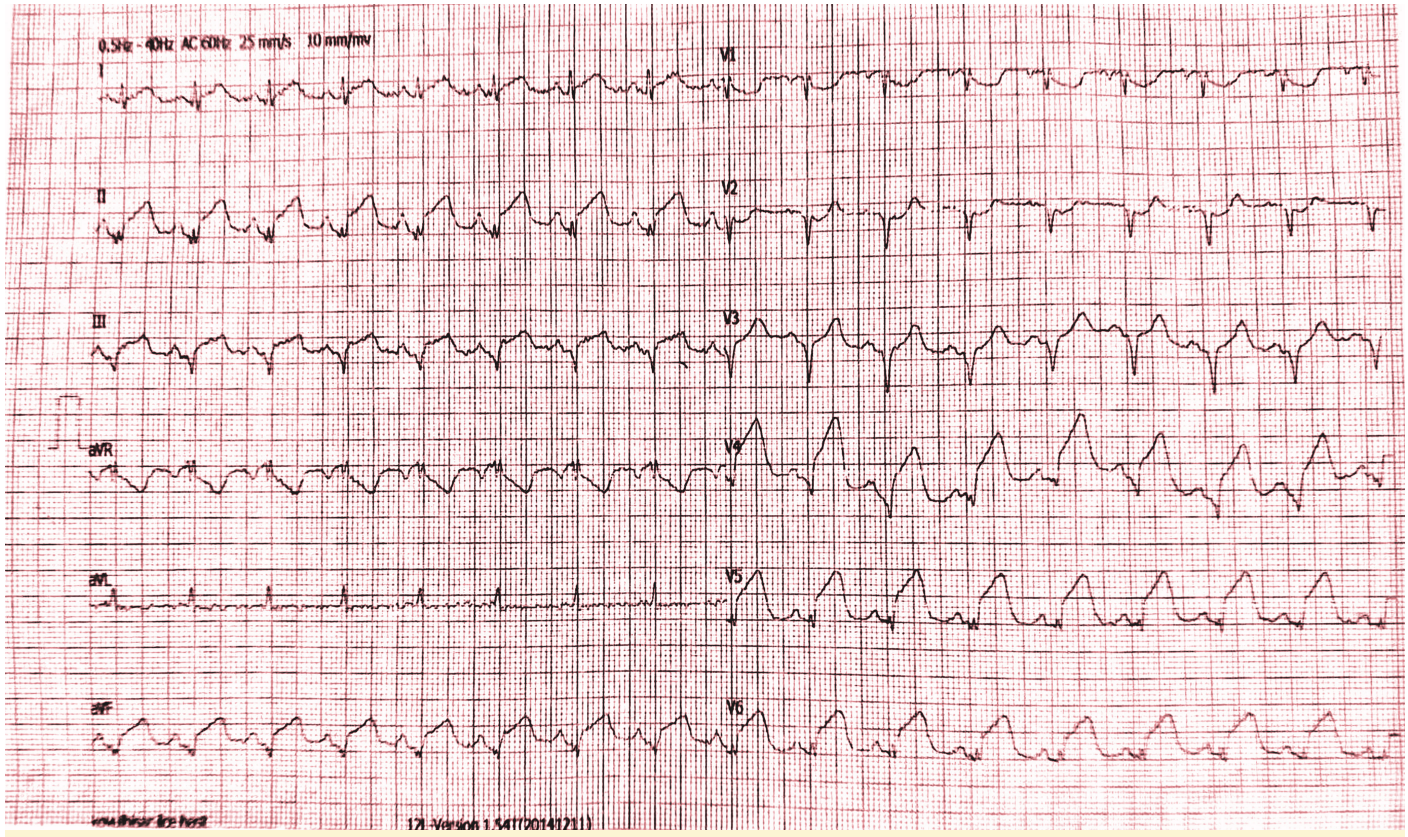



**Figure 2.** Twelve-lead electrocardiogram obtained on admission demonstrating ST-segment elevation in the inferolateral leads (II, III, aVF, and V4–V6), consistent with acute myocardial injury.

disease and had experienced no previous allergic reactions to bee stings. His cardiovascular risk profile was notable for a 12-pack-year smoking history, with no family history of premature coronary artery disease. His body weight was 85 kg and height was 175 cm, corresponding to a body mass index of 27.8 kg/m$^2$. His glycated hemoglobin (HbA1c) level was 5.7%. The lipid profile showed a total cholesterol level of 186 mg/dL, LDL-C of 98 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 29 mg/dL, triglycerides of 83 mg/dL, and non-HDL-C of 157 mg/dL. Apolipoprotein B (ApoB) and lipoprotein(a) levels were not available. There was no history of recreational drug use or other relevant substance exposure, previous thrombotic events, autoimmune disease, or vasculitis. Thrombophilia testing was not performed. The peripheral eosinophil count was 0.4×10$^9$/L, within the high-normal range; serum total immunoglobulin E (IgE) and tryptase levels were not measured.

On admission, he was conscious, with a blood pressure of 90/55 mmHg, a heart rate of 60 beats/min, and an oxygen saturation of 97% on room air. Physical examination revealed facial swelling and multiple sting marks without rash, urticaria, or respiratory distress. A 12-lead electrocardiogram (ECG) demonstrated ST-segment elevation in the inferolateral leads (II, III, aVF, and V4–V6) (Figure 2). Bedside transthoracic echocardiography demonstrated hypokinesia of the basal and mid-inferior wall, with mild left ventricular systolic dysfunction and a left ventricular ejection fraction (LVEF) of 45%. No significant valvular abnormalities or pericardial effusion were observed. Dual antiplatelet therapy consisting of acetylsalicylic acid (300 mg) and ticagrelor (180 mg) was administered, together with a single intravenous dose of unfractionated heparin (4,000 IU). Nitrates were not administered because of the borderline blood pressure (90/55 mmHg) and the initial suspicion of inferior ST-segment elevation myocardial infarction (STEMI). The patient received 500 mL of intravenous isotonic saline, with subsequent improvement in blood pressure. For the allergic manifestations, pheniramine maleate 22.75 mg intravenously (half of a 45.5-mg/2-mL ampoule) and famotidine 20 mg intravenously were administered. Corticosteroids and epinephrine were not administered because the available clinical findings did not fulfill the diagnostic criteria for anaphylaxis.

During transfer, the patient's chest pain gradually resolved, and his vital signs remained stable. Upon arrival, emergency coronary angiography revealed nonobstructive plaques in the proximal left anterior descending and left circumflex arteries, without obstructive coronary artery disease (Figure 3). At presentation, high-sensitivity troponin T (hs-TnT) was 48 ng/L, exceeding the assay upper reference limit of 14 ng/L. Repeat measurement 2 hours after presentation showed a value of 768 ng/L, representing the highest recorded hs-TnT level during the available observation period. Measurements were performed using the Elecsys® Troponin T hs assay (Roche Diagnostics GmbH, Mannheim, Germany). Repeat ECG showed complete resolution of ST-segment elevation and restoration of normal sinus rhythm. Given the close temporal relationship between multiple bee stings and the acute coronary presentation, together with the presence of pre-existing nonobstructive coronary atherosclerotic

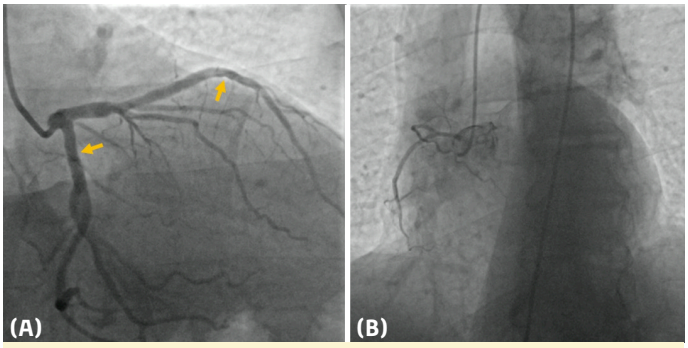



**Figure 3.** Coronary angiographic findings. (A) Left coronary angiography in the right anterior oblique (RAO) caudal view demonstrating the left anterior descending (LAD) and left circumflex (LCx) coronary arteries. Yellow arrows indicate nonobstructive atherosclerotic plaques in the LAD and LCx. (B) Right coronary angiography demonstrating a nondominant right coronary artery (RCA) without significant obstructive coronary artery disease.

plaques, the case was considered probable Type II KS, although the precise coronary mechanism could not be definitively established. The patient remained clinically stable but elected to leave the hospital against medical advice after approximately five hours of observation. No subsequent clinical follow-up was available; therefore, follow-up ECG, cardiac biomarker measurements, and echocardiographic assessment could not be performed, and his subsequent clinical course and long-term outcome remain unknown. Information regarding subsequent allergy/immunology evaluation, prescription of an epinephrine auto-injector, consideration of venom immunotherapy, and continuation of cardiovascular secondary prevention was also unavailable.

## Literature Review

### Baseline Characteristics

A total of 46 previously reported cases of bee sting–associated KS were identified through the systematic review. Together with our index case, 47 patients were included in the final analysis. The mean age was 55.7±13.0 years (range, 22–81 years). Most patients were male (39/47, 83.0%), whereas females accounted for 17.0% (8/47). A history of allergy was documented in 5/38 patients (13.2%). Cardiovascular risk factors were frequently reported. Diabetes mellitus was present in 13/41 patients (31.7%), dyslipidemia in 10/40 (25.0%), and hypertension in 13/41 (31.7%).

The number of bee stings varied considerably, ranging from a single sting to more than 100 stings. Multiple stings were reported in 29/47 patients (61.7%), whereas a single sting occurred in 18/47 patients (38.3%).

The head, face, and neck region was the most frequently involved anatomical site, reported in 20/33 patients (60.6%), followed by the upper extremities in 13/33 patients (39.4%). Generalized or whole-body involvement was reported in 3/33 patients (9.1%), whereas the sting location was not specified in 14/47 patients (29.8%). Cases were reported from 17 countries across four continents, with the largest proportion originating from Türkiye (12/47, 25.5%), followed by India (8/47, 17.0%), the United States (6/47, 12.8%), and Greece (4/47, 8.5%) (Table S1).

### Clinical Presentation

The interval from bee sting to symptom onset was generally short, with 29/47 patients (61.7%) developing symptoms within the first 30 minutes after envenomation. Nevertheless, delayed presentations were observed, with symptom onset ranging from several hours to a maximum of 34 hours after exposure. A single numerical sting-to-symptom interval was available for 22/47 patients (46.8%). Among these patients, the mean interval was 4.6±7.8 hours, and the median interval was 1.5 hours (interquartile range [IQR], 1.0–4.0 hours), with values ranging from 15 minutes to 34 hours.

Chest pain was the predominant presenting symptom, occurring in 41/47 patients (87.2%). Notably, six patients initially presented with isolated allergic manifestations and were subsequently diagnosed with MI during further diagnostic evaluation. Cutaneous manifestations were less common, with rash reported in 24/47 patients (51.1%) and swelling in 15/47 patients (31.9%). Wheezing was observed in 9/47 patients (19.1%), whereas drowsiness was reported in 15/47 patients (31.9%). Anaphylaxis was reported in 22/47 patients (46.8%). Among these patients, symptom onset occurred within 30 minutes of the bee sting in 16/22 (72.7%), whereas delayed onset was reported in six patients: three at 1 hour, two at 2 hours, and one at 12 hours (Table S2).

In an exploratory descriptive analysis stratified by the sting-to-symptom interval, anaphylaxis was reported in 16/29 patients (55.2%) in the ≤30-minute group and in 6/18 (33.3%) in the >30-minute group. Cardiogenic shock occurred in 8/29 (27.6%) and 3/17 patients (17.6%), respectively. Clinical outcome data were available for 28/29 patients in the ≤30-minute group and all 18 patients in the >30-minute group; reported recovery occurred in 27/28 (96.4%) and 18/18 (100%), respectively. One patient in the ≤30-minute group had persistent symptoms.

### Laboratory, Electrocardiographic, and Imaging Findings

Among the 43 patients for whom the KS subtype was available, KS was classified as Type I in 11/43 cases (25.6%), Type II in 29/43 (67.4%), and Type III in 3/43 (7.0%). STEMI was the predominant clinical presentation, occurring in 37/47 patients (78.7%), whereas non-ST-segment elevation myocardial infarction (NSTEMI) was reported in 10/47 patients (21.3%). Troponin levels were reported in 31/47 patients (66.0%) and were elevated in 30/31 (96.8%), whereas a normal troponin level was reported in only one patient (3.2%). Peripheral eosinophil counts were available in only 7/47 patients (14.8%); eosinophilia was present in 2/7 patients (28.5%), whereas eosinophil counts were within the normal range in the remaining 5/7 patients (71.4%).

Echocardiographic findings were available in 30/47 patients (63.8%). Numerical left ventricular ejection fraction (LVEF) values were reported in 18 patients, with a mean LVEF of 44.0±10.9%. Regional wall motion abnormalities, hypokinesia, akinesia, and varying degrees of left ventricular dysfunction were common findings, although several patients demonstrated preserved ventricular function or no wall motion abnormalities.

### Treatment and Outcome Characteristics

Coronary angiography most frequently demonstrated thrombotic lesions, significant coronary stenosis, coronary

occlusion, vasospasm, coronary dissection, or stent thrombosis. Revascularization was performed in 27/47 patients (57.4%), including percutaneous coronary intervention (PCI) in 25/47 patients (53.2%) and coronary artery bypass grafting (CABG) in 2/47 patients (4.3%). Regarding medical management, antiplatelet therapy was administered in 40/45 patients (88.9%) with available data, antihistamines in 30/45 patients (66.7%), and corticosteroids in 26/45 patients (57.8%). Epinephrine administration was explicitly reported in 10/47 patients (21.3%), whereas four patients were explicitly reported not to have received epinephrine; epinephrine use was not reported in the remaining cases. Treatment data were unavailable for two patients.

Cardiac rhythm and conduction disturbances were observed in 7/46 patients (15.2%), including ventricular tachycardia, atrial fibrillation/ventricular fibrillation, second-degree atrioventricular block, and complete atrioventricular block. Cardiogenic shock and cardiac arrest were reported in 11/46 (23.9%) and 5/46 (10.9%) patients with available data, respectively. Length of hospital stay was available for 26/47 patients (55.3%). The median duration of hospitalization was 5.5 days (range, 1–19 days). Among the 46 patients with reported clinical outcome data, recovery at the last available assessment was described in 45 patients (97.8%), whereas persistent symptoms were reported in one patient (2.2%). No deaths were reported among the included cases. However, the duration and completeness of follow-up varied substantially across reports. Detailed electrocardiographic, imaging, angiographic, treatment, and outcome characteristics are summarized in Tables S2 and S3.

**Comparison Between Younger and Older Patients**

Thirteen of 47 patients (27.7%) were aged ≤45 years, whereas 34/47 (72.3%) were older than 45 years. Given the small number of younger patients and the heterogeneous availability of patient-level data, age-based comparisons were considered exploratory and are presented descriptively. Male patients accounted for 11/13 (84.6%) of the younger group and 28/34 (82.4%) of the older group. Diabetes mellitus was reported in 2/12 (16.7%) younger and 11/29 (37.9%) older patients, dyslipidemia in 2/12 (16.7%) and 8/28 (28.6%), and hypertension in 3/12 (25.0%) and 10/29 (34.5%), respectively.

Chest pain was reported in 11/13 (84.6%) younger and 30/34 (88.2%) older patients. Rash was observed in 4/13 (30.8%) and 20/34 (58.8%), drowsiness in 3/13 (23.1%) and 12/34 (35.3%), wheezing in 2/13 (15.4%) and 7/34 (20.6%), and anaphylaxis in 5/13 (38.5%) and 17/34 (50.0%), respectively. Swelling was numerically more frequent in younger patients (8/13 [61.5%]) than in older patients (7/34 [20.6%]).

The distribution of KS types differed numerically between the age groups. Among patients aged ≤45 years with available KS subtype data, Type II KS was more frequent than Type I KS (8/11 [72.7%] vs. 3/11 [27.3%]), whereas no Type III cases were observed. Among patients aged >45 years, Type II KS also predominated (21/32 [65.6%]), followed by Type I (8/32 [25.0%]) and Type III KS (3/32 [9.4%]). All Type III cases occurred in patients aged >45 years. STEMI was the predominant presentation in both groups, occurring in 11/13 (84.6%) younger and 26/34 (76.5%) older patients. Revascularization was performed in 6/13 (46.2%) younger and 21/34 (61.8%) older patients, with PCI representing the most commonly used revascularization strategy in both groups. Among patients with available numerical echocardiographic data, the mean LVEF was numerically higher in patients aged ≤45 years than in those aged >45 years (45.3±2.6% vs. 43.5±12.8%, respectively). Cardiac rhythm or conduction disturbances were observed in 1/12 (8.3%) younger patients and 6/34 (17.6%) older patients with available data.

## Discussion

In this study, we presented a case of bee sting–associated KS manifesting as acute MI in a 44-year-old man and systematically reviewed 46 previously reported cases. The present systematic review provides an updated, trigger-specific synthesis of published cases of bee sting–associated KS and includes an exploratory age-stratified comparison. Bee sting–associated KS predominantly affected middle-aged and older men, although more than one-quarter of cases occurred in patients aged ≤45 years. Chest pain was the most common presenting symptom, and symptom onset typically occurred within 30 minutes of envenomation. Type II KS and STEMI were the predominant clinical phenotypes, and more than half of the patients required coronary revascularization. Finally, serious complications, including cardiogenic shock, cardiac arrest, and arrhythmias, were frequently reported, although no deaths were documented among the published cases.

Previous systematic evidence provides complementary but differently scoped perspectives on KS. Elmezayen et al.[11] identified 17 cases of bee sting–induced MI, whereas the present review identified 46 previously reported cases of bee sting–associated KS, likely reflecting broader search terminology and eligibility criteria, the inclusion of earlier reports, and a later search date. More recently, Kalambay et al.[12] performed a systematic review and meta-analysis including 71 extractable cases of KS across heterogeneous triggers and provided pooled estimates of demographic characteristics, clinical presentation, management, and outcomes. In contrast, the present review was restricted specifically to bee sting–associated KS, allowing a trigger-specific synthesis of clinical characteristics and outcomes, together with an exploratory age-stratified descriptive comparison.

KS is characterized by the concurrence of acute coronary syndromes and allergic or hypersensitivity reactions. Its pathophysiology involves mast cell activation and degranulation, with the release of inflammatory and vasoactive mediators, including histamine, platelet-activating factor, leukotrienes, thromboxane, tryptase, and cytokines, which may promote coronary vasoconstriction, endothelial dysfunction, platelet activation, plaque destabilization, and thrombosis. In bee sting–induced KS, this response may be further amplified by venom components such as melittin, phospholipase A2, hyaluronidase, and apamin. Through these overlapping immunologic and coronary mechanisms, bee stings may precipitate myocardial ischemia or infarction in patients with pre-existing atherosclerosis as well as in those without previously recognized coronary artery disease.[5]

One clinically relevant observation from our review was the broad age distribution of bee sting–associated KS, with more than one-quarter of cases occurring in patients aged ≤45 years. Importantly, significant coronary atherosclerosis is not

a prerequisite for KS in younger individuals, as Type I KS may occur through hypersensitivity-mediated coronary vasospasm in angiographically normal coronary arteries. Nevertheless, Type II KS was the predominant subtype overall, accounting for 29/43 (67.4%) classified cases, suggesting that hypersensitivity-mediated plaque destabilization, thrombosis, or superimposed vasospasm frequently occurred in the presence of underlying atherosclerosis. These findings highlight the heterogeneous coronary mechanisms underlying bee sting–associated KS across the age spectrum.[2,6]

STEMI was reported in 37/47 patients (78.7%), and coronary revascularization was performed in 27/47 (57.4%), consistent with the predominance of Type II KS and the frequent presence of stenotic, thrombotic, or occlusive coronary lesions. These proportions should be interpreted cautiously because more severe cases undergoing coronary angiography or intervention may be preferentially reported. Türkiye was the most frequently represented country, followed by India and the United States; however, this distribution likely reflects differences in clinical awareness, publication practices, and access to coronary angiography rather than true geographic variation in disease incidence.

The diagnosis of bee sting–associated KS remains challenging because its clinical manifestations may overlap with both anaphylaxis and conventional acute coronary syndromes. In our index case, the close temporal relationship between the bee stings and acute chest pain, transient inferolateral ST-segment elevation, and troponin elevation supported a diagnosis of probable bee sting–associated KS. Coronary angiography demonstrated only nonobstructive plaques without a culprit lesion, placing the presentation within the MINOCA framework. Transient allergic coronary vasospasm or spontaneous reperfusion of a transient thrombotic occlusion were plausible mechanisms, although neither was directly documented. Because cardiac magnetic resonance (CMR) imaging, serum tryptase measurement, and formal allergy evaluation were unavailable, myocarditis, Takotsubo syndrome, and other causes of myocardial injury could not be definitively excluded. Careful assessment of recent allergen exposure and recognition of the temporal relationship between a bee sting and symptom onset remain crucial components of diagnosis.[13]

Beyond the specific diagnosis of KS, the present case also highlights the importance of considering both traditional and nontraditional etiologies in younger patients presenting with MI. Although premature MI is frequently associated with conventional cardiovascular risk factors, its etiologic spectrum also includes nonatherosclerotic mechanisms such as coronary vasospasm, thrombophilia, spontaneous coronary artery dissection, coronary anomalies, autoimmune or inflammatory disorders, genetic susceptibility, and allergic or hypersensitivity reactions.[14–16] KS should therefore be considered within this broader etiologic framework, particularly when myocardial ischemia occurs in close temporal association with a potential allergen.[3] Our index patient had established cardiovascular risk factors, including hypertension, dyslipidemia, and smoking, as well as nonobstructive coronary atherosclerosis; however, the immediate onset of chest pain and transient ST-segment elevation following multiple bee stings suggested an additional hypersensitivity-mediated coronary mechanism. This case illustrates that the presence of conventional cardiovascular risk factors in a young patient should not preclude evaluation for less common triggers of MI when supported by the clinical context.

Management of bee sting–induced KS requires simultaneous treatment of the allergic reaction and acute coronary syndrome, and reported therapies have included antihistamines, corticosteroids, intravenous fluids, vasodilators, and standard acute coronary syndrome treatment. Epinephrine remains the cornerstone of anaphylaxis management but may theoretically exacerbate myocardial ischemia by increasing myocardial oxygen demand and inducing coronary vasoconstriction.[17] Likewise, beta-blockers may interfere with the response to epinephrine during severe allergic reactions.[18] These competing therapeutic considerations underscore the importance of individualized management strategies and multidisciplinary decision-making. Despite the absence of reported mortality, serious cardiovascular complications were frequent, including cardiogenic shock in 11/46 patients (23.9%), cardiac arrest in 5/46 (10.9%), and rhythm or conduction disturbances in 7/46 (15.2%) patients with available data. Accordingly, the apparently favorable reported outcomes should be interpreted cautiously given the potential for publication bias, selective reporting, incomplete follow-up, and survival bias inherent in case-report literature. Therefore, the absence of mortality in our review should not be interpreted as evidence of a generally favorable prognosis for bee sting–associated KS. Rather, the occurrence of severe cardiovascular complications underscores the potentially life-threatening nature of this condition and the importance of continued clinical vigilance.[3]

Several limitations should be acknowledged. First, the available evidence consisted primarily of case reports and small case series, making the findings susceptible to publication bias. Second, only the PubMed/MEDLINE and Scopus databases were searched; therefore, some relevant cases may have been missed. The restriction to English-language articles may also have introduced language bias by excluding relevant cases published in other languages. Third, reporting was incomplete and heterogeneous across the included reports, limiting patient-level comparisons. Cardiac biomarker data were particularly inconsistent: numerical troponin values were available in only 31 of 47 patients, whereas assay type, measurement units, reference limits, and timing of sampling varied across reports, precluding meaningful quantitative comparison of biomarker magnitude. Fourth, the age-stratified analysis was exploratory and limited by the relatively small number of patients aged ≤45 years. Finally, because only published cases were included, our findings may not fully represent the entire spectrum of bee sting–associated KS.

The index case also had important diagnostic limitations. Serum tryptase and total IgE levels were not measured, and formal allergy/immunology evaluation was not performed, precluding definitive confirmation of the allergic mechanism. In addition, ApoB and lipoprotein(a) levels were unavailable, and thrombophilia testing was not performed, limiting a comprehensive etiologic evaluation of premature MI. Furthermore, the patient left the hospital against medical advice after approximately five hours, precluding CMR imaging and limiting further diagnostic

evaluation, documentation of troponin normalization, and assessment of subsequent clinical outcomes. Consequently, myocarditis, Takotsubo syndrome, and other potential causes of myocardial injury could not be definitively excluded. Despite these limitations, this study provides an updated synthesis of bee sting–associated KS and includes a descriptive age-based analysis of reported cases.

In conclusion, bee sting–associated KS is an uncommon acute coronary syndrome that may occur across a broad age range, including younger individuals. The published cases demonstrate considerable heterogeneity in clinical presentation, coronary findings, management strategies, and outcomes. STEMI and Type II KS were the most frequently reported presentations in our review, highlighting the clinically relevant coronary manifestations that may accompany allergic reactions to bee stings. Larger studies with systematic data collection are needed to more clearly define the clinical spectrum of bee sting–associated KS, explore potential age-related differences, and guide diagnostic and therapeutic approaches.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-83835/TKDA-83835_(0)_Supplementary_Materials.pdf

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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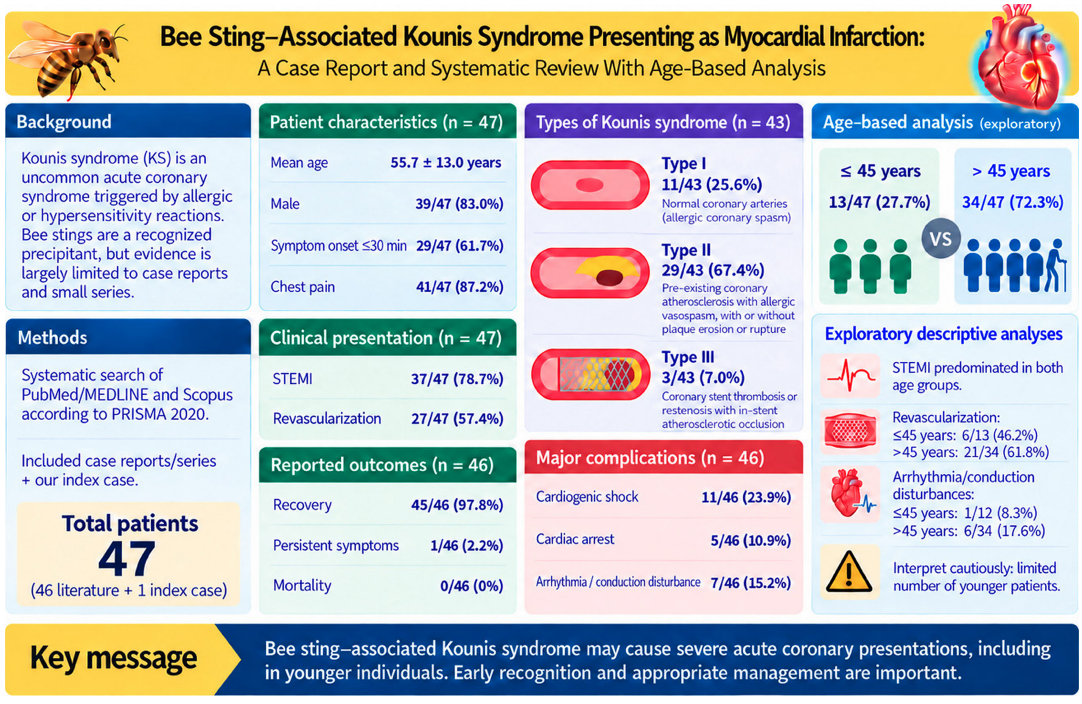
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# Late Drug-Eluting Stent Thrombosis Presenting with Out-of-Hospital Cardiac Arrest in a Young Patient with Primary Antiphospholipid Syndrome

## Primer Antifosfolipid Sendromlu Genç Bir Hastada Hastane Dışı Kardiyak Arrest ile Seyreden Geç İlaç Salınımlı Stent Trombozu

**ABSTRACT**

Late stent thrombosis is an uncommon but potentially fatal complication following percutaneous coronary intervention. In young patients presenting with recurrent myocardial infarction despite appropriate secondary prevention, underlying prothrombotic disorders should be considered. A 39-year-old man presented with out-of-hospital cardiac arrest nine months after implantation of a 2.75×28 mm drug-eluting stent in the left anterior descending artery for anterior ST-segment elevation myocardial infarction. Coronary angiography demonstrated late thrombotic occlusion of the previously implanted stent with TIMI 0 flow. Successful balloon angioplasty followed by kissing balloon inflation restored TIMI 3 flow in both the left anterior descending artery and the diagonal branch. Because of recurrent myocardial infarction due to late stent thrombosis at a young age, the presence of limited conventional risk factors sufficient to explain the clinical presentation, and no reported history of nonadherence to medical therapy, a systematic laboratory evaluation for thrombophilia and antiphospholipid syndrome was performed. Persistent lupus anticoagulant positivity was demonstrated on repeated testing, whereas anticardiolipin and anti-β2-glycoprotein I antibodies were negative. Following multidisciplinary evaluation by the Departments of Cardiology and Rheumatology, the findings supported a clinical diagnosis of primary antiphospholipid syndrome. Long-term vitamin K antagonist therapy was recommended but declined by the patient. At the four-month follow-up after implantable cardioverter-defibrillator implantation, no recurrent thrombotic events or ICD therapies were observed. Young patients presenting with recurrent myocardial infarction secondary to late stent thrombosis, particularly in the absence of documented interruption of dual antiplatelet therapy, should be considered for systematic evaluation of thrombophilic disorders, including antiphospholipid syndrome.

**Keywords:** Antiphospholipid syndrome, cardiac arrest, drug-eluting stent, late stent thrombosis, young myocardial infarction.

**ÖZET**

Geç stent trombozu, perkütan koroner girişim sonrası nadir görülen ancak yaşamı tehdit edebilen bir komplikasyondur. Uygun sekonder korunma tedavisine rağmen rekürren miyokard enfarktüsü gelişen genç hastalarda altta yatan trombofilik durumlar göz önünde bulundurulmalıdır. Otuz dokuz yaşındaki erkek hasta, anterior ST-segment elevasyonlu miyokard enfarktüsü nedeniyle sol ön inen koroner artere 2,75×28 mm ilaç salınımlı stent implantasyonundan dokuz ay sonra hastane dışı kardiyak arrest ile başvurdu. Koroner anjiyografide, daha önce implante edilen stent içerisinde TIMI 0 akımla seyreden geç trombotik oklüzyon saptandı. Balon anjiyoplasti ve ardından uygulanan kissing balon tekniği ile hem sol ön inen koroner arterde hem de diyagonal dalda TIMI 3 akım sağlandı. Mevcut tıbbi kayıtlar ve yakınlarından alınan öyküye göre aspirin veya tikagrelor tedavisinde belgelenmiş bir kesinti bulunmamasına rağmen rekürren miyokard enfarktüsü gelişmesi, hastanın genç yaşı ve hipertansiyon, diyabetes mellitus, tedavi altında belirgin dislipidemi veya prematür aterosklerotik kardiyovasküler hastalık aile öyküsünün bulunmaması nedeniyle trombofili ve antifosfolipid sendromu açısından sistematik laboratuvar değerlendirmesi yapıldı. Tekrarlanan testlerde kalıcı lupus antikoagülan pozitifliği gösterilirken, antikardiyolipin ve anti-β2-glikoprotein I antikorları negatif bulundu. Kardiyoloji ve Romatoloji bölümlerinin multidisipliner değerlendirmesi sonrasında elde edilen bulgular, primer antifosfolipid sendromunun klinik tanısını destekledi. Uzun dönem vitamin K antagonisti tedavisi önerildi, ancak hasta bu tedaviyi kabul etmedi. İmplante edilebilir kardiyoverter-defibrilatör implantasyonundan dört ay sonraki takipte rekürren trombotik olay veya ICD tedavisi gerektiren aritmi izlenmedi. İkili antiplatelet tedavide belgelenmiş bir kesinti olmaksızın geç stent trombozuna bağlı rekürren miyokard enfarktüsü gelişen genç hastalarda, antifosfolipid sendromu başta olmak üzere trombofilik hastalıklar açısından sistematik değerlendirme düşünülmelidir.

**Anahtar Kelimeler:** Antifosfolipid sendromu, kardiyak arrest, ilaç salınımlı stent, geç stent trombozu, genç miyokard enfarktüsü.

**CASE REPORT**
OLGU SUNUMU

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Myocardial infarction in young adults represents an important clinical entity associated with substantial long-term morbidity, premature disability, and socioeconomic burden. Although traditional cardiovascular risk factors remain the leading contributors to myocardial infarction in this population, nonatherosclerotic etiologies should also be considered, particularly in patients presenting with recurrent thrombotic events, stent thrombosis, or unexpectedly severe clinical manifestations. A systematic etiological evaluation is essential in such patients, as identifying an underlying disorder may significantly influence both secondary prevention strategies and long-term clinical outcomes.[1-3]

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilic disorder characterized by persistent antiphospholipid antibodies and arterial and/or venous thrombosis. Although venous thromboembolism is the predominant clinical manifestation, coronary artery thrombosis may also occur and present as acute myocardial infarction or stent thrombosis. Recognition of APS is clinically important because it has direct implications for long-term antithrombotic management and requires multidisciplinary collaboration.[4,5]

Herein, we report a young patient who presented with out-of-hospital cardiac arrest secondary to late stent thrombosis in the left anterior descending (LAD) artery, in whom a systematic etiological investigation beyond conventional cardiovascular risk factors led to the diagnosis of primary APS This case highlights the importance of considering acquired thrombophilic disorders in young patients with recurrent myocardial infarction despite appropriate guideline-directed secondary prevention therapy.

**Case Report**

A 39-year-old man was admitted to our emergency department after an out-of-hospital cardiac arrest. Nine months earlier, he had undergone successful percutaneous coronary intervention (PCI) with stent implantation in the LAD artery for anterior ST-segment elevation myocardial infarction. According to the available medical records and information obtained from the patient's relatives, he had no history of hypertension or diabetes mellitus, no family history of premature atherosclerotic cardiovascular disease or thrombotic disorders, and was an occasional smoker. According to the available medical records and collateral history, there was no documented interruption of the patient's medical therapy between the index PCI and the current event. The patient's chronological clinical course is summarized in Figure 1.

Following successful cardiopulmonary resuscitation and return of spontaneous circulation, a 12-lead electrocardiogram demonstrated anterior ST-segment elevation myocardial infarction (Figure 2). The patient was immediately transferred to the cardiac catheterization laboratory. Coronary angiography demonstrated late thrombotic occlusion within the previously implanted LAD stent, with initial TIMI 0 flow (Figure 3). Balloon angioplasty was performed to restore coronary perfusion. During the procedure, plaque shift resulted in compromise of the diagonal branch. Therefore, kissing balloon inflation was successfully performed to preserve the side branch and optimize bifurcation flow. Final angiography demonstrated restoration of TIMI 3 flow in both the LAD and diagonal branch without the need for additional stent implantation (Figure 3).

## ABBREVIATIONS

| | |
|---|---|
| APS | Antiphospholipid syndrome |
| ARC | Academic Research Consortium |
| ICD | Implantable cardioverter-defibrillator |
| LAD | Left anterior descending |
| LVEF | Left ventricular ejection fraction |
| PCI | Percutaneous coronary intervention |

Following successful revascularization, the patient was admitted to the tertiary cardiac intensive care unit for post-resuscitation management. He was successfully extubated after stabilization. Transthoracic echocardiography demonstrated a left ventricular ejection fraction (LVEF) of 30%. Despite three months of guideline-directed medical therapy, severe left ventricular systolic dysfunction persisted; therefore, an implantable cardioverter-defibrillator (ICD) was implanted for primary prevention of sudden cardiac death.

Considering the patient's young age, recurrent myocardial infarction due to late stent thrombosis in the absence of a history suggestive of nonadherence to medical therapy, and the absence of hypertension, diabetes mellitus, marked on-treatment dyslipidemia, or a family history of premature atherosclerotic cardiovascular disease, an extended etiological evaluation was undertaken.

The results of the laboratory evaluation for APS and thrombophilia are summarized in Table 1. A summary of the diagnostic features supporting the clinical diagnosis of primary APS is presented in Table 2.[6] Baseline cardiovascular risk factors and biochemical findings are presented in Table 3.

Laboratory investigations demonstrated persistent lupus anticoagulant positivity on two occasions approximately 20 weeks apart, whereas anticardiolipin antibodies and anti-β2 glycoprotein I antibodies remained negative. The repeat lupus anticoagulant test was performed approximately 20 weeks after the initial test while the patient was receiving dual antiplatelet therapy without anticoagulant treatment. The initial lupus anticoagulant test was performed after the anticoagulant effect of unfractionated heparin had resolved, making clinically relevant heparin interference unlikely. Protein C, protein S, and antithrombin III activities were within normal limits (Table 1). The patient was evaluated by the Rheumatology Department. Additional evaluation, including antinuclear antibody testing, complement (C3 and C4) levels, and assessment for alternative autoimmune and vasculitic disorders, including Behçet disease and Takayasu arteritis, did not identify an underlying autoimmune or vasculitic disorder suggestive of secondary APS. Following multidisciplinary evaluation by the Cardiology and Rheumatology departments, primary APS was considered the most likely diagnosis. Long-term vitamin K antagonist therapy was recommended after multidisciplinary consultation; however, the patient declined anticoagulation despite detailed counseling and continued dual antiplatelet therapy.

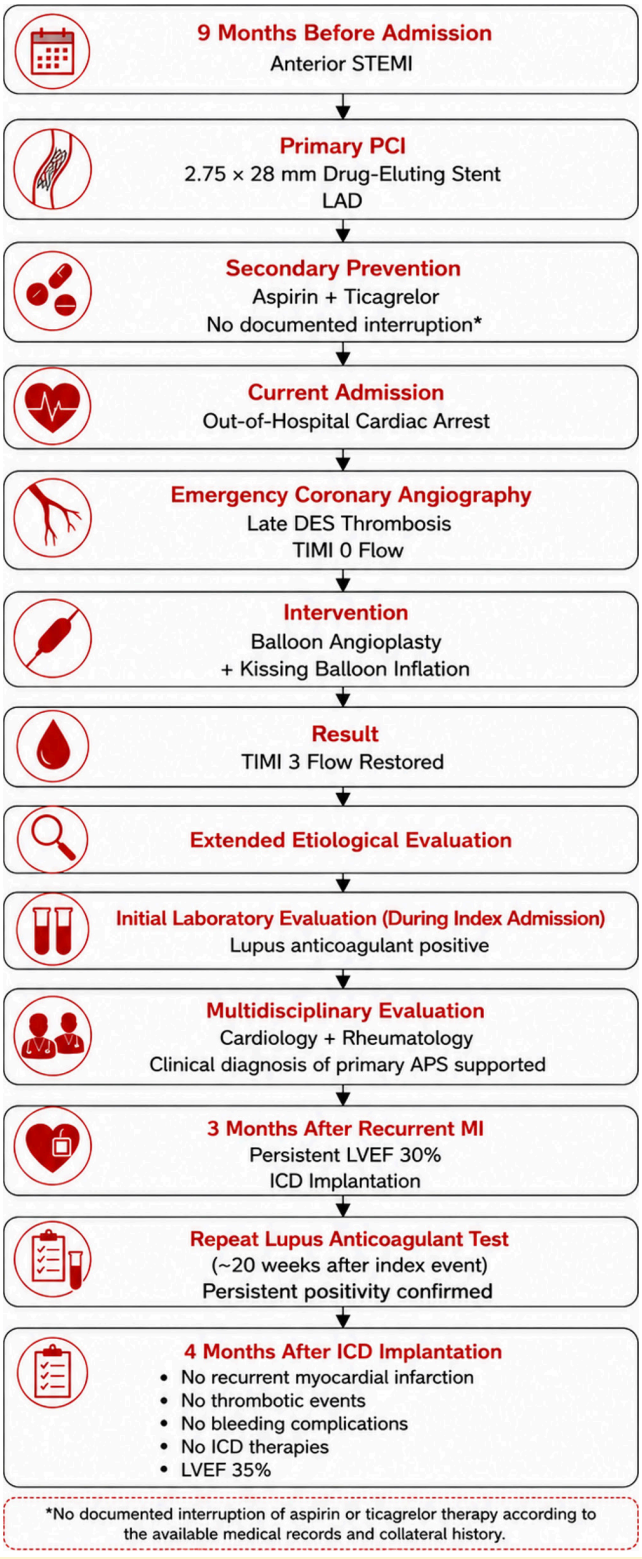



**Figure 1.** Chronological clinical course of the patient.

Clinical timeline illustrating the patient's course from the index anterior ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention and drug-eluting stent implantation in the left anterior descending artery to recurrent myocardial infarction caused by late stent thrombosis, etiological evaluation, confirmation of persistent lupus anticoagulant positivity, multidisciplinary assessment supporting a clinical diagnosis of primary antiphospholipid syndrome, implantable cardioverter-defibrillator implantation, and follow-up. No documented interruption of aspirin or ticagrelor therapy was identified based on the available medical records and collateral history.

At the 4-month follow-up after ICD implantation, the patient remained free of recurrent myocardial infarction, thrombotic events, bleeding complications, or ICD therapies. Left ventricular systolic function showed partial recovery, with an LVEF of 35%, and regular outpatient follow-up was continued.

## Discussion

Recurrent myocardial infarction in young adults remains a significant diagnostic challenge because conventional cardiovascular risk factors do not fully explain every case. Although smoking, hypertension, diabetes mellitus, dyslipidemia, and a positive family history account for the majority of premature myocardial infarctions, clinicians should consider alternative etiologies when recurrent thrombotic events occur despite appropriate secondary prevention therapy.[1-3] In the present case, recurrent anterior ST-segment elevation myocardial infarction developed nine months after implantation of a 2.75 × 28 mm drug-eluting stent because of late stent thrombosis. Given the patient's young age, recurrent myocardial infarction secondary to late stent thrombosis, and the absence of conventional atherosclerotic cardiovascular risk factors that could adequately explain this clinical presentation, a systematic evaluation for acquired and inherited thrombophilic disorders was undertaken.

Late stent thrombosis is an uncommon but potentially fatal complication of PCI. According to the Academic Research Consortium (ARC), late stent thrombosis is defined as thrombosis occurring between 30 days and one year after stent implantation.[7] Despite advances in stent technology and antiplatelet therapy, late stent thrombosis continues to be associated with high mortality and recurrent myocardial infarction. Recent studies have also identified several clinical and biochemical factors associated with an increased risk of stent thrombosis.[8,9] Its pathophysiology is multifactorial and includes procedural factors such as stent underexpansion and malapposition, as well as delayed endothelial healing, neoatherosclerosis, premature discontinuation of dual antiplatelet therapy, and systemic prothrombotic conditions.[7-9] In our patient, there was no documented interruption of aspirin or ticagrelor therapy according to the available medical records and collateral history, making treatment interruption a less likely explanation for the recurrent thrombotic event. Although intravascular imaging was not available to exclude mechanical factors such as stent underexpansion or malapposition, the overall clinical and laboratory findings supporting a clinical diagnosis of primary APS suggested that an acquired prothrombotic mechanism likely contributed to the recurrent thrombotic event.

APS is an acquired autoimmune thrombophilic disorder characterized by recurrent arterial and/or venous thrombosis associated with persistent antiphospholipid antibodies.[10] Although venous thromboembolism represents the most common clinical manifestation, arterial thrombosis accounts for approximately one-third of thrombotic events, with ischemic stroke being the predominant presentation.[10] Coronary artery involvement is relatively uncommon but may manifest as acute myocardial infarction, recurrent coronary thrombosis, or stent thrombosis.[11] Similar coronary thrombotic manifestations associated with APS have also been described in the literature.[12] Therefore, APS should be considered in young patients presenting with recurrent

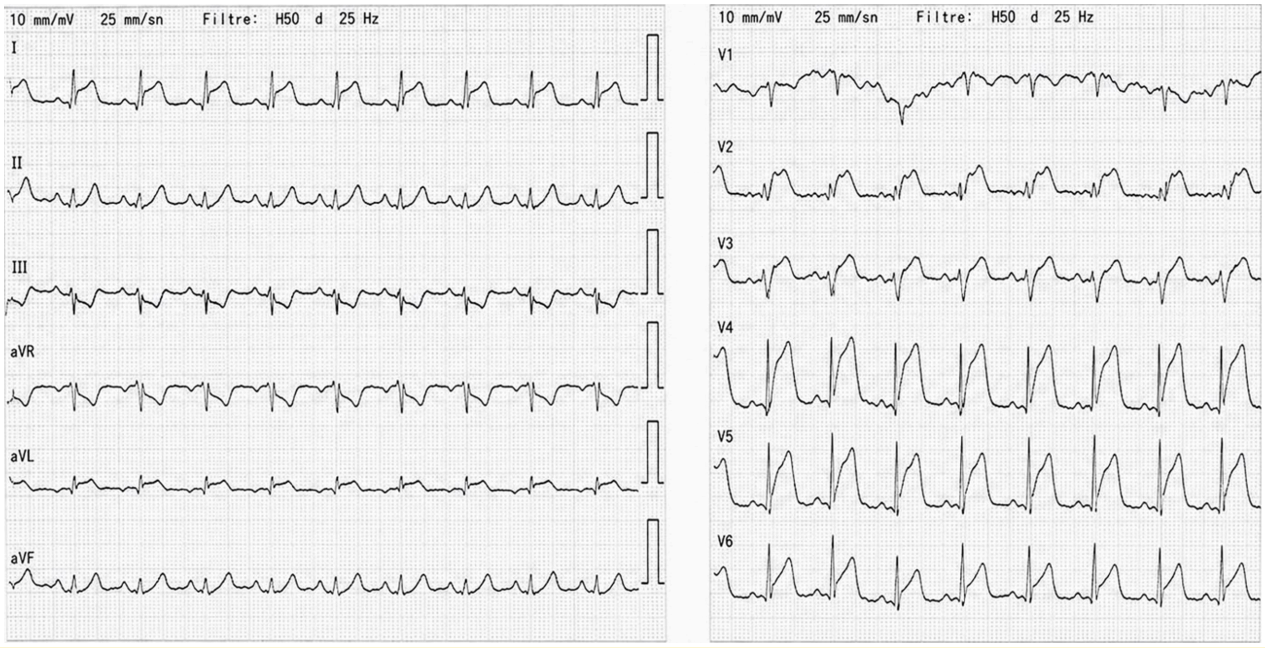



**Figure 2.** Twelve-lead electrocardiogram at presentation.

Twelve-lead electrocardiogram obtained after successful cardiopulmonary resuscitation and return of spontaneous circulation, demonstrating recurrent anterior ST-segment elevation myocardial infarction.

coronary thrombosis when conventional cardiovascular risk factors are insufficient to explain the clinical presentation.

APS screening is not routinely recommended in all young patients presenting with myocardial infarction. In the present case, however, the decision to investigate for APS was prompted by recurrent myocardial infarction due to late drug-eluting stent thrombosis despite appropriate medical therapy, the patient's young age, the absence of conventional atherosclerotic cardiovascular risk factors that could adequately explain the recurrent myocardial infarction, and the lack of an alternative explanation after coronary angiographic evaluation. Taken together, these clinical findings prompted a systematic etiological evaluation.

Repeated lupus anticoagulant positivity together with recurrent arterial thrombosis prompted consultation with the Rheumatology Department. Additional evaluation, including antinuclear antibody testing, complement (C3 and C4) levels, and assessment for alternative autoimmune and vasculitic disorders, including Behçet disease and Takayasu arteritis, did not identify an underlying autoimmune or vasculitic disorder suggestive of secondary APS. Protein C, protein S, and antithrombin III activities were within normal limits, whereas anticardiolipin antibodies and anti-β2 glycoprotein I antibodies were negative. Taken together, the clinical and laboratory findings were consistent with primary APS in the appropriate clinical context. This case illustrates the importance of integrating clinical findings with laboratory results when evaluating young patients with unexplained recurrent coronary thrombosis.

The optimal antithrombotic strategy for APS-related arterial thrombosis remains controversial. Current EULAR recommendations support long-term vitamin K antagonist therapy in patients with thrombotic APS, particularly after arterial thrombotic events, whereas direct oral anticoagulants are generally not recommended in high-risk APS because of concerns regarding recurrent arterial thrombosis.[13] In accordance with these recommendations, long-term vitamin K antagonist therapy was recommended for our patient. However, despite detailed counseling regarding the risk of recurrent thrombosis, the patient declined anticoagulant therapy and continued dual antiplatelet therapy alone. This scenario reflects a common challenge in clinical practice and underscores the importance of shared decision-making and careful patient education.

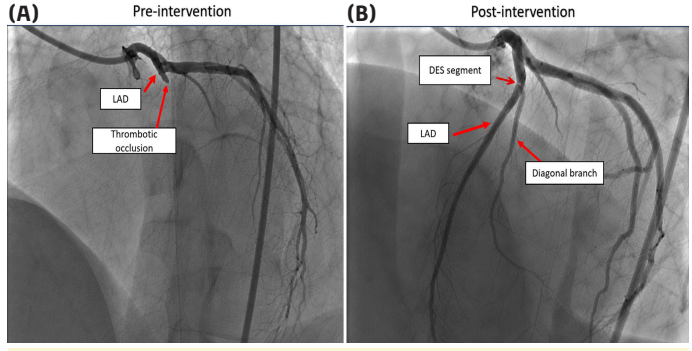



**Figure 3.** Coronary angiographic findings in late stent thrombosis before and after intervention.

(A) Coronary angiography demonstrating thrombotic occlusion within the previously implanted drug-eluting stent (DES) segment in the proximal left anterior descending artery (LAD), resulting in TIMI 0 flow. The labels and red arrows indicate the LAD, DES segment, and thrombotic occlusion. (B) Final angiographic result after balloon angioplasty and kissing balloon inflation, demonstrating restoration of TIMI 3 flow in both the LAD and diagonal branch without additional stent implantation. The labels and red arrows indicate the LAD, previously implanted DES segment, and diagonal branch.

**Table 1.** Laboratory evaluation for antiphospholipid syndrome and thrombophilia

| Investigation | Clinical timing | Result | Reference range/ cut-off | Interpretation |
|---|---|---|---|---|
| Lupus anticoagulant (screen) | During current admission following recurrent MI | 49.6 s | 31–44 s | Positive screening test |
| Lupus anticoagulant (confirm) | During current admission following recurrent MI | 39.6 s | 30–38 s | Positive confirmatory test |
| Lupus anticoagulant ratio | During current admission following recurrent MI | 1.30 | Positive | Positive |
| Lupus anticoagulant ratio (repeat) | Approximately 20 weeks later | 1.46 | Positive (external laboratory) | Persistent positivity fulfilling the APS laboratory criterion |
| Anticardiolipin IgG | During rheumatology evaluation | 0.84 GPL-U/mL | <10 GPL-U/mL | Negative |
| Anticardiolipin IgM | During rheumatology evaluation | 3.01 MPL-U/mL | <7 MPL-U/mL | Negative |
| Anti-β2 glycoprotein I IgG | During rheumatology evaluation | <0.5 IU/mL | Negative | Negative |
| Anti-β2 glycoprotein I IgM | During rheumatology evaluation | <1.0 IU/mL | Negative | Negative |
| Protein C activity | During rheumatology evaluation | 86.2% | 60–175% | Within normal limits |
| Protein S activity | During rheumatology evaluation | 113.4% | 50–143% | Within normal limits |
| Antithrombin III activity | During rheumatology evaluation | 116.8% | 70–130% | Within normal limits |
| Antinuclear antibody (ANA) | During rheumatology evaluation | Negative | Negative | No evidence of connective tissue disease |

ANA, Antinuclear antibody; APS, Antiphospholipid syndrome; GPL, IgG phospholipid units; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IU, International units; LA, Lupus anticoagulant; MI, Myocardial infarction; MPL, IgM phospholipid units; s, Seconds.

**Table 2.** Practical considerations in the interpretation of Antiphospholipid Antibody Testing

| **What should be considered when measuring and interpreting antiphospholipid antibodies?** |
|---|
| Antiphospholipid antibodies should be assessed using three laboratory tests:<br>1. Lupus anticoagulant (LA)<br>2. Anticardiolipin antibodies (aCL IgG and IgM)<br>3. Anti-β2 glycoprotein I antibodies (anti-β2GPI IgG and IgM)<br>Clinically significant positivity is defined as a value above the laboratory-specific 99$^{th}$ percentile.<br>Positive results should be confirmed by repeat testing at least 12 weeks later. |
| Antiphospholipid antibodies may become temporarily positive in the following situations:<br>1. Acute infections<br>2. Acute thrombosis or severe inflammation<br>3. Recent viral infections<br>4. Certain medications<br>5. Acute illness or hospitalization |
| **Use of anticoagulants during testing**<br>This is particularly important for LA testing:<br>● Heparin<br>● Warfarin<br>● Apixaban, rivaroxaban, dabigatran, and other DOACs<br>These anticoagulants may interfere with LA testing and can produce false-positive or, occasionally, false-negative results. Therefore, the timing of testing should be coordinated with the hematology and coagulation laboratory, and the anticoagulant used and the time of the last dose should be reported. Anticoagulant therapy should not be discontinued solely for testing purposes without clinical supervision.[6]<br>Because aCL and anti-β2GPI are solid-phase immunological tests, they are less affected by anticoagulants than LA testing. |

LA, Lupus anticoagulant; aCL, Anticardiolipin antibody; anti-β2GPI, Anti-β2 glycoprotein I antibody; DOACs, Direct oral anticoagulants; IgG, Immunoglobulin G; IgM, Immunoglobulin M.

A systematic etiological evaluation should be considered when recurrent coronary thrombosis occurs without an apparent explanation after appropriate clinical and angiographic evaluation, particularly in young patients without conventional atherosclerotic cardiovascular risk factors. Finally, close collaboration between cardiologists and rheumatologists is essential for identifying the underlying cause and optimizing long-term management in these patients.

## Limitations

This report has several limitations. First, as a single-patient case report, its findings cannot be generalized. Second, intravascular imaging was not performed during either coronary intervention; therefore, mechanical causes of late stent thrombosis, such as stent underexpansion or malapposition, could not be completely excluded. Third, platelet function testing was not performed, and adherence to dual antiplatelet therapy was assessed based on patient history and medical records rather than by an objective adherence measure. Fourth, although the patient was referred for genetic thrombophilia testing, the results were not available in the institutional medical records because they were released directly to the patient and were therefore unavailable for retrospective review. In addition, Lp(a), ApoB, and pretreatment lipid values were unavailable, limiting a comprehensive assessment of cardiovascular risk factors. Finally, the follow-up period was relatively short, particularly considering the patient's decision to decline vitamin K antagonist therapy. Nevertheless, persistent lupus anticoagulant positivity confirmed on two occasions approximately 20 weeks apart, together with recurrent arterial thrombosis, was consistent with primary APS in the appropriate clinical context.

## Conclusion

This case highlights the importance of considering acquired thrombophilic disorders, particularly APS, in young patients

**Table 3.** Baseline cardiovascular risk factors and biochemical profile

| Parameters | Values |
|---|---|
| Age | 39 years |
| Sex | Male |
| Body mass index | 28.9 kg/m² |
| Blood pressure | Normotensive (no history of hypertension) |
| Diabetes mellitus | No history of diabetes mellitus |
| Smoking | Occasional smoker |
| Family history of premature ASCVD | Absent |
| Total cholesterol | 111 mg/dL |
| LDL-C | 58.6 mg/dL |
| HDL-C | 39 mg/dL |
| Triglycerides | 67 mg/dL |
| Non-HDL-C | 72 mg/dL |
| Serum creatinine | 0.66 mg/dL |
| eGFR | 122.7 mL/min/1.73 m² |
| Glucose* | 125 mg/dL |
| HbA1c | 6.2% (prediabetic range) |
| Statin therapy | High-intensity statin therapy |
| ApoB | Not available |
| Lp(a) | Not available |

ApoB, Apolipoprotein B; ASCVD, Atherosclerotic cardiovascular disease; BMI, Body mass index; eGFR, Estimated glomerular filtration rate; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); non-HDL-C, Non-high-density lipoprotein cholesterol. *Random plasma glucose measured during the index hospitalization.

with recurrent myocardial infarction secondary to late drug-eluting stent thrombosis when conventional atherosclerotic cardiovascular risk factors do not adequately explain the clinical presentation. A systematic etiological evaluation may facilitate timely diagnosis and appropriate long-term management in selected patients.

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent was obtained from the patient for publication of this case report.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Peer-review:** Externally peer-reviewed.

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# Cardiac Arrest in Premature Myocardial Infarction: A Window for Etiologic Evaluation

## Prematür Miyokard Enfarktüsünde Kalp Durması: Etiyolojik Değerlendirme İçin Bir Fırsat

**EDITORIAL COMMENT**
EDİTORYAL YORUM

The presented case by Tunçez et al.[1] provides an important illustration of primary antiphospholipid syndrome diagnosed after recurrent anterior myocardial infarction (MI) caused by late drug-eluting stent thrombosis and complicated by out-of-hospital cardiac arrest in a young patient. Beyond the recurrent coronary event itself, the occurrence of cardiac arrest at only 39 years of age highlights a broader educational message: premature MI should be regarded as an opportunity for etiologic assessment from the first event rather than simply as an isolated coronary episode.

At the time of the index MI, the patient was only 39 years old and had no documented hypertension or diabetes mellitus, family history of premature atherosclerotic cardiovascular disease, or thrombotic disorders. Although occasional smoking, overweight, and mild abnormalities in glycemic status may have contributed to premature atherosclerosis, the unusually young age at presentation warranted consideration of additional etiologic contributors. This raises an important clinical question: was a broader etiologic evaluation considered at the time of the index MI, and could earlier investigation have identified an underlying prothrombotic condition before recurrent coronary thrombosis occurred?

Premature MI should not automatically be attributed solely to conventional atherosclerotic mechanisms. In young patients, additional or alternative etiologies should be considered, including acquired thrombophilic disorders, inflammatory or autoimmune diseases, coronary vasospasm, substance-related coronary injury, coronary anomalies, and other nonatherosclerotic causes. Importantly, the presence of one or more conventional cardiovascular risk factors should not preclude consideration of these alternative mechanisms. In patients presenting with MI before the age of 40 years, evaluation for nontraditional contributors has been emphasized because conventional and nonconventional mechanisms may coexist in the same patient.[2]

This principle should nevertheless be distinguished from indiscriminate thrombophilia screening. Current guidance does not support routine testing for inherited thrombophilia after arterial thrombosis because such findings rarely influence clinical management. In contrast, testing for antiphospholipid antibodies may be appropriate in younger patients with arterial thrombosis, particularly when other vascular risk factors or significant atherosclerosis are absent, because the diagnosis may substantially influence long-term antithrombotic management.[3] In this context, the patient's index MI already represented a clinical scenario in which an acquired thrombophilic disorder, including antiphospholipid syndrome, could reasonably have been considered. Earlier recognition might have influenced secondary prevention before the subsequent episode of late stent thrombosis. At the same time, the recurrent event should not necessarily be attributed to a single systemic mechanism. Because intravascular imaging was not performed, mechanical contributors to late stent thrombosis, such as stent underexpansion or malapposition, could not be definitively excluded. Thus, an underlying prothrombotic state and local mechanical factors should be regarded as potentially complementary rather than mutually exclusive mechanisms.

Cardiovascular risk assessment at the time of the index event is also relevant. In the current report, pretreatment lipid levels, apolipoprotein B, and lipoprotein(a) values were unavailable. In a patient presenting with MI at such a young age, these measurements may provide important information regarding previously unrecognized

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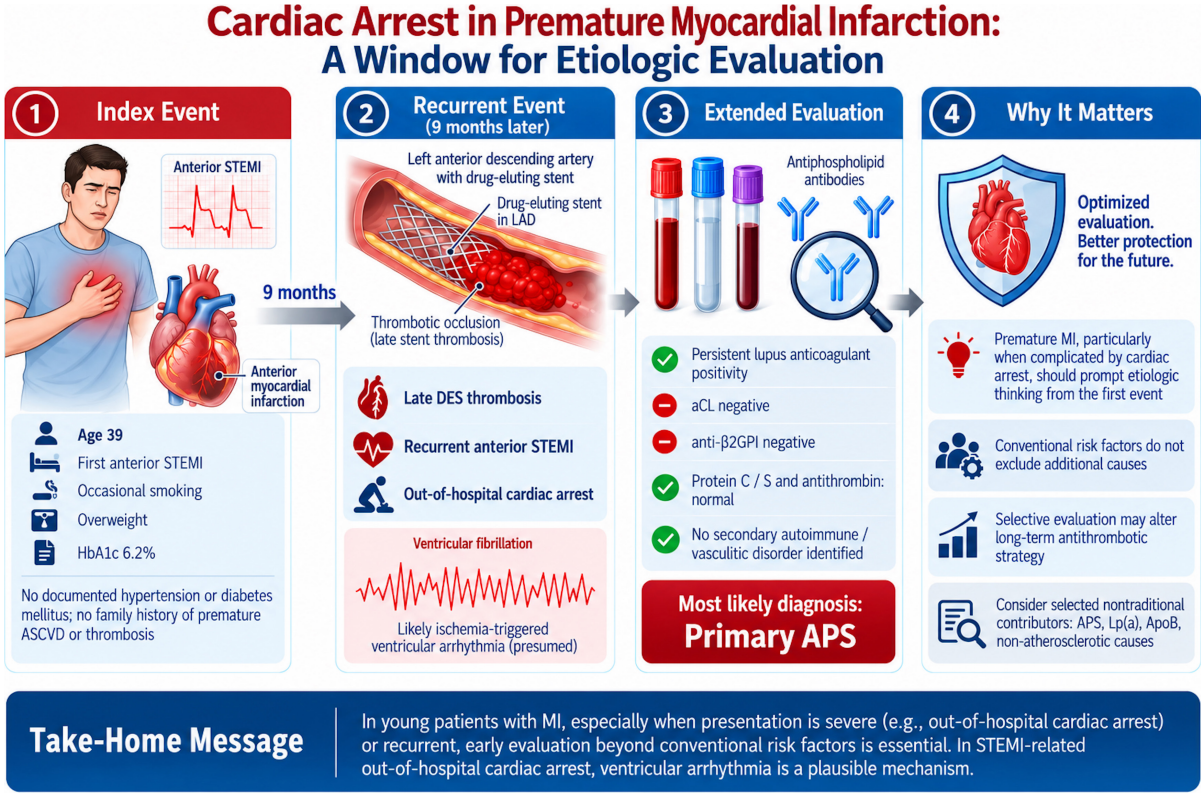
inherited or nontraditional atherogenic risk. Contemporary dyslipidemia guidelines recommend measurement of lipoprotein(a) at least once during adulthood and emphasize its particular relevance in individuals with premature atherosclerotic cardiovascular disease.[4] Thus, the evaluation of premature MI should extend beyond conventional risk factors and selected prothrombotic conditions to include less apparent lipid-related and nonatherosclerotic contributors.

A particularly distinctive feature of this case is the out-of-hospital cardiac arrest accompanying the recurrent STEMI. The report establishes the presence of an acute anterior ST-segment elevation MI due to late thrombotic occlusion of the previously implanted left anterior descending artery stent after return of spontaneous circulation. However, the initial rhythm responsible for the cardiac arrest is not reported. In acute ST-segment elevation MI, ongoing myocardial ischemia is a well-recognized trigger for malignant ventricular arrhythmias, particularly ventricular tachycardia and ventricular fibrillation.[5] Accordingly, in this patient, an ischemia-triggered ventricular arrhythmia secondary to stent thrombosis represents a highly plausible mechanism for the out-of-hospital cardiac arrest. Nevertheless, unless the initial rhythm was documented by emergency medical services or an automated external defibrillator, this mechanism should be regarded as presumed rather than established. If such rhythm documentation is available, its inclusion would further strengthen the clinical narrative. Contemporary European Society of Cardiology guidelines also emphasize the systematic evaluation of survivors of sudden cardiac arrest to identify the underlying mechanism.[6]

In conclusion, this case illustrates that premature MI, particularly when the clinical course is severe, recurrent, or complicated by out-of-hospital cardiac arrest, should prompt careful etiologic consideration. Conventional cardiovascular risk factors may contribute to premature atherosclerosis, but their presence should not preclude consideration of additional prothrombotic, inflammatory, genetic, metabolic, or other nonatherosclerotic contributors. Recognition of such factors at the first cardiovascular event may significantly influence secondary prevention and potentially reduce the risk of recurrence (Graphical Abstract).

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# Very Young ST-Segment Elevation Myocardial Infarction Associated with Chronic Nonmedical Anabolic-Androgenic Steroid Use: A Case Report

## Kronik Tıbbi Endikasyon Dışı Anabolik-Androjenik Steroid Kullanımı ile İlişkili Çok Genç Yaşta ST Yükselmeli Miyokard Enfarktüsü: Olgu Sunumu

**ABSTRACT**

Myocardial infarction (MI) before the age of 40 years is uncommon and warrants a comprehensive evaluation of potential etiologies. Chronic nonmedical anabolic-androgenic steroid (AAS) use has been associated with endothelial dysfunction, accelerated atherosclerosis, and a prothrombotic state, all of which may contribute to premature coronary artery disease. A 29-year-old man with no known medical history and approximately two years of nonmedical testosterone and stanozolol use presented with acute chest pain. Electrocardiography revealed an anterior ST-segment elevation myocardial infarction (STEMI). Emergency coronary angiography demonstrated a thrombotic total occlusion of the mid-left anterior descending coronary artery. Primary percutaneous coronary intervention restored coronary blood flow. The patient presented with Killip class II acute heart failure requiring temporary continuous positive airway pressure (CPAP) and inotropic support. Transthoracic echocardiography (TTE) revealed a left ventricular ejection fraction (LVEF) of 30–35%, with anterior and apical hypokinesia. Admission laboratory tests revealed marked atherogenic dyslipidemia (total cholesterol, 302 mg/dL; low-density lipoprotein cholesterol, 250 mg/dL; high-density lipoprotein cholesterol, 29 mg/dL; triglycerides, 113 mg/dL; and non-high-density lipoprotein cholesterol, 273 mg/dL). In addition to the culprit lesion, nonobstructive atherosclerotic plaques were identified in other coronary segments. At the one-month follow-up, low-density lipoprotein cholesterol had decreased to 85 mg/dL following statin therapy and the reported discontinuation of AAS use. At three months, the patient remained clinically stable, although LVEF remained at 30%. AAS exposure may have contributed to accelerated atherosclerosis and coronary thrombosis in a susceptible young individual. However, alternative causes of MI at a very young age should be systematically considered.

**Keywords:** Dyslipidaemias, myocardial ischemia, myocardial revascularization, percutaneous coronary intervention, young myocardial infarction.

**ÖZET**

Kırk yaşından önce gelişen miyokard enfarktüsü nadir görülür ve olası etiyolojilerin kapsamlı biçimde değerlendirilmesini gerektirir. Kronik tıbbi endikasyon dışı anabolik-androjenik steroid (AAS) kullanımı, endotel disfonksiyonu, hızlanmış ateroskleroz ve protrombotik durum ile ilişkilendirilmiş olup bu mekanizmaların tümü erken koroner arter hastalığı gelişimine katkıda bulunabilir. Bilinen herhangi bir hastalık öyküsü bulunmayan ve yaklaşık iki yıldır tıbbi endikasyon dışı testosteron ve stanozolol kullanan 29 yaşındaki erkek hasta, akut göğüs ağrısı ile başvurdu. Elektrokardiyografide anterior ST yükselmeli miyokard enfarktüsü (STEMI) saptandı. Koroner anjiyografide sol ön inen koroner arterin (LAD) orta segmentinde trombotik total oklüzyon izlendi. Primer perkütan koroner girişim ile koroner kan akımı yeniden sağlandı. Hastada, geçici sürekli pozitif hava yolu basıncı (CPAP) ve inotropik destek gerektiren Killip sınıf II akut kalp yetersizliği mevcuttu. İşlem sonrasında yoğun bakımda izleme alındı. Transtorasik ekokardiyografide (TTE), anterior ve apikal hipokinezi ile birlikte sol ventrikül ejeksiyon fraksiyonu (LVEF) %30–35 olarak saptandı. Başvuru sırasında yapılan laboratuvar incelemelerinde belirgin aterojenik dislipidemi saptandı: total kolesterol 302 mg/dL, düşük yoğunluklu lipoprotein kolesterol (LDL-K) 250 mg/dL, yüksek yoğunluklu lipoprotein kolesterol (HDL-K) 29 mg/dL, trigliserid 113 mg/dL ve yüksek yoğunluklu lipoprotein dışı kolesterol (non-HDL kolesterol) 273 mg/dL. Diğer koroner segmentlerde de obstrüktif olmayan aterosklerotik plaklar saptandı. Birinci ay kontrolünde, statin tedavisi ve hastanın AAS kullanımını bıraktığını bildirmesinin ardından LDL-K düzeyi 85 mg/dL'ye geriledi. Üçüncü ayda hasta klinik olarak stabil olmasına rağmen LVEF %30 düzeyinde kalmaya devam etti. AAS maruziyeti, yatkınlığı bulunan genç bir bireyde hızlanmış ateroskleroz ve koroner tromboz gelişimine katkıda bulunmuş olabilir. Bununla birlikte, çok genç yaşta gelişen miyokard enfarktüsünün alternatif nedenleri sistematik olarak değerlendirilmelidir.

**Anahtar Kelimeler:** Dislipidemiler, miyokard iskemisi, miyokard revaskülarizasyonu, perkütan koroner girişim, genç yaşta miyokard enfarktüsü.

**CASE REPORT**
OLGU SUNUMU

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Although myocardial infarction (MI) in young individuals is commonly defined as MI occurring before the age of 45 years, events occurring before the age of 40 years are frequently classified as very young MI.[1] Very young MI is uncommon and represents a distinct clinical entity requiring comprehensive etiological evaluation. Although premature atherosclerosis remains the leading cause, inherited disorders, thrombophilia, inflammatory diseases, coronary anomalies, substance abuse, spontaneous coronary artery dissection, and other nontraditional cardiovascular risk factors should also be systematically considered in this population. Therefore, identifying potentially reversible causes is particularly important for both secondary prevention and family risk assessment.

Nonmedical use of anabolic-androgenic steroids (AAS) has become increasingly prevalent among recreational athletes and bodybuilders seeking to increase muscle mass and improve physical performance. Beyond their anabolic effects, chronic AAS exposure has been associated with multiple adverse cardiovascular effects, including endothelial dysfunction, accelerated atherosclerosis, coronary vasomotor abnormalities, and a prothrombotic state.[2–6] Nevertheless, the relationship between chronic AAS use and premature MI remains complex, and causality cannot be established from individual case reports because conventional and nonconventional cardiovascular risk factors frequently coexist.

Herein, we report the case of a 29-year-old man who presented with anterior ST-segment elevation myocardial infarction (STEMI) in the setting of chronic nonmedical testosterone and stanozolol use, severe dyslipidemia, extensive intracoronary thrombus burden, and angiographic evidence of nonculprit atherosclerotic plaques. This case highlights the importance of obtaining a detailed history of performance-enhancing drug use while emphasizing the need for a systematic etiological evaluation in patients presenting with MI at a very young age.

## Case Report

A 29-year-old man presented to the emergency department with severe retrosternal chest pain radiating to the left arm that had persisted for approximately two hours. He had no history of hypertension, diabetes mellitus, chronic kidney disease, or known cardiovascular disease. His body mass index was 23.2 kg/m$^2$. He had a 5-pack-year smoking history and reported approximately two years of chronic nonmedical testosterone and stanozolol use to increase muscle mass and enhance physical performance (Table 1).

The patient denied any recent febrile illness or infectious symptoms. He also had no history of autoimmune or inflammatory rheumatic disease, venous or arterial thromboembolism, or other thrombotic events. There was no family history of premature coronary artery disease or sudden cardiac death. He denied using cocaine, amphetamines, or other recreational drugs.

On admission, his blood pressure was 110/70 mmHg, heart rate was 80 beats/min, and oxygen saturation was 95% on room air. Electrocardiography demonstrated ST-segment elevation in the anterior precordial leads, consistent with an acute anterior STEMI. The patient was immediately transferred to the cardiac catheterization laboratory for primary percutaneous coronary intervention (PCI).

## ABBREVIATIONS

| | |
|---|---|
| AAS | Anabolic-androgenic steroid |
| ALT | Alanine aminotransferase |
| ARNI | Angiotensin receptor–neprilysin inhibitor |
| AST | Aspartate aminotransferase |
| CPAP | Continuous positive airway pressure |
| HDL-C | High-density lipoprotein cholesterol |
| ICD | Implantable cardioverter-defibrillator |
| LAD | Left anterior descending |
| LDL-C | Low-density lipoprotein cholesterol |
| LVEF | Left ventricular ejection fraction |
| MI | Myocardial infarction |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| PCI | Percutaneous coronary intervention |
| STEMI | ST-segment elevation myocardial infarction |
| TTE | Transthoracic echocardiography |

**Table 1.** Baseline demographic and clinical characteristics of the patient

| Variables | Finding |
|---|---|
| Age (years) | 29 |
| Sex | Male |
| Body mass index (kg/m$^2$) | 23.2 |
| Smoking history | 5 pack-years |
| Hypertension | No |
| Diabetes mellitus | No |
| Chronic kidney disease | No |
| Family history of premature coronary artery disease | None |
| Autoimmune or rheumatic disease | None reported |
| Recent infection | None reported |
| History of thromboembolic events | None |
| Recreational drug use | Denied |
| Anabolic-androgenic steroid exposure | Approximately 2 years of nonmedical testosterone and stanozolol use |
| Presenting symptom | Retrosternal chest pain radiating to the left arm |
| Symptom duration | Approximately 2 hours |
| Killip class | II |
| Electrocardiographic findings | Anterior ST-segment elevation myocardial infarction |
| Initial left ventricular ejection fraction (%) | 30–35 |

AAS, anabolic-androgenic steroid.

Initial laboratory evaluation revealed marked myocardial injury, with a high-sensitivity cardiac troponin T level exceeding 10,000 ng/L. The white blood cell count was elevated at 18.18 × 10$^9$/L, whereas hemoglobin and platelet counts were within normal limits. Serum creatinine was 0.91 mg/dL (estimated glomerular filtration rate [eGFR], 113.49 mL/min/1.73 m$^2$), and electrolyte levels were within normal limits (Table 2).

**Table 2.** Laboratory findings at admission and at the 1-month follow-up

| Parameters | Admission | 1-month follow-up |
|---|---|---|
| White blood cell count (×10⁹/L) | 18.18 | 7.16 |
| Hemoglobin (g/dL) | 15.9 | 16.4 |
| Platelet count (×10⁹/L) | 359 | 347 |
| Serum creatinine (mg/dL) | 0.91 | 1.25 |
| Estimated glomerular filtration rate (mL/min/1.73 m²) | 113.49 | 77.31 |
| Aspartate aminotransferase (IU/L) | 638 | 50 |
| Alanine aminotransferase (IU/L) | 148 | 88 |
| N-terminal pro-B-type natriuretic peptide (pg/mL) | 398.6 | 1329 |
| Total cholesterol (mg/dL) | 302 | 184 |
| Low-density lipoprotein cholesterol (mg/dL) | 250 | 85 |
| High-density lipoprotein cholesterol (mg/dL) | 29 | 35 |
| Triglycerides (mg/dL) | 113 | 318 |
| Non-high-density lipoprotein cholesterol (mg/dL) | 273 | 149 |
| Lipoprotein(a) (g/L) | Not measured | <0.085 |
| Glycated hemoglobin (%) | Not measured | 5.22 |
| Fasting glucose (mg/dL) | Not measured | 79 |

Liver enzyme levels were elevated (aspartate aminotransferase [AST], 638 IU/L; alanine aminotransferase [ALT], 148 IU/L). The N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 398.6 pg/mL. Thyroid function tests were within normal limits.

The lipid profile revealed severe atherogenic dyslipidemia, with total cholesterol of 302 mg/dL, low-density lipoprotein cholesterol (LDL-C) of 250 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 29 mg/dL, triglycerides of 113 mg/dL, and non-HDL cholesterol of 273 mg/dL. Lipid measurements obtained before the index MI could not be verified because the patient's historical laboratory records were not accessible through the national electronic health record system (e-Nabız).

Transthoracic echocardiography (TTE) demonstrated a left ventricular ejection fraction (LVEF) of 30–35%, with hypokinesia of the anterior and apical left ventricular segments, consistent with extensive anterior MI.

Emergency coronary angiography revealed a thrombotic total occlusion of the mid-left anterior descending (LAD) coronary artery. In addition to the culprit lesion, nonobstructive atherosclerotic plaques were observed in the remaining coronary arteries (Figure 1A).

Primary PCI was performed immediately. Following predilation, a large thrombus burden (Thrombolysis in Myocardial Infarction [TIMI] thrombus grade 4) was observed. Selective manual thrombus aspiration was performed because of the substantial thrombus burden, followed by intracoronary administration of tirofiban (Figure 1B). A drug-eluting stent was subsequently implanted in the mid-LAD, restoring TIMI grade 3 flow and achieving an optimal angiographic result.

Intravascular imaging using intravascular ultrasound or optical coherence tomography was not performed because the patient presented with an acute STEMI requiring immediate reperfusion in the presence of a large thrombus burden.

Following successful primary PCI, the patient was admitted to the coronary intensive care unit (Figure 1C). During the acute phase, he developed Killip class II acute heart failure requiring temporary continuous positive airway pressure (CPAP) support. Short-term inotropic therapy was administered because of transient hemodynamic compromise characterized by hypotension and concern for reduced cardiac output in the setting of extensive anterior MI. His hemodynamic status subsequently stabilized, and he did not develop cardiogenic shock during hospitalization.

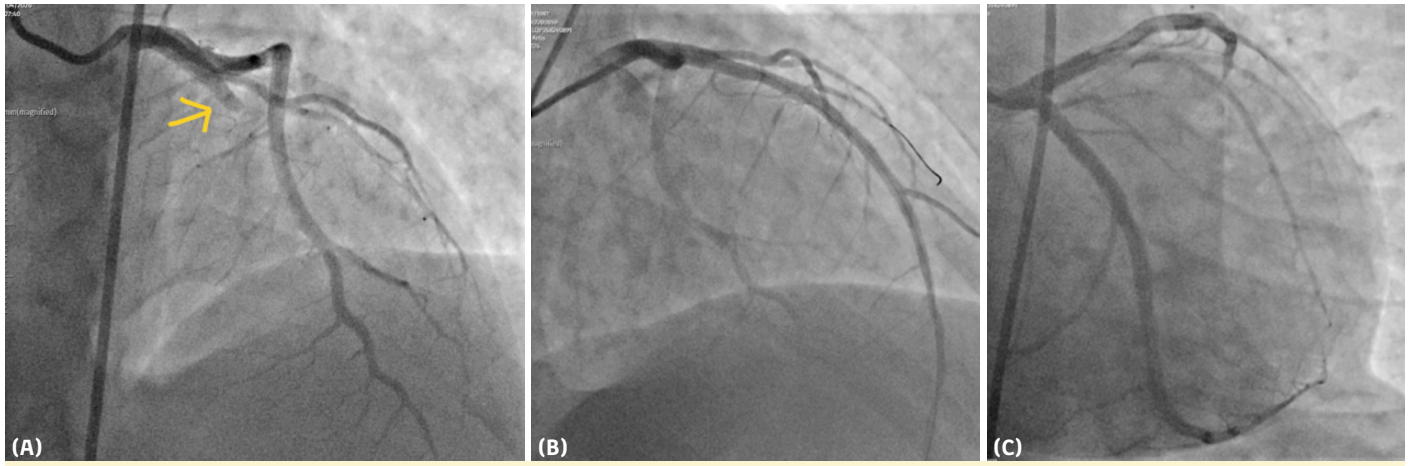



**Figure 1.** (A) Preprocedural coronary angiography demonstrating a thrombotic total occlusion of the mid-left anterior descending coronary artery, with a Thrombolysis in Myocardial Infarction (TIMI) thrombus grade of 4 and TIMI flow grade 0, in an anteroposterior cranial projection. The arrow indicates the culprit lesion. (B) Coronary angiography following selective manual thrombus aspiration and drug-eluting stent implantation, demonstrating restoration of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the left anterior descending coronary artery in a right anterior oblique cranial projection. (C) Final coronary angiography obtained in a right anterior oblique (RAO) caudal projection following percutaneous coronary intervention, demonstrating an optimal postprocedural angiographic result with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow.

The patient was discharged after six days on dual antiplatelet therapy with aspirin and ticagrelor, atorvastatin 40 mg/day, ramipril, metoprolol succinate, spironolactone, and dapagliflozin. Atorvastatin 40 mg/day was initially prescribed because of markedly elevated transaminase levels of uncertain origin, with plans to reassess liver biochemistry and intensify lipid-lowering therapy during follow-up.

He was strongly advised to permanently discontinue anabolic-androgenic steroid use and abstain from smoking.

At the one-month follow-up, the patient remained clinically stable, without recurrent angina or heart failure symptoms. Serum creatinine increased from 0.91 to 1.25 mg/dL, with a corresponding decrease in eGFR from 113.49 to 77.31 mL/min/1.73 $m^2$. This change may have partly reflected the hemodynamic effects of recently initiated guideline-directed heart failure therapy; however, its precise mechanism could not be determined retrospectively. Total cholesterol decreased from 302 to 184 mg/dL, and LDL-C decreased from 250 to 85 mg/dL. HDL-C increased modestly from 29 to 35 mg/dL, whereas triglycerides increased to 318 mg/dL. The fasting status of the admission and follow-up lipid samples could not be verified retrospectively. LDL-C concentrations were calculated using the Friedewald equation. Although the Friedewald equation was applicable at the follow-up triglyceride level of 318 mg/dL, the calculated LDL-C concentration of 85 mg/dL should be interpreted with caution because its accuracy may be reduced in the presence of elevated triglyceride levels.

Liver enzyme levels also improved substantially (AST, from 638 to 50 IU/L; ALT, from 148 to 88 IU/L). Lipoprotein(a) was <0.085 g/L. NT-proBNP was 1329 pg/mL despite the absence of recurrent heart failure symptoms or clinical evidence of decompensation. LDL-C had decreased by more than 50% following discontinuation of AAS use and treatment with atorvastatin 40 mg/day. Nevertheless, because the guideline-recommended LDL-C target for this very-high-risk patient is <55 mg/dL, the atorvastatin dose was subsequently increased to 80 mg/day. Ezetimibe was not initiated at that stage, with additional lipid-lowering therapy to be considered if the LDL-C target was not achieved despite maximally tolerated high-intensity statin therapy.

At the three-month follow-up, repeat TTE demonstrated persistent left ventricular systolic dysfunction, with an LVEF of approximately 30%. The patient remained clinically stable on guideline-directed medical therapy comprising ramipril, metoprolol succinate, spironolactone, and dapagliflozin, with treatment optimized according to clinical tolerance. Transition from ramipril to an angiotensin receptor–neprilysin inhibitor (ARNI) was considered as part of further optimization of heart failure therapy. Given the persistent LVEF of approximately 30% three months after MI and revascularization, the patient was scheduled for formal reassessment of eligibility for a primary-prevention implantable cardioverter-defibrillator (ICD) after completing at least three months of guideline-directed medical therapy.

**Discussion**

MI occurring before the age of 40 years is uncommon and represents a distinct clinical entity that generally requires a more comprehensive etiological evaluation than MI in older adults. In addition to conventional cardiovascular risk factors, inherited lipid disorders, thrombophilic conditions, inflammatory and autoimmune diseases, coronary embolism, spontaneous coronary artery dissection, congenital coronary abnormalities, and exposure to recreational or performance-enhancing substances should be considered in very young patients.[1,7] Identifying reversible or coexisting risk factors is particularly important because these findings may influence secondary prevention, long-term management, and family screening.

The present patient had relatively few documented conventional cardiovascular risk factors. He had a normal body mass index and no known history of hypertension, diabetes mellitus, chronic kidney disease, inflammatory rheumatic disease, previous thromboembolism, or a family history of premature coronary artery disease. Cigarette smoking was an established conventional risk factor. In addition, he reported approximately two years of nonmedical testosterone and stanozolol use for bodybuilding purposes. At presentation, he had severe atherogenic dyslipidemia, including a LDL-C level of 250 mg/dL and a HDL-C level of 29 mg/dL. Coronary angiography revealed a thrombotic total occlusion of the mid-LAD coronary artery, accompanied by mild nonobstructive atherosclerotic plaques causing approximately 10–20% luminal stenosis in the nonculprit coronary arteries. These findings are consistent with acute coronary thrombosis occurring in the presence of premature atherosclerotic disease rather than an isolated thrombotic event in an otherwise angiographically normal coronary circulation. Nevertheless, the relative contributions of AAS exposure, cigarette smoking, severe dyslipidemia, and a possible underlying inherited lipid disorder cannot be determined with certainty.

The cardiovascular effects of supraphysiological AAS exposure involve several interacting mechanisms. Chronic AAS use has been associated with reduced HDL-C, elevated LDL-C, endothelial dysfunction, oxidative stress, vascular inflammation, and accelerated atherosclerosis.[2–4,6,8] In addition, AAS exposure may affect platelet activation, the thromboxane–prostacyclin balance, fibrinolytic activity, and vascular tone, potentially promoting coronary thrombosis.[5,6] Nevertheless, these associations do not establish that AAS exposure was the sole or direct cause of the index event.

The markedly elevated admission LDL-C level also raises the possibility of familial hypercholesterolemia or another inherited dyslipidemia. Although the patient reported no family history of premature coronary artery disease or sudden cardiac death, the absence of a recognized family history does not exclude an inherited lipid disorder.[9] Furthermore, the reduction in LDL-C from 250 mg/dL to 85 mg/dL at the one-month follow-up should not be interpreted as evidence against familial hypercholesterolemia. Statin therapy, dietary changes, reported discontinuation of AAS exposure, acute-phase effects, and biological variability may all have contributed to the observed reduction in LDL-C. Pre-event lipid measurements, apolipoprotein B and apolipoprotein A-I concentrations, genetic testing, and family lipid screening

were unavailable. Similarly, the measured lipoprotein(a) [Lp(a)] level was not elevated; however, this finding does not exclude familial hypercholesterolemia or another inherited dyslipidemia and should be interpreted in the context of ongoing AAS exposure. Therefore, the severe lipid abnormality in this patient should be considered potentially multifactorial rather than attributed exclusively to AAS exposure. In contrast to the marked reductions in total cholesterol and LDL-C, triglyceride levels increased from 113 to 318 mg/dL at the one-month follow-up. The reason for this divergent change remains uncertain and may have been influenced by fasting status, dietary factors, alcohol intake, or other secondary metabolic factors that could not be fully assessed retrospectively.

The large thrombus burden observed in the culprit vessel suggests that acute thrombosis played a central role in the clinical presentation. However, the presence of nonobstructive plaques in other coronary segments also supports an underlying atherosclerotic substrate. Without intravascular imaging, the precise morphology of the culprit lesion cannot be established, and plaque rupture, plaque erosion, or other less common mechanisms cannot be distinguished with certainty. Similarly, although the angiographic findings did not support spontaneous coronary artery dissection, the incomplete evaluation of other inherited and acquired prothrombotic conditions precludes definitive attribution of the thrombotic event to a single mechanism.

Importantly, the metabolic effects of individual AAS compounds are not interchangeable. In a six-week crossover study involving 11 male weightlifters, Thompson et al.[8] compared oral stanozolol (6 mg/day) with supraphysiological intramuscular testosterone enanthate (200 mg/week). Stanozolol decreased HDL-C by 33%, $HDL_2$ by 71%, and apolipoprotein A-I by 40%, while increasing LDL-C by 29%. In contrast, testosterone enanthate decreased HDL-C by approximately 9% and apolipoprotein A-I by approximately 8%, whereas LDL-C decreased by 16% in the same study. Stanozolol also increased postheparin hepatic triglyceride lipase activity by 123%, whereas the maximum increase observed during testosterone treatment (25%) was not statistically significant. These findings highlight the particularly adverse effects of oral 17α-alkylated stanozolol on HDL-related metabolism compared with parenteral testosterone. These compound-specific differences are particularly relevant when interpreting the severe dyslipidemia observed in our patient during prolonged combined testosterone and stanozolol exposure. Although the lack of reliable information regarding individual doses, routes of administration, cycling patterns, and pre-exposure lipid levels precludes attributing these abnormalities to either compound or quantifying their respective contributions, the abnormalities may have contributed to his premature coronary event. Based on the available data, the patient had a Dutch Lipid Clinic Network score of at least 5 points (3 points for an LDL-C level of 191–250 mg/dL and 2 points for premature coronary artery disease), corresponding to "possible familial hypercholesterolemia." However, a complete phenotypic and genetic assessment was unavailable. Although underlying familial hypercholesterolemia cannot be excluded in this patient, concomitant AAS exposure may have further altered an already adverse lipid profile. Notably, the lipoprotein(a) [Lp(a)] level measured in our patient should be interpreted with caution because both testosterone and stanozolol have been reported to reduce Lp(a) levels; therefore, the measured value may not necessarily reflect the patient's untreated lifelong baseline.[10,11]

Although the patient remained clinically stable without heart failure symptoms at one month, NT-proBNP increased from 398.6 to 1329 pg/mL. The relatively low admission level may partly reflect the early timing of sampling after symptom onset, whereas the subsequent elevation may be associated with persistent severe left ventricular systolic dysfunction and postinfarction remodeling. The concomitant modest decline in renal function may also have contributed to the elevated NT-proBNP level. Another clinically relevant finding was the marked elevation in liver transaminase levels at presentation. Elevations in AST and ALT in this setting were likely multifactorial. Extensive myocardial necrosis may contribute substantially to AST elevation, whereas transient hepatic hypoperfusion associated with acute heart failure may also cause acute hepatocellular injury.[12] In addition, hepatotoxicity associated with 17α-alkylated anabolic steroids, particularly stanozolol, represents another potential contributing mechanism.[13] The substantial reductions in AST and ALT levels during follow-up support a predominantly acute and reversible process; however, the relative contributions of myocardial injury, hepatic hypoperfusion, and AAS-related hepatotoxicity cannot be determined from the available data.

This case highlights the importance of obtaining a detailed, nonjudgmental history of performance-enhancing substance use in young patients presenting with acute coronary syndromes. Identification of AAS exposure should prompt counseling regarding permanent cessation and intensive secondary prevention while ensuring a systematic evaluation for coexisting inherited or acquired cardiovascular risk factors.

**Limitations**

This report has several limitations. First, as a single case report, it cannot establish a causal relationship between AAS exposure and MI. The history of AAS use was based on the patient's self-report, and detailed information regarding the formulations, sources of the substances, and concomitant use of other performance-enhancing agents could not be reliably obtained retrospectively. In particular, the exact doses, routes of administration, duration of individual AAS cycles, and interval between the last AAS exposure and the index MI could not be established.

Second, pre-event lipid measurements were unavailable, and lipid values obtained during the acute presentation may have been influenced by the acute-phase response and biological variability. A comprehensive evaluation for familial hypercholesterolemia or another inherited dyslipidemia could not be completed because measurements of apolipoprotein B and apolipoprotein A-I, additional clinical and family history data required for a complete Dutch Lipid Clinic Network assessment, genetic testing, and family lipid screening were unavailable. Historical lipid measurements could not be verified because the patient's previous laboratory records were not accessible through the national electronic health record system (e-Nabız). Therefore, it remains uncertain whether the severe dyslipidemia observed at presentation predated AAS exposure or was partly attributable to it.

Third, inherited and acquired thrombophilic disorders, antiphospholipid antibodies, and other autoimmune or inflammatory conditions were not comprehensively investigated. Accordingly, an underlying inherited dyslipidemia or prothrombotic disorder cannot be definitively excluded, representing an important limitation in the etiological interpretation of this case.

Fourth, intravascular imaging using optical coherence tomography or intravascular ultrasound was not performed. Therefore, the morphology of the culprit lesion and the relative contributions of plaque rupture, plaque erosion, and other potential mechanisms could not be definitively determined.

Finally, clinical and echocardiographic follow-up was limited to three months.

## Conclusion

This case suggests that chronic nonmedical AAS exposure may contribute to premature coronary atherosclerosis and acute coronary thrombosis in susceptible young individuals. However, a causal relationship cannot be established from a single case, and alternative or coexisting inherited and acquired etiologies should be systematically investigated in patients presenting with MI at a very young age. Obtaining a detailed history of image- and performance-enhancing substance use, permanently discontinuing nonmedical AAS exposure, smoking cessation, and implementing intensive guideline-directed secondary prevention are essential components of long-term management.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-65746/TKDA-65746_(0)_Supplementary_Materials.pdf

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent for the publication of this case report was obtained from the patient.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Author Contributions:** Concept – A.İ.B.; Design – A.İ.B.; Supervision – O.Ş.; Resource – S.E.; Materials – O.Ş.; Data Collection and/or Processing – S.E.; Analysis and/or Interpretation – A.İ.B.; Literature Review – O.Ş.; Writing – O.Ş.; Critical Review – G.S.

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# Anabolic-Androgenic Steroid Use and Acute Coronary Thrombosis: Lessons From a Very Young Patient with ST-Elevation Myocardial Infarction

## Anabolik-Androjenik Steroid Kullanımı ve Akut Koroner Tromboz: ST-Segment Elevasyonlu Miyokard Enfarktüsü Geçiren Çok Genç Bir Hastadan Çıkarılacak Dersler

**EDITORIAL COMMENT**
EDİTORYAL YORUM

We read with interest the case reported by the authors describing a 29-year-old man who presented with anterior ST-segment elevation myocardial infarction (STEMI) after approximately two years of nonmedical anabolic-androgenic steroid (AAS; testosterone and stanozolol) use.[1] The presence of a large intracoronary thrombus despite only limited atherosclerotic disease elsewhere in the coronary tree makes this an important and thought-provoking presentation. The authors should be commended for bringing this case to our attention. Although a single case cannot establish causality, the report underscores a cardiovascular problem that may be more common than currently recognized.

The clinical phenotype is particularly striking: a very young patient with relatively mild angiographic disease but a substantial thrombotic burden. Similar presentations have been described in AAS users, including a report from the Turkish literature of STEMI associated with intracoronary thrombus.[2] Several mechanisms may contribute, including increased platelet reactivity, disturbances in coagulation and fibrinolysis, endothelial dysfunction, and potentially altered coronary vasomotor function.[3] Nevertheless, STEMI at such a young age warrants a systematic etiological assessment beyond a single potential trigger. AAS exposure is clinically relevant, but it should be interpreted within a broader differential diagnosis rather than regarded as the default explanation. Familial hypercholesterolemia (FH), elevated lipoprotein(a), thrombophilia, other substance or drug exposures, inflammatory or immune-mediated diseases, and relevant coronary abnormalities, such as spontaneous dissection, anomalous origin, or embolism, deserve consideration when clinically appropriate.[4,5] This comprehensive approach is particularly important in premature STEMI, in which multiple inherited and acquired risk factors may coexist.

The markedly elevated low-density lipoprotein cholesterol (LDL-C) level in this case deserves particular attention. An LDL-C concentration of approximately 250 mg/dL in a 29-year-old patient with STEMI raises concern for substantial underlying lipid-related risk, irrespective of concomitant AAS use. According to the Dutch Lipid Clinic Network criteria, the combination of an LDL-C level in the 191–250 mg/dL range (3 points) and premature coronary artery disease (2 points) already yields at least 5 points, placing the patient in the "possible FH" category even before family history, physical findings, or genetic information are taken into account.[5] Clinical assessment for FH should therefore be performed using validated criteria, with cascade screening and genetic testing considered when appropriate.

Interpretation of the admission lipid profile nevertheless requires caution. Acute myocardial infarction may lower LDL-C levels during the acute-phase response. One prospective study reported a decrease of approximately 9% within 24 hours and 17% by day 4.[6] This interpretation is further complicated by the differing effects of individual anabolic agents on lipid metabolism. In a crossover study of male weightlifters, oral stanozolol increased LDL-C by 29% and hepatic triglyceride lipase activity by 123%, whereas intramuscular testosterone enanthate lowered LDL-C by 16%.[7] Consequently, the patient's untreated baseline LDL-C level cannot be reliably reconstructed from the admission measurement alone. However, even after accounting for these uncertainties, the combination of very premature STEMI and an LDL-C level of approximately 250 mg/dL makes FH or another severe primary dyslipidemia a highly relevant competing or coexisting contributor to the clinical presentation. AAS exposure should therefore be

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viewed as one component of a multifactorial cardiovascular risk profile rather than as an isolated explanation.

This case also emphasizes the importance of routinely asking about AAS exposure in very young patients presenting with STEMI. Such use may not be disclosed spontaneously, and in a meta-analysis of more than 10,000 users, only approximately one-third had sought medical support.[8] Patients should therefore be asked directly and without judgment about AAS use, particularly in this age group.

Finally, this case highlights an important evidence gap. Current knowledge regarding AAS use and coronary thrombosis is based largely on case reports and observational studies, and the magnitude of any associated risk remains uncertain. Prospective studies combining detailed exposure histories with lipid, hematological, and vascular assessments are needed to characterize individuals at risk and determine whether associated abnormalities regress after AAS discontinuation.

We thank the authors for this clinically relevant case, which reminds clinicians to consider nonmedical AAS use when evaluating STEMI in very young patients.

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# Recurrent Spontaneous Coronary Artery Dissection Leading to Advanced Heart Failure and LVAD Implantation

## Tekrarlayan Spontan Koroner Arter Diseksiyonuna Bağlı İleri Kalp Yetersizliği ve LVAD İmplantasyonu

**ABSTRACT**

Spontaneous coronary artery dissection (SCAD) is an important cause of acute myocardial infarction in women without significant atherosclerotic coronary artery disease. Recurrent SCAD progressing to advanced heart failure requiring durable mechanical circulatory support is exceptionally uncommon. A 45-year-old woman with a mechanical mitral valve prosthesis presented with non-ST-segment elevation myocardial infarction caused by multivessel SCAD involving the circumflex artery (Type 1) and the first obtuse marginal branch (OM1) (Type 2A). Because coronary flow was preserved (TIMI 3), conservative management was adopted. Follow-up angiography demonstrated healing of the OM1 lesion and a stable residual circumflex dissection. Two years later, she presented with anterior ST-segment elevation myocardial infarction. Coronary angiography demonstrated an abrupt, near-total occlusion of the left anterior descending artery, which was considered most compatible with recurrent Type 4 SCAD after alternative diagnoses, including coronary thromboembolism, were excluded. Despite intracoronary vasodilator therapy, persistent ischemia necessitated percutaneous coronary intervention with drug-eluting stent implantation, restoring TIMI 3 flow. Severe left ventricular systolic dysfunction developed despite successful revascularization and optimal medical therapy. During follow-up, the patient underwent implantation of an implantable cardioverter-defibrillator (ICD) for primary prevention and, after recurrent heart failure hospitalizations over 18 months, durable left ventricular assist device (LVAD) implantation as a bridge to heart transplantation. This case demonstrates that angiographic healing after conservatively managed SCAD does not eliminate the risk of recurrence in previously unaffected coronary territories. It underscores the diagnostic challenges of Type 4 SCAD in patients with competing causes of myocardial infarction and illustrates that recurrent SCAD may rarely progress to advanced heart failure requiring durable mechanical circulatory support.

**Keywords:** Heart failure, left ventricular assist device, spontaneous coronary artery dissection.

**ÖZET**

Spontan koroner arter diseksiyonu (SKAD), belirgin aterosklerotik koroner arter hastalığı bulunmayan kadınlarda akut miyokard enfarktüsünün önemli nedenlerinden biridir. İleri kalp yetersizliğine ilerleyerek uzun süreli mekanik dolaşım desteği gerektiren tekrarlayan SKAD ise son derece nadirdir. Mekanik mitral kapak protezi bulunan 45 yaşındaki kadın hasta, sirkumfleks arter (Tip 1) ve birinci obtus marjinal dalı (Tip 2A) tutan çok damarlı SKAD'a bağlı non-ST-segment elevasyonlu miyokard enfarktüsü ile başvurdu. Koroner akımın korunmuş olması (TIMI 3) nedeniyle konservatif tedavi tercih edildi. Kontrol koroner anjiyografide OM1 lezyonunda iyileşme, sirkumfleks arterde ise stabil rezidüel diseksiyon izlendi. İki yıl sonra hasta anterior ST-segment elevasyonlu miyokard enfarktüsü ile yeniden başvurdu. Koroner anjiyografide sol ön inen arterde ani gelişen tama yakın oklüzyon saptandı. Koroner tromboembolizm başta olmak üzere en olası alternatif tanılar dışlandıktan sonra bu lezyon, tekrarlayan Tip 4 SKAD ile en uyumlu bulgu olarak değerlendirildi. İntrakoroner vazodilatör tedaviye rağmen devam eden iskemi nedeniyle ilaç salınımlı stent implantasyonu ile perkütan koroner girişim uygulanarak TIMI 3 akım yeniden sağlandı. Başarılı revaskülarizasyona ve kılavuz önerilerine uygun optimal medikal tedaviye rağmen ciddi sol ventrikül sistolik disfonksiyonu gelişti. Takip sürecinde primer korunma amacıyla implante edilebilir kardiyoverter-defibrilatör (ICD) implantasyonu yapıldı. Kalp yetersizliği nedeniyle 18 ay boyunca tekrarlayan hastane yatışlarının ardından, kalp nakline köprüleme amacıyla uzun süreli sol ventrikül destek cihazı (LVAD) implante edildi. Bu olgu, konservatif olarak yönetilen SKAD sonrasında anjiyografik iyileşmenin, daha önce etkilenmemiş koroner segmentlerde rekürrens riskini ortadan kaldırmadığını göstermektedir. Ayrıca, miyokard enfarktüsünün farklı nedenlerinin ayırıcı tanısında Tip 4 SKAD'ın oluşturduğu tanısal güçlükleri vurgulamakta ve tekrarlayan SKAD'ın nadir de olsa ileri kalp yetersizliğine ilerleyerek uzun süreli mekanik dolaşım desteği gerektirebileceğini ortaya koymaktadır.

**Anahtar Kelimeler:** Kalp yetersizliği, spontan koroner arter diseksiyonu, sol ventrikül destek cihazı.

**CASE REPORT**
OLGU SUNUMU

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Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of acute coronary syndrome, particularly among younger and middle-aged women without significant atherosclerotic coronary artery disease or traditional cardiovascular risk factors.[1] Although the exact pathophysiological mechanisms remain incompletely understood, separation of the coronary arterial wall by intramural hematoma and/or intimal disruption may compromise coronary blood flow and result in acute myocardial infarction. Contemporary registries suggest that SCAD accounts for up to one-third of myocardial infarctions in women younger than 50 years.[2]

Unlike atherosclerotic coronary artery disease, spontaneous angiographic healing is common after conservatively managed SCAD, supporting current recommendations that favor an initial conservative strategy in clinically stable patients.[3,4] Nevertheless, recurrent SCAD occurs in approximately 10%–20% of patients during long-term follow-up, frequently affecting coronary arteries different from those involved in the index event.[2] Although progression to advanced heart failure requiring durable mechanical circulatory support or heart transplantation has been reported, such outcomes remain exceptionally uncommon.[5–9]

We report a case of recurrent SCAD involving different coronary territories despite angiographic healing of the initial lesions. This case adds to the limited literature by demonstrating that recurrent SCAD affecting a previously unaffected coronary territory may rarely progress to advanced heart failure requiring an implantable cardioverter-defibrillator (ICD) and durable left ventricular assist device (LVAD) support. The recurrent event also posed a diagnostic challenge in a patient with a mechanical mitral valve prosthesis. This case emphasizes the importance of careful etiological evaluation and long-term follow-up, even after apparently favorable angiographic outcomes.

**Case Report**

A 45-year-old premenopausal woman with a mechanical mitral valve prosthesis implanted for severe mitral stenosis at the age of 39 presented in June 2021 with acute chest pain. The etiology of the underlying mitral valve disease could not be confirmed because the original surgical records were unavailable. She had no history of hypertension, diabetes mellitus, dyslipidemia, smoking, connective tissue disease, or coronary artery disease. She was receiving chronic warfarin therapy. Peak cardiac troponin was 339 ng/L, serum creatinine was 0.4 mg/dL, and the international normalized ratio (INR) was 2.01.

Coronary angiography demonstrated spontaneous coronary artery dissection involving both the circumflex artery (CX) and the first obtuse marginal branch (OM1). The lesion extending from the ostial segment into the proximal CX was classified as Type 1 SCAD, whereas the OM1 lesion was consistent with Type 2A SCAD (Figures 1–2, Video 1). Distal coronary flow was preserved (TIMI 3), there was no left main coronary artery involvement, and the patient's symptoms improved during hospitalization. Electrocardiography demonstrated findings consistent with non-ST-segment elevation myocardial infarction (Figure 3). Transthoracic echocardiography demonstrated preserved left ventricular systolic function (LVEF 55%). Given the preserved coronary flow, hemodynamic stability, and absence of ongoing ischemia, a conservative treatment strategy was adopted.

**ABBREVIATIONS**

| | |
|---|---|
| CX | Circumflex artery |
| FMD | Fibromuscular dysplasia |
| ICD | Implantable cardioverter-defibrillator |
| INR | International normalized ratio |
| IVUS | Intravascular ultrasound |
| LVAD | Left ventricular assist device |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| NYHA | New York Heart Association |
| OCT | Optical coherence tomography |
| OM1 | Obtuse marginal branch |
| SCAD | Spontaneous coronary artery dissection |
| TEE | Transesophageal echocardiography |

Repeat coronary angiography five days later demonstrated persistent dissections without progression and preserved TIMI 3 flow. The patient was discharged on warfarin, clopidogrel, short-term aspirin, atorvastatin, metoprolol, and guideline-directed secondary prevention therapy. Follow-up angiography performed two months later demonstrated marked healing of the OM1 lesion, whereas the residual CX dissection remained stable without progression (Figure 4, Video 2). Conservative management was therefore continued.

Approximately two years later, in October 2023, the patient was admitted with sudden severe chest pain and diaphoresis. Electrocardiography demonstrated an acute anterior ST-segment elevation myocardial infarction (Figure 5). Initial and peak cardiac troponin concentrations were 6,473 ng/L and 11,996 ng/L, respectively, while the INR remained within the therapeutic range (2.89). Emergency coronary angiography demonstrated an abrupt, near-total (≈99%) occlusion of the mid-left anterior descending artery (LAD) at the level of the first diagonal branch (Figure 6, Video 3). Because previous angiograms had shown normal LAD and right coronary arteries without significant atherosclerosis, and therapeutic anticoagulation together with transesophageal echocardiography (TEE) made coronary thromboembolism less likely, the findings were considered most compatible with recurrent Type 4 SCAD.

Because coronary vasospasm remained in the differential diagnosis, intracoronary nitroglycerin and diltiazem were administered without improvement in coronary flow or symptoms. Ongoing ischemia prompted percutaneous coronary intervention with balloon predilatation, implantation of a 3.0 × 37 mm drug-eluting stent, and post-dilatation with a noncompliant balloon, restoring TIMI 3 flow (Figure 7). During the same angiographic procedure, the previously affected CX and first OM1 demonstrated complete angiographic healing (Figure 6). Intracoronary imaging was not performed because optical coherence tomography (OCT) was unavailable, and delaying reperfusion for intravascular ultrasound (IVUS) was considered inappropriate. Although definitive confirmation of Type 4 SCAD was therefore not possible, the overall clinical and angiographic findings were considered most compatible with recurrent SCAD.

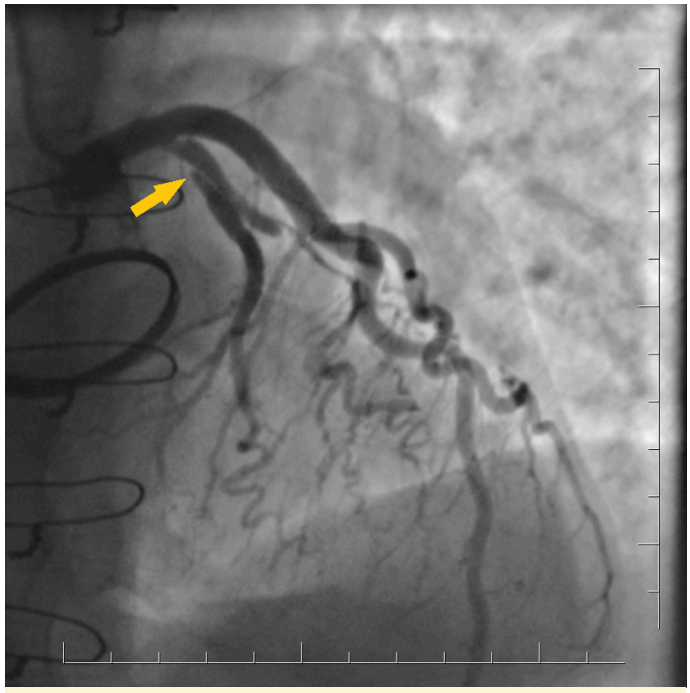


**Figure 1.** Initial coronary angiography showing Type 1 spontaneous coronary artery dissection of the circumflex artery extending from the ostium to the proximal segment (arrow).

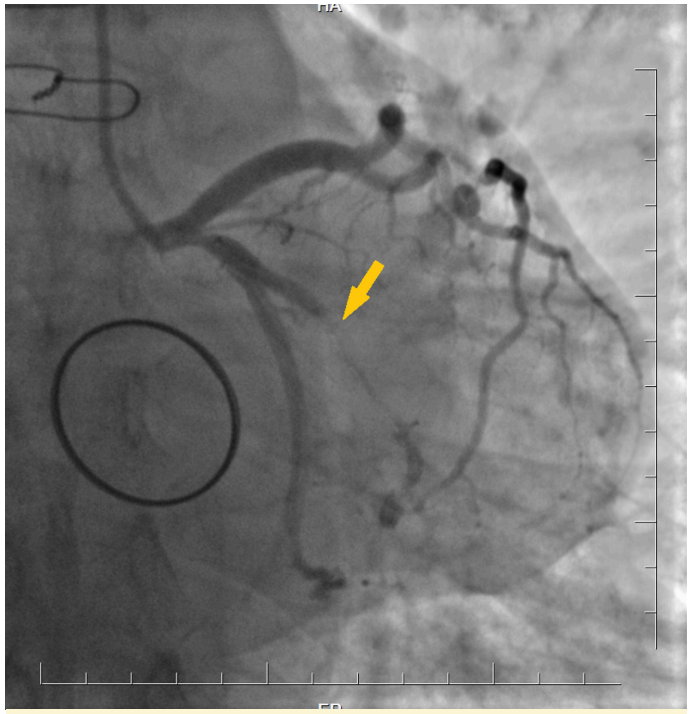


**Figure 2.** Initial coronary angiography showing Type 2A spontaneous coronary artery dissection of the first obtuse marginal branch (arrow).

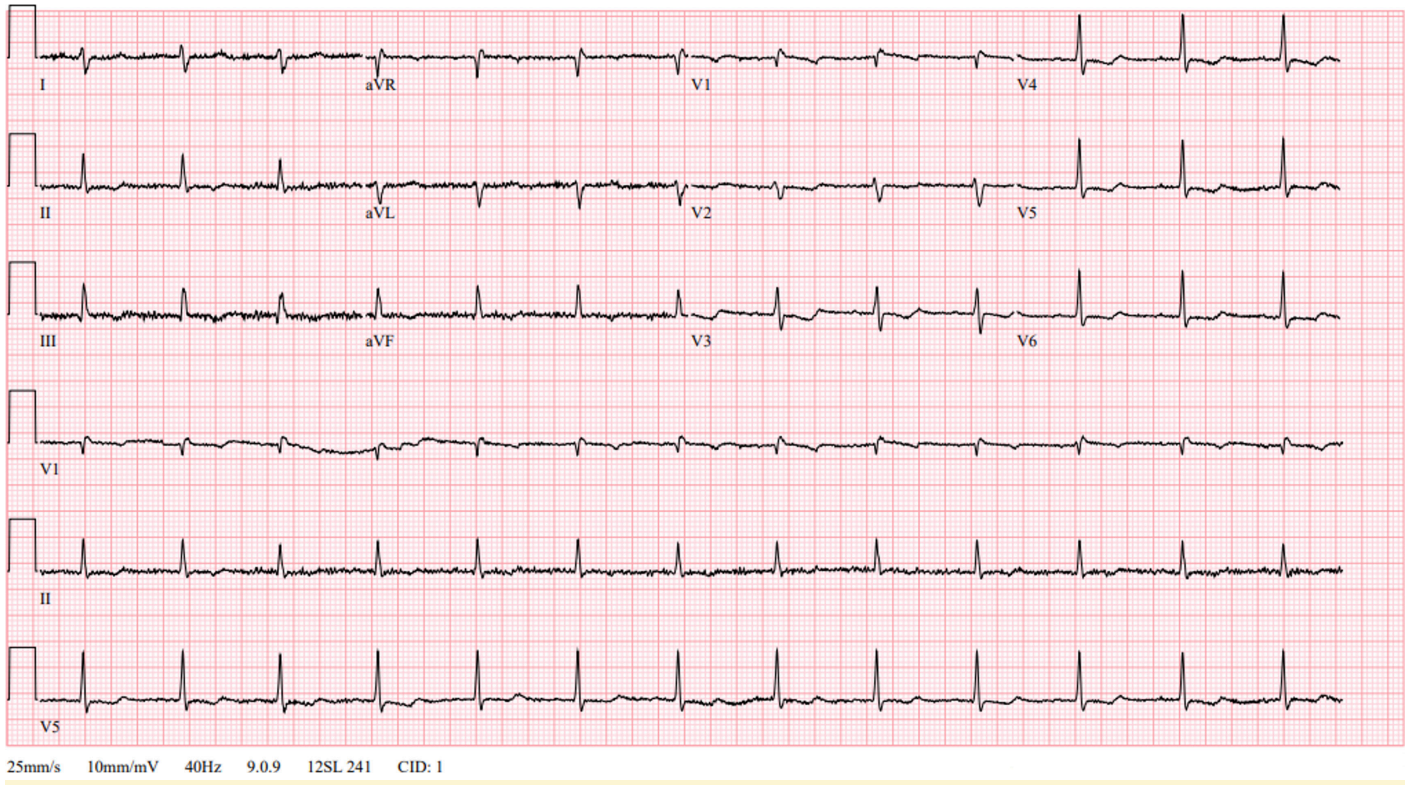



**Figure 3.** Initial 12-lead electrocardiogram showing non-ST-segment elevation myocardial infarction during the index SCAD event.

Postprocedural echocardiography demonstrated severe left ventricular systolic dysfunction (LVEF 25%–30%) with extensive anterior, apical, and septal wall-motion abnormalities. The mechanical mitral valve functioned normally, with only mild paravalvular regurgitation, and TEE excluded left atrial or left atrial appendage thrombus. Follow-up coronary angiography performed five days later confirmed a patent LAD stent with preserved TIMI 3 flow. The patient was subsequently discharged on guideline-



**Figure 4.** Initial coronary angiography showing Type 1 spontaneous coronary artery dissection of the circumflex artery extending from the ostium to the proximal segment (arrow).

directed heart failure therapy together with triple antithrombotic therapy consisting of warfarin, aspirin, and clopidogrel. Aspirin was discontinued after one week, followed by one year of warfarin plus clopidogrel and lifelong warfarin thereafter (target INR, 2.5–3.5). No clinically significant bleeding occurred.

Despite optimal guideline-directed medical therapy, progressive ischemic cardiomyopathy led to persistent severe left ventricular systolic dysfunction and recurrent hospitalizations for worsening heart failure. Because left ventricular systolic function remained severely reduced despite an appropriate post-myocardial infarction waiting period, a primary prevention ICD was implanted on October 18, 2024. No documented sustained ventricular arrhythmias occurred before ICD implantation.

Despite continued optimal medical therapy, the patient's heart failure progressively worsened, with persistent New York Heart Association (NYHA) functional class III–IV symptoms and recurrent hospitalizations. Before LVAD implantation, left ventricular ejection fraction remained severely reduced at 20% despite guideline-directed medical therapy with metoprolol 50 mg twice daily, sacubitril/valsartan 24/26 mg twice daily, spironolactone 25 mg once daily, and furosemide 40 mg once daily. Peak N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration reached 16,312 pg/mL. Preimplantation right heart catheterization demonstrated elevated filling pressures (pulmonary capillary wedge pressure, 29 mmHg) and increased pulmonary vascular resistance (5 Wood units), prompting the addition of sildenafil therapy. The patient was classified as INTERMACS Profile 3 and subsequently underwent durable LVAD implantation as a bridge to heart transplantation on February 10, 2025. The specific LVAD model could not be confirmed because the procedure was performed at an external referral center and detailed operative records were unavailable.

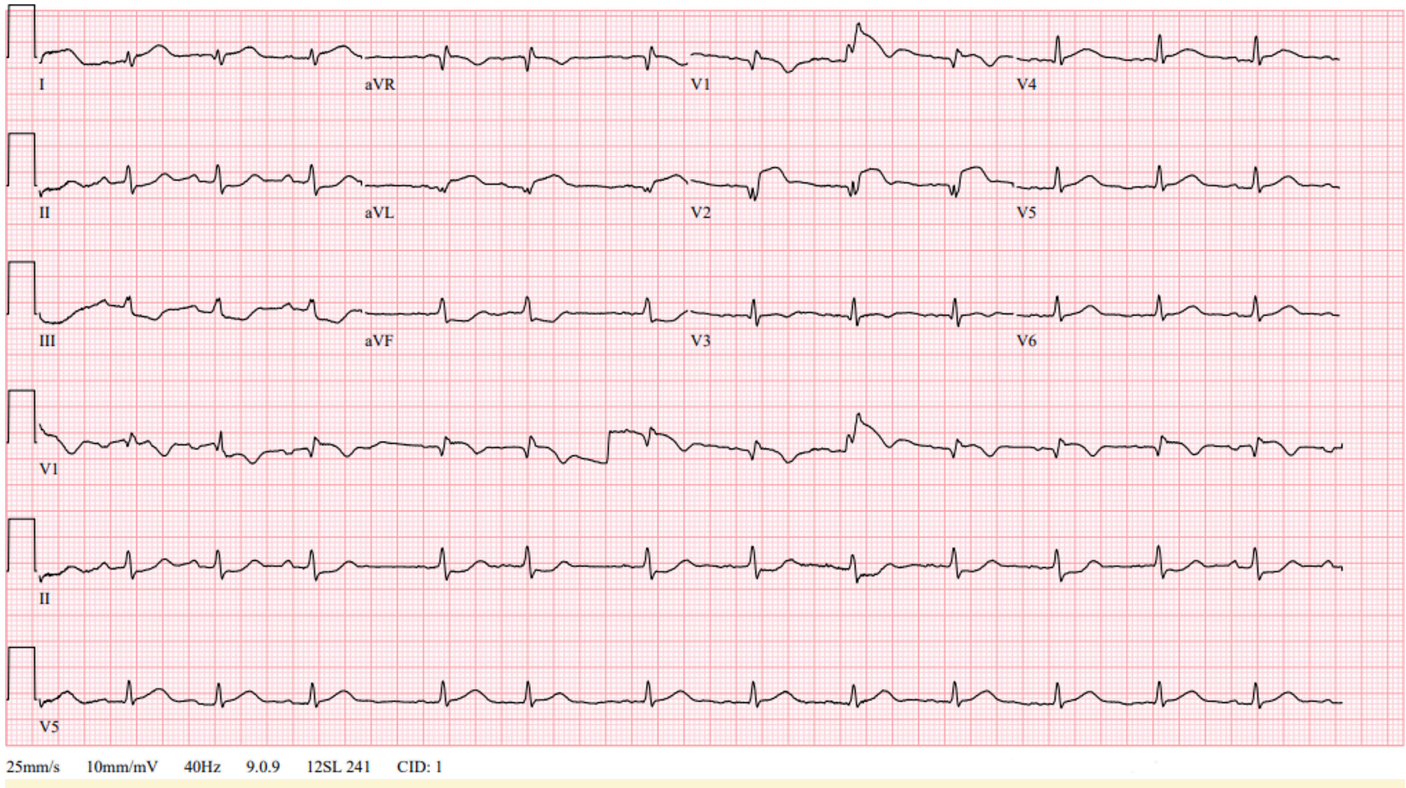



**Figure 5.** 12-lead electrocardiogram showing anterior ST-segment elevation myocardial infarction during the recurrent SCAD event.

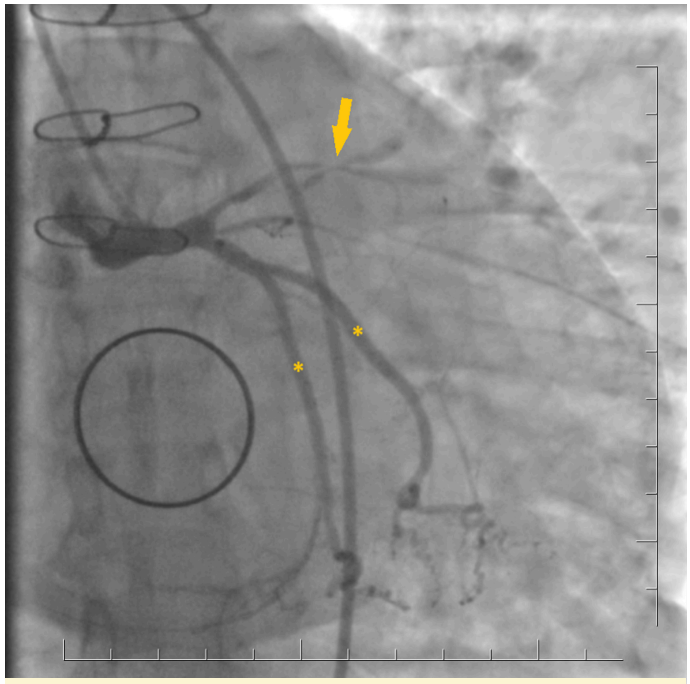


**Figure 6.** Coronary angiography during the recurrent event showing near-total occlusion of the mid-left anterior descending artery, most compatible with Type 4 spontaneous coronary artery dissection (arrow). The previously affected circumflex artery and first obtuse marginal branch show complete angiographic healing (asterisks).

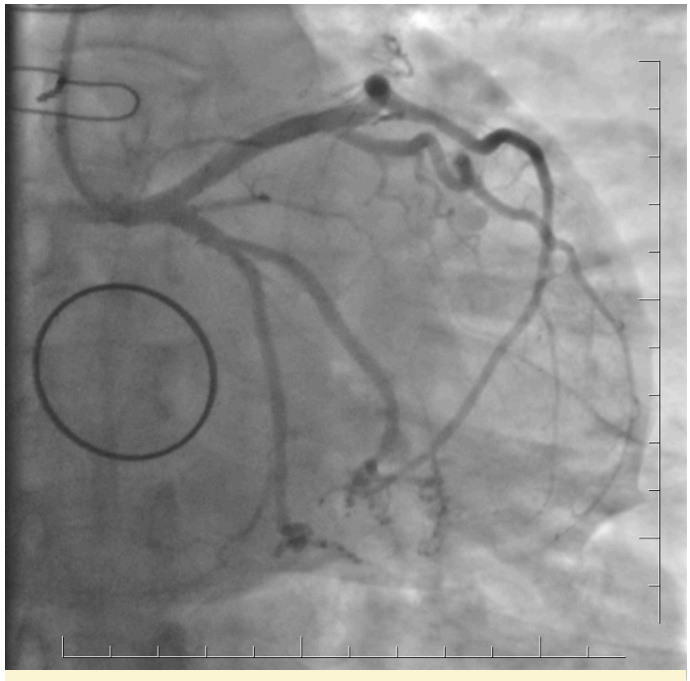


**Figure 7.** Final coronary angiography after percutaneous coronary intervention showing successful restoration of TIMI 3 flow in the left anterior descending artery.

At the most recent follow-up, approximately five years after the initial SCAD event and 16 months after LVAD implantation, the patient remained clinically stable on LVAD support with NYHA functional class II symptoms. Follow-up echocardiography demonstrated improvement in left ventricular systolic function

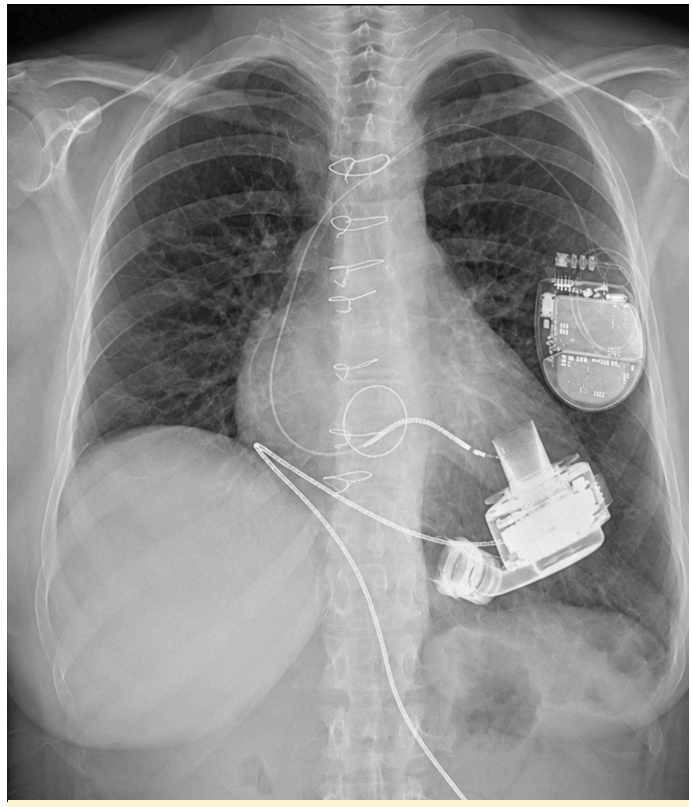


**Figure 8.** Follow-up chest radiograph showing the left ventricular assist device (LVAD), implantable cardioverter-defibrillator (ICD), and mechanical mitral valve prosthesis.

(LVEF 45%–50%). No major LVAD-related complications, recurrent ischemic events, or documented sustained ventricular arrhythmias had occurred, and the patient remained on the waiting list for heart transplantation (Figure 8). The chronological clinical course is summarized in Figure 9.

**Diagnostic Work-up**

An etiological evaluation was performed to investigate potential predisposing conditions for recurrent SCAD and to assess alternative causes of myocardial infarction. The baseline clinical characteristics, laboratory findings, and etiological evaluation are summarized in Table 1.

Because the patient had a mechanical mitral valve prosthesis, coronary thromboembolism was considered in the differential diagnosis of the second acute coronary syndrome. At presentation, the INR was within the therapeutic range (2.89). TEE demonstrated a normally functioning mechanical mitral valve with only mild paravalvular regurgitation and revealed no thrombus in the left atrium or left atrial appendage. These findings made a cardioembolic mechanism less likely, although it could not be completely excluded.

Dedicated screening for fibromuscular dysplasia (FMD) with head-to-pelvis computed tomography angiography was not performed because the patient continued follow-up at another institution after the index hospitalization. However, subsequent carotid and vertebral Doppler ultrasonography demonstrated normal arterial caliber, wall morphology, and flow characteristics without evidence of stenosis or other vascular abnormalities. Bilateral lower-

**Table 1.** Baseline clinical characteristics, diagnostic work-up, and etiological evaluation

| **Variables** | **Findings** | | |
|---|---|---|---|
| Age | 45 years | | |
| Sex | Female | | |
| Blood pressure | 122/72 mmHg | | |
| Heart rate | 98 bpm | | |
| BMI | 28.07 kg/m² | | |
| Hypertension | No | | |
| Diabetes mellitus | No | | |
| Hyperlipidemia | No | | |
| Smoking | No | | |
| Family history | CAD in paternal uncle; no first-degree family history of SCAD or sudden cardiac death | | |
| Mechanical mitral valve | Implanted at age 39 for severe mitral stenosis; exact etiology unavailable | | |
| Pregnancy history | G3P3 | | |
| Pregnant/postpartum | | | |
| Menopause | Premenopausal | | |
| Oral contraceptive/HRT | None | | |
| **Laboratory findings** | | | |
| **First NSTEMI** | **Result** | **Second STEMI** | **Result** |
| Peak troponin | 339 | Initial troponin | 6473 |
| CK-MB | 15.9 | Peak troponin | 11996 |
| Creatinine | 0.4 mg/dL | INR | 2.89 |
| INR | 2.01 | Hemoglobin | 10.6 g/dL |
| LDL-C | 110 mg/dL | WBC | 11.66 ×10⁹/L |
| Hemoglobin | 9.4 g/dL | Platelet count | 446 ×10⁹/L |
| WBC | 5.21 ×10⁹/L | ESR | 3 mm/h |
| Platelet count | 258 ×10⁹/L | CRP | 1.5 mg/L |
| ESR | 7 mm/h | LVEF | 25% |
| CRP | 2.9 mg/L | Vitamin B12 | 218 ng/L (reference range, 197–771 ng/L) |
| LVEF | 55% | Folate | 10.8 ng/L (reference range, 3.89–26.3 ng/L) |
| Total cholesterol | 160 mg/dL | | |
| LDL-C | 107 mg/dL | | |
| HDL-C | 36 mg/dL | | |
| Triglycerides | 87 mg/dL | | |
| Non-HDL-C | 124 mg/dL | | |
| Lipoprotein(a) | Not available | | |
| Homocysteine | Not available | | |
| Glucose | 96 mg/dL | | |
| HbA1c | 5.3% | | |
| **Diagnostic work-up** | | | |
| **Investigation** | **Result** | | |
| Mechanical valve function | Normal | | |
| Prosthetic valve gradient | 8/3 mmHg | | |
| Paravalvular leak | Mild | | |
| Left atrial thrombus | None | | |
| Left atrial appendage thrombus | None | | |
| TEE | Negative for thrombus | | |
| Coronary embolism | No supporting evidence | | |
| IVUS | Not performed | | |
| OCT | Not available | | |

extremity arterial Doppler ultrasonography also demonstrated patent arteries without plaque formation or thrombosis. In addition, contrast-enhanced thoracic computed tomography revealed no abnormalities of the mediastinal great vessels, although it was not designed for dedicated FMD assessment.

Evaluation for inherited thrombophilia included measurements of antithrombin III, protein C, and protein S. Antithrombin III activity was within the normal range, whereas protein C antigen and protein S activity were reduced. However, these measurements were obtained while the patient was receiving chronic warfarin therapy for her mechanical mitral valve, which may affect the interpretation of vitamin K-dependent coagulation proteins. Therefore, these findings were not considered diagnostic of an inherited thrombophilic disorder.

No genetic testing for inherited arteriopathies was performed. Likewise, testing for Factor V Leiden, prothrombin G20210A, antiphospholipid antibodies, or a rheumatologic or autoimmune panel was not performed.

Regarding female-specific risk factors, the patient had a history of three pregnancies and three live births. She was neither pregnant nor in the postpartum period during either SCAD event, had not reached menopause, and was not receiving oral contraceptives or hormonal therapy. Family history was notable only for coronary artery disease in a paternal uncle, whereas there was no history of SCAD or sudden cardiac death among first-degree relatives.

Review of the clinical history did not identify recent infection, vigorous physical exertion, or pregnancy-related triggers preceding either event. A significant emotional stressor was documented before the initial presentation, whereas no definite precipitating factor could be identified before the recurrent event.

## Discussion

This case highlights three uncommon but clinically important aspects of SCAD. First, recurrent SCAD developed in a different coronary territory despite favorable angiographic healing of the initially affected vessels. Second, the recurrent event presented with an

**Table 1 (cont).** Baseline clinical characteristics, diagnostic work-up, and etiological evaluation

| **FMD evaluation** | |
|---|---|
| **Investigation** | **Result** |
| Dedicated head-to-pelvis CTA | Not performed |
| Carotid Doppler US | Normal |
| Vertebral Doppler US | Normal |
| Lower-extremity arterial Doppler US | Normal |
| Thoracic contrast-enhanced CT | No major vascular abnormality |
| **Thrombophilia evaluation** | |
| **Investigation** | **Result** |
| Antithrombin III | 92.7% (normal) |
| Protein C antigen | 25.3% ↓* |
| Protein C activity | 74% |
| Protein S activity | 34.2% ↓* |
| Protein S antigen | 73.7% |
| Comment | Measured during chronic warfarin therapy |
| **Other etiological evaluation** | |
| **Investigation** | **Result** |
| Genetic testing | Not performed |
| Factor V Leiden | Not performed |
| Prothrombin G20210A | Not performed |
| ANA/ENA/ANCA | Not performed |
| Antiphospholipid antibodies | Not performed |
| **Potential SCAD triggers** | |
| **Variables** | **Result** |
| Emotional stress | Present before the first event |
| Heavy exercise | None |
| Pregnancy | No |
| Postpartum period | No |
| Infection | None documented |
| Hormonal therapy | None |

ANA, Antinuclear antibody; ANCA, Antineutrophil cytoplasmic antibody; BMI, Body mass index; CAD, Coronary artery disease; CK-MB, Creatine kinase-MB; CRP, C-reactive protein; CTA, Computed tomography angiography; ENA, Extractable nuclear antigen; ESR, Erythrocyte sedimentation rate; FMD, Fibromuscular dysplasia; G3P3, Gravida 3, para 3; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; HRT, Hormone replacement therapy; INR, International normalized ratio; IVUS, Intravascular ultrasound; LDL-C, Low-density lipoprotein cholesterol; LVEF, Left ventricular ejection fraction; NSTEMI, Non-ST-segment elevation myocardial infarction; OCT, Optical coherence tomography; SCAD, Spontaneous coronary artery dissection; STEMI, ST-segment elevation myocardial infarction; TEE, Transesophageal echocardiography; US, Ultrasonography; WBC, White blood cell. Protein C antigen and protein S activity were measured during chronic warfarin therapy and therefore cannot be reliably interpreted as evidence of inherited deficiency.

angiographic pattern most compatible with Type 4 SCAD in a patient with a mechanical mitral valve prosthesis, creating a challenging differential diagnosis that included coronary thromboembolism and acute atherosclerotic coronary occlusion. Third, the recurrent event resulted in extensive myocardial injury that progressed to advanced heart failure requiring ICD implantation and durable LVAD support. Although each of these features has been reported individually, their coexistence in a single patient appears to be exceptionally uncommon and provides several important clinical insights into the diagnosis, management, and long-term follow-up of SCAD.

Healing of the dissected coronary artery is one of the characteristic features of SCAD and provides the rationale for conservative management in hemodynamically stable patients with preserved coronary flow.[1,3] Observational studies have demonstrated spontaneous angiographic healing in the majority of conservatively managed lesions, supporting current guideline recommendations that favor an initial conservative approach whenever feasible. However, angiographic healing should not be interpreted as resolution of the underlying disease process. Contemporary SCAD registries have shown that recurrent SCAD occurs in approximately 10%–20% of patients during long-term follow-up, frequently involving coronary segments different from those affected during the index event rather than the previously affected vessel.[2] In our patient, the initial CX and OM1 dissections healed or remained stable after conservative treatment, yet a new LAD dissection developed two years later. This clinical course supports the concept that angiographic healing reflects local vessel recovery rather than resolution of the underlying arteriopathy, emphasizing the need for long-term surveillance even after favorable angiographic outcomes.

The recurrent event also emphasizes the diagnostic challenges associated with Type 4 SCAD.[1,5] Unlike the classic angiographic appearance of Type 1 SCAD, Type 4 lesions present as abrupt vessel occlusions and may closely mimic acute thrombotic coronary occlusion or coronary embolism, particularly in patients with predisposing conditions such as prosthetic heart valves.[4,5] In our patient, therapeutic anticoagulation, previously normal coronary angiograms, the absence of intracardiac thrombus on TEE, and the lack of significant coronary atherosclerosis strongly favored recurrent SCAD over coronary thromboembolism. Nevertheless, because intracoronary imaging was unavailable, plaque rupture and coronary embolism could not be completely excluded, and the diagnosis relied on integration of the clinical and angiographic findings.[4]

Although conservative management remains the preferred treatment strategy for most patients with SCAD, revascularization is recommended in selected high-risk situations, including ongoing ischemia, hemodynamic instability, left main involvement, or persistent impairment of coronary flow.[1,4] Because the patient had an ongoing anterior myocardial infarction with persistent ischemia, PCI was performed despite the technical challenges associated with SCAD.[3,4] Although intracoronary imaging might have provided additional diagnostic confirmation, delaying reperfusion was considered inappropriate, and OCT was unavailable at our institution.

Despite successful revascularization and implementation of guideline-directed medical therapy, the patient developed progressive ischemic cardiomyopathy leading to advanced heart failure. Although left ventricular systolic function often recovers after SCAD, extensive myocardial injury, particularly after proximal dissections or those involving a large myocardial territory, may result in irreversible ventricular remodeling and

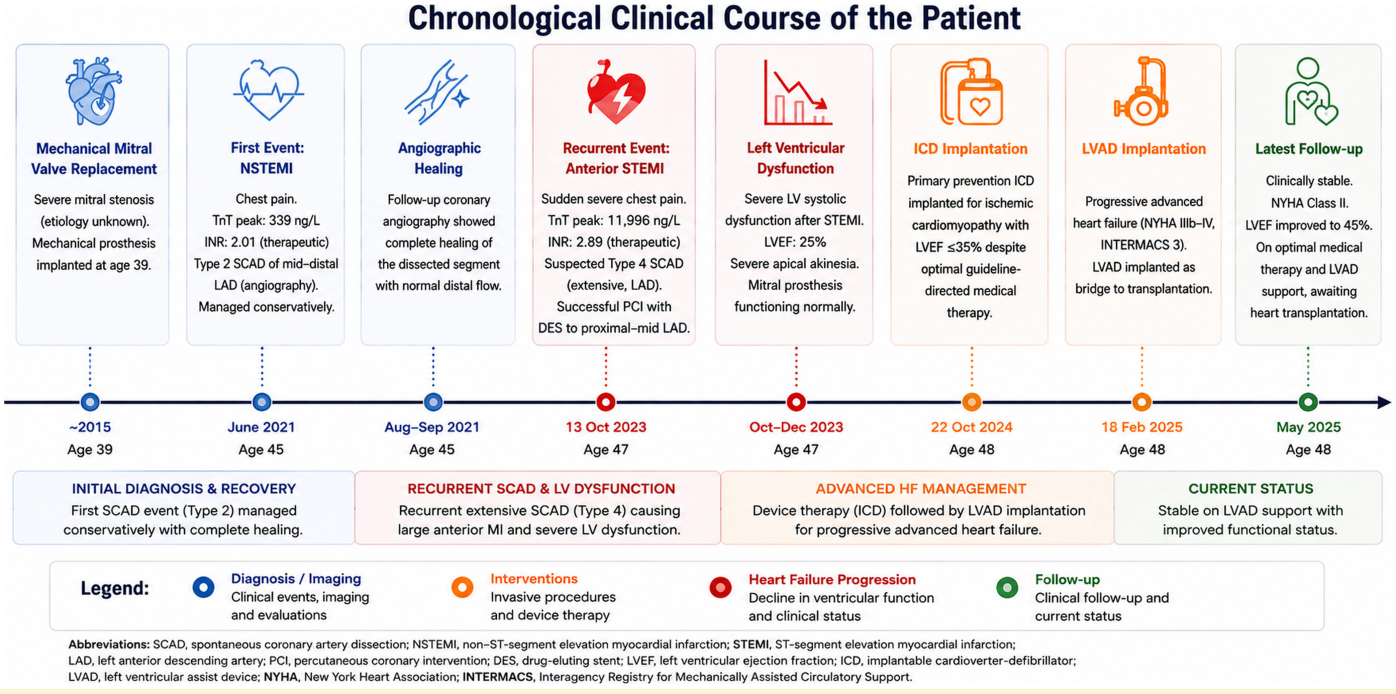



**Figure 9.** Clinical timeline summarizing the patient's course from the initial presentation with multivessel spontaneous coronary artery dissection to recurrent spontaneous coronary artery dissection of the left anterior descending artery, implantable cardioverter-defibrillator implantation, and durable left ventricular assist device support.

chronic heart failure.[6] Progression from SCAD to advanced heart failure requiring durable mechanical circulatory support or heart transplantation remains exceptionally uncommon. Recent case reports have described catastrophic SCAD culminating in LVAD support or heart transplantation despite contemporary management, with only a limited number of such cases reported.[7–9] Despite optimization of guideline-directed medical therapy, our patient experienced recurrent heart failure hospitalizations and persistent severe left ventricular dysfunction, ultimately requiring primary prevention ICD implantation followed by durable LVAD support as a bridge to heart transplantation. Although SCAD is generally associated with favorable long-term outcomes, recurrent disease may rarely progress to advanced heart failure when a large myocardial territory is affected.

## Limitations

Several limitations of this case should be acknowledged. First, intracoronary imaging with OCT or IVUS was not performed during the recurrent event. Consequently, definitive confirmation of Type 4 SCAD and complete exclusion of alternative diagnoses, including plaque rupture or coronary thromboembolism, were not possible. Nevertheless, the diagnosis was considered most compatible with the overall clinical presentation, angiographic findings, previously angiographically confirmed SCAD, therapeutic anticoagulation, and absence of intracardiac thrombus on TEE

Second, evaluation for extracoronary arteriopathies was incomplete. Dedicated head-to-pelvis computed tomography angiography for FMD was not performed because the patient continued follow-up at another institution after the index hospitalization. However, carotid, vertebral, and lower-extremity arterial Doppler ultrasonography, together with contrast-enhanced thoracic computed tomography, did not demonstrate vascular abnormalities suggestive of FMD.

Third, genetic testing for inherited arteriopathies, rheumatologic evaluation, antiphospholipid antibody testing, and molecular thrombophilia studies, including Factor V Leiden and prothrombin G20210A variant analyses, were not performed. In addition, protein C and protein S measurements were obtained during chronic warfarin therapy and therefore could not be reliably interpreted as evidence of inherited thrombophilia.

Given the patient's young age and premenopausal status, the etiological assessment of SCAD and myocardial infarction was incomplete, particularly with respect to vascular imaging, selected thrombophilia testing, autoimmune markers, and lipoprotein(a), which was not measured.

Finally, cardiac magnetic resonance imaging was not performed; therefore, infarct size, myocardial scar burden, transmurality, and ventricular remodeling could not be assessed.

## Conclusion

Recurrent SCAD may occur despite angiographic healing of previously affected coronary arteries and may rarely progress to advanced heart failure. This case highlights the importance of careful diagnostic evaluation, particularly in patients with competing causes of myocardial infarction, and emphasizes the need for long-term follow-up, as recurrent SCAD may ultimately require advanced heart failure therapies, including durable LVAD support.

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** The patient provided written informed consent for publication of the clinical information and accompanying images included in this report.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Use of AI for Writing Assistance:** Artificial intelligence tools were used solely for language editing. All clinical interpretation, scientific content, and final manuscript approval were performed by the authors.

**Author Contributions:** Concept – Y.A., E.Ö.; Design – Y.A., E.Ö.; Supervision – Y.A., E.Ö.; Resource – Y.A., E.Ö.; Materials – Y.A., E.Ö.; Data Collection and/or Processing – Y.A., E.Ö.; Analysis and/or Interpretation – Y.A., E.Ö.; Literature Review – Y.A.; Writing – Y.A.; Critical Review – Y.A., E.Ö.

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**Peer-review:** Externally peer-reviewed.

**Video 1.** Initial coronary angiography showing Type 1 spontaneous coronary artery dissection of the circumflex artery and Type 2A spontaneous coronary artery dissection of the first obtuse marginal branch, with preserved TIMI 3 flow.

**Video 2.** Two-month follow-up coronary angiography showing marked healing of the first obtuse marginal branch lesion and a stable residual dissection of the circumflex artery.

**Video 3.** Coronary angiography during the recurrent event showing near-total occlusion of the left anterior descending artery, most compatible with Type 4 spontaneous coronary artery dissection, followed by guidewire passage, percutaneous coronary intervention, and restoration of TIMI 3 flow. The previously affected circumflex artery and first obtuse marginal branch show complete angiographic healing.

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# No-Stent Management of High Coronary Thrombus Burden in Young Patients with STEMI: A Four-Case Series

## STEMI'li Genç Hastalarda Yüksek Koroner Trombüs Yükünün Stentsiz Yönetimi: Dört Olguluk Seri

**ABSTRACT**

Atherosclerotic plaque rupture is the most common mechanism underlying ST-segment elevation myocardial infarction (STEMI); however, young patients (≤50 years old) may present with a massive coronary thrombus in the absence of clearly demonstrated flow-limiting severe atherosclerotic stenosis. Routine direct stent implantation in these highly thrombotic lesions may increase the risk of distal embolization, impaired coronary blood flow, and long-term stent thrombosis. This report describes the angiographic outcomes of a retrospective case series of four young male patients managed without permanent stent implantation using tirofiban-based antithrombotic therapy, with or without initial mechanical reperfusion, guided by clinical stabilization and Thrombolysis in Myocardial Infarction (TIMI) flow. Tirofiban-based antithrombotic therapy was followed by substantial thrombus regression, while mechanical reperfusion was used when necessary to restore epicardial flow. In carefully selected patients with preserved coronary flow, a high thrombus burden, and no clearly demonstrated flow-limiting fixed lesion, a no-stent management strategy, with or without initial mechanical reperfusion, may be considered following individualized assessment and close angiographic follow-up.

**Keywords:** Coronary thrombus, glycoprotein IIb/IIIa inhibitor, ST-segment elevation myocardial infarction.

**ÖZET**

ST-segment elevasyonlu miyokard enfarktüsünün (STEMI) en sık görülen mekanizması aterosklerotik plak rüptürüdür; ancak genç hastalar (≤50 yaş), net olarak gösterilmiş akım kısıtlayıcı ciddi bir aterosklerotik darlık olmaksızın masif koroner trombüs ile başvurabilir. Bu yoğun trombotik lezyonlarda rutin direkt stent implantasyonu, distal embolizasyon, bozulmuş koroner kan akımı ve uzun dönem stent trombozu riskini artırabilir. Bu yazıda, klinik stabilizasyon ve Miyokard Enfarktüsünde Tromboliz (TIMI) akımı rehberliğinde, kalıcı stent implantasyonu yapılmadan, başlangıç mekanik reperfüzyon eşliğinde veya tek başına glikoprotein IIb/IIIa inhibitörü (tirofiban) temelli antitrombotik tedavi ile yönetilen dört genç erkek hastadan oluşan retrospektif olgu serisinin anjiyografik sonuçları sunulmaktadır. Gerektiğinde epikardiyal akımı sağlamak amacıyla mekanik reperfüzyon uygulanırken, tirofiban temelli antitrombotik tedaviyi takiben belirgin trombüs regresyonu gözlenmiştir. Korunmuş koroner akımı olan, yüksek trombüs yüküne sahip ve net olarak gösterilmiş akım kısıtlayıcı sabit bir lezyonu bulunmayan özenle seçilmiş hastalarda, bireyselleştirilmiş değerlendirme ve yakın anjiyografik takip sonrasında, başlangıç mekanik reperfüzyonu içeren veya içermeyen stentsiz bir yönetim stratejisi düşünülebilir.

**Anahtar Kelimeler:** Koroner trombüs, glikoprotein IIb/IIIa inhibitörü, ST-segment elevasyonlu miyokard enfarktüsü.

**CASE REPORT**
OLGU SUNUMU

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The predominant mechanism underlying ST-segment elevation myocardial infarction (STEMI) is the rupture of a lipid-rich atherosclerotic plaque.[1] However, the etiology of STEMI in younger patients (≤50 years old) often differs from the classical pathophysiology. Although approximately 80–85% of premature myocardial infarction (MI) remains associated with conventional atherosclerotic factors, nonatherosclerotic mechanisms account for a higher proportion (15–20%) than in older cohorts. In this population, plaque erosion with an intact fibrous cap accounts for more than one-third of cases. Additionally, transient hypercoagulable

states, severe vasospasm, and spontaneous coronary artery dissection (SCAD) are significant contributors to massive coronary thrombus formation.[2,3] In scenarios in which the underlying mechanism is suspected to involve activation of a local or systemic coagulation cascade rather than mechanical stenosis, routine direct stent implantation may increase the risk of microvascular obstruction (no-reflow) and long-term stent thrombosis.[4] Targeted pharmacological approaches using glycoprotein IIb/IIIa inhibitors have demonstrated efficacy in reducing thrombus burden.[5] The OCT-guided EROSION study, for example, demonstrated the feasibility of an antithrombotic strategy without stenting in carefully selected patients with OCT-confirmed plaque erosion, further supporting this conservative approach.[5] Accordingly, a no-stent strategy has been explored in carefully selected patients, particularly when significant residual fixed stenosis is absent. This report presents the angiographic outcomes of four young male patients treated with a no-stent strategy, with or without initial mechanical reperfusion, using the glycoprotein IIb/IIIa inhibitor tirofiban.

## ABBREVIATIONS

| | |
|---|---|
| CAG | Coronary angiography |
| DAPT | Dual antiplatelet therapy |
| IVUS | Intravascular ultrasound |
| LAD | Left anterior descending artery |
| MI | Myocardial infarction |
| OCT | Optical coherence tomography |
| PDA | Posterior descending artery |
| RCA | Right coronary artery |
| SCAD | Spontaneous coronary artery dissection |
| STEMI | ST-segment elevation myocardial infarction |
| TIMI | Thrombolysis in Myocardial Infarction |

## Case Report

### Case 1

A 46-year-old male presented with an acute inferior STEMI. Coronary angiography (CAG) revealed a massive thrombus

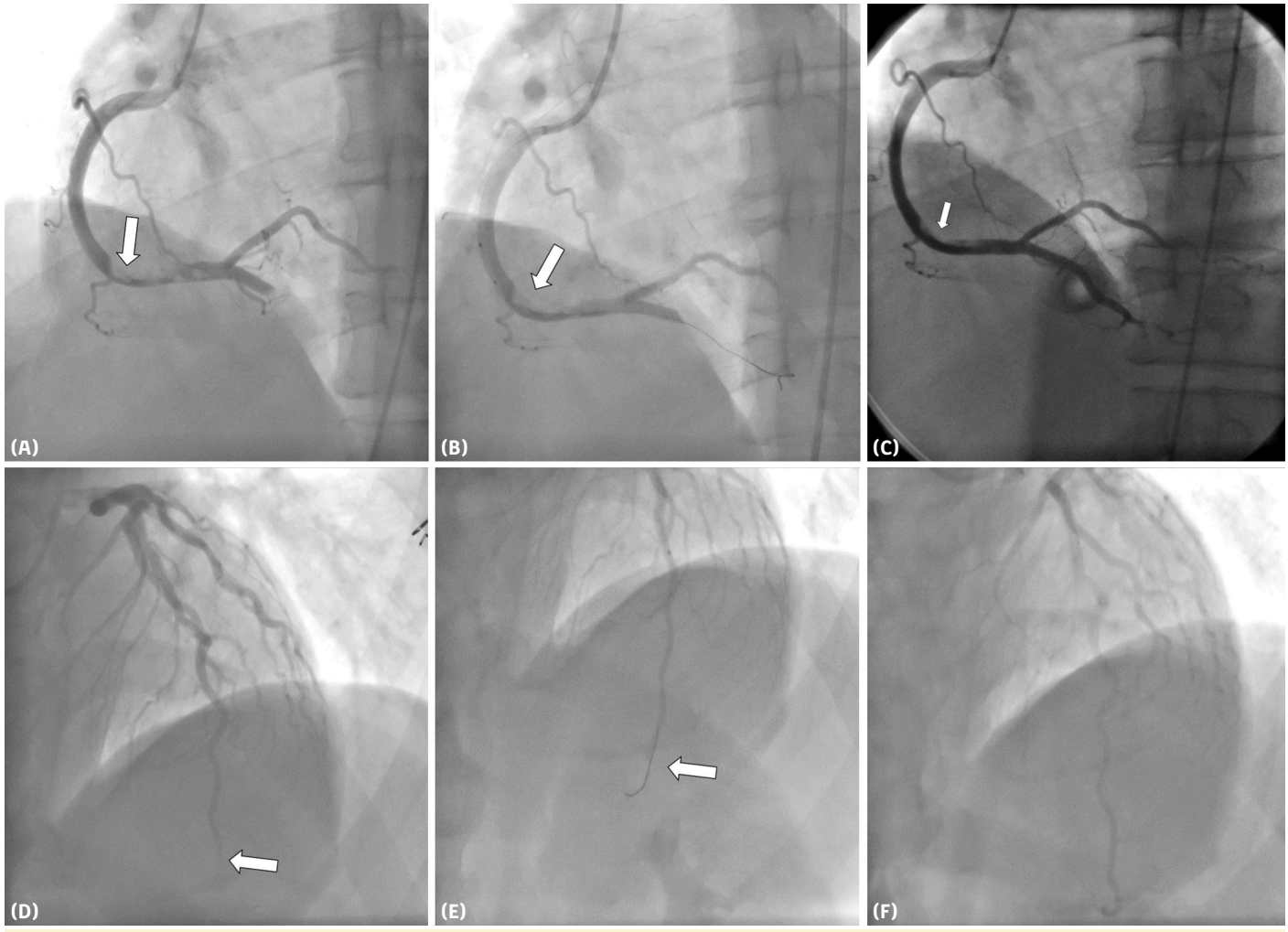



**Figure 1.** Coronary angiography images of Cases 1 and 2. (A–C) Case 1: (A) Baseline heavy thrombus burden in the right coronary artery (RCA) with an occluded posterior descending artery (PDA). (B) Inadequate result with persistent large thrombus burden after balloon angioplasty (PTCA). (C) Final control angiography showing substantially reduced thrombus burden with preserved TIMI III epicardial flow, which had initially been restored by mechanical intervention. (D–F) Case 2: (D) Baseline large thrombus causing total occlusion of the distal left anterior descending artery (LAD). (E) Restoration of flow after balloon dilatation, with the guidewire visible in the lumen. (F) Control angiography showing preserved normal distal flow after balloon dilatation and thrombus regression following tirofiban infusion. Note: Arrows indicate thrombi.

burden (TIMI thrombus grade 5) in the right coronary artery (RCA) proximal to the posterior descending artery (PDA) and posterolateral artery (PLA), with total occlusion of the PDA branch. Balloon angioplasty (PTCA) with a 3.0×12 mm balloon, followed by manual thrombus aspiration, was performed on the PDA lesion, and a 2.5×15 mm balloon was used to treat the thrombus in the PLA. However, a large thrombus burden persisted within the lumen after the procedure (Figure 1A, B); therefore, stent implantation was not performed, and a tirofiban infusion was initiated. As the patient became asymptomatic and hemodynamically stable, he was discharged on maintenance antiplatelet therapy. Because the patient remained asymptomatic, follow-up CAG was scheduled based on individualized clinical judgment and performed 1 month later, demonstrating a significant reduction in thrombus burden (TIMI thrombus grade 2) with preserved TIMI III flow (Table 1; Figure 1C; Video 1). Given the optimal distal flow and absence of critical flow-limiting stenosis, definitive permanent stenting was avoided.

**Case 2**

A 33-year-old male presented with an acute anterior STEMI. CAG showed 40–50% ostial narrowing, suspected to be thrombotic, and total occlusion of the distal left anterior descending artery (LAD) (TIMI thrombus grade 5) (Figure 1D). PTCA was performed with a 2.0×12 mm balloon in the distal LAD, resulting in TIMI III flow (Figure 1E). Because of the residual thrombus burden, tirofiban was initiated. Control CAG performed 24 hours later showed significant regression of the distal LAD thrombus (TIMI thrombus grade 1–2) without compromised flow (Table 1; Figure 1F; Video 2).

**Case 3**

A 27-year-old male presented with an acute anterior STEMI. CAG revealed a thrombus impairing distal flow in the LAD (TIMI thrombus grade 4) (Figure 2A). After an intracoronary tirofiban bolus of 25 μg/kg, a maintenance infusion was initiated. Without any mechanical intervention, including balloon angioplasty or stent implantation, control CAG demonstrated complete thrombus resolution and preserved normal coronary anatomy (Table 1; Figure 2B; Video 3).

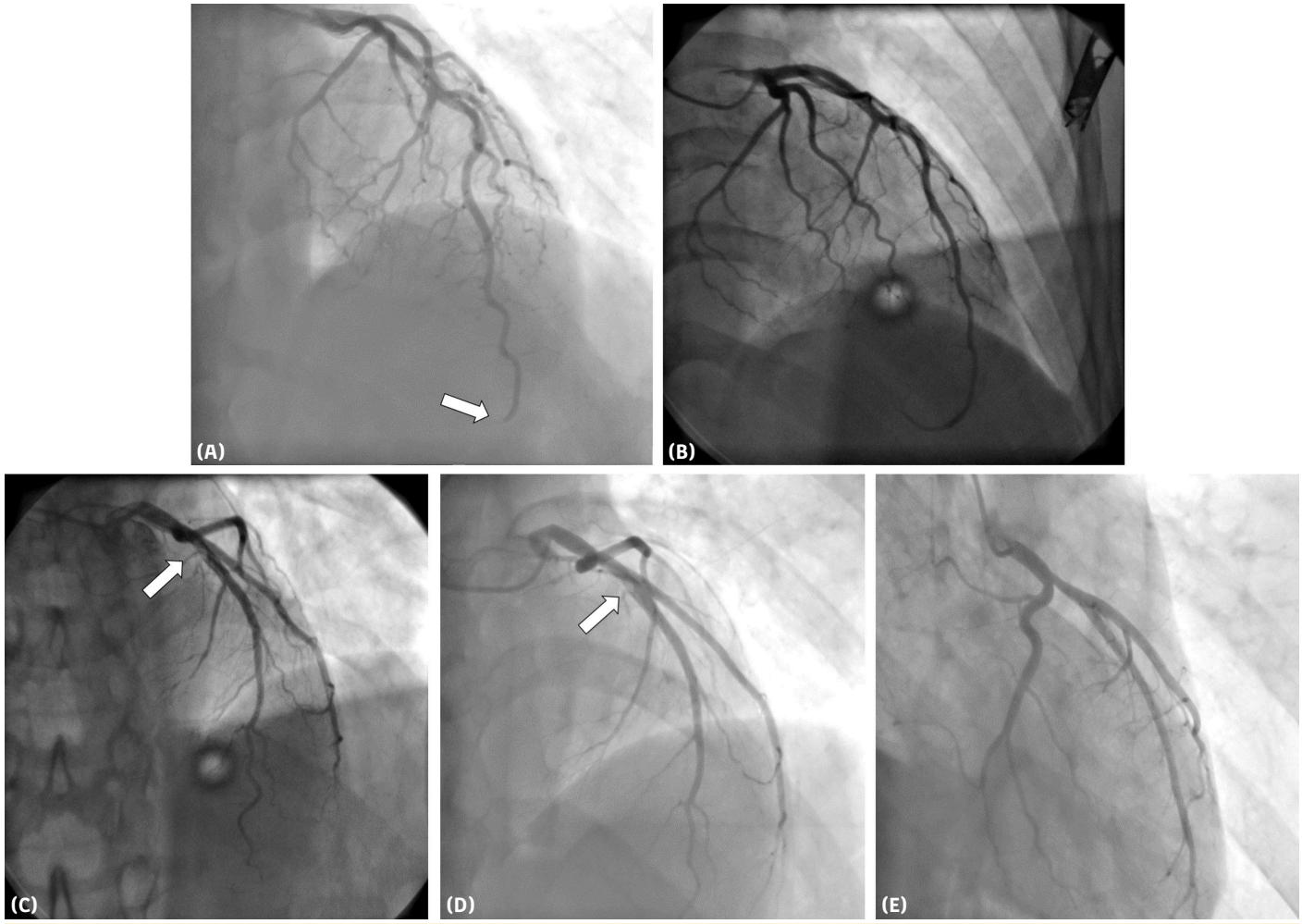



**Figure 2.** Coronary angiography images of Cases 3 and 4. (A, B) Case 3: (A) Baseline image showing a thrombus disrupting distal flow in the left anterior descending artery (LAD). (B) Control angiography demonstrating complete resolution of the thrombus after a tirofiban bolus and maintenance infusion, without mechanical intervention. (C–E) Case 4: (C) Baseline angiography showing a suspected thrombotic culprit lesion with an overlying mobile thrombus and preserved TIMI flow in the proximal LAD. (D) Early control angiography showing partial persistence of the thrombus after tirofiban infusion. (E) Final angiography showing complete thrombus resolution after a 3-week course of dual antiplatelet therapy (DAPT) and low-molecular-weight heparin (LMWH). Note: Arrows indicate thrombi.

**Table 1.** Clinical, angiographic, and therapeutic characteristics of the patients

| Variables | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Clinical presentation | | | | |
| Clinical presentation | Acute inferior STEMI | Acute anterior STEMI | Acute anterior STEMI | Acute anterior STEMI |
| Presenting symptoms and duration | Chest pain (unknown duration) | Chest pain (unknown duration) | Chest pain (unknown duration) | Chest pain (unknown duration) |
| Age/Sex | 46/Male | 33/Male | 27/Male | 43/Male |
| Comorbidities (HTN, DM) | HTN | None documented | None documented | None documented |
| Smoking status | N/A | N/A | N/A | N/A |
| Substance/cocaine use | N/A | N/A | N/A | N/A |
| Family history of CAD | N/A | N/A | N/A | N/A |
| ECG findings | ST elevation in leads II, III, and aVF | ST elevation in leads V2–V6 | ST elevation in leads V1–V6 | ST elevation in leads V1–V6 |
| Hemodynamic status | Stable | Stable | Stable | Stable |
| GRACE score | N/A | N/A | N/A | N/A |
| Peak troponin I (ng/L) | N/A | 30,543.4 | 17,792.1 | 2,691.3 |
| Peak CK-MB (U/L) | N/A | 176.9 | 199.6 | 40.9 |
| Laboratory parameters | | | | |
| Platelet count (before/after) | 340/318 | 338/290 | 401/320 | 207/140 |
| Creatinine (mg/dL) | 0.73 | 1.11 | 0.81 | 0.90 |
| HbA1c (%)/Glucose (mg/dL) | 4.9/163 | 5.6/98 | 6.1/88 | N/A/92 |
| Lipid profile (total cholesterol/LDL/HDL/TG) | 137/81.7/43.1/61.0 | 181/121.9/30.5/143.0 | 158/98.5/37.1/112.0 | 126/63.9/37.3/124.0 |
| Non-HDL cholesterol (mg/dL) | 93.9 | 150.5 | 120.9 | 88.7 |
| Thrombophilia | Not measured | Not measured | Low protein S level (36%); hyperhomocysteinemia (>50 μmol/L) | Not measured |
| Lipoprotein(a) | Not measured | Not measured | Not measured | Not measured |
| Angiographic findings | | | | |
| Culprit vessel | RCA (PDA/proximal PLA) | Distal LAD | Distal LAD | Proximal LAD |
| Multivessel disease | No | No | No | No |
| Initial TIMI thrombus grade | Grade 5 | Grade 5 | Grade 4 | Grade 4 |
| Initial TIMI flow | TIMI 0 | TIMI 0 | TIMI 2/3 | TIMI 3 |
| Treatment strategy | | | | |
| Stenting strategy | Stenting avoided | Stenting avoided | Definitive no-stent strategy | Definitive no-stent strategy |
| Mechanical intervention | Balloon angioplasty + aspiration | Balloon-only PCI | None | None |
| Tirofiban regimen (standard) | 25 μg/kg IV bolus + 0.15 μg/kg/min for 24 h | 25 μg/kg IV bolus + 0.15 μg/kg/min for 24 h | 25 μg/kg intracoronary bolus + 0.15 μg/kg/min IV for 24 h | 25 μg/kg IV bolus + 0.15 μg/kg/min for 24 h |
| Renal function adjustment | None required | None required | None required | None required |
| Activated clotting time (ACT) | Not measured | Not measured | Not measured | Not measured |
| P2Y12 inhibitor and aspirin | Ticagrelor (180-mg loading dose, 90 mg BID) + ASA (300-mg loading dose, 100 mg daily) | Ticagrelor (180-mg loading dose, 90 mg BID) + ASA (300-mg loading dose, 100 mg daily) | Ticagrelor (180-mg loading dose, 90 mg BID) + ASA (300-mg loading dose, 100 mg daily) | Ticagrelor (180-mg loading dose, 90 mg BID) + ASA (300-mg loading dose, 100 mg daily) |
| Planned DAPT duration | 12 months | 12 months | 12 months | 12 months |
| Anticoagulant | UFH (IV during PCI) | UFH (IV during PCI) | Enoxaparin (1 mg/kg SC twice daily for 3 days) | Enoxaparin (1 mg/kg SC twice daily for 3 weeks) |

**Table 1 (cont).** Clinical, angiographic, and therapeutic characteristics of the patients

| Variables | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Outcomes (follow-up) | | | | |
| Echocardiography (1 month) | LVEF 50–55%; inferobasal hypokinesia; LVH (+) | LVEF 60%; no RWMA | LVEF 60%; no RWMA | LVEF 60%; no RWMA |
| Timing of repeat angiography | 1 month | 24 hours | 14 days | 24 hours and 3 weeks |
| Final TIMI thrombus grade | Significant reduction (TIMI thrombus grade 2) | Significant regression (TIMI thrombus grade 1–2) | Complete resolution | Complete resolution |
| Final TIMI flow | TIMI III | TIMI III | TIMI III | TIMI III |
| In-hospital mortality/stroke/heart failure | None | None | None | None |
| Urgent revascularization | None | None | None | None |
| Bleeding complications | None | None | None | None |
| Recurrent ischemia/MI | None | None | None | None |
| Follow-up duration | 1 month | 1 month | 1 month | 1 month |

ACT, activated clotting time; ASA, acetylsalicylic acid; BID, twice daily; CAD, coronary artery disease; CK-MB, creatine kinase-myocardial band; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HTN, hypertension; IV, intravenous; LAD, left anterior descending artery; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; N/A, not available; PCI, percutaneous coronary intervention; PDA, posterior descending artery; PLA, posterolateral artery; RCA, right coronary artery; RWMA, regional wall motion abnormality; SC, subcutaneous; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin. Lipid samples were obtained at admission before the initiation of lipid-lowering therapy.

**Case 4**

A 43-year-old male presented with an acute anterior STEMI. The proximal LAD showed a mild angiographically suspected thrombotic culprit lesion with an overlying mobile thrombus and preserved TIMI flow (TIMI thrombus grade 4) (Figure 2C). A conservative approach with tirofiban infusion was chosen without balloon angioplasty or stent implantation. Early control CAG performed at 24 hours showed partial persistence of the thrombus (Figure 2D). Continuation of therapeutic-dose low-molecular-weight heparin (LMWH; enoxaparin 1 mg/kg subcutaneously twice daily) alongside dual antiplatelet therapy (DAPT) for 3 weeks was a highly individualized management decision based on the persistent massive thrombus burden. During this period, Case 4 showed a decrease in platelet count from $207\times10^9$/L to $140\times10^9$/L without severe thrombocytopenia or overt bleeding. Final CAG performed 3 weeks later demonstrated complete thrombus resolution (Table 1; Figure 2E; Video 4). A subsequent exercise stress test was negative.

**Discussion**

As observed in our cases, tirofiban-based antithrombotic treatment was followed by thrombus regression in the management of a high coronary thrombus burden in young patients with STEMI.[6] In selected young patients with a large thrombus burden and limited angiographically evident fixed stenosis, plaque erosion, thrombosis related to prothrombotic conditions, or other nonclassical mechanisms may be considered.[2,3] In such scenarios, pharmacological antithrombotic treatment may allow permanent stenting to be avoided in selected cases, thereby avoiding exposure to potential long-term metallic stent-related complications.[4]

The decision to pursue a no-stent strategy, with or without initial mechanical reperfusion, should be highly individualized.[5] Features that may support consideration of such an approach include hemodynamic stability with preserved or restored TIMI III flow, a high thrombus burden without clearly demonstrated flow-limiting (≥70%) fixed severe stenosis, and the absence of critical left main or proximal bifurcation lesions. Importantly, this does not represent a guideline-defined selection algorithm.[5,6] Conversely, patients with ongoing ischemia, hemodynamic instability, or significant residual obstructive lesions after thrombus resolution should undergo conventional mechanical revascularization.[1] However, this conservative approach is not without risks, including early reocclusion, recurrent MI, distal embolization, missed plaque rupture or dissection, and bleeding complications associated with intensive antithrombotic therapies, including tirofiban-induced thrombocytopenia.[6]

A key component of this conservative approach is follow-up CAG. After resolution of the massive thrombus burden, the underlying coronary anatomy becomes more apparent. Re-evaluation of the coronary arteries is recommended to objectively confirm thrombus resolution and identify any latent obstructive lesions that may require mechanical intervention. Although manual thrombus aspiration was used in one case (Case 1) as a bailout strategy to restore initial flow, current guidelines do not recommend the routine use of aspiration thrombectomy, although bailout aspiration may be considered in selected cases with a large residual thrombus burden or inadequate flow. Understanding the underlying mechanisms is essential for tailoring interventional strategies in STEMI.[3,7–9] Managing massive intracoronary thrombus requires a careful clinical balance between mechanical reperfusion and pharmacological therapy. Additionally, identifying the underlying etiology is essential in young patients with STEMI. In cases without significant fixed atherosclerosis, a comprehensive diagnostic

evaluation for nonclassical causes, such as coronary embolism, hypercoagulable states (including inherited thrombophilia and antiphospholipid syndrome), malignancy, or systemic prothrombotic disorders, should be strongly considered, particularly in patients with recurrent events or an absence of traditional risk factors.

The primary limitations of this retrospective series include the absence of long-term clinical follow-up and the lack of intravascular imaging modalities such as optical coherence tomography (OCT) or intravascular ultrasound (IVUS). Without OCT-guided confirmation, the diagnosis of plaque erosion remains speculative. Additionally, the "stentless" strategies applied were heterogeneous, ranging from conservative pharmacological treatment alone to balloon angioplasty and manual thrombus aspiration, indicating that this report does not represent a uniform treatment protocol. Furthermore, although the detailed treatment characteristics presented in this report are limited to antithrombotic and interventional management, all patients received guideline-directed secondary prevention, including high-intensity statin therapy at discharge. Comprehensive etiological data, including body mass index, smoking status, family history, drug or substance exposure, recent infections, and autoimmune diseases, could not be retrospectively obtained from the medical records. A thrombophilia evaluation in Case 3 revealed a low protein S level (36%) and severe hyperhomocysteinemia (>50 µmol/L), suggesting a possible prothrombotic contribution. However, because the protein S sample was obtained during the acute STEMI phase without subsequent confirmatory testing, a definitive diagnosis of hereditary deficiency cannot be established. Furthermore, a retrospective review of the patient's medical records revealed documented vitamin B12 (152.0 ng/L) and folate (2.7 µg/L) deficiencies, supporting a nutritional contribution to the hyperhomocysteinemia. Such systematic data could not be retrospectively obtained for the other three patients, which constitutes a limitation. Additionally, this case series is highly selected and nonconsecutive, introducing vulnerability to selection bias that may favor cases with successful clinical and angiographic outcomes. Furthermore, routine monitoring of post-treatment platelet counts confirmed that no severe tirofiban-induced thrombocytopenia occurred across the cohort. Case 4 demonstrated a decrease in platelet count from $207\times10^9$/L to $140\times10^9$/L without severe thrombocytopenia or overt bleeding. Despite these limitations, short-term outcomes were favorable: all patients maintained left ventricular ejection fractions above 50% and experienced no recurrent angina at 1-month follow-up, as determined through outpatient clinic visits and hospital electronic medical records. Although a 12-month DAPT regimen is standard following STEMI, adherence beyond the 1-month follow-up period remains unknown.

## Conclusion

In carefully selected patients with preserved coronary flow, a high thrombus burden, and no clearly demonstrated flow-limiting fixed lesion, a no-stent management strategy, with or without initial mechanical reperfusion, may be considered after individualized assessment and close angiographic follow-up.

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent was obtained from all individual patients for the publication of this case series and its accompanying images.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Video 1.** Angiographic assessment of Case 1. The sequences demonstrate the baseline thrombus burden in the RCA, persistent poor flow after balloon angioplasty, and subsequent restoration of epicardial flow following mechanical intervention, followed by a reduction in thrombus burden after tirofiban-based therapy.

**Video 2.** Angiographic assessment of Case 2. The video demonstrates total occlusion of the distal LAD, balloon angioplasty with the guidewire in place, successful restoration of epicardial flow after balloon angioplasty, and subsequent thrombus regression after tirofiban infusion.

**Video 3.** Angiographic assessment of Case 3. The first segment shows the thrombus in the LAD at baseline, while the second segment shows complete thrombus resolution after tirofiban therapy without stent implantation or balloon angioplasty.

**Video 4.** Angiographic assessment of Case 4. The sequences show the baseline thrombus in the proximal LAD with preserved flow, persistent thrombus on early control angiography despite tirofiban infusion, and complete resolution after 3 weeks of maintenance therapy.

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# High-Voltage Electrical Injury Presenting with ST-Segment Elevation and Transient Myocardial Dysfunction without Obstructive Coronary Artery Disease

## Obstrüktif Koroner Arter Hastalığı Olmaksızın ST-Segment Elevasyonu ve Geçici Miyokardiyal Disfonksiyonla Seyreden Yüksek Voltajlı Elektrik Yaralanması

**ABSTRACT**

Electrical injury may cause various cardiac complications, including electrocardiographic (ECG) changes that mimic acute myocardial infarction. We present a 38-year-old man who developed cardiopulmonary arrest after exposure to a 25,000-volt electrical source. The admission ECG showed inferolateral ST-segment elevation, raising suspicion for acute myocardial infarction. Cardiac biomarkers were markedly elevated, and transthoracic echocardiography demonstrated a left ventricular ejection fraction (LVEF) of 35% with inferoposterolateral wall hypokinesia accompanied by moderate mitral regurgitation. Emergency coronary angiography demonstrated no significant obstructive coronary artery disease. The post-coronary angiography ECG showed greater than 50% resolution of the ST-segment elevation. A 24-hour follow-up ECG demonstrated near-complete resolution of the ST-segment abnormalities, while repeat echocardiography showed complete recovery of left ventricular systolic function, resolution of the previously detected regional wall motion abnormalities, and regression of mitral regurgitation to a trivial degree. Although ventricular function normalized within 24 hours, the patient subsequently developed dialysis-requiring acute kidney injury, neurological deterioration, suspected pneumonia, and refractory septic shock and died on hospital day 10. This case highlights that high-voltage electrical injury may present with ST-segment elevation despite the absence of obstructive coronary artery disease, accompanied by reversible myocardial dysfunction, emphasizing the importance of considering ST-segment elevation myocardial infarction (STEMI) mimics in the differential diagnosis.

**Keywords:** Electrical injury, myocardial injury, ST-segment elevation, transient myocardial dysfunction.

**ÖZET**

Elektrik yaralanmaları, akut miyokart enfarktüsünü taklit eden elektrokardiyografik (EKG) değişiklikler de dahil olmak üzere çeşitli kardiyak komplikasyonlara neden olabilir. Bu olgu sunumunda, yaklaşık 25.000 voltluk elektrik kaynağına maruz kaldıktan sonra kardiyopulmoner arrest gelişen 38 yaşında bir erkek hasta sunulmaktadır. Başvuru EKG'sinde akut miyokart enfarktüsünü düşündüren inferolateral ST-segment elevasyonu saptandı. Kardiyak biyobelirteçler belirgin derecede yüksek bulundu ve transtorasik ekokardiyografide inferoposterolateral duvar hipokinezisi ile birlikte sol ventrikül ejeksiyon fraksiyonu (LVEF) %35 olarak ölçüldü; ayrıca orta derecede mitral yetersizliği saptandı. Acil koroner anjiyografide anlamlı obstrüktif koroner arter hastalığı saptanmadı. Koroner anjiyografi sonrasında çekilen EKG'de ST-segment elevasyonunda %50'den fazla gerileme izlendi. Başvurudan 24 saat sonra çekilen kontrol EKG'sinde ST-segment değişikliklerinin büyük ölçüde düzeldiği, kontrol ekokardiyografisinde ise sol ventrikül sistolik fonksiyonlarının tamamen normale döndüğü, daha önce saptanan bölgesel duvar hareket bozukluklarının tamamen kaybolduğu ve mitral yetersizliğinin eser düzeye gerilediği izlendi. Sol ventrikül fonksiyonları 24 saat içinde normale dönmesine rağmen hastada daha sonra diyaliz gerektiren akut böbrek hasarı, nörolojik kötüleşme, şüpheli pnömoni ve refrakter septik şok gelişti ve hasta yatışının 10. gününde kaybedildi. Bu olgu, yüksek voltajlı elektrik yaralanmasının obstrüktif koroner arter hastalığı bulunmamasına rağmen ST-segment elevasyonu ve geri dönüşümlü miyokardiyal disfonksiyon ile prezente olabileceğini göstermekte ve ayırıcı tanıda ST-segment yükselmeli miyokart enfarktüsünü (STEMI) taklit eden tabloların göz önünde bulundurulmasının önemini vurgulamaktadır.

**Anahtar Kelimeler:** Elektrik yaralanması, miyokardiyal hasar, ST-segment elevasyonu, geçici miyokardiyal disfonksiyon.

**CASE REPORT**
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Electrical injuries are generally classified as low-voltage (<1000 V) and high-voltage (≥1000 V) injuries and may result in a broad spectrum of cardiovascular complications, ranging from benign electrocardiographic abnormalities to life-threatening arrhythmias, myocardial injury, and sudden cardiac death.[1,2] High-voltage electrical injuries are associated with more severe cardiovascular complications and greater morbidity and mortality than low-voltage injuries.[1,2]

Cardiac manifestations following electrical injury are most commonly limited to transient electrocardiographic abnormalities and cardiac arrhythmias, whereas ST-segment elevation in the absence of obstructive coronary artery disease has been reported only rarely.[1,3] The underlying mechanisms of cardiac injury following electrical exposure remain incompletely understood and are thought to involve direct thermal myocardial injury, coronary vasospasm, endothelial injury, and thrombotic vascular damage.[4] Herein, we present a case of high-voltage electrical injury associated with ST-segment elevation and transient left ventricular systolic dysfunction without obstructive coronary artery disease.

**Case Report**

A 38-year-old man with no known chronic medical conditions was brought to the emergency department after cardiopulmonary arrest following a high-voltage electrical injury. According to the patient's history, he had been exposed to an electrical source of approximately 25,000 volts while working on an electrical pole. Following electrical exposure, the patient was thrown from the source. The duration of contact and environmental conditions at the time of injury were unknown. The current entered through the right upper extremity and exited through the left foot. He developed cardiopulmonary arrest at the scene, with pulseless ventricular tachycardia documented as the initial rhythm. Although the exact no-flow interval was unknown, the low-flow time was approximately 25 minutes. During cardiopulmonary resuscitation, three 200-J defibrillation shocks were delivered, along with intravenous adrenaline (1 mg every 3 minutes) and a 300-mg amiodarone bolus, resulting in return of spontaneous circulation (ROSC). Following restoration of spontaneous circulation, transient bradycardia developed and responded to a total of 2 mg of atropine, with no further doses required. An intravenous amiodarone infusion, planned at 900 mg over 24 hours, was subsequently initiated. Serum magnesium levels remained within the normal range; therefore, magnesium replacement was not required. Induced hypothermia was not performed because extensive burn injuries precluded the safe application of surface-cooling devices. No active temperature-control protocol was applied; however, the patient remained spontaneously normothermic and afebrile during the first 72 hours. Upon admission, the patient was intubated, unconscious, and in poor general condition. Physical examination revealed extensive second- and third-degree electrical burns involving both upper extremities, the trunk, and the left foot, affecting approximately 35% of the total body surface area. The distribution of the burn injuries was consistent with the presumed current entry through the right upper extremity and exit through the left foot. The estimated height of the fall was unknown. As part of the initial trauma evaluation, cranial, cervical, thoracic, and abdominal computed tomography (CT) imaging was performed. No intracranial hemorrhage, cervical spine fracture, traumatic intra-abdominal injury, or hemorrhage was identified. Multiple rib fractures were observed and were considered most likely related to cardiopulmonary resuscitation. Abdominal CT raised suspicion of subileus; however, this finding was not supported by subsequent direct abdominal radiography after bowel movements. No other traumatic fractures or major internal organ injuries were identified. The patient received intravenous crystalloid fluid resuscitation with close monitoring of hemodynamic status, urine output, fluid balance, and serial electrolyte levels. Detailed data regarding the initial crystalloid volume and weight-based burn resuscitation protocol were not available. Serial potassium, calcium, magnesium, and phosphate levels were monitored. Burn surgery consultation was obtained, and the burn injuries were managed predominantly with supportive treatment.

The first electrocardiogram (ECG), obtained approximately 35 minutes after the electrical exposure and shortly after ROSC, showed sinus rhythm at 103 beats/min, a QRS duration of 116 ms, and a manually calculated corrected QT interval (QTc) of 472 ms, with marked ST-segment elevation in leads II, III, aVF, and V4–V6, accompanied by reciprocal ST-segment depression in leads I and aVL, raising suspicion of acute ST-segment elevation myocardial infarction (STEMI) (Figure 1). Initial laboratory evaluation revealed severe metabolic acidosis and hyperlactatemia, accompanied by markedly elevated cardiac and skeletal muscle injury biomarkers. Serial laboratory findings during hospitalization are summarized in Table 1. High-sensitivity troponin I was >25 ng/mL on admission and remained above the assay's upper measurement limit at 6 and 24 hours, decreased to 23.24 ng/mL on Day 3, and further declined to 2.1 ng/mL on Day 10. Bedside transthoracic echocardiography demonstrated a left ventricular ejection fraction (LVEF) of 35%, calculated using the modified biplane Simpson method, with regional hypokinesia involving the inferior, posterior, and lateral left ventricular wall segments. Right ventricular systolic function was preserved. Moderate mitral regurgitation and trivial tricuspid regurgitation were present, and no pericardial effusion was detected (Video 1).

## ABBREVIATIONS

| | |
|---|---|
| CMR | Cardiac magnetic resonance |
| CRRT | Continuous renal replacement therapy |
| CT | Computed tomography |
| ECG | Electrocardiogram |
| EEG | Electroencephalography |
| LAD | Left anterior descending artery |
| LCx | Left circumflex artery |
| LMCA | Left main coronary artery |
| LVEF | Left ventricular ejection fraction |
| MINOCA | Myocardial infarction with non-obstructive coronary arteries |
| MRI | Magnetic resonance imaging |
| RCA | Right coronary artery |
| ROSC | Return of spontaneous circulation |
| STEMI | ST-segment elevation myocardial infarction |
| TIMI | Thrombolysis in myocardial infarction |

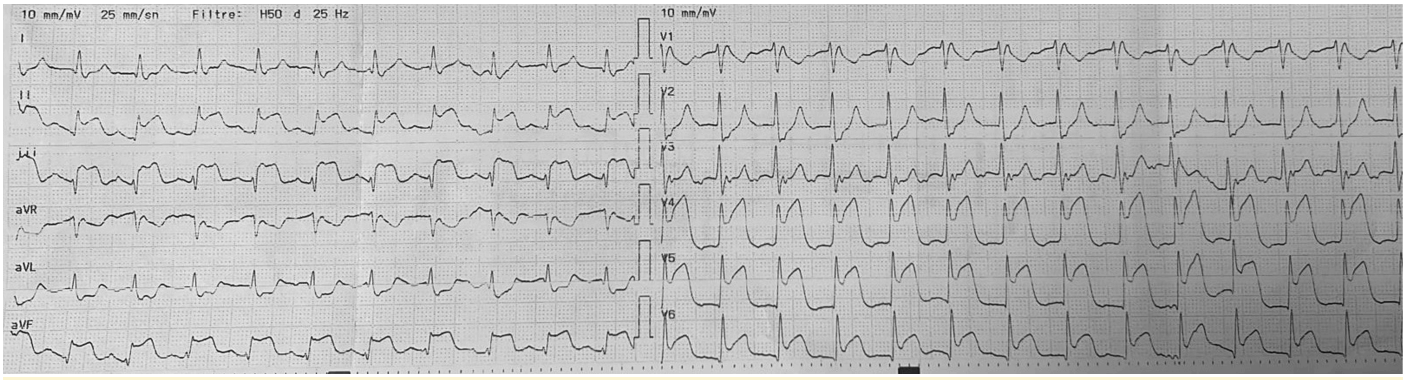



**Figure 1.** Initial electrocardiogram obtained approximately 35 minutes after electrical exposure and shortly after return of spontaneous circulation, showing sinus rhythm at 103 beats/min, marked ST-segment elevation in leads II, III, aVF, and V4–V6 with reciprocal ST-segment depression in leads I and aVL, and a manually calculated QTc of 472 ms.

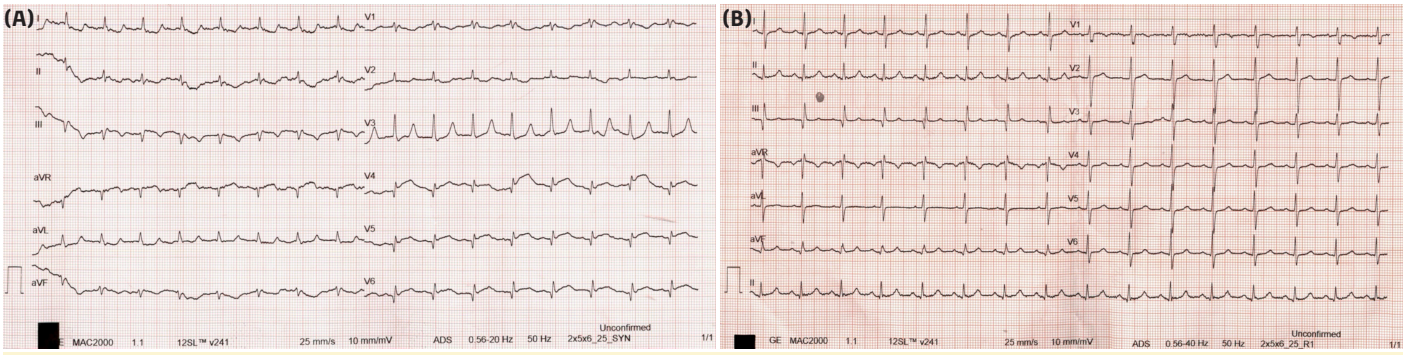



**Figure 2.** (A) Electrocardiogram obtained after coronary angiography, approximately 2 hours after electrical exposure. Despite the automated interpretation suggesting an accelerated junctional rhythm, manual ECG assessment demonstrated sinus rhythm at 102 beats/min, greater than 50% resolution of the ST-segment elevations, and a manually calculated QTc of 522 ms. (B) Electrocardiogram obtained 24 hours after electrical exposure, showing sinus rhythm at 93 beats/min, near-complete resolution of the ST-segment abnormalities, and a manually calculated QTc of 452 ms.

Given the electrocardiographic findings, marked elevation of cardiac biomarkers, and regional left ventricular wall motion abnormalities, the patient underwent emergency coronary angiography. Before coronary angiography, 300 mg of aspirin was administered via a nasogastric tube. Given the extensive burn injury, possible associated trauma, and consequent bleeding and procedural risks, neither a P2Y12 receptor inhibitor nor unfractionated heparin was administered before delineation of the coronary anatomy. No nitrate therapy, including intracoronary nitrates, was administered before or during coronary angiography. Angiographic evaluation of the left main coronary artery (LMCA), left anterior descending artery (LAD), left circumflex artery (LCx), and right coronary artery (RCA) demonstrated Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow throughout the coronary tree, with no evidence of obstructive coronary artery disease, coronary slow flow, ectasia, congenital coronary anomalies, distal embolization, angiographically visible thrombus, or features suggestive of spontaneous coronary artery dissection. A mild myocardial bridge was observed in the mid-LAD, with approximately 20–30% systolic compression, and was considered an incidental angiographic finding (Video 2). The second ECG, obtained after coronary angiography approximately 2 hours after the electrical exposure, showed sinus rhythm at 102 beats/min, with greater than 50% resolution of the ST-segment elevations and a manually calculated QTc of 522 ms (Figure 2A). In view of the QTc prolongation, the amiodarone infusion was discontinued.

The patient remained in the coronary intensive care unit for 24 hours under continuous cardiac monitoring. No malignant ventricular arrhythmias were observed during this period. Repeat transthoracic echocardiography performed 24 hours after admission demonstrated complete resolution of the previously detected regional wall motion abnormalities, with recovery of the LVEF to 62%. Moderate mitral regurgitation had regressed to trivial, while trivial tricuspid regurgitation remained unchanged. The third ECG, obtained 24 hours after the electrical exposure, showed sinus rhythm at 93 beats/min, with near-complete resolution of the ST-segment abnormalities and a manually calculated QTc of 452 ms (Figure 2B).

Following stabilization of the cardiac condition, the patient was transferred to the tertiary intensive care unit for further multidisciplinary management. The patient remained unconscious after resuscitation and was evaluated by the neurology team. Brain CT revealed no acute intracranial pathology; brain magnetic resonance imaging (MRI) and electroencephalography (EEG) were not performed. Because of recurrent seizures, intravenous levetiracetam was initiated with a loading dose of 2,500 mg followed by 500 mg twice daily. Intermittent seizures during follow-up were treated with 5 mg of intravenous diazepam as needed, and close neurological monitoring was continued.

During the subsequent hospital course, the patient developed acute kidney injury requiring renal replacement therapy, with

intermittent hemodialysis initiated on hospital day 3. On hospital day 7, anuria developed, and intermittent hemodialysis could no longer be performed because of persistent hemodynamic instability; continuous renal replacement therapy (CRRT) was therefore administered during the final 3 days. Following consultation with the infectious diseases team, empirical piperacillin–tazobactam therapy was initiated on hospital day 1 because of clinical suspicion of aspiration pneumonia and the presence of extensive burn injuries. Subsequently, persistent fever of approximately 39°C, a progressive increase in C-reactive protein despite antimicrobial therapy, and growth of Klebsiella pneumoniae in blood cultures prompted escalation of antimicrobial therapy to meropenem and vancomycin, as recommended by the infectious diseases team. The isolated Klebsiella pneumoniae was susceptible to meropenem. Tracheal aspirate cultures showed no growth, and the source of the bacteremia could not be definitively established. The patient subsequently developed refractory septic shock with multiorgan failure. Despite high-dose norepinephrine support, profound hypotension persisted, and dopamine was added because of intermittent bradycardia. Despite combined vasoactive support, profound hypotension persisted, followed by cardiac arrest on hospital day 10. Resuscitation was unsuccessful. Refractory septic shock with multiorgan failure was considered the immediate cause of death, with acute kidney injury, suspected pneumonia, and severe neurological deterioration as major contributing conditions. No additional cardiac complications occurred during follow-up.

## Discussion

Although transient electrocardiographic abnormalities and cardiac arrhythmias are well-recognized manifestations of electrical injury, ST-segment elevation in the absence of obstructive coronary artery disease remains an uncommon clinical presentation. As summarized in Table 2, selected previously reported cases of electrical injury presenting with ST-segment elevation demonstrate considerable heterogeneity in the severity of myocardial dysfunction, angiographic findings, and clinical outcomes. These cases were selected to provide a concise clinical comparison with the present case and do not represent an exhaustive review of all published cases.[3,5–9] Our patient shared several features with these reports, including marked ST-segment elevation and non-obstructive coronary arteries, but also exhibited transient inferoposterolateral left ventricular systolic dysfunction, with complete recovery within 24 hours despite an initially reduced LVEF. Although cardiac function recovered rapidly, the patient ultimately died from refractory septic shock with multiorgan failure. This case highlights the importance of integrating electrocardiographic, echocardiographic, and coronary angiographic findings when evaluating patients with suspected STEMI following electrical injury.

Several overlapping mechanisms may account for the myocardial abnormalities observed in this case. Direct electrical myocardial injury may result from thermal damage, altered cell membrane permeability, and injury to the coronary endothelium, whereas vasospasm and transient thrombosis with spontaneous recanalization may produce temporary myocardial ischemia despite a subsequently non-obstructive angiogram.[3,4] The prolonged cardiac arrest introduces additional confounding mechanisms. Post-resuscitation myocardial dysfunction is characterized by reversible contractile dysfunction after restoration of spontaneous circulation and is not necessarily limited to a global pattern. It may therefore substantially confound the interpretation of early echocardiographic findings after cardiac arrest.[10] Given the rapid recovery of LVEF from 35% to 62% within 24 hours, post-resuscitation myocardial dysfunction should be considered a leading potential mechanism in this case.[10,11] Furthermore, profound metabolic acidosis, hyperlactatemia, hypoperfusion, hypoxia, increased sympathetic activity, and electrolyte disturbances may have contributed to the observed ST-segment abnormalities and transient myocardial dysfunction. These systemic factors therefore represent important confounders when interpreting the cardiac findings in this case.[12]

The differential diagnosis also includes Takotsubo syndrome and myocarditis, both of which may present with ST-segment elevation, elevated cardiac troponin levels, transient left

**Table 1.** Serial laboratory parameters during hospitalization

| Parameters | Reference range | Admission | 6 h | 24 h | Day 3 | Last available value |
|---|---|---|---|---|---|---|
| White blood cell count (×10⁹/L) | 4–10 | 22.9 | 23.13 | 14.0 | 5.97 | 23.15 |
| Creatinine (mg/dL) | 0.5–1.3 | 1.4 | 1.5 | 1.7 | 4.31 | 2.02 |
| Potassium (mmol/L) | 3.5–5.5 | 5.3 | 5.5 | 5.24 | 5.13 | 3.34 |
| pH | 7.35–7.45 | 6.78 | 7.10 | 7.19 | 7.33 | 6.92 |
| Lactate (mmol/L) | 0.5–1.6 | 9.9 | 7.4 | 5.52 | 2.06 | 8.19 |
| Bicarbonate (mmol/L) | 21.8–26.9 | 9.1 | 15.3 | 18.9 | 20.6 | 18.3 |
| High-sensitivity troponin I (ng/mL) | 0–0.06 | >25.0 | >25.0 | >25.0 | 23.24 | 2.1 |
| Creatine kinase (U/L) | 0–171 | 21,383 | NR | 19,813 | 15,678 | 9,887 |
| CK-MB (U/L) | 0–25 | 1,405 | NR | 1,375 | NR | 193 |
| Lactate dehydrogenase (U/L) | 120–246 | 1,619 | 3,409 | 2,421 | 1,470 | 1,233 |
| Aspartate aminotransferase (U/L) | 0–34 | 846 | 2,106 | 2,090 | 878 | 456 |
| Alanine aminotransferase (U/L) | 5–49 | 331 | 565 | 451 | 270 | 150 |
| C-reactive protein (mg/L) | 0–7 | 1.9 | NR | 40.2 | 212.8 | 275.9 |

CK, Creatine kinase; CK-MB, Creatine kinase–myocardial band; CRP, C-reactive protein; LDH, Lactate dehydrogenase; NR, Not recorded. Last available values represent the final laboratory measurements obtained before death.

ventricular dysfunction, and non-obstructive coronary arteries. Takotsubo syndrome was clinically plausible because of the profound physical stress and rapid ventricular recovery, although the regional wall-motion pattern was not typical and cardiac magnetic resonance imaging (CMR) was unavailable. Myocarditis was less strongly supported by the immediate temporal relationship with electrical exposure and the rapid resolution of dysfunction, but it could not be excluded without tissue characterization. Myocardial infarction with non-obstructive coronary arteries (MINOCA) formed part of the differential diagnosis after exclusion of obstructive coronary disease.[11] Electrical injury should not itself be regarded as a definitive MINOCA mechanism, but it may trigger recognized ischemic mechanisms such as coronary vasospasm, microvascular dysfunction, or transient thrombosis. Conversely, direct electrical injury, post-resuscitation stunning, Takotsubo syndrome, and myocarditis represent alternative causes of myocardial injury that may mimic MINOCA. Because CMR, intravascular imaging, and coronary functional testing were not performed, the case remained a provisional MINOCA-like presentation rather than an etiologically confirmed MINOCA diagnosis.[13,14]

This case also underscores the diagnostic challenge posed by electrical injury presenting with ST-segment elevation. Despite the absence of obstructive coronary artery disease, the initial electrocardiographic, biomarker, and echocardiographic findings were highly suggestive of acute myocardial infarction, making emergency coronary angiography justified to exclude acute coronary occlusion. In addition, the rapid normalization of both the electrocardiographic abnormalities and left ventricular systolic function emphasizes that myocardial injury following electrical exposure may be reversible in selected patients.[1,3] Therefore, serial electrocardiographic and echocardiographic assessments may provide valuable information regarding the evolution and recovery of cardiac involvement after electrical injury.

This case has several limitations. CMR, intracoronary imaging, and provocative testing for coronary vasospasm were not performed, precluding definitive tissue characterization and identification of the underlying coronary mechanism. In addition, EEG was not performed despite persistent unconsciousness and recurrent seizures, limiting the objective assessment of post-cardiac arrest neurological injury and seizure activity. Interpretation of myocardial injury was further complicated by prolonged cardiopulmonary resuscitation, hypoxia, extensive burns, and rhabdomyolysis, while assessment of troponin kinetics was limited by the upper analytical measurement limit of the assay. In addition, cardiac imaging follow-up was restricted to the first 24 hours because of the patient's subsequent multisystem deterioration and death. Therefore, the precise mechanism responsible for the ST-segment elevation and transient left ventricular dysfunction could not be established.

**Table 2.** Comparison of selected previously reported cases of electrical injury presenting with ST-segment elevation

| Study | Electrical exposure | Electrocardiographic findings | Coronary angiography | Left ventricular findings | Clinical outcome |
|---|---|---|---|---|---|
| Kinney, 1982[5] | 23,000-V high-voltage power line | ST-segment elevation in II, III, and aVF; subsequent inferior Q waves | Performed 2 months later; subtotal LCx obstruction distal to a 30–40% ostial lesion; mild LAD/RCA atherosclerosis | Inferior wall-motion abnormality; LVEF NR | Discharged on day 13; persistent exertional symptoms and controlled heart failure |
| Walton et al., 1988[6] | 240-V alternating-current power line | Pronounced anterior ST-segment elevation evolving to anterior Q-wave infarction | Normal coronary arteries | Regional wall-motion abnormality; preserved LV function; LVEF NR | Survived; good recovery with limited residual myocardial damage |
| Al et al., 2012[7] | High-voltage power line (>1000 V) | Inferior MI pattern; ECG normalized within 6 h | Normal coronary arteries | Myocardial involvement; LVEF NR | Discharged in good condition after surgical treatment |
| Ertem et al., 2013[8] | Electrical installation; voltage NR | ST-segment elevation in V1–V6 and I–aVL | No coronary occlusion or significant stenosis | Depressed LV function with apical hypokinesia; LVEF NR | Died on ICU day 4 |
| Gursul et al., 2015[9] | 220-V, 50-Hz alternating current | AF with inferior ST-segment elevation and reciprocal ST-segment depression in V1–V3 | Normal coronary arteries; RCA dominant | LVEF 58%; no regional wall-motion abnormality | Recovered completely; discharged after 4 days |
| Belen et al., 2015[3] | Conducted electrical weapon; voltage NR | Inferior ST-segment elevation (II, III, aVF) with reciprocal depression | Normal coronary arteries | Minimal inferior wall hypokinesia; LVEF NR | No cardiac complications; normal ECG and echocardiography at 3 months |
| Present case | 25,000-V high-voltage electrical injury | ST-segment elevation in II, III, aVF, and V4–V6 with reciprocal depression in I and aVL | TIMI 3 flow; no obstructive CAD, thrombus, or dissection; mild mid-LAD myocardial bridge | Initial LVEF 35% with inferoposterolateral hypokinesia; recovered to 62% within 24 h | Cardiac recovery; died on day 10 from refractory septic shock with multiorgan failure |

AF, Atrial fibrillation; CAD, Coronary artery disease; ECG, Electrocardiogram; ICU, Intensive care unit; LAD, Left anterior descending artery; LCx, Left circumflex artery; LV, Left ventricle; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NR, Not reported; RCA, Right coronary artery; TIMI, Thrombolysis in myocardial infarction.

In conclusion, although uncommon, high-voltage electrical injury may present with a STEMI-like clinical picture, marked elevation of cardiac biomarkers, and transient left ventricular systolic dysfunction despite the absence of obstructive coronary artery disease. This case highlights the importance of comprehensive electrocardiographic, echocardiographic, and coronary angiographic evaluation in patients presenting with suspected acute myocardial infarction after electrical injury. Recognition of this uncommon presentation may facilitate timely diagnosis and appropriate clinical management while avoiding premature conclusions regarding the underlying mechanism.

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent for publication of this case report and accompanying images was obtained from the patient's next of kin.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Peer-review:** Externally peer-reviewed.

**Video 1.** Admission transthoracic echocardiography.

**Video 2.** Coronary angiography.

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# Anterior ST-Segment Elevation Myocardial Infarction Followed by Acute Popliteal Artery Occlusion in a 25-Year-Old Tobacco Smoker with Cannabis Use

## Yirmi Beş Yaşında, Esrar Kullanımı Olan Bir Sigara İçicisinde Anterior ST-Segment Yükselmeli Miyokard Enfarktüsünü İzleyen Akut Popliteal Arter Oklüzyonu

**ABSTRACT**

Myocardial infarction before 30 years of age warrants evaluation beyond conventional atherosclerosis, particularly when a second arterial event occurs in another vascular bed. A 25-year-old man with a nine-pack-year history of tobacco smoking and occasional cannabis use presented with anterior ST-segment elevation myocardial infarction and underwent primary percutaneous coronary intervention of the left anterior descending artery. Left ventricular ejection fraction was 30%, with severe apical wall-motion abnormality. Twelve days after discharge, he developed acute left popliteal artery occlusion (Rutherford IIb), which improved to IIa and subsequently to I during therapeutic anticoagulation and was managed without revascularization. Fasting homocysteine measured on day 21 was 18.4 µmol/L, with a vitamin B12 level of 121 pg/mL and a folate level of 1.9 ng/mL. Vitamin B12 replacement and folic acid 5 mg/day were prescribed; fasting homocysteine remained mildly elevated at approximately 6 and 18 months (21.6 and 20.7 µmol/L, respectively), with follow-up folate levels of 5.2 and 4.7 ng/mL. Renal and thyroid function were not reassessed at these later measurements. Genotyping showed compound heterozygosity for *MTHFR* C677T (Methylenetetrahydrofolate reductase) and A1298C, which was considered an accompanying finding rather than a causal thrombophilia. A missed or transient left ventricular apical thrombus represents a plausible, and possibly the most likely, explanation for the limb event. The patient remained free of recurrent thrombotic or bleeding events for 18 months while receiving an individualized warfarin regimen.

**Keywords:** Cannabis, homocysteine, myocardial infarction, peripheral arterial disease, tobacco smoking.

**ÖZET**

Otuz yaşından önce görülen miyokart enfarktüsü, özellikle kısa süre içinde farklı bir arteriyel yatakta ikinci bir olay geliştiğinde, konvansiyonel ateroskleroz dışındaki nedenlerin araştırılmasını gerektirir. Dokuz paket-yıl tütün maruziyeti ve aralıklı esrar kullanımı olan 25 yaşındaki erkek hasta, anterior ST-segment yükselmeli miyokart enfarktüsü ile başvurdu ve sol ön inen artere primer perkütan koroner girişim uygulandı. Sol ventrikül ejeksiyon fraksiyonu %30'du ve belirgin apikal duvar hareket bozukluğu mevcuttu. Taburculuktan 12 gün sonra akut sol popliteal arter oklüzyonu (Rutherford IIb) gelişti; terapötik antikoagülasyon sırasında Rutherford IIa'ya ve ardından kategori I'e geriledi ve revaskülarizasyon uygulanmadan izlendi. Yirmi birinci günde ölçülen açlık homosistein düzeyi 18,4 µmol/L idi; eş zamanlı olarak B12 vitamini 121 pg/mL ve folat 1,9 ng/mL ile düşük düzeydeydi. B12 vitamini replasmanı ve folik asit 5 mg/gün reçete edildi; yaklaşık 6. ve 18. aylardaki açlık homosistein düzeyleri sırasıyla 21,6 ve 20,7 µmol/L ile hafif yüksek kalırken, folat düzeyleri 5,2 ve 4,7 ng/mL idi. Bu iki takip ölçümünde renal ve tiroid fonksiyonları yeniden değerlendirilmedi. Genotiplemede *MTHFR* C677T ve A1298C bileşik heterozigotluğu saptandı ve nedensel bir trombofili olarak değil, eşlik eden bir bulgu olarak değerlendirildi. Gözden kaçmış veya geçici bir sol ventrikül apikal trombüsü, ekstremite olayı için olası ve muhtemelen en olası açıklamadır. Hasta, bireyselleştirilmiş varfarin tedavisi altında 18 ay boyunca tekrarlayan trombotik olay veya kanama yaşamadı.

**Anahtar Kelimeler:** Esrar, homosistein, miyokart enfarktüsü, periferik arter hastalığı, tütün kullanımı.

**CASE REPORT**
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Myocardial infarction before 30 years of age is uncommon and warrants evaluation beyond conventional atherosclerosis. When a second arterial occlusion occurs within days in another vascular bed, embolic sources, thrombophilia, substance exposure, and nonatherosclerotic coronary mechanisms should also be considered.[1,2]

We report the case of a 25-year-old man with anterior ST-segment elevation myocardial infarction followed 12 days after discharge by acute popliteal artery occlusion. This case illustrates how competing mechanisms can be weighed when none is definitively established and why homocysteine levels should be interpreted only in the context of the timing of measurement and the patient's vitamin status.

## ABBREVIATIONS

| | |
|---|---|
| HDL-C | High-density lipoprotein cholesterol |
| INR | International normalized ratio |
| LA | Lupus anticoagulant |
| LDL-C | Low-density lipoprotein cholesterol |
| LVEF | Left ventricular ejection fraction |
| *MTHFR* | Methylenetetrahydrofolate reductase |
| *MTRR* | Methionine synthase reductase |
| TIMI | Thrombolysis in Myocardial Infarction |

### Case Report

A 25-year-old man (body mass index, 19.2 kg/m$^2$) presented with acute, typical ischemic chest pain. He had no history of cardiovascular disease and was not receiving any chronic medication. He had smoked one pack of cigarettes daily since the age of 16 (nine pack-years) and reported smoking herbal cannabis on approximately four to five social occasions per year for six years, usually with tobacco; the quantity used per occasion could not be reliably quantified. His last cannabis use was three days before symptom onset. He specifically denied the use of synthetic cannabinoids, cocaine, amphetamines, anabolic steroids, energy drinks, and dietary supplements; toxicological screening was not performed. He discontinued both tobacco and cannabis use after the infarction.

A three-generation family history was obtained. The patient was the eldest of four siblings; his three siblings, aged 22, 18, and 14 years, were healthy. Both parents were alive and free of known disease (mother, 49 years; father, 51 years). All four grandparents were alive and aged 69–79 years; both grandmothers had hypertension and type 2 diabetes mellitus, and both grandfathers had hypertension. No first- or second-degree relative had a history of myocardial infarction, stroke, peripheral arterial disease, premature cardiovascular death, venous thromboembolism, known severe hypercholesterolemia, tendon xanthoma, lipid-lowering therapy initiated at a young age, or recurrent pregnancy loss. The parents were nonconsanguineous. On systematic physical examination, the patient had no tendon xanthoma, xanthelasma, or corneal arcus.

The admission electrocardiogram showed ST-segment elevation in leads V1–V6 with reciprocal inferior ST-segment depression (Figure 1). High-sensitivity cardiac troponin T was 59 ng/L and peaked at 6521 ng/L the following day. Emergency coronary angiography showed a long culprit lesion extending from the proximal to the mid left anterior descending artery, with up to 90% stenosis and angiographic features suggestive of superimposed thrombus; the remaining coronary arteries were normal. Intracoronary imaging was not performed. Primary percutaneous coronary intervention consisted of implantation of two drug-eluting stents and drug-coated balloon angioplasty of the diagonal branch, resulting in final TIMI grade 3 flow (Thrombolysis in Myocardial Infarction) (Figures 2A, B; Supplementary Video S1).

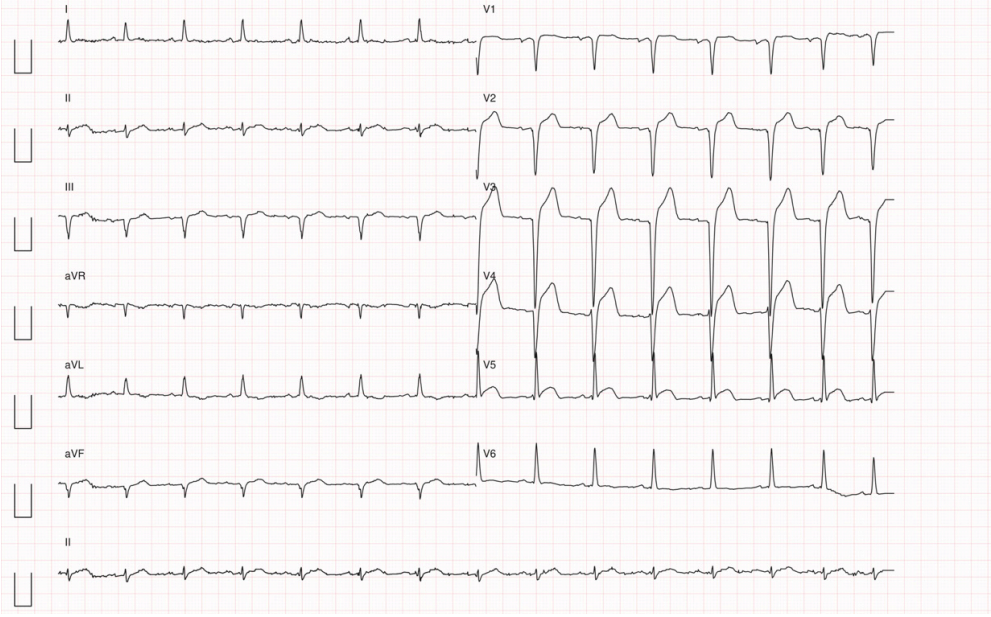



**Figure 1.** Admission 12-lead electrocardiogram showing ST-segment elevation in leads V1–V6 with reciprocal inferior ST-segment depression, consistent with anterior STEMI.

ECG, electrocardiogram; STEMI, ST-segment elevation myocardial infarction.

Transthoracic echocardiography on day 1 showed a left ventricular ejection fraction (LVEF) of 30%, with marked anterior and apical hypokinesis and no intracardiac thrombus (Supplementary Video S2). Contrast echocardiography and acute cardiac magnetic resonance imaging were not performed. At the subsequent admission for the limb event, repeat transthoracic and transesophageal echocardiography again showed no definite embolic source.

A comprehensive etiological evaluation was performed in consultation with medical genetics, hematology, and endocrinology; numerical results and reference ranges are provided in Supplementary Table S1, and the timing of assessments is provided in Supplementary Table S2. The lipid profile showed a total cholesterol level of 149 mg/dL, low-density lipoprotein cholesterol (LDL-C) of 101 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 40 mg/dL, triglycerides of 136 mg/dL, and apolipoprotein B of 88 mg/dL; lipoprotein(a) and sitosterol levels were normal. Renal, hepatic, thyroid, and inflammatory testing was otherwise unremarkable; fasting glucose was 101 mg/dL, HbA1c was 5.1%, and autoimmune and infectious screening results were negative. Hematocrit (52.7%), leukocyte count ($14.63\times10^3$/μL), absolute neutrophil count ($10.22\times10^3$/μL), and D-dimer (0.66 μg/mL) were above the reference range during the acute phase and had substantially normalized at follow-up (Supplementary Table S1).

At the admission for the limb event, before the first dose of anticoagulant therapy, protein C, protein S, antithrombin, factors VII and VIII, and lupus anticoagulant (LA) screening results were within the reference ranges; Factor V Leiden, prothrombin G20210A, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies were negative. At 12 weeks, testing during warfarin therapy (international normalized ratio (INR), 1.96) showed a weakly positive LA with concomitant reductions in vitamin K-dependent factors. Because the pretreatment LA test was negative and the repeat test was confounded by vitamin K antagonist therapy, antiphospholipid syndrome was not diagnosed; confirmatory testing after discontinuation of anticoagulation remains unavailable.

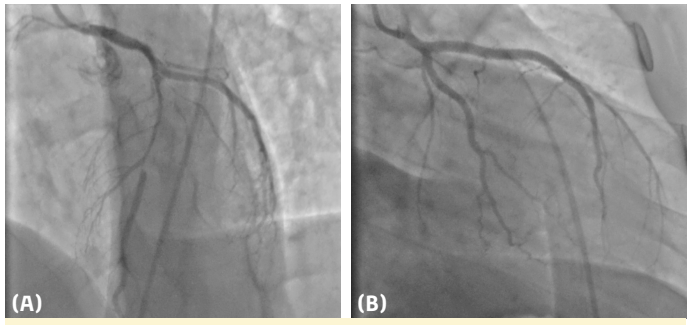



**Figure 2.** (A) Primary percutaneous coronary intervention. The left anterior descending artery showed a long proximal-to-mid obstructive culprit lesion with angiographic features suggestive of superimposed thrombus; the remaining coronary arteries were angiographically normal. Intracoronary imaging was not performed; therefore, the lesion mechanism remained uncertain. (B) Final angiographic result after implantation of two drug-eluting stents in the left anterior descending artery and drug-coated balloon angioplasty of the diagonal branch, with TIMI grade 3 flow and no procedural complications.

LMCA, left main coronary artery; PCI, percutaneous coronary intervention; DCB, drug-coated balloon; DES, drug-eluting stent; LAD, left anterior descending artery; TIMI, Thrombolysis in Myocardial Infarction.

The first fasting homocysteine measurement was obtained on day 21 after the index infarction, when the patient was already receiving anticoagulation: 18.4 μmol/L, with a vitamin B12 level of 121 pg/mL and a folate level of 1.9 ng/mL. Vitamin replacement consisted of one week of intramuscular B-complex vitamin therapy, followed by an oral B-complex preparation containing thiamine 250 mg, pyridoxine 250 mg, and cyanocobalamin 1 mg once daily, together with folic acid 5 mg once daily. At approximately 6 months, fasting homocysteine was 21.6 μmol/L, with a vitamin B12 level of 971 pg/mL and a folate level of 5.2 ng/mL. At 18 months, while documented as being off supplementation, fasting homocysteine was 20.7 μmol/L, with a vitamin B12 level of 371 pg/mL and a folate level of 4.7 ng/mL. Renal and thyroid function were not reassessed at the 6- or 18-month homocysteine measurements; treatment adherence was not independently quantified.

After the index infarction, he was discharged after 72 hours on aspirin 100 mg once daily, prasugrel 10 mg once daily, rosuvastatin 40 mg once daily, bisoprolol 5 mg once daily, ramipril 5 mg once daily, spironolactone 25 mg once daily, and empagliflozin 10 mg once daily (Supplementary Table S2).

Twelve days after discharge, he developed sudden left lower-extremity pain and presented approximately six hours after symptom onset. The foot was cold, with impaired capillary refill, paresthesia, and incomplete motor deficit; distal arterial Doppler signals remained audible but were monophasic, with minimal low-velocity dorsalis pedis flow. The limb was classified as Rutherford IIb, and he was admitted under cardiovascular surgery for planned revascularization.[3]

Doppler ultrasonography and computed tomography angiography showed a single continuous 126-mm thrombus extending from the distal popliteal artery through the tibioperoneal trunk into the proximal posterior tibial artery, explaining the different segments emphasized in the two reports. No plaque, aneurysm, or significant proximal arterial stenosis was observed. The index percutaneous coronary intervention had been performed via radial access.

Therapeutic anticoagulation was initiated immediately. Before intervention, the motor deficit resolved while distal Doppler flow persisted, prompting reclassification to Rutherford IIa; the sensory findings subsequently resolved, and the limb was reclassified as Rutherford I. Revascularization was therefore deferred, with immediate intervention planned in the event of recurrent motor deficit or loss of Doppler signals; this decision reflected documented improvement from class IIb rather than conservative management of persistent class IIb ischemia. Recent drug-eluting stent implantation and dual antiplatelet therapy also increased the hemorrhagic risk and the potential consequences of stent thrombosis associated with thrombolysis or interruption of antiplatelet therapy.

Genotyping findings are detailed in Supplementary Table S1. The principal findings were compound heterozygosity for *MTHFR* C677T (methylenetetrahydrofolate reductase) and A1298C and homozygosity for *MTRR* A66G (methionine synthase reductase);

Factor V Leiden and prothrombin G20210A were absent. These common variants were considered accompanying findings rather than established thrombophilias.

For the limb event, enoxaparin was initiated with warfarin loading, and prasugrel was switched to clopidogrel because triple therapy was required. Aspirin was discontinued after one month and clopidogrel after 12 months. Warfarin (INR target, 2.0–3.0) was selected by the treating cardiology and cardiovascular surgery teams because the event was considered potentially embolic from a postinfarction apical source and the teams preferred a vitamin K antagonist in this evidence-limited setting; this is not presented as evidence of superiority over a direct oral anticoagulant. No fixed discontinuation date was established, and the optimal duration of anticoagulation remains uncertain. Continued treatment is reassessed at each follow-up visit and should be periodically reconsidered in light of recovery of left ventricular function, the absence of recurrent events, bleeding risk, and the absence of a demonstrable persistent embolic source. Complete resolution of the peripheral thrombus at one year, improvement in LVEF to 39% at month 16, freedom from recurrent events, and the lack of any demonstrated persistent embolic source are therefore findings that would support reconsideration or discontinuation of warfarin, provided this pattern is maintained. Mild hyperhomocysteinemia was not used as an indication for long-term anticoagulation.

Rosuvastatin 40 mg daily reduced LDL-C from 101 to 37 mg/dL at 18 months. During follow-up, there were no recurrent coronary, peripheral, or venous thrombotic events or bleeding events. The patient reported continued abstinence from tobacco and cannabis and adherence to prescribed medical therapy.

At one year, Doppler ultrasonography and computed tomography angiography showed complete thrombus resolution, with restoration of peripheral pulses and no residual limb symptoms. Follow-up echocardiography showed an LVEF of 35%–40%; cardiac magnetic resonance imaging at month 16 showed evidence of a prior anterior infarction with an LVEF of 39%.

**Discussion**

This case involved several plausible contributors but no single proven mechanism. Tobacco use was the strongest conventional exposure, whereas the coronary and peripheral events required separate mechanistic assessment.

The mechanism of the coronary lesion was not established. Angiography showed an obstructive proximal-to-mid left anterior descending artery lesion with suspected superimposed thrombus; however, without intravascular ultrasound or optical coherence tomography, plaque rupture, plaque erosion, spontaneous coronary artery dissection, intramural hematoma, vasospasm with secondary thrombosis, and primary in situ thrombosis could not be distinguished.[4,5] We therefore describe the angiographic appearance without assigning a specific mechanism.

For the popliteal event, abrupt occlusion in an otherwise nonatherosclerotic arterial tree favors embolism over in situ thrombosis.[6] A missed or transient left ventricular apical thrombus represents a plausible, and possibly the most likely, explanation for the limb event: the patient had a large anterior infarction, an LVEF of 30%, and severe apical wall-motion abnormality, and ventricular thrombus commonly forms early after anterior infarction.[7] Negative unenhanced transthoracic and transesophageal echocardiographic studies do not exclude a small apical thrombus; contrast echocardiography and acute thrombus-sensitive cardiac magnetic resonance imaging were not performed.[8]

Tobacco exposure began in adolescence and continued until the infarction, supporting a clinically important contribution.[9] Cannabis exposure was infrequent and self-reported, with the last use occurring approximately 72 hours before chest pain. Because the strongest reported temporal association with myocardial infarction occurs shortly after use,[10,11] we regard cannabis as an exposure of uncertain relevance rather than an acute trigger.

Homocysteine requires similarly cautious interpretation. The first value, 18.4 μmol/L, was obtained on day 21 in the presence of marked vitamin B12 and folate deficiencies and therefore cannot establish a nonnutritional abnormality. After vitamin B12 replacement and prescription of folic acid 5 mg/day, fasting homocysteine levels remained mildly elevated at approximately 6 and 18 months (21.6 and 20.7 μmol/L, respectively), with folate levels of 5.2 and 4.7 ng/mL. However, renal and thyroid function were not reassessed at those later measurements, adherence was not independently quantified, and the patient was documented as being off supplementation at month 18. Persistence is therefore reproducible, but its mechanism cannot be determined.

The *MTHFR* C677T/A1298C genotype therefore does not explain the clinical events. These are common polymorphisms, routine *MTHFR* testing is not recommended as a stand-alone thrombophilia assessment, and folate-based homocysteine lowering has not reduced cardiovascular events in randomized trials.[12,13] Population allele frequencies and family segregation data were not available, further limiting genetic attribution.[14] The genotype is therefore reported as an accompanying observation.

Antiphospholipid syndrome and major inherited thrombophilias were investigated because of the patient's young age and arterial presentation. Anticardiolipin and anti-β2-glycoprotein I antibodies were negative on both occasions. Pretreatment LA testing was negative; the weakly positive LA result at 12 weeks was obtained during warfarin therapy and cannot be interpreted independently. The available data therefore did not establish an acquired or inherited thrombophilia.[15]

The cardiovascular effects attributed to cannabis and homocysteine are summarized in Table 1. $\Delta^9$-Tetrahydrocannabinol produces dose-dependent sympathetic activation, with increased heart rate, a transient increase in blood pressure, and increased myocardial oxygen demand, and has also been associated with endothelial dysfunction and platelet activation.[10] Smoking cannabis may rarely trigger myocardial infarction, and in a premature myocardial infarction registry cohort, cocaine or cannabis use was associated with long-term atherosclerotic cardiovascular disease and all-cause mortality.[9] Observational studies have associated cannabis use with acute myocardial infarction in adults younger than 45 years, with the reported risk concentrated shortly after inhalation.[10,11] Cardiovascular harm is therefore biologically plausible but is confounded by concomitant

tobacco use, unquantified potency, and reliance on self-report, supporting our cautious interpretation of this exposure.[10]

Homocysteine metabolism represents a second biologically plausible axis (Table 1). Hyperhomocysteinemia is regarded as an independent risk factor for atherosclerotic cardiovascular disease and has been detected in up to 40% of patients with premature coronary artery disease, peripheral vascular disease, or recurrent venous thrombosis; proposed mechanisms include endothelial dysfunction, impaired nitric oxide-dependent vasodilation, plaque instability, and increased thrombosis, while deficiencies of the cofactors vitamin B6, vitamin B12, and folic acid increase homocysteine concentrations.[9] In this patient, the initial elevation coincided with vitamin B12 and folate deficiencies, both potentially reversible nutritional causes; after replacement, vitamin levels increased, but homocysteine remained mildly elevated. The *MTHFR* C677T substitution produces a thermolabile variant with reduced enzyme activity and higher homocysteine concentrations, but a meta-analysis of the *MTHFR* mutation reported a relative risk of only 1.05 (95% CI, 0.86–1.27) for myocardial infarction; the variants carried by this patient are common polymorphisms and are not established causal thrombophilias, and routine *MTHFR* testing is not recommended as a stand-alone thrombophilia assessment.[9,12] Homocysteine lowering with folic acid and B vitamins did not reduce cardiovascular events in randomized trials.[13] It is therefore plausible, but not demonstrated, that reduced folate-cycle capacity in the setting of vitamin deficiency and concurrent cannabis and tobacco exposure contributed to a transiently prothrombotic milieu. No interaction between cannabis exposure and *MTHFR* genotype was tested or demonstrated, and this remains a hypothesis generated by a single case.

In practical terms, an elevated homocysteine concentration measured early after an arterial event in the presence of vitamin deficiency should not be assigned causal significance. Repeat testing after vitamin replacement can establish reproducibility, but interpretation must take into account the treatment actually received, adherence, and contemporaneous renal, thyroid, and vitamin status rather than infer an independent thrombophilia.

**Limitations**

Limitations include the absence of intracoronary imaging and thrombus histology; uncertainty regarding embolic versus in situ mechanisms for the limb event; the absence of contrast echocardiography, a dedicated bubble study, prolonged rhythm monitoring, or acute thrombus-sensitive cardiac magnetic resonance imaging; no formal documentation of apical endocardial border quality; warfarin interference with repeat LA testing; no repeat renal or thyroid testing at the 6- and 18-month homocysteine measurements; no independent assessment of adherence to vitamin therapy; and self-reported substance exposure without toxicological confirmation. A single case cannot establish genetic causality or support a general antithrombotic strategy.

**Table 1.** Potential cardiovascular and thrombotic effects relevant to cannabis exposure and hyperhomocysteinemia

| Exposure or factor | Proposed cardiovascular or thrombotic effect | Potential mechanism | Relevance to the present case | Key references |
|---|---|---|---|---|
| Cannabis ($\Delta^9$-tetrahydrocannabinol) | Increased heart rate, transient hypertension, and increased myocardial oxygen demand | Cannabinoid receptor-mediated sympathetic activation | Occasional inhaled use together with tobacco | 10 |
| Cannabis | May rarely trigger acute myocardial infarction, with the reported risk concentrated shortly after inhalation | Supply-demand mismatch, vasospasm, and plaque destabilization | Last use approximately 72 hours before chest pain; exposure of uncertain relevance rather than an acute trigger | 9–11 |
| Cannabis | Endothelial dysfunction and platelet activation | Platelet activation and impaired endothelial function | Plausible but unproven contribution to either event | 10 |
| Cannabis | Peripheral arterial disease and cannabis-associated arteritis | Endothelial injury; strongly confounded by tobacco use | Popliteal occlusion in a nonatherosclerotic arterial tree without arteritic features | 10 |
| Hyperhomocysteinemia | Independent risk factor for atherosclerotic cardiovascular disease; elevated in up to 40% of patients with premature coronary, peripheral, or recurrent venous thrombotic disease | Endothelial dysfunction, impaired nitric oxide-dependent vasodilation, plaque instability, and increased thrombosis | Fasting values of 18.4, 21.6, and 20.7 µmol/L; treated as an accompanying finding | 9 |
| Vitamin B12 and folate deficiency | Elevated homocysteine, potentially reversible | Deficiency of cofactors required for homocysteine remethylation | Vitamin B12 121 pg/mL and folate 1.9 ng/mL on day 21; corrected with replacement | 9 |
| *MTHFR* C677T and A1298C | Thermolabile variant with reduced activity and higher homocysteine levels; relative risk 1.05 (95% CI, 0.86–1.27) for myocardial infarction | Reduced methylenetetrahydrofolate reductase activity | Compound heterozygosity; routine testing is not recommended as a stand-alone thrombophilia assessment | 9,12 |
| Homocysteine lowering with B vitamins | No reduction in cardiovascular events in randomized trials | Homocysteine may be a marker rather than a cause of vascular risk | Vitamins were administered for documented deficiency, not for cardiovascular prevention | 13 |

*MTHFR*, methylenetetrahydrofolate reductase.

## Conclusion

A 25-year-old tobacco smoker developed anterior STEMI followed 12 days after discharge by acute popliteal artery occlusion. The coronary mechanism remained uncertain, and a missed or transient left ventricular apical thrombus represents a plausible, and possibly the most likely, explanation for the limb event. Mild hyperhomocysteinemia was reproducible on serial fasting measurements, but the day-21 value was obtained in the presence of vitamin deficiency, and later measurements lacked contemporaneous renal and thyroid testing; common *MTHFR* variants therefore cannot be assigned causal significance. In young patients with arterial thrombosis, homocysteine should be interpreted only within the clinical and metabolic context in which it is measured.

**Appendix Online File:** https://jag.journalagent.com/tkd/abs_files/TKDA-47908/TKDA-47908_(0)_Supplementary_Materials.pdf

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent was obtained from the patient for publication of this case report and the accompanying images and videos.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Video 1.** Baseline coronary angiography showing the long proximal-to-mid left anterior descending artery culprit lesion with suspected superimposed thrombus. LAD, left anterior descending artery; PCI, percutaneous coronary intervention.

**Video 2.** Transthoracic echocardiography after anterior STEMI showing reduced left ventricular systolic function with anterior and apical wall-motion abnormalities; contrast was not used. LV, left ventricle; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; TTE, transthoracic echocardiography.

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# Anterior ST-Segment Elevation Myocardial Infarction With Coronary Thrombosis in a Young Man with Newly Diagnosed HIV Infection and *Pneumocystis jirovecii* Pneumonia

## Yeni Tanı HIV Enfeksiyonu ve *Pneumocystis jirovecii* Pnömonisi Olan Genç Bir Erkekte Koroner Tromboz Eşliğinde Anterior ST-Segment Elevasyonlu Miyokard Enfarktüsü

**ABSTRACT**

Human immunodeficiency virus (HIV) infection is associated with an increased cardiovascular risk through chronic inflammation, immune dysregulation, endothelial dysfunction, and prothrombotic mechanisms. However, the mechanisms underlying acute coronary events in young patients with newly diagnosed advanced HIV infection remain incompletely understood. We report the case of a 36-year-old man with newly diagnosed HIV infection and severe immunosuppression who was initially evaluated for suspected systemic vasculitis and subsequently diagnosed with *Pneumocystis jirovecii* pneumonia. His initial CD4 cell count was 13.56 cells/mm$^3$, and his HIV RNA level was 14,095,323 copies/mL. Twenty-five days after the initiation of antiretroviral therapy, he developed an acute anterior ST-segment elevation myocardial infarction. Peak high-sensitivity cardiac troponin T was 1051 ng/L. Coronary angiography demonstrated a 90–99% thrombotic lesion at the ostium of the left anterior descending artery with preserved TIMI 3 flow. Given his clinical stability, preserved coronary flow, and potential procedural risks, percutaneous coronary intervention was deferred, and treatment with abciximab, unfractionated heparin, aspirin, and ticagrelor was continued. Repeat angiography after 72 hours demonstrated marked regression of the thrombotic lesion without significant residual stenosis, and no coronary intervention was required. Antiphospholipid antibody testing was negative; however, a comprehensive evaluation for inherited and acquired thrombophilia was not performed. The coexistence of profound immunosuppression, active opportunistic infection, systemic inflammation, and acute coronary thrombosis raises the possibility of a multifactorial prothrombotic state. However, causality cannot be established based on a single case. This case highlights the importance of considering acute coronary thrombosis in young patients with severe HIV-related immunosuppression and active opportunistic infection while recognizing alternative thrombotic mechanisms.

**Keywords:** Coronary thrombosis, human immunodeficiency virus, ST-segment elevation myocardial infarction.

**ÖZET**

İnsan immün yetmezlik virüsü (HIV) enfeksiyonu; kronik inflamasyon, immün disregülasyon, endotelyal disfonksiyon ve protrombotik mekanizmalar aracılığıyla artmış kardiyovasküler risk ile ilişkilidir. Bununla birlikte, yeni tanı almış ileri evre HIV enfeksiyonu olan genç hastalarda gelişen akut koroner olayların altında yatan mekanizmalar tam olarak aydınlatılamamıştır. Bu olguda, yeni tanı HIV enfeksiyonu ve ciddi immünsüpresyonu bulunan, başlangıçta sistemik vaskülit şüphesiyle değerlendirilen ve sonrasında *Pneumocystis jirovecii* pnömonisi tanısı alan 36 yaşındaki erkek hasta sunulmaktadır. Başlangıç CD4 hücre sayısı 13,56 hücre/mm$^3$, HIV RNA düzeyi ise 14.095.323 kopya/mL idi. Antiretroviral tedavinin başlanmasından 25 gün sonra hastada akut anterior ST-segment elevasyonlu miyokard enfarktüsü gelişti. Pik yüksek duyarlılıklı kardiyak troponin T düzeyi 1051 ng/L idi. Koroner anjiyografide, sol ön inen arter ostiyumunda TIMI 3 akımın korunduğu ve %90–99 oranında darlığa neden olan trombotik lezyon izlendi. Hastanın klinik olarak stabil olması, koroner akımın korunmuş olması ve girişimsel tedaviye bağlı olası komplikasyonlar nedeniyle perkütan koroner girişim uygulanmadı; abciximab, fraksiyone olmayan heparin, aspirin ve tikagrelor tedavisine devam edildi. Yetmiş iki saat sonra yapılan kontrol anjiyografisinde, anlamlı rezidüel darlık olmaksızın trombotik lezyonda belirgin gerileme izlendi ve koroner girişime gereksinim duyulmadı. Antifosfolipid antikor testi negatifti; ancak kalıtsal ve edinilmiş trombofiliyi kapsayan kapsamlı bir değerlendirme yapılmadı. Belirgin immünsüpresyon, aktif fırsatçı enfeksiyon, sistemik inflamasyon ve akut koroner trombozun birlikte bulunması, multifaktöriyel bir protrombotik durum olasılığını düşündürmektedir. Bununla birlikte, tek bir olgudan nedensel bir ilişki kurulamaz. Bu olgu, ciddi HIV ile ilişkili immünsüpresyon ve aktif fırsatçı

**CASE REPORT**
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enfeksiyonu bulunan genç hastalarda akut koroner trombozun göz önünde bulundurulmasının önemini ve alternatif trombotik mekanizmaların da dikkate alınması gerektiğini göstermektedir.

**Anahtar Kelimeler:** Koroner tromboz, insan immün yetmezlik virüsü, ST-segment elevasyonlu miyokard enfarktüsü.

Advances in antiretroviral therapy (ART) have substantially improved the life expectancy of people living with human immunodeficiency virus (HIV). As survival has increased, cardiovascular disease has emerged as an important cause of morbidity and mortality in this population. Persistent immune activation, chronic inflammation, endothelial dysfunction, platelet activation, and coagulation abnormalities have all been implicated in the development of cardiovascular complications among individuals with HIV.[1,2]

People living with HIV have a higher risk of atherosclerotic cardiovascular disease (ASCVD) than the general population, and conventional risk assessment tools may underestimate this risk. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) demonstrated a significant reduction in major adverse cardiovascular events with pitavastatin in people with HIV who were considered to have low-to-moderate traditional cardiovascular risk.[3] Accordingly, contemporary guidelines have adopted a more proactive approach to cardiovascular risk assessment and prevention in people with HIV.[4]

Despite these advances, acute myocardial infarction (MI) in younger individuals remains challenging because traditional cardiovascular risk factors may not fully explain the event. In addition to smoking, dyslipidemia, hypertension, and family history, young patients may have nontraditional risk factors, such as thrombophilia, substance exposure, immune-mediated disease, coronary abnormalities, allergic reactions, and other prothrombotic conditions.[5] In people with HIV, chronic immune activation and uncontrolled viral replication may further contribute to endothelial dysfunction and a prothrombotic state.[2] However, the mechanisms underlying acute coronary thrombosis in young patients with newly diagnosed advanced HIV infection and active opportunistic infection remain incompletely understood.

We report the case of a 36-year-old man with newly diagnosed HIV infection, severe immunosuppression, and *Pneumocystis jirovecii* pneumonia who developed an acute anterior ST-segment elevation MI with a predominantly thrombotic lesion at the ostium of the left anterior descending artery. This case highlights the diagnostic complexity of acute coronary thrombosis in a young patient with advanced HIV infection and active opportunistic infection and emphasizes the importance of considering both HIV-related and alternative thrombotic mechanisms.

## ABBREVIATIONS

| | |
|---|---|
| ART | Antiretroviral therapy |
| ASCVD | Atherosclerotic cardiovascular disease |
| HIV | Human immunodeficiency virus |
| MI | Myocardial infarction |
| PJP | Pneumocystis *jirovecii pneumonia* |

### Case Report

A 36-year-old man was admitted with a 1-year history of progressive dyspnea, intermittent fever, arthralgia, and approximately 15 kg of unintentional weight loss. During the month preceding admission, his respiratory and musculoskeletal symptoms worsened, and he developed a productive cough. He had no known history of cardiovascular disease, hypertension, diabetes mellitus, or dyslipidemia. He was an active smoker with a 10-pack-year history. There was no family history of premature coronary artery disease, sudden cardiac death, venous thromboembolism, or known thrombophilia. He denied the use of cocaine, amphetamines, methamphetamine, marijuana, anabolic steroids, energy drinks, other stimulants, intravenous recreational drugs, or other recreational substances; he reported alcohol use, with his last intake approximately 6 months before the MI.

Because of dyspnea, proteinuria, and positive PR3-ANCA (32.72 RU/mL; reference range, 0–20), systemic vasculitis was initially suspected; the patient was evaluated by nephrology and rheumatology, renal biopsy was planned, and high-dose corticosteroid therapy (120 mg/day) was initiated on March 12, 2026. Subsequent evaluation revealed newly diagnosed HIV infection and *Pneumocystis jirovecii* pneumonia (PJP). HIV infection was diagnosed on March 15, 2026, with an HIV RNA level of 14,095,323 copies/mL and a CD4 cell count of 13.56 cells/mm$^3$. Bronchoalveolar lavage polymerase chain reaction confirmed *P. jirovecii* infection. Chest imaging demonstrated bilateral parenchymal involvement (Figure 1), and the patient required supplemental oxygen at 3–4 L/min via nasal cannula. Hepatitis B surface antigen and hepatitis B core antibody were negative, and hepatitis C testing was also negative. C-reactive protein and procalcitonin levels were 36 mg/L and 1.1 ng/mL, respectively. Following the diagnosis of HIV infection and PJP, corticosteroid therapy was gradually tapered to 20 mg/day by the time of MI.

ART consisting of dolutegravir, emtricitabine, and tenofovir disoproxil fumarate was initiated on March 26, 2026. Because of a previous trimethoprim-sulfamethoxazole allergy, PJP was treated with clindamycin and primaquine. A CD4 cell count obtained on April 4, 2026, was 49.57 cells/mm$^3$. A trimethoprim-sulfamethoxazole desensitization attempt performed approximately 20 days before the MI was unsuccessful because of a recurrent allergic reaction. No new medication had been initiated during the 3 days immediately preceding the coronary event.

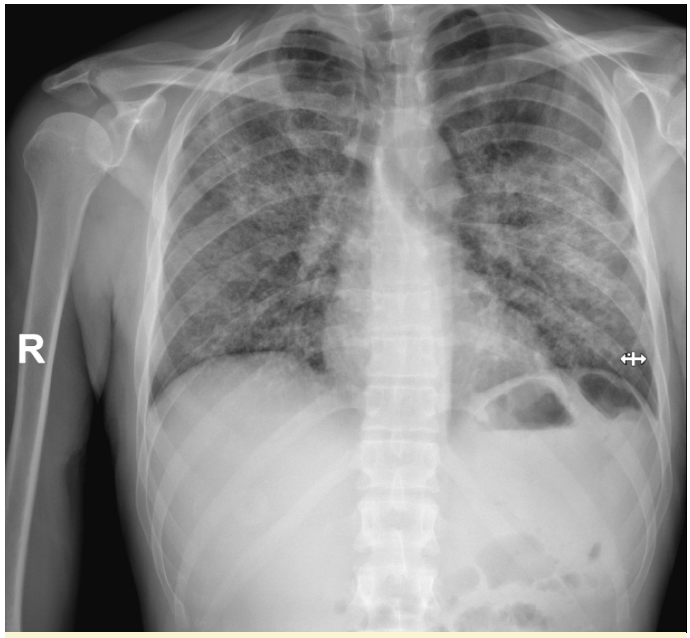



**Figure 1.** Posteroanterior chest radiograph showing bilateral pulmonary infiltrates consistent with *Pneumocystis jirovecii* pneumonia.

Twenty-five days after the initiation of ART, on April 21, 2026, the patient developed an acute anterior ST-segment elevation MI. Electrocardiography showed sinus rhythm with 4–5 mm ST-segment elevation in leads V2–V5, without reciprocal changes, at a heart rate of 112 beats/min (Figure 2). Peak high-sensitivity cardiac troponin T was 1051 ng/L (upper reference limit, 14 ng/L). At the time of MI, his blood pressure was 120/70 mmHg, and oxygen saturation was 97%. Laboratory evaluation at the time of MI demonstrated elevated inflammatory and coagulation markers, with preserved renal function (Table 1). A lipid profile obtained before the HIV diagnosis, on December 8, 2025, at 11:20 AM, showed a total cholesterol level of 190 mg/dL, LDL-C of 98 mg/dL, HDL-C of 31 mg/dL, and triglycerides of 304 mg/dL. On the day of MI, April 21, 2026, at 10:00 AM, total cholesterol was 192 mg/dL, LDL-C was 110 mg/dL, HDL-C was 38.3 mg/dL, and triglycerides were 219 mg/dL. At the 4-month follow-up after MI, on August 18, 2026, total cholesterol was 116 mg/dL, LDL-C was 68 mg/dL, HDL-C was 32.2 mg/dL, and triglycerides were 80 mg/dL.

Emergency coronary angiography demonstrated a 90–99% thrombotic lesion involving the ostium of the left anterior descending artery, with preserved TIMI 3 flow (Figure 3A; Video 1). The left circumflex artery showed plaque formation without significant stenosis, whereas the left main and right coronary arteries were angiographically normal. No angiographic evidence of coronary spasm, distal embolization, or another obvious coronary embolic source was identified. Because the patient remained clinically stable, his chest pain decreased during the procedure, and TIMI 3 flow was preserved, immediate percutaneous coronary intervention was deferred. Thrombus aspiration was not performed. The potential procedural risks associated with intervention at the LAD ostium, including distal embolization and dissection, were considered. Intravascular ultrasound was not performed because of these procedural concerns and the expectation that its findings would not alter the initial management strategy, whereas optical coherence tomography was unavailable at the institution.

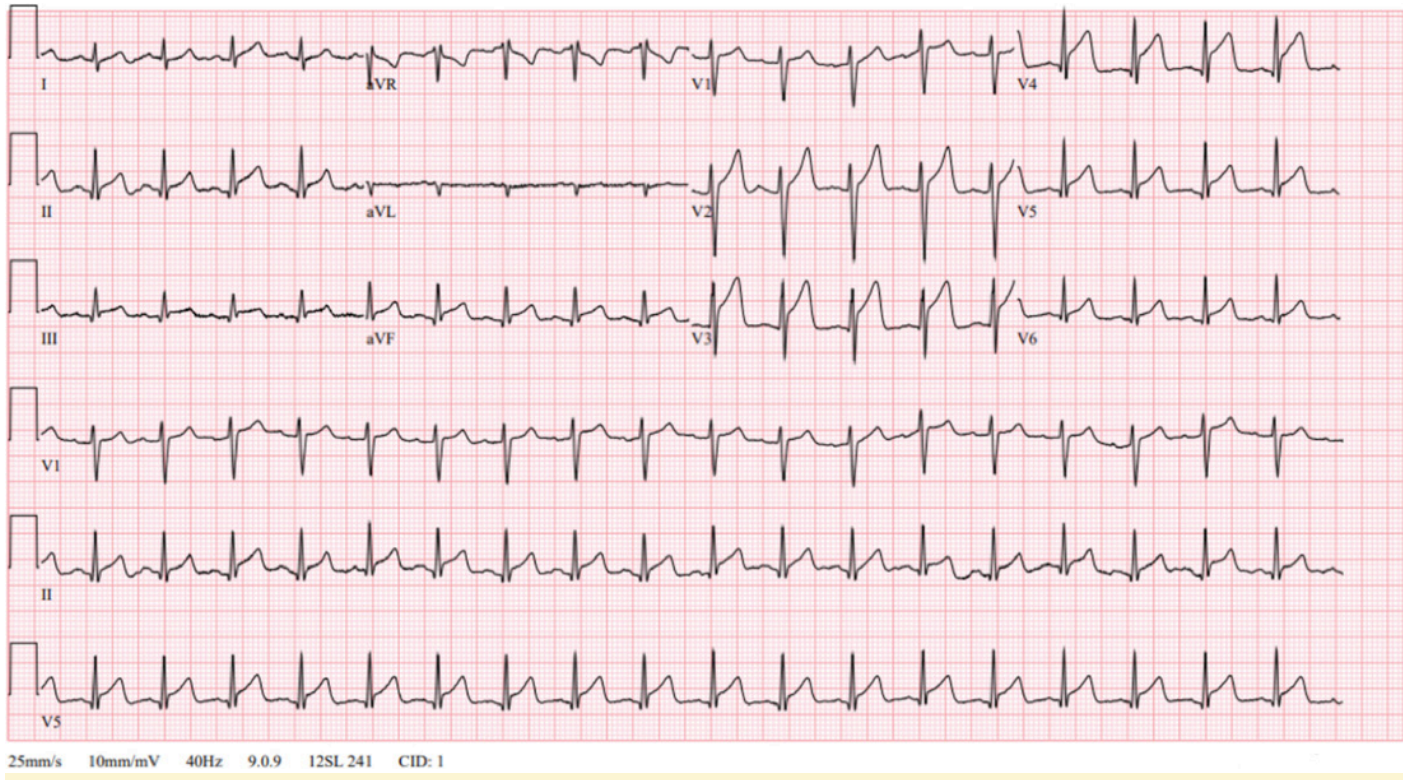



**Figure 2.** Twelve-lead electrocardiogram showing 4–5 mm ST-segment elevation in leads V2–V5 at a heart rate of 112 beats/min (25 mm/s, 10 mm/mV).

**Table 1.** Clinical and laboratory characteristics of the patient

| Parameters | Findings |
|---|---|
| Demographics and cardiovascular risk factors | |
| Age | 36 years |
| Sex | Male |
| Smoking | Active smoker, 10 pack-years |
| Hypertension | No |
| Diabetes mellitus | No |
| Previously diagnosed dyslipidemia | No |
| Previous cardiovascular disease | No |
| Family history of premature CAD | No |
| Family history of thrombosis/thrombophilia | No |
| Clinical status at MI | |
| Blood pressure | 120/70 mmHg |
| Heart rate | 112 beats/min |
| Oxygen saturation | 97% |
| Weight loss | Approximately 15 kg |
| BMI | 20.24 kg/m$^2$ |
| Fasting glucose | 89 mg/dL |
| HbA1c | 6.04% |
| Waist circumference | Not available |
| HIV and PJP | |
| HIV RNA at diagnosis | 14,095,323 copies/mL |
| HIV RNA at MI | 2,090,000 copies/mL |
| HIV RNA at follow-up | 826,000 copies/mL (May 21); 215,000 copies/mL (June 25) |
| CD4 count at diagnosis | 13.56 cells/mm$^3$ |
| CD4 count before MI (April 4, 2026) | 49.57 cells/mm$^3$ |
| CD4 count after MI (April 28, 2026) | 143.55 cells/mm$^3$ |
| CD4 count at follow-up | 302.66 cells/mm$^3$ (May 21); 329.56 cells/mm$^3$ (June 25) |
| P. jirovecii pneumonia | Confirmed by BAL PCR |
| Oxygen requirement | 3–4 L/min |
| HBsAg | Negative |
| Anti-HBc | Negative |
| Laboratory findings at MI | |
| Hemoglobin | 12.6 g/dL |
| Platelet count | 502×10$^9$/L |
| Creatinine | 0.82 mg/dL |
| CRP | 47 mg/L |
| Fibrinogen | 6.08 g/L |
| D-dimer | 1.04 mg/L |
| Peak hs-cTnT | 1051 ng/L |
| hs-cTnT upper reference limit | 14 ng/L |
| Homocysteine | Not measured |
| Vitamin B12 | 606 ng/L (reference range, 197–771 ng/L) |
| Folate | 8 ng/L (reference range, 3.89–26.3 ng/L) |
| Lipid profile | |
| Lipid profile before HIV diagnosis (December 8, 2025) | TC 190 mg/dL; LDL-C 98 mg/dL; HDL-C 31 mg/dL; TG 304 mg/dL; non-HDL-C 159 mg/dL |
| Lipid profile at MI (April 21, 2026) | TC 192 mg/dL; LDL-C 110 mg/dL; HDL-C 38.3 mg/dL; TG 219 mg/dL; non-HDL-C 153.7 mg/dL |
| Lipid profile at 4-month follow-up (August 18, 2026) | TC 116 mg/dL; LDL-C 68 mg/dL; HDL-C 32.2 mg/dL; TG 80 mg/dL |
| Lipoprotein(a) [Lp(a)] | Not measured |
| Apolipoprotein B [ApoB] | Not measured |
| Autoimmune evaluation | |
| PR3-ANCA | 32.72 RU/mL (reference range, 0–20) |
| Repeat PR3-ANCA | 15.42 RU/mL |
| ANA | Negative |
| Anti-dsDNA | Negative |
| Antiphospholipid antibodies | Negative |
| Proteinuria | 468 mg/L |
| Urine protein/creatinine ratio | 0.78 |
| Hematuria/casts | Absent |
| Relevant clinical evaluation | |
| Transthoracic echocardiography on April 21, 2026 | LVEF 55%, with mild apical hypokinesia; no intracardiac thrombus or significant structural abnormality |
| Repeat transthoracic echocardiography on April 28, 2026 | LVEF 55–60%, with no regional wall-motion abnormalities; no intracardiac thrombus or significant structural abnormality |
| Blood cultures | Negative |
| Atrial fibrillation | Not documented |

ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-HBc, hepatitis B core antibody; ApoB, apolipoprotein B; BAL, bronchoalveolar lavage; BMI, body mass index; CAD, coronary artery disease; CD4, cluster of differentiation 4; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; hs-cTnT, high-sensitivity cardiac troponin T; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction; MI, myocardial infarction; non-HDL-C, non-high-density lipoprotein cholesterol; PCR, polymerase chain reaction; PJP, Pneumocystis jirovecii pneumonia; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; RNA, ribonucleic acid; TC, total cholesterol; TG, triglycerides.

The patient was treated with aspirin (300 mg loading dose followed by 100 mg/day), ticagrelor (180 mg loading dose followed by 90 mg twice daily), unfractionated heparin (50 U/kg loading dose followed by 12 U/kg/h for 48 hours), and abciximab (0.25 mg/kg bolus followed by 0.125 µg/kg/min infusion for 48 hours). During the subsequent 72 hours, he remained hemodynamically stable without recurrent chest pain, new ST-segment changes, bleeding, or recurrent thrombotic events. Repeat coronary angiography performed 72 hours after the initial procedure demonstrated marked regression of the thrombotic lesion, with no visible residual thrombus or significant residual stenosis and preserved TIMI 3 flow (Figure 3B; Video 2). PCI was therefore not performed.

Immediately after coronary angiography, transthoracic echocardiography performed on April 21, 2026, showed a left ventricular ejection fraction of 55% with mild apical hypokinesia. Repeat transthoracic echocardiography performed on April 28, 2026, after the patient had been transferred to the ward, showed a left ventricular ejection fraction of 55–60% without regional wall-motion abnormalities, intracardiac thrombus, significant valvular disease, or pericardial effusion. No atrial fibrillation was identified clinically, and blood cultures showed no growth or evidence of infective endocarditis. Transesophageal echocardiography and Holter monitoring were not performed. The patient was discharged on April 28, 2026, receiving aspirin 100 mg/day, ticagrelor 90 mg twice daily, atorvastatin 40 mg/day, metoprolol 50 mg/day, and continued ART. Dual antiplatelet therapy was planned for 12 months. Potential drug–drug interactions between the antiretroviral and cardiovascular therapies were reviewed, and no major interactions were identified.

Following the initiation of ART, the CD4 cell count increased from 13.56 cells/mm³ at HIV diagnosis to 49.57 cells/mm³ on April 4, 2026. At the time of MI on April 21, 2026, the most recent available CD4 cell count was 49.57 cells/mm³. A subsequent CD4 cell count obtained on April 28, 2026, 7 days after MI, was 143.55 cells/mm³, while HIV RNA at the time of MI had decreased to 2,090,000 copies/mL. PR3-ANCA decreased from 32.72 to 15.42 RU/mL on April 27, 2026, and the remainder of the autoimmune evaluation was unrevealing. Antiphospholipid antibodies were negative; however, inherited thrombophilia testing was not performed. At follow-up on May 21, 2026, the CD4 cell count was 302.66 cells/mm³, and HIV RNA was 826,000 copies/mL. On June 25, 2026, the CD4 cell count had increased to 329.56 cells/mm³, while HIV RNA had decreased to 215,000 copies/mL. The patient remained on ART and, approximately 4 months after MI, had experienced no recurrent MI, angina, heart failure, thrombosis, major bleeding, or death.

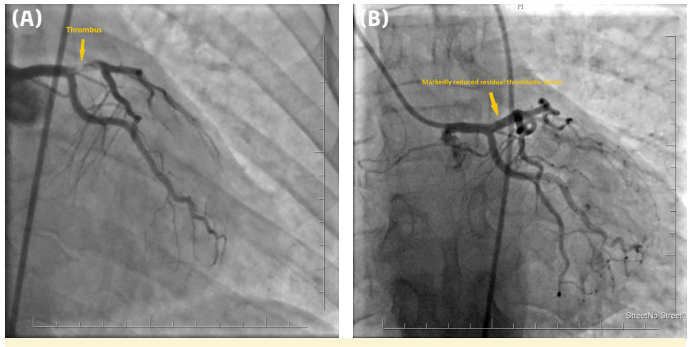



**Figure 3.** (A) Initial coronary angiography showing a large thrombotic lesion at the ostium of the left anterior descending artery, causing critical luminal narrowing. (B) Repeat coronary angiography performed 72 hours after antithrombotic therapy, showing no visible residual thrombus or significant residual stenosis, with preserved coronary flow.

## Discussion

This case describes an anterior ST-segment elevation myocardial infarction in a 36-year-old man with newly diagnosed advanced HIV infection and active *Pneumocystis jirovecii* pneumonia. Coronary angiography demonstrated a predominantly thrombotic ostial LAD lesion with limited angiographic evidence of atherosclerosis, which markedly regressed after antithrombotic therapy. However, the underlying mechanism cannot be determined from angiography alone, and HIV infection and PJP should be considered potential contributors rather than established causes.

HIV infection is associated with an increased risk of MI through a combination of traditional cardiovascular risk factors, persistent immune activation, inflammation, endothelial dysfunction, platelet activation, and coagulation abnormalities (Table 2).[1,2,6–14] In our patient, the degree of immunosuppression was particularly pronounced, with a CD4 count of 13.56 cells/mm³ and an HIV RNA level exceeding 14 million copies/mL at diagnosis. Following the initiation of ART, the CD4 count increased to 49.57 cells/mm³ by April 4, 2026. At the time of MI on April 21, 2026, 25 days after ART initiation, the most recent available CD4 count was 49.57 cells/mm³. A subsequent measurement on April 28, 2026, 7 days after MI, showed a CD4 count of 143.55 cells/mm³. The patient also had active PJP and evidence of systemic inflammation, including elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, platelet count, and D-dimer levels. These findings are consistent with an inflammatory and prothrombotic milieu that may have contributed to thrombus formation. Experimental and clinical data indicate that HIV-related immune activation can promote endothelial dysfunction, platelet activation, and activation of coagulation pathways, providing a biologically plausible link between advanced HIV infection and thrombotic cardiovascular events.[2,6,15]

PJP may have further amplified this inflammatory state, particularly in the setting of profound CD4 depletion. The coexistence of severe immunosuppression, active PJP, systemic inflammation, and acute coronary thrombosis raises the possibility of a multifactorial prothrombotic state but does not establish causality. The rapid increase in the CD4 count after ART also raises the theoretical possibility of immune restoration-related inflammation; however, the available data are insufficient to diagnose IRIS.

MI occurring before 40 years of age represents a particularly young subgroup and warrants systematic assessment beyond conventional atherosclerotic risk factors. Smoking, dyslipidemia, substance exposure, thrombophilia, coronary abnormalities, immune-mediated disease, and allergic conditions may all contribute to MI in younger individuals.[5] Our patient was an active smoker with a 10-pack-year history and had no history of hypertension, diabetes, or known coronary artery disease. Although LDL-C was not elevated, a lipid profile obtained before HIV diagnosis on December 8, 2025, showed hypertriglyceridemia (triglycerides, 304 mg/dL) and low HDL-C (31 mg/dL). Although the patient did not have diabetes mellitus, the HbA1c level was 6.04%, which was within the prediabetic range. Thus, traditional cardiovascular risk factors were not entirely absent and may have contributed

to underlying coronary vulnerability. Conversely, the angiographic appearance was predominantly thrombotic, with no significant obstructive disease in the remaining coronary arteries, making a purely conventional atherosclerotic explanation less compelling.

Several alternative mechanisms of coronary thrombosis were therefore considered. Coronary angiography cannot reliably distinguish thrombus superimposed on plaque rupture or plaque erosion from other mechanisms, such as spontaneous recanalization, coronary embolism, or vasospasm. Intravascular imaging with OCT or IVUS would have provided additional information regarding plaque morphology and could have helped differentiate plaque rupture from plaque erosion.[16] In our patient, neither modality was used to establish the underlying substrate of the thrombotic lesion. The absence of a clear embolic source on transthoracic echocardiography, clinically documented atrial fibrillation, and positive blood cultures or other evidence of infective endocarditis argues against some potential embolic causes, but transesophageal echocardiography and prolonged rhythm monitoring were not performed. Therefore, a coronary embolic mechanism cannot be completely excluded.

Antiphospholipid antibody testing was negative; however, inherited thrombophilia testing, including Factor V Leiden, prothrombin G20210A, protein C, protein S, and antithrombin levels, was not performed. Accordingly, an inherited hypercoagulable state cannot be definitively excluded. This limitation is particularly relevant in a patient younger than 40 years presenting with a predominantly thrombotic coronary lesion.[5]

Kounis syndrome was another potential differential diagnosis because of the patient's previous trimethoprim–sulfamethoxazole hypersensitivity. Kounis syndrome represents an acute coronary syndrome occurring in the setting of an allergic or hypersensitivity reaction and may involve coronary vasospasm, plaque-related thrombosis, or coronary thrombosis.[17] In this case, however, the most recent hypersensitivity reaction occurred approximately 20 days before the MI, no new medication had been initiated during the 3 days preceding the coronary event, and there were no documented acute allergic manifestations at the time of STEMI. The mildly elevated tryptase level obtained 17 days before MI also cannot establish an acute hypersensitivity-mediated coronary event. Thus, Kounis syndrome appears less likely, although it cannot be completely excluded retrospectively.

The initial positive PR3-ANCA and proteinuria also raised concern for systemic vasculitis. PR3-ANCA subsequently decreased from 32.72 to 15.42 RU/mL, and the remainder of the autoimmune evaluation was unrevealing, reducing the clinical suspicion of active systemic vasculitis. However, renal biopsy was not performed; therefore, vasculitis cannot be definitively excluded. Importantly, the reduction in PR3-ANCA should not itself be interpreted as proof that the initial findings were solely related to HIV-associated immune dysregulation.

**Table 2.** Cardiovascular effects of HIV infection and antiretroviral therapy

| Pathophysiologic mechanism | Cardiovascular effect | Clinical consequence |
|---|---|---|
| Chronic inflammation and immune activation (↑ IL-6 and TNF signaling; monocyte/macrophage activation) | Vascular inflammation, endothelial activation, accelerated atherosclerosis, and plaque formation | Premature atherosclerosis, coronary artery disease, myocardial infarction, and stroke.[7,8] |
| Endothelial dysfunction | ↓ Nitric oxide bioavailability, impaired vasodilation, increased endothelial permeability, and leukocyte adhesion | Atherosclerosis, coronary ischemia, and thrombotic cardiovascular events.[7,8] |
| HIV proteins (Nef, Tat, gp120) | Endothelial injury, oxidative stress, increased expression of adhesion molecules, and impaired ABCA1-mediated cholesterol efflux with macrophage foam-cell formation | Accelerated coronary plaque development and plaque instability.[7,9] |
| Dyslipidemia and metabolic abnormalities associated with HIV and ART | Increased atherogenic lipoproteins, insulin resistance, altered adipose distribution, and weight gain; effects vary by antiretroviral regimen | Increased ASCVD risk.[7,10] |
| Prothrombotic state and vascular inflammation | Increased coagulation and platelet activation and activation of thrombosis-related pathways | Arterial and venous thrombosis, myocardial infarction, and stroke.[7,8] |
| Direct myocardial effects and chronic inflammation | Myocardial fibrosis, impaired systolic and diastolic function, and structural myocardial disease | Heart failure and arrhythmias.[7,11] |
| Pulmonary vascular endothelial dysfunction/inflammation | Pulmonary vascular remodeling and increased pulmonary vascular resistance | HIV-associated pulmonary arterial hypertension and right-sided heart failure.[7,12] |
| Autonomic/electrical abnormalities and myocardial disease | Altered conduction, QTc prolongation, ventricular arrhythmogenic substrate, and myocardial fibrosis | Arrhythmias and an increased risk of sudden cardiac death.[11] |
| Antiretroviral therapy: abacavir | Association with increased cardiovascular risk in some observational cohorts, particularly with recent or current exposure | Potentially increased MI/ASCVD risk in susceptible patients.[10,13] |
| Antiretroviral therapy: protease inhibitors (especially lopinavir/ritonavir; some data for ritonavir-boosted darunavir) | Dyslipidemia and other cardiometabolic effects; cumulative exposure may increase cardiovascular risk | Potentially increased MI/ASCVD risk.[10,14] |
| Tenofovir formulations and contemporary ART | TDF is generally associated with a more favorable lipid profile than TAF; integrase inhibitor-associated weight and metabolic effects remain an area of ongoing study | Changes in cardiometabolic risk profile; clinical effects depend on the regimen and patient-specific factors.[10,13] |
| Opportunistic infection and systemic inflammatory activation | Acute inflammatory and prothrombotic state superimposed on chronic HIV-related vascular risk | Potential triggering or amplification of acute coronary thrombosis or other cardiovascular events.[7,8] |

ABCA1, ATP-binding cassette transporter A1; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HIV, human immunodeficiency virus; IL-6, interleukin-6; MI, myocardial infarction; Nef, negative factor; NO, nitric oxide; PAH, pulmonary arterial hypertension; TAF, tenofovir alafenamide; TNF, tumor necrosis factor; TDF, tenofovir disoproxil fumarate.

The marked regression of the LAD thrombotic lesion with antithrombotic therapy and preserved TIMI 3 flow allowed PCI to be avoided. This response supports the role of acute thrombus in the clinical presentation but does not establish its underlying cause. Overall, the clinical course favors a multifactorial interpretation involving advanced HIV infection, active opportunistic infection, systemic inflammation, and conventional cardiovascular risk factors.

### Limitations

This report has several limitations. First, the conclusions are based on a single case and therefore cannot establish a causal relationship between HIV infection, *Pneumocystis jirovecii* pneumonia, and coronary thrombosis. Second, although coronary angiography demonstrated marked regression of the thrombotic lesion after antithrombotic therapy, intracoronary imaging with optical coherence tomography or intravascular ultrasound was not performed; therefore, plaque rupture, plaque erosion, or another underlying coronary substrate could not be definitively distinguished. No pathological confirmation of the thrombotic material was available. Third, acquired thrombophilia was evaluated with negative antiphospholipid antibody testing, but inherited thrombophilia testing was not performed. Lipoprotein(a), apolipoprotein B, and homocysteine levels were also not measured, representing additional limitations of the etiological evaluation. Vitamin B12 and folate levels were measured and were 606 ng/L (reference range, 197–771 ng/L) and 8 ng/L (reference range, 3.89–26.3 ng/L), respectively. In addition, transesophageal echocardiography and prolonged rhythm monitoring were not performed, limiting the exclusion of a potential embolic source. Renal biopsy was also not performed; therefore, systemic vasculitis could not be excluded histopathologically. Finally, the lipid profile was obtained during an active infectious and inflammatory state and may not accurately reflect the patient's baseline lipid status. The clinical course may also have been influenced by active infection, substantial preceding weight loss, corticosteroid exposure, and recently initiated ART. Although the patient remained clinically stable without recurrent cardiovascular events during approximately 4 months of follow-up, longer-term follow-up was not available.

### Conclusion

This case highlights the diagnostic complexity of acute coronary thrombosis in a young patient with newly diagnosed advanced HIV infection and active *Pneumocystis jirovecii* pneumonia. The marked regression of the LAD thrombotic lesion following antithrombotic therapy suggests that acute thrombosis played a major role in the clinical presentation. However, the precise mechanism of thrombosis could not be established, and a causal relationship with HIV infection or PJP cannot be inferred. In young patients with advanced HIV infection and acute coronary syndrome, clinicians should consider both HIV-related inflammatory and prothrombotic mechanisms and alternative causes of coronary thrombosis.

**Ethics Committee Approval:** This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

**Informed Consent:** Written informed consent was obtained from the patient for publication of this case report and accompanying images.

**Conflict of Interest:** The author have no conflicts of interest to declare.

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**Use of AI for Writing Assistance:** Author declares that artificial intelligence tools were used solely for language editing. All clinical interpretation, scientific content, and final manuscript approval were performed by the author.

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**Peer-review:** Externally peer-reviewed.

**Video 1.** Initial coronary angiography showing the thrombotic lesion at the ostium of the left anterior descending artery.

**Video 2.** Repeat coronary angiography performed 72 hours after antithrombotic therapy, showing marked regression of the thrombotic lesion.

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