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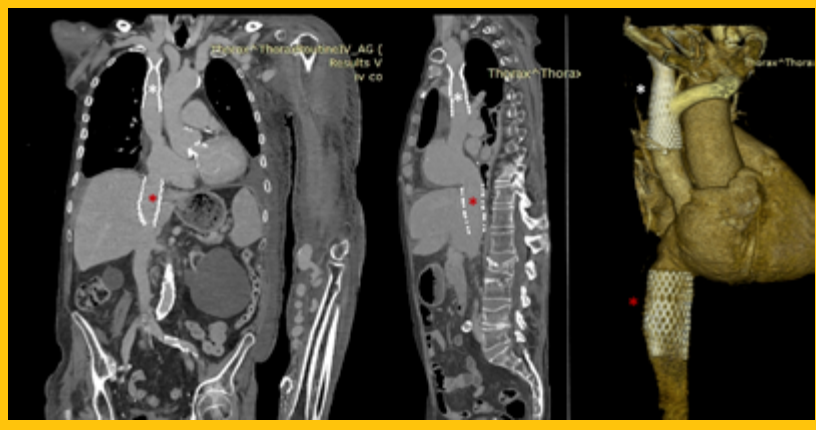

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CONTENTS/İÇİNDEKİLER

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ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Legal Artificial Intelligence in Interventional Cardiology: Ethical Boundaries and Decision Support Opportunities in the Turkish Legal Context

Girişimsel Kardiyolojide Yasal Yapay Zeka: Türk Hukuk Sistemi Bağlamında Etik Sınırlar ve Karar Destek Olanakları

PERSPECTIVE
GÖRÜŞ

Artificial intelligence (AI) is increasingly applied to legal reasoning across various fields. Physicians in Türkiye and worldwide are beginning to consult AI tools for matters such as malpractice evaluation, labor disputes, compensation claims, and criminal liability.[1,2] Although these systems offer efficiency and accessibility, their use in clinical decision-making—especially in high-risk specialties like interventional cardiology—poses significant ethical and legal challenges.[3,4] In this context, we believe that this manuscript not only highlights theoretical concerns but also attempts to link AI-assisted legal reasoning with practical cardiology settings, aiming to provide more clinically grounded insights.

For instance, in a complex percutaneous coronary intervention (PCI), an AI system could theoretically provide real-time alerts regarding informed consent deficiencies, previous litigation patterns, or guideline deviations.[5]. In practice, such alerts could directly influence operator behavior during high-risk PCI by prompting immediate consent review or recommending documentation updates, thereby connecting abstract legal oversight with actual procedural workflow. If properly implemented, such tools may help mitigate risk, streamline documentation, and enhance patient safety. This conceptual analysis argues that while legal AI can serve as a valuable decision-support tool in interventional cardiology by improving medico-legal awareness, its integration into the Turkish healthcare system must be strictly circumscribed by ethical guidelines and regulatory frameworks to prevent unauthorized practice of law and protect physicians from increased liability.

The Rise of Legal AI: A Global Overview

Globally, legal AI systems such as IBM Watson Legal, ROSS Intelligence, DoNotPay, and CaseMine have been developed to analyze case law, statutory text, and regulatory codes.[1] In the United States, the United Kingdom (UK), and Singapore, these tools assist in contract review, litigation risk assessment, and legal precedent extraction.[2] China's XiaoFa system goes further by assisting courts with sentencing and drafting basic legal documents.[3]

In healthcare, particularly in malpractice risk assessment, some U.S. hospitals and insurers have adopted AI to predict indemnity ranges and guide pre-litigation settlement discussions.[4] However, these platforms are generally used by legal professionals, not by physicians acting independently.

Legal Competence and Interpretive Limitations in Türkiye

Türkiye's legal system is jurisprudential and evolves through constitutional court rulings and legislative updates. AI lacks the interpretive flexibility to navigate this legal environment effectively. Medical liability, under Article 36 of the Turkish Penal Code and Law No. 6098, often hinges on contextual evidence and expert testimony—factors beyond the current capabilities of AI systems.[6,7]

Moreover, the Attorneyship Law (Article 35) prohibits non-lawyers, including AI, from offering legal counsel.[7] Labor law miscalculations can lead to financial penalties, further emphasizing the need for authorized legal interpretation.

Most Turkish physicians—especially in invasive specialties—receive minimal training on legal liability during their education.[8] Legal AI could play a supplementary role by flagging incomplete documentation before procedures such as device implantation or off-label interventions,[1,4] helping bridge knowledge gaps without supplanting legal counsel.

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Materials and Methods

This study adopted a qualitative conceptual analysis approach, involving a systematic review and synthesis of relevant national and international legal documents, ethical guidelines, and AI system functionalities. The analysis focused on identifying core tensions, opportunities, and limitations at the intersection of legal AI and clinical practice in interventional cardiology.

Key legal documents, including the Turkish Penal Code, Personal Data Protection Law (PDPL), and Turkish Medical Association (TMA) guidelines, were reviewed, along with international documentation from legal AI systems such as ROSS, XiaoFa, and DoNotPay.[1,3,7,8]

Three simulated scenarios were constructed to test legal AI applications in cardiology:

1. PCI in an elderly multimorbid patient;
2. Pacemaker implantation with incomplete consent;
3. Transcatheter aortic valve implantation (TAVI) in a patient with limited decision-making capacity.[5]

Each scenario was analyzed in terms of how AI might offer real-time legal alerts regarding documentation, consent, or procedural compliance. Scenarios were assessed through the lens of Turkish constitutional law and medical ethics.[6,9,10]

Results

The analysis revealed five key limitations:

1. Legal inadmissibility: AI cannot offer binding legal advice under Turkish law.[7]
2. Judicial non-delegability: Courts retain sole authority over legal interpretation.[9]
3. Professional liability: Medical responsibility is non-transferable.[8]
4. Data privacy risks: Inputting sensitive data into AI systems without consent may breach the PDPL.[10]
5. Educational deficits: Cardiologists often lack legal training, leaving them vulnerable to liability exposure.[5,11]

While AI systems can highlight red flags in documentation, they are not capable of rendering context-sensitive legal interpretations under Turkish law.[7]

Discussion

Interventional cardiology involves high-stakes, time-sensitive procedures, often performed with limited legal oversight. Legal AI could function analogously to clinical decision support systems (CDSS), providing alerts about documentation gaps or evolving regulations.[11] For example, before scheduling a rotational atherectomy, the system might advise revising consent documents due to recent complications in similar cases. Similarly, during transcatheter aortic valve implantation, AI could flag incomplete risk disclosure in patients with frailty, thereby directly linking legal oversight with procedural ethics.

However, reliance on AI must be tempered. A critical issue beyond regulation is the "black box" problem of some AI systems, where the rationale for a legal alert may not be transparent. This lack of explainability could undermine a physician's ability to trust and appropriately act upon the AI's suggestions, potentially creating a false sense of security or unnecessary alarm.

Unregulated use could violate constitutional boundaries and increase malpractice exposure.[7,12] These systems should function as supportive informational tools, not legal arbiters.[12] By incorporating such concrete cardiology examples, the conceptual framework gains greater clinical applicability and avoids repetitive theoretical assertions.

Integration with hospital information systems (HIS) and catheterization laboratory workflows could allow AI to assist with real-time documentation and consent processes,[5] provided there are ethical and legal safeguards in place.[8,10]

Recommendations

1. Restrict AI to supportive roles: AI should assist only with regulatory indexing, not final legal interpretation.[7,12]
2. Create ethical guidelines: The TMA and the Bar Association should define the ethical limits of legal AI in healthcare.[8,12]
3. Mandate disclaimers: All AI tools must clearly state that outputs are not legally binding.[12]
4. Regulatory action: Dedicated national legislation is needed to govern legal AI in clinical settings.[11]

Conclusion

Legal AI holds promise for enhancing medico-legal awareness in interventional cardiology.[5] However, without ethical constraints, regulatory oversight, and proper training, such tools could become liabilities rather than safeguards.[7,12] This paper emphasizes that the integration of legal AI must be contextualized through clinical scenarios (e.g., PCI, pacemaker implantation, TAVI) to remain relevant for practitioners. Thus, the recommendations bridge conceptual analysis with daily interventional cardiology practice. Structured integration through legislation, education, and interdisciplinary collaboration is essential to ensure AI functions as an aid, not an authority.[8,11]

Future research should focus on empirical validation of the conceptual framework presented in this paper. Real-world studies integrating AI-assisted legal alerts into interventional cardiology procedures such as PCI, pacemaker implantation, and TAVI are essential to assess feasibility, physician acceptance, and medico-legal outcomes. Such validation would provide stronger evidence for policy development and safe implementation in the Turkish healthcare context.

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Comparison of Ultrathin-Strut Sirolimus-Eluting Stents Versus Drug-Coated Balloons in Small Coronary Vessels: Real-World Data

Küçük Çaplı Koroner Arter Hastalığında Ultra-ince Strutlu Sirolimus Salınımlı Stent ile İlaç Kaplı Balon Tedavisinin Karşılaştırılması: Gerçek Yaşam Verileri

ABSTRACT

Objective: Drug-coated balloons (DCBs) and ultrathin-strut sirolimus-eluting stents (SES) are both treatment options for small-vessel coronary artery disease. However, comparative real-world data between these strategies are limited.

Method: In this single-center retrospective study, 178 consecutive patients with stable angina who underwent percutaneous coronary intervention with either a DCB (n = 89) or an ultrathin-strut SES (n = 89) between January 2017 and May 2025 were analyzed. Baseline demographics, angiographic and procedural features, and clinical outcomes were assessed. The primary outcome of this study was major adverse cardiac events (MACE), defined as a composite of target-lesion revascularization (TLR), long-term all-cause mortality, stroke, and myocardial infarction.

Results: Baseline characteristics were generally comparable, although SES-treated patients were older and had higher SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores. During a median follow-up of 293 days, MACE occurred in 2.2% of the DCB group and 5.6% of the SES group (P = 0.441). Rates of TLR, myocardial infarction, bleeding, and all-cause mortality were not significantly different. Kaplan–Meier analysis likewise demonstrated no significant difference in cumulative MACE between the two groups (log-rank P = 0.068).

Conclusion: In this real-world study, DCB treatment demonstrated similar safety and efficacy compared to ultrathin-strut SES for small-vessel coronary artery disease. DCB therapy may represent a viable alternative to DES in selected patients, supporting the "leave nothing behind" strategy.

Keywords: Drug-coated balloon, drug-eluting stent, sirolimus-eluting stent, small-vessel disease, ultrathin-strut

ÖZET

Amaç: İlaç kaplı balonlar (DCB) ve ultra-ince strut sirolimus salınımlı stentler (SES), küçük damar koroner arter hastalığının tedavisinde kullanılan iki seçenektir. Bu stratejilerin karşılaştırılması açısından gerçek yaşam verileri sınırlıdır.

Yöntem: Bu tek merkezli, retrospektif çalışmaya, Ocak 2017 ile Mayıs 2025 tarihleri arasında küçük damar koroner arter hastalığı nedeniyle perkütan koroner girişim uygulanan 178 hasta dahil edilmiştir. Hastaların 89'una DCB, 89'una ise ultra-ince strut SES uygulanmıştır. Başlangıç özellikleri, prosedürel ayrıntılar ve sonuçlar karşılaştırılmıştır. Birincil sonlanım noktası, tüm nedenlere bağlı ölüm, miyokard enfarktüsü, inme ve hedef lezyon revaskülarizasyonunu (TLR) içeren majör advers kardiyak olaylardır (MACE).

Bulgular: Başlangıç özellikleri ve komorbiditeler büyük ölçüde benzer olmakla birlikte, SES grubundaki hastaların daha yaşlı ve SYNTAX skorlarının daha yüksek olduğu görülmüştür. Medyan takip süresi 293 gün olarak bulunmuştur. MACE, DCB grubunda %2,2, SES grubunda ise %5,6 oranında saptanmıştır (P = 0,441). Tüm nedenlere bağlı mortalite, TLR, miyokard enfarktüsü ve majör kanama oranları benzer olarak bulunmuştur. Kaplan–Meier analizi, kümülatif MACE açısından anlamlı fark göstermemiştir (log-rank P = 0,068).

Sonuç: Bu gerçek yaşam kohortunda, küçük damar koroner arter hastalığının tedavisinde DCB, ince strutlu SES'e benzer güvenlik ve etkinlik sağlamıştır. DCB tedavisi, seçilmiş hastalarda ilaç-kalplı stentlere alternatif oluşturabilir ve "geride hiçbir şey bırakmama" stratejisini destekleyebilir.

Anahtar Kelimeler: İlaç kaplı balon, ilaç salınımlı stent, sirolimus salınımlı stent, küçük damar hastalığı, ince strut

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Although drug-eluting stents (DES) are a well-established treatment option for small coronary vessel disease, in-stent restenosis and adverse events remain significant concerns in this patient population.[1]. Several randomized controlled trials have demonstrated that drug-coated balloons (DCBs) provide comparable efficacy to DES with respect to adverse events, including target-lesion revascularization (TLR), mortality, myocardial infarction, and bleeding.[2-8] DCBs may offer additional advantages, such as enabling shorter durations of dual antiplatelet therapy (DAPT), avoiding the need for overly long or multiple stents in extensive coronary artery disease (CAD), and providing greater flexibility, particularly in calcified or tortuous coronary vessels.[9] Despite the favorable outcomes reported in randomized controlled trials, data reflecting real-world results are critically important at this stage.

Advances in drug-eluting stent technology have aimed to further reduce in-stent restenosis and adverse outcomes in small-vessel CAD. Innovations such as ultrathin struts, enhanced biocompatibility, and the use of bioresorbable materials have been employed to lower complications such as stent thrombosis, inflammation, and in-stent restenosis (ISR).[10] ISR remains a particularly significant concern in small-vessel disease. The Orsiro sirolimus-eluting coronary stent (SES) (Biotronik, Buelach, Switzerland), with an ultrathin strut thickness of 60 μm for diameters ≤ 3 mm, is designed to provide improved flexibility and deliverability, as well as to promote earlier endothelialization, potentially reducing in-stent restenosis rates.[10] Owing to these properties, Orsiro coronary stents have attracted particular interest in patients with small-vessel disease. Subgroup analyses from several previous studies on small-vessel disease.[11-15] including the BIO-RESORT trial (Randomized Trial Comparing Three Contemporary Drug-Eluting Stents with Different Polymer Coatings in All-Comers Patients Undergoing PCI)[11] and BIO-FLOW II trial (Randomized Trial of the Orsiro Biodegradable Polymer Sirolimus-Eluting Stent Versus Xience Everolimus-Eluting Stent in Patients With CAD),[12] have demonstrated that the Orsiro ultrathin-strut coronary stent is associated with lower TLR rates and, in the BIO-FLOW II trial, even reduced mortality.[12] These findings highlight the potential advantages of ultrathin-strut SES over second-generation everolimus-eluting DES in small-vessel coronary artery disease, particularly regarding adverse events such as target lesion revascularization.

Previous studies and randomized clinical trials on drug-coated balloons have primarily used first- or second-generation DES as comparators rather than ultrathin-strut SES.[2-8] Moreover, the effectiveness of DCBs in real-world settings for small-vessel coronary artery disease needs to be fully established. Therefore, this study aims to compare the Orsiro ultrathin-strut coronary stent with DCB treatment in small-vessel coronary artery disease in terms of clinical outcomes.

Materials and Methods

Study Population

This single-center, retrospective study included patients who underwent DCB or ultrathin-strut SES treatment for small-vessel coronary artery disease due to stable angina pectoris between January 1, 2017 and May 31, 2025. Patients were consecutively enrolled, and the following strict exclusion criteria were applied:

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
AF	Atrial fibrillation
ARBs	Angiotensin II receptor blockers
ARNi	Angiotensin receptor neprilysin inhibitor
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloon
DES	Drug-eluting stents
DM	Diabetes mellitus
HDL	High-density lipoprotein
HT	Hypertension
ISR	In-stent restenosis
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
MRA	Mineralocorticoid receptor antagonist
PASP	Pulmonary artery systolic pressure
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography
SES	Sirolimus-eluting stents
TIMI	Thrombolysis in myocardial infarction
TLR	Target-lesion revascularization
TVR	Target vessel restenosis

- Percutaneous coronary intervention (PCI) for small-vessel disease involving chronic total occlusion or a bifurcation segment (n = 11)
- Acute coronary syndrome or shock requiring inotropic support (n = 5)
- Severe anemia (hemoglobin < 8 mg/dL) (n = 2)
- Active malignancy (n = 1)
- End-stage renal disease with glomerular filtration rate < 30 mL/min/1.73 m^2 or maintenance dialysis (n = 3)
- Severe valvular heart disease (n = 2)
- Missing data (n = 12)
- Bail-out DES implantation after DCB application due to flow-limiting dissection or recoil (n = 3).

After applying these criteria, the remaining patients constituted the study cohort (Figure 1). Baseline characteristics, laboratory values, medications, and imaging data were obtained from the hospital information system and patient files, and recorded anonymously. Transthoracic echocardiographic examinations were performed at discharge using a Vivid E95 ultrasound device (General Electric Vingmed Ultrasound, Milwaukee, WI). The evaluated parameters were left ventricular ejection fraction (LVEF) by visual estimation, pulmonary artery systolic pressure (PASP) using the Bernoulli equation based on tricuspid regurgitant jet velocity, and valvular pathologies.

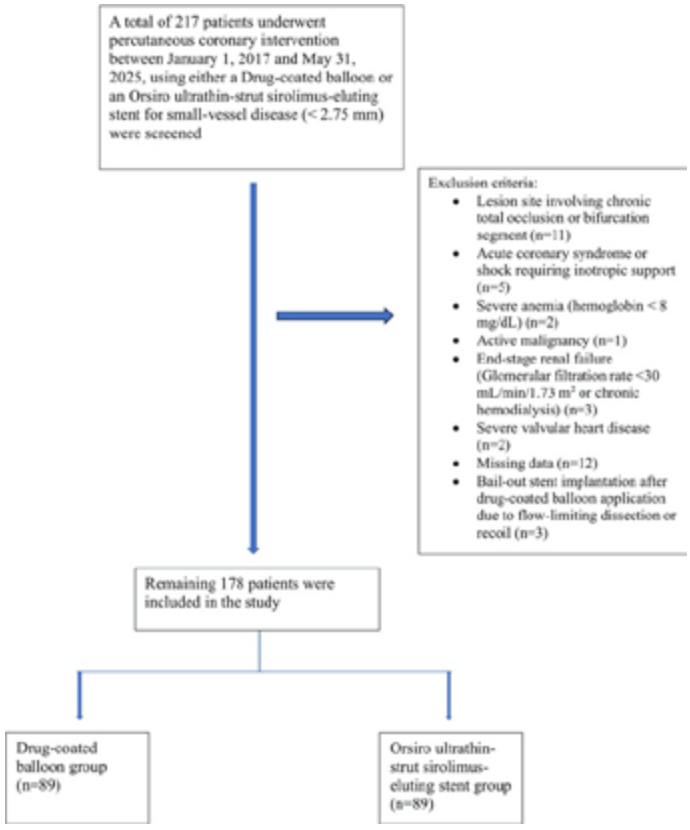

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patient selection.

Given the retrospective design of this study, the risk of selection bias cannot be excluded, as lesion characteristics may have influenced the decision between DES and DCB implantation. To reduce this potential bias, consecutive patient enrollment was applied. Lesion complexity was characterized by reporting the SYNTAX I score, which integrates factors such as calcification, tortuosity, and lesion length. Furthermore, the presence of LMCA stenting, device length (as a surrogate for lesion length), and the number of diseased vessels were also reported, thereby providing detailed information on lesion characteristics in the cohort.

The study was approved by Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval Number: E-10840098-202.3.02-5214, Date: 14.08.2025), and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients at admission and prior to invasive procedures, allowing the use of their data for scientific purposes.

Procedural Details

Loading doses of aspirin (300 mg) and clopidogrel (600 mg) were administered to all patients prior to the procedure. A left or right radial arterial approach was used in all cases. Pre-dilation of lesions with a plain balloon (balloon-to-vessel ratio 1:1) was routinely performed, and adjunctive devices such as scoring or cutting balloons, rotational atherectomy, intravascular lithotripsy, or orbital atherectomy were used when necessary. Following pre-dilation, a drug-coated balloon or an ultrathin-strut SES sized 1:1 was deployed. The following paclitaxel-coated balloons were used in the DCB procedures: Pantera Lux® (Biotronik AG, Buelach, Switzerland), Essential Pro® paclitaxel-coated balloon (iVascular, Barcelona, Spain), Elutax® paclitaxel-coated balloon (Aachen Resonance GmbH, Aachen, Germany), Agent™ sirolimus-coated balloon (Boston Scientific, Marlborough, MA, USA), IN.PACT® Admiral paclitaxel-coated balloon (Medtronic, Minneapolis, MN, USA), SeQuent® Please NEO paclitaxel-coated balloon (B. Braun Melsungen AG, Berlin, Germany), and Danubio® paclitaxel-coated balloon (Minvasys, Gennevilliers, France). For DCB procedures, balloon inflation at nominal pressure was maintained for at least 60 seconds. Procedural success was defined as ≤ 30% residual stenosis, restoration of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, and absence of flow-limiting dissection. A re-evaluation was performed after a five-minute waiting period, following the administration of an intracoronary vasodilator, to exclude vessel recoil or other complications. Bail-out DES implantation was performed in unsuccessful DCB cases according to predefined criteria. In the DES group, routine post-dilation with non-compliant balloons was carried out. When additional interventions for other lesions were required, these were generally performed during the same procedure; however, in cases where excessive contrast administration or prolonged procedural time was anticipated, a staged approach was preferred. Following PCI, all participants were prescribed dual antiplatelet therapy with aspirin and clopidogrel for a minimum of six months.

Definitions and Outcomes

Definitions were based on the consensus document of the Drug-Coated Balloon Academic Research Consortium.[16] Small-vessel coronary artery disease was defined as a reference vessel diameter < 2.75 mm. In this study, vessel diameter was primarily determined by quantitative coronary angiography (QCA). When QCA was not feasible, visual estimation by experienced interventional cardiologists was performed. The primary outcome was major adverse cardiac events (MACE), defined as a composite of all-cause death, any myocardial infarction, stroke, and target-lesion revascularization. Each component of MACE was also analyzed individually. Significant bleeding events were classified according to the Bleeding Academic Research Consortium (BARC) criteria, with type 3 to 5 bleeding considered clinically relevant.[17] Follow-up data were collected through review of hospital records and outpatient clinic visits, and, when necessary, by structured telephone contact with patients or their relatives.

Statistical Analysis

The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test, supported by visual inspection of histograms. Categorical variables were summarized as counts and percentages, while continuous variables were presented as mean ± standard deviation if normally distributed, or as median with interquartile ranges otherwise.

Comparisons between the DCB and ultrathin-strut SES groups were performed using the independent samples t-test or Mann–Whitney U test for continuous data, depending on distribution. For categorical comparisons, the Chi-square test or Fisher's exact test was applied.

Table 1. Comparison of drug-coated balloon (DCB) and ultrathin-strut sirolimus-eluting stent (SES) groups regarding baseline clinical characteristics, comorbidities, and medications

Variables	DCB (n = 89)	Ultra-thin strut SES (n = 89)	*P*
Baseline clinical characteristics and comorbidities			
Age (years)	57.4 ± 11.2	61.9 ± 9.0	0.003
Male sex	79 (88.8%)	80 (89.9%)	1.000
Smoking	47 (52.8%)	50 (56.2%)	0.763
Hypertension	65 (73.0%)	65 (73.0%)	1.00
Diabetes mellitus	42 (47.2%)	43 (48.3%)	1.00
Chronic kidney disease	2 (2.2%)	7 (7.9%)	0.171
Congestive heart failure	3 (3.4%)	7 (7.9%)	0.329
Chronic obstructive pulmonary disease	3 (3.4%)	0	0.244
Previous cerebrovascular accident	1 (1.1%)	0	1.00
Atrial fibrillation	6 (6.7%)	4 (4.5%)	0.745
Peripheral arterial disease	0	1 (1.1%)	1.00
Pre-existing coronary artery disease	37 (41.6%)	29 (32.6%)	0.277
Previous PCI	35 (39.3%)	25 (28.1%)	0.154
Previous CABG	3 (3.4%)	5 (5.6%)	0.718
Medications during Follow-up			
ß-blocker usage	69 (77.5%)	85 (95.5%)	0.001
ACEi/ARB usage	58 (65.2%)	61 (68.5%)	0.750
Statin usage	89 (100%)	88 (98.9%)	1.00
SGLT-2i usage	25 (28.1%)	27 (30.3%)	0.869
MRA usage	3 (3.4%)	4 (4.5%)	1.00
ARNI usage	2 (2.2%)	0	0.477
Insulin usage	6 (6.7%)	10 (11.2%)	0.432
DAPT duration (months)	15.8 ± 18.5	12.2 ± 12.7	0.139

ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; ARNI: Angiotensin receptor neprilysin inhibitor; CABG, Coronary artery bypass graft surgery; DAPT, Dual antiplatelet therapy; MRA, Mineralocorticoid receptor antagonist; PCI, Percutaneous coronary intervention; SGLT-2i, Sodium-glucose cotransporter-2 inhibitor.

Time-to-event outcomes, including cumulative incidence of MACE, were analyzed with Kaplan–Meier survival curves, and statistical differences were evaluated using the log-rank test. All statistical analyses were conducted with Python 3.11 (Python Software Foundation, Wilmington, DE, USA). A two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 178 patients were included in this study, with 89 in each group (DCB vs. ultrathin-strut SES). The ultrathin-strut SES group was older (61.9 ± 9.0 vs. 57.4 ± 11.2 years, P = 0.003), while gender distribution (male: 88.8% vs. 89.9%, P = 1.00) and smoking prevalence (52.8% vs. 56.2%, P = 0.763) were similar. Comorbidities, including hypertension (HT), atrial fibrillation (AF), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), chronic kidney disease (CKD), prior cerebrovascular accident, and peripheral arterial disease, did not differ between groups (Table 1). Rates of pre-existing CAD (41.6% vs. 32.6%, P = 0.277), previous percutaneous coronary intervention (39.3% vs. 28.1%, P = 0.154), and previous coronary artery bypass grafting (CABG) (3.4% vs. 5.6%, P = 0.718) were also comparable (Table 1).

The use of medications, including statins, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNi), mineralocorticoid receptor antagonists (MRAs), sodium-glucose cotransporter-2 inhibitors (SGLT-2i), and insulin during follow-up, was similar between groups, except for ß-blockers, which were more frequently prescribed in the ultrathin-strut SES group (95.5% vs. 77.5%, P = 0.001) (Table 1). Mean DAPT durations did not differ significantly (15.8 ± 18.5 vs. 12.2 ± 12.7 months, P = 0.139).

Laboratory parameters at admission were comparable between groups, including hemoglobin (14.2 ± 1.7 vs. 13.7 ± 1.8 g/dL, P = 0.079), creatinine (0.9 ± 0.2 vs. 1.0 ± 0.3 mg/dL, P = 0.174), hemoglobin A1c, C-reactive protein (CRP) values, and lipid profile (total cholesterol, low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides). The ultrathin-strut SES group had a lower albumin level, with borderline statistical significance (4.3 ± 0.4 vs. 4.7 ± 0.2, P = 0.041) (Table 2). Left ventricular ejection fraction at discharge was slightly lower in the ultrathin-strut SES group (55.2 ± 11.1% vs. 58.9 ± 7.6%, P = 0.013) (Table 2).

Table 2. Comparison of laboratory and echocardiographic parameters between drug-coated balloon (DCB) and ultrathin-strut sirolimus-eluting stent (SES) groups

Variables	DCB (n = 89)	Ultra-thin strut SES (n = 89)	*P*
Laboratory parameters			
Hemoglobin (g/dL)	14.2 ± 1.7	13.7 ± 1.8	0.079
WBC (cell count/L)	(8.2 ± 2.3) ×10^3	(8.5 ± 2.4) ×10^3	0.460
Platelets (cell count/mcL)	(238.7 ± 57.7) ×10^3	(241.8 ± 62.5) ×10^3	0.731
CRP (mg/dL)	5.5 ± 8.7	7.7 ± 13.3	0.390
Creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.3	0.174
Urea (mg/dL)	31.0 ± 10.6	37.2 ± 19.0	0.069
AST (IU/L)	28.5 ± 27.5	24.5 ± 20.0	0.463
ALT (IU/L)	29.2 ± 17.1	22.1 ± 9.5	0.027
Albumin (g/dL)	4.7 ± 0.2	4.3 ± 0.4	0.041
Sodium (mEq/L)	139.1 ± 3.1	138.2 ± 2.5	0.084
Potassium (mEq/L)	4.3 ± 0.4	4.2 ± 0.4	0.389
Hemoglobin A1c (%)	6.7 ± 1.3	6.5 ± 1.6	0.624
Total cholesterol (mg/dL)	189.1 ± 50.1	184.2 ± 54.3	0.726
LDL cholesterol (mg/dL)	118.0 ± 47.4	111.0 ± 49.3	0.368
HDL cholesterol (mg/dL)	42.1 ± 9.7	41.5 ± 12.1	0.806
Triglycerides (mg/dL)	197.8 ± 122.1	212.0 ± 165.6	0.703
TSH (mIU/L)	1.9 ± 1.0	1.9 ± 1.2	0.860
Echocardiographic parameters			
Left ventricular ejection fraction (%)	58.9 ± 7.6	55.2 ± 11.1	0.013
Pulmonary artery systolic pressure (mmHg)	26.4 ± 5.8	25.3 ± 5.5	0.507

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; TSH, Thyroid-stimulating hormone; WBC, White blood cell count.

Regarding angiographic characteristics, the number of diseased vessels was similar between groups (2.0 ± 0.8 vs. 2.2 ± 0.7, P = 0.109). However, the ultrathin-strut SES group had a higher SYNTAX I score (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) (18.9 ± 0.5 vs. 13.8 ± 10.3, P = 0.002), indicating more complex anatomic disease (Table 3). Device diameters were comparable (2.4 ± 0.3 vs. 2.4 ± 0.1 mm, P = 0.304), but device length was greater in the ultrathin-strut SES group (32.0 ± 8.1 vs. 25.7 ± 5.5 mm, P < 0.001) (Table 3). In the DCB group, 83 (93.3%) patients received paclitaxel-coated balloons, while six (6.7%) received sirolimus-coated balloons.

The median follow-up for the overall patient population was 293 (170–456) days, ranging from 71 to 2807 days, and was similar between groups (296 (189–456) vs. 256 (158–456) days, P = 0.906). The primary outcome, MACE, occurred in 5.6% of patients in the ultrathin-strut SES group and 2.2% in the DCB group (P = 0.441) (Table 3, Figure 2). Rates of all-cause mortality, TLR, cerebrovascular accident, and myocardial infarction were also comparable (Table 3, Figure 2). No cases of procedural mortality or early (< 30 days) mortality occurred in either group. Coronary angiography during follow-up was performed in six patients (6.7%) in the DCB group and seven (7.9%) in the ultrathin-strut SES group, with identical rates of TLR and restenosis > 50% (2.2% vs. 2.2%, P = 1.00). BARC type 3–5 bleeding occurred in one patient (1.1%) in each group (P = 1.00) (Table 3, Figure 2). Kaplan–Meier analysis did not demonstrate a statistically significant difference in cumulative MACE between the groups (log-rank P = 0.068) (Figure 3).

Discussion

Small-vessel coronary artery disease is associated with a higher incidence of restenosis despite advancements in DES technology, with target vessel failure reported in over 40% of patients at 10-year follow-up.[18] Drug-coated balloons emerged as an alternative after studies consistently demonstrated superior outcomes compared with plain balloon angioplasty.[19] Whereas DES exert their effect through controlled, sustained release of antiproliferative drugs, DCBs act via rapid drug uptake by the vessel wall to achieve persistent drug bioavailability.[1] Consequently, adequate lesion preparation and, when necessary, the use of adjunctive devices—such as cutting balloons, scoring balloons, and rotational atherectomy—are critical for optimal drug delivery. Sufficient balloon inflation time (≥ 30 seconds) is also essential to ensure adequate drug transfer.[1] In the first PICCOLETO trial (Paclitaxel-Coated Balloon Versus Drug-Eluting Stent for the Treatment of Small Coronary Vessels)[20] for small-vessel disease, DCB use was associated with higher MACE and target vessel restenosis (TVR) rates within six months, leading to early trial termination. However, only 25% of patients in that study underwent pre-dilation before DCB deployment, and the unfavorable outcomes were attributed to insufficient lesion preparation.

Table 3. Comparison of angiographic characteristics and outcomes between drug-coated balloon (DCB) and ultrathin-strut sirolimus-eluting stent (SES) groups

Variables	DCB (n = 89)	Ultra-thin Strut SES (n = 89)	*P*
Angiographic characteristics			
Diseased vessel number	2.0 ± 0.8	2.2 ± 0.7	0.109
Device length (mm)	25.7 ± 5.5	32.0 ± 8.1	<0.001
Device diameter (mm)	2.4 ± 0.3	2.4 ± 0.1	0.304
SYNTAX I score	13.8 ± 10.3	18.9 ± 10.5	0.002
Patients with LMCA stent	19 (21.3%)	26 (29.2%)	0.301
Outcomes			
Follow-up duration (days)	256 (158, 456)	296 (189, 456)	0.906
Procedural mortality	0	0	1.00
30-day mortality	0	0	1.00
MACE	2 (2.2%)	5 (5.6%)	0.441
All-cause mortality	0	3 (3.4%)	0.244
Target-lesion revascularization	2 (2.2%)	2 (2.2%)	1.00
Cerebrovascular accident	0	0	1.00
Myocardial infarction	0	0	1.00
BARC type 3-5 bleeding	1 (1.1%)	1 (1.1%)	1.00

BARC, Bleeding Academic Research Consortium; LMCA, Left main coronary artery; MACE, Major adverse cardiac events.

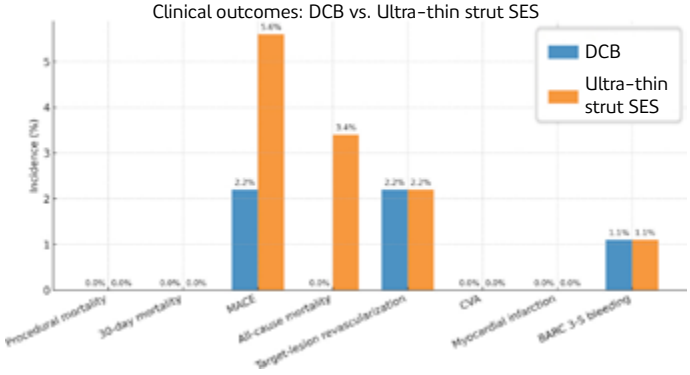

Figure 2. Clinical outcomes in the drug-coated balloon and ultrathin-strut sirolimus-eluting stent groups.

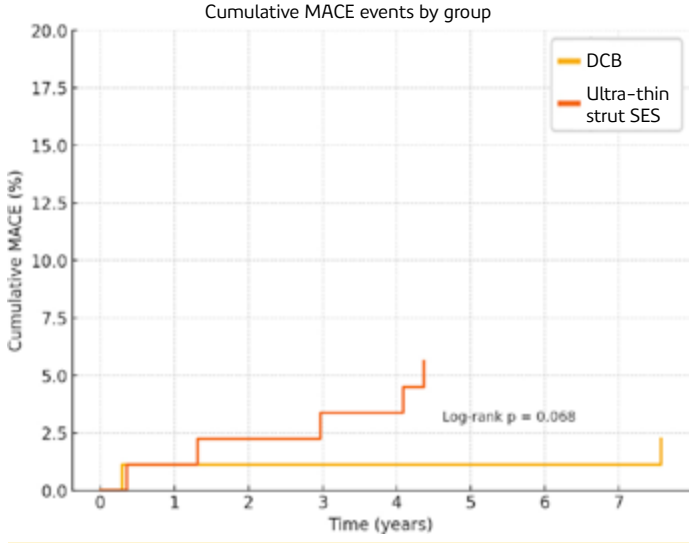

Figure 3. Kaplan-Meier curves depicting cumulative major adverse cardiac events (MACE) events during follow-up in the drug-coated balloon and ultrathin-strut sirolimus-eluting stent groups.

Subsequent randomized controlled trials were designed to evaluate the non-inferiority of DCBs compared with DES in small-vessel CAD. In the BELLO trial (Balloon Elution and Late Loss Optimization),[3] DCBs were compared with first-generation DES, with pre-dilation prior to DCB performed in 97% of cases. Although MACE and TLR rates were similar at six months, DCB use was associated with lower MACE rates at three years.[3] Later trials compared DCBs with second-generation DES in small-vessel CAD. In the BASKET-SMALL 2 trial (Basel Stent Kosten Effektivitäts Trial–Small Vessels 2), MACE, cardiovascular death, myocardial infarction, and TVR were similar between DCB and DES groups at both 12 months and three years.[4,5] The RESTORE SVD trial (Randomized Comparison of the Restenosis Rate Between Drug-Eluting Stent and Drug-Coated Balloon in Small Vessel Coronary Artery Disease) also demonstrated comparable efficacy of the two devices at 12- and 24-month follow-up.[6] Similarly, the PICCOLETO II trial (Paclitaxel-Coated Balloon Versus Drug-Eluting Stent for the Treatment of Small Coronary Vessels II)[7] and the study by Yu et al.[8] reported no significant differences in MACE, myocardial infarction, and TVR at 12 months. Angiographic outcomes were also evaluated in these randomized clinical trials. In the PICCOLETO II trial,[7] late lumen loss was lower in the DCB group, although minimal lumen diameter at six months was comparable between groups. Similarly, Yu et al.[8] reported no significant difference in late lumen loss at nine months. Meta-analyses have also demonstrated comparable long-term clinical outcomes

between DCBs and DES.[19,21,22] However, the use of DCBs for de novo lesions in non-small coronary vessels has not been adequately investigated, despite promising findings from observational studies.[23,24] Further randomized trials with long-term follow-up are warranted before definitive conclusions can be reached for this patient subset.

Drawbacks of DES include early and late stent thrombosis, long-term inflammatory reactions, reduced flexibility and deliverability—particularly in tortuous or calcified vessels—ISR, and the requirement for prolonged DAPT.[9] DCBs may overcome many of these limitations. For example, stent thrombosis is not a concern with DCB treatment. Enhanced deliverability and flexibility can facilitate and shorten procedures while reducing procedural complications. By preserving the vessel's natural flexibility, DCBs may be particularly advantageous in situations where vessel mobility is critical, such as in tortuous segments and bifurcation lesions. Furthermore, DCB use eliminates stent-related complications such as malapposition and fracture, and is especially beneficial for diffuse coronary lesions by avoiding the need for excessively long stents, which may increase restenosis risk and complicate potential future coronary artery bypass grafting.[9] Although newer-generation DES have demonstrated high efficacy and safety even in patients with diffuse CAD,[25] the "leave nothing behind" strategy offered by DCB therapy remains appealing to clinicians for the reasons outlined above. Real-world studies are essential to validate clinical trial findings and strengthen confidence in their application.

DCB treatment may also allow for shorter DAPT duration and potentially reduce bleeding risk, particularly in patients at high risk for bleeding. Cortese et al.[26] demonstrated lower BARC type 3–5 bleeding events in patients receiving single antiplatelet therapy after DCB treatment, without compromising efficacy compared with those receiving DAPT following DCB application. However, clinical trials have not demonstrated superiority of DCB over DES in terms of bleeding outcomes in patients with small-vessel disease. In our study, DAPT duration and bleeding rates were comparable between groups. The high proportion of DES use in other coronary segments and the potential presence of extensive CAD in patients with small-vessel involvement may explain these findings. Real-world practice may not always align with theoretical expectations; nevertheless, bleeding rates could be reduced in patients with isolated small-vessel disease treated exclusively with DCB.

Coronary dissection after DCB application is a common phenomenon, occurring in up to 40% of cases. However, these dissections usually do not impair distal flow and may be left untreated. In the study by Gitto et al.,[27] target lesion failure rates at two years were similar between patients without dissection and those with untreated dissections in the absence of flow limitation. Current guidelines likewise recommend leaving non-flow-limiting dissections untreated.[1] Regarding device type, previous studies suggest that the choice of DCB—paclitaxel-coated versus sirolimus-coated—does not significantly affect outcomes. This finding is supported by the comparative study of Vlieger et al.,[28] the randomized clinical trial by Ahmad et al.,[29] and the meta-analysis by Shin et al.[30]

Several studies have investigated the potential advantages of the Orsiro SES (Biotronik, Buelach, Switzerland), particularly in small-vessel disease. While some studies[31,32] found no significant difference between ultrathin-strut SES and second-generation DES, other investigations, including randomized-controlled trials and meta-analyses, have reported superior outcomes with ultrathin-strut SES compared with second-generation DES in this patient population.[10–15] Previous randomized controlled trials comparing DCBs have primarily used first- or second-generation DES as comparators. To our knowledge, this is the first study to compare DCBs with ultrathin-strut SES in small-vessel coronary artery disease with respect to clinical outcomes. Our findings suggest that DCBs offer a comparable efficacy and safety profile to ultrathin-strut DES; however, larger randomized studies with longer follow-up are warranted to confirm these results. The presence of longer lesion lengths and higher SYNTAX scores in the ultrathin-strut SES group should be considered when interpreting the results of this study. More complex anatomic disease may contribute to higher TLR rates and poorer clinical outcomes, potentially creating a pre-existing disadvantage for the ultrathin-strut SES group. Nevertheless, this study demonstrated comparable efficacy of the two devices in small-vessel coronary artery disease and reflected real-world practice, in which clinicians tend to prefer DES implantation in the setting of more complex CAD rather than DCB.

Limitations

This study has various limitations. First, it was conducted at a single center using a retrospective design, which may introduce selection and information bias. To minimize this risk, patients were enrolled consecutively. Second, the sample size was modest, reducing statistical power to detect differences in infrequent clinical outcomes. Third, although baseline characteristics were generally well balanced, residual confounding from unmeasured variables cannot be excluded. Because of the very low number of MACE events (n = 7), Cox regression analysis with hazard ratios and confidence intervals could not be reliably performed, and survival comparisons were therefore limited to Kaplan–Meier curves with log-rank testing. Finally, the median follow-up duration was less than one year, and longer-term differences between treatment strategies may not have been captured.

Conclusion

In this real-world, retrospective analysis of patients with small-vessel coronary artery disease, treatment with drug-coated balloons demonstrated comparable efficacy and safety outcomes to ultrathin-strut sirolimus-eluting stents. Rates of MACE, all-cause mortality, target-lesion revascularization, and major bleeding were similar between the two strategies. Larger randomized trials with extended follow-up are warranted to confirm these observations and further define the optimal revascularization strategy for small-vessel coronary artery disease.

Ethics Committee Approval: Ethics committee approval was obtained from Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval Number: E-10840098-202.3.02-5214, Date: 14.08.2025).

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Gender Differences in Mechanical Circulatory Support, Heart Transplantation, and Survival Among Patients with Advanced Heart Failure

İleri Düzey Kalp Yetersizliği Hastalarında Mekanik Dolaşım Desteği, Kalp Nakli ve Yaşam Süresi Açısından Cinsiyet Farklılıkları

ABSTRACT

Objective: Despite growing awareness of sex-based disparities in heart failure (HF), their impact on clinical outcomes in advanced stages remains poorly understood, largely due to confounding in observational data. This study aimed to assess the independent effect of biological sex on clinical outcomes in advanced HF.

Method: In this retrospective cohort study, 522 patients with advanced HF (85.2% male) evaluated between 2021 and 2024 underwent comprehensive assessments, including echocardiography, cardiopulmonary exercise testing, and cardiac catheterization. Covariate balance was achieved using inverse probability weighting (IPW) based on propensity scores. Primary outcomes included left ventricular assist device (LVAD) implantation, heart transplantation, all-cause mortality, and a composite of these events. Cox proportional hazards models were applied, with a median follow-up of 864 days.

Results: At baseline, male patients were older (54.0 vs. 49.5 years; P = 0.025), had higher rates of ischemic etiology (49.9% vs. 22.7%; P < 0.001), larger cardiac dimensions, and superior exercise capacity. Following IPW adjustment, female sex was associated with a significantly lower risk of LVAD implantation (hazard ratio [HR]: 0.13; 95% confidence interval [CI]: 0.04–0.40; P < 0.001). In contrast, no significant sex-related difference was found in all-cause mortality (HR: 0.75; 95% CI: 0.36–1.58; P = 0.43). The composite outcome showed a non-significant trend toward better outcomes in women (HR: 0.53; 95% CI: 0.26–1.06; P = 0.076). These findings should be interpreted in the context of the relatively small female cohort (14.8%).

Conclusion: In patients with advanced HF, female sex was associated with a lower likelihood of LVAD implantation without an effect on overall mortality. These findings suggest that advanced HF may follow distinct pathophysiological trajectories in women and men, underscoring the importance of sex-informed clinical decision-making frameworks to optimize management and outcomes.

Keywords: Advanced heart failure, sex differences, left ventricular assist device, mechanical circulatory support, inverse probability weighting, propensity score

ÖZET

Amaç: İleri düzey kalp yetersizliği (KY) yönetiminde ve sonuçlarında cinsiyete dayalı farklılıklar tam olarak anlaşılamamıştır. Bu çalışma, biyolojik cinsiyetin mekanik dolaşım desteği (LVAD) uygulanması, kalp nakli ve mortalite üzerindeki bağımsız etkisini değerlendirmeyi amaçlamıştır.

Yöntem: 522 ileri KY hastasından oluşan (%85,2'si erkek) retrospektif bir kohort analiz edilmiştir. Klinik, ekokardiyografik, hemodinamik ve laboratuvar verileri cinsiyete göre karşılaştırılmıştır. Birincil birleşik sonlanım; LVAD implantasyonu, kalp nakli veya tüm nedenlere bağlı ölüm olarak belirlenmiştir. Kafa karıştırıcı etkenleri ayarlamak için eğilim skoru kullanılarak ters olasılık ağırlıklı (IPW) analiz ve çok değişkenli Cox regresyon modelleri uygulanmıştır.

Bulgular: Başlangıçta, erkek hastalar daha yaşlıydı (54,0 yaşa karşı 49,5 yaş; P = 0,025), iskemik etiyoloji oranları daha yüksekti (%49,9'a karşı %22,7; P < 0,001), kalp boyutları daha büyüktü ve egzersiz kapasiteleri daha üstündü. IPW ayarlamasından sonra, kadın cinsiyeti LVAD implantasyonu riskinde anlamlı olarak daha düşük bir riskle ilişkiliydi (HR: 0,13; %95 GA: 0,04–0,40; P < 0,001). Buna karşın, tüm nedenlere bağlı mortalitede cinsiyetle ilişkili önemli bir fark bulunmamıştır (HR: 0,75; %95 GA: 0,36–1,58; P = 0,43). Bileşik sonuç, kadınlarda daha iyi sonuçlara doğru anlamlı olmayan bir eğilim gösterdi (HR: 0,53; %95 GA: 0,26–1,06; P = 0,076). Sonuçların yorumlanması, nispeten küçük kadın kohortu (%14,8) bağlamında değerlendirilmelidir.

ORIGINAL ARTICLE
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Sonuç: İleri düzeyde kalp yetersizliği olan hastalarda, kadın cinsiyeti genel mortaliteyi etkilemeksizin LVAD implantasyonu ihtiyacının daha düşük olmasıyla ilişkilendirilmiştir. Bu bulgular, ileri düzeyde kalp yetmezliğinin kadınlarda ve erkeklerde farklı patofizyolojik seyir izleyebileceğini göstermekte ve tedaviyi ve sonuçları optimize etmek için cinsiyete dayalı klinik karar verme çerçevelerinin önemini vurgulamaktadır.

Anahtar Kelimeler: İleri kalp yetersizliği, ters olasılık ağırlıklandırması, sol ventrikül destek cihazı, mekanik dolaşım desteği, eğilim skoru, cinsiyet farklılıkları

Heart failure (HF) represents a major global health burden, affecting over 64 million individuals worldwide and contributing substantially to morbidity and mortality.[1] Despite significant advances in both pharmacologic and device-based therapies, a considerable proportion of patients progress to advanced HF, characterized by persistent symptoms, frequent hospitalizations, and markedly reduced quality of life.[2]

Advanced HF is typically defined as New York Heart Association (NYHA) Class III–IV or American College of Cardiology/American Heart Association (ACC/AHA) Stage D, where conventional treatment options fail to provide adequate relief.[2] At this critical stage, mechanical circulatory support (MCS), particularly left ventricular assist devices (LVADs), is frequently employed either as a bridge to transplantation or recovery or as destination therapy.[3,4] Although LVAD therapy has improved survival and quality of life, growing evidence suggests that sex-based disparities may influence access to these therapies and the outcomes they produce.

Prior studies have highlighted potential sex differences in HF etiology, clinical phenotype, hemodynamics, and treatment response.[5,6] Women are more likely to exhibit non-ischemic causes, HF with preserved ejection fraction (HFpEF), and different patterns of ventricular remodeling, while men are more often diagnosed at a younger age with ischemic HF and undergo invasive interventions more frequently.[7,8] Despite this, women remain underrepresented in advanced HF therapies such as LVAD implantation.[9–11] These disparities likely reflect not only clinical heterogeneity but also biological variation, health system factors, and decision-making biases.

Understanding these disparities is complicated by confounding factors common to observational research. Traditional multivariable modeling often fails to fully adjust for numerous sex-related clinical and demographic differences. In this context, inverse probability weighting (IPW) using propensity scores offers a more robust framework by achieving covariate balance between comparison groups.[12,13]

Therefore, the objective of this study was to determine the independent impact of biological sex on clinical outcomes—including LVAD implantation, mortality, and heart transplantation—in patients with advanced HF by applying IPW methodology. This approach aims to clarify the role of sex in clinical progression and risk stratification, with the potential to inform more equitable and personalized HF management strategies. Specifically, we hypothesized that sex-related differences in cardiovascular pathophysiology, including variations in neurohormonal activation, inflammatory responses, and metabolic adaptation, may influence the trajectory toward mechanical circulatory support requirements.

ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
BIOSTAT-CHF	BIOlogy Study to TAilored Treatment in Chronic Heart Failure
BMI	Body Mass Index
BNP	B-type natriuretic peptide
CPET	Cardiopulmonary exercise testing
HF	Heart failure
HFpEF	HF with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IPW	Inverse probability weighting
LVAD	Left ventricular assist device
LVEDD	Left ventricular end-diastolic dimension
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic dimension
MCAR	Missing completely at random
MCS	Mechanical circulatory support
MET	Metabolic equivalent
NYHA	New York Heart Association
PASP	Pulmonary artery systolic pressure
RER	Respiratory exchange ratio
RHC	Right heart catheterization
SMD	Standardized mean difference
TAPSE	Tricuspid annular plane systolic excursion
TSH	Thyroid-stimulating hormone

Materials and Methods

Study Population

This retrospective cohort study included patients with advanced HF who were admitted to the heart transplantation outpatient clinic between 2021 and 2024. All patients underwent comprehensive clinical evaluation, including echocardiographic examination, cardiopulmonary exercise testing (CPET), and right heart catheterization (RHC). Clinical, laboratory, echocardiographic, and hemodynamic data were obtained within a maximum of two weeks from the CPET date to ensure temporal consistency of measurements.

Inclusion criteria comprised patients with advanced HF (predominantly New York Heart Association Class III–IV or ACC/AHA Stage D) who had complete clinical, echocardiographic, exercise testing, and hemodynamic evaluation. Patients with

left ventricular ejection fraction (LVEF) >25%, severe lung disease, or contraindications to CPET or RHC were excluded from the study. To ensure accurate assessment of exercise capacity, patients with a peak respiratory exchange ratio (RER) < 1.05, indicating submaximal effort, were excluded from the analysis, as such values are associated with poor reproducibility of peak VO_2 in multicenter trials.[14] Demographics, clinical characteristics, and laboratory results were retrieved from electronic hospital records.

The study was approved by the Koşuyolu High Specialization Training and Research Hospital Ethics Committee (Approval Number: 2025/12/1199, Date: 22.07.2025), and conducted in accordance with the Declaration of Helsinki. All patients provided informed consent for the procedures and data collection.

Clinical Data Collection

Comprehensive clinical evaluation included documentation of cardiovascular risk factors, comorbidities, medication history, and functional status. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Smoking history, diabetes mellitus, hypertension, hyperlipidemia, and previous cardiovascular interventions were systematically recorded. Heart failure etiology was classified as ischemic or non-ischemic based on clinical history, imaging findings, and coronary angiography when available.

Echocardiographic Assessment

Transthoracic echocardiography was performed by a single experienced cardiology echocardiographer using EPIQ CVx v9.0.5 with an X5-1 transducer (Philips Medical Systems, Andover, MA, USA) to minimize inter-observer variability. LVEF was measured using the biplane method of disk summation (modified Simpson's rule). The left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), and left atrial dimension were measured in the parasternal long-axis view.

Doppler echocardiography was performed in accordance with current American Society of Echocardiography guidelines.[15] Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode imaging in the apical four-chamber view. The severity of tricuspid regurgitation was assessed using color Doppler and graded as mild, moderate, or severe. Echocardiographic estimation of pulmonary artery systolic pressure (PASP) was determined by summing the peak velocity of tricuspid regurgitation (calculated using the Bernoulli equation) and the estimated central venous pressure, derived from inferior vena cava diameter and collapsibility.

Cardiopulmonary Exercise Testing

Maximal CPET was performed using a continuous, incremental treadmill protocol based on individualized ramp design, conducted on a JAEGER Vyntus CPX system (Vyaire Medical, Germany). Oxygen uptake was measured breath-by-breath using an automated system, with data collected at rest, during graded exercise, and throughout a two-minute recovery period.

Exercise capacity was expressed in metabolic equivalents (METs), calculated by dividing the VO_2max value by 3.5 mL/kg/min. VO_2, VCO_2, and respiratory exchange ratio (RER = VCO_2/VO_2) were computed and averaged every 10 seconds. Maximal effort was defined as achieving an RER greater than 1.05. Peak VO_2 was defined as the highest 10-second averaged VO_2 during the final stage of exercise testing. Blood pressure was measured before testing, every three minutes during exercise, and during the recovery phase.

Right Heart Catheterization

Right heart catheterization was performed using a 7Fr balloon-tipped Swan–Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) or a pigtail catheter introduced through the right jugular or femoral vein. Hemodynamic measurements included right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure. Cardiac output was estimated using the indirect Fick method. Stroke volume was calculated as cardiac output divided by heart rate. Systemic vascular resistance was calculated using standard hemodynamic formulas.

All pressure tracings were visually inspected for physiological accuracy, and end-expiratory pressure values were recorded to minimize respiratory variation effects. Measurements were obtained after hemodynamic stabilization and averaged over multiple cardiac cycles.

Laboratory Assessment

Blood samples were obtained in the fasting state within two weeks of hemodynamic evaluation. Laboratory parameters included complete blood count (hemoglobin, hematocrit), comprehensive metabolic panel (creatinine, electrolytes), lipid profile (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides), liver function tests, thyroid-stimulating hormone (TSH), and B-type natriuretic peptide (BNP) or N-terminal pro-BNP, when available.

Clinical Outcomes

The primary outcomes of interest were: (1) LVAD implantation, (2) heart transplantation, (3) all-cause mortality, and (4) a composite outcome defined as the occurrence of any of the above events. Patients were followed from the date of initial evaluation until the occurrence of an endpoint, loss to follow-up, or study closure. Follow-up data were obtained through electronic medical records, outpatient clinic visits, and telephone contact when necessary.

Statistical Analysis

Baseline characteristics were reported as means ± standard deviations (SD) for continuous variables and as counts with percentages for categorical variables. Comparisons between men and women were made using t-tests or chi-square tests, as appropriate.

To address potential confounding by indication and achieve balance in baseline characteristics between men and women, we employed IPW using propensity scores. The propensity score represented the probability of being female conditional on observed baseline covariates. We compared propensity scores derived from logistic regression and gradient boosting machine (GBM) algorithms based on their ability to balance clinical covariates between men and women, assessed by standardized mean differences after weighting. The logistic regression-based IPW was selected because it provided superior covariate balance and more stable weights. The propensity score model included cardiovascular risk factors, comorbidities, demographic variables,

laboratory parameters, echocardiographic measurements, hemodynamic variables, and exercise testing results. Variables were selected based on: (1) differences observed between groups in unadjusted analyses, (2) clinical importance based on expert judgment, and (3) established associations with heart failure outcomes in the literature. IPWs were calculated as 1/propensity score for women and 1/(1–propensity score) for men. Extreme weights were trimmed at the 1st and 99th percentiles to stabilize estimates, resulting in 49 patients being trimmed. Standardized mean differences were used to evaluate the balance of patient characteristics following weighting, with values < 0.2 considered indicative of adequate balance.

Cox proportional hazards regression models were employed to assess the association between sex and clinical outcomes. Using the IPWs, weighted Cox proportional hazards models were fitted. To implement a doubly robust approach, the same covariates used in propensity score estimation were included in the multivariable model, providing protection against misspecification of either the propensity score model or the outcome model. Additionally, a weighted ridge-penalized Cox model was fitted, with all covariates except the sex variable subject to penalization, allowing for regularized coefficient estimation while preserving the unpenalized effect of sex. A traditional multivariable Cox model without weighting was also fitted for comparison.

The proportional hazards assumption was tested using Schoenfeld residuals and was not found to be violated for the primary analyses. Hazard ratios with 95% confidence intervals were calculated for all models. Due to the retrospective design, no a priori sample size calculation was performed; however, post hoc power analyses for LVAD implantation and the composite outcome were conducted and are provided in the Appendix 1.

Overall, 7.9% of the dataset contained missing values. Missing data were assumed to be missing completely at random (MCAR) and were imputed using the missForest algorithm.

The Kaplan-Meier method was used to visualize the cumulative incidence of outcomes, including the composite endpoint and LVAD implantation separately, stratified by sex. Comparisons were made using the log-rank test. Time-to-event analyses were conducted with patients censored at the time of last follow-up or study closure.

All statistical analyses were performed using R 4.4.1 software (R Foundation for Statistical Computing, Vienna, Austria) with the following packages: "WeightIt," "survey," "survival," "survminer," "ggplot2," "cobalt," "tableone," "naniar," "missForest," and "powerSurvEpi." A two-tailed P value <0.05 was considered statistically significant.

Results

A total of 522 patients diagnosed with advanced HF were included in the study. Of the participants, 85.2% were male (n = 445) and 14.8% were female (n = 77). When evaluated by sex, significant differences were identified in demographic characteristics, body composition, heart failure etiology, comorbidities, hemodynamic parameters, and laboratory findings (Table 1).

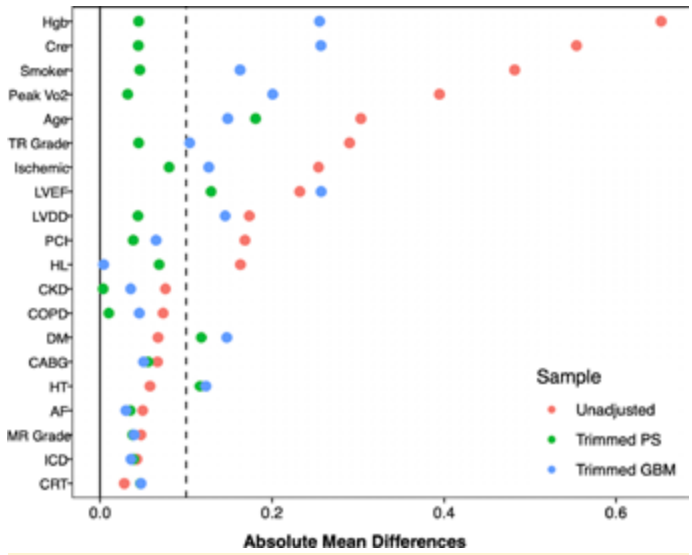

Figure 1. Covariate balance assessment before and after propensity score weighting. Standardized mean differences (SMD) for key covariates comparing patients by sex with advanced heart failure. Red dots represent unadjusted differences showing substantial imbalances between groups. Green dots show results after propensity score weighting (trimmed PS), and blue dots show results after gradient boosting machine weighting (trimmed GBM). The solid vertical line at 0.0 represents perfect balance, while the dashed vertical line at 0.2 indicates the threshold for adequate balance. All covariates achieved SMD < 0.2 after propensity score weighting, demonstrating successful covariate balance and supporting the validity of causal inference analyses.

Hgb, Hemoglobin; Cre, Creatinine; LVEF, Left ventricular ejection fraction; LVDD, Left ventricular diastolic dysfunction; PCI, Percutaneous coronary intervention; HL, Hyperlipidemia; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; HT, Hypertension; AF, Atrial fibrillation; ICD, Implantable cardioverter defibrillator; CRT, Cardiac resynchronization therapy.

Male patients were older than female patients (median age: 54.0 [interquartile range [IQR]: 44.0–59.0] vs. 49.5 [IQR: 41.0–58.0]; P = 0.025), taller (172 vs. 158 cm; P < 0.001), and heavier (80 vs. 69.5 kg; P < 0.001), but there was no difference in BMI (P = 0.155). Ischemic etiology (49.9% vs. 22.7%; P < 0.001), history of PCI (39.0% vs. 22.1%; P = 0.004), hyperlipidemia (42.4% vs. 26.0%; P = 0.007), and smoking (78.0% vs. 29.9%; P < 0.001) were more frequent in men.

Echocardiographic evaluation revealed significantly larger left ventricular and atrial dimensions in men: LVEDD (6.90 vs. 6.05 cm; P < 0.001), LVESD (6.00 vs. 5.40 cm; P < 0.001), and left atrium (LA) (4.70 vs. 4.25 cm; P < 0.001). LVEF values were similar (P = 0.066). Tricuspid regurgitation was more prominent in women (P < 0.001) (Table 2).

Invasive hemodynamic measurements showed higher stroke volume (41.0 vs. 36.8 mL; P = 0.001) and cardiac output (3.40 vs. 2.90 L/min; P < 0.001) in men, while women had higher systemic vascular resistance (25.90 vs. 22.05 Wood units; P < 0.001) and aortic systolic pressure (120 vs. 112 mmHg; P = 0.009) (Table 2).

Table 1. Baseline clinical characteristics, laboratory assessment and outcomes stratified by sex

Variables	Overall	Male	Female	*P*
Demographic and follow-up data				
Follow-up (days)	864.5 (517.25–1461.0)	830.0 (507.0–1482.0)	1018.0 (529.0–1281.0)	0.328
Age (years)	53.0 (44.0–59.0)	54.0 (44.0–59.0)	49.50 (41.0–58.0)	0.0254
Height (cm)	170.0 (165.0–176.0)	172.0 (168.0–178.0)	158.0 (153.75–162.0)	<0.001
Weight (kg)	79.0 (70.0–90.0)	80.0 (71.0–91.0)	69.50 (59.0–80.0)	<0.001
BMI (kg/m²)	27.0 (24.0–30.0)	27.0 (24.0–30.0)	28.0 (23.75–33.0)	0.155
Comorbidities				
Ischemic	231 (45.8)	214 (49.9)	17 (22.7)	<0.001
PCI	191 (36.5)	174 (39)	17 (22.1)	0.004
CABG	57 (10.9)	53 (11.9)	4 (5.2)	0.082
HT	185 (35.4)	154 (34.5)	31 (40.3)	0.331
DM	173 (33.1)	152 (34.1)	21 (27.3)	0.241
AF	97 (18.5)	86 (19.3)	11 (14.3)	0.298
HL	209 (40)	189 (42.4)	20 (26)	0.007
CKD	102 (19.5)	92 (20.6)	10 (13)	0.118
CVD	42 (8)	38 (8.5)	4 (5.2)	0.321
PAD	26 (5)	24 (5.4)	2 (2.6)	0.299
Smoker	371 (70.9)	348 (78)	23 (29.9)	<0.001
COPD	60 (11.5)	56 (12.6)	4 (5.2)	0.061
Laboratory parameters				
Urea (mg/dL)	43.0 (34.35–55.95)	43.8 (35.10–56.95)	40.0 (31.1–48.3)	0.00672
Cre (mg/dL)	1.0 (0.83–1.2)	1.03 (0.86–1.23)	0.81 (0.70–0.96)	<0.001
AST (U/L)	20.6 (15.6–27.2)	20.95 (15.70–27.33)	19.2 (14.8–26.6)	0.336
ALT (U/L)	20.65 (14.22–30.95)	21.1 (14.90–32.1)	16.7 (13.0–25.3)	0.00448
Total Bil (mg/dL)	0.75 (0.5–1.2)	0.79 (0.52–1.28)	0.6 (0.41–0.94)	0.00154
Direct Bil (mg/dL)	0.3 (0.19–0.54)	0.32 (0.2–0.55)	0.26 (0.17–0.36)	0.0159
Pro-BNP (pg/mL)	2232.0 (1000.0–4411.0)	2236.5 (998.0–4384.75)	2022.0 (1081.0–4835.0)	0.659
Trig (mg/dL)	122.0 (88.05–172.3)	121.15 (86.8–175.07)	126.25 (97.43–160.57)	0.715
LDL (mg/dL)	92.3 (65.3–121.83)	92.06 (64.98–121.76)	93.59 (78.31–122.3)	0.692
HDL (mg/dL)	38.8 (32.02–48.32)	38.2 (31.95–47.7)	43.0 (35.8–51.45)	0.0305
Sodium (mEq/L)	138.0 (136.0–140.0)	138.0 (136.0–140.0)	139.0 (137.0–141.0)	0.0381
Potassium (mEq/L)	4.49 (0.52)	4.48 (0.52)	4.55 (0.48)	0.275
Total prot (g/dL)	71.0 (67.0–75.0)	72.0 (67.0–75.0)	71.0 (68.0–75.0)	0.813
Alb (g/dL)	44.0 (41.0–47.0)	44.0 (40.0–47.0)	44.0 (41.75–46.0)	0.914
LDH (U/L)	216.0 (185.0–265.0)	213.0 (185.0–263.0)	221.0 (195.0–276.5)	0.0949
GFR (mL/min/1.73m²)	82.0 (66.0–98.0)	82.0 (66.0–98.0)	84.78 (69.0–103.0)	0.393
TSH (mIU/L)	1.92 (1.23–3.09)	1.84 (1.22–2.98)	2.45 (1.55–4.19)	0.0203
INR	1.18 (1.06–1.40)	1.19 (1.06–1.38)	1.17 (1.06–1.43)	0.84
Hgb (g/dL)	13.9 (12.5–15.1)	14.1 (12.7–15.3)	12.7 (11.8–13.9)	<0.001
Hct (%)	42.66 (5.54)	43.11 (5.52)	40.11 (4.93)	<0.001
PLT (×10³/μL)	249.0 (205.0–291.0)	245.5 (205.0–288.0)	260.0 (205.0–328.0)	0.137
Neu (×10³/μL)	5.07 (4.04–6.26)	5.07 (4.10–6.27)	5.12 (3.62–6.21)	0.396
Lym (×10³/μL)	1.93 (1.42–2.52)	1.92 (1.41–2.5)	1.94 (1.53–2.53)	0.725
Devices and outcomes				
ICD	128 (24.5)	112 (25.1)	16 (20.8)	0.414
CRT	33 (6.3)	30 (6.7)	3 (3.9)	0.346
LVAD	66 (12.6)	60 (13.5)	6 (7.8)	0.165
TX	4 (0.8)	3 (0.7)	1 (1.3)	0.473
Death	113 (21.6)	97 (21.8)	16 (20.8)	0.841

AF, Atrial fibrillation; Alb, Albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; Bil, Bilirubin; CABG, Coronary artery bypass grafting; CKD, Chronic kidney disease; Cre, Creatinine; COPD, Chronic obstructive pulmonary disease; CRT, Cardiac resynchronization therapy; CVD, Cerebrovascular disease; DM, Diabetes mellitus; GFR, Glomerular filtration rate; HL, Hyperlipidemia; Hct, Hematocrit; Hgb, Hemoglobin; HT, Hypertension; ICD, Implantable cardioverter defibrillator; INR, International normalized ratio; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; Lym, Lymphocyte count; LVAD, Left ventricular assist device; Neu, Neutrophil count; PCI, Percutaneous coronary intervention; PLT, Platelet count; Pro-BNP, Pro-B-type natriuretic peptide; TX, Heart transplantation; Trig, Triglycerides; TSH, Thyroid-stimulating hormone; WBC, White blood cell count; LDH, Lactate dehydrogenase.

Table 2. Echocardiographic assessment, invasive hemodynamic parameters and Cardiopulmonary Exercise Testing parameters stratified by sex

Variable	Overall	Male	Female	*P*
Echocardiography parameters				
LVEF (%)	22.0 (20.0–25.0)	22.0 (20.0–25.0)	24.0 (20.0–25.0)	0.0656
LVEDD (mm)	6.7 (6.2–7.4)	6.9 (6.3–7.4)	6.05 (5.8–6.62)	<0.001
LVESD (mm)	5.9 (5.4–6.6)	6.0 (5.5–6.6)	5.4 (4.8–6.0)	<0.001
LA (mm)	4.6 (4.3–5.0)	4.7 (4.34–5.0)	4.25 (3.98–4.6)	<0.001
LVDD				0.027
0		1 (0.2)	0 (0)	
1		86 (20.2)	14 (20.3)	
2		82 (19.3)	24 (34.8)	
3		256 (60.2)	31 (44.)	
Echo-PASP (mm Hg)	40.0 (30.0–53.0)	40.0 (30.0–55.0)	36.0 (25.0–50.0)	0.341
TAPSE (mm)	1.6 (1.36–2.0)	1.62 (1.36–2.0)	1.60 (1.33–2.0)	0.7
IVC (mm)	1.9 (1.6–2.2)	1.90 (1.60–2.20)	1.80 (1.50–2.10)	0.0346
Plethorea (0/1)	132 (27.0)	108 (25.9)	24 (33.8)	
MR grade				0.960
0		1 (0.2)	0 (0)	
1		156 (36.1)	26 (36.1)	
2		181 (41.9)	29 (40.3)	
3		94 (21.8)	17 (23.6)	
TR grade				<0.001
1		246 (55.8)	40 (52.6)	
2		141 (32)	13 (17.1)	
3		54 (12.2)	22 (28.9)	
4		0 (0)	1 (1.3)	
AVR (0/1)	9 (1.7)	8 (1.8)	1 (1.3)	0.757
MVR (0/1)	19 (3.7)	15 (3.4)	4 (5.3)	0.428
Invasive hemodynamic parameters				
Aort Sys (mmHg)	113.0 (100.0–129.5)	112.0 (99.0–128.0)	12.0 (110.0–142.0)	0.00921
Aort Dia (mmHg)	70.0 (62.0–79.0)	70.0 (62.0–78.0)	71.0 (67.0–84.0)	0.0842
Aort Mean (mmHg)	86.0 (78.0–96.0)	85.0 (76.25–95.0)	88.0 (82.0–104.0)	0.0099
LVEDP (mmHg)	24.0 (15.0–28.0)	24.0 (16.0–28.0)	22.0 (12.0–27.0)	0.0746
Cath_PASP (mmHg)	50.0 (35.0–63.0)	50.0 (35.0–64.0)	45.0 (36.0–59.0)	0.155
Cath_PADP (mmHg)	23.0 (14.0–29.0)	23.0 (14.0–30.0)	20.0 (13.0–28.0)	0.0684
Cath_PAMP (mmHg)	33.0 (22.0–42.0)	34.0 (23.0–42.0)	31.0 (21.0–40.0)	0.149
RVSP (mmHg)	48.0 (36.0–62.0)	49.0 (36.0–62.0)	45.0 (35.0–58.0)	0.137
RAP (mmHg)	8.0 (5.0–13.5)	8.0 (5.0–13.0)	8.0 (6.0–14.0)	0.425
TPG (mmHg)	9.0 (5.0–14.0)	8.0 (5.0–14.0)	9.0 (5.0–13.0)	0.998
TSG (mmHg)	76.0 (66.0–87.0)	75.0 (66.0–86.0)	80.0 (72.0–90.0)	0.0216
SV (mL)	40.02 (32.31–51.0)	41.0 (33.2–52.0)	36.8 (28.25–43.85)	0.00141
SVI (mL/m²)	20.8 (17.12–25.66)	21.0 (17.5–25.85)	19.0 (16.15–24.6)	0.204
CO (L/min)	3.32 (2.80–4.12)	3.4 (2.84–4.2)	2.9 (2.44–3.62)	<0.001
CI (L/min/m²)	1.7 (1.5–2.06)	1.7 (1.5–2.07)	1.64 (1.39–2.01)	0.23
PVR (Wood units)	2.45 (1.36–4.3)	2.38 (1.33–4.29)	2.98 (1.75–4.32)	0.211
SVR (Wood units)	22.8 (18.96–27.0)	22.05 (18.0–26.4)	25.9 (22.27–32.15)	<0.001
RVSWI (g·m/m²)	6.55 (4.68–9.12)	6.7 (4.79–9.2)	5.80 (4.0–8.0)	0.0349

Table 2 (cont). Echocardiographic assessment, invasive hemodynamic parameters and Cardiopulmonary Exercise Testing parameters stratified by sex

Variables	Overall	Male	Female	*P*
Cardiopulmonary exercise test				
Duration (minutes)	6.58 (4.18–9.3)	7.02 (4.39–9.32)	5.57 (2.56–8.52)	0.0178
Load (watts)	90.0 (45.0–140.0)	100.0 (50.0–150.0)	65.0 (26.25–115.0)	<0.001
VE (L/min)	46.0 (38.0–54.0)	48.0 (41.0–56.0)	35.0 (30.0–40.75)	<0.001
VO_2 (mL/min)	1072.0 (801.5–1370.0)	1111.0 (834.0–1445.0)	850.5 (660.0–1104.25)	<0.001
Peak VO_2 (mL/min/kg)	13.6 (10.4–16.95)	13.9 (10.6–17.1)	12.05 (9.43–14.7)	0.00157
Pred percent (%)	29.0 (25.13–33.88)	29.5 (26.17–34.52)	23.75 (19.50–28.88)	<0.001
RER (unitless)	1.03 (0.98–1.08)	1.03 (0.98–1.08)	1.03 (0.98–1.09)	0.905
METS (unitless)	3.9 (3.0–4.8)	4.0 (3.0–4.9)	3.45 (2.7–4.2)	0.00195
HR (bpm)	116.99 (25.6)	116.95 (26.06)	117.24 (23.14)	0.928
HRR (bpm)	53.0 (39.75–70.25)	53.0 (39.0–70.0)	55.0 (41.0–73.0)	0.605
Peak Sat (%)	98.0 (95.0–99.0)	98.0 (95.0–99.0)	98.0 (94.0–98.0)	0.124
$VECO_2$ (unitless)	38.04 (31.5–52.34)	37.95 (31.38–51.1)	38.52 (33.09–81.0)	0.236
VO_2WS (mL/min/kg)	3.6 (2.02–5.27)	3.66 (2.14–5.2)	2.93 (1.46–6.87)	0.633
HRO_2WS (bpm)	2.21 (0.99–3.3)	2.21 (0.99–3.3)	2.13 (1.07–3.24)	0.842
MECKI score	15.36 (5.68–31.83)	18.42 (7.28–32.12)	7.94 (4.97–13.33)	0.231

Aort Sys/Dia/Mean, aortic systolic/diastolic/mean pressure; AVR, Aortic valve replacement; Bil, Bilirubin; Cath_PASP/PADP/PAMP, Catheter-derived pulmonary artery systolic/diastolic/mean pressure; CI, Cardiac index; CO, Cardiac output; Echo-PASP, Echocardiographic pulmonary artery systolic pressure; HR, Heart rate; HRO_2WS, Heart rate at anaerobic threshold; HRR, Heart rate reserve; IVC, Inferior vena cava diameter; LA, Left atrial dimension; LVDD, Left ventricular diastolic dysfunction (0, normal, 1, mild, 2, moderate, 3, severe); LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic dimension; LVEDP, Left ventricular end-diastolic pressure; LVESD, Left ventricular end-systolic dimension; MECKI, Metabolic Exercise Test data combined with Cardiac and Kidney Indexes; METS, Metabolic equivalents; MR, Mitral regurgitation (0, none, 1, mild, 2, moderate, 3, severe); MVR, Mitral valve replacement; Peak Sat, Peak oxygen saturation; Peak VO_2, Peak oxygen consumption normalized to body weight; Pred Percent, Predicted percentage of normal peak VO_2; PVR, Pulmonary vascular resistance; RAP, Right atrial pressure; RER, Respiratory exchange ratio; RVSP, Right ventricular systolic pressure; RVSWI, Right ventricular stroke work index; SV, Stroke volume; SVI, Stroke volume index; SVR, Systemic vascular resistance; TAPSE, Tricuspid annular plane systolic excursion; TPG, Transpulmonary gradient; TR, Tricuspid regurgitation (1, mild, 2, moderate, 3, severe, 4, torrential); TSG, Total systemic gradient; VE, Minute ventilation; $VECO_2$, Ventilatory equivalent for carbon dioxide; VO_2, Absolute oxygen consumption; VO_2WS, Oxygen consumption at anaerobic threshold.

Laboratory evaluation demonstrated significantly higher hemoglobin (14.1 vs. 12.7 g/dL; P < 0.001), hematocrit (43.1% vs. 40.1%; P < 0.001), and creatinine (1.03 vs. 0.81 mg/dL; P < 0.001) levels in men. Women had higher HDL cholesterol (43.0 vs. 38.2 mg/dL; P = 0.031) and TSH (2.45 vs. 1.84 mIU/L; P = 0.020) levels (Table 1).

Regarding functional capacity, men exhibited higher values across all parameters compared to women: exercise duration (7.02 vs. 5.57 minutes; P = 0.018), maximum workload (100 vs. 65 watts; P < 0.001), peak VO_2 (13.9 vs. 12.05 mL/min/kg; P = 0.002), and METs value (4.0 vs. 3.45; P = 0.002) (Table 2).

To isolate the independent effect of sex on clinical outcomes, IPW was applied. The propensity score model was comprehensively constructed to include demographic data, comorbidities, laboratory findings, and echocardiographic and hemodynamic parameters. After weighting, standardized mean difference (SMD) values < 0.2 were achieved for all covariates, indicating successful balancing between female and male groups (Appendix 2). Figure 1 demonstrates the elimination of significant imbalances present before weighting (red dots) and the achievement of excellent balance after IPW (green dots).

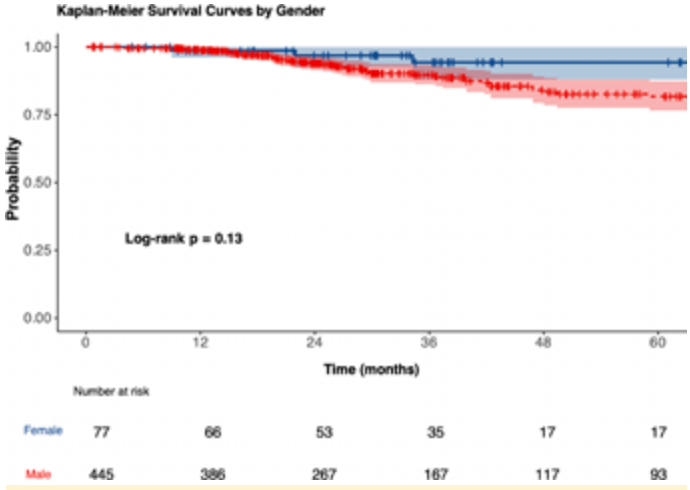

Figure 2. Kaplan-Meier curves for left ventricular assist device-free (LVAD-free) survival by sex. Kaplan-Meier survival curves showing the cumulative probability of remaining free from left ventricular assist device (LVAD) implantation over a 60-month follow-up period, stratified by sex. Female patients demonstrated a consistently lower risk of LVAD implantation compared to male patients, although the difference did not reach statistical significance (log-rank P = 0.13). The number at risk at each time point is displayed below the plot.

Table 3. Cox proportional hazards models for LVAD implantation risk by sex

Model	Info	Gender HR	*P*	Concordance	LR df	LR *P* value
1	Weighted and adjusted (double robust)	0.125 (0.039–0.398)	<0.001	0.812	21	<0.001
2	Unweighted and adjusted	0.226 (0.082–0.614)	0.004	0.804	21	<0.001
3	Unweighted univariate	0.532 (0.082–0.614)	0.141	0.538	1	0.10
4	Weighted univariate	0.196 (0.064–0.591)	0.004	0.556	1	0.005
5	Weighted and penalized	0.128 (0.040–0.400)	<0.001	0.812	20.45	<0.001

HR, Hazard ratio; LVAD, Left ventricular assist device; LR df, Degrees of freedom for likelihood ratio test; LR p value, P-value for overall model significance via likelihood ratio test.

Table 4. Cox proportional hazards models for composite outcome by sex

Model	Info	Gender HR	*P* value	Concordance	LR df	LR *P* value
1	Weighted and adjusted (double robust)	0.527 (0.259–1.069)	0.076	0.716	21	<0.001
2	Unweighted and adjusted	0.501 (0.288–0.872)	0.014	0.707	21	<0.001
3	Unweighted univariate	0.759 (0.475–1.212)	0.248	0.515	1	0.2
4	Weighted univariate	0.604 (0.291–1.252	0.175	0.53	1	0.07
5	Weighted and penalized	0.532 (0.263–1.073)	0.078	0.717	20	<0.001

HR, Hazard ratio; LR df, Degrees of freedom for likelihood ratio test; LR p value, P-value for overall model significance via likelihood ratio test.

Table 5. Cox proportional hazards models for all-cause mortality risk by sex

Model	Info	Gender HR	*P* value	Concordance	LR df	LR *P* value
1	Weighted and adjusted (double robust)	0.75 (0.366–1.533)	0.43	0.719	21	<0.001
2	Unweighted and adjusted	0.69 (0.364–1.293)	0.25	0.707	21	<0.001
3	Unweighted univariate	0.92 (0.544–1.571)	0.77	0.504	1	0.8
4	Weighted univariate	0.82 (0.370–1.800)	0.62	0.52	1	0.5
5	Weighted and penalized	0.75 (0.368–1.536)	0.43	0.72	21	<0.001

Model Descriptions: ●Model 1 (Weighted and adjusted – double robust): Inverse probability weighted Cox model with all covariates included, providing protection against misspecification of either propensity score or outcome model. ●Model 2 (Unweighted and adjusted): Traditional multivariable Cox model including all baseline covariates without propensity score weighting. ●Model 3 (Unweighted univariate): Simple univariate Cox model with sex as the only predictor. ●Model 4 (Weighted univariate): Inverse probability weighted Cox model with sex as the only predictor. ●Model 5 (Weighted and penalized): Ridge penalized Cox model with inverse probability weighting, where all covariates except sex were subject to L2 regularization. Statistical Measures: HR, hazard ratio for female vs. male sex; P value, statistical significance of the sex coefficient; Concordance, C-index measuring model's discriminative ability (0.5 = no discrimination, 1.0 = perfect discrimination); LR df, Degrees of freedom for likelihood ratio test; LR p value, P-value for overall model significance via likelihood ratio test.

The median follow-up period was 864 days (approximately 28.8 months). During this period, 66 patients (12.6%) underwent LVAD implantation, 113 patients (21.6%) died, and 4 patients (0.8%) received heart transplantation. The composite outcome (LVAD, transplantation, or death) occurred in a total of 161 patients (30.8%). Although female patients had a lower absolute incidence of these events, the differences were not statistically significant.

A notable finding was the consistent association between female sex and lower observed LVAD implantation rates. Kaplan-Meier analyses showed better LVAD-free survival in female patients, although this difference did not reach statistical significance (Figure 2, log-rank P = 0.13). In the IPW-weighted, doubly robust model, LVAD requirement was lower in women (hazard ratio [HR]: 0.13; P < 0.001). This finding demonstrated consistency across all analyses, including penalized and traditional multivariable Cox models (Table 3).

In multivariable Cox regression analysis, female sex was associated with a lower risk for the composite outcome (HR: 0.50; 95% confidence interval [CI]: 0.29–0.87; P = 0.015). However, after IPW weighting, this association weakened and approached the significance threshold (HR: 0.53; 95% CI: 0.26–1.06; P = 0.076) (Table 4). Kaplan-Meier curves also showed a trend toward better event-free survival in female patients, but this difference was not significant (Figure 3, log-rank P = 0.25).

No significant difference was found between sexes regarding all-cause mortality. IPW-adjusted models showed a slightly lower risk in women (e.g., doubly robust model: HR: 0.75; P = 0.43), but this difference was not statistically significant (Table 5). Due to the very low number of heart transplantation events (n = 4), we did not analyze transplantation separately and instead focused on LVAD implantation and the composite outcome (LVAD, transplantation, or death). Female patients appeared to remain stable for longer periods and required less invasive treatment. Risk tables supported this trend. The protective effect was not observed for outcomes other than LVAD (mortality and transplantation).

In conclusion, when all measurable clinical and hemodynamic variables were balanced, female sex did not have an independent effect on mortality in advanced heart failure. However, female patients had lower observed LVAD implantation rates; this

association is hypothesis-generating and should not be interpreted as evidence of causal clinical superiority.

Figure 4 provides a visual summary of the observed lower LVAD implantation rates in female patients, while showing no significant effect on mortality or composite outcomes. The consistent results obtained across five different Cox regression models reinforce the validity and reliability of these findings (Appendix 3).

Discussion

This study evaluated the effect of biological sex on clinical outcomes in patients with advanced HF using IPW. After achieving excellent covariate balance across 522 patients (all SMD < 0.2), female sex was associated with lower observed LVAD implantation rates; however, this represents an observational association and should not be interpreted as evidence of clinical superiority. Alternative explanations, including referral bias, provider decision-making, and systemic barriers, may contribute to this finding.

These findings are consistent with the growing literature suggesting sex-specific pathophysiological mechanisms.[6,8] Women demonstrate enhanced lipid metabolism and fatty acid utilization, which may contribute to more efficient myocardial energy use under stress.[6] In contrast, men exhibit more prominent neuroinflammatory activation and maladaptive cytokine signaling, potentially accelerating progression toward mechanical circulatory support.[6] Additionally, estrogen's beneficial effects on endothelial function and calcium handling,[8,16] along with greater parasympathetic tone and a predisposition to HFpEF phenotypes, may contribute to a more favorable hemodynamic trajectory in women.[5,16]

The lower prevalence of ischemic etiology among women (22.7% vs. 49.9%) and more preserved ventricular-arterial coupling offer further physiological explanations.[5,17] The association between female sex and lower LVAD utilization observed in this study is hypothesis-generating and should not be overinterpreted as causal. In unadjusted analyses, female sex was associated with a lower risk of the composite outcome (HR: 0.50; P = 0.015), but this effect attenuated after IPW adjustment (HR: 0.53; P = 0.076), indicating that the lower composite event rate was primarily driven by lower LVAD utilization rather than differences in mortality. The small number of female patients (n = 77, 14.8%) limits statistical power and precision, as reflected in the attenuation of the composite outcome after IPW adjustment (HR: 0.53, P = 0.076), highlighting the potential for type II error.

Interestingly, despite lower use of LVADs, women showed comparable long-term survival to men. This finding mirrors that of Gruen et al.,[10] who reported higher complication rates—including bleeding, stroke, and device malfunction—in female LVAD recipients. Similarly, Hsich et al.(18) found that women on transplant waitlists, particularly those with UNOS 1A/1B status, had higher mortality risk, suggesting that women may progress more gradually, potentially reaching similar clinical stages as men. Studies by Rubinstein,[19] Rose,[11] and Steinberg[20] also indicate that systemic barriers in referral and decision-making may contribute to sex-based disparities in access to advanced therapies. Thus, the lower LVAD implantation rate in women may reflect a combination of biological differences, disease trajectory, and systemic factors, rather than inherent clinical advantage. Further supporting this, Diaz-Arocutipa et al.[21] reported that women in acute cardiogenic shock were 23% less likely to receive mechanical circulatory support and experienced higher mortality when devices were implanted—highlighting context-specific sex differences in pathophysiologic response.

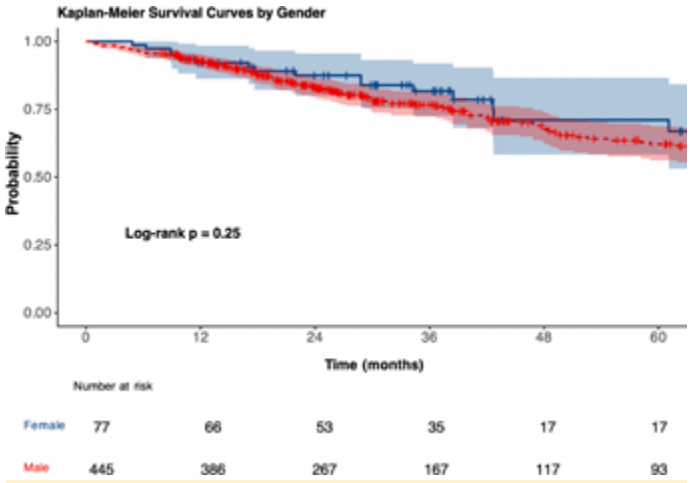

Figure 3. Kaplan-Meier curves for freedom from composite outcome (LVAD, transplantation, or death) by sex. Kaplan-Meier curves depicting the probability of remaining free from the composite outcome of left ventricular assist device (LVAD) implantation, heart transplantation, or all-cause death over a 60-month follow-up period, stratified by sex. Although female patients exhibited a trend toward better event-free survival, the difference was not statistically significant (log-rank P = 0.25). Risk tables display the number of patients at risk in each group at specified time points.

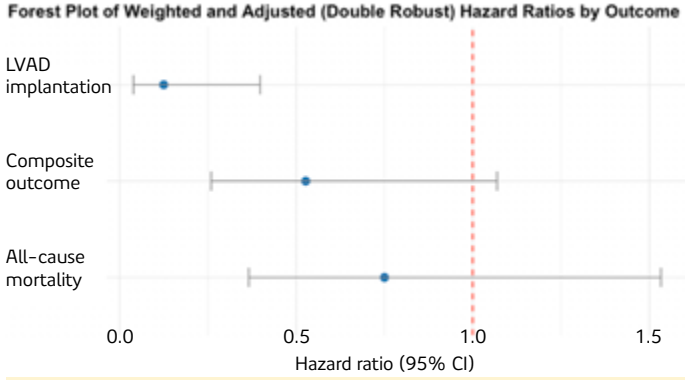

Figure 4. Forest plot of weighted and adjusted (doubly robust) hazard ratios by outcome. Forest plot of hazard ratios (HRs) for female sex in advanced heart failure. Shown are HRs (95% CI) for LVAD implantation, composite outcome (LVAD, heart transplantation, or death), and all-cause mortality, derived from IPW-weighted and doubly robust Cox models. HR < 1 indicates lower risk for female patients. Female sex was consistently associated with reduced LVAD implantation, with no significant effect on mortality or the composite outcome.

Pharmacological data also reinforce these disparities. In the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) trial, women achieved similar therapeutic benefit with lower doses of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, yet treatment strategies are still primarily based on male-centric dosing thresholds.[22] This cautious approach may partially explain the reduced LVAD use observed in women. The long-standing underrepresentation of women in cardiovascular trials further amplifies these issues.

Whitelaw et al.[23] found that in more than 70% of heart failure studies, women were underrepresented relative to disease prevalence, hindering the development of sex-specific clinical guidelines. By applying IPW methodology, this study helps bridge that gap, isolating the effect of sex on outcomes that previous studies lacked the statistical power to detect.[13]

The biological mechanisms underlying these differences likely reflect complex interactions among hormonal regulation, metabolic efficiency, and inflammatory tone. While enhanced lipid metabolism may help women maintain cardiac function, it may also create distinct anticoagulation-related complication profiles in the context of device therapy. Conversely, more active inflammatory profiles in men may influence their physiological response to LVAD implantation.[6,8,16]

Our methodological approach—incorporating five analytic models and rigorous IPW implementation—ensured consistent and robust findings, with all models showing a consistent association between female sex and lower observed LVAD implantation rates.[12,13] The single-center design enhanced internal validity, and standardized protocols helped reduce confounding.

Future studies should aim to clarify whether reduced LVAD use in women reflects undertreatment, differences in disease progression, or both. Integrating hormonal, genetic, and inflammatory parameters into risk stratification and device therapy selection may facilitate more personalized and equitable care. Aligning these strategies with current echocardiographic guidelines and evidence-based management frameworks will help optimize outcomes for all patients with advanced heart failure.

Limitations

Several constraints warrant consideration. The observational design limits causal inferences, while unmeasured confounders, including hormonal levels, genetic polymorphisms, and epigenetic modifications, influence outcomes. The low female representation (14.8%) constrains statistical power for subgroup analyses, and the single-center design limits external generalizability.

Selection bias in referral patterns also affects interpretation, as women receive advanced HF evaluation at different disease stages. Unmeasured socioeconomic factors—such as insurance coverage, social support, and caregiver availability—may differentially impact treatment decisions. Furthermore, the ethnically homogeneous Turkish population limits generalizability to other demographic groups with different genetic backgrounds and cardiovascular risk profiles. Evidence from other cohorts suggests that survival and HF progression may vary across ethnic groups; a Danish registry study comparing immigrants with native Danish patients with heart failure with reduced ejection fraction (HFrEF) found differences in comorbidities and outcomes that diminished after age- and sex-matching.[24] Therefore, the findings should be interpreted with caution when applied outside this setting. Our binary approach focused solely on biological sex, without evaluating gender identity, sexual orientation, or the broader gender spectrum. Limited LGBTI+ representation obscures health patterns relevant to these populations. Social determinants, including socioeconomic status, educational attainment, and cultural factors, were not systematically assessed. Additionally, patient-reported quality-of-life outcomes were not included in this study, which could have provided additional context for LVAD decision-making.

Conclusion

Female sex was associated with a significant reduction in LVAD requirement in advanced HF without demonstrating differences in overall mortality. These findings indicate that heart failure may progress through distinct pathophysiological pathways in women, highlighting the importance of developing tailored clinical evaluation approaches. For female patients, mechanical support decisions should incorporate comprehensive evaluations that account for unique complication profiles and pathophysiological differences, thereby contributing to improved patient safety and optimized clinical outcomes. Prospective multicenter studies are warranted to further validate these observations and guide clinical practice.

Ethics Committee Approval: Ethics committee approval was obtained from Koşuyolu High Specialization Training and Research Hospital (Approval Number: 2025/12/1199, Date: 22.07.2025).

Informed Consent: All patients provided informed consent for the procedures and data collection.

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Appendix 1

Post-hoc Power Analysis

Post-hoc power analysis was performed using the powerSurvEpi R package.[1] For LVAD implantation, based on 66 events among 522 patients and a hazard ratio of 0.125, the study had nearly 100% power to detect sex differences. For the composite outcome of LVAD implantation, heart transplantation, or death, based on 165 events and a hazard ratio of 0.527, the post-hoc power was 86.1%, indicating sufficient sensitivity to detect sex-related effects. Mortality alone had fewer events, resulting in lower power, which explains why sex differences were not statistically significant for this endpoint.

Missing Data Handling

Dataset and Missingness Overview

The analysis dataset comprised 522 patients with advanced heart failure and approximately 50 clinical, laboratory, echocardiographic, hemodynamic, and exercise testing variables. Overall, 7.9% of the data were missing. The pattern of missing data across patients and variables was visualized using a heatmap, where red indicates missing values and blue indicates observed values.

Assumption

Missing values were assumed to be missing completely at random (MCAR), based on the distribution and lack of systematic patterns in observed data.

Imputation Method

Imputation was performed using the MissForest algorithm (from the missForest R package). MissForest is a non-parametric method based on random forests that can handle mixed-type data (continuous and categorical variables) and accounts for non-linear relationships.[2] This approach iteratively predicts missing values for each variable using other observed variables until convergence is achieved.

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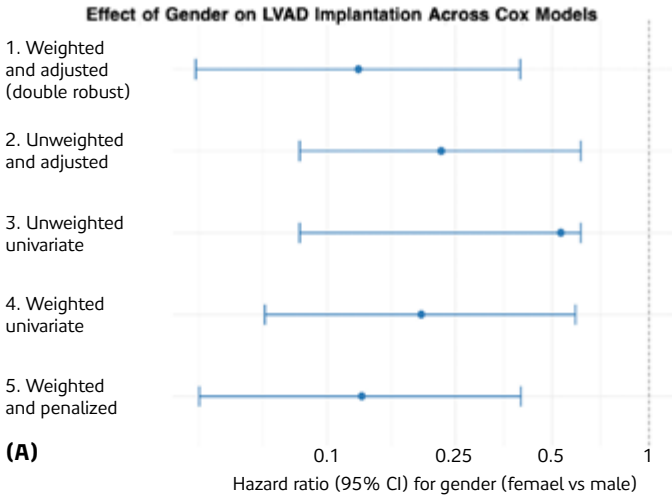
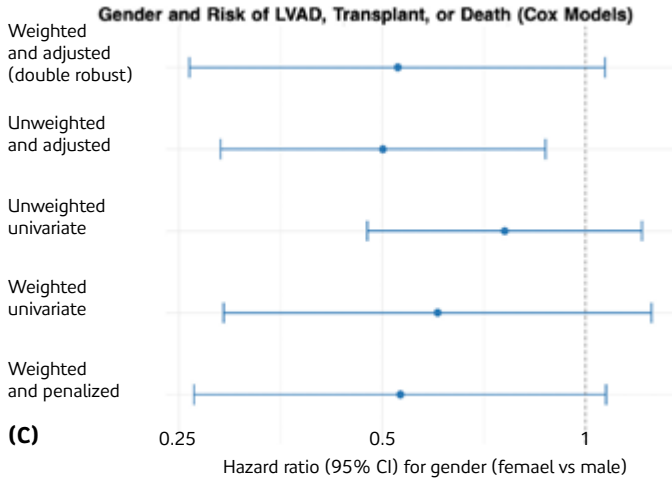
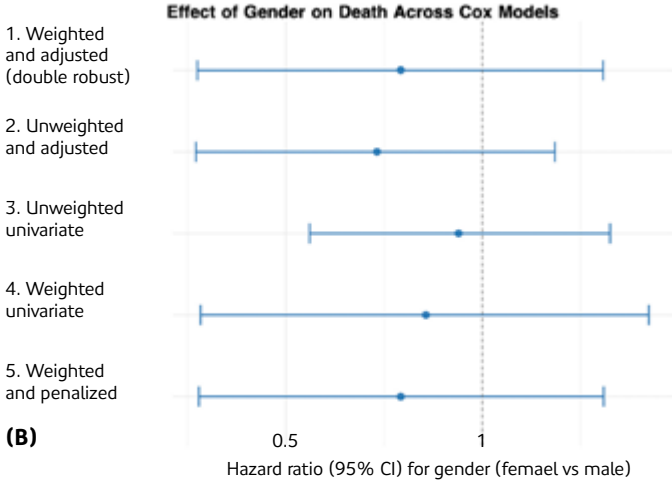
Appendix 2. Standardized mean differences (smd) of covariates by sex after inverse probability weighting

Covariate	Type	Adjusted SMD
Age	Continu-ous	-0.181
Ischemic	Binary	-0.080
LVEF	Continu-ous	0.129
MR grade	Continu-ous	-0.038
TR grade	Continu-ous	0.045
LVDD	Continu-ous	-0.044
Creatinine	Continu-ous	-0.045
Hemoglobin	Continu-ous	-0.045
Peak VO_2	Continu-ous	-0.032
Hypertension	Binary	0.116
Diabetes mellitus	Binary	-0.118
Atrial fibrillation	Binary	0.035
Hyperlipidemia	Binary	0.069
Chronic kidney disease	Binary	-0.004
Smoker	Binary	-0.046
COPD	Binary	-0.010
PCI	Binary	-0.039
CABG	Binary	-0.056
ICD	Binary	0.039
CRT	Binary	-0.047

LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; TR, Tricuspid regurgitation; LVDD, Left ventricular diastolic dysfunction; Peak VO_2, Peak oxygen consumption; COPD, Chronic obstructive pulmonary disease; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; ICD, Implantable cardioverter defibrillator; CRT, Cardiac resynchronization therapy. Interpretation: ●SMD < 0.1: Negligible difference (excellent balance). ●SMD 0.1–0.2: Small difference (adequate balance). ●SMD > 0.2: Meaningful imbalance (inadequate balance).







Appendix 3. Forest plot demonstrating the effect of female sex on clinical outcomes across different Cox regression models. Forest plot panels display hazard ratios (HRs) and 95% confidence intervals for the effect of female sex (vs. male) on (A) LVAD implantation, (B) all-cause mortality, and (C) the composite outcome (LVAD, transplantation, or death), evaluated across five Cox regression models: unweighted univariate, unweighted multivariable, weighted univariate, weighted multivariable (doubly robust), and weighted penalized models. Panel A illustrates a consistently significant inverse association between female sex and LVAD implantation risk across all models. Panel B shows no significant association between sex and mortality. Panel C suggests a nonsignificant trend toward lower composite event risk in female patients. These consistent findings across diverse modeling approaches reinforce the robustness of the observed sex-based difference in LVAD implantation.

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Detection of Hypokalemia, Hyponatremia, and Hyperkalemia in Heart Failure Patients Using Artificial Intelligence Techniques via Electrocardiography

Kalp Yetersizliği Hastalarında Yapay Zeka Teknikleri Kullanarak Elektrokardiyografi Aracılığıyla Hipokalemi, Hiponatremi ve Hiperkaleminin Tespiti

ABSTRACT

Objective: Detection and monitoring of electrolyte imbalances are essential for the appropriate treatment of many metabolic diseases. However, no reliable and noninvasive tool currently exists for such detection. Electrolyte disorders, particularly in heart failure patients, can lead to life-threatening situations, which may often develop as a result of medications used in routine treatment.

Method: In this study, we developed a deep learning model (DLM) using electrocardiography (ECG) to detect electrolyte imbalances in heart failure patients and evaluated its performance in a multicenter setting. Seventeen different centers participated in this study. Heart failure patients (ejection fraction ≤ 45%) who had blood electrolyte measurements and ECG taken on the same day were included. Patients were divided into four groups: those with normal electrolyte values, those with hypokalemia, those with hyperkalemia, and those with hyponatremia. Patients who developed electrolyte disorders due to medications used for heart failure were classified in the relevant group. Confidence intervals (CI): We computed 95% CIs for area under the receiver operating characteristic curve (AUROC) via stratified bootstrap (2,000 resamples at the patient level) and 95% CIs for accuracy using the Wilson score interval for binomial proportions.

Results: The accuracy rates of the DLM in detecting hyponatremia, hypokalemia, and hyperkalemia were 83.33%, 95.33%, and 95.77%, respectively.

Conclusion: The proposed DLM demonstrated high performance in detecting electrolyte imbalances. These results suggest that a DLM can be used to detect and monitor electrolyte imbalances using ECG on a daily basis.

Keywords: Artificial intelligence, deep learning, electrocardiography, electrolytes

ÖZET

Amaç: Elektrolit dengesizliğinin tespiti ve izlenmesi, birçok metabolik hastalığın uygun tedavisi için gereklidir. Ancak bu dengesizlikleri güvenilir ve invaziv olmayan şekilde tespit edebilen bir araç henüz mevcut değildir. Özellikle kalp yetmezliği hastalarında görülen elektrolit bozuklukları, hastalığın rutin tedavisinde kullanılan ilaçlara bağlı olarak gelişebilen ve yaşamı tehdit eden durumlara yol açabilir.

Yöntem: Bu çalışmada, kalp yetmezliği hastalarında elektrolit dengesizliğini tespit etmek amacıyla elektrokardiyografi (EKG) kullanan bir derin öğrenme modeli (DLM) geliştirdik ve performansını çok merkezli bir çalışmada test ettik. Çalışmaya 17 farklı merkez dahil edildi. Aynı gün kan elektrolit değerleri ve EKG'si alınan, ejeksiyon fraksiyonu (EF) ≤ %45 olan kalp yetmezliği hastaları çalışmaya alındı. Hastalar dört gruba ayrıldı: normal elektrolit değerleri olanlar, hipokalemisi olanlar, hiperkalemisi olanlar ve hiponatremisi olanlar. Kalp yetmezliği tedavisinde kullanılan ilaçlara bağlı elektrolit bozukluğu gelişen hastalar ilgili gruba dahil edildi. Güven aralıkları (GA), AUROC için %95 GA, hasta düzeyinde 2.000 tekrar örnekleme (stratified bootstrap) yöntemiyle, Accuracy için ise binom oranları için Wilson skor aralığı kullanılarak hesaplandı.

Bulgular: Hiponatremi, hipokalemi ve hiperkalemi gruplarında DLM doğruluk oranları sırasıyla %83,33, %95,33 ve %95,77 olarak belirlendi.

Sonuç: Önerilen DLM, elektrolit dengesizliğini tespit etmede yüksek performans göstermiştir. Bu sonuçlar, DLM'nin EKG kullanılarak elektrolit dengesizliğinin günlük olarak tespit edilmesi ve izlenmesinde kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Yapay zeka, derin öğrenme, elektrokardiyografi, elektrolitler

ORIGINAL ARTICLE
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Electrolyte balance is critical for maintaining homeostasis and preserving cellular function, as imbalances can disrupt numerous physiological processes.[1] Electrolytes, including sodium, potassium, calcium, and magnesium, are precisely regulated between intracellular and extracellular compartments to sustain the normal physiological function of muscles and nerves, thereby influencing neuromuscular excitability and contractility.[2] Certain electrolyte imbalances, such as hyperkalemia or hypocalcemia, can cause fatal arrhythmias and sudden cardiac death, making early diagnosis essential for effective intervention.[3]

Screening for critical electrolyte imbalances is particularly important in patients with conditions that impair electrolyte retention and excretion, such as renal failure, as well as in patients taking medications that affect electrolyte excretion, including diuretics, which can exacerbate these imbalances.[4] Moreover, the symptoms of electrolyte imbalance are often vague and nonspecific, making diagnosis based solely on patient history and clinical examination difficult until the condition progresses and life-threatening complications arise.[5]

The gold standard for diagnosing electrolyte imbalance remains laboratory testing, which quantitatively measures electrolyte concentrations in biological fluids. However, laboratory tests can be invasive, costly, and dependent on specialized equipment and infrastructure, including trained medical personnel to collect blood samples and hematology analyzers to perform biochemical reagent assessments.[6] Daily electrolyte assessment is vital for monitoring health status and preventing life-threatening events; however, reliance on laboratory tests is suboptimal for timely and effective monitoring, emphasizing the need for more accessible and rapid diagnostic alternatives.

The condition of the cardiac cell membrane is critically dependent on maintaining a normal electrolyte balance across the membrane.[7] Previous studies have demonstrated that alterations in electrolyte balance can significantly affect the morphological characteristics of the electrocardiogram (ECG) waveform. However, diagnosing electrolyte disturbances through subtle variations in ECG signals poses considerable challenges for clinicians.[8]

Deep learning techniques have previously been applied in various medical contexts to detect lesions and are now increasingly utilized for diagnosing conditions such as heart failure, valvular disease, anemia, and coronary artery disease, as well as for analyzing ECGs. The ECG is a widely accepted, noninvasive test that records heart voltage over time.

Deep learning technology, a sophisticated application of artificial intelligence, effectively mimics the data-processing capabilities of the human brain and has achieved remarkable success in disease screening, diagnosis, and prognosis. Unlike traditional machine learning approaches, deep learning algorithms demonstrate superior learning capacity and can automatically extract relevant features without extensive data preprocessing or manual feature extraction. This capability makes deep learning particularly well-suited for analyzing complex, high-dimensional data. With ongoing advances in computing power and the growing availability of digitized data, deep learning offers opportunities to enhance ECG interpretation with greater efficiency and accuracy, and, more importantly, to expand the functional utility of the ECG. Such progress could potentially transform current clinical monitoring and management strategies.[9]

Deep learning models developed through artificial intelligence algorithms serve as robust tools that emulate the data-processing patterns of the human brain to facilitate informed decision-making. In the past five years, deep learning has demonstrated exceptional promise in medical applications, encompassing disease screening, diagnosis, and prognosis.[10]

For digital ECG data, deep learning algorithms can detect subtle changes in ECGs associated with cardiac structural or functional abnormalities. Studies have shown that the application of deep learning provides significant improvements in the interpretation of ECG data with high efficiency and accuracy. Rapid algorithmic and computational advances are allowing us to reconsider the role of deep learning in ECG analysis. Regarding digital ECG data, deep learning algorithms are capable of detecting subtle changes in ECGs that may be indicative of underlying cardiac structural or functional abnormalities. Empirical studies have shown that the application of deep learning leads to significant improvements in the interpretation of ECG data, providing enhancements in both efficiency and accuracy. Rapid advancements in algorithmic and computational technologies are enabling a reevaluation of the role of deep learning within the context of ECG analysis.[11]

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ABBREVIATIONS

ANOVA	Analysis of Variance
AUROC	Area under the receiver operating characteristic curve
CE	Conformité Européenne
CHF	Congestive heart failure
CI	Confidence intervals
CNN	Convolutional neural network
DLM	Deep learning model
ECG	Electrocardiogram
EF	Ejection fraction
FDA	Food and Drug Administration
MCC	Matthews Correlation Coefficient
XAI	Explainable Artificial Intelligence

Despite the promising performance exhibited by deep learning methodologies, several challenges persist. The lack of standardization in ECG data may present obstacles for subsequent research initiatives, as there currently exists no unified ECG input type or established data preprocessing protocol. While the majority of studies have utilized 10-second, 12-lead ECGs recorded in the supine position as input data, other studies have opted for segmented ECGs.[12]

There is a lack of uniformity in how ECG data is prepared prior to analysis, with preprocessing techniques differing significantly between studies. This inconsistency complicates reproducibility and may compromise the effectiveness of deep learning applications. The accuracy of these models is highly dependent on the integrity and volume of the input data, yet ECG signals are often subject to considerable variability. Many investigations utilize data from a single institution or rely on open-access datasets, which may not reflect broader population characteristics. The ECG recording process itself is susceptible to numerous variables, such as device specifications, technician skill, electrical interference, muscle activity, electrode positioning and adherence, as well as individual anatomical and demographic differences. While larger datasets can reduce these sources of error, studies based on fewer than 100 subjects are particularly prone to overfitting, limiting their clinical utility. Furthermore, imbalanced class distributions remain a persistent challenge, often distorting the perceived performance of machine learning algorithms.[13]

Individuals with congestive heart failure (CHF) often develop disturbances in acid-base balance and electrolyte levels. These imbalances arise from neurohumoral system activation and the effects of commonly prescribed treatments such as diuretics. Such abnormalities not only indicate the progression of CHF but are also linked to reduced functional capacity and unfavorable long-term outcomes. Frequently observed electrolyte issues include low sodium (hyponatremia), low potassium (hypokalemia), and elevated potassium levels (hyperkalemia).[14]

Hyponatremia can serve as an indicator of neurohormonal activation and may reflect the severity of heart failure, yet it can also be a side effect of its treatment. Diuretics are among the most frequent contributors to hyponatremia in these patients. While thiazide diuretics are most commonly linked to this condition, non-thiazide medications such as furosemide, spironolactone, and indapamide have also been associated with sodium depletion. Numerous clinical studies have demonstrated that hyponatremia correlates with poorer outcomes and reduced survival rates in individuals with heart failure.[15]

Hypokalemia is frequently observed in patients with congestive heart failure and serves as a strong, independent predictor of mortality. It tends to be more severe in individuals with advanced CHF, particularly those undergoing intensive diuretic treatment and experiencing elevated activation of the renin-angiotensin system. Low serum potassium levels often reflect elevated neurohormonal activity and disease progression. Hypokalemia is inversely correlated with plasma renin activity, serum potassium concentration, and plasma norepinephrine levels. Increased catecholamine release contributes to potassium depletion and elevates the risk of arrhythmias. Both the prevalence of ventricular ectopy and the incidence of sudden cardiac death are closely linked to serum and total body potassium stores. Notably, around half of all heart failure-related deaths occur suddenly, likely due to arrhythmic events. Studies have found that individuals who suffer from sudden cardiac death often have lower myocardial potassium levels than controls, while survivors frequently exhibit hypokalemia, likely resulting from intracellular potassium shifts.[16]

Table 1. Patient and beat distribution

Group	Patients	Beats	Median (IQR) beats/patient
Hyperkalemia	40	117	2 (2–3)
Hypokalemia	73	166	2 (2–2)
Hyponatremia	98	266	2 (2–3)
Normal electrolytes	230	722	3 (2–3)
Total	441	1271	–

IQR: Interquartile range.

Hyperkalemia can pose a serious, potentially life-threatening condition, particularly in individuals with heart failure, chronic kidney disease, or diabetes. The risk is further elevated in patients receiving medications that affect the renin-angiotensin-aldosterone system, including mineralocorticoid receptor antagonists.[17]

In the heart failure patient group, electrolyte disorders, both caused by the disease and due to treatment, may increase morbidity and mortality. Therefore, early and easy recognition of these disorders in this patient group may contribute to disease management.

Materials and Methods

Study Design

This was a prospective multicenter study conducted across 17 hospitals. In our study, we developed a deep learning model (DLM) using ECG to detect electrolyte imbalance in heart failure patients and tested its performance in a multicenter setting. Patients from 17 different centers were included. Heart failure (left ventricular ejection fraction (LVEF) ≤ 45%) patients whose blood electrolyte values and ECG were obtained on the same day were included in the study. The patients were divided into four groups: those with normal electrolyte values, those with hypokalemia, those with hyperkalemia, and those with hyponatremia. Patients who developed electrolyte disorders due to medications used in heart failure were included in the relevant group. The devices used in different centers were Nihon Kohden [Nihon Kohden ECG-3150: Nihon Kohden Corporation (Tokyo, Japan)] and Mindray [Mindray BeneHeart R700: Mindray Bio-Medical Electronics Co., Ltd. (Shenzhen, China)]. All patients were informed about the content of the study and provided written consent. Our study was conducted in accordance with the Declaration of Helsinki. Approval for this study was received from Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Clinical Research Ethics Committee (Approval Number: 2022/108, Date: 19.12.2022). Patient counts and pulse data are presented in Table 1.

Two patients included in the study had multiple electrolyte disturbances. These patients were excluded from the study in order not to affect the results.

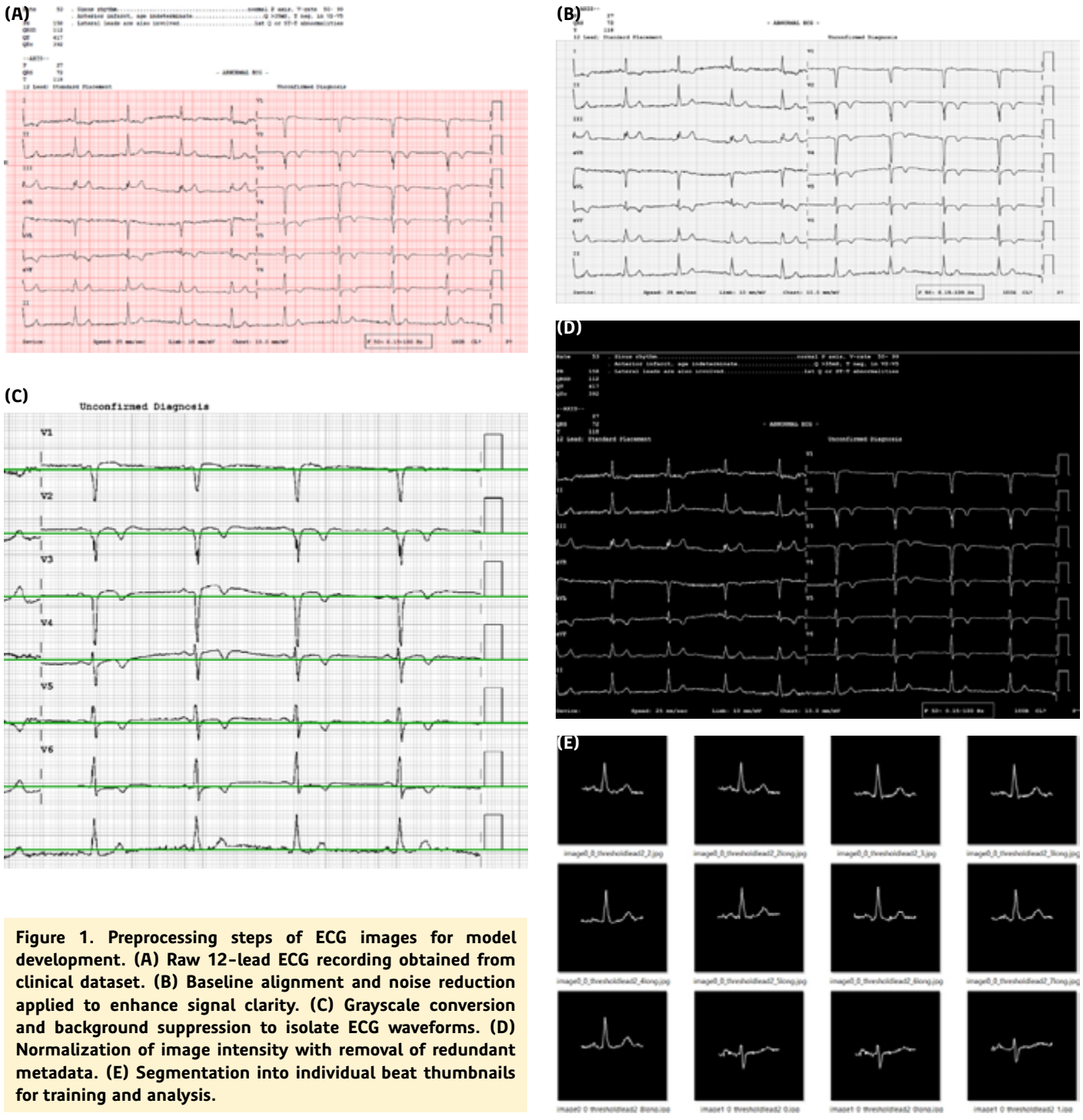

Figure 1. Preprocessing steps of ECG images for model development. (A) Raw 12-lead ECG recording obtained from clinical dataset. (B) Baseline alignment and noise reduction applied to enhance signal clarity. (C) Grayscale conversion and background suppression to isolate ECG waveforms. (D) Normalization of image intensity with removal of redundant metadata. (E) Segmentation into individual beat thumbnails for training and analysis.

Preprocessing

After grouping, ECGs were converted to grayscale format (Figure 1A–B).

Afterwards, a line was drawn showing the baseline in order to create a reference before digitizing the data (Figure 1C).

The background was removed using the threshold technique (Figure 1D).

Contour detection was performed using the OpenCV library. The aim of this process was to find the longest contour and eliminate the others to identify the true waveform (Algorithm: Satoshi, Suzuki and others. Topological structural analysis of digitized binary images by border following. Computer Vision, Graphics, and Image Processing, 30(1):32– 46, 1985).

Contour detection was again performed using the OpenCV library, with the goal of finding the longest contour and eliminating the others to obtain the true waveform (Figure 1E).

R-peak was detected using the NeuroKit2 library (https://joss.theoj.org/papers/10.21105/joss.02621).

Table 2. Overall performance metrics

Group	Accuracy (95% CI)	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Precision (95% CI)	NPV (95% CI)	F1-Score (95% CI)	MCC (95% CI)
Hyperkalemia	89.47% (77.40–95.61)	0.94 (0.87–0.98)	88.00% (71.37–95.68)	90.48% (77.37–96.57)	88.00% (71.05–96.00)	90.48% (77.37–96.77)	0.88 (0.71–0.96)	0.79 (0.62–0.91)
Hypokalemia	86.84% (74.01–94.01)	0.84 (0.76–0.91)	80.00% (62.65–90.52)	89.47% (76.52–95.64)	80.00% (62.65–90.52)	89.47% (76.52–95.64)	0.80 (0.63–0.91)	0.70 (0.54–0.82)
Hyponatremia	83.33% (68.64–92.05)	0.91 (0.82–0.96)	85.71% (62.41–95.11)	82.05% (64.62–91.41)	85.71% (62.41–95.11)	82.05% (64.62–91.41)	0.86 (0.62–0.95)	0.67 (0.48–0.84)

AUROC, Area under the receiver operating characteristic curve; CI, Confidence interval; MCC, Matthews correlation coefficient; NPV, Negative predictive value; PPV, Positive predictive value.

The signaling of a single heartbeat was captured and saved as a CSV file (Figure 2).

Single beats were obtained from D2 leads of all ECGs. While single beats were selected, beats considered as interference were excluded from the evaluation with the approval of the cardiologist. Since it is important for the data to be the same size in order to be comparable, a padding process was applied to all CSV files. Each CSV file was then tagged:

- Hyperkalemia: 1, Normal: 0
- Hypokalemia: 1, Normal: 0
- Hyponatremia: 1, Normal: 0.

The dataset was split at the patient level (70% training, 15% validation, 15% test). To prevent data leakage, no patient contributed beats to more than one subset. Group-aware cross-validation (GroupKFold) keyed by patient ID was used.

Model Architecture

The complete Python code for model development, training, and evaluation is provided in the Supplementary Material as Supplementary Code 1 (cnn_models.py).

Results

This study was designed as a multicenter, prospective investigation and included a total of 211 patients. The mean age was 56 years (range: 21–94), with 48 female and 163 male participants. The average left ventricular ejection fraction was 33%. Among the cohort, 82 patients had a history of hypertension, 67 had diabetes mellitus, and 54 had documented coronary artery disease. Exclusion criteria included individuals under 18 years of age, pregnant women, those with left or right bundle branch block on baseline ECG, patients with atrial fibrillation, and individuals with implanted cardiac pacemakers. These criteria were selected to eliminate conditions that could alter the baseline ECG and potentially compromise the performance of the proposed deep learning model. For analysis, single-lead ECG recordings (lead D2) were used after preprocessing.

A total of 266 single beats were obtained from the D2 lead in the hyponatremia patient group. The number of single beats obtained from the normal group was 722. When we applied our proposed model, the accuracy rate was 83.33% in the hyponatremia group.

Diagnosis of hyponatremia by ECG is challenging due to non-specific ECG findings. Despite this, the model we created

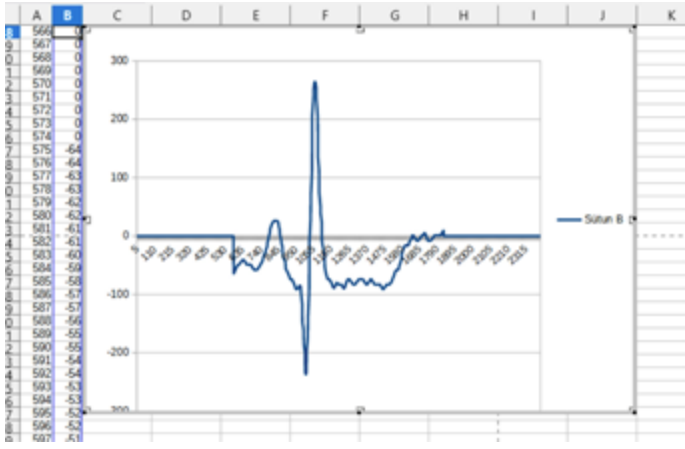

Figure 2. Single heartbeat was captured and saved as CSV file.

achieved an Area Under the Receiver Operating Characteristic curve (AUROC) of 95.62% and a recall of 93.94%, showing that hyponatremia could be identified with acceptable precision. The situation in the final validation set shows that caution should be exercised to avoid overfitting with strong learning. This indicates that future studies should be conducted with a larger dataset. The lower Matthews Correlation Coefficient (MCC) score (0.450) compared to potassium-based models underscores the difficulty of this evaluation. Adding additional parameters may help improve model performance. Although slightly lower in our study, the model achieved an accuracy rate of 83.33%, which can be considered acceptable given the limited number of beats and the difficulty of detecting ECG changes associated with hyponatremia.

In the hypokalemia group, 166 single beats were obtained from lead D2. When we applied the proposed model to 722 beats obtained from the normal patient group, we reached 95.33% accuracy, with an AUROC of 92.83%, precision of 96.75%, and recall of 97.54%.

The hypokalemia classifier achieved strong discrimination across all metrics. Patients with hypokalemia often exhibit ST depression, flattened T waves, and prominent U waves. The Convolutional Neural Network (CNN) model used in our study was successful in capturing these changes, with an AUROC of 92.83%. The minimal variance across the validation sets supports the consistency of these findings. Additionally, the model exhibited excellent precision (96.75%) and recall

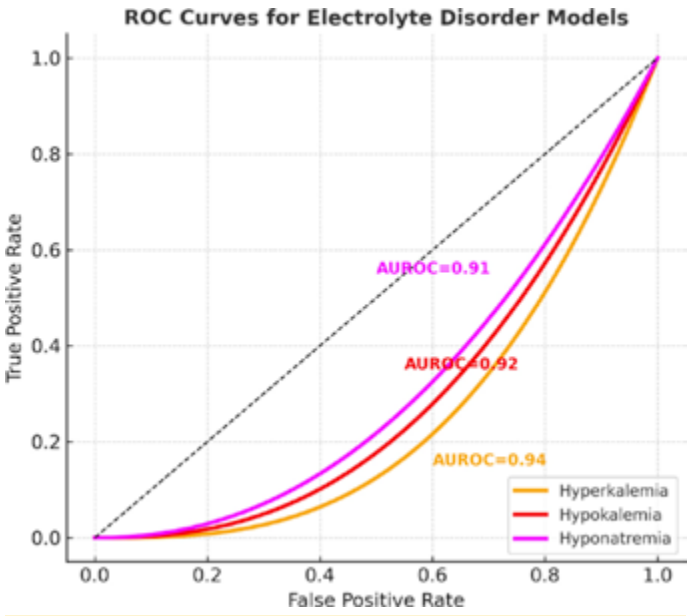

Figure 3. ROc curves for electrolyte disorder models.

AUROC, Area under the receiver operating characteristic curve; ROC, Receiver operating characteristic.

(97.54%), which are critical for clinical utility. The slightly higher performance on the final validation set supports the hypothesis that the network successfully generalizes the learned representations beyond the training data. At the same time, our model achieved an accuracy of 95.33%, indicating consistent classification across the training and validation sets.

In the hyperkalemia group, 117 single beats were obtained from the D2 lead. When we applied the proposed model to 722 single beats obtained from the normal patient group, we reached an accuracy of 95.77%.

Overall performance metrics are shown in Table 2.

The full implementation code (cnn_models.py) is provided in the Supplementary Material for reproducibility.

Comprehensive ECG Analysis and Explainable AI Using Saliency Maps

Theoretical Framework of Explainable AI (XAI)

Explainable Artificial Intelligence (XAI) comprises methodologies that make the decision-making processes of machine learning models understandable and interpretable. In clinical settings, XAI is crucial for the following reasons:

- Clinical Reliability: Allows physicians to validate model decisions
- Legal Accountability: Meets transparency requirements of regulatory bodies such as the U.S. Food and Drug Administration (FDA) and Conformité Européenne (CE)
- Patient Safety: Minimizes misdiagnoses
- Scientific Validation: Ensures alignment between learned model patterns and medical literature.

Algorithm and Methodology

Saliency pipeline: preprocessing (zero-padding removal, normalization), gradient computation, saliency map generation, critical segment detection.

Dataset Characteristics and Findings

Sample distribution: Hyperkalemia (Normal = 20, Pathologic = 107), Hypokalemia (Normal = 25, Pathologic = 109), Hyponatremia (Normal = 14, Pathologic = 24).

Performance metrics: AUROC = 0.92 ± 0.05, Accuracy = 0.89 ± 0.07, Sensitivity = 0.91 ± 0.06, Specificity = 0.87 ± 0.08 (Figure 3).

Confusion matrices for the classification of hyperkalemia, hypokalemia, and hyponatremia are shown in Figure 4.

Temporal Localization Analysis and Clinical Interpretation

- Hyperkalemia: Salient in segments 60–100, temporal shift +20, peak saliency 0.67; correlates with QRS widening and T-peak

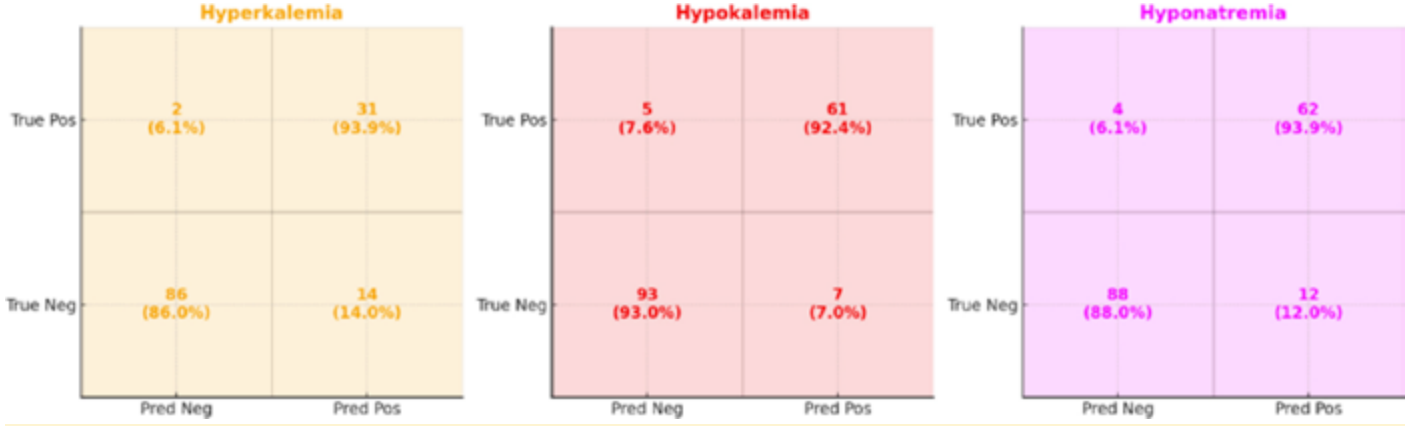

Figure 4. Confusion matrices for electrolyte disorder classification. Confusion matrices for hyperkalemia, hypokalemia, and hyponatremia classification. Each cell shows both raw counts (n) and row percentages (%). Orange: Hyperkalemia, Red: Hypokalemia, Magenta: Hyponatremia.

AUROC, Area under the receiver operating characteristic curve; CI, Confidence interval; MCC, Matthews correlation coefficient; PPV, Positive predictive value; NPV, Negative predictive value.

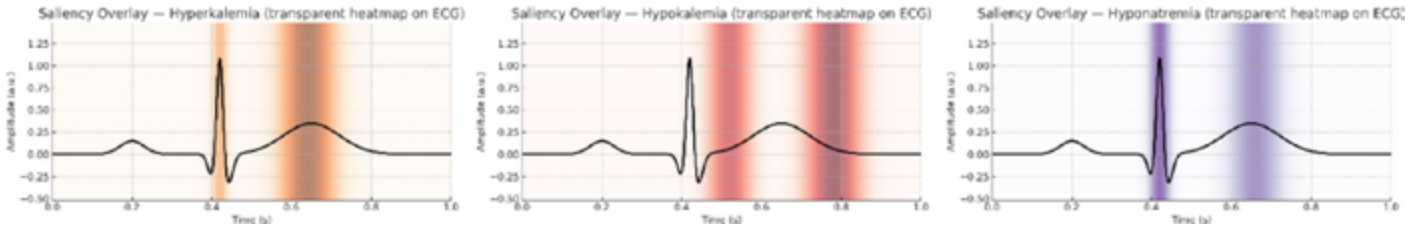

Figure 5. The saliency overlay visualizes the ECG segments most influential in the model's decision-making process.

- Hypokalemia: Segments 50–90, shift +15, saliency 0.54; correlates with QT prolongation and U-waves
- Hyponatremia: Segments 50–100, shift +17, saliency 0.61; correlates with ST changes and arrhythmogenic substrate

Comparative Analysis and Shared Patterns

Electrolyte-specific temporal signatures identified:

- Hyperkalemia: +20 shift, 0.67 saliency
- Hypokalemia: +15 shift, 0.54 saliency
- Hyponatremia: +17 shift, 0.61 saliency

All conditions exhibit temporal shifts, higher saliency in pathological groups, and variability in gradient magnitude.

Methodological Validity and Clinical Relevance

Pathophysiological validation was confirmed by matching saliency regions with known ECG changes.

Statistical Significance: Temporal shifts ($P < 0.001$, Analysis of Variance [ANOVA]), saliency differences ($P < 0.01$, Kruskal-Wallis), inter-group variability ($P < 0.05$, Levene's test).

This study confirms that CNN models with gradient-based saliency maps can successfully identify temporal features specific to electrolyte disorders. XAI adds transparency and enables real-time decision support. The saliency analysis presented in this report offers a robust framework for interpreting CNN-based ECG classification in the context of electrolyte disorders. By aligning salient temporal segments with known pathophysiological markers—such as QRS widening in hyperkalemia, QT prolongation and U-waves in hypokalemia, and ST changes in hyponatremia—the model not only demonstrates high performance (AUROC 0.92, accuracy 0.89) but also clinical interpretability. This alignment enhances trust in model outputs and supports their potential application in real-time decision-making. Importantly, the observed temporal shifts and saliency peaks were statistically significant, confirming that the model's focus corresponds meaningfully to clinically relevant waveform segments. Figure 5 illustrates the saliency overlay, which visualizes the ECG segments most influential in the model's decision-making process.

Saliency focus regions are shown in Table 3.

Table 3. Saliency focus per class

Condition	Primary ECG focus	Clinical correlation
Hyperkalemia	T-wave region	Peaked T-waves
Hypokalemia	T-U transition	Flattened T, prominent U
Hyponatremia	Post-QRS/diffuse	Subtle, non-specific changes

Limitations

Although the results obtained in our study support meaningful conclusions that electrolyte disorders can be detected from ECG using artificial intelligence methods, it is important to repeat these findings with larger datasets in order to evaluate their applicability and achieve more effective results. In future studies, models incorporating additional patient parameters may provide more efficient results. Additionally, this study did not adopt two suggested approaches—multi-beat input matrices and a single multi-label classifier. These remain acknowledged limitations. Future work will explore multi-beat input representations to capture temporal dynamics across successive beats and multi-label classification approaches to enable simultaneous detection of multiple electrolyte disorders, once larger and more balanced datasets become available.

In our study, it was planned to take ECG samples and blood electrolyte measurements on the same day. Minimizing the time between laboratory measurements and ECG may be more appropriate to detect ECG changes that can occur due to electrolyte disturbances.

Discussion

Analyzing ECG data via deep learning models has recently been shown to be effective in detecting dyskalemia, a finding that suggests significant potential for this technology within clinical contexts.[18]

Our study focused on developing a DLM specifically for detecting hypokalemia, hyperkalemia, and hyponatremia. The model was trained using a comprehensive dataset of ECG samples acquired from patients, employing advanced deep learning techniques. Specifically, patients diagnosed with the aforementioned conditions were systematically grouped and then compared with carefully defined normal patient cohorts. The results showed that our model achieved accuracy rates of 83.33% for the hyponatremia group, 95.33% for the hyperkalemia group, and 95.77% for the hypokalemia group, underscoring the clinical relevance of our approach.

In a related study, Lin et al.[18] introduced ECG12Net, a deep learning model designed to detect dyskalemias through comprehensive ECG analysis. Using a training set of more than 50,000 ECGs and a sophisticated deep convolutional network to identify numerous ECG features, ECG12Net demonstrated higher performance than clinicians in detecting dyskalemias, specifically showing sensitivity rates of 95.6% for severe hypokalemia and 84.5% for severe hyperkalemia.[19] The results of our work are generally consistent with these previous findings, reinforcing the effectiveness of deep learning models.

While serum potassium concentration can be rapidly assessed in hospital settings using venous blood tests, diagnosing hypokalemia outside those settings remains a considerable problem, partly because affected patients often do not exhibit clear symptoms. Consequently, using ECGs to screen patients noninvasively for hypokalemia could significantly improve early detection and, by extension, patient care and outcomes. Furthermore, numerous wearable devices for monitoring ECGs have emerged in recent years, providing additional support in this area.[12]

The limitations of our study, specifically the sample size, warrant further confirmatory and controlled investigations. Still, our findings suggest that deep learning models can detect subtle changes that may elude even experienced cardiologists. This aligns with other studies in the literature, bolstering the transformative potential of deep learning in ECG analysis.[6]

Although we applied our model to more data than the other two electrolyte disorders (hypokalemia and hyperkalemia) in our study, the accuracy rate in the hyponatremia group was 83.33%, lower than in the other groups. One reason for this may be that ECG findings due to hyponatremia are less obvious than in the other two groups. To increase accuracy rates, studies involving evaluation with larger datasets are needed.

Datasets created with patients who have pure electrolyte disorders may produce more efficient results in detecting changes due to these conditions. However, because most electrolyte disorders coexist with other diseases and many medications are used in these patient groups, ECG parameters may be affected. This may cause the applied model to reach incorrect results. In our study, the frequency of diabetes mellitus, hypertension, and coronary artery disease was high, and the number of medications used for these was also high. To reduce the effects that may arise from this situation, future studies with similar groups in terms of disease and drug use are needed.

One of the main problems in studies based on ECG and deep learning models is that standardization has not yet been achieved. It can be seen from publications in the literature that models can be applied to data taken from different leads in different studies.[12] While some ECG studies are carried out on raw data, in others, ECGs in formats such as JPEG and PDF are used. Data received from different devices in different centers can lead to a number of difficulties such as a more costly data processing phase, longer processing times, and greater reliance on human-dependent processes. In our study, the difference in the number of centers and the types of devices used caused the data processing phase to be longer.

In the future, applications that contribute to routine monitoring, especially for patients at risk of electrolyte disorders, can be developed for smartphones capable of taking photographs and recording a single-lead ECG signal. This may accelerate with advances in sensor technology and the resulting improvement in the quality of data signals received from patients. Continuous collection of individual changes and their use in personalized medicine applications will open up broad horizons for the future.

On the other hand, as the success rate of evaluations using photographic ECGs increases, application-based systems can also be used as assistive tools for physicians and patients in disadvantaged regions where cardiologists are not available or laboratory services are inadequate.

These systems can further be integrated into remote monitoring platforms, providing benefits such as more qualified treatment and early detection of potentially life-threatening conditions in disadvantaged groups at risk, such as heart failure patients.

This study demonstrates that computer vision-based AI models can accurately detect diagnostic features on ECG images. To facilitate the integration of this technology into routine clinical practice, future research should aim to develop models capable of generalizing across diverse ECG image formats and originating from multiple sources, while encompassing a wider spectrum of clinically relevant diagnoses. These models can be designed to accommodate various ECG styles and layouts, enhancing their applicability across settings. Furthermore, the underlying algorithms may be adapted for innovative applications—such as smartphone-based tools or smart health platforms—to enable the detection of electrolyte imbalances directly from ECG photographs.

Future work will explore multi-beat input representations to capture temporal dynamics across successive beats, potentially enhancing the model's sensitivity to subtle intra-patient variations.

Conclusion

The proposed DLM exhibited strong performance in accurately identifying electrolyte imbalances, underscoring its potential value in clinical settings. These findings indicate that such a model could be integrated into routine practice for the detection and monitoring of electrolyte disturbances using ECG data, offering a promising tool to enhance patient care and outcomes, particularly in high-risk populations. Supporting this model with further studies to ensure its compatibility with clinical practice may increase the power and value.

Online Supplementary Link: Supplementary Code 1 may be accessed via this link.

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Clinical and Demographic Characteristics of Dipper and Non-Dipper Hypertensive Patients at Moderate Altitude

Orta Rakımda Yaşayan Dipper ve Dipper Olmayan Hipertansif Hastaların Klinik ve Demografik Özellikleri

ABSTRACT

Objective: Hypertension (HT) is a complex clinical syndrome influenced by lifestyle, genetics, mental stress, and environmental factors. High-altitude (H-ALT) is one environmental factor that affects the development of HT. This study aimed to analyze the clinical and demographic features of patients residing at moderate altitude (M-ALT).

Method: A total of 515 patients with hypertension, confirmed through 24-hour ambulatory blood pressure monitoring (ABPM), were screened. After exclusions, the final study population consisted of 452 patients. Participants were divided into two groups: dippers and non-dippers.

Results: Patients in the non-dipper group were older (standard deviation [SD]: 61 ± 13 vs. 54 ± 12 years, P < 0.001) and had a significantly higher waist circumference (SD: 104 ± 13 vs. 107 ± 12 cm, P = 0.022). However, patients in the dipper group had a significantly higher daytime mean systolic blood pressure (SBP) (SD: 144 ± 16 vs. 141 ± 17 mmHg, P = 0.027) and daytime mean diastolic blood pressure (DBP) (SD: 89 ± 12 vs. 87 ± 13 mmHg, P = 0.037). Patients in the non-dipper group also had a significantly higher proportion of abnormal left ventricular global longitudinal strain (LVGLS) (n = 218 (65.6%) vs. n = 53 (46.7%), P = 0.009).

Conclusion: In our study, patients with a non-dipper pattern of hypertension, which is associated with poor multisystemic outcomes, were found to have a higher waist circumference and subclinical left ventricular dysfunction (abnormal LVGLS). Furthermore, patients with a non-dipper pattern of hypertension comprised 76% of the study population.

Keywords: Altitude, demography, dipper hypertension, hypertension, non-dipper hypertension

ÖZET

Amaç: Hipertansiyon (HT), yaşam tarzı, genetik, zihinsel stres ve çevresel faktörlerle ilişkili karmaşık bir klinik sendromdur. Yüksek rakım (H-ALT), HT gelişimini etkileyen çevresel faktörlerden biridir. Bu çalışma, orta rakımda (M-ALT) yaşayan hastaların klinik ve demografik özelliklerini analiz etmeyi amaçlamaktadır.

Yöntem: 24 saatlik ambulatuvar kan basıncı ölçümü (ABPM) ile hipertansiyonu doğrulanan toplam 515 hasta taranmıştır. Çalışma dışı bırakılanların ardından, nihai çalışma popülasyonu 452 hastadan oluşmuştur. Hastalar, dipper hipertansiyon ve non-dipper hipertansiyon olmak üzere iki gruba ayrıldı.

Bulgular: Non-dipper grubundaki hastalar daha yaşlıydı (SD: 61 ± 13 - 54 ± 12 yıl, P < 0,001) ve anlamlı derecede daha yüksek bel çevresine sahipti (SD: 104 ± 13 - 107 ± 12 cm, P = 0,022). Ancak dipper grubundaki hastaların gündüz ortalama sistolik kan basıncı (SKB) (SD: 144 ± 16 - 141 ± 17 mm Hg, P = 0,027) ve diyastolik kan basıncı (DKB) (SD: 89 ± 12 - 87 ± 13 mm Hg, P = 0,037) anlamlı derecede daha yüksekti. Non-dipper grubundaki hastalarda anormal sol ventrikül global longitudinal strain oranı anlamlı olarak daha yüksekti (n = 218 (%65,6) - n = 53 (%46,7), P = 0,009).

Sonuç: Çalışmamızda, multisistemik sonuçların kötü olduğu non-dipper hipertansiyon paternine sahip hastalarda, daha yüksek bel çevresi ve subklinik sol ventrikül disfonksiyonu (anormal LVGLS) olduğu tespit edildi. Ayrıca, non-dipper hipertansiyon paternine sahip hastalar çalışma popülasyonunun %76'sını oluşturuyordu.

Anahtar Kelimeler: Rakım, demografi, dipper hipertansiyon, hipertansiyon, non-dipper hipertansiyon

ORIGINAL ARTICLE
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Hypertension (HT) is the most common chronic non-communicable disease and a major contributor to global illness and death.[1] Recent data show that about 1.4 billion people worldwide have HT.[2] Blood pressure follows a consistent circadian rhythm, with endogenous neuroendocrine oscillations and other factors leading to a 10%–20% decrease at night compared to daytime.[3] In hypertensive patients, systolic and diastolic blood pressure (BP) typically decrease by more than 10% during sleep compared to daytime. These changes often follow a pattern known as dipper HT. In contrast, non-dipper HT patients do not exhibit this circadian variation, with BP reductions falling below 10%.[4] Non-dipper hypertension has been associated with an increased risk of heart disease and damage to target organs compared to dipper hypertension.[5,6]

Hypertension is a multifaceted clinical condition influenced by lifestyle, genetics, and mental stress.[7] As understanding of hypertension risk factors advances, environmental factors have gained increased attention in recent research, one of which is residential altitude.[2] High-altitude (H-ALT) is an ecological, racial, geographic, and genetic factor that influences the development of systemic HT. The threshold for H-ALT is generally defined as above 2,500 meters above sea level.[8] Studies conducted in H-ALT regions show that the prevalence and risk of hypertension increase with altitude.[9-11] However, there are very few studies on hypertension at moderate altitudes (M-ALT) (1,500-2,500 m). This study aimed to examine the clinical and demographic characteristics of patients residing at M-ALT.

This study received approval from the Research Ethics Committee of Kafkas University (Approval Number: 80576354-050-99/669, Date: 28.05.2025). As it was a single-center retrospective study, informed consent was waived by the Ethics Committee. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Materials and Methods

Study Participants

A total of 515 patients with hypertension, confirmed by 24-hour ambulatory blood pressure monitoring (ABPM), were screened. The study included participants who were at least 18 years old; had no prior diagnosis of hypertension; had their blood pressure measured with ABPM; were diagnosed with hypertension based on guideline threshold values using ABPM (a 24-hour average ABPM of ≥ 130 and/or ≥ 80 mmHg); and had resided at a moderate altitude for at least two years. Participants were excluded from the study if they had a left ventricular ejection fraction (LVEF) of less than 35%; primary severe heart valve disease requiring intervention or surgery; a history of stroke, myocardial infarction, or coronary artery bypass graft surgery within the previous 30 days; congenital heart disease; were on dialysis; or were pregnant. After applying these criteria, 452 patients remained in the final sample (Figure 1).

The patients' baseline demographic and clinical characteristics, along with their medical history—including comorbidities and education level—were retrieved from the hospital's electronic database and patient charts. Education level was categorized as illiterate/primary/secondary school (combined as one group) and high school or above (as another group).

ABBREVIATIONS

2CH	Two-chamber
2DS	Two-dimensional strain
4CH	Four-chamber
ABPM	Ambulatory blood pressure monitoring
ASE	American Society of Echocardiography
BNP	B-type natriuretic peptide
BP	Blood pressure
BSA	Body surface area
CAD	Coronary artery disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
GLS	Global longitudinal strain
H-ALT	High-altitude
HbA1C	Hemoglobin A1C
HBPM	Home blood pressure monitoring
HT	Hypertension
LVEF	Left ventricular ejection fraction
LVGLS	Left ventricular global longitudinal strain
LVM	Left ventricular mass
LVMI	Left ventricular mass index
M-ALT	Moderate altitude
OBP	Office blood pressure
SBP	Systolic blood pressure
TDI	Tissue Doppler imaging

24-Hour ABPM Recordings

Using an ABPM device (SunTech Medical Inc., Morrisville), hypertension was diagnosed according to current guidelines.[12] Twenty-four-hour ABPM recordings were taken every 15 minutes during the day (6:00 a.m. to 10:00 p.m.) and every 30 minutes at night (10:00 p.m. to 6:00 a.m.). From the collected data, patients' awake and sleep periods were identified. The nocturnal blood pressure dip was calculated using the formula: 100 × [1 – (sleep systolic BP / awake systolic BP)]. Circadian blood pressure patterns were classified as dipper (0.8 < ratio ≤ 0.9) or non-dipper (ratio > 0.9) based on nocturnal blood pressure decline.[13] Consequently, if mean systolic and diastolic blood pressure levels decreased by more than 10%, the patient was considered a dipper with hypertension; if they decreased by less than 10%, the patient was classified as a non-dipper; and if they showed an increase, the patient was considered a reverse-dipper.[14] Patients were then divided into two categories for evaluation: dipper and non-dipper (including non-dippers and reverse dippers).

Electrocardiographic (ECG) Analysis

All patients' standard 12-lead electrocardiograms (ECGs) were obtained from the hospital's records. All ECG strips were scanned, uploaded to a computer, and analyzed using ImageJ digital image processing software (available at imagej.nih.gov/ij/).

Echocardiographic Evaluation

All patients underwent transthoracic echocardiography using a Philips HD 11 XE ultrasound machine (Andover, MA). Measurements adhered to the American Society of Echocardiography (ASE)[15] guidelines. All echocardiographic

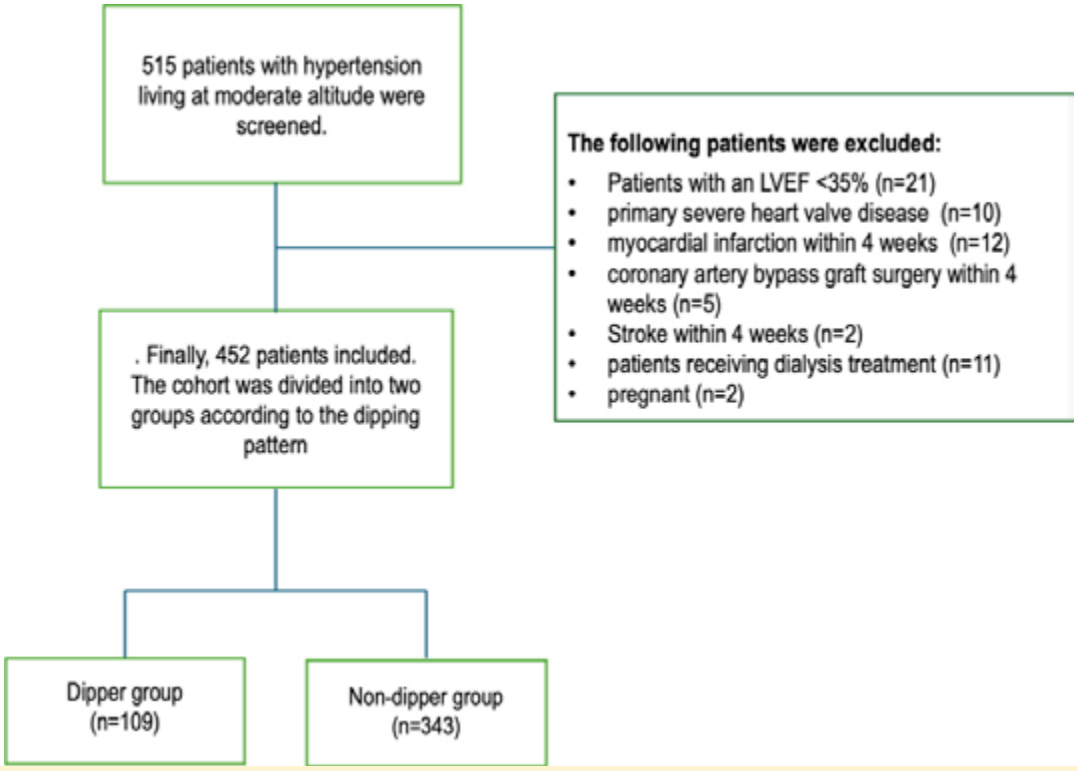

Figure 1. A flow chart illustrating the study design.

measurements were performed transthoracically while the patient was in the left lateral decubitus position. Standard 2D, M-mode, pulsed-wave Doppler, and tissue Doppler imaging (TDI) procedures were carried out according to ASE guidelines.[15] The LVEF was determined using the modified Simpson method. Transmitral inflow velocities (E and A waves) were measured using pulsed-wave Doppler in the apical four-chamber view, with the sample volume positioned at the mitral leaflet tips. TDI was performed at both the septal and lateral mitral annuli to record early diastolic velocity (Em) and late diastolic velocity (Am). Left ventricular global longitudinal strain (LVGLS) was analyzed in three apical left ventricular-focused (LV-focused) views (the apical long-axis, four-chamber (4CH), and two-chamber (2CH) views) using the two-dimensional strain speckle-tracking application (2DS).

The echocardiographic value of left ventricular mass (LVM) was indexed to body surface area (BSA) according to ASE guideline recommendations.[15]

LVM was calculated as follows:

$$LVM = 0.8 \times 1.04 \times [(IVS + LVEDD + PW)^3 - LVEDD^3] + 0.6\,g$$

where

- LVM = Left ventricular mass
- IVS = Interventricular septal thickness
- LVEDD = Left ventricular end-diastolic diameter
- PW = Posterior wall thickness.

Left ventricular hypertrophy (LVH) was defined as LVM/BSA > 115 g/m² in men or > 95 g/m² in women.

Statistical Analyses

Statistical analyses were conducted using SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, New York, USA, 2013). Descriptive statistics are presented as mean ± standard deviation (SD) for normally distributed continuous variables, medians with 0.25 and 0.75 quantiles for non-normally distributed variables, and percentages for categorical data. The t-test or Mann-Whitney U test was used to compare continuous variables between groups, while Fisher's exact test or the chi-square test was applied for categorical data.

Results

The study included 233 females (51.5%) and 219 males (48.5%), with an average age of 59 ± 13 years. Overall, 109 (24.1%) patients had a dipper blood pressure pattern, while 343 (75.9%) had a non-dipper pattern. Table 1 presents the baseline demographic features, clinical characteristics, and 24-hour ABPM data of the study population. Patients in the non-dipper group were older (mean age: 61 ± 13 vs. 54 ± 12 years, P < 0.001) and had a significantly higher waist circumference (104 ± 13 vs. 107 ± 12 cm, P = 0.022). They also exhibited higher night-time mean systolic blood pressure (SBP) (139 ± 18 vs. 123 ± 14 mmHg, P < 0.001) and night-time mean diastolic blood pressure (DBP) (83 ± 13 vs. 75 ± 11 mmHg, P < 0.001). Additionally, these patients had higher rates of coronary artery disease (CAD) (77 [22.4%] vs. 12 [11%], P = 0.006), diabetes mellitus (DM) (130 [37.8%] vs. 24 [22%], P = 0.002), and chronic obstructive pulmonary disease (COPD) (32 [9.3%] vs. 2 [1.8%], P = 0.010), as well as higher smoking rates (77 [22.4%] vs. 37 [33.9%], P = 0.016). However, patients in the dipper group had significantly higher daytime mean SBP (144 ± 16 vs. 141 ± 17 mmHg, P = 0.027) and daytime mean DBP (89 ± 12 vs. 87 ± 13 mmHg, P = 0.037).

Table 1. Comparison of baseline demographic, clinical, and ambulatory blood pressure characteristics

Variables	Hypertension			P
	Dipper group n = 109 (24.1%)	Non-dipper group n = 343 (75.9%)	Total n = 452	
Age, years (SD)	54 ± 12	61 ± 13	59 ± 13	<0.001
Gender, female, n (%)	56 (51.4%)	177 (51.6%)	233 (51.5%)	0.96
Education				0.48
Less than high school, n (%)	63 (57.8%)	211 (61.5%)	274 (60.6%)	
High school or more, n (%)	46 (42.2%)	132 (38.5%)	178 (39.4%)	
BSA, m^2 (SD)	1.94 ± 0.22	1.94 ± 0.21	1.94 ± 0.21	0.658
BMI, (kg/m^2) (SD)	29.7 ± 5	30.2 ± 5	30.1 ± 5	0.360
Waist circumference, cm (SD)	104 ± 13	107 ± 12	106 ± 12	**0.022**
Mid-upper arm circumference, cm (SD)	32 ± 4	32 ± 6	32 ± 5	0.389
Neck circumference, cm (SD)	39 ± 5	40 ± 4	40 ± 4	0.190
Daytime mean SBP, mmHg (SD)	144 ± 16	141 ± 17	141 ± 17	**0.027**
Daytime mean DBP, mmHg (SD)	89 ± 12	87 ± 13	87 ± 13	**0.037**
Night-time mean SBP, mmHg (SD)	123 ± 14	139 ± 18	135 ± 18	**<0.001**
Night-time mean DBP, mmHg (SD)	75 ± 11	83 ± 13	81 ± 13	**<0.001**
Coronary artery disease, n (%)	12 (11%)	77 (22.4%)	89 (19.7%)	**0.006**
Diabetes mellitus, n (%)	24 (22%)	130 (37.8%)	154 (34.1%)	**0.002**
Chronic renal disease, n (%)	4 (3.7%)	16 (4.7%)	20 (4.4%)	0.660
Hyperlipidemia, n (%)	20 (18.3%)	80 (23.3%)	100 (22.1%)	0.276
COPD, n(%)	2 (1.8%)	32 (9.3%)	34 (7.5%)	**0.010**
CVA/TIA, n (%)	3 (2.8%)	14 (4.1%)	17 (3.8%)	0.522
OSA, n (%)	1 (0.9%)	12 (3.5%)	13 (2.9%)	0.154
Asthma, n (%)	13 (11.9%)	33 (9.6%)	46 (10.2%)	0.500
Smokers, n (%)	37 (33.9%)	77 (22.4%)	114 (25.2%)	**0.016**

BMI, Body mass index; BSA, Body surface area; COPD, Chronic obstructive pulmonary disease; CVA, Cerebrovascular accident; DBP, Diastolic blood pressure; OSA, Obstructive sleep apnea; SBP, Systolic blood pressure; SD, Standard deviation; TIA, Transient ischemic attack.

Table 2. Medications

Variables	Hypertension			P
	Dipper group n = 109	Non-Dipper group n = 343	Total n = 452	
Hydropyridine CCB, n (%)	25 (22.9%)	88 (25.7%)	113 (25%)	0.558
ACEI, n (%)	18 (16.5%)	69 (20.1%)	87 (19.2%)	0.399
ARB, n (%)	33 (30.3%)	103 (30%)	136 (30.1%)	0.975
Beta-blocker, n (%)	20 (18.3%)	98 (28.6%)	118 (26.1%)	**0.034**
MRA, n (%)	2 (1.8%)	5 (1.5%)	7 (1.5%)	0.784
Thiazide, n (%)	26 (23.9%)	86 (25.1%)	112 (24.8%)	0.786
Indapamide, n (%)	0	6 (1.7%)	6 (1.3%)	0.164
Loop diuretic, n (%)	0	8 (2.3%)	8 (1.8%)	0.108

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; MRA, Mineralocorticoid receptor antagonist.

Table 2 shows the drug treatment of the groups. There was no difference between the groups except for the rate of beta-blocker use, which was significantly higher in the non-dipper group (n = 98 (28.6%) vs. n = 20 (18.3%), P = 0.034).

Table 3 presents the baseline electrocardiographic, echocardiographic, and laboratory characteristics of the patients. Patients in the non-dipper group had a significantly lower mean e' (SD: 7.52 ± 2.04 vs. 8.21 ± 2.03 cm/sec, P = 0.003) and a significantly higher rate of abnormal LVGLS (n = 218 [65.6%] vs. n = 53 [46.7%], P = 0.009). Additionally, they showed significantly elevated hemoglobin A1C (HbA1C) levels (SD: 6.2 ± 1.2 vs. 5.9 ± 1%, P < 0.001), urea levels (SD: 37 ± 14 vs. 34 ± 12 mg/dl, P =

Table 3. Comparison of electrocardiographic, echocardiographic, and laboratory characteristics in patients

Variables	Hypertension			P
	Dipper group n = 109	Non-dipper group n = 343	Total n = 452	
Rhythm				0.205
Sinus rhythm, n (%)	107 (98.2%)	331 (96.5%)	438 (96.9%)	
Atrial fibrillation, n (%)	0	4 (1.2%)	4 (0.9%)	
Paced rhythm, n (%)	0	1 (0.3%)	1 (0.2%)	
Heart rate, bpm	77 ± 13	76 ± 14	76 ± 14	0.386
Left BBB, n (%)	1 (0.9%)	16 (4.7%)	17 (3.8%)	0.070
Right BBB, n (%)	2 (1.8%)	15 (4.4%)	17 (3.8%)	0.216
QRS duration, msec (SD)	100 ± 14	102 ± 18	102 ± 17	0.318
LVEF, %	60 ± 7	59 ± 8	59 ± 8	0.156
E/A ratio (SD)	0.84 ± 0.23	0.83 ± 0.32	0.83 ± 30	0.079
E/e' ratio (SD)	8.59 ± 2.59	8.97 ± 3.33	8.88 ± 3.17	0.294
e' mean, cm/sec (SD)	8.21 ± 2.03	7.52 ± 2.04	7.69 ± 2.06	**0.003**
Left ventricular mass index, g/m^2	88 ± 22	89 ± 23	89 ± 22	0.963
Left ventricular hypertrophy, n (%)	18 (16.5)	76 (22.2)	94 (20.8)	0.206
Left atrial AP diameter, cm (SD)	3.5 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	0.115
Tricuspid RV, m/sec (SD)	1.99 ± 0.53	2.02 ± 0.55	2.02 ± 0.54	0.835
LVGLS				**0.009**
GLS >-16%	56 (51.3%)	125 (36.4%)	181 (40%)	
GLS <-16%	53 (46.7%)	218 (65.6%)	271 (60%)	
White blood cell count, ×10^3/μL(SD)	7.5 ± 1.9	7.2 ± 1.9	7.3 ± 1.9	0.142
Hemoglobin, g/dl (SD)	15 ± 1.9	14.4 ± 1.9	14.5 ± 1.9	**0.018**
Hematocrit, %	45 ± 6	43 ± 6	44 ± 6	**0.020**
Platelet count, ×10^3/μL (SD)	235 ± 60	240 ± 80	239 ± 76	0.537
Fasting blood glucose, mg/dl (SD)	103 ± 38	108 ± 45	107 ± 43	0.564
Hemoglobin A1C, %	5.9 ± 1	6.2 ± 1.2	6.1 ± 1.1	**<0.001**
Albumin, g/L (SD)	4.4 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	**<0.001**
eGFR, ml/min/1.73 m^2 (SD)	86 ± 18	81 ± 17	82 ± 17	**0.009**
Urea, mg/dl (SD)	34 ± 12	37 ± 14	36 ± 14	**0.016**
Serum sodium, mmol/l (SD)	139 ± 2	139 ± 2	139 ± 2	0.916
Serum potassium, mmol/l (SD)	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	0.554
ALT, U/l (IQR)	22 (17-28)	19 (14-17)	20 (15-29)	0.074
AST, U/l (IQR)	20 (16-23)	19 (16-24)	20 (16-24)	0.683
TSH, mIU/L (IQR)	1.56 (1.13-2.31)	1.70 (0.93-2.46)	1.64 (0.99-2.43)	0.876
HDL-C, mg/dl (SD)	51 ± 12	50 ± 12	50 ± 12	0.583
LDL-C, mg/dl (SD)	126 ± 33	122 ± 40	123 ± 39	0.275
Triglycerides, mg/dl (IQR)	129 (99-210)	139 (99-203)	136 (99-204)	0.708
NT-proBNP, ng/ml (IQR)	25 (14-55)	39 (19-75)	34 (17-65)	**0.002**

ALT, Alanine transaminase; AST, Aspartate transaminase; eGFR, Estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; IQR, Interquartile range; LDL-C, Low-density lipoprotein cholesterol; LVEF, Left ventricular ejection fraction; LVGLS, Left ventricular global longitudinal strain; RV, Regurgitant velocity; SD, Standard deviation; TSAT, Transferrin saturation; TSH, Thyroid-stimulating hormone.

0.016), and B-type natriuretic peptide (BNP) levels (interquartile range [IQR]: 39 [19-75] vs. 25 [14-55] ng/ml, P = 0.002). In contrast, patients in the non-dipper group had significantly lower hemoglobin (SD: 14.4 ± 1.9 vs. 15 ± 1.9 g/dl, P = 0.018), hematocrit (SD: 43 ± 6 vs. 45 ± 6%, P = 0.020), platelet counts (SD: 239 ± 81 vs. 246 ± 63 ×103/μL, P = 0.025), albumin levels (SD: 4.2 ± 0.4 vs. 4.4 ± 0.4 g/dL, P < 0.001), and estimated glomerular filtration rate (eGFR) (SD: 81 ± 17 vs. 86 ± 18 ml/min/1.73 m^2, P = 0.009).

Discussion

Patients with a non-dipper pattern of hypertension made up 76% of the study population. The non-dipper group was older and had higher rates of smoking, abnormal LVGLS, CAD, DM, and COPD based on our analysis of the study population. Furthermore, waist circumference was associated with the non-dipper group, although there were no differences between the HT groups in terms of Body Mass Index (BMI), BSA, arm circumference, or neck circumference. As expected, we examined the differences between the groups and observed that the non-dipper group had higher mean nocturnal SBP and DBP but lower mean daytime SBP and DBP.

In the systematic review by Aryal et al.,[16] the prevalence of HT at H-ALT in the general population appeared to be higher in men. However, there was no gender difference between the groups in our study sample, which included individuals living at altitudes between 1,500 and 2,500 meters. This may be due to factors such as small sample size, ethnic characteristics, study design limitations, and limited geographic areas.

We found that patients in the dipper group had significantly higher mean SBP and DBP levels during the daytime compared to patients in the non-dipper group. However, the non-dipper group had significantly higher nighttime SBP and DBP. This characteristic of the non-dipper group might be related to different types of end-organ damage in this patient population. For example, some parameters reflecting left ventricular systolic and diastolic mechanics and function, such as global longitudinal strain (GLS) and e' mean, were lower. Previous studies suggest that non-dipper HT can lead to either clinical or subclinical LV dysfunction.[17,18] In our study, no significant differences were observed between the groups in echocardiographic measurements of LVEF, E/A ratio, and E/e' ratio. However, LVGLS was significantly lower in the non-dipper group. This is one of the key findings of our study. A low LVGLS, which is increasingly recognized for its role in indicating LV subclinical dysfunction,[19] can be seen as an early sign of organ dysfunction in non-dipper hypertension. Additionally, the mean e' obtained by tissue Doppler, used to assess LV diastolic dysfunction, was found to be decreased. Our findings are consistent with these earlier studies. In our study, left ventricular hypertrophy and the left ventricular mass index (LVMI) showed no differences between the groups. Reviewing the literature, we found some studies[20-22] reporting no difference between patients with LVH and different blood pressure patterns (dipper and non-dipper hypertension). Our study results were similar in this regard. The reasons for this may be that our sample size was small and/or consisted of newly diagnosed patients. An important finding is that the non-dipper pattern group had lower daytime mean BP than the dipper group. It is well known that non-dipper hypertensive patients experience more severe target organ damage—either clinical or laboratory evidence of early hypertensive damage in vascular organs—than dipper patients.[4] In their study, Tanrıverdi et al.[23] demonstrated a significant association between carotid intima-media thickness, a key indicator of atherosclerosis, and non-dipper hypertension. Patients diagnosed, followed-up, and treated based on home blood pressure monitoring (HBPM) or office blood pressure (OBP) may have a higher risk of end-organ damage that could be overlooked or diagnosed late. All patients in our study were diagnosed using ABPM, emphasizing the significance of pattern diagnosis alongside blood pressure measurement.

Previous studies have indicated that non-dippers show a stronger association with organ injury compared to patients with normal nocturnal BP decline, including renal dysfunction, DM, and cardiovascular damage.[24-26] Long-term effects of H-ALT include eGFR, reduced renal plasma and blood flow, and increased filtration fraction.[27] The development of increased erythrocytosis due to persistent hypoxia is a proposed explanation for impaired renal function at H-ALT.[28] Although these effects of high altitude have been examined in various studies, our study population was at M-ALT, yet a significantly lower eGFR was observed in the non-dipper group. This finding suggests that a combination of altitude, ethnicity, hypertension, diet, and other environmental factors may contribute to similar outcomes at different elevations.

Living at H-ALT is known to increase hemoglobin levels.[29-31] In our study, neither group was anemic[32] based on mean hemoglobin levels. However, we found that the non-dipper group had lower hemoglobin and hematocrit levels. This may be due to the negative effects of the non-dipper pattern, as well as the small study population, nutritional factors, and ethnicity. We believe that further research into hemoglobin differences related to impaired circadian blood pressure regulation is necessary.

In their MAPEC trial (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares/Ambulatory Blood Pressure Monitoring for the Prediction of Cardiovascular Events), Hermida et al.[33] found that after a 5.6-year follow-up, abnormal nighttime blood pressure measured by ABPM was independently associated with the development of diabetes. Condoleo et al.[34] and Santilli et al.[35] also found a significant correlation between DM and HT, particularly with the non-dipper pattern.[34-36] Aryal et al.[37] provided evidence that prediabetes and living at H-ALT are linked. To compare hypertensive individuals regarding diabetes, our study did not include a normotensive group. However, diabetes was more common in the non-dipper group. We believe that this notable adverse effect of the non-dipper pattern should be further investigated in populations living at moderate-to-high altitudes, with larger sample sizes and across different geographic regions. Ambulatory mean systolic BP (particularly nighttime systolic blood pressure) has been shown in previous population studies to better predict cardiovascular events than clinic BP.[38] Inflammation contributes to both HT and CAD, as demonstrated in various studies.[39-41] The connection between chronic inflammation, hypertension, and accelerated atherosclerosis can be explained by increased endothelial dysfunction and decreased vasodilation due to persistently high cytokine levels.[42] Additionally, prior research indicates that both hypertensive and normotensive individuals with a non-dipping blood pressure pattern exhibit a more pronounced inflammatory response.[43-45] Although our study population included hypertensive individuals living at M-ALT, the non-dipper group showed a stronger association with CAD.

Approximately 78% of the risk for primary HT in men and 65% in women is attributed to excessive weight gain, which has long been recognized as a major cause of HT.[46] Studies have indicated that body fat distribution may explain the differences in obesity-related risk, since excess subcutaneous fat is less harmful than abdominal fat accumulation.[47,48] BMI remains the most important measure for estimating body fat and assessing

the cardiometabolic risk associated with obesity.[49] Despite high BMIs, there was no difference between the two groups in our study sample. However, waist circumference was significantly higher in the non-dipper group. Therefore, BMI alone cannot fully represent the cardiometabolic risk associated with obesity. Waist circumference shows a significant relationship with the absolute amount of abdominal fat compared to BMI.[50,51] The statistically significant finding of higher waist circumference in the non-dipper group in our study is important. We believe it is necessary to investigate this finding in a larger cohort of patients from different regions and to establish the potential relationship with more substantial evidence.

Limitations of the Study

The main limitations of this study include its single-center, retrospective design and relatively small sample size. Additionally, ethnic differences could not be identified because the cohort was primarily from one geographic location. Another limitation is the lack of comparison between our patient population and a control (normotensive) group, as well as with hypertensive patients living at sea level.

Conclusion

This study showed that the non-dipper pattern rate may be high in hypertensive individuals living at M-ALT. Since the non-dipper phenotype is associated with worse outcomes related to overall cardiovascular and end-organ damage, the importance of ABPM in diagnosing non-dipper hypertension is emphasized. It is also noteworthy that the mean daytime systolic and diastolic blood pressures in patients with non-dipper hypertension may be lower than in those with dipper patterns, which is an important finding that clinicians should not overlook. Waist circumference is another measure that should be considered in hypertensive patients when evaluating clinical outcomes, even though the link between high BMI and HT is well known. Clinicians should recognize that hypertensive patients living at M-ALT may have elevated mean nocturnal blood pressure levels; therefore, appropriate testing, treatment, and follow-up plans should be implemented.

Ethics Committee Approval: This study received approval from the Research Ethics Committee of Kafkas University (Approval Number: 80576354-050-99/669, Date: 28.05.2025).

Informed Consent: As it was a single-center retrospective study, informed consent was waived by the Ethics Committee.

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Pan-Immune-Inflammation Value as an Independent Indicator of Isolated Coronary Artery Ectasia

İzole Koroner Arter Ektazisinin Bağımsız Bir Göstergesi Olarak Pan-İmmün-İnflamasyon Değeri

ABSTRACT

Objective: Coronary artery ectasia (CAE) is increasingly recognized as an active inflammatory vascular disorder rather than a benign anatomical variant. The pan-immune-inflammation value (PIV) is a novel biomarker integrating neutrophil, monocyte, platelet, and lymphocyte counts, providing a comprehensive measure of systemic inflammation. This study aimed to evaluate the association between PIV and CAE and to compare their diagnostic performance with that of conventional inflammatory indices.

Method: In this retrospective case-control study, 17,538 patients who underwent elective coronary angiography between 2018 and 2024 were screened. A total of 228 patients with isolated CAE and 296 age-, sex-, and Body Mass Index (BMI)-matched controls with normal coronary arteries were included. Hematologic and biochemical parameters were analyzed, and inflammatory indices were calculated. Logistic regression and receiver operating characteristic (ROC) analyses were performed to identify independent predictors and assess diagnostic performance.

Results: Patients with CAE had significantly higher PIV levels compared to controls (801.6 [504.4–1301.8] vs. 491.8 [302.4–872.7], P < 0.001). In multivariable logistic regression, log-transformed PIV remained independently associated with CAE (odds ratio [OR]: 1.987, 95% confidence interval [CI]: 1.057–3.737, P = 0.033), along with hypertension, triglycerides, high-density lipoprotein (HDL) cholesterol, and serum creatinine. PIV demonstrated the highest discriminative ability among all inflammatory indices (area under the curve [AUC]: 0.674, 95% CI: 0.623–0.722), and correlated strongly with the Systemic Immune-Inflammation Index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Systemic Inflammation Response Index (SIRI) (P = 0.75–0.94).

Conclusion: Elevated PIV levels are independently associated with CAE, reflecting the pivotal role of systemic inflammation in its pathogenesis. Given its simplicity and availability, PIV may serve as a practical adjunctive marker for identifying patients at risk of CAE, warranting validation in larger prospective studies.

Keywords: Atherosclerosis, coronary artery ectasia, inflammatory biomarkers, pan-immune-inflammation value, systemic inflammation

ÖZET

Amaç: Koroner arter ektazisi (KAE), giderek artan şekilde iyi huylu bir anatomik varyanttan ziyade aktif bir inflamatuvar damar hastalığı olarak kabul edilmektedir. Pan-immün-inflamasyon değeri (PIV), nötrofil, monosit, trombosit ve lenfosit sayılarının birleşimiyle oluşturulan ve sistemik inflamasyonun bütüncül bir göstergesini sağlayan yeni bir biyobelirteçtir. Bu çalışmanın amacı, PIV ile KAE arasındaki ilişkiyi değerlendirmek ve tanısal performansını geleneksel inflamatuvar indekslerle karşılaştırmaktır.

Yöntem: Bu retrospektif olgu-kontrol çalışmasında, 2018–2024 yılları arasında elektif koroner anjiyografi uygulanan 17,538 hasta tarandı. İzole KAE'si olan 228 hasta ve yaş, cinsiyet ve BKİ açısından eşleştirilmiş normal koroner anatomili 296 kontrol çalışmaya dahil edildi. Hematolojik ve biyokimyasal parametreler analiz edildi, inflamatuvar indeksler hesaplandı. Bağımsız prediktörleri belirlemek ve tanısal performansı değerlendirmek amacıyla lojistik regresyon ve ROC analizleri yapıldı.

Bulgular: KAE'li hastalarda PIV düzeyleri kontrol grubuna göre anlamlı olarak daha yüksekti (801.6 [504.4–1301.8] vs. 491.8 [302.4–872.7], P < 0.001). Çok değişkenli lojistik regresyon analizinde, log-dönüştürülmüş PIV düzeyi hipertansiyon, trigliserid, HDL-kolesterol ve serum kreatinin ile birlikte KAE ile bağımsız olarak ilişkili kalmıştır (OR: 1.987, %95 GA: 1.057–3.737, P =

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0.033). PIV, tüm inflamatuvar indeksler arasında en yüksek ayırt edici güce sahipti (AUC: 0.674, %95 GA: 0.623–0.722) ve SII, NLR, PLR ve SIRI ile güçlü korelasyon göstermiştir (P = 0.75–0.94).

Sonuç: Yükselmiş PIV düzeyleri KAE varlığıyla bağımsız olarak ilişkilidir ve bu durum hastalığın patogenezinde sistemik inflamasyonun temel rolünü yansıtmaktadır. Basit, ulaşılabilir ve düşük maliyetli bir belirteç olarak PIV, KAE riski altındaki hastaların belirlenmesinde pratik bir tamamlayıcı araç olabilir. Bulgularımızın, daha geniş ve prospektif çalışmalarda doğrulanması gerekmektedir.

Anahtar Kelimeler: Ateroskleroz, koroner arter ektazisi, inflamatuvar biyobelirteçler, panoimmün-inflamasyon değeri, sistemik inflamasyon

Coronary artery ectasia (CAE) refers to a localized or diffuse dilatation of an epicardial coronary artery, where the vessel diameter is at least 1.5-fold greater than that of the normal adjacent segment.[1] The prevalence of CAE ranges from 1.2% to 4.9%, with males affected three times more often than females.[2] CAE may manifest across a wide clinical spectrum, ranging from incidental detection in asymptomatic individuals to symptoms such as exertional angina, exertional ischemia, and acute coronary syndrome (ACS).[3] While atherosclerosis is considered the primary etiopathogenetic mechanism of CAE, other contributing factors include chronic inflammation, matrix metalloproteinase (MMP) hyperactivity, connective tissue diseases, genetic conditions, infections, and iatrogenic injury following percutaneous coronary interventions.[4,5]

Several previous investigations have explored the link between inflammation and CAE, reporting significant associations with parameters such as the neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), Systemic Immune-Inflammation Index (SII), red cell distribution width (RDW), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and high-sensitivity CRP (hs-CRP).[6-8] Recent research has emphasized the importance of the pan-immune inflammation value (PIV) as a marker of systemic inflammatory status.[9-12] This biomarker incorporates the counts of four key immune cell types in peripheral blood: neutrophils, monocytes, platelets, and lymphocytes.[9-12] Recent studies have demonstrated the prognostic value of PIV in individuals with ST-elevation myocardial infarction (STEMI), non-STEMI, contrast-induced nephropathy, acute decompensated heart failure, coronary slow flow, and hypertrophic cardiomyopathy.[10,13-17]

Although PIV has demonstrated prognostic importance in multiple cardiovascular diseases, its association with CAE remains unexamined. This study represents the first investigation of PIV specifically in patients with CAE.

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
BMI	Body Mass Index
CAD	Coronary artery disease
CAE	Coronary artery ectasia
CAG	Coronary angiography
CRP	C-reactive protein
DM	Diabetes mellitus
ELR	Eosinophil-to-lymphocyte ratio
HDL	High-density lipoprotein
ICD	International Classification of Diseases
IL-6	Interleukin-6
LAD	Left anterior descending
MMP	Matrix metalloproteinase
NLR	Neutrophil-to-lymphocyte ratio
PIV	Pan-immune inflammation value
PLR	Platelet-to-lymphocyte ratio
RCA	Right coronary artery
RCS	Restricted cubic spline
RDW	Red cell distribution width
ROC	Receiver operating characteristic
SII	Systemic Immune-Inflammation Index
SIRI	Systemic Inflammation Response Index
STEMI	ST-elevation myocardial infarction
TNF-α	Tumor necrosis factor-alpha

Materials and Methods

Study Population

This retrospective case-control study screened 22,843 individuals undergoing elective coronary angiography (CAG) between January 2018 and December 2024. Of these, 17,538 patients remained after applying the exclusion criteria, among whom 228 patients (1.3%) had isolated CAE, as shown in Figure 1. Exclusion criteria included ACS, obstructive coronary artery disease (CAD), history of percutaneous coronary intervention or coronary artery bypass grafting, any acute or chronic infection, systemic inflammatory or autoimmune disorders, heart failure with reduced or mildly reduced ejection fraction, liver disease (defined as liver function tests > 3× the upper normal limit), significant endocrine, hematologic, respiratory, or metabolic conditions, malignancy, pregnancy, inadequate CAG imaging, and missing laboratory data.

The control group included 296 subjects with angiographically normal coronary arteries, matched to the CAE group by age, sex, and Body Mass Index (BMI). Baseline demographic and relevant clinical data were obtained from electronic medical records. The study protocol received approval from the Ankara Etlik City Hospital Scientific Research Ethics Committee (Approval Number: AEŞH-BADEK2-2025-136, Date: 27.05.2025), and was conducted in accordance with the Declaration of Helsinki. Given the retrospective design, informed consent was waived.

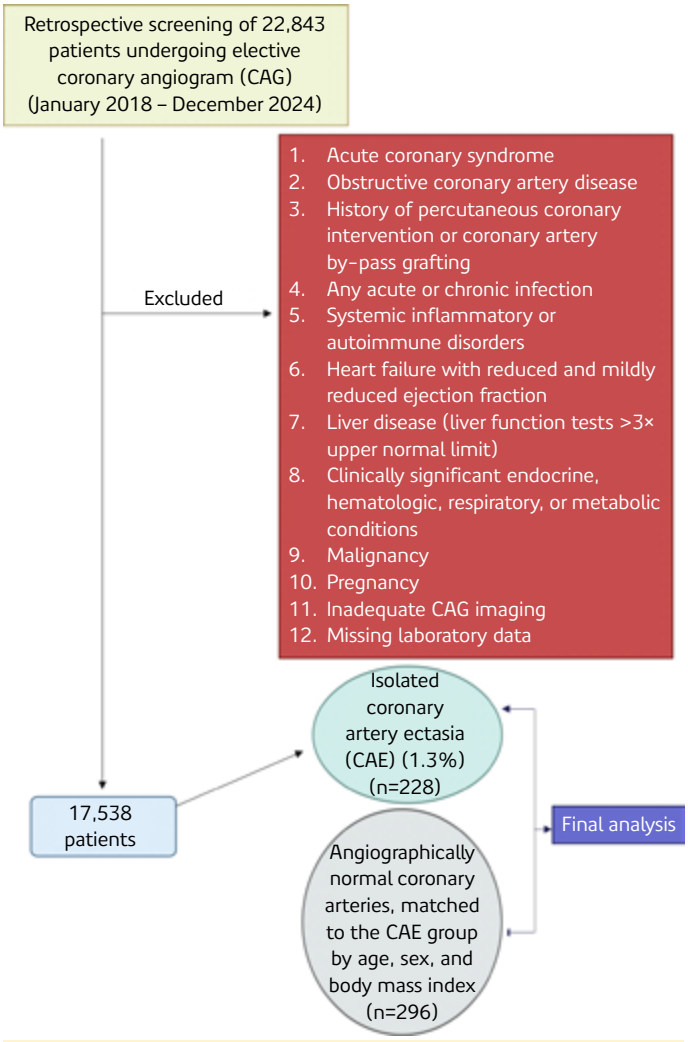

Figure 1. Flowchart of the study population.

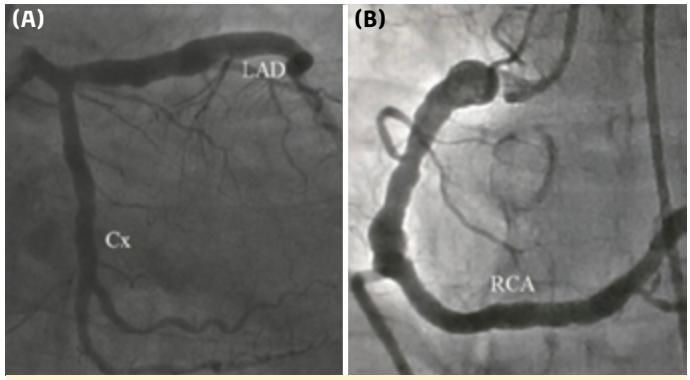

Figure 2. Coronary angiographic images demonstrating coronary artery ectasia (CAE), with (A) showing diffuse ectasia involving the left anterior descending (LAD) and circumflex (Cx) arteries, and (B) depicting marked segmental ectasia of the right coronary artery (RCA), characterized by localized dilatation.

Coronary Angiography and Measurements

All participants underwent coronary angiography using the General Electric Healthcare (GE) Innova™ IGS 530 system, equipped with AutoRight™ CAG devices (Chicago, Illinois, USA). Both normal and ectatic vessels were measured using specialized software (InnovaSpinTM, one-touch analysis, GE Healthcare). CAE is defined as an abnormal enlargement of the coronary artery lumen, occurring either locally or diffusely. This condition is characterized by a vessel diameter that exceeds 1.5 times that of the adjacent healthy segments or the maximal coronary artery.[18] CAE is further classified into three categories based on luminal diameter: small (< 5 mm), medium (5–8 mm), and large (> 8 mm).[19] A representative CAG image of CAE is presented in Figure 2.

Biochemical Analysis

At our institution, blood samples were obtained from the antecubital vein via atraumatic puncture before coronary angiography and delivered to the laboratory for analysis within one hour. For all participants undergoing CAG, blood was drawn into K3 EDTA-containing (ethylenediaminetetraacetic acid-containing) tubes to measure hematological indices. Hematological indices were assessed using a complete blood count analysis conducted with a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Biochemical parameters were measured using a Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, USA).

Definitions

Hypertension was considered present in participants who were receiving antihypertensive therapy. Patients were classified as having diabetes mellitus (DM) if they had a fasting serum glucose level greater than 126 mg/dL, a hemoglobin A1c level of 6.5% or higher, or were taking antidiabetic medications. Atrial fibrillation (AF) was identified based on electrocardiogram recordings and/or the use of anticoagulants. The diagnosis of peripheral arterial disease, cerebrovascular events, chronic obstructive pulmonary disease, and malignancy were established using ICD (International Classification of Diseases) codes and medical records.

Inflammatory Indices

We calculated the NLR by dividing the absolute neutrophil count by the absolute lymphocyte count; the platelet-to-lymphocyte ratio (PLR) by dividing the platelet count by the lymphocyte count; the SII using the formula (neutrophil count × platelet count) / lymphocyte count; the Systemic Inflammatory Response Index as (neutrophil count × monocyte count) / lymphocyte count; and the PIV using the formula: (neutrophil count × platelet count × monocyte count) / lymphocyte count.

Statistical Analysis

We performed all statistical analyses using SPSS software (version 27.0, IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages. In contrast, continuous variables were presented as mean ± standard deviation or median with interquartile range, depending on the data distribution, which was assessed using the Kolmogorov–Smirnov test. We compared groups using the Student's t-test or the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Logistic regression was performed to identify independent predictors of CAE, using only variables with P-values < 0.05 in the univariable analysis, after checking for multicollinearity and excluding highly collinear covariates

to ensure robustness. In the multivariable logistic regression model, individual hematological parameters (white blood cell count [WBC], platelet, neutrophil, lymphocyte, monocyte) and their derived inflammatory indices (NLR, SII, PLR, SIRI) were not included simultaneously with the PIV to avoid multicollinearity, as these variables constitute components of the PIV formula. Thus, the PIV was considered a representative composite marker integrating the overall inflammatory burden. To evaluate potential non-linear relationships between PIV and CAE, a restricted cubic spline (RCS) was fitted within a multivariable logistic regression framework. The model was adjusted for hypertension, high-density lipoprotein (HDL) cholesterol, triglycerides, and serum creatinine, which were identified as significant covariates in the multivariable analysis. Knots were placed at the 5th, 25th, 50th, 75th, and 95th percentiles of the PIV distribution. The overall association and nonlinearity of PIV with CAE were assessed using Wald and likelihood-ratio tests, respectively. Predicted probabilities with 95% confidence intervals (CI) were visualized to illustrate the adjusted association between PIV and CAE. We assessed the PIV's predictive capability for CAE via receiver operating characteristic (ROC) curve analysis and computed the area under the curve (AUC) to determine its discriminative power. Comparative predictive performances of inflammatory indices (PIV, SII, NLR, PLR, and SIRI) were assessed using ROC curve analysis. Differences between AUCs were evaluated by bootstrap resampling. Correlations among these indices were analyzed using Spearman's rank correlation test, and results were visualized as a correlation heatmap. A two-tailed P-value < 0.05 was deemed statistically significant in all analyses.

Results

Table 1 shows the baseline demographic, clinical, and laboratory features of the study population. No significant differences were found between the CAE and control groups for age, sex, BMI, smoking status, DM, hemoglobin, low-density lipoprotein cholesterol, glucose, or thyroid-stimulating hormone levels. However, hypertension was significantly more prevalent in the CAE group (74.6 vs. 53.0%, P < 0.001), as were cerebrovascular events (4.4 vs. 1.0%, P < 0.001) and AF (9.7 vs. 1.0%, P < 0.001). Baseline medications did not differ significantly between groups, except for angiotensin-converting enzyme (ACE) inhibitor and anticoagulant use, which were significantly more common among CAE patients (both P < 0.001). Statin, acetylsalicylic acid, clopidogrel, and beta-blocker use did not differ significantly between groups. Laboratory analyses revealed significantly greater white blood cell, platelet, neutrophil, and monocyte counts, along with lower lymphocyte counts in the CAE group. The erythrocyte sedimentation rate and CRP levels were similar between the groups. In contrast, CAE patients had higher serum creatinine and uric acid levels, lower high-density lipoprotein cholesterol, and higher triglyceride concentrations compared with controls. Inflammatory indices, including NLR, PIV, SII, PLR, and SIRI, were also significantly elevated in CAE patients. Regarding anatomical distribution, ectatic involvement was most commonly observed in the right coronary artery (RCA) (51.8%), followed by the circumflex (LCx) artery (24.6%) and the left anterior descending (LAD) artery (23.7%). Additionally, 37.7% of patients had small, 52.6% medium-sized, and 9.6% giant ectasia.

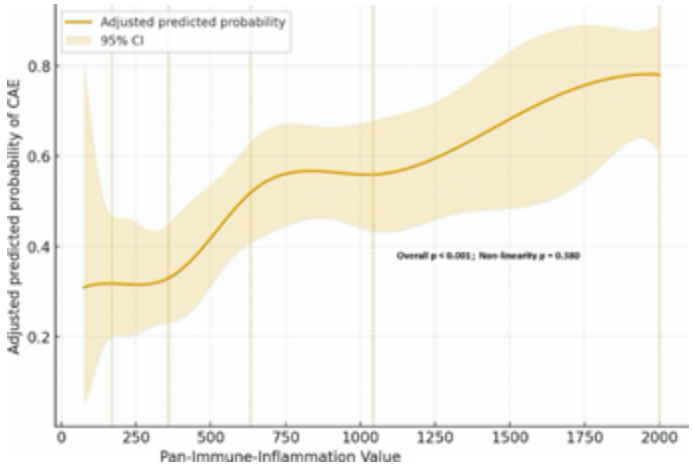

Figure 3. Adjusted restricted cubic spline illustrating the association between the pan-immune-inflammation value (PIV) and the probability of coronary artery ectasia (CAE), adjusted for hypertension, high-density lipoprotein (HDL) cholesterol, triglycerides, and creatinine. The overall association of PIV with CAE was significant (Wald test, P < 0.001), whereas evidence for deviation from linearity was not (likelihood-ratio test vs. linear term, P = 0.380). The shaded area denotes the 95% confidence interval (CI); vertical dashed lines indicate knot locations.

Table 2 summarizes the findings of the univariable and multivariable logistic regression analyses, which identified factors independently associated with CAE. In univariable analysis, multiple clinical and laboratory parameters—including hypertension, AF, ACE-inhibitor and anticoagulant use, triglycerides, HDL-cholesterol, WBC, platelet, neutrophil, lymphocyte, and monocyte counts, serum creatinine, serum uric acid, and inflammatory indices (log-transformed PIV, SII, and PLR, as well as non-transformed NLR and SIRI)—showed significant associations with CAE (all P < 0.05). However, in the multivariable model, only hypertension (odds ratio [OR]: 2.310, 95% CI: 1.463–3.647; P < 0.001), serum creatinine (OR: 4.441, 95% CI: 1.587–12.431; P = 0.005), triglycerides (OR: 1.008, 95% CI: 1.004–1.013; P < 0.001), HDL-cholesterol (OR: 0.953, 95% CI: 0.928–0.978; P < 0.001), and log PIV (OR: 1.987, 95% CI: 1.057–3.737; P = 0.033) remained independently associated with CAE.

In a multivariable logistic regression model adjusted for hypertension, HDL-cholesterol, triglycerides, and serum creatinine, restricted cubic spline analysis demonstrated a significant overall association between the PIV and the probability of CAE (P < 0.001 for overall association). The relationship appeared approximately linear, with no strong evidence of non-linearity (P = 0.380). As illustrated in Figure 3, higher PIV values were associated with a higher adjusted probability of CAE, and this trend persisted after controlling for potential confounders.

Figure 4 illustrates the predictive performance of the clinical and laboratory parameters identified as significant in the multivariable analysis for detecting CAE. Hypertension demonstrated an AUC of 0.608 (95% CI: 0.566–0.651, P < 0.001), with a sensitivity of 77.4% and specificity of 44.1%. HDL cholesterol showed an

Table 1. Baseline demographic, clinical, and laboratory characteristics of the groups

	Control group (n = 296)	CAE group (n = 228)	P
Demographic characteristics			
Age, years	60.8 ± 10.4	60.3 ± 10.2	0.452
Female sex, n (%)	80 (27.0)	65 (28.5)	0.755
Body Mass Index (kg/m^2)	27.5 ± 4.2	27.8 ± 4.1	0.637
Smoker, n (%)	58 (19.6)	62 (20.9)	0.658
Medical history, n (%)			
Hypertension	157 (53.0)	170 (74.6)	<0.001
Diabetes mellitus	143 (48.3)	113 (49.6)	0.552
Cerebrovascular event	3 (1.0)	10 (4.4)	<0.001
Atrial fibrillation	3 (1.0)	22 (9.7)	<0.001
Baseline medications, n (%)			
ACE inhibitor	139 (47.0)	154 (67.5)	<0.001
Anticoagulant	3 (1.0)	25 (11.0)	<0.001
Statin	57 (19.3)	52 (22.8)	0.318
Acetylsalicylic acid	75 (25.3)	69 (30.3)	0.184
Clopidogrel	3 (1.0)	6 (2.6)	0.168
Beta-blocker	76 (25.7)	70 (30.7)	0.204
Laboratory findings			
Hemoglobin (g/dl)	13.89 ± 1.43	13.90 ± 2.11	0.951
White blood cells (10^3/μL)	8.15 ± 2.09	8.72 ± 2.61	0.005
Platelets (10^3/μL)	272.1 ± 67.4	289.1 ± 70.1	0.005
Neutrophils (10^9/L)	5.10 ± 2.19	6.31 ± 2.99	<0.001
Lymphocytes (10^9/L)	1.83 ± 0.83	1.56 ± 0.71	<0.001
Monocytes (10^9/L)	0.69 ± 0.21	0.75 ± 0.19	0.008
HDL-cholesterol (mg/dl)	45.6 ± 8.9	41.7 ± 11.5	<0.001
LDL-cholesterol (mg/dl)	117.4 ± 37.1	114.2 ± 38.8	0.335
Triglycerides (mg/dl)	140.3 ± 44.5	169.3 ± 75.9	<0.001
Blood glucose (mg/dl)	96 (88-104)	100 (89-109)	0.658
Erythrocyte sedimentation rate (mm/hr)	5.2 (4.0-10.0)	6.0 (3.1-12.0)	0.447
C-reactive protein (mg/L)	4.7 (3.0-7.2)	5.0 (2.6-10.3)	0.255
Serum creatinine (mg/dl)	0.8 (0.7-0.9)	0.9 (0.8-1.0)	<0.001
Serum uric acid (mg/dl)	5.0 (4.2-5.5)	5.5 (4.8-6.5)	<0.001
TSH (μIU/ml)	1.8 (1.2-2.1)	1.6 (1.0-2.2)	0.108
Inflammatory indices			
Neutrophil-to-lymphocyte ratio	2.8 (1.9-4.3)	4.1 (2.5-5.8)	<0.001
Pan-immune inflammation value	491.8 (302.4-872.7)	801.6 (504.4-1301.8)	<0.001
Systemic immune-inflammation index	727.2 (471.3-1217.1)	1125.3 (698.4-1746.8)	<0.001
Platelet-to-lymphocyte ratio	152 (105-228)	196.8 (131.0-294.1)	<0.001
Systemic inflammation response index	1.8 (1.2-2.9)	2.9 (1.7-4.7)	<0.001
Ectasia artery, (n, %)			
LAD	-	54 (23.7)	N/A
LCx	-	56 (24.6)	N/A
RCA	-	118 (51.8)	N/A
Ectasia size, (n, %)			
Small	-	86 (37.7)	N/A
Medium	-	120 (52.6)	N/A
Giant	-	22 (9.6)	N/A

ACE, Angiotensin-converting enzyme; CAE, Coronary artery ectasia, HDL, High-density lipoprotein; LAD, Left anterior descending artery; LCx, Circumflex artery; LDL, Low-density lipoprotein; N/A, Not applicable; RCA, Right coronary artery; TSH, Thyroid-stimulating hormone.

Table 2. Univariable and multivariable logistic regression analyses of inflammatory and clinical parameters associated with coronary artery ectasia

	Univariable regression analysis		Multivariable regression analysis	
	OR (95% CI)	P	OR (95% CI)	P
Hypertension	2.592 (1.781–3.774)	<0.001	2.310 (1.463–3.647)	<0.001
Atrial fibrillation	10.433 (3.081–35.324)	<0.001	3.055 (0.324–28.809)	0.329
ACE inhibitor	2.352 (1.640–3.362)	<0.001	1.834 (0.750–4.487)	0.184
Anticoagulant	12.021 (3.581–40.373)	<0.001	8.823 (0.934–83.324)	0.057
Triglycerides	1.012 (1.010–1.022)	<0.001	1.008 (1.004–1.013)	<0.001
HDL-cholesterol	0.961 (0.943–0.982)	<0.001	0.953 (0.928–0.978)	<0.001
White blood cells	1.114 (1.031–1.190)	0.006	–	–
Platelets	1.004 (1.001–1.006)	0.005	–	–
Neutrophils	1.201 (1.114–1.303)	<0.001	–	–
Lymphocytes	1.381 (1.132–1.542)	<0.001	–	–
Monocytes	3.512 (1.372–8.963)	0.008	–	–
Serum creatinine	9.630 (4.142–22.361)	<0.001	4.441 (1.587–12.431)	0.005
Serum uric acid	1.530 (1.312–1.781)	<0.001	1.179 (0.966–1.439)	0.105
Neutrophil-to-lymphocyte ratio	1.125 (1.052–1.204)	<0.001	–	–
Log PIV*	1.903 (1.412–2.552)	<0.001	1.987 (1.057–3.737)	0.033
Log SII*	1.614 (1.280–2.031)	<0.001	–	–
Log PLR*	2.981 (1.122–7.901)	<0.001	–	–
Systemic Inflammation Response Index	1.170 (1.071–1.272)	<0.001	–	–

ACE, Angiotensin-converting enzyme; CI, Confidence interval; HDL, High-density lipoprotein; OR, Odds ratio; PIV, Pan-immune inflammation value; PLR, Platelet-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index. *Log PIV, Log SII, and Log PLR correspond to the logarithmically transformed values of PIV, SII, and PLR, respectively. A logarithmic transformation was applied to achieve normality prior to regression analysis.

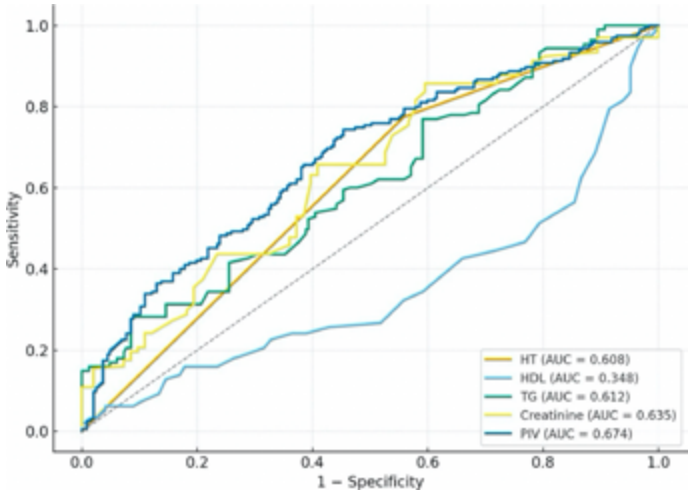

Figure 4. Receiver operating characteristic curves demonstrating the predictive performance of hypertension (HT), high-density lipoprotein (HDL) cholesterol, triglyceride (TG), creatinine, and the pan-immune-inflammation value (PIV) for identifying coronary artery ectasia. PIV exhibited the highest discriminative ability (AUC = 0.674, 95% CI: 0.623–0.722), while all parameters showed statistically significant AUC values (P < 0.001). AUC, Area Under the Curve.

inverse association with CAE, yielding an AUC of 0.348 (95% CI: 0.297–0.403, P < 0.001) and demonstrating high specificity (96.0%) but low sensitivity (6.2%) at the optimal cut-off value of 63 mg/dL. Triglyceride levels yielded an AUC of 0.612 (95% CI: 0.556–0.661, P < 0.001), with a sensitivity of 27.7% and specificity of 91.5% at a threshold of 187 mg/dL. Serum creatinine yielded an AUC of 0.635 (95% CI: 0.584–0.686, P < 0.001), with a sensitivity of 85.6% and specificity of 40.5% at an optimal cut-off value of 0.71 mg/dL. Among the evaluated variables, the PIV demonstrated the highest discriminative performance, with an AUC of 0.674 (95% CI: 0.623–0.722, P < 0.001), sensitivity of 74.4%, and specificity of 54.7%, using an optimal threshold of 533.8. Although PIV outperformed conventional biochemical and clinical markers, its diagnostic power remained moderate.

Comparative ROC analysis of PIV and conventional inflammatory indices (SII, NLR, PLR, and SIRI) revealed that PIV had the highest discriminative ability for predicting CAE (Figure 5A). Although PIV outperformed SII, NLR, and SIRI, the differences were not statistically significant (P = 0.260, P = 0.142, and P = 0.549, respectively). However, PIV showed a significantly higher predictive value than PLR (P = 0.001). Spearman correlation analysis demonstrated strong positive correlations between PIV and other indices (P = 0.75–0.94), indicating that these inflammatory markers share common biological pathways and reflect overlapping immune–inflammatory activity. The correlation heatmap (Figure 5B) visually illustrates these strong associations, supporting the conceptual interrelatedness among the inflammatory indices.

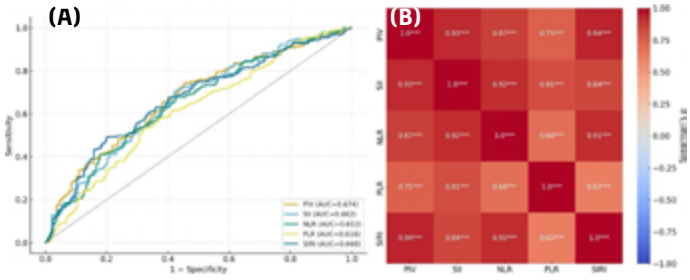

Figure 5. (A) Receiver operating characteristic curves of the pan-immune inflammation value (PIV) and other inflammatory indices for predicting coronary artery ectasia. PIV demonstrated the highest discriminative performance among the indices. (B) Spearman correlation matrix between PIV and other inflammatory indices. Strong positive correlations were observed among all indices, indicating shared inflammatory activity. SII, Systemic Immune-Inflammation Index; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SIRI, Systemic Inflammation Response Index.

Discussion

This research is the first to examine the relationship between PIV and CAE. The analysis found that patients with CAE had significantly higher PIV levels compared to those with normal coronary anatomy, and PIV remained an independent predictor of CAE even after accounting for traditional cardiovascular risk factors and other inflammatory markers. While these findings underscore the potential importance of PIV in the pathophysiological assessment of CAE, its diagnostic accuracy was moderate, as shown by an ROC analysis indicating only fair discriminative ability. This suggests that although PIV may be a useful marker of systemic inflammation, it should be viewed as a supplementary parameter within a broader clinical and laboratory context rather than a standalone diagnostic tool.

Inflammation plays a key role in CAE development, triggering both local vascular changes and systemic immune activation. Levels of adhesion molecules, such as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, are significantly higher in patients with isolated CAE than in those with obstructive CAD or normal coronary arteries on angiography, and they positively correlate with the extent of ectatic involvement.[20] These molecules facilitate monocyte adhesion and migration across the endothelium, thereby worsening local inflammation and endothelial dysfunction.[20] Vascular endothelial growth factor, a major regulator of inflammation and new blood vessel formation, is elevated in diffuse CAE cases, aligning with pathological neovascularization and its role in activating MMPs and breaking down the extracellular matrix.[21,22] Additionally, leukotrienes, proinflammatory lipids commonly found in atherosclerotic plaques, have been linked to the development of increased atherosclerosis and aneurysms.[23,24] Experimental studies show that overexpression of the 5-lipoxygenase gene increases the risk of aortic aneurysms and is associated with MMP secretion by macrophages in the vessel wall.[24,25] Overall, these findings emphasize the complex inflammatory processes underlying CAE and suggest that targeted anti-inflammatory treatments could benefit patients with this condition.

These findings align with an expanding body of literature that emphasizes the role of systemic inflammation in the development of CAE. Vrachatis et al.[8] conducted a comprehensive meta-analysis showing that inflammatory markers, including NLR, hs-CRP, interleukin-6 (IL-6), TNF-α, and RDW, were significantly higher in CAE patients compared to controls, indicating an inflammatory imbalance underlying the condition. Similarly, Tosu et al.[7] reported that SII was notably higher in patients with isolated CAE and had better diagnostic value than NLR. Yılmaz et al.[26] introduced the ELR as a new marker elevated in CAE patients and correlated with disease severity, supporting its usefulness in assessing diffuse or high-grade ectasia. Argan et al.[6] further demonstrated that CRP and serum uric acid levels were independently associated with CAE in patients with concomitant CAD, suggesting that CAE may be a manifestation of increased vascular inflammation beyond atherosclerosis. The current study found that PIV, a broader index including neutrophils, monocytes, lymphocytes, and platelets, was independently associated with CAE and showed moderate discriminative ability. Furthermore, our analysis revealed that PIV was strongly correlated with other inflammatory indices, including SII, NLR, PLR, and SIRI, further supporting the interrelated inflammatory mechanisms observed in previous studies. Collectively, these findings reinforce the notion that CAE is an active inflammatory vascular disorder rather than a passive anatomic variant, and that composite inflammatory indices such as PIV, SII, and ELR may serve as valuable tools in the diagnosis, risk stratification, and possibly future therapeutic targeting of CAE.

Fucà et al.[11] introduced the PIV in 2020 as a systemic inflammation-related predictive biomarker for metastatic colorectal cancer. PIV differs from other systemic inflammatory indices by providing a more comprehensive assessment of the inflammatory response, as it simultaneously incorporates neutrophils, monocytes, and platelets into its numerator. While indices such as the NLR, PLR, and SII include lymphocyte count in the denominator to reflect immune competence, PIV's unique strength lies in integrating three key pro-inflammatory cell types, thereby amplifying the overall inflammatory burden. Including monocytes enhances its clinical relevance, given their central role in vascular inflammation, endothelial dysfunction, and arterial remodeling, making PIV especially promising for inflammation-related cardiovascular conditions such as CAE.[27] The PIV has been shown to outperform other inflammatory indices in various clinical settings, including multiple types of cancer, ACS, acute heart failure, the coronary slow-flow phenomenon, and contrast-induced nephropathy.[10,11,13,16,28,29] Elevated PIV levels, indicative of increased inflammatory burden, may contribute to microvascular dysfunction and thus play a role in the pathogenesis of CAE. From a clinical perspective, PIV's practicality and affordability, especially in resource-limited settings, highlight its potential utility for cardiovascular risk stratification. Incorporating PIV into diagnostic algorithms may improve the detection of CAE, particularly in patients undergoing CAG for atypical chest pain or with non-obstructive lesions. However, despite its independent predictive value, PIV should not be used alone. Accurate diagnosis and risk stratification of CAE require a comprehensive approach that integrates clinical, angiographic, and laboratory findings.

Consistent with previous literature, most patients in our cohort were male (about 72%), aligning with the commonly cited male-to-female ratio of 3:1 in CAE[2] Regarding coronary artery involvement, the RCA was the most frequently affected vessel, involved in 51.8% of cases. This finding matches earlier studies that identify the RCA as the primary site of ectatic changes.[30] The LCx and LAD arteries were affected in 24.6% and 23.7% of cases, respectively. Additionally, single-vessel ectasia was observed in 41% of our patients, which agrees with previous reports indicating that CAE usually presents as a localized vascular abnormality rather than a diffuse process.[31] Overall, these findings demonstrate that the demographic and angiographic characteristics of our study population are consistent with established patterns of CAE, supporting the external validity of our results.

Hypertension was the most common comorbidity among patients with CAE in our study, affecting 74.6% of the CAE group. This rate is notably higher than those reported in previous studies by Harikrishnan (45.4%), Gunes (47.5%), Lam (58%), and Almansori (64%).[32-35] Moreover, hypertension independently predicted CAE in the multivariable logistic regression analysis, suggesting a potential pathogenic role beyond mere coexistence. These findings support the hypothesis that elevated blood pressure may contribute to vascular remodeling processes underlying ectasia formation.[36] In contrast to previous findings,[37] although serum uric acid levels were significantly higher in the CAE group and showed moderate discriminatory power in ROC analysis, they did not reach statistical significance in the multivariable model. This indicates that while uric acid may reflect systemic inflammation or endothelial dysfunction, it may not be a strong independent marker of CAE. Interestingly, in our cohort, traditional cardiovascular risk factors such as smoking and DM were not significantly associated with CAE. This aligns with recent studies reporting a weak or even inverse association between these factors and ectatic coronary changes, despite earlier evidence linking them to vascular dysfunction.[36,38] Although statins and ACE inhibitors are known to exert anti-inflammatory and endothelial-protective effects,[39,40] their specific influence on CAE remains a matter of controversy. In our study, statin use was not significantly different between the CAE and control groups. Additionally, ACE inhibitor therapy, although significant in univariable analysis, did not retain independent predictive value in the multivariable analysis. Prior evidence suggests that both drug classes may attenuate vascular inflammation and enhance endothelial function by reducing circulating inflammatory mediators, including hs-CRP and adhesion molecules. Özbay et al.[41] demonstrated that combined statin and ACE inhibitor therapy reduced hs-CRP levels in CAE patients after three months of treatment, suggesting a potential modulatory effect on vascular inflammation. Similarly, recent reviews have proposed that statins and ACE inhibitors may have favorable effects in CAE by improving endothelial stability and suppressing chronic inflammation, although large-scale prospective trials are lacking.[42] Our findings did not demonstrate any independent or protective association between the use of statins or ACE inhibitors and the presence of CAE. These results suggest that although these medications may exert systemic anti-inflammatory effects, as reported in prior studies, their influence on CAE itself appears limited in our study population. Collectively, these observations underscore the complex, multifaceted nature of CAE and highlight the potential utility of incorporating new inflammatory and metabolic markers into risk assessment models.

Study Limitations

This research presents certain limitations. This was a single-center study with a relatively small sample size, which may limit the generalizability of the findings; therefore, validation in larger, multicenter prospective studies is warranted. Given the retrospective and cross-sectional design of our study, causal relationships between PIV and CAE cannot be established. Although rigorous exclusion criteria were applied to minimize confounding, unrecognized subclinical inflammatory or immune conditions, dietary factors, and medication effects (particularly anti-inflammatory or lipid-lowering agents) could still have influenced the results. Additionally, a proportion of patients were on statin therapy, which exerts anti-inflammatory and endothelial-protective effects that may influence inflammatory indices such as the PIV; this potential confounding factor was not specifically addressed in our analysis. Inflammatory indices were derived from a single blood sample collected before angiography. Therefore, potential temporal fluctuations in inflammatory status could not be assessed. Serial measurements might provide a more robust evaluation in future prospective studies. Furthermore, advanced biomarkers, including cytokines (e.g., IL-6, TNF-α), oxidative stress markers, and genetic markers, were unavailable in this retrospective dataset. Despite employing automated software, the diagnosis of CAE based on CAG measurements may still be subject to interobserver variability. The control group consisted of individuals with angiographically normal coronary arteries. Inclusion of an additional comparison group with atherosclerotic but non-ectatic coronary arteries might have provided deeper insight into the inflammatory differences between CAE and atherosclerotic CAD. Additionally, the potential impact of medical therapy on PIV levels or CAE progression was not evaluated, as treatment data were limited to baseline use at the time of CAG. Finally, although PIV was identified as an independent predictor of CAE, its moderate sensitivity and specificity may limit its diagnostic utility as a standalone biomarker.

Conclusion

The study revealed that PIV levels are significantly higher in patients with CAE and are independently associated with its occurrence. This emphasizes the possible role of systemic inflammation in the development of CAE. Due to its simplicity and ease of use, PIV could serve as a helpful additional marker in the diagnostic process for patients suspected of having CAE. Further prospective studies are needed to determine its prognostic significance and to explore how it can be effectively incorporated into clinical decision-making.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara Etlik City Hospital Scientific Research Ethics Committee (Approval Number: AEŞH-BADEK2-2025-136, Date: 27.05.2025).

Informed Consent: Informed consent was waived due to the study's retrospective nature.

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

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Author Contributions: Concept – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Design – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Supervision – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Resource – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Materials – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Data Collection and/or Processing – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Analysis and/or Interpretation – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Literature Review – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Writing – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.; Critical Review – Ç.T., M.T.Ö., B.N.E., S.B.G., A.T., H.A.K., K.A., V.O.T., B.Ö.

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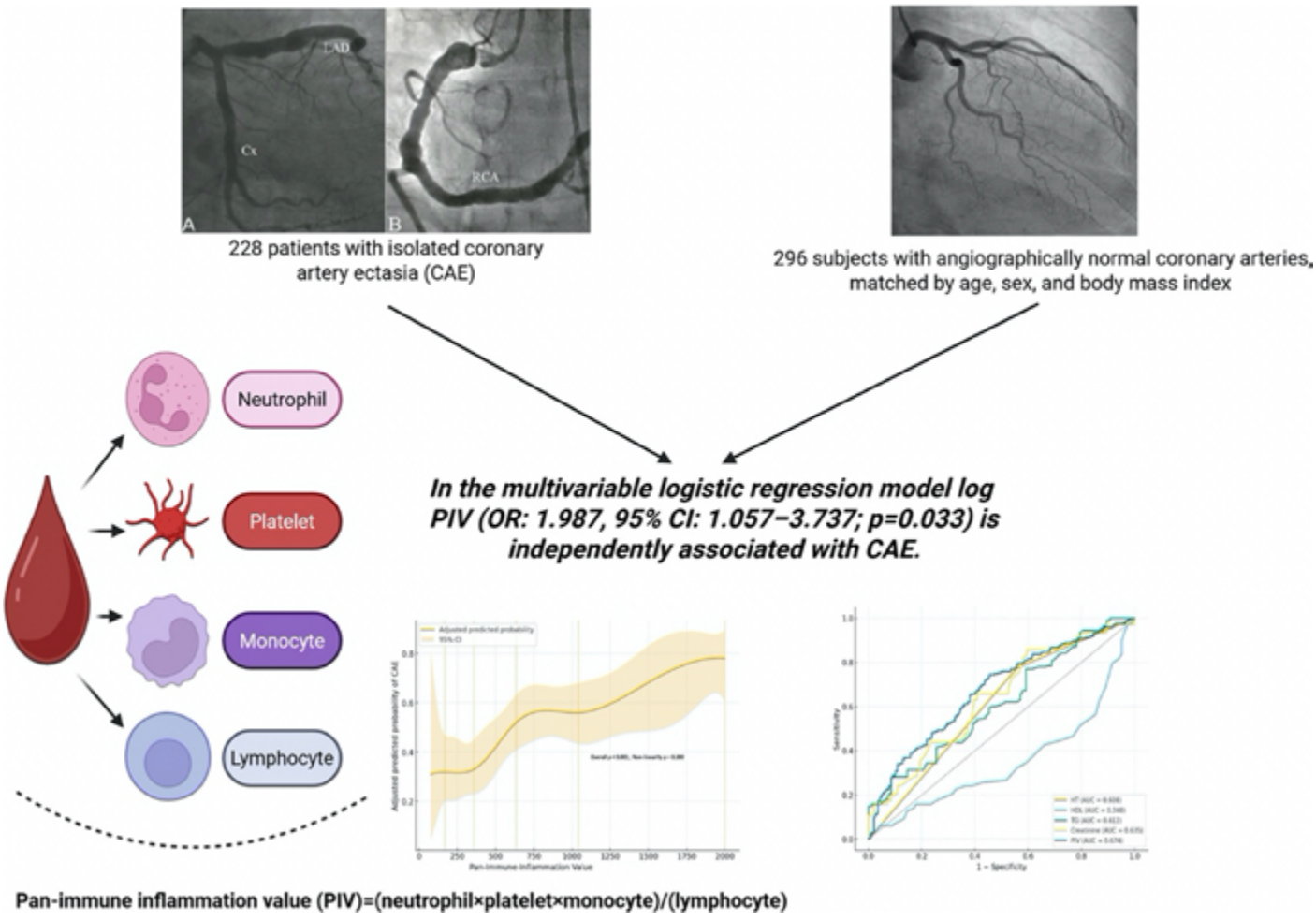

Graphical Abstract. Schematic summary of the study design and main findings. Among 17,538 patients undergoing elective coronary angiography, 228 patients with isolated coronary artery ectasia (CAE) and 296 controls with normal coronary anatomy were compared. The pan-immune-inflammation value (PIV), calculated as (neutrophil × platelet × monocyte) / lymphocyte, was significantly higher in CAE patients. In multivariable logistic regression, log-transformed PIV was independently associated with CAE (OR: 1.987, 95% CI: 1.057–3.737, P = 0.033).

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Awareness of Cardiovascular Disease as the Primary Cause of Mortality in Women: Insights from a Survey of 7,920 Individuals

Kadınlarda Kardiyovasküler Hastalıkların Birincil Ölüm Nedeni Olduğuna Dair Farkındalık: 7920 Kişilik Anket Çalışmasından Elde Edilen Bulgular

ABSTRACT

Objective: Cardiovascular disease (CVD) remains the main cause of mortality worldwide for both women and men. However, women are often overlooked as victims of CVD, leading to underdiagnosis and undertreatment. We aimed to assess public awareness of CVD as the leading cause of death in women.

Method: This nationwide survey was conducted to evaluate awareness of CVD as the primary cause of female mortality. Individuals aged 18 to 80 years from across Türkiye were invited to complete a brief, structured questionnaire.

Results: A total of 7,920 individuals were surveyed, of whom 59% were female. Only 34% of women and 38% of men correctly identified CVD as the leading cause of death in women (P = 0.0001). In contrast, malignant diseases—particularly breast cancer—were cited as the leading cause by 46% of women and 42% of men. Educational attainment was not associated with greater awareness. Among women, age was the only factor independently correlated with awareness, while in men both age and a history of coronary artery disease (CAD) were significantly associated with awareness.

Conclusion: Public awareness of CVD as the leading cause of death in women remains alarmingly low in Türkiye. Neither higher education nor the presence of cardiovascular risk factors was associated with increased awareness. Age emerged as the primary correlate in women, and both age and CAD history in men. These findings suggest that awareness of female CVD mortality may be shaped more by personal experience than by formal education, highlighting a critical gap in national health literacy.

Keywords: Awareness, cardiovascular disease, female heart, mortality

ÖZET

Amaç: Kardiyovasküler hastalıklar (KVH), halen dünya genelinde hem kadınlar hem de erkekler için en önemli ölüm nedenidir. Ancak kadınlar KVH'nin mağduru olarak yeterince dikkate alınmamakta, bu da yetersiz tanı ve tedaviye yol açmaktadır. Bu çalışmada, kadınlarda KVH'nin başlıca ölüm nedeni olduğuna yönelik toplumsal farkındalık düzeyini değerlendirmeyi amaçladık.

Yöntem: Bu ulusal çaplı anket çalışması, kadınlarda KVH'nin en yaygın ölüm nedeni olduğuna dair farkındalığı değerlendirmek amacıyla tasarlandı. Ülke genelinde 18 ila 80 yaşları arasındaki bireylerin, kısa ve yapılandırılmış bir anketi yanıtlamaları istenildi.

Bulgular: Toplam 7920 birey çalışmaya katıldı; bunların %59'u kadındı. Kadınların sadece %34'ü ve erkeklerin %38'i KVH'nin kadınlardaki başlıca ölüm nedeni olduğunu doğru şekilde bildirdi (P = 0.0001). Buna karşın, özellikle meme kanseri olmak üzere malign hastalıklar, kadınların %46'sı ve erkeklerin %42'si tarafından ilk sıradaki ölüm nedeni olarak belirtildi. Eğitim düzeyi, farkındalıkla ilişkili bulunmadı. Kadınlarda yaş, farkındalıkla bağımsız olarak ilişkili tek faktörken; erkeklerde hem yaş hem de koroner arter hastalığı (KAH) öyküsü farkındalıkla anlamlı düzeyde ilişkiliydi.

Sonuç: Türkiye'de KVH'nin kadınlardaki en yaygın ölüm nedeni olduğuna dair farkındalık alarm verici düzeyde düşüktür. Daha yüksek eğitim düzeyi ya da kardiyovasküler risk faktörlerinin varlığı artmış farkındalıkla ilişkili bulunmamıştır. Kadınlarda farkındalıkla en çok ilişkili faktör yaşken, erkeklerde yaş ve KAH öyküsü öne çıkmıştır. Bu bulgular, kadınlardaki KVH'ye bağlı ölümlere dair farkındalığın daha çok kişisel deneyimlerle şekillendiğini, eğitimle yeterince desteklenmediğini ve bu alanda ciddi bir sağlık okuryazarlığı eksikliğini ortaya koymaktadır.

Anahtar Kelimeler: Farkındalık, kardiyovasküler hastalıklar, kadın kalbi, mortalite

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Cardiovascular disease (CVD) remains the major cause of mortality worldwide for both men and women.[1] However, CVD in women continues to be under-recognized and undertreated.[2,3] Historically, women have been underrepresented in biological research and clinical trials, partly due to the exclusion of women of childbearing potential and older women with comorbidities.[2] This exclusion has limited our understanding of sex-specific differences in the pathophysiology, clinical presentation, and management of CVD.

While traditional CVD risk factors become more prominent with advancing age, women face additional sex-specific and inflammatory risk factors that contribute to their cardiovascular risk earlier in life. These include early menarche, premature menopause, gestational hypertension and diabetes, preterm delivery, use of oral contraceptives, and hormone replacement therapy.[4-6] Furthermore, autoimmune and inflammatory conditions—such as systemic lupus erythematosus, rheumatoid arthritis, and scleroderma—occur more frequently in women and substantially increase their risk of cardiovascular events.[7] In many of these contexts, women may not meet conventional criteria for cardiovascular risk, resulting in delayed recognition and treatment.

There is a paucity of data on many aspects of CVD in women, which may contribute to poor awareness of CVD as a leading cause of female mortality. Low awareness results in inadequate modification of risk factors and delayed diagnosis and treatment of CVD, thereby exposing women to greater cardiovascular risk.[8,9] In a 2019 American Heart Association (AHA) survey, only 44% of female respondents were aware that CVD is the main cause of mortality in women.[9] A recent review analyzed 36 studies from countries including the United States, Italy, Malaysia, South Korea, the United Arab Emirates, France, Jordan, Argentina, Canada, South Africa, and Chile, and revealed consistently low awareness of CVD in women across diverse populations, with particularly lower awareness in developing countries.[8] As such data are lacking in Türkiye, we aimed to investigate awareness of CVD as the leading cause of female mortality.

Materials and Methods

This nationwide, cross-sectional survey enrolled individuals (men and women) aged 18–80 years through random sampling across all cities of Türkiye. Subjects with overt mental disability hindering participation or the ability to provide informed consent were excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki (1975), as revised in 2008. Koşuyolu High Specialty Research and Training Hospital Clinical Trials Ethics Committee approved the study (Approval Number: 2023/18/747, Date: 21.11.2023), and informed consent was obtained from all participants.

Participants completed a structured 12-item questionnaire developed specifically for this study by a cardiologist (MK) experienced in survey design, preventive cardiology, and epidemiology. Data were collected through face-to-face interviews conducted by trained volunteers. The instrument collected information on demographics (age, sex, height, weight, educational attainment, and profession), cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia), and lifestyle behaviors (smoking status, exercise habits). The core question assessing awareness was:

ABBREVIATIONS

AHA	American Heart Association
ANOVA	Analysis of variance
APC	Annual percentage change
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
IQR	Interquartile range
MI	Myocardial infarction
TURKMI	Turkish Myocardial Infarction
VIRGO study	The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients

"In your opinion, what is the primary cause of mortality in women?" Response options included: heart attack/heart vessel disease, various cancers (breast, lung, genital), cerebral bleeding, and an open-ended option for other causes. While the questionnaire was reviewed for face validity by experts and pilot-tested on a small group representative of the study population to assess clarity, feasibility, and relevance, definitions of comorbidities were based on participant self-report. Obesity was defined as a body mass index (BMI) greater than 30 kg/m^2.

Statistical analyses were performed using SPSS software (IBM Corp., SPSS Statistics for Windows, Version 25.0, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR), depending on distributional characteristics. Categorical variables were expressed as numbers of subjects and percentages. Given the large sample size (n > 2,000), assessment of variable distribution was conducted primarily using histograms, along with evaluations of skewness and kurtosis. Variables with non-normal distributions were reported as medians with IQRs.

The chi-square test was used to compare categorical variables. Differences between the sexes for continuous variables were assessed using the independent-samples t-test or the Mann-Whitney U test, as appropriate. Mean values were compared using the independent-samples t-test or one-way analysis of variance (ANOVA). Logistic regression analysis was performed to model relationships between dependent and independent variables. A p value less than 0.05 was considered statistically significant.

Results

A total of 7,920 respondents were included in the analysis. Females constituted 59% (n = 4,643) of the study population. Table 1 presents the demographic and clinical characteristics of the participants. The mean age was 57.27 ± 11.47 years, with no significant difference between women and men (Figure 1).

Educational background varied widely: 13% of participants were university graduates, while another 13% reported no formal education. Notably, 20% of women and 3.8% of men were illiterate—rates considerably higher than official figures from the Turkish Statistical Institute. Moreover, 85% of participants were primary school graduates or above—a proportion far lower than that of the general population.[10] Employment status also revealed a marked gender gap, with substantially fewer women in the workforce.

Table 1. Baseline characteristics of the population and comparison of awareness of CVD as the primary cause of death in women according to sex

	All (n = 7,920)	Female (n = 4,643)	Male (n = 3,277)	P
Age (years) (mean ± SD) (min–max)	57.27 ± 11.47 (18-80)	57.42 ± 11.48 (18-80)	57.05 ± 11.45 (18-80)	0.168
BMI (kg/m^2), (mean ± SD)	27.89 ± 4.25	28.25 ± 4.72	27.39 ± 3.42	< 0.001
Educational status, n (%)				< 0.001
Illiterate	1059 (13.4)	935 (20.1)	124 (3.8)	
Primary school graduate	3063 (38.7)	2016 (43.4)	1047 (31.9)	
Secondary/high school graduate	2739 (34.6)	1283 (27.6)	1456 (44.4)	
Bachelor's degree or higher	1059 (13.4)	409 (8.8)	650 (19.8)	
In employment, n (%)	2549 (32.1)	794 (17.1)	1755 (53.6)	< 0.001
Cardiovascular risk factors, n (%)				
Hypertension, n (%)	2557 (32.28)	1575 (33.92)	982 (29.96)	< 0.001
Diabetes mellitus, n (%)	715 (9.02)	422 (9.1)	293 (8.9)	0.427
Hyperlipidemia, n (%)	2871 (36.3)	1652 (35.6)	1219 (37)	0.073
Obesity, n (%)	2082 (26.3)	1432 (30.8)	650 (19.8)	< 0.001
Smoking, n (%)				< 0.001
Non-smoker	5194 (65.6)	3804 (81.9)	1390 (42.4)	
Ex-smoker	1015 (12.8)	297 (6.4)	718 (21.9)	
Current smoker	1711 (21.6)	542 (11.7)	1169 (35.7)	
Regular exercise habit, n (%)				
No-exercise	6820 (86.1)	4154 (89.5)	2666 (86.1)	< 0.001
≤ 3 hours/week	904 (11.4)	417 (8.9)	487 (14.9)	< 0.001
> 3 hours/week	196 (2.5)	72 (1.5)	124 (3.8)	< 0.001
Coronary artery disease, n (%)	1467 (18.5)	628 (13.5)	839 (25.6)	< 0.001
Awareness of CVD as the primary cause of death in women	2813 (35.5)	1572 (33.8)	1241 (37.8)	< 0.001

BMI, Body mass index; CVD, Cardiovascular disease; N, Number; SD, Standard deviation.

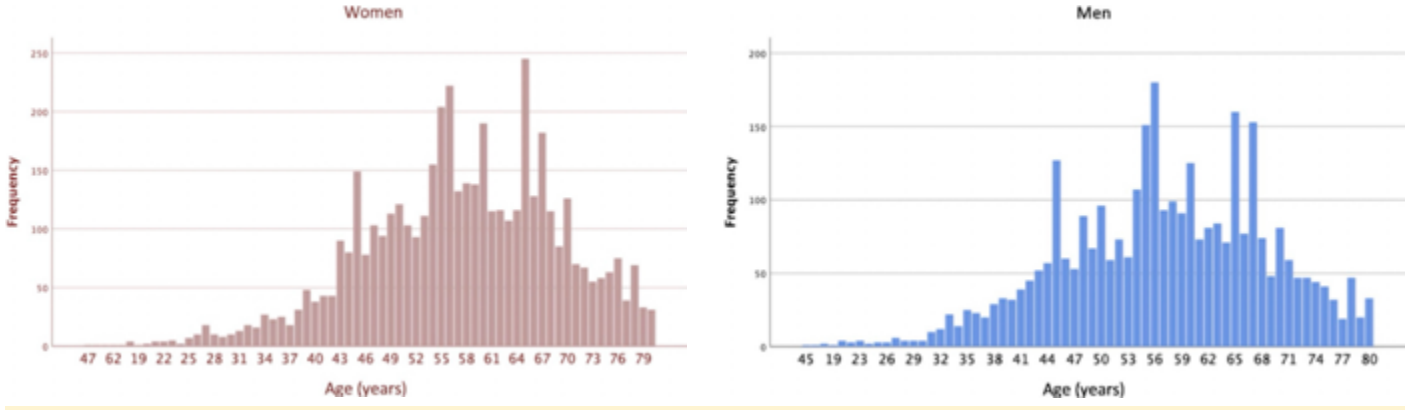

Figure 1. Age distribution of female and male respondents.

Almost 36% of male and 12% of female respondents were current smokers (P < 0.001). In terms of physical activity, 86% of men and 89.5% of women did not engage in regular exercise (P < 0.001). Obesity and self-reported hypertension were more frequent in women. Self-reported diabetes mellitus and hyperlipidemia did not differ significantly between the sexes (Table 1).

When asked about the leading cause of death in women, only 34% of female and 38% of male participants correctly identified CVD (P < 0.001) (Figure 2). In contrast, 46% of women and 42% of men believed malignancies—particularly breast cancer—were the main cause (Figure 3). Overall, 27% of women and 22% of men selected breast cancer as the major cause, totaling 25% of the entire study population (n = 2.015).

Table 2. Comparison of those aware and non-aware of cardiovascular disease as the leading cause of female mortality in each sex according to baseline characteristics of the population

	Female (n = 4,643)			Male (n = 3,277)		
	Aware	Non-Aware	P[a]	Aware	Non-Aware	P[b]
n (%)	1572 (33.8)	3071 (66.1)	0.0001	1241 (37.9)	2036 (62.1)	0.001
Age (years) (mean ± SD)	58.78 ± 11.27	56.73 ± 11.51	0.0001	57.56 ± 11.45	56.74 ± 11.43	0.047
BMI (kg/m^2), (mean ± SD)	28.53 ± 4.72	28.11 ± 4.71	0.004	27.37 ± 3.42	27.40 ± 3.41	0.86
Educational status, n (%)			0.002			0.805
Illiterate	355 (22.5)	580 (18.9)		46 (3.7)	78 (3.8)	
Primary school graduate	690 (43.8)	1326 (43.2)		394 (31.7)	653 (32)	
Secondary/high school graduate	412 (26.2)	871 (28.3)		544 (43.8)	912 (44.8)	
Bachelor's degree or higher	115 (7.3)	294 (9.5)		257 (20.7)	393 (19.3)	
In employment	226 (14.3)	568 (18.5)	0.0001	674 (54.3)	1081 (53.1)	0.261
Cardiovascular risk factors, n (%)						
Hypertension, n (%)	531 (33.7)	1044 (33.9)	0.455	367 (29.5)	615 (30.2)	0.366
Diabetes mellitus, n (%)	139 (8.8)	283 (9.2)	0.706	115 (9.3)	178 (8.7)	0.614
Hyperlipidemia, n (%)	574 (36.5)	1078 (35.1)	0.179	453 (39.7)	766 (37.6)	0.272
Obesity, n (%)	513 (32.6)	919 (29.9)	0.0001	243(19.6)	407 (20)	< 0.001
Smoking, n (%)			0.009			0.607
Non-smoker	1325 (82.3)	2479 (80.7)		540 (43.5)	850 (41.7)	
Ex-smoker	92 (5.9)	205 (6.7)		268 (21.6)	450 (22.1)	
Current smoker	155 (9.9)	387 (12.6)		433 (34.9)	736 (36.1)	
Regular exercise habit, n (%)			0.207			0.976
No-exercise	1421 (90.4)	2733 (89)		1008 (81.2)	1658 (81.4)	
≤ 3 hours/week	125 (8)	292 (9.5)		186 (14.9)	301 (14.8)	
> 3 hours/week	26 (1.7)	46 (1.5)		47 (3.8)	77 (3.8)	
Coronary artery disease, n (%)	245 (15.6)	383 (12.5)	0.002	344 (27.7)	495 (24.3)	0.017

BMI, Body mass index; CVD, Cardiovascular disease; N, Number; SD, Standard deviation. a: P value compares aware vs. non-aware females; b: P value compares aware vs. non-aware males.

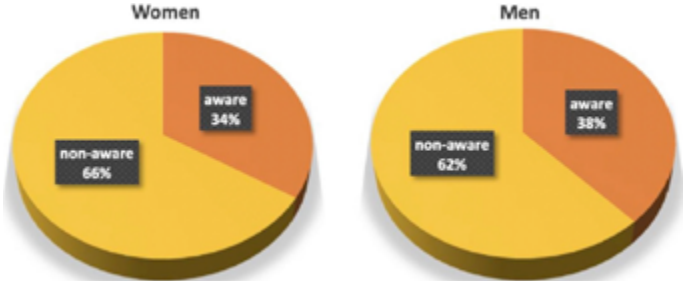

Figure 2. Percentage of individuals for each sex who are aware of cardiovascular disease as the leading cause of female mortality.

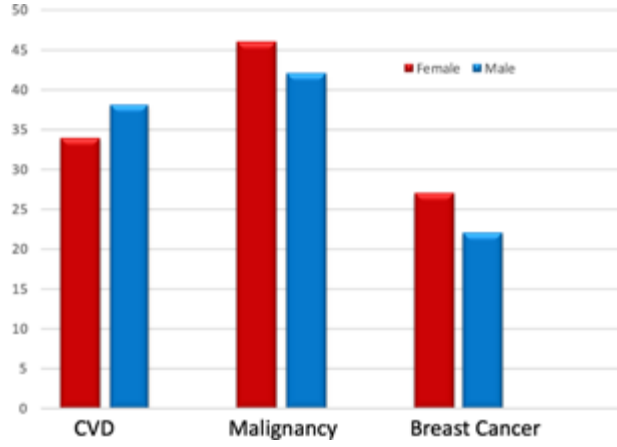

Figure 3. Presumed causes of death in women, identified by sex.

Interestingly, overall educational level was not associated with greater awareness (P = 0.377). In gender-stratified analyses, however, a paradox emerged: illiterate women were more aware of CVD as the leading cause of female mortality, while awareness was lowest among university-educated women (Table 2).

With increasing age, participants were more likely to recognize CVD as the leading cause of death in women. This finding was especially pronounced among those over 65 years (P < 0.001).

In sex-specific analyses, age was significantly correlated with awareness in women (P < 0.001) but showed only borderline statistical significance in men (P = 0.047).

Subjects with a medical history of coronary artery disease (CAD) were more aware, but having hypertension, diabetes mellitus, or

hyperlipidemia did not increase awareness of CVD as the leading cause of death in women. Obese subjects and non-smoking women were more aware, whereas current-smoking women were less aware. Smoking status did not affect awareness in men, and the reverse was also true (Table 2).

When we explored whether awareness translated into healthier behaviors, the results were less encouraging. Education level, a medical history of CAD, or the presence of CVD risk factors did not appear to motivate risk factor modification. Participants with CAD were less likely to engage in regular exercise. Higher educational attainment did not alter smoking or exercise habits. Hypertensive or diabetic subjects did not exercise more, and patients with CAD did not smoke less. However, those with hyperlipidemia reported more exercise, and people with diabetes or hypertension were somewhat less likely to smoke.

Finally, logistic regression analysis demonstrated that when multiple factors were examined simultaneously, age was the only variable associated with awareness in women, while both age and a personal history of CAD were significantly associated with greater awareness in men.

Discussion

Our nationwide survey documented that public awareness of CVD as the leading cause of death in women is extremely low, with even lower awareness among women themselves. Participants were more likely to identify cancer as the primary cause of female mortality. Neither higher educational attainment nor a history of cardiovascular risk factors was linked to increased awareness. However, logistic regression analysis identified age as the sole factor associated with awareness in women, while both age and a history of CAD were significantly correlated with awareness in men.

Awareness of CVD as the main health problem of women is extremely critical to prevention, timely diagnosis, and appropriate treatment of CVD. Lack of awareness also contributes to resistance against primary preventive measures. The Nurses' Health Study revealed that 82% of ischemic heart disease events were attributable to a lack of adherence to lifestyle measures involving diet, exercise, and smoking.[11] Another study indicated that 41% of women did not seek help within the first 12 hours of chest pain onset, likely reflecting a lack of awareness regarding cardiovascular risk in women.[12]

To reduce mortality and morbidity among women, many countries and organizations have launched campaigns to raise awareness of CVD-related deaths in women and periodically assess public awareness levels. However, gender inequality in cardiovascular care remains evident in many parts of the world, a disparity first described as the "Yentl syndrome" in 1991.[13] Notably, the term Yentl syndrome is derived from the main character in Isaac Bashevis Singer's story, who had to conceal her gender and present herself as a man to receive education.[14] Yentl syndrome highlights the persistent sex bias in the management of CVD.[13] Women with acute or chronic coronary syndromes, or those presenting with chest pain, are still less likely to undergo coronary angiography or receive coronary revascularization procedures.[15] It appears that women must first present with severe CAD or experience a myocardial infarction (MI) to receive the same standard of care afforded to men. The core challenge lies in convincing both the public and the medical community that CVD is equally a women's disease.[13] Since the recognition of this bias, many public awareness initiatives—including Go Red for Women, HER Disease Campaign, #29daysofheart, The Heart Truth Campaign, and Make the Call, Don't Miss a Beat—have been launched in the United States and the European countries to raise awareness of CVD as the number one killer of women.

In Türkiye, there is currently no structured, nationwide campaign or research initiative specifically targeting awareness of CVD in women. Age-adjusted mortality rates for ischemic heart disease, based on the world standard population, demonstrated an upward trend between 2009 and 2019; however, this trend was not statistically significant [annual percentage change (APC) = 1.7 (-0.8; 4.3), P = 0.166]. The APC value for women (2.2 [-0.7; 5.2, P = 0.121]) was higher compared with men (1.4 [-1.1; 3.9, P = 0.235]).[16] Turkish women also exhibit more adverse cardiovascular risk profiles than men, except for smoking.[17] Likewise, treatment goals for low-density lipoprotein (LDL) cholesterol, blood pressure, and blood glucose are less frequently achieved in women with CVD compared with their male counterparts.[18] In addition, both early and one-year mortality following acute MI are almost threefold higher in women than in men (11.2% vs 3.8%, respectively; P < 0.001).[18] The results of the Turkish MI (TURKMI) Registry showed that women with ST-segment elevation MI are more likely than men to delay seeking medical attention for chest pain, experience longer total ischemic times, and have higher in-hospital mortality rates.[19,20] These sex-based disparities have been attributed to a greater burden of comorbidities, delayed treatment, and lower implementation of guideline-recommended therapies in women presenting with acute MI.[19] Our finding that only one-third of female participants were aware that CVD is the leading cause of death in women suggests that low awareness may play a key role in these delays—particularly the prolonged total ischemic time and delay in treatment. This highlights the potential influence of awareness not only on preventive behaviors but also on the urgency with which women seek care during acute cardiovascular events.

Since 1997, the AHA has conducted national surveys to assess women's awareness and understanding of CVD. Between 1997 and 2012, awareness of ischemic heart disease as the leading cause of death among women nearly doubled—from 30% to 56%.[9] This significant improvement has been largely attributed to the impact of large-scale public awareness campaigns. However, the 2019 AHA survey showed a concerning reversal: awareness declined to 43.7% compared with 64.8% in 2009 (P < 0.05). Overall, awareness among women increased steadily from 1997 to 2009, plateaued until 2012, and then declined markedly by 2019.[9] In Türkiye, historical data are lacking, making comparable trend analyses impossible. Nevertheless, global data highlight the persistent gap in awareness: only 14.4% of women in Chile, 9% in Singapore, and 4% in the United Arab Emirates recognized CVD as the leading cause of female death.[21,22] Similarly, a nationwide Korean survey reported that almost half of the women surveyed did not consider CVD a significant health concern for women.[21]

The age-adjusted mortality rates from CVD in women are four times higher than those from breast cancer.[23] Despite this, both male and female participants in our survey most frequently cited malignancies—particularly breast cancer—as the leading cause of death in women, with women doing so at a higher rate. This discrepancy between perceived and actual mortality causes is striking. According to data from the Turkish Statistical Institute, CVD accounts for twice as many deaths in women as all malignancies combined.[24,25] In Türkiye, nationwide awareness campaigns and educational efforts targeting malignant neoplasms, especially breast cancer, have been implemented effectively. Annual diagnostic screening for breast and gastrointestinal cancers is widely encouraged and often supported by health insurance providers. In contrast, there has been no equivalent effort to raise awareness about women's cardiovascular health. Our findings reflect this imbalance: public health messaging around cancer has been effective, while messaging about CVD in women remains insufficient. This disparity likely contributes to widespread misperceptions about the leading cause of female mortality and underscores the urgent need for targeted awareness campaigns focused on CVD.

Interestingly, our study did not demonstrate a positive association between educational attainment and awareness of CVD mortality in women, contrary to findings from both the Korean nationwide survey[21] and the 2019 AHA survey,[9] which reported that lower educational levels were independently associated with reduced awareness. This discrepancy may point to limitations within the Turkish education system in fostering functional health literacy. Indeed, a prior study found that only 28% of Turkish adults possessed adequate health literacy, highlighting the need to prioritize health literacy initiatives in Türkiye.[26] Notably, in our study, illiterate women demonstrated higher levels of awareness compared to university-educated women. This controversial finding may be attributed to age differences: the mean age of illiterate women was 64.7 ± 8.93 years, while that of literate women was significantly lower at 55.6±11.3 years. A similar age gap was observed among men; illiterate men were older (65.1 ± 10 years) than their literate counterparts (56.7 ± 11.4 years). Among men, cumulative educational attainment was not associated with awareness levels. Logistic regression analysis further confirmed that age was the only independent correlate of awareness in women, while both age and a history of CAD were significantly associated with awareness in men. These findings suggest that, in Türkiye, awareness of CVD as the leading cause of female mortality is likely driven more by lived experience and personal observation—particularly among older individuals—than by formal education. Another important finding in our population is the higher awareness we observed among individuals over 65 years of age in both sexes. Similarly, the marked decline in CVD awareness among women in the AHA survey between 2009 and 2019, affecting all racial, ethnic, and demographic groups, did not occur in those aged ≥ 65 years.[9] These parallel findings emphasize the need for renewed, age-targeted educational efforts, particularly for younger women and high-risk populations.

Interestingly, we did not observe any relationship between awareness of CVD mortality in women and the presence of traditional cardiovascular risk factors such as hypertension, diabetes mellitus, or hyperlipidemia, consistent with the findings of the 2019 AHA survey.[9] Only a personal history of CAD was significantly associated with increased awareness. These findings suggest that individuals may only recognize the cardiovascular threat to women after experiencing or witnessing a major clinical event. The VIRGO study (The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) further supports this interpretation, showing that physicians were less likely to inform women of their CVD risk or to discuss preventive strategies.[27] Overall, these results indicate a broader failure in risk communication, particularly at the level of primary prevention, and emphasize the importance of proactive, sex-specific education and counseling in routine care.

Our results underscore the urgent need to implement national action plans aimed at increasing public awareness of CVD as the leading cause of death in women. A dedicated, large-scale public awareness campaign focused on women's cardiovascular health could play a pivotal role in reducing the high burden of female cardiovascular mortality in Türkiye. Equally important is the active involvement of healthcare professionals, who should be encouraged and supported to engage in regular, evidence-based risk communication—especially with women at elevated risk. Finally, integrating health literacy education into school curricula may provide long-term, population-level benefits by equipping individuals with the tools to understand and act on cardiovascular health risks early in life.

Strengths and Limitations

Our study has several important strengths. First, it was conducted across all provinces of Türkiye, ensuring broad national representation. The large sample size and inclusion of participants from a wide range of educational and literacy backgrounds enhanced the generalizability of the findings. Notably, the use of face-to-face interviews allowed for the participation of illiterate individuals, improving inclusivity and reducing sampling bias.

However, certain limitations must be acknowledged. The questionnaire, although developed by an expert cardiologist with experience in epidemiology and survey methodology, was not subjected to formal validation in an independent population. While it was reviewed for face validity and pilot-tested, the absence of full psychometric validation may affect interpretability and limit its generalizability.

In addition, the survey relied on self-reported data for comorbid conditions and lifestyle behaviors, which may be subject to recall or reporting bias. Furthermore, the study did not collect socioeconomic or region-specific data, and awareness of CVD as the leading cause of death in men was not assessed. Therefore, comparisons between male and female awareness levels should be interpreted with caution.

Despite these limitations, to the best of our knowledge, this is the first nationwide study in Türkiye to investigate public awareness of CVD as the leading cause of death among women, highlighting a critical gap in national cardiovascular health literacy.

Conclusion

The findings of this survey reveal alarmingly low public awareness of CVD as the leading cause of death in women, a gap that persists across both genders. Surprisingly, neither higher educational attainment nor a history of cardiovascular risk factors was associated with greater awareness. Instead, age emerged as the only factor

significantly associated with awareness in women, while both age and a history of CAD were correlated with awareness in men. These results suggest that awareness of female mortality causes may arise more from personal experiences than from formal education, underscoring a potential gap in health literacy.

Collectively, these findings highlight the urgent need for targeted public awareness campaigns addressing CVD as the leading cause of death among women in Türkiye. Furthermore, we advocate for the integration of health literacy into school curricula. Equipping individuals—particularly women—with the knowledge and skills to make informed decisions about their cardiovascular health is essential for improving outcomes and reducing preventable mortality.

Ethics Committee Approval: Ethics committee approval was obtained from Koşuyolu High Specialty Research and Training Hospital Clinical Trials Ethics Committee (Approval Number: 2023/18/747, Date: 21.11.2023).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest: Meral Kayikcioglu has received honoraria from Abbott, Abdi Ibrahim, Chiesi, LIB Therapeutics, Novartis, NovoNordisk, TR-pharma, and Ultragenix; research funding from Amryt Pharma, and has participated in clinical trials with Amgen, Ionis, LIB Therapeutics, Lilly, Novartis, Novo Nordisk, during the past 3 years. Müge Ildızlı Demirbaş has no conflicts of interest.

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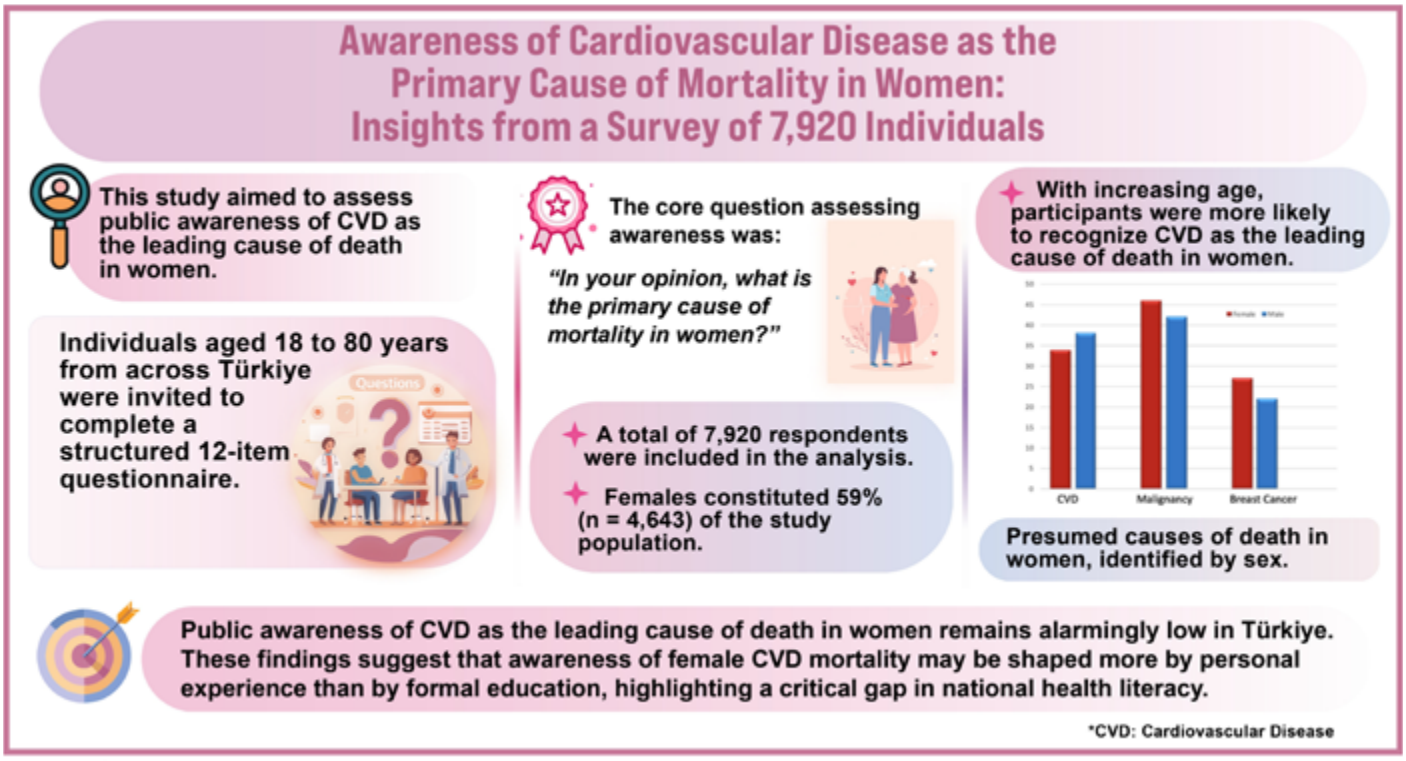
Awareness of Cardiovascular Disease as the Primary Cause of Mortality in Women: Insights from a Survey of 7,920 Individuals
This study aimed to assess public awareness of CVD as the leading cause of death in women.
Individuals aged 18 to 80 years from across Türkiye were invited to complete a structured 12-item questionnaire.
Questions
The core question assessing awareness was:
"In your opinion, what is the primary cause of mortality in women?"
A total of 7,920 respondents were included in the analysis.
Females constituted 59% (n = 4,643) of the study population.
With increasing age, participants were more likely to recognize CVD as the leading cause of death in women.
CVD
Malignancy
Breast Cancer
Presumed causes of death in women, identified by sex.
Public awareness of CVD as the leading cause of death in women remains alarmingly low in Türkiye. These findings suggest that awareness of female CVD mortality may be shaped more by personal experience than by formal education, highlighting a critical gap in national health literacy.
*CVD: Cardiovascular Disease
@PAY 2026
Ildızlı DM. et al. Turk Kardiyol Dern Ars. 2026;54(1):51–57.

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When Everything Else Fails: TricValve® in a Dialysis-Dependent Patient with Advanced Right Heart Failure

Diğer Her Şey Başarısız Olduğunda: İleri Derecede Sağ Kalp Yetersizliği Olan Diyalize Bağımlı Hastada TricValve®

ABSTRACT

We report the case of a 72-year-old man with end-stage renal disease on maintenance dialysis and advanced right heart failure with severe tricuspid regurgitation, chronic atrial fibrillation, and cardiac cachexia. The patient presented with profound hypotension and cardiogenic shock, leading to recurrent failure of renal replacement therapy despite inotropic support. Given the prohibitive surgical risk, transcatheter edge-to-edge repair was deemed unsuitable due to extensive annular dilation, and the patient underwent urgent percutaneous caval valve implantation with the TricValve® system. The procedure was technically successful, resulting in immediate hemodynamic stabilization, improved tolerance of dialysis, and rapid clinical recovery. Follow-up imaging confirmed optimal device positioning without complications. To our knowledge, this represents the first TricValve® implantation in a dialysis-dependent patient in Europe, demonstrating the feasibility and therapeutic value of this approach in carefully selected, high-risk patients with severe tricuspid regurgitation.

Keywords: Advanced, chronic, heart failure, hemodialysis, interventional cardiology, tricuspid regurgitation, ultrafiltration

ÖZET

Son dönem böbrek yetmezliği olan, idame diyalizi uygulanan ve şiddetli triküspit yetmezliği, kronik atriyal fibrilasyon ve kardiyak kaşeksi ile ileri derecede sağ kalp yetmezliği olan 72 yaşındaki bir erkek hastanın vakasını sunuyoruz. Hasta, inotropik destek olmasına rağmen böbrek replasman tedavisinin tekrar tekrar başarısız olmasına neden olan şiddetli hipotansiyon ve kardiyojenik şok ile başvurdu. Cerrahi riskin çok yüksek olması ve yaygın anüler dilatasyon nedeniyle transkateter kenardan kenara onarım uygun görülmedi ve hastaya TricValve® sistemi ile acil perkütan kaval kapak implantasyonu uygulandı. İşlem teknik olarak başarılı oldu ve hemen hemodinamik stabilizasyon, diyaliz toleransında iyileşme ve hızlı klinik iyileşme sağlandı. Takip görüntüleme, komplikasyon olmaksızın cihazın optimal konumlandırıldığını doğruladı. Bildiğimiz kadarıyla, bu, Avrupa'da diyalize bağımlı bir hastaya yapılan ilk TricValve® implantasyonu olup, ciddi triküspit yetmezliği olan, dikkatle seçilmiş yüksek riskli hastalarda bu yaklaşımın uygulanabilirliğini ve terapötik değerini göstermektedir.

Anahtar Kelimeler: İleri düzey, kronik, kalp yetmezliği, hemodiyaliz, girişimsel kardiyoloji, triküspit yetmezliği, ultrafiltrasyon

CASE REPORT
OLGU SUNUMU

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Right heart failure (HF) due to severe tricuspid regurgitation is a growing clinical challenge, particularly in elderly patients with multiple comorbidities.[1,2] While optimal medical therapy remains the cornerstone of management, many patients continue to experience persistent congestion, poor functional status, and intolerance to renal replacement therapy. Surgical repair or replacement of the tricuspid valve is associated with high perioperative risk, and transcatheter edge-to-edge repair may be unsuitable in cases of advanced annular dilation or large coaptation gaps.[3,4] In this context, novel percutaneous approaches such as bicaval valve implantation (TricValve® system) have emerged as promising palliative strategies to reduce systemic venous congestion while preserving native valve anatomy.[5,6] We present the case of a dialysis-dependent patient with advanced right HF and prohibitive surgical risk, in whom TricValve® implantation provided immediate hemodynamic stabilization and restored tolerance to renal replacement therapy.

Case Report

A 72-year-old male with end-stage renal disease, on renal replacement therapy for the past 30 years, had longstanding advanced right HF with severe tricuspid regurgitation, cardiac cachexia, and permanent atrial fibrillation (AF). He was on maximally tolerated HF medication. His renal replacement therapy had become increasingly challenging over the preceding years due to chronically low arterial blood pressure and persistent congestion. During a recent dialysis session, he developed discomfort, dizziness, and profound hypotension, leading to his urgent transfer to our center.

On presentation, the patient was hemodynamically unstable, exhibiting signs of cardiogenic shock, and was admitted to the intensive care unit (ICU) requiring inotropic support. On physical examination, auscultation of the lung fields revealed bilateral crackles, while signs of peripheral congestion were also evident. Cardiac auscultation detected a prominent holosystolic murmur over the tricuspid area, consistent with severe tricuspid regurgitation, and a softer systolic murmur at the aortic area. Peripheral pulses were weak and thready. Electrocardiography showed AF with a rapid ventricular response. Laboratory evaluation indicated a borderline hematocrit, markedly elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (~18,000 pg/mL), and increased serum creatinine levels, as the patient was already on maintenance dialysis. Chest X-ray demonstrated bilateral pleural effusions (predominantly right-sided), interlobar fluid collection, and radiographic signs of pulmonary congestion.

Transthoracic echocardiography revealed preserved left ventricular ejection fraction, significant dilation of the right heart chambers, and severe tricuspid regurgitation. Right ventricular (RV) function was borderline, with a tricuspid annular plane systolic excursion (TAPSE) of 17 mm and an estimated RV systolic pressure of 58 mmHg (Figure 1). In addition, moderate aortic stenosis and mild aortic regurgitation were noted.

ABBREVIATIONS

AF	Atrial fibrillation
CT	Computed tomography
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II
HF	Heart failure
ICU	Intensive care unit
IVC	Inferior vena cava
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
RV	Right ventricular
SVC	Superior vena cava
TAPSE	Tricuspid annular plane systolic excursion

The patient remained in the ICU on inotropic support. Several attempts at renal replacement therapy were made, but blood pressure response remained poor, reflecting the severity of his clinical condition. Given the high surgical risk (European System for Cardiac Operative Risk Evaluation II [EuroSCORE II]: 38.1% and Society of Thoracic Surgeons [STS] score: 53%), a surgical approach for the severe tricuspid regurgitation was deemed prohibitive.

After multidisciplinary discussion, we opted for urgent percutaneous caval valve implantation (TricValve® system). Transcatheter edge-to-edge repair with TriClip™ was initially considered but ultimately rejected due to extensive tricuspid annular dilation, a wide coaptation gap, and a high predicted risk of procedural failure.

Pre-procedural computed tomography (CT) angiography of the venous system [inferior vena cava (IVC), superior vena cava (SVC), and peripheral veins] confirmed favorable anatomy for TricValve® implantation. Under sedation, and following administration of intravenous unfractionated heparin, the procedure was initiated via the right femoral vein.

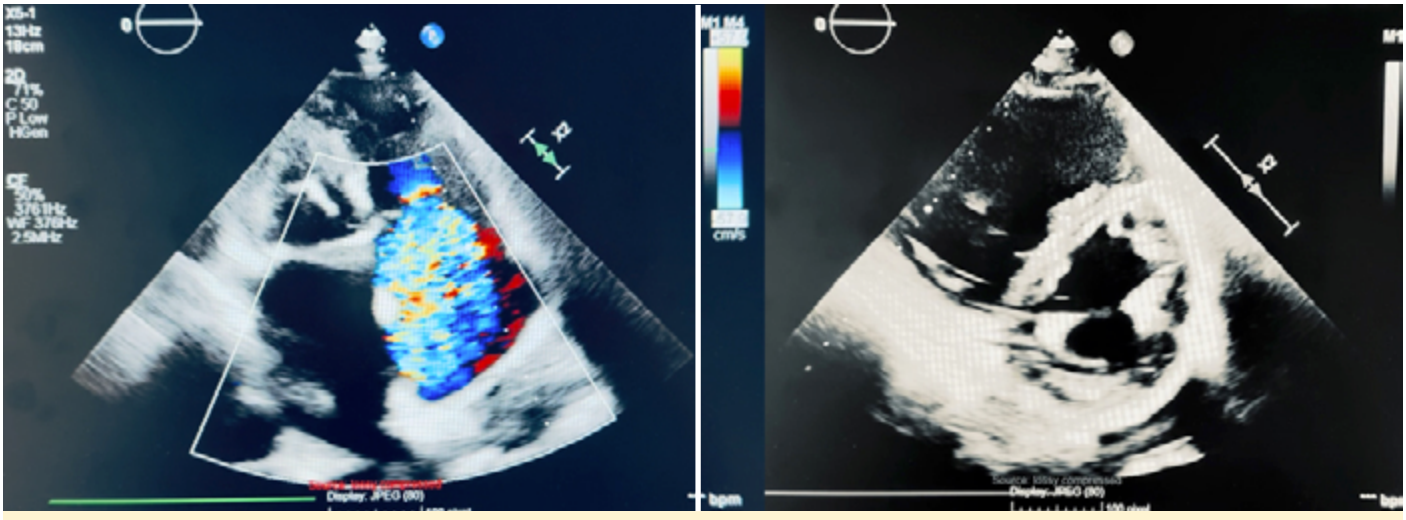

Figure 1. Transthoracic echocardiography. (Left) Apical four-chamber view with color Doppler demonstrating severe tricuspid regurgitation with a broad, high-velocity regurgitant jet. (Right) Corresponding grayscale image showing significant dilatation of the right ventricle and a D-shaped left ventricle, corresponding to increased right heart pressures.

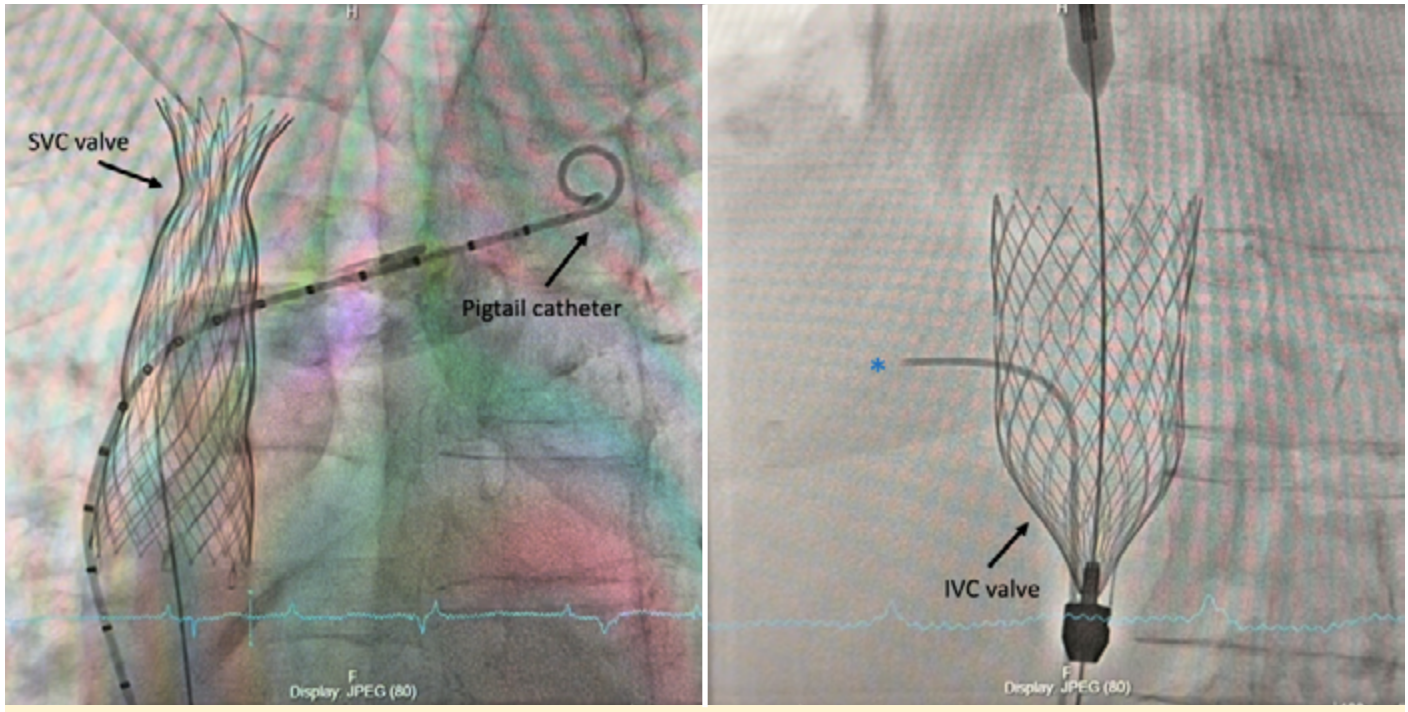

Figure 2. Fluoroscopic guidance during TricValve® implantation. (Left) Deployment of the superior caval valve with positioning relative to the superior vena cava. A pigtail catheter was placed in the right atrium for pressure tracking. (Right) Deployment of the inferior caval valve under fluoroscopic control, with appropriate visualization confirming stable device release. A catheter was positioned in the hepatic veins to confirm that the device did not cause any obstruction (blue star).

The superior caval valve was first advanced and deployed under fluoroscopic guidance. Angiography confirmed appropriate positioning relative to the orifice of the left subclavian vein. Subsequently, the inferior caval valve was introduced and deployed with concurrent angiographic visualization of the hepatic veins to ensure correct placement (Figure 2, Video 1).

Valve positioning was excellent, with no significant paravalvular leak observed. Hemodynamic measurements were performed before and after valve deployment. Before implantation, mean right atrial pressure was approximately 26 mmHg, consistent with severe systemic venous congestion. Following deployment of both valves, right atrial pressure decreased markedly to about 8 mmHg, confirming substantial hemodynamic improvement. During the procedure, a pigtail catheter was placed in the right atrium, confirming a significant reduction in right atrial pressure following implantation (Figures 2 and 3).

The post-procedural course was uneventful. The patient remained in the ICU for 24 hours and was then transferred to the cardiology ward, where he stayed for an additional three days. He showed rapid clinical improvement with stabilization of hemodynamics, improving from New York Heart Association (NYHA) class IV at presentation to class III by early post-procedural follow-up. Tolerance of renal replacement therapy was excellent; whereas preprocedural sessions were often limited or aborted due to hypotension, postprocedural treatments were completed uneventfully, with stable blood pressure and no signs of intradialytic intolerance. A post-procedural CT angiography was performed, confirming correct positioning of the prosthetic valve and excluding paravalvular leak or other complications (Figure 4, Video 2).

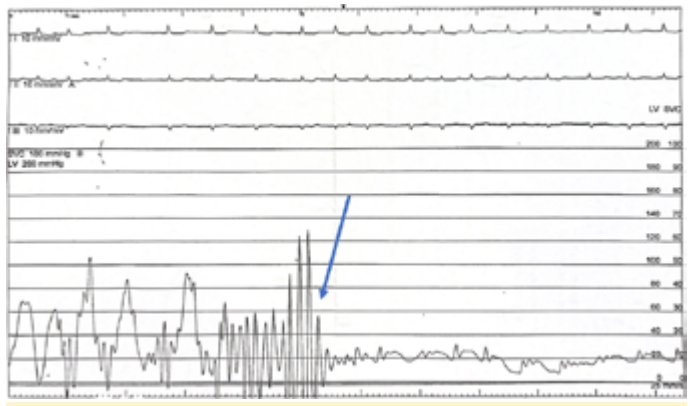

Figure 3. Hemodynamic tracings before and after TricValve® implantation. The blue arrow indicates a significant reduction in right atrial pressure immediately following device deployment, reflecting effective relief of systemic venous congestion.

Guideline-directed HF therapy was continued, and antithrombotic treatment with low-molecular-weight heparin was initiated under close nephrologist supervision.

Discussion

The TricValve® system is a novel percutaneous solution for patients with symptomatic severe tricuspid regurgitation and right HF who are inoperable or not suitable for transcatheter edge-to-edge repair. It consists of two self-expanding bioprosthetic valves implanted in the SVC and IVC, aiming to reduce systemic venous reflux while preserving native valve anatomy.

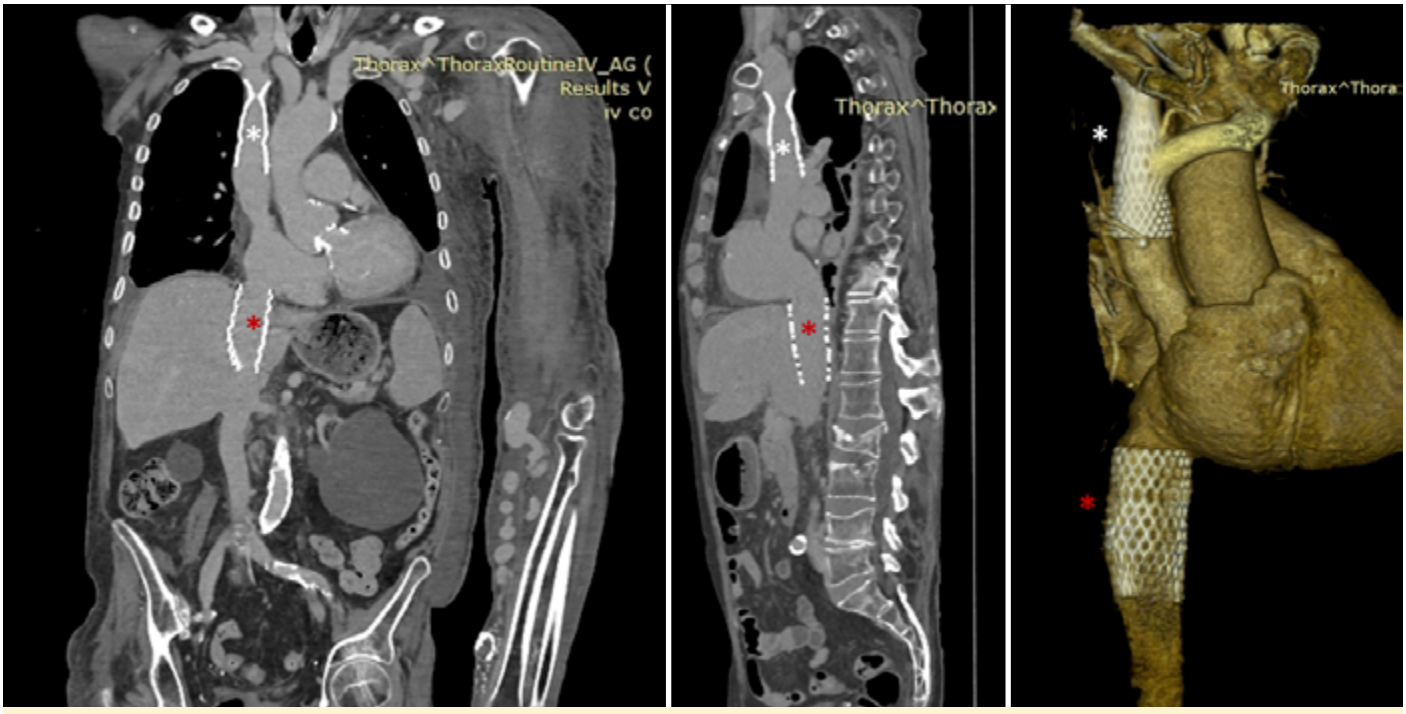

Figure 4. Post-procedural cardiac computed tomography (CT) angiography. Coronal (left) and sagittal (middle) views demonstrate the TricValve® prostheses in the superior (white stars) and inferior (red stars) vena cava with correct positioning. (Right) Three-dimensional reconstruction confirming stable device deployment and absence of paravalvular leak or migration (white star: superior vena cava valve; red star: inferior vena cava valve).

In this case, multimodality cardiovascular imaging played a pivotal role in both patient selection and procedural success. Transthoracic echocardiography demonstrated the extent of right heart dilation, severity of tricuspid regurgitation, and borderline RV function, while CT angiography provided a detailed assessment of the venous anatomy (IVC, SVC, hepatic and subclavian veins), confirming suitability for TricValve® implantation and guiding device sizing and positioning. Fluoroscopy and angiography were essential intra-procedurally to verify deployment accuracy and valve function.

Dialysis dependence is typically an exclusion criterion in TricValve® trials and registries due to concerns regarding venous anatomy alterations, intraprocedural instability, and increased thrombotic risk. Our case expands current knowledge by demonstrating that caval valve implantation may be feasible and clinically effective even in this population. This experience suggests that selected dialysis-dependent patients with refractory venous congestion may benefit from TricValve® therapy and highlights the need for future studies to re-evaluate candidacy criteria.

In this patient, alternative management strategies were carefully considered but ultimately deemed insufficient. Medical therapy had already been optimized, yet persistent systemic venous congestion and profound intradialytic hypotension continued to limit effective renal replacement therapy. Intensified ultrafiltration strategies were unsuccessful, as even minimal volume removal triggered hemodynamic instability. Balloon tricuspid valvuloplasty was also evaluated but was unlikely to provide durable benefit given the marked tricuspid annular dilation and torrential regurgitation. These limitations underscored the need for a more definitive approach to reduce venous reflux and improve circulatory support. CT imaging also confirmed adequate SVC and IVC diameters, appropriate landing zones without excessive tapering, and favorable hepatic and subclavian vein takeoff, allowing safe anchoring of the prostheses. Importantly, there were no venous obstructions, such as IVC filters, thrombus, or significant SVC/IVC stenosis, which would contraindicate caval valve implantation. These anatomical features, combined with the patient's refractory venous congestion, intolerance to dialysis, and prohibitive risk for surgery or edge-to-edge repair, supported the decision to proceed with TricValve® implantation.

To our knowledge, this case represents the first reported TricValve® implantation in a dialysis-dependent patient in Europe. Beyond its novelty, it highlights the potential of caval valve implantation as a life-saving option in severe tricuspid regurgitation and advanced right HF when surgery and transcatheter edge-to-edge repair are not feasible. In this critically ill patient, the intervention provided immediate hemodynamic stabilization and restored tolerance to renal replacement therapy, demonstrating its feasibility even in complex, high-risk scenarios. While multimodality imaging was essential for diagnosis, procedural planning, and follow-up, the most important lesson from this case is that advanced percutaneous therapies may offer meaningful benefit when conventional treatment strategies reach their limits. Broader clinical experience and dedicated studies will be required to define the role of TricValve® in this high-risk population.

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 the publication of this case report.

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

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Use of AI for Writing Assistance: No artificial intelligence-assisted technologies were used in the preparation of this manuscript.

Author Contributions: Concept – P.C., D.Z., D.D.; Design – A.B., D.D.; Supervision – D.D.; Resource – D.Z., D.D.; Materials – D.D.; Data Collection and/or Processing - A.B., A.K, D.D.; Analysis and/or Interpretation - A.B., C.P.; Literature Review – A.B., P.C., D.K.; Writing – A.B., A.K., D.D.; Critical Review – D.Z., C.P., D.D.

Peer-review: Internally peer-reviewed.

Video 1. Angiography demonstrating successful expansion of the TricValve® system, with both the inferior and superior vena cava valves in the appropriate position.

Video 2. Computed tomography (CT) scan demonstrating the implanted TricValve® system, with visualization of both the inferior and superior vena cava valves in situ.

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The Dilemma of Edoxaban Interruption and Heparin Bridging Before Upgrading to Cardiac Resynchronization Therapy in an Older Patient with Atrial Fibrillation, Chronic Kidney Disease, and a Mitral Bioprosthesis

Atriyal Fibrilasyon, Kronik Böbrek Hastalığı ve Mitral Biyoprotezli Yaşlı Bir Hastada Kardiyak Resenkronizasyon Terapisine Yükseltme İşleminden Önce Edoksaban Kesintisi ve Heparinle Köprüleme İkilemi

ABSTRACT

The peri-procedural management of novel oral anticoagulants (NOAC) should be individualized based on patient-specific factors (age, body weight, renal function, concomitant medications, history of thromboembolic or bleeding events, and the presence of prosthetic valve) as well as procedural characteristics (bleeding risk). Less invasive procedures carry a relatively low bleeding risk and may be performed with minimal or no interruption of NOAC therapy. However, upgrading from an implantable cardioverter-defibrillator (ICD) to cardiac resynchronization therapy (CRT) is more complex than initial implantation. Therefore, the timing of the last NOAC dose before an elective procedure requires careful judgment, balancing individual risks and benefits. Herein, we present the case of an elderly patient with atrial fibrillation, grade IIIb chronic renal disease, low body weight, and a bioprosthetic mitral valve, who underwent an upgrade from an implantable cardioverter-defibrillator (ICD) to cardiac resynchronization therapy with a defibrillator (CRT-D). The patient developed bioprosthetic valve thrombosis 24 hours after edoxaban interruption without heparin bridging, which was successfully treated with ultraslow tissue plasminogen activator (tPA) therapy.

Keywords: Edoxaban, interruption, novel oral anticoagulant, thrombosis

ÖZET

Yeni oral antikoagülanların (NOAK) girişimsel işlemlerden önce yönetimi, hastaya (yaş, vücut ağırlığı, böbrek fonksiyonu, ilaçlar, önceki tromboembolik/kanama olayı, protez kapak varlığı) ve işlemin (kanama riski) özelliklerine göre kişiselleştirilmelidir. Daha az girişimsel işlemler nispeten düşük kanama riski taşır ve minimal veya kesintisiz NOAK tedavisi altında gerçekleştirilebilir. Ancak, implante edilebilir defibrilatörden (ICD) kardiyak resenkronizasyon tedavisine (KRT) yükseltme, ilk implantasyon işleminden daha karmaşıktır. Bu nedenle, elektif bir prosedürden önce son NOAK alımının zamanlaması, bireysel fayda/risk oranına dayalı karar vermeyi gerektirir. Burada, atriyal fibrilasyon, evre 3b kronik böbrek hastalığı, düşük vücut ağırlığı ve biyoprotez mitral kapağı olan ve ICD'den KRT-D'ye yükseltme işlemi sürecinde, heparin köprülemesi olmadan edoksaban tedavisinin kesilmesinden 24 saat sonra biyoprotez kapak trombozu yaşayan ve ultra yavaş tPA tedavisiyle başarılı bir şekilde tedavi edilen yaşlı bir hastanın yönetimini sunduk.

Anahtar Kelimeler: Edoksaban, ara verme, yeni oral antikoagülan, tromboz

Physicians must carefully balance the risk of thromboembolic events and bleeding during the peri-procedural management of novel oral anticoagulants (NOACs). Many low bleeding-risk procedures can be performed with minimal or no interruption of NOAC therapy. However, both patient-specific factors (such as age, body weight, renal function, concomitant medications, history of thromboembolic or bleeding events, and the presence of a prosthetic valve) and procedural characteristics

CASE REPORT
OLGU SUNUMU

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(particularly bleeding risk) must be taken into account when deciding on the discontinuation and resumption of a NOAC. Although earlier guidelines have provided standard NOAC interruption intervals, these recommendations should be individualized based on a careful assessment of the patient's risk-benefit profile.[1] Pre-procedural heparin bridging is generally not recommended in patients receiving NOACs, as it is associated with an increased risk of bleeding.[2,3] In this case report, we present the peri-procedural management of an elderly patient with atrial fibrillation (AF), grade 3b chronic renal disease, low body weight, heart failure with reduced ejection fraction (HFrEF), and a bioprosthetic mitral valve, who underwent an upgrade from an implantable cardioverter-defibrillator (ICD) to cardiac resynchronization therapy (CRT). The patient developed bioprosthetic valve thrombosis 24 hours after edoxaban interruption without heparin bridging, which was successfully treated with ultraslow tissue plasminogen activator (tPA) therapy.

ABBREVIATIONS

BNP	Brain natriuretic peptide
CIED	Cardiovascular implantable electronic device
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with a defibrillator
ECG	Electrocardiogram
ICD	Implantable cardioverter-defibrillator
LAA	Left atrial appendage
LVEF	Left ventricular ejection fraction
NOAC	Novel oral anticoagulants
SEC	Spontaneous echo contrast
TEE	Transesophageal echocardiography
tPA	Tissue plasminogen activator
TTE	Transthoracic echocardiography
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
Vp	Ventricular pacing

Case Report

An 81-year-old male patient presented to our clinic with complaints of exertional dyspnea, classified as New York Heart Association class II. His medical history included AF, with a CHA2DS2-VASc score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke/transient ischemic attack) of 4 and a HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol) of 3, chronic kidney disease, a diagnosis of non-ischemic dilated cardiomyopathy ten years earlier, and implantation of a dual-chamber ICD. Ten months prior, the patient had undergone mitral valve replacement with a bioprosthesis (Hancock II Bioprosthesis, size 27, Medtronic, USA) and tricuspid Kay annuloplasty. On physical examination, his body weight was 57 kg. Bilateral rales were heard at the lung bases, and +2 pitting edema was observed in the pretibial region bilaterally. A 12-lead electrocardiogram (ECG) revealed a ventricular paced (Vp) rhythm at 81 beats per minute. The patient remained in AF, with a paced QRS duration of 184 msec (Figure 1A). Device interrogation of the ICD showed a ventricular pacing (Vp) burden of 92.6%. Laboratory findings included a hemoglobin level of 15.0 gr/dL, serum creatinine of 1.58 mg/dL (corresponding to an estimated glomerular filtration rate [eGFR] of 40 mL/min), and a brain natriuretic peptide (BNP) level of 743.52 pg/mL. Transthoracic echocardiography (TTE) revealed a left ventricular (LV) end-diastolic diameter of 56 mm, a left ventricular ejection fraction (LVEF) of 21%, and a left atrial diameter of 45 mm. The bioprosthetic mitral valve was functioning with a mean transvalvular gradient of 3 mmHg. The repaired tricuspid valve showed moderate tricuspid regurgitation, and systolic pulmonary artery pressure was estimated at 45 mmHg. One year earlier, the patient's LVEF had been 38%, with a Vp burden of 31.2%. Given the current findings, right ventricular pacing-induced cardiomyopathy was suspected. Therefore, an upgrade from ICD to CRT-D was planned. The patient had been on edoxaban 30 mg/day as oral anticoagulation therapy. Due to advanced age, impaired renal function, low body weight, and the anticipated complexity of the procedure, edoxaban was interrupted for 48 hours without bridging with heparin prior to the CRT-D upgrade. Upon hospitalization the day before the procedure, 24 hours after edoxaban interruption, a follow-up TTE was performed. There was a three-day interval between the two echocardiographic assessments. A 13 × 16 mm hyperechogenic mobile mass, moving toward the left atrium and ventricle, was detected on the posterior leaflet of the mitral bioprosthetic valve (Figure 2A-C, Video 1). This mass had not been present prior to the interruption of edoxaban therapy. An increase in the mean transvalvular gradient to 8 mmHg was also observed. Transesophageal echocardiography (TEE) confirmed the presence of the hyperechogenic mobile mass attached to the mitral bioprosthetic valve.

Additionally, a fresh thrombus in the form of sludge was observed in the left atrial appendage, along with grade III spontaneous echo contrast (SEC) in the left atrium (Video 2). The patient had no fever or signs of systemic infection. Acute-phase reactant levels were within normal limits, and blood cultures were negative. Given the rapid appearance of the mass and other findings suggestive of blood stasis on TEE, a diagnosis of mitral bioprosthetic valve thrombosis was considered. Although the patient experienced no clinical thromboembolic events or further deterioration after hospitalization, and despite current guideline recommendations favoring anticoagulation with a vitamin K antagonist (VKA) or unfractionated heparin (UFH) prior to re-intervention, we opted for thrombolytic therapy to minimize the time to treatment of bioprosthetic valve thrombosis. The patient's clinical status (critically ill due to decompensated heart failure), the size of the thrombus (>10 mm), the high surgical risk associated with advanced heart failure, and the increased mean transvalvular gradient were the primary factors influencing the decision to initiate thrombolytic therapy at the first-line option. Tissue plasminogen activator was administered via an ultraslow protocol (25 mg of tPA infusion over 25 hours). On follow-up TTE after the first tPA infusion, the mass on the mitral bioprosthesis valve had completely resolved, and the mean mitral transvalvular gradient had decreased to 4 mmHg (Figure 2D, Video 3). The sludge and fresh thrombus in the left atrial appendage (LAA) also disappeared after the tPA infusion, as confirmed by follow-up TEE. The CRT implantation procedure was performed six hours after completion of thrombolytic treatment. UFH

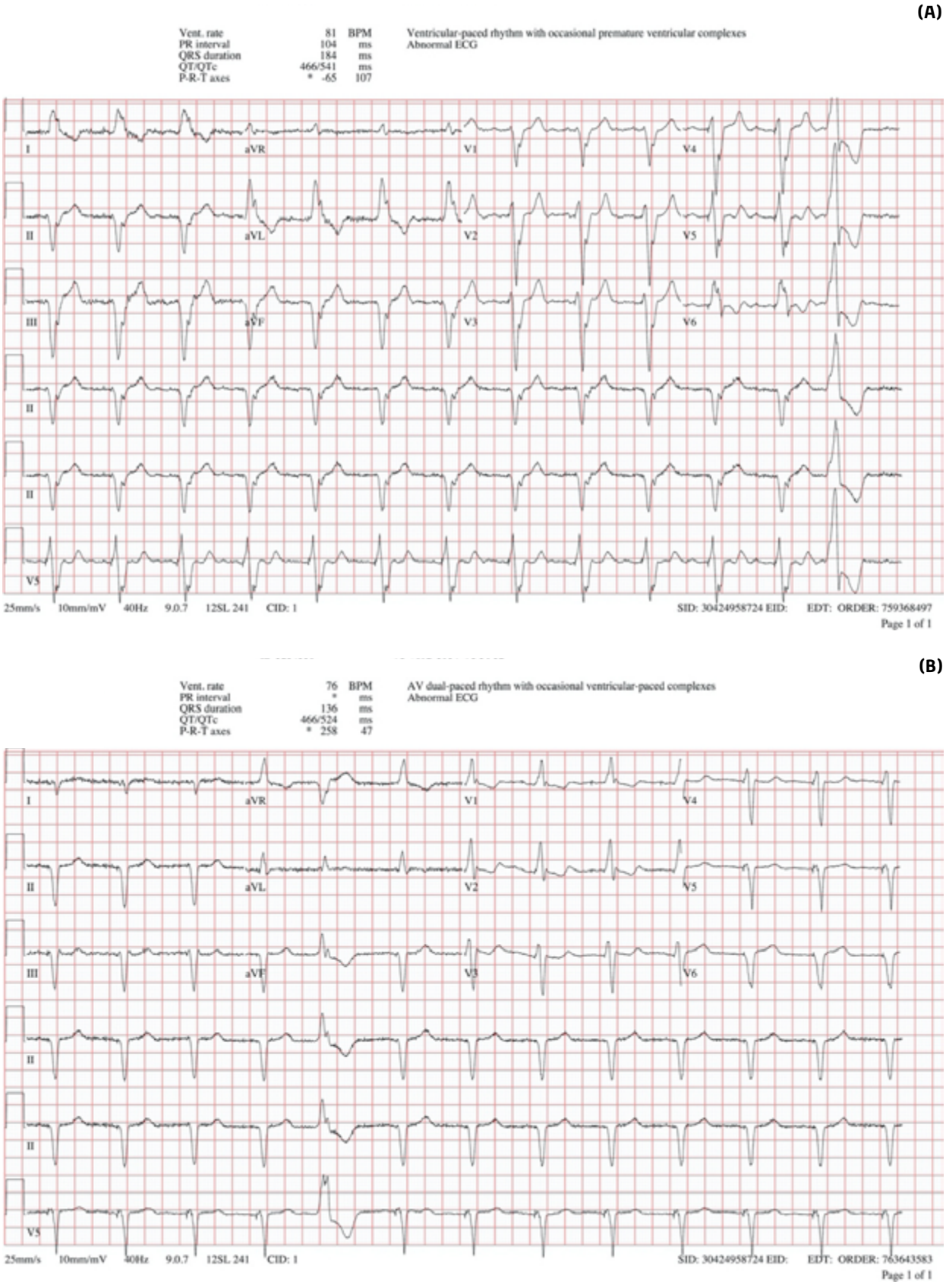

Figure 1. (A) On admission, a 12-lead electrocardiogram (ECG) revealed a right ventricular paced (Vp) rhythm at 81 beats per minute. The patient remained in AF, with a paced QRS duration of 184 msec. (B) The biventricular paced QRS duration on the postprocedural ECG was 136 milliseconds.

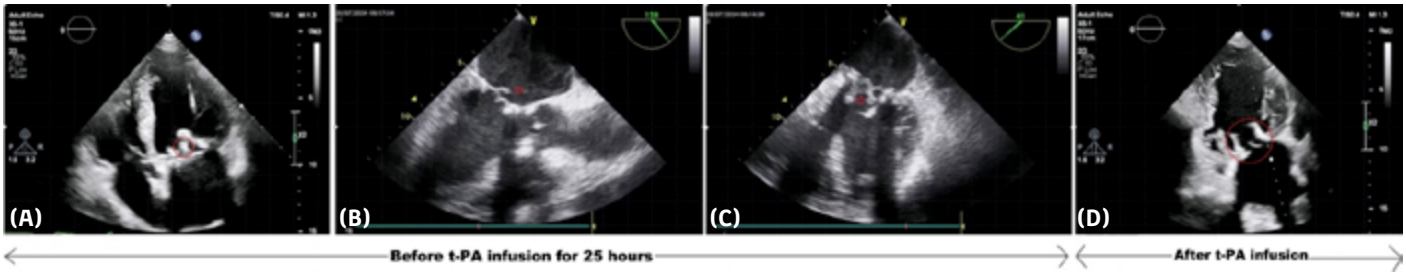

Figure 2. Transthoracic echocardiography (A) and transesophageal echocardiography (B–C) showed a hyperechogenic, mobile mass on the posterior leaflet of the bioprosthetic mitral valve 24 hours after edoxaban interruption. The mass disappeared following ultraslow tissue plasminogen activator (tPA) therapy (D).

bridging was used during this interval and was discontinued two hours before the procedure. The patient was then taken to the catheterization laboratory for the CRT-D upgrade. After a single axillary vein puncture, the coronary sinus was cannulated using a delivery sheath (Selectra Catheter Extended Hook-45 Lead Delivery System, Biotronik), and a coronary sinus electrode (Sentus ProMRI OTW QP S-xx/49, Biotronik) was positioned in the posterolateral branch of the coronary sinus. The CRT-D generator (Inlexa 3 HF-T, Biotronik) was successfully implanted. Electrical cardioversion was performed, and sinus rhythm was achieved following the procedure. The paced QRS duration on the postprocedural ECG was 136 milliseconds (Figure 1B). Edoxaban 30 mg was reinitiated six hours after the CRT-D upgrade procedure. The remainder of the hospital stay was uneventful. The patient was discharged on edoxaban 30 mg orally once daily, acetylsalicylic acid 100 mg orally once daily, amiodarone 200 mg orally once daily, along with optimized heart failure therapy.

Discussion

Balancing the risks of bleeding versus thromboembolic events during cardiovascular implantable electronic device (CIED) implantation in patients receiving NOACs is challenging. Patient-specific factors, such as age, body weight, renal function, concomitant medications, prior thromboembolic events, and the presence of a prosthetic valve, as well as procedural bleeding risk, are critical in the decision-making process.[1] The optimal management of NOACs during CIED implantation is uncertain. Current evidence suggests that an uninterrupted or minimally interrupted NOAC strategy, without heparin bridging, may be appropriate for NOAC-treated patients undergoing non-major surgeries such as CIED implantation.[4-7] While initial CIED implantation procedures (e.g., pacemaker or ICD) are considered low risk for bleeding, procedures involving an upgrade from ICD to CRT-D may be more complex. Due to the patient's advanced age, low body weight, grade IIIb chronic renal disease, and the anticipated complexity of the procedure, we elected to interrupt edoxaban 48 hours prior to the procedure without heparin bridging. However, a bioprosthetic valve thrombosis was detected on TTE 24 hours after edoxaban interruption. In the Global EMIT-AF/VTE (Edoxaban Management in Therapeutic Pathways for Patients With Atrial Fibrillation or Venous Thromboembolism) study, Santamaria et al.[8] identified predictors of edoxaban interruption, the use of heparin bridging strategies, and associated adverse clinical outcomes. Heparin bridging was used in approximately 15% of patients whose edoxaban therapy was interrupted. The study results showed that a HAS-BLED score greater than 3 and high European Heart Rhythm Association (EHRA) procedural risk predicted both edoxaban interruption and the use of a heparin bridging strategy. In contrast, the CHA2DS2-VASc score was not a significant predictor. Peri-procedural heparin bridging in this study was associated with a two-fold increase in bleeding risk without a corresponding reduction in thromboembolic events. Therefore, Santamaria and colleagues[8] concluded that patient and procedural bleeding risks influence clinicians' decisions regarding heparin bridging more than stroke risk. Due to the elevated patient- and procedure-related bleeding risks in our case, we opted to interrupt edoxaban therapy for 48 hours without heparin bridging before the procedure. However, a bioprosthetic valve thrombosis developed within a short time interval. Although the incidence of prosthetic valve thrombosis is approximately 0.4%, it is a significant, though rare, cause of morbidity and mortality.[9] Atrial fibrillation, SEC, HFrEF, and left atrial enlargement have all been identified as risk factors for thrombus formation in mitral valve prostheses, and our patient exhibited all of these risk factors.[10] Therefore, interruption of NOAC therapy with heparin bridging may be considered, particularly in patients with similar thromboembolic risk profiles. The effectiveness and safety of ultraslow thrombolytic therapy have been demonstrated in cases of prosthetic valve thrombosis.[11] In our patient, the prosthetic mitral valve thrombus was also successfully treated with an ultraslow infusion of 25 mg of tPA, without any complications. Video 2 further confirms the presence of spontaneous echo contrast, sludge, and fresh thrombus in the left atrial appendage. The presence of left atrial appendage thrombus in patients with prosthetic valve thrombosis favors surgical intervention over thrombolytic therapy.[12] While thrombolysis may be effective in patients with mitral prosthesis thrombosis,[11] only a limited number of cases have been reported,[13,14] and data regarding associated bleeding or embolic risks are scarce. Fresh and poorly organized thrombi, such as those observed in our patient, are more likely to dissolve effectively with thrombolytic therapy. In contrast, the efficacy of thrombolysis in cases involving organized or partially organized thrombi is unknown.

Although heparin bridging therapy is not routinely recommended in current practice when NOACs are interrupted, it may be considered in selected cases, such as ours, to balance the risks of thromboembolic events and bleeding.

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 was provided with detailed information regarding the potential contribution of the case report to the medical literature. Written and verbal consent for publication was obtained from the patient.

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Video 1. Transthoracic echocardiography 24 hours after edoxaban interruption revealed a hyperechogenic, mobile mass.

Video 2. Transesophageal echocardiography confirmed the presence of a hyperechogenic, mobile mass attached to the mitral bioprosthetic valve. Additionally, a fresh thrombus in the form of sludge was observed in the left atrial appendage, along with grade III spontaneous echo contrast in the left atrium.

Video 3. Transthoracic echocardiography performed immediately after ultraslow tissue plasminogen activator (tPA) therapy demonstrated complete resolution of the hyperechogenic, mobile mass on the mitral bioprosthetic valve.

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Uninvited Guest in the Left Ventricle: Cardiac Lipoma

Sol Ventrikülde Davetsiz Misafir: Kardiyak Lipom

ABSTRACT

Cardiac lipoma is a rare primary tumor of the heart. With advances in diagnostic and treatment methods, an increasing number of cases have been reported. This trend suggests that the clinical presentation, previously believed to follow classic patterns, may actually exhibit atypical features. In such cases, multimodal imaging facilitates accurate diagnosis and the selection of the most appropriate treatment. This case report presents a 28-year-old female with progressive exertional dyspnea. Transthoracic and transesophageal echocardiography revealed a large mass in the left ventricle, originating from the posteromedial papillary muscle. The mass exhibited a low-density focus with a well-defined boundary and regular shape and, fortunately, had no significant effect on the valves or hemodynamics. Cardiac magnetic resonance imaging confirmed the diagnosis of a cardiac lipoma. Although surgical intervention was offered, the patient ultimately declined the procedure. Most patients diagnosed with cardiac lipoma are asymptomatic, and the diagnosis is often made incidentally. The use of multimodality imaging greatly aids in diagnosis. Echocardiography is a suitable modality for ongoing monitoring.

Keywords: Cardiac tumors, intracardiac mass, lipoma, multimodality imaging

ÖZET

Kardiyak lipom, kalbin nadir görülen bir primer tümörüdür ve tanı ve tedavi yöntemleri geliştikçe daha fazla vaka bildirilmiştir. Bu durum, daha önce klasik özelliklere sahip olduğu düşünülen klinik sunumun aslında atipik belirtilere sahip olabileceğini düşündürmektedir. Bu olgu sunumunda, ilerleyici efor dispnesi olan 28 yaşında bir kadın hasta sunulmaktadır. Transtorasik ve transözofageal ekokardiyografide, sol ventrikülde posteromedial papiller kastan kaynaklanan büyük bir kitle görüldü. Kitle iyi tanımlanmış bir sınıra ve düzenli bir şekle sahip düşük yoğunluklu bir odak izlenimi verdi ve neyse ki kapaklar veya hemodinami üzerinde önemli bir etkisi yoktu. Kardiyak manyetik rezonans görüntüleme kardiyak lipom tanısını doğruladı. Hastaya lipom eksizyon ameliyatı önerildi, ancak hasta operasyonu reddetti. Lipom genellikle asemptomatiktir ve tesadüfen teşhis edilir. Cerrahi eksizyon ana terapötik müdahaledir. Multimodalite görüntüleme kullanımı tanıya büyük ölçüde yardımcı olur. Ekokardiyografi daha sonraki izlem için uygun bir yöntemdir.

Anahtar Kelimeler: Kardiyak tümörler, intrakardiyak kitle, lipoma, multimodalite görüntüleme

CASE REPORT
OLGU SUNUMU

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In population studies, the frequency of primary cardiac tumors ranges from 0.0017% to 0.02%.[1] Cardiac lipomas account for 8.4% of benign primary tumors and vary widely in shape and size.[2] Fang et al.[2] reported that cardiac lipomas represent 2.4% of benign primary cardiac tumors. They can occur in all heart chambers, with a preference for subepicardial and subendocardial locations. In rare cases, they may also develop within the myocardium or valve leaflets. Symptomatology depends on the size and location of the mass.[3] In this case report, we discuss a patient who presented to a cardiology outpatient clinic with atypical dyspnea and was diagnosed with a large lipoma.

Case Report

A 28-year-old woman presented with exertional dyspnea that had progressively worsened over the past two years. She was initially evaluated at a local hospital, where a cardiac mass was detected. The patient was then referred for further assessment and treatment. Her medical and family histories were unremarkable. Both pulmonary and cardiac examinations were within normal limits. Electrocardiography showed normal sinus rhythm with no significant ST-T segment changes. Laboratory tests revealed no abnormalities.

Transthoracic echocardiography (TTE) revealed the following measurements: a normal-sized left ventricular cavity (50 x 35 mm), aorta 30 mm, left atrium 35 mm, and a hyperechogenic mass measuring 37 x 28 mm located in the mid-apical region of the posterior left ventricular wall (Figure 1A-B, Video 1). Transesophageal echocardiography (TEE) confirmed a hyperechogenic, well-circumscribed mass originating from the posteromedial papillary muscle of the left ventricle. The mass caused thickening of the papillary muscle and its attachment to the left ventricle (Figure 1C, Video 2). For more detailed characterization of the mass, the patient underwent cardiovascular magnetic resonance imaging (MRI). The scan revealed a mass approximately 33 x 19 mm in size, located at the mid-level of the left ventricle, extending to the posteromedial papillary muscle and the left ventricular wall. The mass appeared hyperintense on all sequences, was suppressed in fat-suppressed sequences, and showed minimal contrast enhancement following intravenous contrast administration (Figure 2A-D).

Surgical intervention was recommended; however, the patient declined to give consent for the procedure.

Discussion

Cardiac lipomas, a type of primary cardiac tumor, are most often diagnosed incidentally. Symptomatology varies depending on the tumor's location and size. A significant number of these tumors are discovered either during autopsy or incidentally during cardiac imaging performed for unrelated reasons. The incidence of cardiac lipomas is not influenced by age or sex, with equal prevalence observed in both sexes across all age groups. The most commonly affected anatomical structures include the left ventricle, right atrium, and interatrial septum.[4] In a systematic review of Shu et al.[5] involving 255 patients with cardiac lipomas, 8.3% of the lipomas originated from cardiac valvular leaflets, and 32.5% were located in the pericardium. Cardiac lipomas can originate from the endocardium, epicardium, myocardium, or pericardium.[6]

Symptoms associated with these tumors may include dyspnea, palpitations, and chest pain, which can range from nonspecific to clinically significant manifestations. The patient presented in this report experienced progressive exertional dyspnea.[2]

ABBREVIATIONS

MRI	Magnetic resonance imaging
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

Multimodal imaging is highly valuable in characterizing cardiac tumors. Echocardiography is typically the first and primary tool for evaluating tumor location, extent, and characteristics (such as whether the mass is single or multiple, intramuscular or intracavitary, solid or cystic). Additionally, color Doppler is essential for assessing the hemodynamic impact of tumors, including obstruction, compression, or valvular leak. Echocardiography is a highly sensitive modality for detecting intraluminal tumors. After the mass is detected, further detail can be obtained with TEE. Although most cardiac lipomas can be detected and localized with high sensitivity and accuracy via TTE, their exact tissue nature cannot be determined based solely on acoustic properties. The acoustic characteristics of lipomas can help differentiate them from malignant cardiac tumors. However, differentiating lipomas from other benign lesions, such as myxomas, remains a challenging diagnostic task. Cardiac MRI and cardiac computed tomography may be required in cases where echocardiography alone does not provide sufficient information.[4,7]

MRI is a valuable diagnostic tool that offers critical insights into the relationship between the tumor, normal myocardium, and surrounding great vessels. Beyond simply identifying the tumor's location, size, and boundaries, MRI can also help characterize the tissue type, such as confirming the presence of a lipoma. It is well established that lipomas and mature adipose tissue are composed of the same elements. Furthermore, the imaging appearances of lipomas and subcutaneous fat on CT and MRI sequences are identical. The signal characteristics of cardiac lipomas are consistent with those of subcutaneous fat across all MRI sequences. Complete signal loss of the mass on fat-suppression sequences is considered a characteristic diagnostic indicator of lipoma. It is important to note that the "black boundary sign" seen on cine sequences, which is attributable to the chemical shift

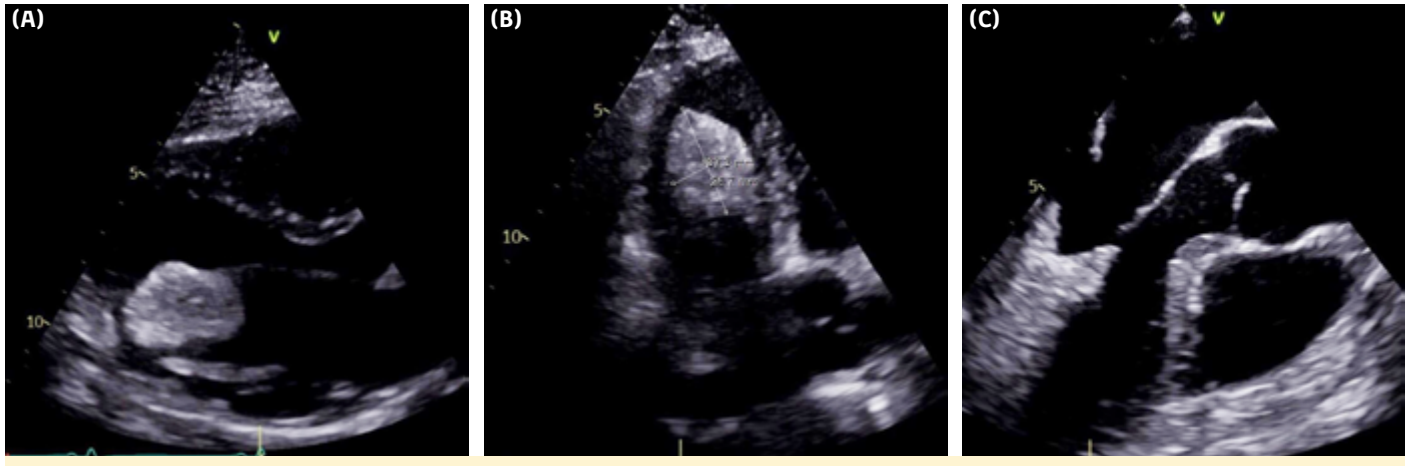

Figure 1. Transthoracic (A, B) and transesophageal echocardiographic (C) views. (A) Parasternal long-axis view; (B) Apical four-chamber view; (C) 135* mid-esophageal view.

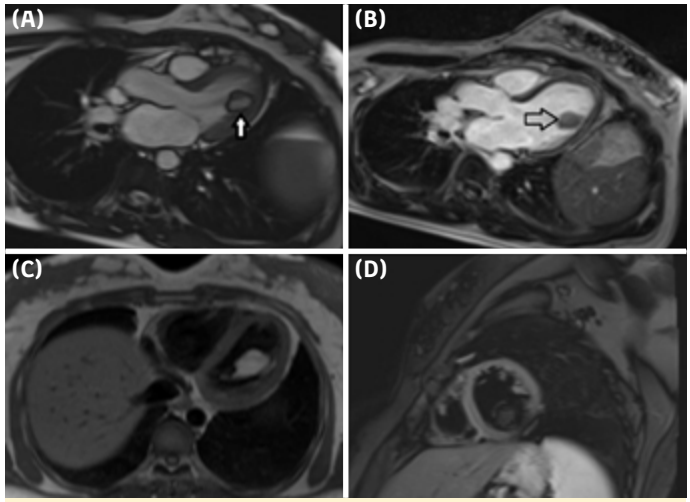

Figure 2. Cardiac magnetic resonance imaging: (A) Long-axis cine view. The mass is characterized by its smooth, well-circumscribed, hyperintense appearance, with evidence of origin from the papillary muscle. The presence of the "Indian ink" around the mass is also noted. (B) Late gadolinium enhancement in the long-axis cine view; (C) Hyperintense mass on transaxial T1-weighted image; (D) Hypointense mass on short-axis T2-weighted fat-suppressed image.

effect, is particularly valuable in diagnosing small lipomas.[5] This feature is especially significant for surgical planning, as it helps determine the extent and feasibility of tumor resection. In this case, cardiac MRI provided detailed information regarding the extent and nature of the tumor. Notably, in the fat-suppressed sequences, the "Indian ink sign," which is a characteristic feature of cardiac lipomas, was observed.[8,9]

Surgical excision is the preferred treatment option for all primary cardiac tumors when feasible. However, extensive myocardial involvement or proximity to critical structures such as coronary arteries or heart valves may limit the possibility of complete resection. Nevertheless, partial resection can still produce satisfactory surgical outcomes. Therefore, total tumor resection should not be considered the sole therapeutic goal. The primary objective should be the preservation of optimal cardiac function, which can often be achieved through partial resection and a conservative surgical approach. The majority of patients with benign tumors are cured by surgical resection, and recurrence is rare.[4,10] In the present case, the surgical intervention was declined by the patient. As a result, pathological examination could not be performed.

Cardiac lipoma is a benign cardiac tumor with a favorable prognosis. The intracardiac location and size are the most important factors influencing the clinical course of the disease. Multimodality imaging can provide detailed and valuable information about these parameters noninvasively. While pathological examination is essential for a definitive diagnosis, the information it offers is also invaluable for surgical planning.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.A.; Design – E.A.; Supervision – E.A., K.M.S.; Materials – E.A., K.M.S., B.U., İ.D.; Analysis and/or Interpretation – E.A.; Literature Review – E.A.; Writing – E.A.; Critical Review – K.M.S., B.U.

Use of AI for Writing Assistance: Artificial intelligence-assisted technologies were not used in the preparation of this article.

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Video 1: Transthoracic echocardiographic short-axis view.

Video 2: Transesophageal echocardiographic 135° view.

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ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Coronary Cameral Fistula from the Right Coronary Artery to a Left Ventricular Aneurysm

Sağ Koroner Arterden Sol Ventrikül Anevrizmasına Koroner Kameral Fistül

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 27-year-old gentleman presented with exertional dyspnea and palpitations for two years. Clinical examination revealed blood pressure of 136/70 mmHg, cardiomegaly, a prominent apical impulse, a soft left ventricular third heart sound, and a continuous murmur at the lower sternal border, more prominent in diastole. The electrocardiogram demonstrated first-degree atrioventricular block, features of left atrial enlargement, T-inversion in D3 and augmented vector foot (aVF), and poor R-wave progression (Figure 1a). Transthoracic echocardiography showed a dilated, dysfunctional left ventricle, moderate mitral regurgitation, and a large thick-walled akinetic accessory chamber in the posteromedial aspect of the left ventricle (Figure 1b, Video 1). Coronary angiography revealed an ectatic right coronary artery (RCA) with a large fistulous communication to the left ventricle. The left system was normal. Computed tomography (CT) angiography delineated the coronary cameral fistula from the RCA draining into the wide-mouthed, thick-walled accessory chamber in the posterobasal left ventricle, with myocardial attenuation characteristics conforming to a true aneurysm (Figure 1c-e, Video 2). There was no thrombus. Viral serology, Treponema pallidum hemagglutination test, rheumatoid factor, and antinuclear antibody profile were negative. The patient had no history of trauma, angina, or prolonged fever, and work-up for Koch's disease was negative. The patient was scheduled for aneurysmectomy, fistula ligation, and distal RCA bypass.

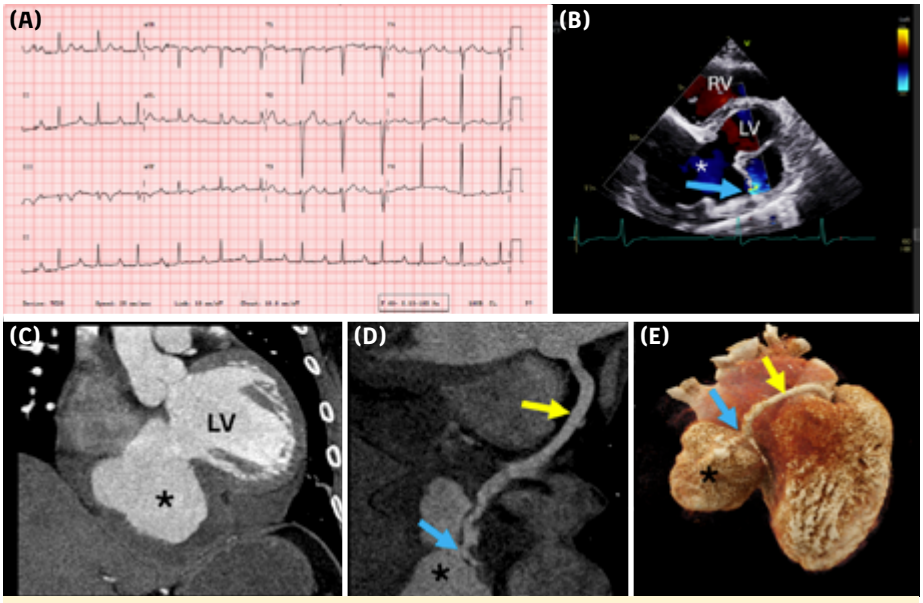

Figure 1. (A) The electrocardiogram of the patient. (B) The modified parasternal short-axis projection demonstrating the large aneurysm (asterisk) from the posterobasal left ventricle (LV). The blue arrow depicts the entry of the coronary cameral fistula into the left ventricle (LV). RV – Right ventricle. (C) The oblique computed tomography (CT) section demonstrating the aneurysm (asterisk) from the posterobasal LV. (D) The CT reconstruction demonstrating the right coronary artery (yellow arrow) opening into the LV aneurysm (blue arrow). (E) The corresponding 3D CT reconstruction.

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The left ventricle is the least common drainage site of coronary cameral fistulae. Failure of regression of embryonic myocardial sinusoids from endothelial protrusions into intertrabecular spaces of the thicker left ventricle is rarer compared to those draining into the right heart. Progressive intimal ulceration, medial degeneration, mural thrombosis, and focal coronary hypoperfusion are possible reasons for aneurysm formation at drainage sites, including the left ventricle.

Ethics Committee Approval: This is a case image, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Informed written consent was obtained from the patient concerned. No patient identity particulars have been disclosed.

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Video 1. Transthoracic echocardiographic cine loop from the modified parasternal short-axis projection demonstrating the large aneurysm (asterisk) from the posterobasal left ventricle (LV).

Video 2. Curved multiplanar reconstructed computed tomography (CT) coronary angiography demonstrating the coronary cameral fistula opening into the left ventricle (LV).

ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Concealed Conduction as an Electrocardiographic Clue for the Origins of Premature Beats

Prematüre Atımların Lokalizasyonu İçin Bir İpucu Olarak Gizli İleti

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 58-year-old woman presented with palpitations. A 12-lead electrocardiogram demonstrated sinus rhythm (SR) with premature contractions displaying a right bundle branch block (RBBB) morphology and a superior axis (Figure 1). Holter monitoring further revealed post-extrasystolic PR prolongation (Figure 2). The PR interval prolongation following interpolated premature complexes is an important clue to the origin of the premature beats. Both concealed conduction (CC) and dual pathway physiology represent important electrophysiological characteristics of the atrioventricular node (AVN). The CC (retrograde, concealed incomplete penetration of the AVN by the premature complexes) is defined as the partial penetration of a cardiac impulse into any component of the conduction system (i.e., the AVN or the His–Purkinje system) without resulting in a directly observable response (Figure 3). Instead, it modifies subsequent conduction by altering tissue refractoriness. The manifestations of CC can be summarized as: (a) conduction prolongation (Figure 4A), (b) failure of impulse propagation, (c) facilitation of conduction by "peeling back" refractoriness, and (d) pauses in the discharge of a spontaneous pacemaker (Figure 4B). Another clue is the similarity of the QRS morphologies between the initial part of the premature complexes and SR (Figure 5). Since the precordial leads used today are considered unipolar leads in that they measure voltage at a given location relative to approximately zero potential, these leads consist of a single active lead and an indifferent electrode, providing accurate information about the direction of electrical activation. The right bundle does not influence the time of arrival of activation to the lateral left ventricle (LV), because activation of the LV occurs via the left septal branch of the left bundle. Therefore, RBBB is characterized by an initial steep upstroke in the QRS complex on a unipolar electrogram, similar to SR, due to early septal activation since the LV has the same initial forces. The similarity of the initial QRS forces between SR and premature complexes indicates comparable early septal activation, supporting a supraventricular origin, with

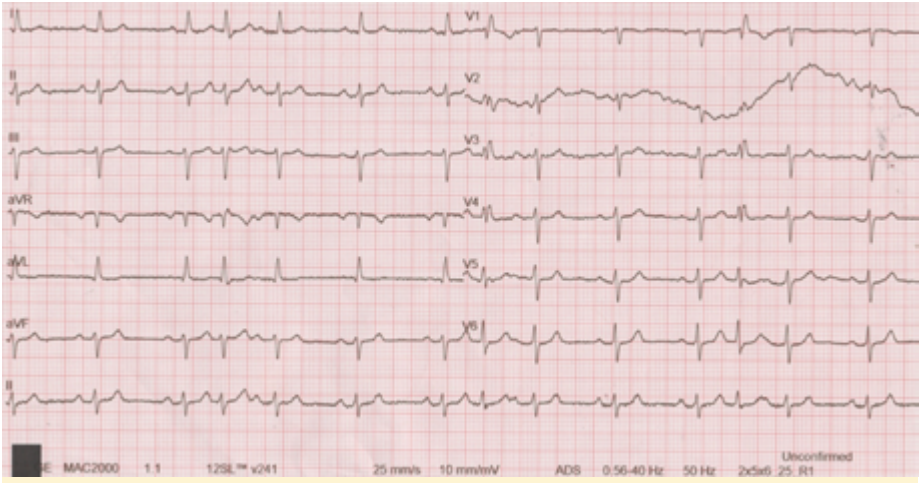

Figure 1. An electrocardiogram (ECG) lead shows sinus rhythm with premature complexes.

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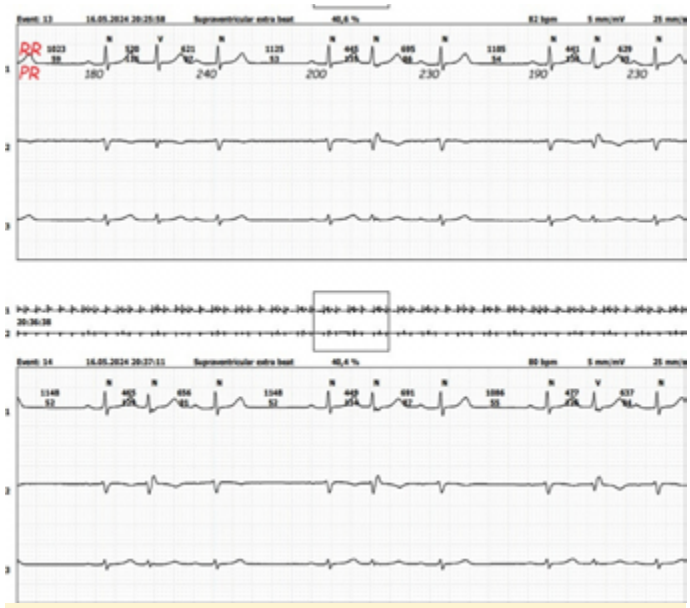

Figure 2. Holter recording showing sinus rhythm with premature beats, including the corresponding RR and PR intervals.

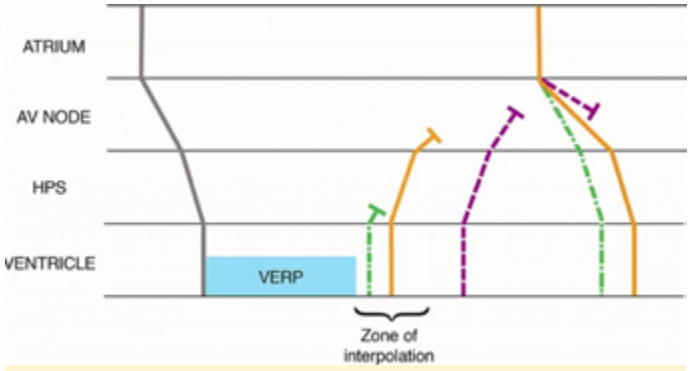

Figure 3. The zone of interpolation and concealed retrograde penetration of the atrioventricular (AV) node and conduction system (Courtesy of Prof. Dr. Eric N. Prystowsky, with permission).

premature atrial contractions or premature Hisian contractions (PHC) as possible sources (Figure 4). The observed PR prolongation after premature beats (Figures 1 and 2), together with the QRS force similarity (Figure 4), suggests retrograde AVN penetration from an infranodal origin (Figures 3 and 4), leaving PHC as the most likely diagnosis, which was also confirmed by three-dimensional mapping (Figure 6).

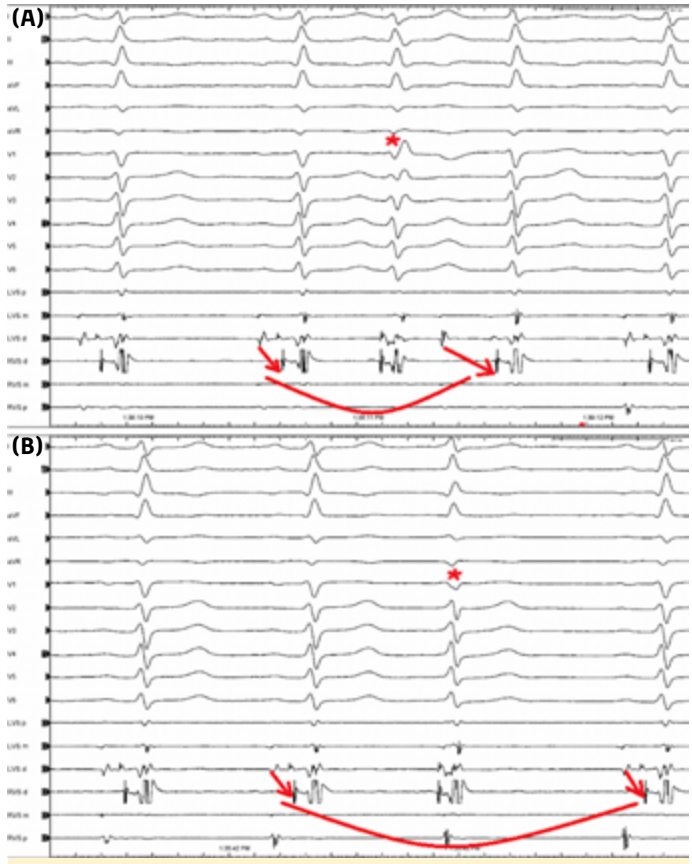

Figure 4. Electrocardiograms demonstrating atrial–His (AH) interval prolongation (red arrows in panel A) following early-coupled premature beats (red star in panel A), but not after a late-coupled premature beat (red star in panel B). LVS, Left ventricular septum; RVS, Right ventricular septum.

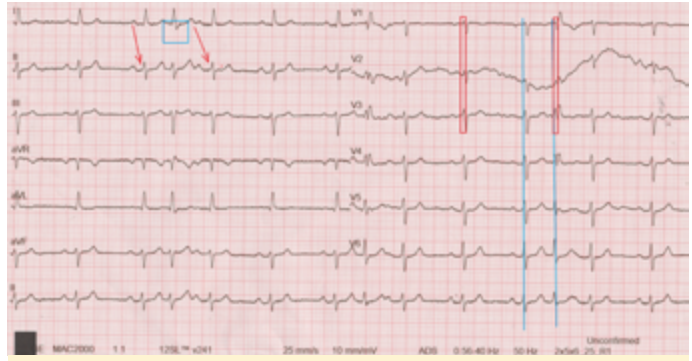

Figure 5. Post-premature ventricular contraction (PVC) PR prolongation (compare the PR intervals indicated by the red arrows). The 4th and 12th beats in the top tracing are premature contractions. The initial forces in V1-3 (red rectangular boxes) and V4-6 (blue straight line) are the same as in sinus rhythm, with a dip in the V5 and V6 leads (blue square box). The relatively narrow QRS, with the same axis and initial QRS section resembling sinus rhythm (SR), suggests an origin in the His-Purkinje system.

Ethics Committee Approval: This is a case image, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Informed consent was obtained from the patient for publication of their data in anonymized form, in compliance with guidance from the Committee on Publication Ethics.

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

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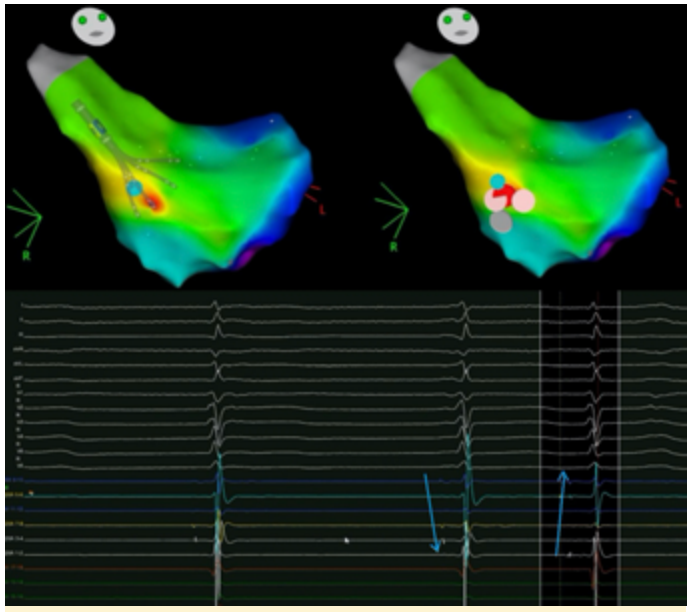

Figure 6. The patient underwent ablation due to severe, drug-refractory symptoms. No conduction abnormalities occurred post-procedure. Three-dimensional activation mapping of the left ventricle localized the premature complexes to the left-sided Hisian region, which was successfully targeted for ablation. The Pentaray catheter demonstrates antegrade His–Purkinje system activation (downward blue arrow) and its reversal during Hisian premature complexes (upward blue arrow).

Use of AI for Writing Assistance: AI-assisted technologies were not used in this article.

Author Contributions: Concept – Ö.Ö., D.A., S.T.; Design – E.H.Ö.Ç.; Supervision – D.A., S.T.; Resource – A.K., Ö.Ö.; Materials – F.Ö.; Data Collection and/or Processing – S.Ç., D.K.B.; Analysis and/or Interpretation – M.K.; Writing – Ö.Ö.

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Frontal QRS-T Angle in Hemodialysis

Hemodiyalizde Frontal QRS-T Açısı

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read with great interest the article by Kaya et al.,[1] who investigated the prognostic value of the frontal QRS-T angle (fQRSTa) in hemodialysis patients and demonstrated its association with long-term mortality. This work addresses a clinically meaningful question, as the fQRSTa represents the vectorial difference between ventricular depolarization and repolarization axes, and increased values have been shown to reflect electrical heterogeneity and arrhythmogenic substrate formation in various cardiovascular conditions, as emphasized by Küçük et al.[2] in non-ST elevation myocardial infarction populations.

However, several methodological aspects merit elaboration. Kaya et al.[1] relied on a single electrocardiogram (ECG) measurement, yet in hemodialysis patients, ventricular repolarization indices, including fQRSTa, QT interval, and Tp-e interval, have been shown to undergo dynamic intradialytic fluctuations influenced by volume status, electrolyte shifts, and autonomic balance. Kalaycı et al.[3] reported that repolarization markers vary in relation to dialysis adequacy, while Korkmaz et al.[4] demonstrated that even the QRS axis may shift during dialysis due to changes in intrathoracic fluid distribution. Thus, a single ECG may not adequately reflect the chronic electrophysiologic milieu of this patient population.

Additionally, the authors evaluated all-cause mortality as the primary endpoint. While clinically relevant, differentiation between arrhythmic and non-arrhythmic death would deepen mechanistic interpretation, considering that fQRSTa reflects repolarization heterogeneity and may indicate vulnerability to malignant ventricular arrhythmias. Prior observations by Kaplan and Kıraslan have highlighted the importance of distinguishing genuine arrhythmic patterns from electrical artifacts when interpreting repolarization abnormalities.[5] Therefore, cause-specific mortality analysis would enhance the understanding of how fQRSTa relates to arrhythmic risk versus systemic disease burden.

Furthermore, renal dysfunction and inflammation have been shown to modulate cardiovascular outcomes in acute coronary syndromes, indicating that the observed prognostic significance of fQRSTa may also be influenced by the underlying cardiorenal-inflammatory pathway.[6] The prognostic value of fQRSTa is not limited to hemodialysis populations. Usalp and Bağırtan demonstrated that elevated fQRSTa was associated with increased total mortality in ischemic stroke patients, suggesting that fQRSTa may serve as a marker of global cardiometabolic stress and inflammatory activation rather than a dialysis-specific electrophysiological phenomenon.[7] Supporting this interpretation, Çoner et al.[8] found that repolarization markers, including the Tp-e interval, may reflect systemic autonomic and inflammatory imbalance, thereby providing prognostic insight across different cardiovascular settings.

In summary, while Kaya et al.[1] contribute valuable data to the literature, future prospective studies incorporating serial ECG assessments and cause-specific mortality analyses are warranted to clarify whether fQRSTa primarily reflects arrhythmogenic risk, systemic disease burden, or both. Such work may refine the use of fQRSTa in risk stratification and clinical decision-making among hemodialysis patients.

In conclusion, while the authors present valuable preliminary findings, prospective studies incorporating serial ECG measurements and stratified evaluation of mortality mechanisms are needed to clarify the applicability of the frontal QRS-T angle as a practical prognostic marker in hemodialysis patients.

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Reply to the Letter: Frontal QRS-T Angle in Hemodialysis

Editöre Mektup Yanıtı: Hemodiyalizde Frontal QRS-T Açısı

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We sincerely thank the author for the valuable comments regarding our study on the prognostic value of the frontal QRS-T angle (fQRSTa) in hemodialysis patients.[1] The relationship between repolarization markers and long-term outcomes is an important area of research, and we welcome the opportunity to clarify several points.

First, we acknowledge the concern about using a single electrocardiogram (ECG) recording. Because our study was retrospective, serial or intradialytic ECGs were not available. We agree that repeated measurements would better reflect the rapidly changing electrical environment in hemodialysis.[2] Future prospective studies incorporating serial ECG recordings are essential to address this limitation. Second, although cause-specific mortality could provide more mechanistic information, reliable classification of arrhythmic versus non-arrhythmic death was not possible in our dataset. To avoid misclassification, we used all-cause mortality, as noted in our limitations. Still, we concur that analyses stratified by mortality mechanisms would meaningfully enhance future research. Evidence from previous studies in the literature also supports a broader interpretation of fQRSTa. Fragmented QRS, another conduction abnormality, has been shown in a previous study to predict ventricular arrhythmias in hemodialysis patients, reflecting the electrical vulnerability of this population.[3] These findings reinforce the concept that ventricular depolarization and repolarization markers may interact and collectively reflect structural-electrical remodeling. Similarly, in ischemic stroke patients, Usalp and Bağırtan demonstrated that an increased frontal QRS-T angle independently predicted five-year mortality, suggesting that its prognostic implications extend beyond dialysis-dependent populations.[4] In addition, a recent 36-month study in patients with type 2 diabetes mellitus showed that fragmented QRS independently predicted major cardiovascular events, linking it to myocardial fibrosis and chronic inflammation.[5] Together, these findings indicate that both fragmented QRS and the frontal QRS-T angle are simple, practical, and clinically useful tools for risk assessment.

In conclusion, we sincerely appreciate the constructive feedback. The points raised support our view that prospective studies with serial ECG recordings and cause-specific mortality data are needed to better define the prognostic role of fQRSTa in hemodialysis patients.

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Lipoprotein(a): The Silent Actor That Hardens the Arteries and Weakens the Bone

Lipoprotein(a): Arterleri Sertleştiren ve Kemikleri Zayıflatan Sessiz Aktör

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

The study by Yurtseven et al.[1] represents an important step toward understanding the vascular–skeletal interplay through the lens of lipoprotein(a) [Lp(a)]. Their findings suggest that elevated Lp(a) levels parallel two seemingly opposite processes (vascular calcification and bone demineralization) inviting a deeper look at the molecular symmetry underlying this phenomenon.

While the authors have made a valuable contribution, several aspects deserve further consideration. The visual assessment of coronary artery calcification, rather than quantitative Agatston scoring, may limit reproducibility and comparability across cohorts.[2] In addition, prior population data linking coronary calcium and thoracic vertebral bone mineral density (BMD) further underline the vascular–skeletal continuum that the present study seeks to illuminate. Furthermore, key modulators of bone metabolism such as menopausal status, estrogen, and vitamin D levels were not incorporated into the analysis; integrating these factors could refine the clinical interpretability of Lp(a)-related bone–vascular interactions.[3,4]

Beyond these methodological nuances, the concurrent increase in coronary calcification and reduction in bone density across Lp(a) strata may not be a mere coincidence but rather the manifestation of a shared molecular paradox—a "calcify-and-resorb" signal driven by the same lipoprotein particle. Lp(a) carries oxidized phospholipids that can activate Runt-related transcription factor 2 (RUNX2) and bone morphogenetic protein 2 (BMP-2)-mediated osteogenic differentiation in vascular smooth muscle cells, while simultaneously promoting osteoclastic bone resorption via pro-inflammatory cytokine pathways.[5,6] Structurally, Lp(a) shares a high degree of homology with plasminogen, particularly within its Kringle IV and V domains, which may partly explain its ability to modulate osteoclast activity through plasminogen-like pathways.[6] This dualistic mechanism positions Lp(a) as a metabolic crossroads molecule, silently orchestrating mineral deposition in arteries and depletion in bone. Such opposing biological symmetry raises a provocative question: could Lp(a) represent the biochemical thread uniting atherosclerosis, aortic valve stenosis, and osteoporosis?

Although measurable for decades, Lp(a) has long remained overshadowed by traditional lipids. Recent studies have repositioned it as a "silent but potent actor" in both atherosclerosis and vascular calcification.[7] The work by Yurtseven et al.[1] extends this narrative to the skeletal domain, potentially redefining Lp(a) as a systemic regulator of mineral homeostasis.

Future translational studies that integrate serial Lp(a) measurements with bone turnover markers and micro-computed tomography (micro-CT) imaging may determine whether this molecule is merely a passive bystander or the molecular conductor of the vascular–skeletal symphony.

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Reply to the Letter to the Editor: ''Lipoprotein(a): The Silent Actor That Hardens the Arteries and Weakens the Bone''

Editöre Mektup Yanıtı: ''Lipoprotein(a): Arterleri Sertleştiren ve Kemikleri Zayıflatan Sessiz Aktör''

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We would like to thank the authors[1] for their thoughtful comments and interest in our study,[2] which examined the association between lipoprotein(a) [Lp(a)], coronary artery calcification (CAC), and bone mineral density (BMD) in elderly, statin-naive individuals. Their contribution is valuable.

The authors note that the use of visual CAC assessment may limit comparability across studies. We are aware of this limitation and have acknowledged it in the manuscript. However, while quantitative Agatston scoring is the reference standard, visual CAC scoring has been demonstrated to be a reliable and clinically meaningful approach, particularly in retrospective cohorts where dedicated calcium scoring protocols are not uniformly performed.[3] Additionally, the scans in our study were independently evaluated by both a cardiologist and a radiologist who were blinded to clinical data, which strengthened reproducibility.

Regarding menopausal status, estrogen levels, and vitamin D, we agree that these factors influence bone metabolism. In our study population (≥ 55 years), the majority of women were postmenopausal, and individuals receiving hormone replacement therapy or those with significant inflammatory or metabolic conditions were excluded to minimize confounding. Nonetheless, we concur that future prospective studies incorporating hormonal parameters and bone turnover markers will help further clarify the underlying mechanisms.

The point raised regarding shared mechanistic pathways is also highly relevant. As noted in the letter, Lp(a) carries oxidized phospholipids that promote osteogenic signaling in vascular smooth muscle cells, while also potentially influencing osteoclastic activity through plasminogen-like structural domains.[4,5] Our findings align with this concept, demonstrating a stepwise increase in both CAC and low BMD prevalence across ascending Lp(a) categories.

In summary, we appreciate the authors' insightful comments, which support the broader implication of our study: Lp(a) may serve as a shared molecular mediator linking atherosclerosis, vascular calcification, and osteoporosis. Further longitudinal and translational research will be essential to determine whether therapeutic targeting of Lp(a) may provide dual benefits for cardiovascular and bone health.

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Can Large Language Models Guide Aortic Stenosis Management? A Comparative Analysis of ChatGPT and Gemini AI

Büyük Dil Modelleri Aort Darlığı Yönetimine Rehberlik Edebilir mi? ChatGPT ve Gemini Yapay Zekanın Karşılaştırmalı Analizi

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read Sezgin et al.'s article titled "Can Large Language Models Guide Aortic Stenosis Management? A Comparative Analysis of ChatGPT and Gemini AI," published in Archives of the Turkish Society of Cardiology, with great interest.[1] The study provides valuable insight into the use of widely accessible large language models (LLMs) in the management of severe aortic stenosis. I would like to share a few constructive observations that may be useful for future research or manuscript refinement.

Large language models, widely used across medical and non-medical domains, are becoming increasingly integrated into everyday life.[2] These models have also become prominent in contemporary medical research due to their potential to support both medical education and clinical decision-making processes. However, when ethical considerations and professional evaluation standards are taken into account, a controlled and supervised use of LLMs appears to be the most appropriate approach.[3] In the context of LLM use, question phrasing is crucial; even slight variations in wording can result in significantly different answers. As prompts become more specific, detailed, and clearly formulated, the responses from LLMs tend to become more accurate, consistent, and aligned with the intended objective.[4]

In this study,[1] each question was asked independently in a separate session, preventing the model from retaining memory of previous interactions. This approach eliminated the risk of biased responses that could arise from content being carried over from earlier questions. We also examined the questions that contributed to this difference. We believe that some of the information provided may be insufficient for both guideline-based evaluation and real-world clinical judgment, particularly in the clinical scenario questions. Question 33 – "Is surgery indicated in a 59-year-old asymptomatic patient with left ventricular (LV) hypertrophy and ejection fraction (EF) 52%?" – does not explicitly refer to aortic stenosis, potentially reducing the question's alignment with the intended evaluation scope. When we tested ChatGPT 5.1 (the current version) by presenting the same question in two different formats, the model generated two distinct answers (Figure 1 and 2). Question 35 – "How should combined treatment be planned for a 64-year-old patient with 90% left anterior descending (LAD) artery stenosis and severe aortic stenosis (AS)?" – appears to be phrased too broadly. In our opinion, the optimal management strategy would depend on additional information such as the anatomical location of the LAD lesion, further echocardiographic parameters, surgical risk stratification, and relevant comorbidities, none of which are specified in the scenario. Although the study was conducted using a general evaluation framework, it is essential to further refine and expand the clinical scenario questions to ensure better alignment with real-world clinical decision-making and patient variability. Although the clinical scenarios lack detailed contextual information, the study still provides valuable insight, particularly in demonstrating Gemini's near-perfect performance.

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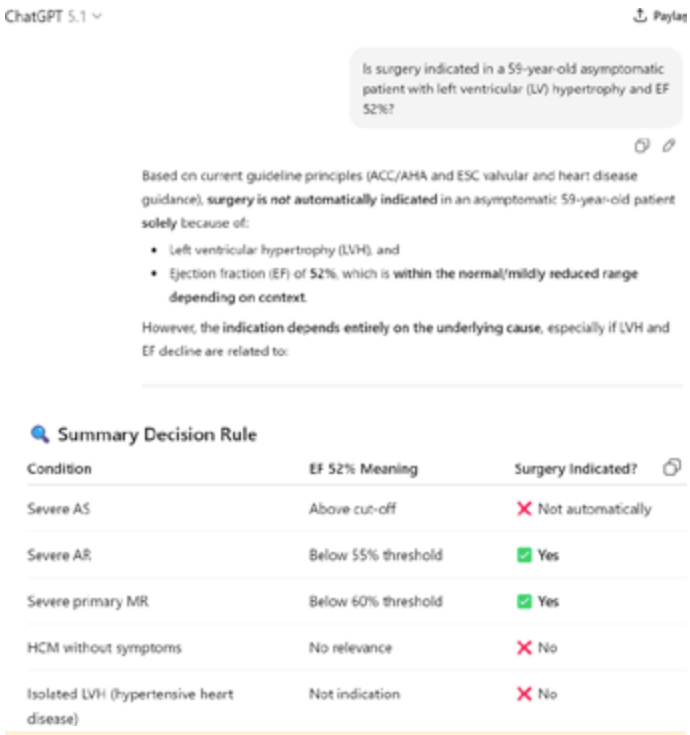

Figure 1. ChatGPT 5.1 response to question 33.

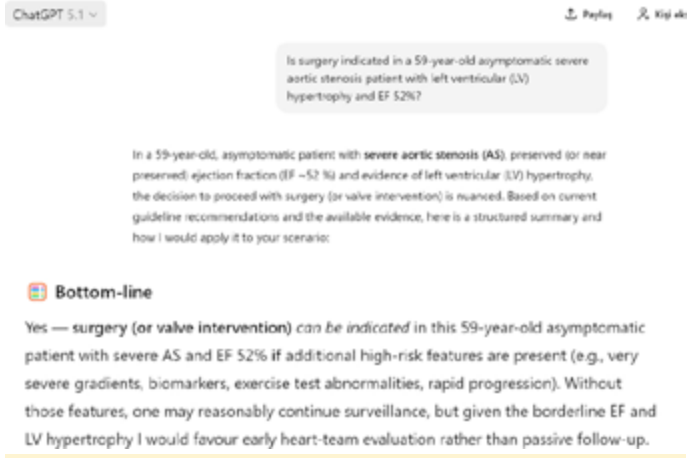

Figure 2. ChatGPT response to question 33 when aortic stenosis is specified.

In conclusion, despite its limitations, the work conducted by Sezgin et al. provides an important foundation for future research exploring the role of large language models in aortic stenosis. Future studies are needed to explore the decision-making mechanisms of LLMs in patients with aortic stenosis, particularly using real-world clinical scenarios.

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Reply to the Letter to the Editor: Can Large Language Models Guide Aortic Stenosis Management? A Comparative Analysis of ChatGPT and Gemini AI

Editöre Mektup Yanıtı: Büyük Dil Modelleri Aort Darlığı Yönetimine Rehberlik Edebilir mi? ChatGPT ve Gemini Yapay Zekanın Karşılaştırmalı Analizi

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We sincerely thank the author for their thoughtful and constructive comments[1] regarding our article[2] titled "Can Large Language Models Guide Aortic Stenosis Management? A Comparative Analysis of ChatGPT and Gemini AI." Their insights contribute meaningfully to the ongoing discussion on the role of large language models (LLMs) in cardiovascular decision-making.

First, we appreciate the author's emphasis on the critical impact of prompt phrasing and contextual completeness on LLM performance. As noted, clinical scenario questions that lack explicit diagnostic or anatomical detail may yield variable model outputs. This observation is particularly relevant for Questions 33 and 35, which the author highlights. We agree that Question 33, in its isolated phrasing, did not explicitly reference aortic stenosis (AS), and that Question 35 intentionally provided limited procedural details to evaluate general decision-making tendencies rather than to simulate a comprehensive real-world case. These points offer valuable guidance for refining future question design, especially for studies aiming to better approximate clinical complexity.

Nonetheless, the primary objective of our study was not to reproduce full clinical scenarios, but rather to compare how two accessible LLMs interpret standardized, open-ended prompts under uniform methodological constraints. All questions were deliberately phrased in a zero-shot, decontextualized format to minimize prompt-engineering bias and to isolate each model's intrinsic behavior. Within this framework, the observed differences in performance—particularly ChatGPT's lower compliance in selected scenarios—reflect the models' reasoning capabilities at the time of evaluation rather than limitations of guideline knowledge per se.

Importantly, we wish to underscore a point also raised in the Letter:[1] LLM outputs are inherently sensitive to model versioning.[3] Our study used ChatGPT-4 (GPT-4-Turbo) in May 2025, whereas the Letter presents examples from ChatGPT-5.1, a substantially more advanced generation with improved clinical reasoning and contextual stability.[4] In the limitations section of our article, we explicitly acknowledged that LLM performance evolves rapidly and that findings represent a "snapshot" of a specific model version at a fixed time point. The differences illustrated by the author—namely, markedly improved responses with ChatGPT-5.1—further reinforce our argument that continuous benchmarking is essential and that LLMs cannot be evaluated as static tools.

Despite these considerations, we appreciate the positive remarks regarding the study's contribution and its value as a foundation for future research. We fully agree that upcoming work should incorporate richer clinical contexts, multimodal data, and mechanistic analyses of LLM decision pathways.

We thank the author once again for their constructive engagement and believe their observations will help inform more refined and clinically meaningful assessments of LLMs in AS management.

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HAKEMLERİMİZE TEŞEKKÜRLER

2025 yılında Türk Kardiyoloji Derneği Arşivi'ne gönderilen makaleler için hakemlik yapan ve bilimsel yetkinlikleriyle dergimize katkıda bulunan tüm hakemlerimize teşekkür ederiz.

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