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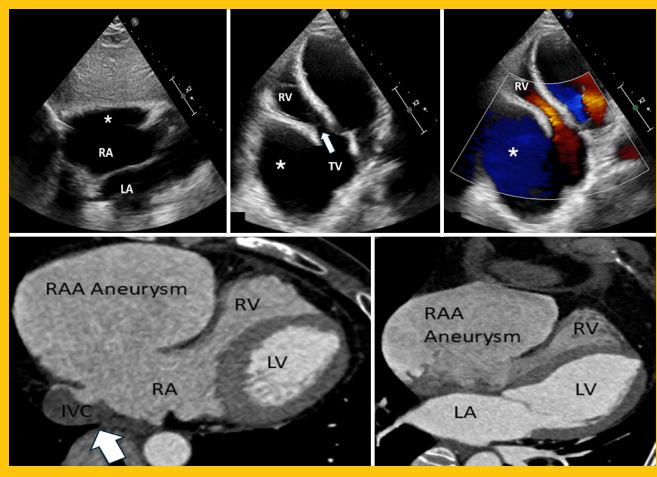

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ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

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ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Artificial Intelligence in Medical Education: Curriculum Design, Assessment Models, and Educational Infrastructure Across Undergraduate and Residency Training – A Narrative Review

Tıp Eğitiminde Yapay Zekâ: Lisans ve Uzmanlık Eğitimi Boyunca Müfredat Tasarımı, Değerlendirme Modelleri ve Eğitim Altyapısı – Anlatı Derlemesi

ABSTRACT

Artificial intelligence (AI) is rapidly becoming an integral part of everyday clinical practice, including cardiology and cardiovascular surgery. As AI increasingly influences diagnostic and therapeutic decisions, physicians are expected to interact with these systems in a critical, safe, and ethically grounded manner. This narrative review aims to explore how AI can be systematically integrated into undergraduate and residency medical education, with a particular focus on curriculum design, teaching strategies, assessment models, and educational infrastructure, while considering the context of the Turkish medical education system. A narrative synthesis of international medical education literature, policy documents, and institutional reports was conducted without quantitative meta-analysis. The review was guided by the principles of human-in-the-loop clinical reasoning, ethical AI use, and patient safety. Effective integration of AI into medical education requires a longitudinal and staged curriculum spanning preclinical, clinical, and residency training. Assessment strategies must explicitly address AI-assisted decision-making and be supported by transparent institutional policies governing AI use in examinations, as well as by secure, regulation-compliant digital infrastructure. Educational approaches should encourage learners to critically appraise and contextualize AI outputs rather than accept them uncritically. The reviewed literature supports a competency-based educational framework that integrates AI literacy, ethical reasoning, and context-aware clinical judgment. AI education should be viewed as a core clinical competency that strengthens rather than replaces human judgment. Particularly in high-risk cardiovascular disciplines, a standardized, ethics-centered, and competency-based educational framework is essential to prepare future physicians for AI-augmented healthcare environments.

Keywords: Artificial intelligence, assessment, clinical decision support, ethics, medical education, residency training

ÖZET

Yapay zekâ (YZ), kardiyoloji ve kardiyovasküler cerrahi dâhil olmak üzere günlük klinik uygulamanın ayrılmaz bir parçası hâline hızla gelmektedir. YZ'nin tanısal ve terapötik kararlar üzerindeki etkisi arttıkça, hekimlerin bu sistemlerle eleştirel, güvenli ve etik temellere dayalı bir şekilde etkileşim kurmaları beklenmektedir. Bu anlatı derlemesi, YZ'nin lisans ve uzmanlık düzeyindeki tıp eğitimine nasıl sistematik olarak entegre edilebileceğini; müfredat tasarımı, öğretim stratejileri, değerlendirme modelleri ve eğitim altyapısı açısından incelemeyi amaçlamakta ve bunu Türkiye'deki tıp eğitimi sistemi bağlamında ele almaktadır. Uluslararası tıp eğitimi literatürü, politika belgeleri ve kurumsal raporlar, nicel bir metaanaliz yapılmaksızın anlatı sentezi yöntemiyle değerlendirilmiştir. Derleme; insan denetimli klinik akıl yürütme, etik YZ kullanımı ve hasta güvenliği ilkeleri doğrultusunda yönlendirilmiştir. YZ'nin tıp eğitimine etkili biçimde entegre edilmesi, preklinik, klinik ve uzmanlık eğitimini kapsayan uzunlamasına ve aşamalı bir müfredat gerektirir. Değerlendirme stratejileri, YZ destekli karar verme süreçlerini açıkça ele almalı; sınavlarda YZ kullanımını düzenleyen şeffaf kurumsal politikalar ve güvenli, mevzuata uygun bir dijital altyapı ile desteklenmelidir. Eğitim yaklaşımları, öğrenenlerin YZ çıktılarının eleştirel değerlendirilmesi ve bağlamsallaştırılması becerilerini geliştirmeli, bu çıktıları sorgulamadan kabul etmelerini engellemelidir. İncelenen literatür, YZ okuryazarlığını, etik akıl yürütmeyi ve bağlama duyarlı klinik yargıyı bütünleştiren yetkinlik temelli bir eğitim çerçevesini desteklemektedir. YZ eğitimi, insan yargısını ikame eden değil, güçlendiren temel bir klinik yetkinlik olarak değerlendirilmelidir. Özellikle yüksek riskli kardiyovasküler alanlarda, YZ destekli sağlık hizmeti ortamlarına hekimleri hazırlamak için standartlaştırılmış, etik temelli ve yetkinlik odaklı bir eğitim çerçevesi gereklidir.

Anahtar Kelimeler: Yapay zekâ, değerlendirme, klinik karar destek, etik, tıp eğitimi, uzmanlık eğitimi

REVIEW
DERLEME

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Artificial intelligence (AI) has become an increasingly integral component of modern healthcare systems. Across disciplines such as radiology, pathology, cardiology, cardiovascular surgery, oncology, intensive care, and primary care, AI-based tools are influencing how clinicians diagnose disease, assess risk, and plan treatment.[1,2] Advances in machine learning-driven diagnostics, predictive models derived from electronic health records, and generative AI systems capable of producing clinical documentation are now affecting everyday clinical decision-making.

In cardiovascular medicine and surgery, AI is being explored for imaging interpretation, perioperative risk assessment, surgical planning, and postoperative follow-up. As these systems become more embedded in clinical workflows, physicians are expected not only to use AI tools but also to understand their limitations, potential biases, and implications for patient safety. This shift creates new expectations for medical education.[3]

In Türkiye, interest in AI within medical education is increasing; however, current initiatives remain fragmented and are often limited to elective courses or short-term educational activities. The absence of a nationally standardized framework highlights the need for a coherent and pedagogically grounded approach. This narrative review therefore examines how AI can be integrated into medical education in a way that strengthens clinical reasoning, protects patient safety, and supports professional accountability.

Against this background, there is an urgent need for a structured, ethically grounded, and pedagogically sound framework for integrating AI into medical education. Rather than positioning AI as a replacement for clinical expertise, educational strategies should emphasize augmentation, critical appraisal, and shared decision-making between human clinicians and intelligent systems. This review aims to synthesize current evidence on AI in medical education, critically evaluate existing training models, and propose guiding principles for responsible and sustainable integration aligned with both educational theory and clinical practice.

However, there remains a lack of assessment-aligned, longitudinal, and nationally adaptable frameworks that systematically span both undergraduate and residency medical training.

Materials and Methods

This study was designed as a narrative review. Relevant literature on artificial intelligence in medical education was identified through searches of major medical and educational databases, including PubMed, Scopus, Web of Science, and ERIC, as well as policy reports from organizations such as the World Health Organization and the Organization for Economic Co-operation and Development. Position statements from leading medical education bodies were also reviewed. The search strategy combined keywords including "artificial intelligence," "medical education," "curriculum," "assessment," "clinical decision support," and "ethics." The literature search primarily focused on publications between 2018 and 2024, reflecting the period during which clinically applicable AI systems and educational frameworks have rapidly expanded. English-language sources were prioritized, with additional consideration given to Turkish policy documents and institutional reports relevant to national medical education. Source selection prioritized conceptual relevance, educational applicability, and ethical considerations rather than quantitative outcomes. Findings were synthesized thematically, with a focus on curriculum structure, assessment strategies, and educational infrastructure, guided by the principles of human-in-the-loop clinical reasoning, ethical AI deployment, and patient safety. Neither formal quantitative quality scoring nor meta-analytic synthesis was performed, in keeping with the narrative design of the review.

ABBREVIATION

AI Artificial intelligence

Results

The identified themes can be conceptualized within a staged educational framework aligned with progressive clinical responsibility and increasing exposure to AI. The synthesis of the literature revealed several consistent and interrelated themes across studies.[3,4]

First, successful AI education requires longitudinal integration across all stages of medical training, including preclinical, clinical, and residency phases, rather than isolated instructional units or elective courses. This approach ensures that AI literacy develops as a continuous professional competency.

Second, traditional assessment models are inadequate in the context of AI-augmented clinical practice. Assessment strategies must evolve to evaluate higher-order competencies such as clinical reasoning, ethical judgment, and the critical appraisal of AI outputs within authentic or simulated clinical scenarios. Reliance on rote memorization is no longer an adequate proxy for clinical competence.[5]

Third, institutional preparedness is essential. This includes the establishment of transparent policies governing appropriate AI use in education and assessment, alongside robust, secure, and regulation-compliant digital infrastructure capable of supporting simulation, data protection, and equitable access to AI tools.[6]

Across the literature, a consistent finding was the importance of fostering critical engagement with AI. Educational models that emphasize the contextual interpretation and validation of AI-generated recommendations are associated with improved clinical reasoning and a reduction in harmful automation bias among trainees.[4,7]

Discussion

The following sections synthesize the reviewed evidence into a practical and educationally grounded framework, translating conceptual findings into actionable components for curriculum design, teaching, and assessment.

Integrating AI into medical education represents an educational and cultural challenge rather than a purely technical one. Early and repeated exposure to AI concepts helps demystify these systems and supports the development of balanced clinical judgment. Embedding AI within existing curricula allows learners to perceive it as a natural component of routine clinical reasoning rather than as a disruptive external force.[3,8]

Table 1. Representative table mapping specific AI competencies to existing accreditation standards

AI competency domain	Description of Competency	Relevant accreditation / qualification criteria	Example evidence for accreditation
AI literacy and conceptual understanding	Knowledge of fundamental AI concepts, including machine learning, natural language processing, and data-driven systems	Program learning outcomes requiring advanced disciplinary knowledge within the national qualifications framework	Written examinations, conceptual quizzes, theoretical assignments
Data literacy and analytical skills	Ability to collect, process, analyze, and interpret structured and unstructured data for informed decision-making	Analytical thinking and problem-solving competencies emphasized in program accreditation standards	Data analysis reports, statistical projects, applied research assignments
Algorithmic and computational thinking	Capacity to understand, evaluate, or design algorithms used in AI systems and digital technologies	Technical and methodological competencies required in computing and engineering-related programs	Programming assignments, algorithm design projects, coding assessments
AI tool application	Ability to effectively use AI-based tools (e.g., large language models, predictive analytics systems) for academic and professional tasks	Digital competency and technology integration outcomes in higher education programs	Practical laboratory exercises, tool-based coursework, applied projects
Human–AI collaboration	Ability to critically evaluate AI-generated outputs and integrate them into human decision-making processes	Critical thinking and professional judgment competencies in quality assurance frameworks	Scenario-based evaluations, case studies, reflective analyses
Ethical and responsible AI use	Understanding ethical considerations including algorithmic bias, data privacy, accountability, and transparency	Ethical responsibility and professional conduct criteria in accreditation frameworks	Ethics reports, policy analyses, reflective essays on responsible AI
AI in professional practice	Application of AI technologies within discipline-specific contexts such as business, healthcare, engineering, or education	Applied knowledge and real-world problem-solving requirements in program outcomes	Capstone projects, internships, applied industry collaborations
AI-supported teaching and learning (education programs)	Ability to design AI-enhanced learning environments and integrate AI into instructional strategies	Pedagogical competence and instructional design outcomes in teacher education accreditation	Instructional design projects, lesson plans integrating AI tools
Research and innovation with AI	Ability to conduct research using AI methodologies or develop innovative AI-driven solutions	Research competence and innovation capacity expected in undergraduate and graduate programs	Research papers, thesis projects, experimental studies
Lifelong learning and adaptability	Capacity to continuously update knowledge and skills in response to rapidly evolving AI technologies	Lifelong learning competency emphasized in national qualifications frameworks	Professional development portfolios, independent learning projects

The Turkish context presents both opportunities and challenges. Centralized governance of medical education may facilitate coordinated implementation of national AI competency standards. Aligning AI education with existing accreditation frameworks from the Turkish Council of Higher Education and the National Medical Specialty Education Board (TUSED, Türkiye) could promote consistency, quality, and sustainability.[9] However, successful implementation depends on substantial investment in faculty development and institutional infrastructure. Although discussed within the Turkish context, these principles are transferable to other centrally governed or resource-constrained medical education systems. The integration of AI competencies into higher education curricula requires alignment with existing accreditation and quality assurance frameworks. In Türkiye, universities design program learning outcomes in accordance with national higher education standards established by the Council of Higher Education (Türkiye) and monitored through quality assurance processes coordinated by the Higher Education Quality Council of Türkiye. To illustrate how emerging AI-related skills can be incorporated within these established frameworks, Table 1 presents a representative mapping between key AI competency domains and corresponding accreditation criteria.[9] The table demonstrates how competencies such as AI literacy, data analysis, ethical AI use, and human–AI collaboration align with widely recognized learning outcomes, including analytical thinking, professional responsibility, research competence, and lifelong learning. This alignment highlights that integrating AI competencies into higher education programs does not require entirely new accreditation structures; rather, these competencies can be embedded within existing outcome-based quality assurance systems through curriculum design, assessment strategies, and program evaluation practices.

It is important to acknowledge that this review is limited by its narrative design and by the rapidly evolving nature of AI technologies, which may outpace curricular adaptations. Additionally, much of the available literature consists of conceptual frameworks, expert perspectives, or early educational initiatives rather than fully implemented and outcome-validated curricula.

The relative scarcity of Türkiye-specific empirical studies on AI integration in medical education further limits the generalizability of localized recommendations. Future research should focus on outcome-based evaluations of AI education, particularly its impact on clinical performance, patient safety, and professional behavior in high-risk fields.

Conceptual Foundations: AI Literacy for Medical Students and Residents

AI literacy in medicine extends beyond basic familiarity with digital tools. Medical trainees must understand that most contemporary AI systems rely on probabilistic pattern recognition rather than causal reasoning.[10] Without this understanding, clinicians may become vulnerable to automation bias, excessive trust in algorithmic outputs, and subsequent diagnostic or therapeutic errors.[4]

Foundational AI education should therefore include core concepts such as supervised and unsupervised learning; model performance metrics, including sensitivity, specificity, and area under the curve; external validation; and common failure modes such as dataset bias and hallucinations in generative models.[11] These topics should be taught using clinically relevant examples and analogies, without requiring programming skills, to ensure accessibility and relevance.

Upon achieving foundational AI literacy, learners should be able to critically evaluate AI-generated clinical recommendations, recognize scenarios in which AI performance may be compromised, and integrate algorithmic outputs with clinical judgment and patient-specific context.

Curriculum Design Across Educational Stages

Undergraduate Medical Education

During the preclinical years, AI concepts should be integrated into existing courses such as biostatistics, epidemiology, and evidence-based medicine. Early exposure to AI-assisted case discussions and algorithmic risk scores helps students develop essential conceptual familiarity.[3]

During clinical clerkships, students should encounter AI tools within real or simulated clinical workflows, such as clinical decision support alerts or radiology assistance systems. These encounters should be supported by structured supervision and guided reflection, enabling learners to critically evaluate the role, benefits, and limitations of AI in patient care.[12]

Residency Training

Residency programs require more advanced and specialty-specific AI education. In cardiovascular surgery and interventional cardiology, AI-enhanced simulations can provide valuable training in preoperative decision-making, complication prediction, and postoperative monitoring.[13]

Residents should also be trained to communicate AI-supported decisions transparently to patients, clearly explaining the role of these technologies in clinical care.[7]

Teaching Methods in AI-Enhanced Medical Education

Effective AI education necessitates a shift from purely didactic instruction toward learner-centered approaches. Case-based discussions, flipped classrooms, and critical appraisal exercises, in which trainees audit AI-generated outputs, promote active learning and deeper engagement.[3] Interdisciplinary teaching involving collaboration among clinicians, data scientists, and ethicists further enriches the educational experience by integrating technical, clinical, and ethical perspectives.[14]

Assessment and Examination Models

Traditional closed-book examinations, which primarily assess factual recall, are poorly suited to evaluating the competencies required for AI-augmented clinical practice.[5] AI-aware assessment models should include open-book examinations permitting the use of artificial intelligence tools with mandatory disclosure and justification; AI-enhanced Objective Structured Clinical Examinations, in which candidates must interpret or communicate AI-generated findings; and portfolio-based assessments documenting reflective and responsible AI use during clinical training. These approaches provide more authentic measures of clinical competence, particularly in high-risk disciplines such as cardiovascular medicine.[15]

Maintaining examination integrity in the era of artificial intelligence requires carefully designed assessment environments that balance authentic AI-supported practice with safeguards against inappropriate reliance on automated tools. In high-stakes assessments, unrestricted use of AI systems may introduce risks such as automation bias, where trainees defer to algorithmic outputs rather than demonstrating independent clinical reasoning.[16] To mitigate this risk, institutions should establish transparent policies defining when and how AI tools may be used during examinations. Structured formats—such as supervised open-book assessments and mandatory disclosure of AI assistance, or scenarios in which learners must explicitly critique AI-generated recommendations—can help ensure that evaluation focuses on higher-order competencies rather than passive acceptance of algorithmic outputs. In addition, secure digital testing environments, proctoring protocols, and clear academic integrity guidelines are essential to prevent unauthorized AI use. Together, these strategies help preserve the validity of assessments while reinforcing the educational objective that AI should augment, rather than replace, human clinical judgment.

Ethical, Legal, and Professional Considerations

Ethical instruction must be embedded throughout AI education rather than treated as an add-on. Core issues requiring longitudinal attention include data privacy and informed consent, algorithmic bias and health equity, professional accountability for AI-influenced decisions, and transparency in patient-clinician communication.[17,18] Teaching the technical aspects of AI without a strong ethical foundation may risk undermining patient trust and safety.[6,11] To support safe interaction with AI-assisted clinical tools, trainees require practical strategies for identifying algorithmic bias and mitigating automation-related risks. The checklist presented in Table 2 provides a structured approach that medical students and residents can apply during real-world clinical encounters to critically evaluate AI-generated recommendations and preserve patient safety.

Integration Strategies for AI Education in Medical Curricula

Rather than introducing AI as a standalone discipline, a more feasible and sustainable strategy is to integrate AI-related competencies into existing components of the medical curriculum. Foundational concepts such as algorithm performance metrics, predictive modeling, and data interpretation can be incorporated into courses already devoted to biostatistics and evidence-based medicine, where students learn to evaluate diagnostic

Table 2. Checklist detailing how trainees can proactively identify and mitigate these biases when interacting with real-world clinical tools

Stage of AI interaction	Key questions for trainees	Practical actions
Before using the AI tool	Is the AI system validated for the patient population and clinical context?	Review the intended use, validation population, and known limitations of the AI system before applying it in clinical decision-making.
	Does the tool rely on datasets that may exclude certain populations?	Consider whether demographic groups such as older patients, women, or minority populations may be underrepresented in the training data.
	Is the clinical question appropriate for AI assistance?	Use AI tools as supportive decision aids rather than replacements for clinical reasoning.
During AI-assisted decision-making	Does the AI recommendation align with the patient's clinical presentation?	Compare the AI output with clinical findings, established guidelines, and differential diagnoses.
	Could automation bias be influencing your interpretation?	Avoid accepting AI outputs automatically; actively question unexpected or unusually confident recommendations.
	Are there inconsistencies between AI outputs and clinical judgment?	Reassess patient data, review alternative diagnoses, and consult senior clinicians when discrepancies arise.
After receiving the AI output	Could dataset bias explain the AI recommendation?	Evaluate whether patient characteristics (age, comorbidities, socioeconomic factors) may fall outside the algorithm's training distribution.
	Is the AI output explainable and clinically interpretable?	Prefer outputs that provide transparent reasoning or supporting variables rather than opaque predictions.
Patient communication and documentation	How should the AI contribution be communicated to the patient?	Explain the supportive role of AI in decision-making and emphasize that clinical responsibility remains with the physician.
	Was the AI tool influential in the final decision?	Document when AI-assisted recommendations were considered and how they were integrated with clinical reasoning.
Reflection and quality improvement	Did the AI tool perform as expected in this case?	Reflect on discrepancies and discuss them during case reviews or morbidity and mortality meetings.
	Could the system demonstrate systematic bias?	Report repeated inconsistencies or potential biases through institutional quality and safety channels.

tests, risk prediction models, and clinical research methodology. For example, discussions of sensitivity, specificity, and receiver operating characteristic curves can be expanded to include the evaluation of machine learning models and clinical decision-support algorithms. Similarly, epidemiology and population health courses can address issues such as dataset bias, representativeness, and fairness in algorithmic systems. During clinical clerkships, AI-supported tools—such as imaging interpretation software or clinical risk calculators—can be introduced within supervised case discussions, enabling trainees to critically assess algorithmic outputs alongside traditional clinical reasoning. This integrative approach minimizes curricular disruption while promoting longitudinal exposure to AI concepts across training stages. By embedding AI literacy within familiar educational contexts, medical schools can foster critical engagement with emerging technologies while maintaining alignment with established competency-based educational frameworks.

Conclusion

Artificial intelligence is no longer a speculative addition to healthcare; it is an operational reality that is reshaping clinical workflows, diagnostic pathways, and health system governance. Medical education must therefore evolve proactively to prepare future physicians not only to use AI tools but also to critically evaluate, ethically govern, and responsibly integrate them into patient care.

Artificial intelligence should be integrated into undergraduate and residency medical education as a core clinical competency. A staged, human-centered, and ethics-driven educational framework can ensure that AI functions as a powerful adjunct that supports and strengthens, rather than replaces, human clinical judgment. This integration is particularly important in cardiovascular and other high-stakes disciplines, where AI-assisted decision-making increasingly influences patient outcomes. Such frameworks are essential to preserve professional accountability, enhance patient safety, and sustain trust in AI-augmented healthcare systems. Future research should focus on evaluating the educational and clinical outcomes of AI-integrated curricula, including their impact on clinical reasoning, patient safety, and professional decision-making in real-world healthcare environments.

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Correlations Between Air Pollutants and Acute Coronary Syndrome Subtypes: A Six-Year Analysis

Hava Kirleticileri ile Akut Koroner Sendrom Alt Tipleri Arasındaki Korelasyonlar: 6 Yıllık Bir Analiz

ABSTRACT

Objective: Air pollution is a major global public health concern and has increasingly been linked to cardiovascular diseases, including acute coronary syndrome (ACS). This study investigated the temporal association between air pollution and ACS case counts in Amasya, northern Türkiye.

Method: In this retrospective study, the medical records of 6,185 ACS patients treated at a single hospital were analyzed, including cases of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris. Environmental air pollutant levels, including particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}), particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), nitric oxide (NO), and nitrogen oxides (NOx) were collected, and their temporal correlations with ACS case counts were evaluated. Seasonal variations in both the number of hospital admissions for ACS and pollutant concentrations were also analyzed.

Results: Seasonal analysis revealed a significantly higher number of hospital admissions for acute coronary syndrome during winter compared with other seasons in this single-center study conducted in northern Türkiye ($P < 0.05$). Levels of particulate matter (PM_{10} and $PM_{2.5}$) were also elevated in winter, with $PM_{2.5}$ showing a moderate positive correlation with STEMI case counts ($r = 0.38$, $P = 0.0005$) and a strong positive correlation with NSTEMI case counts ($r = 0.55$, $P < 0.0001$). Nitrogen oxides (NO and NOx) also increased during winter but did not show significant correlations with overall ACS case counts.

Conclusion: Targeted public health strategies are required to mitigate pollution exposure, particularly during high-risk seasons. Further research using more accurate and higher-resolution pollution metrics and longitudinal data is warranted to deepen our understanding of the cardiovascular impacts of specific pollutants and to support the development of effective intervention strategies.

Keywords: Acute coronary syndrome, air pollution, particulate matter, seasonal variation

ÖZET

Amaç: Hava kirliliği, küresel çapta önemli bir halk sağlığı sorunudur ve akut koroner sendrom (AKS) da dahil olmak üzere kardiyovasküler hastalıklarla giderek artan bir şekilde ilişkilendirilmektedir. Bu çalışma, Türkiye'nin kuzeyindeki Amasya'da hava kirliliği ile AKS vaka sayısı arasındaki zamansal ilişkiyi araştırmıştır.

Yöntem: Bu retrospektif çalışmada, tek bir hastanede ST yükselmeli miyokard enfarktüsü (STEMI), ST yükselmesiz miyokard enfarktüsü (NSTEMI) ve kararsız angina pektoris vakaları da dahil olmak üzere 6185 AKS hastasının tıbbi kayıtları analiz edilmiştir. Çevresel hava kirleticileri (örneğin PM_{10}, $PM_{2.5}$, NO, NOx) düzeyleri derlenmiş ve bunların AKS vaka sayısı ile zamansal korelasyonları belirlenmiştir. Hem AKS vakalarının hastane başvuru sayısı hem de hava kirletici konsantrasyonlarındaki mevsimsel değişimler değerlendirilmiştir.

Bulgular: Türkiye'nin kuzeyinde yürütülen bu tek merkezli çalışmada, mevsimsel analiz, kış aylarında akut koroner sendrom nedeniyle hastaneye yatış sayısının diğer mevsimlere kıyasla anlamlı derecede daha yüksek olduğunu ortaya koymuştur ($P < 0.05$). Partikül madde (PM_{10} ve $PM_{2.5}$) seviyeleri de kış aylarında yükselmiş ve $PM_{2.5}$, STEMI vaka sayısıyla orta düzeyde pozitif bir korelasyon ($r = 0,38$, $P = 0,0005$) ve NSTEMI vaka sayısıyla güçlü bir pozitif korelasyon ($r = 0,55$, $P < 0,0001$) göstermiştir. Azot oksitler (NO ve NOx) kış aylarında artış göstermiş, ancak genel AKS vaka sayısıyla anlamlı bir korelasyon göstermemiştir.

Sonuç: Özellikle yüksek riskli mevsimlerde hava kirliliğine maruziyeti azaltmayı hedefleyen halk sağlığı stratejilerine ihtiyaç vardır. Belirli hava kirleticilerin kardiyovasküler etkilerine ilişkin anlayışımızı derinleştirmek ve etkili müdahale stratejileri geliştirmek için daha doğru ve daha yüksek çözünürlüklü hava kirlilik ölçümleri ve uzunlamasına verilerle daha fazla araştırmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Akut koroner sendrom, hava kirliliği, partikül madde, mevsimsel değişim

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

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Cardiovascular diseases (CVDs) persist as the foremost cause of global mortality and morbidity,[1] with acute coronary syndrome (ACS) representing one of the most severe clinical manifestations.[2] Acute coronary syndrome encompasses a continuum of conditions, including unstable angina and myocardial infarction, both of which result from an abrupt reduction in myocardial perfusion.[2] These ischemic episodes are often precipitated by the rupture of a vulnerable atherosclerotic plaque followed by thrombus formation, leading to significant hemodynamic compromise.[3] Despite significant advances in diagnostic modalities and therapeutic strategies, including percutaneous coronary intervention and the widespread use of antiplatelet therapies,[4] the burden that ACS places on patients and healthcare systems worldwide continues to increase.

Air pollution has emerged as a critical public health issue worldwide, with profound implications for human health and the environment. According to the World Health Organization, approximately 7 million premature deaths each year are attributable to exposure to ambient air pollution, with outdoor air pollution alone accounting for approximately 60% of these deaths.[5,6] These findings highlight the urgency of addressing this global health crisis. Among the many health consequences associated with air pollution, its impact on CVDs has attracted substantial attention in recent years.

The etiology of ACS is multifactorial, with hypertension, diabetes, hyperlipidemia, and smoking, among others, established as risk factors.[7,8] However, growing evidence suggests that environmental factors, particularly air pollution, also play a significant role in triggering or exacerbating acute cardiovascular events. Fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) are among the key air pollutants implicated in the pathophysiology of CVDs through mechanisms involving systemic inflammation, oxidative stress, and endothelial dysfunction.[9-11] These processes collectively destabilize atherosclerotic plaques, increasing the likelihood of plaque rupturing and subsequent thrombotic occlusion of coronary arteries. Furthermore, oxidative stress induced by exposure to pollutants compromises mitochondrial function and promotes apoptosis of vascular endothelial cells, rendering the cardiovascular system more vulnerable to adverse events.[12] Urbanization has led to the exposure of a larger proportion of the population to harmful air pollutants, with residents in metropolitan areas experiencing chronic exposure to elevated levels of $PM_{2.5}$, nitrogen oxides (NOx), and other pollutants.[13] Epidemiological studies have demonstrated a temporal association between spikes in air pollution levels and increases in ACS-related hospital admissions, particularly in urban environments characterized by poor air quality and limited green spaces.[14-16] However, much remains unclear regarding which pollutants predominate in different regions, the nature of dose-response relationships, and how the age structure of different populations influences these clinical outcomes.

Against this background, the present study aimed to evaluate the relationship between air pollution and ACS case counts through a retrospective analysis of the temporal association between hospital admissions and environmental air quality data, with the goal of contributing to strategies aimed at mitigating the cardiovascular risks associated with air pollution.

ABBREVIATIONS

ACS	Acute coronary syndrome
CO	Carbon monoxide
CVDs	Cardiovascular diseases
NO	Nitric oxide
NO_2	Nitrogen dioxide
NOx	Nitrogen oxides
NSTEMI	Non-ST-elevation myocardial infarction
O_3	Ozone
$PM_{2.5}$	Particulate matter with a diameter of 2.5 μm or less
PM_{10}	Particulate matter with a diameter of 10 μm or less
STEMI	ST-elevation myocardial infarction
USAP	Unstable angina pectoris

Materials and Methods

Study Design and Population

This retrospective, observational study was designed to assess the impact of air pollution on ACS case counts in Amasya in northern Türkiye. Patients admitted to the Cardiology Clinic of Amasya Training and Research Hospital were included in the study, and patient data collected between January 1, 2018 and September 30, 2024 were analyzed. The study adhered to the principles outlined in the Declaration of Helsinki and was approved by Amasya University Non-Interventional Clinical Research Ethics Committee (Approval Number: 2024/122, Date: 27.11.2024). As the study was retrospective in nature and used anonymized patient data, the requirement for informed consent was waived by the committee. Official permission to access patient files in the hospital's archived medical records was obtained from the hospital directorate. Patient confidentiality was maintained throughout the study by anonymizing all data.

The study population included adult patients aged 18 years and older who were admitted to the cardiology clinic with a clinical diagnosis of ACS and who underwent coronary angiography during the study period.

ACS Subtypes and Clinical Definitions

Acute coronary syndrome subtypes were identified using appropriate International Classification of Diseases (ICD) codes: ST-elevation myocardial infarction (STEMI; I21.0, I21.1, I21.2, I21.3), non-ST-elevation myocardial infarction (NSTEMI; I21.4), and unstable angina pectoris (I20.0). Broad ischemic heart disease codes were used only for the initial electronic screening. Final diagnoses were confirmed through detailed review of clinical records, laboratory findings, and coronary angiography results. Clinical definitions were as follows: STEMI was defined as ischemic symptoms with persistent ST-segment elevation (or new/presumed new left bundle branch block, where applicable) accompanied by a rise and/or fall in cardiac troponin levels. NSTEMI was defined as ischemic symptoms with a rise and/or fall in troponin levels without persistent ST-segment elevation. Unstable angina pectoris (USAP) was defined as ischemic symptoms without troponin elevation consistent with myocardial injury and without persistent ST-segment elevation.

Patients who underwent coronary angiography, regardless of whether significant obstructive coronary lesions were present, were included in the study. Patients who died before undergoing

Table 1. Total number and baseline demographic characteristics of the patients

Total ACS cases, n	6,185
STEMI, n (%)	1,948 (31.5)
NSTEMI, n (%)	3,400 (54.9)
USAP, n (%)	837 (13.6)
Age (years)	63.60 ± 11.32
Male, n (%)	3,866 (62.5)
DM, n (%)	2,158 (34.9)
HT, n (%)	3,593 (58.1)
CVA, n (%)	488 (7.9)

ACS, Acute coronary syndrome; CVA, Cerebrovascular accident; DM, Diabetes mellitus; HT, Hypertension; NSTEMI, Non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; USAP, Unstable angina pectoris.

coronary angiography or for whom incomplete clinical data were available were excluded. To improve diagnostic accuracy and minimize misclassification of ACS subtypes, a known limitation in retrospective registry-based studies, only patients who underwent coronary angiography were included, allowing non-coronary etiologies to be ruled out inpatients with a preliminary diagnosis of chest pain.

Data Collection

Following ethics committee approval, patient data were retrospectively collected from hospital electronic medical records and registry databases beginning on December 16, 2024. International Classification of Diseases codes (I21.0, I21.1, I21.2, I21.3, I21.4, and I20.0) were used to identify patients diagnosed with myocardial infarction. The monthly numbers of hospital admissions for STEMI, NSTEMI, and USAP were recorded for the entire study period. Seasons were defined as winter (December–February), spring (March–May), summer (June–August), and fall (September–November).

Environmental air pollution data were obtained from the Amasya Provincial Directorate of Environment, Urbanization, and Climate Change on December 16, 2024, following ethics committee approval. Monthly average concentrations of key air pollutants between January 1, 2018 and September 30, 2024, including particulate matter aerodynamic diameters ≤ 2.5 μm and ≤ 10 μm ($PM_{2.5}$ and PM_{10}, respectively), carbon monoxide (CO), nitrogen dioxide, nitrogen oxides, and ozone (O_3), were collected for the study period.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism v8.0 (GraphPad Software Inc., California, USA, 2019). Continuous variables were tested for normality using the Shapiro–Wilk test. Variables were analyzed using one-way analysis of variance (ANOVA), and post hoc analyses were conducted using Dunn's multiple comparisons test. For non-normally distributed variables, the Kruskal–Wallis test was employed, and multiple comparisons were performed using Dunn's test.

The correlations between air pollution parameters and ACS case counts were analyzed using Pearson's correlation coefficient for normally distributed variables and Spearman's rho for non-normally distributed variables. Statistical significance was set at $P < 0.05$.

Results

Among the 6,185 ACS cases recorded at our hospital between January 2018 and September 2024, 1,948 were STEMI, 3,400 were NSTEMI, and 837 were USAP. The total number of patients included in the study and their baseline demographic characteristics are shown in Table 1. The numbers of STEMI, NSTEMI, and total ACS cases were significantly higher in winter than in spring and summer (all $P < 0.05$) (Table 2). Additionally, the numbers of NSTEMI and total ACS cases were significantly higher in winter than in fall (both $P < 0.01$) (Table 2).

The concentrations of various air pollutants, including PM_{10}, $PM_{2.5}$, CO, O_3, NO, NO_2, and NOx, were compared across the four seasons. PM_{10} levels were significantly higher in winter than in spring ($P < 0.01$), summer ($P < 0.0001$), and fall ($P < 0.05$) (Figure 1A). Similarly, $PM_{2.5}$ levels were significantly elevated in winter compared with spring ($P < 0.01$), summer ($P < 0.0001$), and fall ($P < 0.05$) (Figure 1B). Moreover, $PM_{2.5}$ levels were significantly higher in fall than in summer ($P < 0.01$) (Figure 1B). CO concentrations peaked in winter, when they were significantly higher than those observed in spring ($P < 0.05$), summer ($P < 0.0001$), and fall ($P < 0.01$) (Figure 1C). Meanwhile, ozone levels showed a distinct seasonal pattern, with significantly higher levels in spring than in winter ($P < 0.01$) and summer ($P < 0.0001$). Additionally, ozone levels in fall were significantly lower than those in summer ($P < 0.001$) (Figure 1D). Moreover, NO levels were highest in winter, significantly exceeding those observed in spring ($P < 0.0001$), while NO levels were also significantly higher in fall than in summer ($P < 0.01$) (Figure 1E). Finally, although NO_2 levels were similar across seasons (Figure 1F), NOx levels were significantly higher in winter than in summer ($P < 0.01$) (Figure 1G).

Table 2. Distribution of acute coronary syndrome (ACS) cases across seasons

	Winter	Spring	Summer	Fall
STEMI	29.05 ± 6.02[a,b]	22.38 ± 5.21[a]	21.38 ± 6.67[b]	23.58 ± 7.34
NSTEMI	55.75 ± 10.25[x,y,z]	40.24 ± 11.27[x]	32.81 ± 9.96[y]	39.53 ± 6.32[z]
USAP	11.10 ± 6.63	10.52 ± 6.48	10.19 ± 6.42	9.47 ± 5.36
Total ACS	95.9 ± 17.77[k,l,m]	73.14 ± 19.28[k]	64.38 ± 17.21[l]	72.58 ± 19.15[m]

ACS, Acute coronary syndrome; NSTEMI, Non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; USAP, Unstable angina pectoris. Statistical analysis: Kruskal–Wallis test followed by Dunn's multiple comparison test. Data are presented as mean ± standard deviation (SD). Post hoc pairwise comparisons and corresponding p values: [a]Winter vs. Spring ($P = 0.0077$); [b]Winter vs. Summer ($P = 0.0016$); [x]Spring vs. Summer ($P = 0.002$); [y]Spring vs. Fall ($P < 0.001$); [z]Summer vs. Fall ($P = 0.007$); [k]Winter vs. Spring for total ACS ($P = 0.0103$); [l]Winter vs. summer for total ACS ($P < 0.0001$); [m]Winter vs. fall for total ACS ($P = 0.0027$).

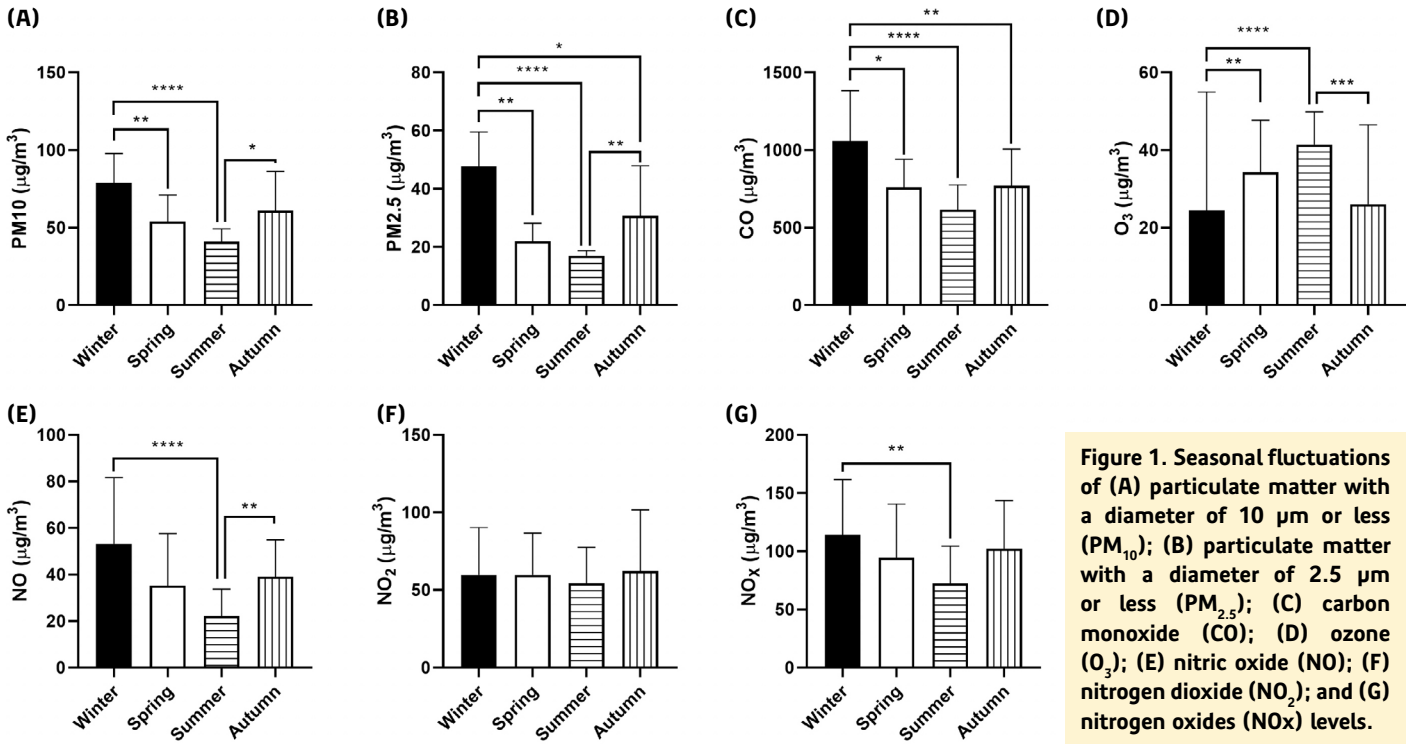

Figure 1. Seasonal fluctuations of (A) particulate matter with a diameter of 10 µm or less (PM_{10}); (B) particulate matter with a diameter of 2.5 µm or less ($PM_{2.5}$); (C) carbon monoxide (CO); (D) ozone (O_3); (E) nitric oxide (NO); (F) nitrogen dioxide (NO_2); and (G) nitrogen oxides (NOx) levels.

Table 3. Correlations between air pollutants and cases of acute coronary syndrome (ACS) and its subtypes

	Spearman's rho (*P* value)			
	STEMI	**NSTEMI**	**USAP**	**Total ACS**
PM_{10}	0.1559 (0.1647)	**0.3088 (0.0050)**	0.0670 (0.5521)	**0.2246 (0.0439)**
$PM_{2.5}$	**0.3778 (0.0005)**	**0.5539 (<0.0001)**	0.1466 (0.1917)	**0.4686 (<0.0001)**
CO	**0.4722 (<0.0001)**	**0.5647 (<0.0001)**	0.0898 (0.4249)	**0.5137 (<0.0001)**
O_3	–0.1725 (0.1236)	**–0.3564 (0.0011)**	0.0496 (0.6598)	**–0.2225 (0.0459)**
NO	0.1170 (0.2983)	0.1616 (0.1494)	–0.0575 (0.6098)	0.1050 (0.3510)
NO_2	0.1303 (0.2462)	–0.0568 (0.6141)	**0.2737 (0.0134)**	0.0714 (0.5264)
NOx	0.1764 (0.1151)	0.1012 (0.3689)	0.1497 (0.1823)	0.1275 (0.2565)

ACS, Acute coronary syndrome; CO, Carbon monoxide; NO, Nitric oxide; NO_2, Nitrogen dioxide; NOx, Nitrogen oxides; NSTEMI, Non-ST-elevation myocardial infarction; O_3, Ozone; $PM_{2.5}$, Particulate matter with a diameter of 2.5 µm or less; PM_{10}, Particulate matter with a diameter of 10 µm or less; STEMI, ST-elevation myocardial infarction; USAP, Unstable angina pectoris.

In line with the seasonal variations of air pollutant concentrations, monthly measurements revealed fluctuations in air pollutant levels throughout the study period, with concentrations generally peaking between fall and spring (Figure 2A–G).

The monthly fluctuations in total ACS cases and its subtypes are shown in Figure 3.

PM_{10} levels demonstrated a mild-to-moderate positive correlation with NSTEMI case counts and a mild positive correlation with total ACS cases. $PM_{2.5}$ levels exhibited a moderate positive correlation with STEMI and strong positive correlations with NSTEMI and total ACS cases (Table 3).

Carbon monoxide concentrations showed moderate-to-strong positive correlations with STEMI and total ACS cases and a strong positive correlation with NSTEMI cases. In contrast, ozone levels showed mild negative correlations with NSTEMI and total ACS cases. NO and NOx levels did not show any correlations with total ACS or any ACS subtypes, whereas NO_2 levels showed a mild-to-moderate positive correlation with USAP cases (Table 3).

Discussion

The current retrospective study demonstrated a significant association between air pollution and the seasonal case counts of ACS, particularly highlighting the roles of particulate matter ($PM_{2.5}$ and PM_{10}) and CO in exacerbating cardiovascular conditions. These findings contribute to the growing body of evidence demonstrating that environmental air pollutants are critical risk factors in the pathogenesis of ACS.

Seasonal variations in the incidence of ACS have been documented in various studies, suggesting that environmental factors such as temperature, as well as lifestyle variations including exercise and alcohol consumption during different

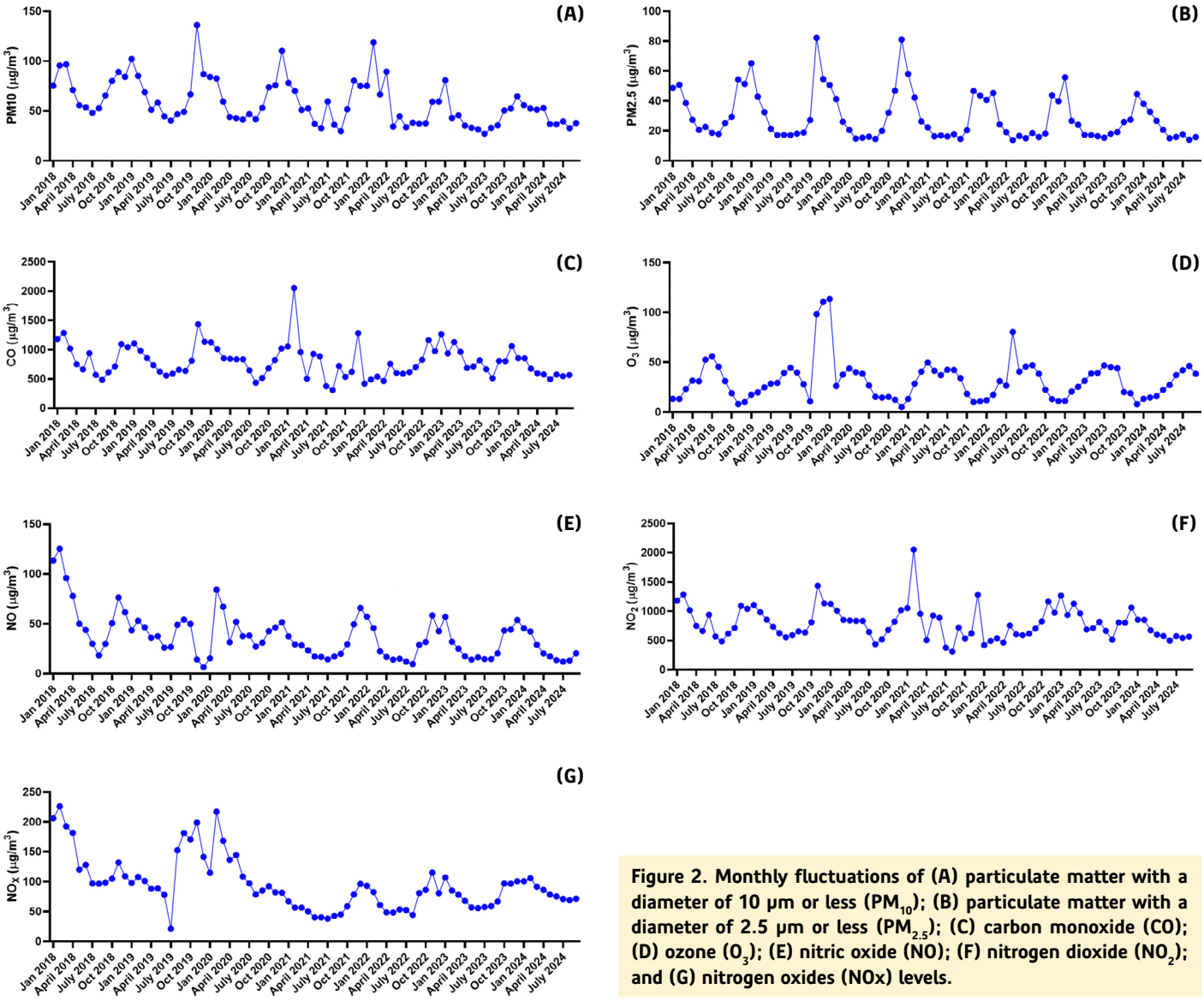

Figure 2. Monthly fluctuations of (A) particulate matter with a diameter of 10 µm or less (PM_{10}); (B) particulate matter with a diameter of 2.5 µm or less ($PM_{2.5}$); (C) carbon monoxide (CO); (D) ozone (O_3); (E) nitric oxide (NO); (F) nitrogen dioxide (NO_2); and (G) nitrogen oxides (NOx) levels.

seasons, may influence cardiovascular events.[17] For instance, in a study conducted in the United States, Vallabhajosyula et al.[18] reported that the management and outcomes of acute myocardial infarction can be affected by seasonal changes, with winter months often associated with increased hospitalizations for myocardial infarction. Lower temperatures in winter may contribute to this phenomenon through increases in blood viscosity and elevated sympathetic nervous system activity, whereas higher temperatures in summer may play a role through increased air pollution associated with high PM_{10} levels and vitamin D deficiency.[19-21]

The clear seasonal variability in air pollutants and their associations with ACS subtypes underscores the complex interactions among meteorological conditions, emission sources, and pathophysiological processes that influence cardiovascular outcomes.[22,23] PM_{10} and $PM_{2.5}$ concentrations, both of which are significantly elevated during winter, reflect pollution from combustion-based heating and vehicular emissions, as well as reduced atmospheric dispersion in colder months worldwide.[24,25]

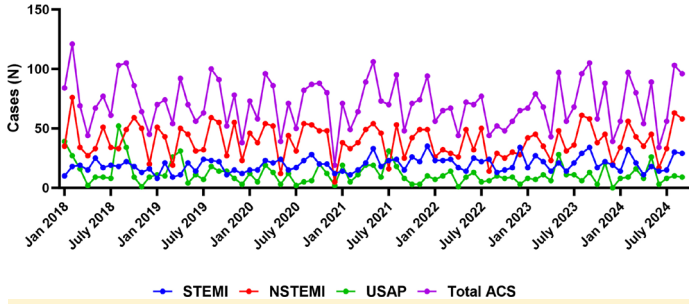

Figure 3. Monthly fluctuations in the total number of acute coronary syndrome (ACS) cases and its subtypes.

These elevated particulate levels coincide with increased ACS incidence. In our analysis, PM_{10} demonstrated a mild-to-moderate positive correlation with NSTEMI and a mild positive correlation with total ACS cases, while $PM_{2.5}$ showed a moderate positive correlation with STEMI and strong positive correlations with the incidences of NSTEMI and total ACS.[26,27] $PM_{2.5}$ poses

a particular cardiovascular risk because its smaller aerodynamic diameter allows particles to penetrate deeply into the respiratory tract, triggering systemic inflammation, endothelial dysfunction and atherogenesis.[28]

Carbon monoxide also peaked in winter at the study site, likely due to incomplete combustion under stable atmospheric conditions and decreased photochemical oxidation during colder months.[29] Notably, CO exhibited moderate-to-strong positive correlations with STEMI and total ACS, and a strong positive correlation with NSTEMI. These findings are consistent with evidence that CO-mediated tissue hypoxia and oxidative stress can exacerbate cardiovascular risk.[30,31] Meanwhile, ozone displayed a distinct seasonal cycle, peaking in spring under more intense sunlight and higher temperatures conducive to photochemical reactions. Interestingly, ozone showed mild negative correlations with NSTEMI and total ACS, a finding that may reflect the different oxidative pathways, precursor availability, and atmospheric dynamics governing ozone compared with those for primary combustion pollutants.[32,33]

Wintertime elevations in NO and total NOx were pronounced; however, these pollutants did not show significant correlations with ACS in this study. Although NO_2 did not vary significantly by season, mild-to-moderate correlations with USAP were observed, suggesting that certain patient subgroups or specific cardiac phenotypes may be more susceptible to NO_2-related oxidative and inflammatory mechanisms.[34-36] Collectively, these results reinforce the notion that winter elevates cardiovascular risk due to concurrent surges in multiple pollutants (PM_{10}, $PM_{2.5}$, CO, NO, and NOx), each of which can trigger overlapping biological pathways of inflammation, platelet activation, and endothelial dysfunction.

Taken together, the findings of this study indicate that the observed seasonal clustering of pollutants and their associations with different ACS subtypes emphasize the importance of targeted public health interventions to mitigate cardiovascular disease exacerbation linked to air pollution, particularly when pollution levels peak in winter.[37] Measures aimed at reducing combustion-related emissions, improving urban air ventilation, and enhancing clinical awareness of high-risk periods could help mitigate the cardiovascular burden associated with air pollution. Future large-scale, longitudinal studies with more accurate and higher-resolution pollution metrics (e.g., source apportionment and personal-level exposure assessment) are warranted to disentangle pollutant-specific impacts and optimize strategies for preventing ACS and related cardiovascular conditions.

Limitations

This study has several limitations. First, its retrospective single-center design limits causal inference. Second, the effects of air pollution on ACS were examined at the monthly and seasonal levels, and short-term acute effects on ACS were not evaluated. Third, only patients who underwent coronary angiography were included, potentially excluding patients managed conservatively or those who died before angiography, which may have influenced the distribution of ACS subtypes. Fourth, the angiographic coronary artery anatomy of ACS patients was not analyzed, and the number of affected vessels was not assessed. Finally, potential confounding factors such as ambient temperature and seasonal infections could not be incorporated into the analysis due to data limitations.

Conclusion

This investigation demonstrated a significant association between air pollution and the seasonal case counts of ACS in Amasya, northern Türkiye. Particulate matter ($PM_{2.5}$ and PM_{10}) and CO were identified as the primary pollutants, with concentrations peaking during the winter months. $PM_{2.5}$ exhibited strong correlations with both STEMI and NSTEMI cases, while CO correlated with NSTEMI and total ACS cases. These observations highlight air pollution as a modifiable risk factor for ACS, particularly during winter. The findings emphasize the need for targeted public health initiatives to reduce pollution exposure in northern Türkiye and elsewhere, especially during high-risk periods. Proposed interventions include reducing combustion-related emissions, enhancing urban air circulation, and increasing clinical awareness of high-risk seasons. Further research is warranted, including large-scale longitudinal studies using refined pollution metrics and investigations of the biological mechanisms linking pollutants to ACS. This study adds to the evidence connecting air pollution to cardiovascular outcomes and highlights the significance of environmental factors in the pathogenesis of ACS. The results have implications for public health policy, urban planning, and clinical practice, underscoring the need for a multidisciplinary approach to address these challenges.

Ethics Committee Approval: Ethics committee approval was obtained from Amasya University Non-Interventional Clinical Research Ethics Committee (Approval Number: 2024/122, Date: 27.11.2024).

Informed Consent: As the study was retrospective in nature and used anonymized patient data, the requirement for informed consent was waived by the committee.

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Stress Hyperglycemia Ratio Is Associated with Intracardiac Thrombus in Acute Ischemic Stroke

Akut İskemik İnmede Stres Hiperglisemi Oranı ile İntrakardiyak Trombüs Arasındaki İlişki

ABSTRACT

Objective: Transthoracic echocardiography (TTE) is widely used for cardiac evaluation in acute ischemic stroke (AIS), but it may miss intracardiac thrombi that can be detected by transesophageal echocardiography (TEE). The stress hyperglycemia ratio (SHR), which adjusts admission glucose for baseline glycemia, has emerged as a novel biomarker in cardiovascular disease. However, its association with intracardiac thrombus undetected by TTE in AIS remains unclear.

Method: This retrospective study included 486 AIS patients who underwent TEE despite negative baseline TTE findings. Demographic, laboratory, and echocardiographic data were evaluated. Logistic regression and receiver operating characteristic (ROC) analysis were used to assess independent associations with intracardiac thrombus.

Results: TEE detected thrombus in 64 patients (13.2%). Patients with thrombus had higher SHR (0.99 ± 0.42 vs. 0.84 ± 0.27, P < 0.001), glucose, C-reactive protein (CRP), and creatinine levels, and lower ejection fraction. In univariable analysis, SHR showed a strong association with intracardiac thrombus (odds ratio [OR] = 3.68, P < 0.001) and remained independently associated after multivariable adjustment (OR = 2.39, 95% confidence interval: 1.11–5.17, P = 0.027), along with CRP, paroxysmal atrial fibrillation, and male sex, while ejection fraction was inversely associated with thrombus presence. The model demonstrated good discriminative performance (area under the curve: 0.796).

Conclusion: SHR is associated with intracardiac thrombus missed by TTE but detected by TEE in AIS. SHR may enhance risk stratification and help guide selective use of TEE.

Keywords: Acute ischemic stroke, cardioembolism, echocardiography, intracardiac thrombus, risk stratification, stress hyperglycemia ratio

ÖZET

Amaç: Transtorasik ekokardiyografi (TTE), akut iskemik inmede (AİS) kardiyak değerlendirmede yaygın olarak kullanılmakla birlikte, transözofageal ekokardiyografi (TEE) ile saptanabilen intrakardiyak trombüsleri gözden kaçırabilmektedir. Başvuru glukozunu bazal glisemik duruma göre düzelten stres hiperglisemi oranı (SHR), kardiyovasküler hastalıklarda yeni bir biyobelirteç olarak ortaya çıkmıştır. Akut iskemik inmede, TTE ile saptanamayan ancak TEE ile gösterilen intrakardiyak trombüs ile ilişkisi henüz net değildir.

Yöntem: Bu retrospektif çalışmaya, başlangıç TTE bulguları negatif olmasına rağmen TEE yapılan 486 AİS hastası dahil edilmiştir. Demografik, laboratuvar ve ekokardiyografik veriler değerlendirilmiş; intrakardiyak trombüs ile bağımsız ilişkileri belirlemek için lojistik regresyon ve ROC analizleri kullanılmıştır.

Bulgular: TEE ile 64 hastada (%13,2) trombüs saptanmıştır. Trombüsü olan hastalarda SHR (0,99 ± 0,42'ye karşı 0,84 ± 0,27; P < 0,001), glukoz, CRP ve kreatinin düzeyleri daha yüksek, ejeksiyon fraksiyonu ise daha düşüktür. Tek değişkenli analizde SHR, intrakardiyak trombüs ile güçlü bir ilişki göstermiştir (OR 3,68; P < 0,001) ve çok değişkenli düzeltme sonrası da CRP, paroksismal atriyal fibrilasyon ve erkek cinsiyet ile birlikte bağımsız olarak ilişkili kalmaya devam etmiştir (OR 2,39; %95 GA 1,11–5,17; P = 0,027). Düşük ejeksiyon fraksiyonu, trombüs varlığı ile ilişkilidir. Model, iyi ayırt edici performans göstermiştir (AUC 0,796).

Sonuç: SHR, akut iskemik inmede TTE ile saptanamayan ancak TEE ile ortaya konulan intrakardiyak trombüs ile ilişkilidir. SHR, risk sınıflandırmasını geliştirebilir ve seçilmiş hastalarda TEE kullanımına rehberlik edebilir.

Anahtar Kelimeler: Akut iskemik inme, kardiyoembolizm, ekokardiyografi, intrakardiyak trombüs, risk sınıflandırması, stres hiperglisemi oranı

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Stroke remains a major global health problem, ranking among the leading causes of long-term disability and representing the second most common cardiovascular cause of mortality worldwide.[1] Acute ischemic stroke (AIS) accounts for approximately 85% of all stroke cases and can be classified into five principal subtypes according to their etiological mechanisms: (i) small-vessel occlusion (lacunar infarction), (ii) large-artery atherosclerosis, (iii) cardioembolic stroke, (iv) stroke due to other determined causes, and (v) stroke of undetermined origin.[2,3] Among these, cardioembolic events are typically associated with worse prognoses, including higher mortality rates, greater disability, and poorer neurological recovery. In routine clinical practice, transthoracic echocardiography (TTE) is the first-line imaging technique for patients presenting with AIS.[4] Although widely accessible and noninvasive, TTE is often inadequate for fully excluding cardioembolic sources. Current guidelines also do not provide definitive recommendations regarding whether patients with unremarkable TTE findings should undergo transesophageal echocardiography (TEE) for further evaluation of potential embolic substrates in AIS.[5,6] Importantly, although TEE is more sensitive, it is semi-invasive and carries procedural risks, particularly in patients with recent ischemic events. Therefore, identifying patients most likely to benefit from TEE is of practical clinical importance.[7]

Stress hyperglycemia, defined as a relative increase in blood glucose during acute illness, has been consistently associated with adverse outcomes across a range of critical conditions, including sepsis, myocardial infarction, and postoperative complications.[8] The stress hyperglycemia ratio (SHR), which standardizes acute glucose levels to baseline glycemic control derived from hemoglobin A1c (HbA1c), is superior to absolute hyperglycemia in predicting short-term mortality and cardiovascular events.[9]

The stress hyperglycemia ratio improves upon glucose or HbA1c alone by adjusting admission glucose to baseline glycemic status, allowing differentiation between acute stress-induced hyperglycemia and chronic dysglycemia.[10] This distinction is important because stress hyperglycemia is more strongly associated with endothelial dysfunction, oxidative stress, platelet activation, and prothrombotic states than chronic hyperglycemia alone.[11] Stress-induced hyperglycemia results from an acute neuroendocrine and inflammatory response characterized by elevated catecholamine and cortisol levels, insulin resistance, and cytokine activation. These effects contribute to a range of prothrombotic actions that likely link elevated SHR to intracardiac thrombus development.[12] Acute hyperglycemia damages the endothelium through oxidative stress and reduced nitric oxide, impairing its antithrombotic function.[13] Simultaneously, stress-induced hyperglycemia stimulates platelet activation and aggregation, upregulates adhesion molecules, and enhances tissue factor-driven coagulation, all of which favor clot formation.[14] Studies also indicate that acute hyperglycemia impairs natural fibrinolysis by elevating plasminogen activator inhibitor-1 levels and producing fibrin clots that are more resistant to breakdown.[15] In the context of AIS, the presence of left atrial thrombus (LAT) is a critical determinant of cardioembolic events and often portends a poor prognosis. Although atrial fibrillation is the most recognized substrate for LAT, many patients without documented AF may also harbor thrombi that remain undetected on transthoracic echocardiography.[16]

ABBREVIATIONS

AF	Atrial fibrillation
AIS	Acute ischemic stroke
CRP	C-reactive protein
EF	Ejection fraction
HbA1c	Hemoglobin A1c
HF	Heart failure
LA	Left atrium
LAA	Left atrial appendage
LAAP	Left atrial anteroposterior diameter
LAT	Left atrial thrombus
LVEF	Left ventricular ejection fraction
MVR	Mitral valve replacement
PAF	Paroxysmal atrial fibrillation
ROC	Receiver operating characteristic
SEC	Spontaneous echo contrast
SHR	Stress hyperglycemia ratio
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography

Based on these considerations, we hypothesized that elevated SHR values are associated with the presence of intracardiac thrombus in patients with acute ischemic stroke without known AF. If validated, SHR could serve as a readily available and cost-effective tool to refine risk stratification, guide the selective use of TEE, and ultimately improve the detection of latent cardioembolic sources in this vulnerable population.

Materials and Methods

Study Design and Patient Selection

This retrospective, cross-sectional study was conducted at a tertiary referral center between March 2018 and May 2023. A total of 486 consecutive patients with acute ischemic stroke who underwent transesophageal echocardiography to evaluate a potential cardioembolic source were included. The inclusion criteria were: (1) confirmed AIS or transient ischemic attack (TIA) based on neurological assessment and brain magnetic resonance imaging; (2) sinus rhythm on admission electrocardiography; (3) absence of intracardiac thrombus on baseline transthoracic echocardiography; (4) availability of admission laboratory data, including glucose and HbA1c levels; (5) technically adequate TEE imaging; and (6) no prior use of oral or parenteral anticoagulant therapy before hospital admission.

The exclusion criteria were: (1) stroke due to clearly identifiable non-cardioembolic etiologies (e.g., large-artery atherosclerosis or small-vessel disease); (2) intracardiac thrombus detected on baseline transthoracic echocardiography (patients with intracardiac thrombus detected on baseline transthoracic echocardiography were excluded because the primary aim of the study was to investigate thrombi not identified by initial TTE but subsequently detected by transesophageal echocardiography); (3) isolated right atrial or left ventricular thrombus; (4) known persistent or permanent atrial fibrillation at presentation; (5) current or prior anticoagulant use, including vitamin K antagonists, direct oral anticoagulants, or parenteral anticoagulants; (6) documented thrombophilia or hypercoagulable states,

including active thrombophlebitis, inherited or acquired coagulation disorders, or systemic conditions associated with increased thrombotic risk; (7) incomplete clinical, laboratory, or echocardiographic data; and (8) inadequate TEE image quality precluding reliable thrombus assessment. All patients underwent 24–72-hour Holter monitoring during hospitalization to screen for paroxysmal atrial fibrillation. Stroke diagnosis and etiological classification were established by an experienced neurologist. The study protocol was approved by Haydarpaşa Numune Training and Research Hospital Clinical Trials Ethics Committee (Approval Number: HNEAH/KAEK/2019/KK/171, Date: 02.12.2019) and conducted in accordance with the Declaration of Helsinki.

Information on medication use before admission was systematically obtained for all patients through a detailed review of electronic medical records, medication reconciliation forms, and admission documentation. Particular attention was given to oral and parenteral anticoagulant therapy, including vitamin K antagonists, direct oral anticoagulants, and heparin-based agents. Patients with documented anticoagulant use before hospital admission were excluded from the study to minimize confounding effects on intracardiac thrombus formation and prevalence. Antiplatelet therapy was recorded separately and evaluated as a potential covariate.

Transesophageal Echocardiography

Transesophageal echocardiography examinations were performed after overnight fasting (≥8 hours) using a multiplane 5 MHz probe (Philips iE33, Philips Medical Systems, Massachusetts, USA). Topical oropharyngeal anesthesia was administered to all patients, and intravenous sedation with diazepam was given when necessary. Two experienced cardiologists performed TEE with patients in the left lateral decubitus position. The left atrium (LA) and left atrial appendage (LAA) were systematically evaluated in multiple planes to detect intracardiac thrombus, defined as a circumscribed, homogenous echogenic mass distinct from the atrial wall and identifiable in at least two views. LAA flow velocities were assessed using pulsed-wave Doppler positioned at the orifice of the appendage. The presence and severity of spontaneous echo contrast (SEC) were also recorded.

Definitions

Acute ischemic stroke was defined as a focal neurological deficit lasting ≥24 hours, whereas transient ischemic attack was defined as symptoms lasting <24 hours without evidence of acute infarction on neuroimaging. Intracardiac thrombus was defined as a discrete echogenic mass distinct from the endocardial border, attached to the LA wall or LAA, and visible in at least two projections. Left ventricular ejection fraction (EF), left atrial anteroposterior diameter (LAAP), and left ventricular dimensions were measured according to current echocardiography guidelines.

The stress hyperglycemia ratio was calculated to account for both the acute glucose level at hospital admission and the individual's baseline glycemic status. Admission blood glucose was normalized to long-term glycemic control, as measured by HbA1c, thereby providing a relative measure of stress-induced hyperglycemia rather than relying solely on absolute glucose values. Specifically, SHR was defined according to the following formula:

[glucose (mg/dL) / 18] / [(1.59 × HbA1c) − 2.59].

This adjustment allows SHR to distinguish transient stress-related hyperglycemia from chronically elevated glucose levels due to diabetes, thereby improving its clinical relevance in outcome discrimination.[17]

Statistical Analysis

Continuous variables were initially assessed for normality using visual inspection (histograms and Q–Q plots) and the Shapiro–Wilk test. Variables with non-normal distributions, particularly laboratory and inflammatory parameters, were analyzed using nonparametric methods. Accordingly, continuous variables are presented as mean ± standard deviation for descriptive purposes, and between-group comparisons were performed using the Mann–Whitney U test, as appropriate. Categorical variables are reported as counts and percentages and were compared using the chi-square test or Fisher's exact test.

Univariate logistic regression analyses were performed to identify potential predictors of intracardiac thrombus. Before multivariable modeling, potential collinearity among candidate variables was assessed, taking into account both clinical relevance and mathematical dependence. Because the stress hyperglycemia ratio is derived from admission glucose and HbA1c, absolute glucose was not entered simultaneously with SHR in the multivariable regression model to avoid collinearity and redundancy. The final multivariable logistic regression model was constructed by including variables that were statistically significant in univariable analyses while also considering clinical relevance, biological plausibility, and model stability, particularly given the limited number of outcome events. By study design, patients receiving oral or parenteral anticoagulant therapy prior to admission were excluded.

Odds ratios with 95% confidence intervals were reported. Model discrimination was evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test; however, calibration metrics in a retrospective, cross-sectional dataset were interpreted cautiously. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA).

Results

Of the 486 study participants, 259 (53.3%) were women and 227 (46.7%) were men. Intracardiac thrombus was detected in 64 patients (13.2%). The mean age of the cohort was 59.7 ± 17.0 years. Patients with thrombus were significantly older (63.6 ± 16.5 vs. 58.6 ± 17.0 years, P = 0.006) and were more frequently male (62.5% vs. 44.3%, P = 0.007) (Table 1).

Baseline Laboratory and Echocardiographic Findings

Patients with thrombus had higher white blood cell counts (9.98 ± 5.27 vs. 7.99 ± 2.51, P < 0.001), glucose levels (134 ± 74 vs. 118 ± 56 mg/dL, P < 0.001), stress hyperglycemia ratio (0.99 ± 0.42 vs. 0.84 ± 0.27, P < 0.001), creatinine levels (1.68 ± 1.94 vs. 1.17 ± 0.71 mg/dL, P = 0.001), C-reactive protein (CRP) levels (63.4 ± 76.3 vs. 27.2 ± 27.1 mg/L, P < 0.001), and lower albumin levels (34.6 ± 5.9 vs. 38.0 ± 7.5 g/L, P = 0.002). They also had reduced ejection fraction (54.3 ± 11.2% vs. 58.8 ± 8.0%, P < 0.001), a larger LA anteroposterior diameter (44.1 ±

Table 1. Baseline clinical characteristics of the study cohort

Variables (n = 486)	Thrombus (-) n = 422	Thrombus (+) n = 64	*P*
Male sex	166 (43.3%)	38 (59.3%)	0.007
Hypertension	229 (54.3%)	39 (60.9%)	0.317
Diabetes mellitus	99 (23.5%)	18 (28.1%)	0.416
Chronic kidney disease	41 (10.7%)	13 (12.6%)	0.012
Smoking	47 (11.1%)	8 (12.5%)	0.748
Paroxysmal atrial fibrillation (PAF)	29 (7.6%)	40 (38.8%)	<0.001
Mitral valve replacement (MVR)	35 (8.3%)	15 (23.4%)	<0.001
Aortic valve replacement (AVR)	20 (4.7%)	2 (3.1%)	0.563
Antiplatelet use	177 (42%)	34 (53%)	0.105
Statin use	48 (11.4%)	9 (14.1%)	0.533

7.5 vs. 42.6 ± 7.2 mm, P = 0.009), and increased left ventricular end-diastolic diameter (LVEDD) (50.1 ± 9.8 vs. 47.8 ± 7.4 mm, P = 0.017). No significant differences were observed in HbA1c (P = 0.099), platelet count (P = 0.260), or liver enzymes (Table 2).

Clinical Characteristics

Paroxysmal atrial fibrillation (PAF) was strongly associated with thrombus (62.5% vs. 6.9%, P < 0.001), as was mitral valve replacement (23.4% vs. 8.3%, P < 0.001). Chronic kidney disease was more frequent among thrombus-positive patients (20.3% vs. 9.7%, P = 0.012). In contrast, hypertension, diabetes, smoking status, antiplatelet use, and statin use did not differ significantly between the groups (Table 1).

Univariate Analysis

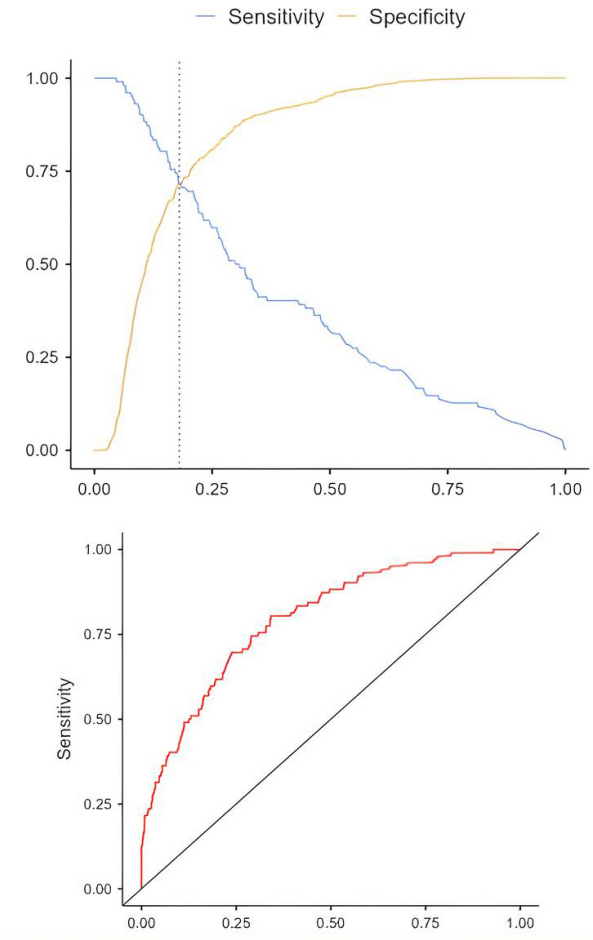
Univariate logistic regression identified age (odds ratio [OR] = 1.018, P = 0.010), male sex (OR = 1.899, P = 0.004), chronic kidney disease (CKD) (OR = 2.473, P = 0.003), SHR (OR = 3.682, P < 0.001), CRP (OR = 1.017, P < 0.001), and PAF (OR = 2.962, 95% confidence interval [CI]: 1.872–4.687, P < 0.001) as variables significantly associated with intracardiac thrombus. Ejection fraction was inversely associated with thrombus (OR = 0.951, P < 0.001) (Table 3).

Multivariate Analysis

After adjustment for covariates, SHR (OR = 2.393, P = 0.027) and CRP (OR = 1.015, P < 0.001) remained independently associated with thrombus. Male sex (OR = 1.657, P = 0.048) and PAF also retained statistical significance (OR = 2.419, 95% CI: 1.381–4.239, P < 0.001). Ejection fraction remained inversely associated with thrombus (OR = 0.956, P < 0.001). CKD lost statistical significance (P = 0.422) and age showed only a borderline association (P = 0.058) (Table 3).

Model Performance

The SHR-based predictive model demonstrated good discriminatory performance, (AUC: 0.796, 95% CI: 0.745–0.852, P < 0.001), indicating reliable differentiation between patients with and without thrombus. At the optimal cut-off probability of 0.18, the model achieved a sensitivity of 71.5% and a specificity of 71.6%, suggesting that SHR provides a balanced ability to detect true thrombus cases while minimizing false positives. Furthermore, the model was well calibrated, as indicated by the Hosmer–Lemeshow test (χ^2 = 6.731, df = 8, P = 0.566). These results highlight the potential of SHR as a practical and clinically relevant parameter for thrombus risk prediction (Figure 1).



Accuracy	Specificity	Sensitivity	AUC	95% CI	P value
0.715	0.715	0.716	0.796	0.745-0.852	<0.001

Note: The cut-off value is set to 0.18

Figure 1. Receiver operating characteristic (ROC) curve for the predictive model of intracardiac thrombus.

Discussion

In this retrospective study, we demonstrated that SHR was independently associated with the presence of intracardiac thrombus detected on transesophageal echocardiography in patients with acute ischemic stroke despite negative transthoracic echocardiography. To our knowledge, this is the first study to establish a direct association between SHR and occult intracardiac thrombus in AIS, highlighting its potential role as a practical biomarker to guide advanced cardiac imaging.

Identifying simple biomarkers to stratify patients who may benefit from further evaluation is essential for improving diagnostic precision and overall patient outcomes. TTE, although widely used, may fail to detect small atrial or ventricular thrombi capable of causing AIS.[18] Therefore, recognizing which patients should undergo TEE could help prevent underdiagnosis. This is particularly relevant because stroke etiology strongly influences treatment strategies. However, the selective use of TEE remains controversial due to its semi-invasive nature.[19]

Table 2. Baseline laboratory and echocardiographic parameters of patients with and without thrombus

Variables (n = 486)	Thrombus (-) (n = 422)	Thrombus (+) (n = 64)	Z	P*
Age (years)	58.64 ± 17.03	63.56 ± 16.48	-2.760	**0.006**
WBC (10^3/μL)	7.99 ± 2.51	9.98 ± 5.27	-3.396	**<0.001**
Hemoglobin (g/dL)	13.02 ± 2.14	11.82 ± 4	-6.154	**<0.001**
Platelet (10^3/μL)	241.29 ± 79.77	232.08 ± 114.89	-1.127	0.260
Creatinine (mg/dL)	1.17 ± 0.71	1.68 ± 1.94	-3.237	**0.001**
HbA1c (%)	6.5 ± 1.3	6.4 ± 1.2	-1.648	0.099
Glucose (mg/dL)	118 ± 56	134 ± 74	-3.317	**<0.001**
Stress hyperglycemia ratio	0.84 ± 0.27	0.99 ± 0.42	-3.869	**<0.001**
CRP (mg/L)	27.22 ± 27.08	63.42 ± 76.3	-4.435	**<0.001**
Total protein (g/L)	62.00 ± 13.81	63 ± 6.76	-1.547	0.122
Albumin (g/L)	37.96 ± 7.45	34.61 ± 5.93	-3.73	**0.002**
AST (U/L)	26.1 ± 17.8	73.4 ± 328.1	-0.953	0.340
ALT (U/L)	26.7 ± 35.7	66.5 ± 237.4	-1.008	0.314
TSH (mIU/L)	1.75 ± 2.33	1.67 ± 1.44	-0.907	0.364
T4 (ng/dL)	1.43 ± 4.95	1.81 ± 5.43	-1.737	0.087
Ejection fraction (%)	58.83 ± 7.97	54.25 ± 11.23	-3.968	**<0.001**
LAAP (mm)	42.6 ± 7.2	44.1 ± 7.5	-2.595	**0.009**
LVESD (mm)	40.9 ± 7.5	40.1 ± 10.7	-1.772	0.076
LVEDD (mm)	47.8 ± 7.4	50.1 ± 9.8	-2.386	**0.017**
TPAP (mmHg)	40 ± 9	38 ± 14	-0.275	0.783

*P-values were calculated using the Mann-Whitney U test. WBC, White blood count; HbA1c, Hemoglobin A1c; CRP, C-reactive protein; AST, Aspartate Aminotransferase; ALT, Alanine aminotransferase; LAAP, Left atrial anteroposterior diameter; LVESD, Left ventricular end-systolic diameter; LVEDD, Left ventricular end-diastolic diameter; TPAP, Pulmonary artery pressure.

Table 3. Univariate and multivariate logistic regression analysis of predictors of intracardiac thrombus

Predictor	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	1.018 (1.004–1.032)	**0.010**	1.016 (0.999–1.032)	0.058
SHR	3.682 (1.914–7.082)	**<0.001**	2.393 (1.107–5.172)	**0.027**
CRP	1.017 (1.011–1.023)	**<0.001**	1.015 (1.009–1.021)	**<0.001**
EF	0.951 (0.930–0.973)	**<0.001**	0.956 (0.933–0.980)	**<0.001**
TPAP	0.988 (0.968–1.009)	0.253	0.982 (0.960–1.004)	0.103
Male sex	1.899 (1.220–2.954)	**0.004**	1.657 (1.003–2.736)	**0.048**
CKD	2.473 (1.355–4.516)	**0.003**	1.342 (0.653–2.755)	0.422
Paroxysmal atrial fibrillation (PAF)	2.962 (1.872–4.687)	**<0.001**	2.419 (1.381–4.239)	**0.002**

CI, Confidence interval; SHR, Stress hyperglycemia ratio; CRP, C-reactive protein; EF, Ejection fraction; TPAP, Pulmonary artery pressure; CKD, Chronic kidney disease.

Our findings suggest that SHR, being simple, inexpensive, and easily obtainable, could refine patient selection for TEE in AIS. Incorporating SHR into risk assessment models may improve diagnostic yield while avoiding unnecessary procedures.

Acute ischemic stroke continues to be a leading cause of mortality and long-term disability. Despite advances in secondary prevention, a substantial proportion of patients experience poor outcomes. Accurate identification of stroke etiology remains the cornerstone of management. Stroke is generally classified into five etiological categories: (i) small-vessel occlusion (lacunar infarction), (ii) large-artery atherosclerosis, (iii) cardioembolic stroke, (iv) other determined causes, and (v) undetermined origin.[20] Among these, cardioembolic strokes often require long-term anticoagulation, and in cases of suspected paroxysmal atrial fibrillation, prolonged cardiac monitoring is recommended.[21,22] However, the coexistence of atherosclerotic disease frequently complicates classification. Failure to detect a cardioembolic source can therefore lead to incomplete or inappropriate treatment.[23,24] Our study underscores that even in patients without embolic sources on TTE, SHR-based risk stratification may identify those who should undergo TEE to ensure accurate diagnosis and optimal therapy, potentially reducing stroke-related mortality and disability.

Our results expand upon prior evidence linking stress hyperglycemia to adverse cerebrovascular outcomes. Previous studies and meta-analyses have demonstrated associations between elevated glucose levels or SHR and larger infarct size, poorer functional recovery, and higher mortality.[25,26] Unlike absolute glucose, SHR incorporates background glycemic status, providing a more accurate reflection of the acute metabolic stress response.[9] The present study extends this concept by identifying SHR not only as a prognostic marker but also as an indicator of cardioembolic risk by detecting intracardiac thrombi missed by routine TTE.

In our cohort, patients with thrombus were significantly older and more often male, consistent with the prothrombotic risk conferred by age-related atrial remodeling and the higher cardiovascular burden observed in men. Several laboratory parameters were also associated with thrombus presence: patients with thrombus exhibited higher white blood cell counts, glucose levels, creatinine levels, CRP levels, and SHR, along with lower hemoglobin levels. This finding aligns with results reported by Wu et al.,[27] who demonstrated that higher hemoglobin levels are protective against ischemic and cardioembolic stroke, suggesting that anemia may contribute to a prothrombotic state. Mechanistically, hyperglycemia may promote endothelial dysfunction, oxidative stress, platelet activation, and systemic inflammation, all of which favor thrombus formation. Elevated CRP and reduced albumin levels in our thrombus group further support the role of inflammatory and metabolic pathways in thrombogenesis.

Reduced left ventricular ejection fraction (LVEF) is associated with intracardiac thrombi, which are frequently observed in patients with cardiovascular diseases, particularly in autopsy studies. In a study analyzing 11,724 autopsies, Vaideeswar et al.[28] identified 276 cases (2.4%) with intracardiac thrombus. Patients with LVEF are particularly prone to intracardiac thrombosis due to structural and functional heart abnormalities compounded by comorbid conditions. Thromboembolic events occur in 1–3% of patients with chronic heart failure (HF) annually, with intracardiac thrombus representing a major underlying cause. Severe systemic arterial embolism and the associated morbidity and mortality related to intracardiac thrombi highlight the importance of further studies investigating the clinical characteristics of these patients.[29] McCarthy et al.[30] reported that HF was the leading cause of intracardiac thrombosis (68.5%), with 86% of patients exhibiting reduced EF (LVEF ≤ 40%). Similarly, our study demonstrated a close relationship between thrombus formation and impaired cardiac function. Although the underlying mechanisms are not fully understood, impaired intracardiac hemodynamics resulting from cardiac dysfunction and reduced LVEF contribute significantly to a hypercoagulable state within the ventricle.[29]

Furthermore, both PAF and mitral valve replacement (MVR) emerged as strong predictors of intracardiac thrombus. This finding is consistent with evidence showing that PAF, which is often underdiagnosed, substantially increases the risk of left atrial thrombus, while prosthetic mitral valves predispose to thrombosis through both mechanical and structural mechanisms. These observations highlight the importance of arrhythmias and valve interventions in thrombus pathogenesis.[31,32] Crucially, our results show that SHR remains a significant predictor even after accounting for atrial fibrillation (AF) and MVR, supporting its value as a complementary biomarker in high-risk subgroups.

Finally, common vascular risk factors such as hypertension, diabetes, and smoking remain highly prevalent among patients with AIS and influence all stroke subtypes. The widespread use of antiplatelet agents and statins may further complicate etiological attribution by modulating thrombosis and inflammation across categories. Against this complex background, SHR offers an accessible and clinically meaningful parameter to improve diagnostic accuracy, guide imaging strategies, and optimize treatment in AIS.

Limitations

Several limitations should be acknowledged. First, the retrospective, single-center design limits causal inference and may affect the generalizability of our findings. In addition, the decision to perform transesophageal echocardiography in routine clinical practice was influenced by physician judgment and patient-related factors rather than a standardized protocol, introducing potential selection bias. Although clearly defined inclusion and exclusion criteria were applied to improve cohort homogeneity, selection bias cannot be fully excluded in retrospective observational studies, and the study population may not fully represent all patients with acute ischemic stroke and negative transthoracic echocardiography findings.

Furthermore, although the stress hyperglycemia ratio incorporates baseline glycemic status through adjustment for HbA1c, residual confounding remains possible. SHR values may still be influenced by the time interval between symptom onset and blood sampling, interindividual variability in acute stress responses, and the presence or severity of diabetes mellitus.

Importantly, ROC-based results should be interpreted as indicators of diagnostic discrimination rather than forward-looking risk prediction. In addition, the optimal SHR cut-off value was derived from the same dataset used for model evaluation, and no external validation cohort was available. These factors increase the risk of overestimating model performance and limit the generalizability of the identified threshold.

Finally, the multivariable regression model was constructed using a combination of univariable statistical significance and clinical judgment to reduce the risk of overfitting.

Conclusion

In summary, this study demonstrates that the stress hyperglycemia ratio is independently associated with the presence of intracardiac thrombus not detected by transthoracic echocardiography but revealed on transesophageal echocardiography in patients with acute ischemic stroke. As a simple, inexpensive, and widely available biomarker, SHR has the potential to improve risk stratification and guide clinical decision-making regarding the selective use of TEE to uncover hidden cardioembolic sources. Prospective multicenter studies are warranted to validate these findings and determine whether integrating SHR into routine stroke evaluation improves diagnostic accuracy, informs therapeutic strategies, and reduces recurrent ischemic events.

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Skeletal Muscle Strength and Waist-to-Height Ratio Serve as Partial Mediators in the Relationship Between Muscle Mass and Exercise Capacity in Individuals with Heart Failure: A Mediation Analysis

Kalp Yetersizliği Olan Bireylerde Kas Kütlesi ile Egzersiz Kapasitesi Arasındaki İlişkide İskelet Kası Kuvveti ve Bel/Boy Oranı Kısmi Aracı Değişkenler Olarak Rol Oynamaktadır: Bir Aracılık Analizi

ABSTRACT

Objective: Exercise intolerance is a hallmark of heart failure (HF), and skeletal muscle abnormalities and abdominal obesity are important noncardiac factors contributing to this limitation. This study aimed to investigate the mediating roles of skeletal muscle strength and waist-to-height ratio (WtHR) in the relationship between muscle mass and exercise capacity in individuals with HF.

Method: This cross-sectional study included 110 patients with HF aged over 18 years who were classified as New York Heart Association (NYHA) functional class II or III. Exercise capacity, skeletal muscle mass, muscle strength, and WtHR were assessed using the six-minute walk test, a Tanita device, a Jamar hydraulic handgrip dynamometer, and a tape measure, respectively. Mediation effects were evaluated using the bootstrapping method with a 95% confidence interval and parallel multiple mediation models. Mediation was considered significant when the intervals did not include zero.

Results: A significant correlation was observed between muscle mass and exercise capacity, with both muscle strength and WtHR acting as partial mediators in this relationship. After adjusting for age, sex, and NYHA class, the mediating effect of WtHR was greater (30.6%) than that of muscle strength (17.9%). Despite these mediating effects, muscle mass maintained a direct effect of 51.5% on exercise capacity.

Conclusion: In individuals with HF, muscle mass is associated with exercise capacity both directly and indirectly through muscle strength and WtHR. Assessing these characteristics together may help account for the impact of abdominal obesity, which is associated with reduced exercise capacity in this population.

Keywords: Abdominal obesity, heart failure, muscle strength, six-minute walk test, waist-to-height ratio

ÖZET

Amaç: Egzersiz intoleransı, kalp yetersizliğinin (KY) temel klinik özelliklerinden biridir. İskelet kası bozuklukları ve abdominal obezite ise bu kısıtlılığın önemli nonkardiyak belirleyicilerindendir. Bu çalışma, KY'li bireylerde kas kütlesi ile egzersiz kapasitesi arasındaki ilişkide kas kuvveti ve bel/boy oranının (WtHR) aracılık rollerini incelemeyi amaçlamaktadır.

Yöntem: Kesitsel olarak tasarlanan araştırmaya, NYHA fonksiyonel sınıf II–III'te olan, 18 yaş ve üzerindeki 110 KY hastası dâhil edildi. Egzersiz kapasitesi, altı dakikalık yürüme testi ile; iskelet kası kütlesi, Tanita analizörü ile; kas kuvveti, Jamar hidrolik el dinamometresi ile ve WtHR, mezura kullanılarak değerlendirildi. Aracılık analizleri, %95 güven aralıklı bootstrapping yöntemi ve paralel çoklu aracılık modelleri kullanılarak gerçekleştirildi; güven aralığının sıfırı içermemesi anlamlı aracılık olarak yorumlandı.

Bulgular: Kas kütlesi ile egzersiz kapasitesi arasında anlamlı bir ilişki gözlendi; kas kuvveti ve WtHR, bu ilişkide kısmi aracı değişkenler olarak belirlendi. Yaş, cinsiyet ve NYHA sınıflaması için düzeltme yapıldıktan sonra, WtHR'nin aracılık etkisi (%30,6), kas kuvvetinin etkisine (%17,9) kıyasla daha yüksek bulundu. Aracılık etkisine rağmen kas kütlesinin, egzersiz kapasitesi üzerinde %51,5 oranında doğrudan etkisi vardı.

ORIGINAL ARTICLE
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Sonuç: KY'li bireylerde kas kütlesi, egzersiz kapasitesi ile hem doğrudan hem de kas kuvveti ve WtHR aracılığıyla dolaylı olarak ilişkilidir. Bu faktörlerin birlikte değerlendirilmesi, KY popülasyonunda egzersiz kapasitesini önemli ölçüde azaltan abdominal obezitenin dikkate alınmasını sağlar.

Anahtar Kelimeler: Abdominal obezite, kalp yetersizliği, kas kuvveti, altı dakika yürüme testi, bel/boy oranı

Heart failure (HF) constitutes a significant public health issue characterized by high mortality, morbidity, and hospitalization rates. Despite advances in treatment that have contributed to reduced mortality, HF remains a serious condition characterized by numerous symptoms and clinical signs.[1] Exercise intolerance is a primary symptom associated with reduced quality of life and an increased risk of mortality in individuals with HF. Exertional dyspnea, fatigue, and ambulatory difficulties are also common symptoms among non-hospitalized patients with HF.[1,2]

Individuals with HF exhibit various histological and metabolic abnormalities in skeletal muscle, including muscle atrophy, a reduction in oxidative fibers and enzymes, and decreased mitochondrial volume density and capillary-to-fiber ratio.[3] Approximately 20% of this population demonstrates reduced muscle mass, which is an independent predictor of mortality.[4,5] Previous studies have indicated that skeletal muscle atrophy and decreased lower-extremity muscle mass lead to reduced peak oxygen uptake (VO_2peak) and decreased muscle strength.[3] Furthermore, the prevalence of sarcopenia, characterized by a decline in both muscle quantity and quality, is higher in individuals with HF than in age-matched populations and is associated with poor prognosis.[5] Impaired muscle function in sarcopenia, when combined with other HF-related symptoms, is linked to an increased risk of functional limitations.[5,6]

Obesity is a significant risk factor for the development of HF. Paradoxically, a higher body mass index (BMI) has been associated with a more favorable prognosis until recently.[7] Nevertheless, the outcomes of anthropometric measurements, which provide a more accurate assessment of the distribution and quantity of ectopic fat, do not support this association, known as the obesity paradox. The waist-to-height ratio (WtHR), which assesses adiposity while accounting for sex and racial variations, has been correlated with hospitalization and mortality rates, as well as cardiorespiratory fitness.[8] Additionally, WtHR is a good predictor of metabolic and cardiovascular risk and has been linked to muscle mass, potentially acting as a confounding variable in the relationship between exercise capacity and muscle mass.[9]

Multisystem dysfunction, including peripheral, pulmonary, and cardiac dysfunctions, contributes to exercise intolerance, a key symptom in the HF population.[3,10] Skeletal muscle abnormalities, worsened by aging and the pathogenesis of HF, are critical factors leading to this exercise intolerance. There is a strong correlation between reduced exercise capacity and skeletal muscle atrophy, characterized by a decrease in muscle fiber size.[11] Furthermore, the loss of muscle mass is known to lead to muscle weakness, which further impairs exercise capacity.[3,6] Abdominal obesity is another peripheral factor that negatively impacts exercise tolerance. Research indicates that exercise capacity diminishes as the WtHR increases.[12] Skeletal muscle is among the body compartments where fatty deposits accumulate.[13] Studies have reported that WtHR values tend to rise alongside increases in skeletal muscle mass across different populations.[9,14] This suggests that the WtHR metric used to assess abdominal obesity may influence the relationship between skeletal muscle mass and exercise capacity. Given these connections, the present study aimed to identify the mediating roles of WtHR and skeletal muscle strength in the relationship between exercise capacity and muscle mass.

ABBREVIATIONS

6MWT	Six-minute walk test
BIA	Bioelectrical impedance analysis
BMI	Body mass index
DEXA	Dual-energy X-ray absorptiometry
EF	Ejection fraction
FFM	Fat-free mass
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HG	Handgrip
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PTCA	Percutaneous transluminal angioplasty
SMMI	Skeletal muscle mass index
WC	Waist circumference
WtHR	Waist-to-height ratio

Materials and Methods

Participants

Participants in this cross-sectional study included individuals with HF who attended the cardiology clinic of a local university hospital. The inclusion criteria were: being older than 18 years, having a diagnosis of HF with mild or reduced ejection fraction, and maintaining a stable medication regimen for at least one month. The exclusion criteria were: decompensated HF, unstable angina pectoris, severe valvulopathy, complex ventricular arrhythmias, obstructive or restrictive pulmonary disease; myocardial infarction, percutaneous transluminal angioplasty (PTCA), or cardiac surgery within the past three months; serum creatinine levels > 2.0 mg/dL; neurological and/or orthopedic conditions restricting movement; and participation in a regular exercise training program within the previous six months.

The study was approved by the Ethics Committee of Giresun Traning and Research Hospital (Approval Number: 16.10.2024/14, Date: 16.10.2024) and was conducted in accordance with the principles of the Declaration of Helsinki. Participants signed a written informed consent form prior to participation in the study.

Outcomes

Descriptive Features

Participants' age, educational background, marital status, and comorbidities were recorded. Routine clinical cardiac examinations and the New York Heart Association (NYHA) classification were performed and documented. Left ventricular ejection fraction (LVEF) was assessed using echocardiography and categorized as heart failure with mildly reduced ejection fraction (HFmrEF) when LVEF was 41–49%, and heart failure with reduced ejection fraction (HFrEF) when LVEF was ≤ 40%2. All cardiac examinations and classifications were performed by a cardiologist.

Anthropometric Measures

Body weight and height were measured, and BMI was calculated by dividing body weight by height squared (m^2). Fat-free mass (FFM) was estimated using bioelectrical impedance analysis (BIA) (Tanita BC-532), with measurements performed under clinically stable and euvolemic conditions in patients who met the predefined inclusion and exclusion criteria. Skeletal muscle mass (SMM) was determined using the formula SMM = FFM * 0.566, which was validated by 24-hour creatinine excretion.[15,16] Subsequently, the skeletal muscle mass index (SMMI) was calculated by dividing SMM by height squared (kg/m^2). The cut-off values for SMMI indicating low muscle mass category were defined as < 9.2 kg/m^2 in men and 7.4 kg/m^2 in women.[16]

Waist circumference (WC) was measured horizontally using a tape measure at the midpoint between the superior iliac crest and the lower border of the 12th rib. The WtHR was calculated by dividing WC (cm) by height (cm). Abdominal obesity was defined as a WtHR ≥ 0.5, a cut-off value generally accepted in the literature as a universal indicator of abdominal obesity in adults.[17]

Skeletal Muscle Strength

Handgrip (HG) strength was measured to assess skeletal muscle strength. Participants were seated in a chair with the elbow flexed at 90°, the forearm in mid-rotation, the wrist in a neutral position, and the shoulder in neutral rotation, according to the criteria of the American Society of Hand Therapists. Measurements were performed three times at one-minute intervals using a Jamar hydraulic hand dynamometer (JLW Instruments, Chicago, IL, USA), and the mean value of the three measurements was recorded.[18] Low muscle strength was defined as HG strength < 27 kg in men and < 16 kg in women.[19]

Exercise Capacity

The six-minute walk test (6MWT) was used to evaluate exercise capacity. The test was performed according to the criteria established by the American Thoracic Society and the European Respiratory Society. Participants were instructed to walk back and forth along an empty 30-meter corridor marked by cones at both ends for six minutes. The total walking distance (m) was recorded.[20]

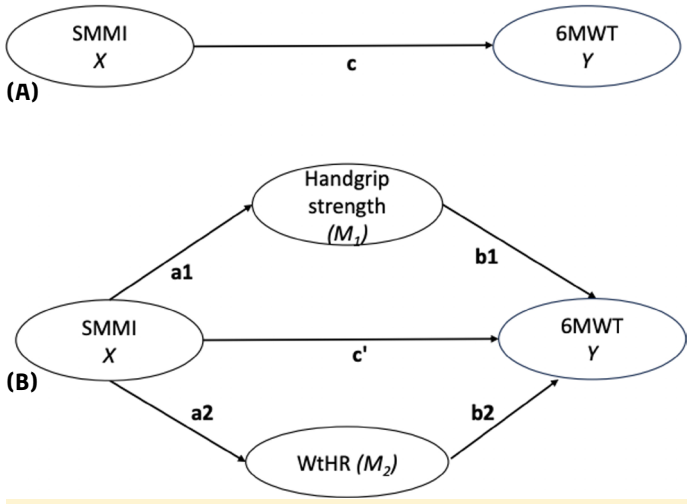

Figure 1. Path diagram showing the total effect and parallel multiple mediator models. (A) Total effect of X on Y (path c). (B) Models demonstrating the relationship between X and Y through parallel multiple mediators. In this model, path c' denotes the direct effect of X on Y after incorporating M_1 and M_2 into the regression analysis. The specific indirect effects of X on Y via M_1 and M_2 are calculated by multiplying paths a and b, with the mediator corresponding to each coefficient indicated by subscripts.

Statistical Analysis

Data analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as mean ± standard deviation for continuous variables and as count (%) for categorical variables. The independent samples t-test was used to compare clinical data according to age, sex, and NYHA categories. The relationships among SMMI, HG strength, WtHR, and 6MWT distance were assessed using Pearson correlation analysis. Correlation coefficients were categorized as negligible (0–0.25), weak (0.26–0.39), moderate (0.40–0.69), high (0.70–0.89), or very strong (0.90–1.00).[21] Statistical significance was set at $P < 0.05$.

Two parallel mediation models were constructed with two potential mediator variables, HG strength and WtHR, to investigate the effect of muscle mass on exercise capacity (Figure 1). Accordingly, three potential paths were examined in both models: indirect path 1 (a1b1), representing the pathway from muscle mass to muscle strength to exercise capacity; indirect path 2 (a2b2), representing the pathway from muscle mass to WtHR to exercise capacity; and the direct path (c'), representing the pathway from muscle mass to exercise capacity. Model 1 included the 6MWT distance as the dependent variable, SMMI as the independent variable, and WtHR and HG strength as potential mediators. Model 2 was constructed by adding age, sex, and NYHA status as covariates to Model 1.

The SPSS PROCESS macro (Model 4) was used to assess the significance of the mediation models.[22] A bootstrapping approach with 5,000 resamples was employed to determine the 95% confidence interval (CI). For the point estimate to be considered statistically significant, the 95% CI should not include zero.[23] The G*Power 3.1 program indicated that, to achieve a medium effect size (f2 = 0.15) with 80% power and a 5% type error for a

multiple regression fixed model with three variables, a minimum of 77 participants was required.[24] For all statistical tests, the level of significance was set at $P < 0.05$.

Results

A total of 122 individuals with HF were evaluated for eligibility. Of these, 12 individuals were excluded: seven had changes in their medication during their last medical visit, three had undergone PTCA within the previous two months, and two had a history of lumbar disc herniation that could impair walking performance. Ultimately, 110 eligible participants with a mean age of 64.25 ± 9.54 years were recruited. Of the sample, 53.6% were aged 65 years or older, and 29.1% were female. Participants were classified as NYHA class II and III, with 73.6% falling into the HFrEF category. The participants' sociodemographic and clinical characteristics are presented in Table 1.

Table 2 presents comparative data on anthropometric measures, muscle strength, and exercise capacity categorized by age, sex, NYHA class, and LVEF category. SMMI showed significant differences only across the sex category, whereas WtHR demonstrated significant differences across both age and sex categories. HG strength and 6MWT distance showed significant differences across age, sex, and NYHA categories.

According to the correlation analysis among SMMI, 6MWT distance, HG strength, and WtHR, a strong association was observed only between 6MWT distance and HG strength ($r = 0.569$, $P < 0.001$). No relationship was found between HG strength and WtHR ($r = -0.127$, $P = 0.187$). Other variables in the correlation matrix showed weak to moderate correlations with each other (Table 3).

The total effect of SMMI on 6MWT distance, without considering any mediators or covariates, was significant ($F(1,108) = 8.884$, $P = 0.004$), with the model explaining 8% of the variance in 6MWT distance. In Model 1, which incorporated HG strength and WtHR as potential mediators, the direct effect of SMMI (B = 10.517) on 6MWT distance remained significant, with HG strength (B = 9.157) and WtHR (-5.496) acting as partial mediators. The 95% bootstrap CI for both direct and indirect effects did not include zero, confirming these findings. The mediation analysis indicated that higher muscle mass was significantly associated with greater HG strength, and greater HG strength was associated with longer 6MWT distances. Consequently, when accounting for SMMI and WtHR, indirect path 1 (a1b1) explained 36.4% of the total effect on 6MWT distance.

Conversely, a positive relationship was observed between SMMI and WtHR (B = 0.016), while a negative relationship was found between WtHR and 6MWT distance (B = -336.414). When considering SMMI and HG strength, indirect path 2 (a2b2) accounted for 21.8% of the total effect on 6MWT distance in a negative direction.

According to Model 2, which included age, sex, and NYHA class as covariates in addition to Model 1, the total effect was significant, with SMMI accounting for 41% of the variation in 6MWT distance ($F(4,105) = 18.82$, $P < 0.001$). Compared with Model 1, the mediating effect of HG strength decreased to 17.9%, whereas the mediating effect of WtHR increased to 30.6%. The direct effect also increased, explaining 51.5% of the variation in 6MWT distance. Overall, more than half of the variance in 6MWT distance was explained by Model 2 ($R2 = 0.53$, $P < 0.001$). In both Model 1 and Model 2, HG strength acted as a positive statistical mediator in the association between SMMI and 6MWT distance, whereas WtHR acted as a negative statistical mediator. When age, sex, and NYHA class were considered, the roles of SMMI and the other mediators in relation to 6MWT distance became clearer. All mediation analysis results are presented in Table 4 and Figure 2.

Table 1. Sociodemographic and clinical characteristic of participants with heart failure

Characteristic	Values
Age, years	64.25 ± 9.54
<65 years	51 (46.4)
≥65 years	59 (53.6)
Sex, n (%)	
Female	32 (29.1)
Male	78 (70.9)
Educational background, n (%)	
Illiterate	15 (13.6)
literate	7 (6.4)
Primary school	32 (29.1)
Secondary school	25 (22.7)
High school	22 (20.0)
College or equivalent	9 (8.2)
Marital status	
Single	3 (2.7)
Married	88 (80.0)
Widowed or divorced	19 (17.3)
NYHA class	
Class II	75 (68.2)
Class III	35 (31.8)
LVEF category, %	
≤40%	81 (73.6)
41–49%	29 (26.4)
Diabetes mellitus history	45 (40.9)
Hypertension history	90 (81.8)
PTCA history	87 (79.1)
CABG history	21 (19.1)
CAD history	93 (84.5)
Pacemaker history	10 (9.1)

Data are presented as means ± standard deviation or n (%). CABG, Coronary arterial bypass graft; CAD, Coronary artery disease; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; PTCA, Percutaneous transluminal coronary angioplasty.

Discussion

This study investigated muscle strength and WtHR as potential mediators in the relationship between muscle mass and exercise capacity in individuals with HF. The findings support our hypothesis and indicate that skeletal muscle strength acts as a positive

Table 2. Comparison of body composition, muscle strength, and exercise capacity according to age, sex, New York Heart Association (NYHA) class, and ejection fraction (EF) categories in participants with heart failure

	Age category			Sex category			NYHA class			LVEF category		
	<65 years (n = 51)	≥65 years (n = 59)	*P*	Female (n = 32)	Male (n = 78)	*P*	Class II (n = 75)	Class III (n = 35)	*P*	HFrEF (n = 81)	HFmrEF (n = 29)	*P*
Height, m	1.67 ± 0.09	1.65 ± 0.08	0.280	1.56 ± 0.06	1.70 ± 0.05	**< 0.001**	1.66 ± 0.08	1.64 ± 0.09	0.162	**1.66 ± 0.09**	**1.65 ± 0.09**	**0.714**
BMI, kg/m²	27.40 ± 4.22	29.58 ± 4.76	**0.013**	31.02 ± 6.09	27.56 ± 3.44	**0.004**	28.65 ± 4.20	28.41 ± 5.49	0.802	**28.30 ± 4.37**	**29.32 ± 5.30**	**0.309**
SMMI	10.80 ± 1.58	10.67 ± 1.39	0.657	10.07 ± 1.67	10.99 ± 1.30	**0.003**	10.74 ± 1.46	10.69 ± 1.51	0.873	**10.67 ± 1.44**	**10.89 ± 1.56**	**0.481**
Low muscle mass, n (%)	7 (13.7)	8 (13.6)	0.598	5 (15.6)	10 (12.8)	0.454	10 (13.3)	5 (14.3)	0.554	**12 (14.8)**	**3 (10.3)**	**0.755**
WtHR, m/cm	0.57 ± 0.06	0.60 ± 0.08	**0.020**	0.61 ± 0.09	0.57 ± 0.05	**0.019**	0.58 ± 0.06	0.59 ± 0.08	0.541	**0.58 ± 0.07**	**0.59 ± 0.08**	**0.201**
Abdominal obesity, n (%)	47 (92.2)	53 (89.8)	0.467	27 (84.4)	73 (93.6)	0.124	69 (92.0)	31 (88.6)	0.398	**72 (88.9)**	**28 (96.6)**	**0.286**
HG strength, kg	31.88 ± 9.93	26.14 ± 7.05	**0.001**	20.25 ± 4.66	32.31 ± 7.84	**< 0.001**	30.05 ± 9.08	26.11 ± 8.10	**0.031**	**28.72 ± 8.27**	**29.03 ± 10.75**	**0.870**
Low muscle strength, n (%)	4 (7.8)	18 (30.5)	**0.003**	8 (25.0)	14 (17.9)	0.277	11 (14.7)	11 (31.4)	**0.039**	**15 (18.5)**	**7 (24.1)**	**0.590**
6MWT, m	415.71 ± 66.76	371.85 ± 77.72	**0.002**	347.87 ± 71.79	410.36 ± 70.01	**< 0.001**	416.32 ± 61.84	340.46 ± 77.74	**< 0.001**	**388.19 ± 70.13**	**403.31 ± 90.13**	**0.359**

Data are presented as mean ± standard deviation. HG strength, Handgrip strength; HFmrEF, Heart failure with mildly reduced ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; WtHR, Waist-to-height ratio; 6MWT, Six-minute walk test.

Table 3. Correlations among muscle mass, waist-to-height ratio (WtHR), muscle strength, and exercise capacity in participants with heart failure

	SSMI (kg/m²)	6MWT distance (m)	HG strength (kg)
6MWT distance (m)	R = 0.276 P = 0.004		
HG strength (kg)	R = 0.397 P < 0.001	R = 0.569 P < 0.001	
WtHR (cm/cm)	R = 0.343 P < 0.001	R = -0.298 P = 0.002	R = -0.127 P = 0.187

Data are presented as mean ± standard deviation. HG strength, Handgrip strength; SSMI, Skeletal muscle mass index; WtHR, Waist-to-height ratio; 6MWT, Six-minute walk test.

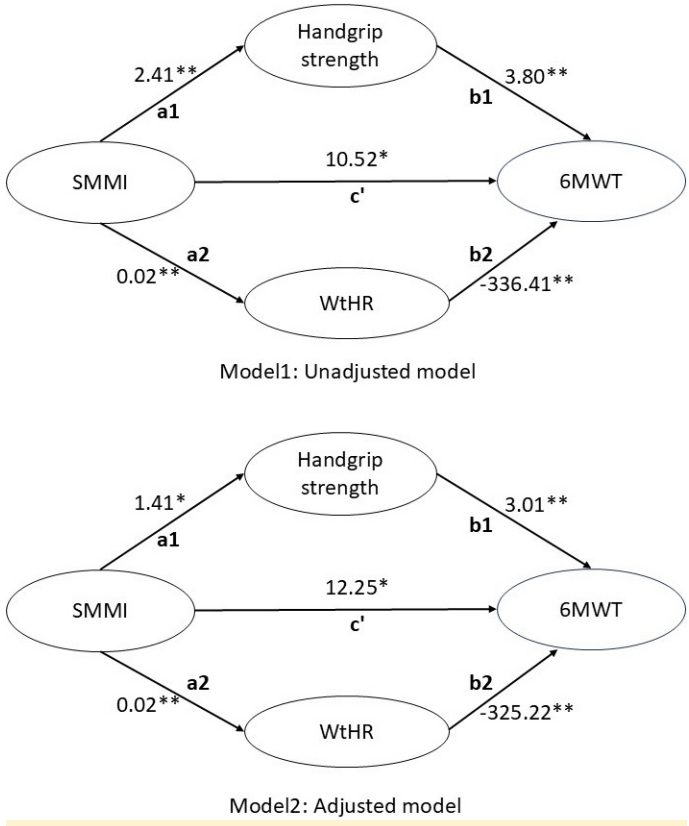

Figure 2. Results of the mediation analysis examining the effects of skeletal muscle mass on exercise capacity in the heart failure (HF) population. Direct and indirect effects of the skeletal muscle mass index on exercise capacity are shown. Unstandardized regression coefficients were used to quantify all paths.

***P < 0.05; **P < 0.001.**

partial mediator, whereas WtHR functions as a negative partial mediator in the association between muscle mass and exercise capacity. Despite these mediating pathways, more than half of the relationship between muscle mass and exercise capacity is attributable to muscle mass itself, even after accounting for age, sex, and the functional status of the participants.

Table 4. Path coefficients, indirect effects, and 95% confidence intervals for each model predicting exercise capacity in participants with heart failure

	Model 1					Model 2				
	Unstandardized B	SE	LLCI	ULCI	Mediation proportion	Unstandardized B	SE	LLCI	ULCI	Mediation proportion
Total effect	14.178	4.756	4.749	23.607	100%	9.240	3.40	1.311	17.170	100%
Direct effect	10.517	4.656	1.285	19.748	41.8%	12.254	4.272	3.782	20.726	51.5%
a1	2.410	0.536	1.347	3.472		1.412	0.421	0.578	2.246	
b1	3.800	0.726	2.359	5.240		3.011	0.839	1.348	4.675	
a2	0.016	0.004	0.007	0.024		0.022	0.004	0.0145	0.030	
b2	-336.414	90.416	-515.673	-157.154		-325.222	88.626	-500.991	-149.453	
Indirect effects										
a1b1	9.157	2.66	4.243	14.629	36.4%	4.252	1.840	1.1456	8.3435	17.9%
a2b2	-5.496	2.321	-10.474	-1.5485	21.8%	-7.266	2.385	-12.120	-2.783	30.6%
Total indirect effect	3.661	4.136	-4.719	11.737		-3.014	2.955	-8.878	2.780	
	R^2 = 0.40, P < 0.001, F = 24.012					R^2 = 0.53, P < 0.001, F = 19.641				

LLCI, Lower limit of the confidence interval; SE, Standard error; ULCI, Upper limit of the confidence interval.

Skeletal muscle abnormalities, such as muscle atrophy, muscle weakness, mitochondrial dysfunction, and fiber-type transition, play a significant role among the non-cardiac factors contributing to exercise intolerance in the HF population. Previous studies have reported a correlation between skeletal muscle mass and peakVO_2[25,26] in this population. In accordance with the existing literature, the present study identified a significant association, showing that greater muscle mass is associated with longer 6MWT distance in individuals with HF.

Handgrip strength has been identified as a significant predictor of clinical outcomes in patients with HF, with decreases in HG strength being associated with reduced exercise capacity.[27] Studies indicate that alterations in skeletal muscle may have a greater impact on exercise capacity than central hemodynamic changes.[6] The effort required to generate force in weakened muscles has been reported to be higher; however, when muscle strength is reduced, maximal effort often fails to produce optimal power output.[28] Moreover, at an equal work rate, individuals with weaker muscles experience higher levels of fatigue.[29] Considering that HG strength is representative of overall muscle strength in the body,[30] lower muscle strength may contribute to reduced exercise capacity through increased fatigue and diminished power output.

Muscle strength is closely correlated with muscle mass,[11] and the present study confirmed that this relationship is also evident in the HF population. An imbalance favoring protein degradation over protein synthesis in muscle cells has been linked to muscle loss and muscle weakness.[11] Our findings indicate that incorporating HG strength alongside muscle mass improves the prediction of changes in 6MWT distance. This finding aligns with the detrimental clinical outcomes associated with sarcopenia, defined as a decrease in both muscle mass and muscle strength. Sarcopenia has been linked to poor prognosis and reduced physical performance.[31] Our results suggest that, within the present model, 6MWT distance is partly explained by the a1b1 indirect pathway—representing the interaction between muscle strength and muscle mass—which accounted for 36.4% of the total effect. However, after adjusting for factors including age, sex, and functional status, this effect was reduced. This attenuation might be related to the strong association of these confounding factors with muscle strength.

Muscle tissue contains fatty deposits located within the fascia, muscle fibers, and intramuscular areas.[13] Therefore, it is not surprising to observe an increase in adipose tissue alongside an increase in muscle mass. Consistent with our findings, WtHR has been shown to correlate positively with muscle mass in patients with type 2 diabetes mellitus.[14] Another study involving elderly participants revealed that individuals with a high BMI had greater muscle mass, and a strong positive correlation was identified between WtHR and BMI.[32] Conversely, elevated fat levels have been associated with reduced insulin sensitivity, increased inflammatory responses, and higher cardiovascular risk.[33] Excessively high fat levels have also been linked to lower muscle mass. A study involving healthy middle-aged and older women identified a WtHR cut-off value of 0.64 for detecting low muscle mass.[34] In our investigation, the average WtHR values did not exceed this threshold in any group. Therefore,

the weak association observed between WtHR and muscle mass may reflect normal muscle physiology within this range. However, due to the cross-sectional design of the study, causal inferences cannot be made.

WtHR is used as a measure of abdominal adiposity and has been associated with mortality risk in patients with HF.[8] In individuals with abdominal obesity, abdominal pressure increases during breathing due to lung inflation and diaphragm descent. This condition is thought to contribute to reduced cardiovascular fitness.[8] Previous studies have examined the association between WtHR and exercise capacity in healthy males and in patients with HF with preserved ejection fraction (EF), demonstrating a significant negative association between WtHR and peak VO_2.[12] The present study is consistent with these findings and further demonstrates that, within the proposed model, WtHR partially and statistically explains the association between muscle mass and exercise capacity in the HF population.

In the present study, after controlling for age, sex, and functional status, WtHR demonstrated a stronger statistical mediating role in the association between muscle mass and 6MWT distance than HG strength. Although no study has specifically examined these relationships in the HF population, abdominal obesity has been reported to have a stronger correlation with functional capacity than HG strength in active women over the age of 50, which parallels our findings. Despite the different methodologies used to assess functional capacity, the results of that study, conducted in a specific population, are consistent with our findings.[35] The association between skeletal muscle weakness and exercise capacity may be related to muscle mass loss but may also occur independently of it.[36] Dynapenia, characterized by a decline in muscle strength without concurrent loss of muscle mass, has been associated with lower exercise capacity in the HF population.[37] This association has been linked to factors including inadequate power generation during exertion, insufficient oxygen consumption, and an earlier onset of fatigue in the context of neuromotor system deficits.[36,38] Abdominal fat has been associated with exercise capacity through metabolic pathways[39] but has also been linked to biomechanical limitations in mobility.[40] Central adipose tissue accumulation has been associated with shifts in the center of gravity, altered knee-joint momentum, and changes in lower-extremity alignment.[40-42] These biomechanical changes may be associated with a higher energy demand for movement and stabilization, which could contribute to exercise intolerance. Moreover, the negative effects of abdominal obesity on respiratory functions in elderly individuals,[43] combined with the association between exercise capacity and dyspnea in the HF population with, irrespective of respiratory muscle strength,[44] may help explain the pronounced mediating role of WtHR on exercise capacity observed in the present model.

In the present investigation, after accounting for clinical variables including functional status, age, and sex, muscle mass exhibited a statistically estimated direct effect, accounting for 51% of the total effect on the 6MWT distance within the mediation model. In the pathophysiological process of HF, early alterations in skeletal muscles have been described as involving disruptions in mitochondrial metabolism. According to a previous study, mitochondrial abnormalities lead to myocyte atrophy and apoptosis, playing a pivotal role in the pathogenesis of muscle dysfunction.[10] Another study involving patients with HF identified skeletal muscle mass as a primary factor associated with peak VO_2, potentially reflecting impairments in oxygen consumption mechanisms.[45] In this context, considering that the 6MWT is an assessment of aerobic exercise capacity, the observed 51% direct effect within the mediation model may be statistically related to alterations in skeletal muscle oxygen consumption mechanisms rather than to the influence of contractile fibers or adipose tissue accumulation. However, this remains a topic for further investigation. On the other hand, our findings indicate that focusing solely on skeletal muscle mass appears insufficient to account for the variation in the 6MWT distance (R^2 = 0.07). In contrast, when assessed together with muscle strength and WtHR, muscle mass contributes significantly to the statistical prediction of the 6MWTdistance (R^2 = 0.53).

From a clinical perspective, these findings may have implications for cardiac rehabilitation (CR) programs in patients with HF. The observed mediation patterns suggest that interventions addressing not only skeletal muscle mass and strength but also abdominal adiposity may be relevant for improving exercise capacity. In this context, comprehensive rehabilitation strategies that consider both muscle-related parameters and central adiposity could be beneficial. Additionally, simple clinical measures such as HG strength and WtHR may serve as useful tools for identifying patients at risk of reduced exercise capacity.

Strength and Limitations

Our study provides a novel contribution to the literature by investigating the relationship between skeletal muscle mass and exercise capacity in symptomatic ambulatory individuals with HF, while considering both facilitating and constraining mediating pathways. By applying a mediation framework, the present model allows for a more comprehensive evaluation of the interrelationships among muscle mass, muscle strength, abdominal adiposity, and exercise capacity.

However, the study has some limitations. First, although an a priori power analysis indicated that the sample size was adequate for the primary regression analyses, the data were collected from a single center, and the sample size may still be considered relatively limited for mediation analysis, particularly with respect to the precision of the estimated indirect effects. This limitation may, in turn, affect the generalizability of the findings. Second, the present study assessed muscle mass using a bioimpedance device commonly used in the literature;[16,46] nevertheless, further research using multi-frequency, multi-electrode bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DEXA) may provide greater clarity regarding our findings. Although measurements were performed under clinically stable and euvolemic conditions, and patients with serum creatinine levels > 2.0 mg/dL were excluded, BIA–derived estimates may still be influenced by minor variations in fluid distribution inherent to HF populations. Moreover, although the applied equation has been widely used in sarcopenia research, including studies conducted in clinically heterogeneous geriatric populations with multiple comorbidities, it has not yet been specifically validated in HF–specific cohorts.

Conclusion

Muscle mass accounted for 51% of the total association with exercise capacity in patients with HF when age, sex, and functional status were considered within the mediation model. This finding suggests that maintaining and/or increasing muscle mass may represent an important consideration for exercise capacity in the context of non-cardiac variables. Additionally, increasing skeletal muscle strength and reducing abdominal fat may enhance the influence of muscle mass on exercise capacity. The study also demonstrated that WtHR had a larger mediating role than muscle strength, which represents an important consideration. Overall, these findings highlight the importance of considering both muscle-related parameters and abdominal adiposity when interpreting exercise capacity in patients with HF.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Giresun Traning and Research Hospital (Approval Number: 16.10.2024/14, Date: 16.10.2024).

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Assessment of Lactate Levels as Prognostic and Predictive Markers in Patients with Complete Atrioventricular Block

Laktat Düzeylerinin Atriyoventriküler Tam Bloklu Hastalarda Prognostik ve Prediktif Belirteç Olarak Değerlendirilmesi

ABSTRACT

Objective: Complete atrioventricular (AV) block complicates management decisions, particularly regarding temporary pacemaker (TP) insertion. Lactate, an anaerobic byproduct, may reflect inadequate cardiac output and help guide this decision. We analyzed the prognostic value of lactate in patients with complete AV block.

Method: We retrospectively evaluated the medical records of adult patients presenting with complete AV block to our coronary care unit. Initial and subsequent venous blood lactate levels were analyzed for associations with adverse in-hospital outcomes, defined as renal injury, cardiac mortality, or the need for TP prior to permanent pacemaker implantation.

Results: The study included 140 patients (46.4% female; median age: 76 years, range: 32–96). Poor outcomes were observed in 22.9% of patients (n = 32), who exhibited significantly higher initial lactate levels (median: 3.1 vs. 2.0 mmol/L; P < 0.001). A lactate cutoff > 1.8 mmol/L predicted poor outcomes with 90.6% sensitivity and 43.5% specificity. Elevated baseline and follow-up lactate levels remained significant predictors, with 83.3% sensitivity and 85.5% specificity compared to normal baseline and follow-up lactate levels.

Conclusion: Increased lactate levels are independent determinants of poor in-hospital outcomes in patients with complete AV block. Lactate measurement may aid decision-making regarding TP even in hemodynamically stable patients. However, these results are hypothesis-generating, and prospective studies are needed to confirm clinical utility.

Keywords: Complete atrioventricular block, temporary pacemaker, venous blood lactate level

ÖZET

Amaç: Atriyoventriküler (AV) tam blok yönetiminde, özellikle geçici pacemaker (GP) endikasyonunun belirlenmesinde karar verme süreci zordur. Anaerobik metabolizmanın bir yan ürünü olan laktat, yetersiz kardiyak debiyi yansıtabilir ve bu süreçte yol gösterici olabilir. Bu çalışmada, AV tam bloklu hastalarda laktat düzeylerinin prognostik değerini ve olumsuz klinik gidişi öngörmedeki rolünü değerlendirmeyi amaçladık.

Yöntem: Koroner yoğun bakım ünitemize kabul edilen AV tam blok tanılı erişkin hastaların kayıtları retrospektif olarak incelendi. Bazal ve takip venöz kan laktat düzeyleri ile kötü hastane içi klinik sonuçlar arasındaki ilişki değerlendirildi. Kötü klinik sonuç; renal hasar, kardiyak nedenli mortalite veya kalıcı pacemaker öncesi GP gereksinimi olarak tanımlandı.

Bulgular: Çalışmaya 140 hasta (yaş ortancası 76 [32–96] yıl; %46,4 kadın) dahil edildi. Kötü klinik gidiş %22,9 (n=32) oranında izlendi. Bu hastalarda bazal laktat düzeyleri anlamlı olarak daha yüksekti (ortanca 3,1 vs. 2,0 mmol/L; P < 0,001). Laktat > 1,8 mmol/L, kötü klinik sonucu %90,6 duyarlılık ve %43,5 özgüllükle öngördü. Normal bazal ve takip laktat düzeylerine kıyasla yüksek bazal ve takip laktat düzeyleri, kötü klinik gidişi %83,3 duyarlılık ve %85,5 özgüllükle öngördü.

Sonuç: Laktat düzeyi, tam AV bloklu hastalarda kötü hastane içi klinik gidişin bağımsız bir öngördürücüsüdür. Hemodinamik olarak stabil hastalarda bile GP gerekliliğine karar verme sürecinde laktat ölçümü yol gösterici olabilir. Ancak bu bulgular hipotez üreten niteliktedir ve klinik faydayı doğrulamak için prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Atriyoventriküler tam blok, geçici kalp pili, venöz kan laktat düzeyi

ORIGINAL ARTICLE
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Managing complete atrioventricular (AV) blocks is challenging, especially when determining the need and timing for temporary pacing. Although immediate temporary pacing is not necessary for all patients with complete AV block, careful clinical assessment is essential.[1-4] Temporary pacing, although a relatively simple intervention, is not without complications, including malfunction, infection, thromboembolic events, and cardiac perforation.[5,6] The inherent risks associated with routine temporary pacing emphasize the need for a cautious and selective approach. Nevertheless, the negative consequences of delayed or omitted temporary pacing should not be disregarded.[7] Maintaining this delicate balance requires careful patient selection. Thorough evaluation of clinical indicators, reversible causes, and the potential for complications is therefore crucial when determining the need and timing of temporary pacing.[8-10]

Lactate, a metabolite generated during both aerobic and anaerobic metabolism, has gained recognition as a valuable biomarker across various medical conditions.[11] Elevated lactate levels may serve as a key indicator of compromised cardiac output and inadequate tissue perfusion, helping to inform decisions regarding the need for temporary pacing in patients with complete AV block.[12] Previous research has demonstrated a strong association between elevated lactate concentrations and mortality in patients with septic shock.[13,14] Likewise, admission lactate levels have been linked to adverse outcomes in individuals with acute coronary syndrome and heart failure.[15,16] Despite these findings, the prognostic significance of lactate in the setting of complete AV block has not been systematically examined. The present study aims to evaluate the prognostic value of lactate levels in this population and to explore their potential role in guiding the timing of temporary pacemaker implantation.

ABBREVIATIONS

AC	Alternating current
AV	Atrioventricular
ECG	Electrocardiogram
KDIGO	The Kidney Disease: Improving Global Outcomes
LVEF	Left ventricular ejection fraction
TP	Temporary pacemaker

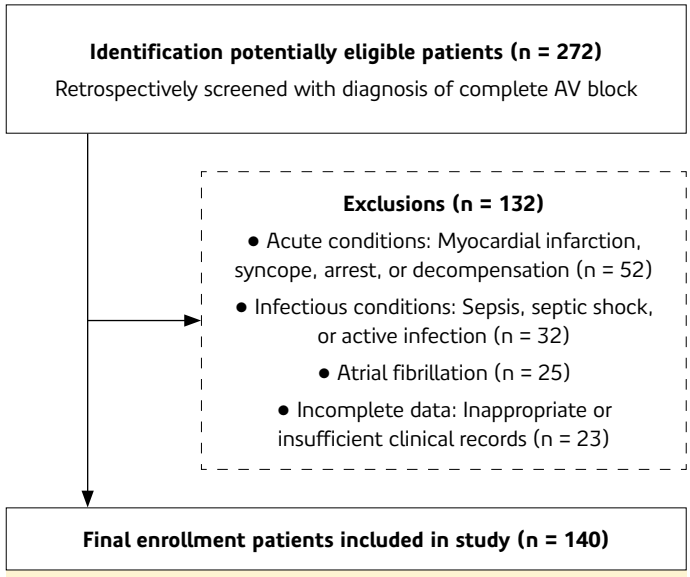

Figure 1. STROBE-style study flow diagram.

Materials and Methods

Study Population

In this retrospective study, we examined the association between serum lactate levels and prognosis in individuals diagnosed with complete AV block. The study initially evaluated data from 272 consecutive patients diagnosed with complete AV block. Exclusion criteria included acute coronary syndrome, atrial fibrillation, active infection or sepsis, decompensated heart failure, the need for inotropes, cardiac arrest, early (< 24 hours) permanent pacemaker implantation, and insufficient clinical or laboratory data (Figure 1). These exclusions were applied to reduce major confounding causes of lactate elevation. In addition, some of these conditions required urgent temporary pacing, leaving no meaningful pre-pacing observation period for analysis. After applying the exclusion criteria, a total of 140 patients were included in the final analysis. The study was conducted in accordance with the Declaration of Helsinki and received approval from Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 56/14, Date: 12.11.2018). Given its retrospective design, the requirement for informed patient consent was waived. This study did not involve the use of artificial intelligence–based technologies, including but not limited to large language models, chatbots, or image-generation tools.

Baseline patient characteristics, including age, sex, comorbidities, and laboratory parameters, were obtained from the hospital database. Patients who underwent temporary pacing were identified. Twelve-lead electrocardiograms (ECGs) were independently evaluated by two cardiologists. ECG recordings were obtained using a filter range of 0.15–100 Hz, an alternating current (AC) filter of 60 Hz, a speed of 25 mm/s, and a sensitivity of 10 mm/millivolt. Echocardiographic examinations were performed using a Philips Healthcare iE33 echocardiography system (xMATRIX, Philips Medical System, Andover, MA, USA) equipped with an S5-1 transducer. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method (biplane method of disks). For the entire study population, the occurrence of acute kidney injury and cardiac-related mortality, as well as the presence of hemodynamic compromise, symptoms, or findings necessitating temporary pacing prior to permanent pacemaker implantation, were regarded as indicators of poor in-hospital clinical outcomes. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used for the diagnosis of acute kidney injury.[17] Acute kidney injury was defined by the presence of any one of the following criteria: an increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours; an increase in serum creatinine to ≥ 1.5 times the known baseline within the previous seven days; or a urine output < 0.5 mL/kg/h for at least 6 hours. Altered mental status, chest pain, worsening bradycardia, or the onset of pulmonary edema were also considered indicators of poor in-hospital clinical outcomes. Conversely, the absence of these conditions during follow-up was considered indicative of a favorable clinical outcome.

Laboratory Analysis

Laboratory analyses included a comprehensive set of parameters recorded at the time of hospital admission, including hemoglobin, creatinine, sodium, potassium, alanine aminotransferase, total bilirubin, low-density lipoprotein, thyroid-stimulating hormone, troponin, and lactate levels. Lactate levels in venous blood gas samples were quantified using a spectrophotometric measurement method on the ABL 800 FLEX device (Radiometer Medical, Denmark). To monitor dynamic changes, follow-up assessments of creatinine and lactate levels were conducted at 12 and 24 hours after admission. Admission lactate was defined as the first lactate measurement obtained at presentation to the emergency department. Follow-up lactate values were defined as measurements obtained approximately 12 and 24 hours after the admission sample based on laboratory timestamps; analyses at each time point included all available cases. For delta lactate, an "increase" was defined as any rise at either follow-up time point compared with the admission value. The maximum delta lactate was calculated using the highest follow-up lactate value (whichever was higher at 12 or 24 hours).

Data Analysis

Statistical analyses were performed using SPSS (version 20.0, IBM Corp., Armonk, NY, USA) and MedCalc (version 22.0, MedCalc Software Ltd., Ostend, Belgium). Data distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables with a normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables were reported as median (min-max). Categorical variables were presented as counts and percentages. To evaluate differences in numerical variables between groups with poor and good clinical outcomes, the Student's t-test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The chi-square test and Fisher's exact test were used to compare categorical data. Multivariable logistic regression analysis was performed to identify independent predictors of poor clinical outcomes from a set of potential risk factors. To evaluate the predictive performance of lactate levels for poor clinical outcomes, receiver operating characteristic (ROC) curve analysis was conducted. The predictive value was then determined using the Youden index. Internal validation was performed using bootstrap resampling. In each bootstrap sample, the multivariable logistic regression model was refitted, and discrimination was assessed by the area under the receiver operating characteristic curve (AUC). Optimism-corrected AUC values with 95% confidence intervals (CI) were derived from the bootstrap distribution. Calibration was evaluated using the calibration intercept and calibration slope. A p-value < 0.05 was considered statistically significant.

Results

During the study period, 272 consecutive patients with complete atrioventricular block were screened; 132 were excluded (acute conditions, n = 52; atrial fibrillation, n = 25; sepsis or active infection, n = 32; inadequate records, n = 23). The final cohort included 140 patients (female, n = 65 [46.4%]; median age 76 years [range: 32–96]). Pre-existing conditions included diabetes mellitus in 17.9% of patients, hypertension in 81.9%, and coronary artery disease in 52.9%. The mean heart rate was 36.0 ± 7.6 beats per minute. At presentation, the mean systolic blood pressure was 124.0 ± 22.6 mmHg in the overall cohort, 125.4 ± 23.4 mmHg in patients with good outcomes, and 119.1 ± 19.4 mmHg in patients with poor outcomes (P = 0.163). Mean diastolic blood pressure was 67.1 ± 14.3 mmHg overall, 67.1 ± 14.2 mmHg in the good-outcome group, and 67.2 ± 14.9 mmHg in the poor-outcome group (P = 0.971). Mean arterial pressure was 86.1 ± 15.9 mmHg overall, 86.5 ± 15.9 mmHg in the good-outcome group, and 84.5 ± 15.8 mmHg in the poor-outcome group (P = 0.523). Senile degeneration was the most common etiological cause (87.9%), followed by drug-related causes (11.4%) and myocarditis (0.7%). On admission, the median serum creatinine level was 1.2 mg/dL (range: 0.6-4.0), increasing to 1.5 mg/dL (range: 1.0-5.1) at follow-up. Serum lactate levels at admission were 2.1 mmol/L (range: 0.7-14.5), with a follow-up median of 2.0 mmol/L (range: 0.5-18.0). The overall rate of poor clinical outcomes was 22.9% (n = 32). During follow-up, acute kidney injury occurred in 13.6% of patients, mortality in 6.4%, and temporary pacing was required in 2.9% of initially untreated patients. A complete overview of the study population's baseline characteristics and clinical outcomes is provided in Table 1.

In patients with poor clinical outcomes, LVEF was significantly lower compared to those with good outcomes (44.0 ± 12.1% vs. 50.3 ± 13.1%; P = 0.016). Notably, in patients with poor clinical outcomes, there was no significant change in lactate levels during follow-up (3.1 mmol/L vs. 3.3 mmol/L; P = 0.468). In contrast, patients with good clinical outcomes demonstrated a significant decrease in lactate levels during follow-up (2.0 mmol/L vs. 1.5 mmol/L; P < 0.001). At admission, patients with poor clinical outcomes had significantly higher serum creatinine levels [1.4 (0.8–3.8) mg/dL vs. 1.2 (0.6–4.0) mg/dL; P = 0.042] and lactate levels [3.1 (0.8–14.5) mmol/L vs. 2.0 (0.7–9.0) mmol/L; P < 0.001] compared to those with good outcomes. Similarly, follow-up assessments revealed significantly higher serum creatinine [2.2 (1.5–5.0) mg/dL vs. 1.3 (1.0–5.1) mg/dL; P < 0.001] and lactate [3.3 (1.0–18.0) mmol/L vs. 1.5 (0.5–12) mmol/L; P < 0.001] levels in patients with poor outcomes (Figure 2). In the good clinical outcome group (n = 108), the median admission lactate level was 2.0 mmol/L (range: 0.7–9.0) and the median follow-up lactate level was 1.5 mmol/L (range: 0.5–12.0). Compared with this group, the mortality subgroup (n = 9) had significantly higher admission and follow-up lactate levels (7.0 [2.8–14.5] and 8.0 [3.6–18.0], respectively; both P < 0.001). The acute kidney injury subgroup (n = 19) also showed higher lactate values at admission (2.3 [1.5–9.0]; P = 0.024) and at follow-up (3.0 [1.0–6.0]; P = 0.002). In contrast, lactate levels in patients requiring temporary pacing (n = 4) were not significantly different from those in the no-event group at admission (2.7 [0.8–5.6]; P = 0.615) or at follow-up (2.1 [1.0–4.0]; P = 0.370). Comparisons of serial lactate levels between the no-event group and adverse outcome subgroups are summarized in Table 2.

The analysis revealed several factors associated with poor clinical outcomes, as detailed in Table 3. Specifically, LVEF (odds ratio [OR]: 0.96, 95% CI: 0.94–0.99; P = 0.018), lactate level at admission (OR: 1.44, 95% CI: 1.17–1.76; P < 0.001), follow-up lactate level (OR: 1.52, 95% CI: 1.23–1.88;

Table 1. Clinical, echocardiographic, and laboratory parameters stratified by clinical course

Parameters	All patients (n = 140)	Patients with good outcomes (n = 108)	Patients with poor outcomes (n = 32)	*P*
Age (years), mean ± SD	74.6 ± 13.1	73.5 ± 13.2	78.1 ± 12.5	0.082
Female, n (%)	65 (46.4)	50 (46.3)	15 (46.9)	0.998
Smoking, n (%)	80 (53.6)	64 (59.3)	16 (50.0)	0.468
Diabetes, n (%)	25 (17.9)	19 (17.6)	6 (18.8)	0.997
Hypertension, n (%)	114 (81.9)	86 (79.6)	28 (87.5)	0.455
CAD, n (%)	74 (52.9)	56 (51.9)	18 (56.2)	0.813
Systolic BP (mmHg), mean ± SD	124.0 ± 22.6	125.4 ± 23.4	119.1 ± 19.4	0.163
Diastolic BP (mmHg), mean ± SD	67.1 ± 14.3	67.1 ± 14.2	67.2 ± 14.9	0.971
Mean BP (mmHg), mean ± SD	86.1 ± 15.9	86.5 ± 15.9	84.5 ± 15.8	0.523
Heart rate (bpm), mean ± SD	36.0 ± 7.6	35.8 ± 8.2	36.0 ± 5.5	0.883
Senile degenerative block, n (%)	123 (87.9)	93 (86.1)	30 (93.8)	0.488
Wide QRS, n (%)	78 (55.7)	61 (56.5)	17 (53.1)	0.840
LVEF (%), mean ± SD	48.0 ± 13.1	50.3 ± 13.1	44.0 ± 12.1	0.016
Hemoglobin (g/dL), mean ± SD	12.7 ± 2.1	12.9 ± 2.0	12.1 ± 2.4	0.069
Potassium (mEq/L), mean ± SD	4.1 ± 0.8	4.0 ± 0.8	4.2 ± 0.9	0.405
LDL (mg/dL), mean ± SD	148.7 ± 42.4	151 ± 42.1	140.9 ± 42.8	0.236
TSH (mIU/L), median (min-max)	1.1 (0.01–9.0)	1.1 (0.01–9.0)	1.1 (0.1–3.2)	0.344
ALT (U/L), median (min-max)	32.0 (8.0–432.0)	32 (8–432)	30 (12–321)	0.994
Total bilirubin (mg/dL), median (min-max)	1.0 (0.2–6.7)	1 (0.2–3.3)	0.9 (0.2–6.7)	0.594
Troponin (pg/mL), median (min-max)	0 (0–1.2)	0 (0–1.2)	0.01 (0–0.9)	0.769
Creatinine (mg/dL), median (min-max)	1.2 (0.6–4.0)	1.2 (0.6–4.0)	1.4 (0.8–3.8)	0.042
Baseline lactate level (mmol/L), median (min-max)	2.1 (0.7–14.5)	2.0 (0.7–9.0)	3.1 (0.8–14.5)	< 0.001
Follow-up lactate level (mmol/L), median (min-max)	2.0 (0.5–18.0)	1.5 (0.5–12)	3.3 (1.0–18.0)	< 0.001

ALT, Alanine aminotransferase; CAD, Coronary artery disease; LDL, Low-density lipoprotein; LVEF, Left ventricular ejection fraction; SD, Standard deviation; TSH, Thyroid-stimulating hormone.

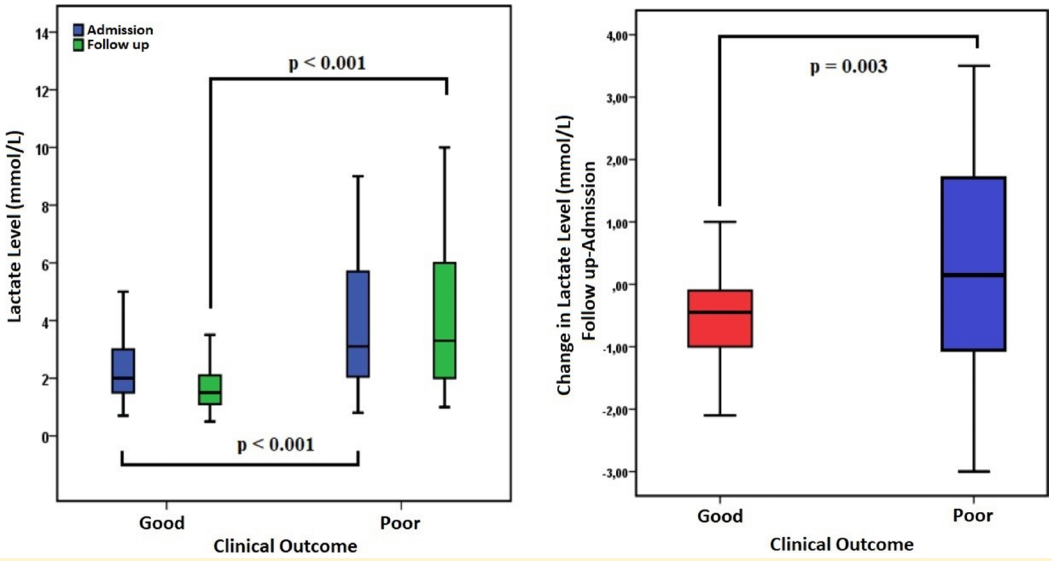

Figure 2. Admission and follow-up lactate levels and lactate change according to clinical outcome.

P < 0.001), and ΔLactate (OR: 1.60, 95% CI: 1.15–2.23; P = 0.005) were associated with poor clinical outcomes. A lactate level > 1.8 mmol/L predicted poor clinical outcomes with 90.6% sensitivity and 43.5% specificity, yielding a positive predictive value of 30.9% and a negative predictive value of 95.3%. When analyzed as a continuous variable, admission

Table 2. Comparison of lactate levels between the good-outcome group and poor-outcome subgroups

Group	n	Lactate at admission	*P*	Lactate at follow-up	*P*
No event	108	2.0 (0.7–9.0)		1.5 (0.5–12.0)	
Mortality	9	7.0 (2.8–14.5)	< 0.001	8.0 (3.6–18.0)	< 0.001
Acute kidney injury	19	2.3 (1.5–9.0)	0.024	3.0 (1.0–6.0)	0.002
Need for temporary pacing	4	2.7 (0.8–5.6)	0.615	2.1 (1.0–4.0)	0.370

P values represent comparisons between each subgroup and the no-event group. Follow-up lactate level refers to the higher value observed at approximately 12 or 24 hours. Lactate levels are reported as median (min–max) in mmol/L.

Table 3. Risk factors associated with poor clinical outcomes

Parameters	OR	95% CI	*P*
LVEF, %	0.96	0.94–0.99	0.018
Admission lactate (mmol/L)	1.44	1.17–1.76	< 0.001
Follow-up lactate (mmol/L)	1.52	1.23–1.88	< 0.001
ΔLactate, (mmol/L)	1.60	1.15–2.23	0.005

OR, Odds ratio; CI, Confidence interval; LVEF, Left Ventricular Ejection Fraction; Δ, Difference between follow-up and admission values.

lactate demonstrated good discrimination, with an area under the receiver operating characteristic curve of 0.712 (95% CI: 0.637–0.792) (Figure 3). The proportion of patients with a baseline lactate level ≤ 1.8 mmol/L and no increase in lactate at follow-up was 25.7%. A baseline lactate level ≤ 1.8 mmol/L with an increase in lactate at follow-up was observed in 10% of patients. The proportion of patients with a baseline lactate level > 1.8 mmol/L and no increase in lactate at follow-up was 47.9%, whereas 16.4% of patients had a baseline lactate level > 1.8 mmol/L with an increase in lactate at follow-up. The proportion of patients with a baseline lactate level > 1.8 mmol/L and an increase in lactate at follow-up was significantly higher among patients with poor outcomes (P < 0.001) (Figure 4). In multivariable regression analysis, Model 1 identified baseline LVEF (OR: 0.97, 95% CI: 0.94–0.99; P = 0.037) and baseline lactate level (OR: 1.39, 95% CI: 1.13–1.70; P = 0.002) as independent predictors of poor clinical outcome. In Model 2, ΔLactate (OR: 1.52, 95% CI: 1.10–2.13; P = 0.010) was identified as an independent predictor of poor clinical outcome. In Model 3, lactate level patterns were categorized as follows: "admission high, no increase at follow-up" (OR: 4.14, 95% CI: 1.12–15.30; P = 0.033) and "admission high, increase at follow-up" (OR: 29.38, 95% CI: 6.90–125.06; P < 0.001). Both patterns were independent predictors of poor clinical outcome. Model 3 demonstrated better performance in explaining poor clinical outcomes compared to the other regression models (Nagelkerke R^2 = 0.523) (Table 4). Relative to a normal admission lactate level, the "admission high, increase at follow-up" lactate pattern demonstrated strong predictive capacity for poor clinical outcomes, with a sensitivity of 83.3% and a specificity of 85.5%. Model 1 (LVEF + admission lactate) showed an optimism-corrected AUC of 0.721 (95% CI: 0.628–0.819) with a calibration slope of 0.948. Model 2 (LVEF + Δlactate) had an optimism-corrected AUC of 0.659 (95% CI: 0.555–0.777) with a calibration slope 0.937. Model 3 (LVEF + lactate pattern) yielded an optimism-corrected AUC of 0.796 (95% CI: 0.715–0.895) with a calibration slope of 0.859.

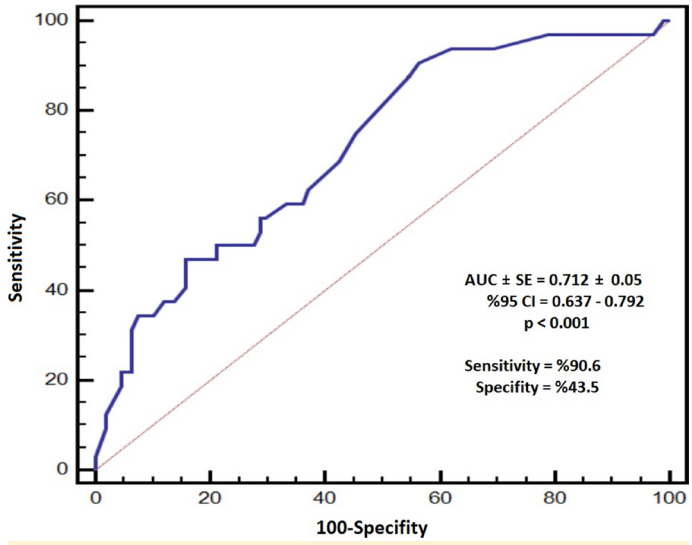

Figure 3. Prediction of poor clinical outcomes by lactate level > 1.8 mmol/L.

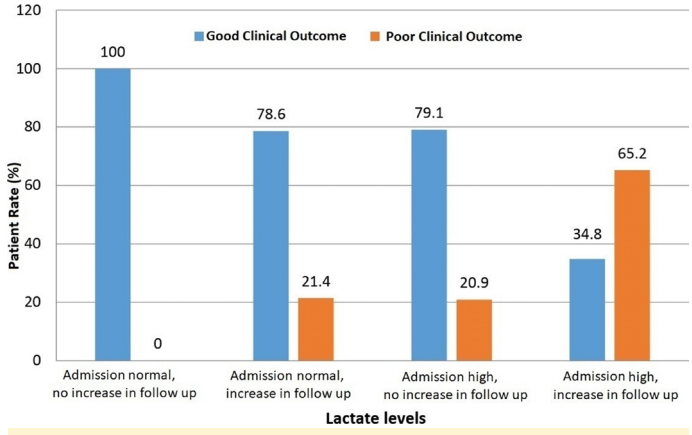

Figure 4. Proportion of patients according to lactate levels at admission and follow-up.

Discussion

This study demonstrates the substantial impact of lactate levels on clinical outcomes in patients with complete AV block, highlighting the association between elevated lactate levels at admission and a subsequent rise in lactate levels during follow-up with poorer in-hospital outcomes. In particular, the lactate profile characterized as "admission high, increase at follow-up" emerged as the most reliable indicator of unfavorable clinical outcomes.

Table 4. Independent predictors of poor clinical outcome

Parameters	OR	95% CI	*P*
Model 1			
LVEF	0.97	0.94–0.99	0.037
Lactate	1.39	1.13–1.70	0.002
Nagelkerke R^2 = 0.352; P < 0.001			
Model 2			
LVEF	0.97	0.94–0.99	0.038
ΔLactate	1.52	1.10–2.13	0.010
Nagelkerke R^2 = 0.411; P < 0.001			
Model 3			
LVEF	0.96	0.93–0.98	0.042
Lactate			
Admission normal	Ref		
Admission high, no increase at follow-up	4.14	1.12–15.30	0.033
Admission high, increase at follow-up	29.38	6.90–125.06	< 0.001
Nagelkerke R^2 = 0.523; P < 0.001			

OR, Odds ratio; CI, Confidence interval; LVEF, Left ventricular ejection fraction; Δ, Difference between follow-up and admission values.

Since its discovery, lactate has traditionally been regarded as a byproduct of glycolysis, viewed primarily as a metabolic waste product with limited physiological significance.[18] However, subsequent research has shed light on the complex role of lactate, revealing its importance beyond that of a mere metabolic byproduct. Lactate is now recognized as a key mediator in organ growth and development, as well as in the coordination of vascular development and progenitor cell behavior during brain development.[19] Moreover, lactate serves as a precursor for gluconeogenesis and can directly or indirectly enter the mitochondrial matrix to contribute to energy production.[20] Lactate also serves as a significant energy source for vital organs such as the heart, brain, and skeletal muscles. Notably, during periods of physical exertion, lactate can supply more than 50% of the energy required by cardiomyocytes. As exercise progresses, lactate production increases to accommodate the heightened metabolic demands.[21]

Lactate production is a complex biochemical process involving multiple tissues, with skeletal muscle being a primary source. Under normal aerobic conditions, pyruvate—produced through glycolysis—enters the Krebs cycle via conversion to acetyl-coenzyme A (acetyl-CoA), allowing efficient energy production without lactate accumulation. However, when oxygen supply is limited—such as in cases of complete AV block where cardiac output is severely compromised—pyruvate is converted to lactate by the enzyme lactate dehydrogenase, facilitating anaerobic glycolysis. This metabolic shift not only results in increased lactate levels but also reflects the severity of tissue hypoxia and systemic perfusion deficits.[22,23]

Clinical and experimental studies have demonstrated significant alterations in lactate levels in several cardiovascular diseases, including atherosclerosis, heart failure, atrial fibrillation, and myocardial infarction.[24-26] Numerous studies have consistently shown that elevated lactate levels are associated with a poor prognosis in patients with heart failure. Specifically, elevated lactate levels at hospital admission are strongly associated with higher mortality rates in patients with acute decompensated heart failure.[25] This rise in blood lactate is primarily caused by several factors, including decreased oxygen delivery to peripheral tissues, impaired tissue oxygen utilization, activation of the neurohumoral system (including the adrenal and sympathetic nervous systems), increased oxygen demand, and organ dysfunction such as liver or kidney issues, which reduce the body's ability to clear lactate.[27-30] During myocardial infarction, coronary occlusion results in a significant reduction in oxygen supply to myocardial cells, impairing mitochondrial oxidative phosphorylation and accelerating glycolysis within the heart muscle.[24,31] This shift leads to increased lactate production in cardiomyocytes, a finding supported by some clinical studies reporting elevated circulating lactate levels in patients with myocardial infarction. It has been consistently demonstrated across multiple studies that circulating lactate levels have substantial prognostic value in predicting unfavorable clinical outcomes in these patients.[32,33] Moreover, compared to initial lactate values, the 24-hour lactate level and lactate clearance rate provide superior predictive power for in-hospital mortality in patients with myocardial infarction.[34] Atrial fibrillation, another common cardiovascular condition, has also been studied in relation to lactate metabolism. Research has shown that lactate levels are elevated in atrial myocytes of patients with atrial fibrillation, a phenomenon associated with oxidative stress-induced damage and cardiomyocyte apoptosis. These findings indicate that this metabolic pathway may contribute to the development and progression of atrial fibrillation by promoting atrial remodeling.[35-38] Atherosclerosis is a chronic inflammatory condition involving multiple cell types, including vascular endothelial cells, monocytes, macrophages, and lymphocytes. In recent years, studies have highlighted the important role of lactate in the development of atherosclerosis. A cross-sectional study demonstrated a positive association between elevated blood lactate levels and carotid atherosclerosis, a finding that remained significant after adjustment for other cardiovascular risk factors.[39,40] In addition, exercise is a well-known protective factor against several cardiovascular diseases, such as atherosclerosis.[41] Recent studies suggest that lactate-induced lactylation may decrease the risk of atherosclerosis by inhibiting lipogenesis and attenuating vascular inflammatory responses.[42] Lactate also exerts similar effects on lipid metabolism in adipose tissue. These findings suggest that the rise in lactate during high-intensity interval training may reduce the risk of atherosclerosis by inhibiting lipogenesis.[43,44]

Profound bradycardia and AV dissociation observed in individuals with complete AV block precipitate a decline in cardiac output. As a result, reduced oxygen delivery to tissues may lead to tissue hypoxia.[45] This physiological state enhances the conversion of pyruvate to lactate through anaerobic glycolysis. Consequently, adverse outcomes such as acute kidney injury and cardiac-related mortality may be more common in individuals with elevated lactate levels. Moreover, patients with good clinical outcomes demonstrated a significant decrease in lactate levels

during follow-up, whereas no such decline was observed in patients with poor clinical outcomes. Therefore, the absence of a decrease in lactate levels during follow-up in a patient with complete AV block may indicate the need for closer clinical monitoring due to the potential risk of clinical complications.[1,2,46]

In critically ill patients, persistent imbalances between oxygen demand and oxygen delivery can lead to global tissue hypoxia, prompting increased anaerobic metabolism and lactate production.[14] While several randomized studies in sepsis use a lactate threshold of ≥ 4 mmol/L as an inclusion criterion, some research suggests that even lactate levels ≥ 2 mmol/L are associated with increased mortality in patients with sepsis.[2,12-15] A retrospective cohort study of 1,865 patients with acute coronary syndrome investigated the association between admission lactate levels and 30-day and 180-day mortality. Patients were categorized into three groups based on lactate levels: < 1.8 mmol/L, 1.8–2.6 mmol/L, and > 2.7 mmol/L. The study reported increased 30-day and 180-day mortality in the third group, in which admission lactate values exceeded 2.7 mmol/L.[15] Additionally, a study involving 754 patients admitted to the coronary intensive care unit with acute decompensated heart failure identified lactate level at presentation as an independent predictor of in-hospital mortality. The lactate threshold with the highest sensitivity and specificity for predicting mortality was determined to be 3.2 mmol/L.[16] Lactate levels have also been increasingly recognized as an important biomarker in cardiac transplantation, particularly in the setting of urgent heart transplantation. Preoperative hyperlactatemia, especially in patients experiencing cardiogenic shock, has been consistently associated with poorer postoperative outcomes, with some studies reporting nearly 50% mortality at one year among patients with preoperative lactate levels ≥ 2 mmol/L. This association highlights the importance of monitoring lactate levels during the perioperative period, as elevated lactate may signal an increased risk of complications, including primary graft failure and multiorgan dysfunction.[47-49] In our study, a lactate level > 1.8 mmol/L was identified as a predictor of poor clinical outcomes, with a sensitivity of 90.6% and a specificity of 43.5%. Among patients with poor outcomes, the proportion of those with a baseline lactate level > 1.8 mmol/L and a subsequent increase in lactate level during follow-up was significantly higher.

Another noteworthy prognostic parameter is LVEF. Extensive evidence has demonstrated that reduced LVEF is associated with an unfavorable prognosis in various cardiovascular diseases, including heart failure and coronary artery disease.[50–52] In our study, we observed significantly lower LVEF values in patients with complete AV block who experienced poor clinical outcomes. One possible explanation is that reduced ejection fraction may be further exacerbated by atrioventricular dissociation and bradycardia in patients with complete AV block.

Current guidelines recommend temporary transvenous pacing primarily for patients with AV block who exhibit symptoms or hemodynamic instability refractory to medical therapy.[1,2] However, a subset of patients who initially do not require temporary pacing may develop cardiac decompensation and hemodynamic deterioration during follow-up, ultimately necessitating temporary pacing. The association between elevated lactate levels and adverse outcomes observed in our study may provide useful guidance, particularly in the management of patients who do not initially require temporary pacing. An important clinical question is whether temporary pacemaker implantation should be considered in patients who, despite being asymptomatic and hemodynamically stable at presentation, exhibit lactate levels exceeding 1.8 mmol/L. Translating the findings of our study into clinical practice suggests that patients without an initial indication for temporary pacing but with elevated admission lactate levels and a subsequent increase during follow-up may require closer monitoring. Additionally, temporary pacing may be considered, particularly when lactate levels become elevated during follow-up despite initially low baseline levels. However, these observations should be considered hypothesis-generating, and prospective studies are required to determine whether incorporating serial lactate measurements into routine decision-making can improve outcomes.

This preliminary study examining the relationship between lactate levels and prognosis in patients with complete AV block has certain limitations. First, as a single-center retrospective study, the generalizability of the findings to broader populations may be limited. Second, the relatively small sample size of the study population limits the statistical power and may affect the reliability of the conclusions. Furthermore, due to its observational design, the study cannot establish a causal relationship between lactate levels and clinical outcomes. Finally, an important limitation of this retrospective study is the lack of reliable documentation regarding the time interval from symptom onset to hospital admission and to the first blood sampling. This interval may influence initial lactate and creatinine measurements and could introduce unmeasured variability into the observed associations.

Conclusion

Our study sheds light on the previously unexplored relationship between lactate levels and clinical outcomes in patients with complete AV block. Our findings highlight the potential importance of lactate as a prognostic marker and as a tool to support clinical decision-making, particularly regarding the need for a temporary pacemaker implantation. Patients with elevated admission lactate levels, especially when accompanied by a further increase during follow-up, demonstrated a higher risk of adverse clinical outcomes. However, these findings are hypothesis-generating and should not be interpreted as sufficient to justify changes in current pacing practice. Prospective, multicenter studies are needed to confirm the clinical utility of lactate measurements in this setting.

Ethics Committee Approval: Ethics committee approval was obtained from Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 56/14, Date: 12.11.2018).

Informed Consent: Given its retrospective design, the requirement for informed patient consent was waived.

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Prevalence and Clinical Course of Methemoglobinemia After Cardiac Device Implantation

Kalp Cihazı İmplantasyonu Sonrası Methemoglobinemi Prevalansı ve Klinik Seyri

ABSTRACT

Objective: Methemoglobinemia is a potentially serious complication of local anesthetic use during cardiac implantable electronic device (CIED) implantation. Although it is mostly asymptomatic, limited awareness may delay diagnosis and treatment.

Method: This prospective observational study included 126 patients undergoing CIED implantation under local anesthesia. Prilocaine 2% was used in all procedures. Arterial blood gases and methemoglobin levels were evaluated at baseline and at 60 and 120 minutes after the procedure. A fractional methemoglobin level > 1.5% was defined as methemoglobinemia. Patients were categorized into three groups based on 60-minute fractional methemoglobin (FMetHb) levels: ≤ 1.5%, 1.5–3%, and > 3%. Clinical parameters, anesthetic dosage, and outcomes were compared between groups.

Results: Methemoglobin levels > 1.5% were observed in 80.2% of patients. Three patients required treatment, and all recovered fully. Patients with FMetHb > 3% received higher anesthetic doses ($P < 0.001$). Differences in drug dose and pCO_2 were observed between groups. Among the clinical parameters, the prilocaine dose demonstrated the strongest predictive value for methemoglobinemia, with an optimal cut-off of ≥ 24.50 mg identified by receiver operating characteristic (ROC) analysis (area under the curve: 0.693, $P < 0.001$).

Conclusion: Methemoglobinemia may occur more frequently than expected following CIED implantation. Early recognition and stratification using practical thresholds, such as FMetHb > 3%, may support timely management and improve clinical outcomes.

Keywords: Cardiac implantable electronic device implantation, ejection fraction, local anesthesia, methemoglobinemia

ÖZET

Amaç: Methemoglobinemi, kardiyak implante edilebilir elektronik cihaz (CIED) implantasyonu sırasında kullanılan lokal anesteziklere bağlı olarak gelişebilen potansiyel olarak ciddi bir komplikasyondur. Çoğu olguda asemptomatik seyretmesine rağmen, farkındalığın sınırlı olması, tanı ve tedavide gecikmelere yol açabilmektedir.

Yöntem: Bu prospektif gözlemsel çalışmaya, lokal anestezi altında CIED implantasyonu uygulanan toplam 126 hasta dahil edildi. Tüm işlemlerde %2 prilokain kullanıldı. Arteriyel kan gazı ve methemoglobin düzeyleri işlem öncesinde (bazal), işlemden 60 ve 120 dakika sonra ölçüldü. Methemoglobin fraksiyonunun (FMetHb) %1,5'in üzerinde olması methemoglobinemi olarak tanımlandı. Hastalar, 60. dakikadaki FMetHb düzeylerine göre ≤ %1,5, %1,5–3 ve > %3 olmak üzere üç gruba ayrıldı. Klinik özellikler, anestezik dozları ve sonuçlar gruplar arasında karşılaştırıldı.

Bulgular: Hastaların %80,2'sinde FMetHb düzeyleri %1,5'in üzerinde saptandı. Üç hastada tedavi gereksinimi gelişti ve tümü tam iyileşme gösterdi. FMetHb >%3 olan hastalarda uygulanan lokal anestezik dozu anlamlı olarak daha yüksekti ($P < 0,001$). Gruplar arasında ilaç dozu ve pCO_2 düzeyleri açısından anlamlı farklılıklar gözlendi. Klinik parametreler arasında, prilokain dozu methemoglobinemi için en güçlü öngördürücü değişken olarak saptandı ve ROC analizinde ≥ 24,50 mg optimal eşik değer olarak belirlendi (AUC: 0,693; $P < 0,001$).

Sonuç: CIED implantasyonu sonrası methemoglobinemi beklenenden daha sık görülebilir. Özellikle FMetHb > %3 gibi pratik eşik değerler kullanılarak erken tanı ve risk sınıflaması yapılması, zamanında tedavi ve daha iyi klinik sonuçlar elde edilmesini destekleyebilir.

Anahtar Kelimeler: Kardiyak implante edilebilir elektronik cihaz implantasyonu, ejeksiyon fraksiyonu, lokal anestezi, methemoglobinemi

ORIGINAL ARTICLE
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Cardiac implantable electronic devices (CIEDs) are increasingly utilized in the management of bradyarrhythmias, heart failure, and other rhythm disorders. These procedures are most commonly performed under local anesthesia, which is considered both effective and safe.[1] However, despite its overall favorable safety profile, the use of local anesthetics may be associated with rare but potentially serious complications. One such complication is methemoglobinemia, a condition characterized by an elevated level of methemoglobin in the blood that can impair oxygen delivery to tissues and organs.[2]

Methemoglobinemia occurs when the iron component of hemoglobin is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state, thereby reducing its capacity to bind and release oxygen effectively.[3] Although the human body possesses enzymatic systems, such as cytochrome b5 reductase, that convert methemoglobin back to hemoglobin, certain medications—including local anesthetics such as benzocaine and prilocaine—can overwhelm these pathways.[4] Clinically, patients may present with symptoms ranging from mild cyanosis and fatigue to life-threatening hypoxia, particularly when methemoglobin levels exceed 5%.[5,6]

The diagnosis of methemoglobinemia requires a high index of suspicion, particularly when patients exhibit oxygen desaturation that does not improve with supplemental oxygen.[7] Definitive diagnosis is established through co-oximetry or arterial blood gas analysis with direct measurement of methemoglobin levels. Mild cases often resolve spontaneously or with supportive care, whereas moderate to severe cases may require pharmacological therapy.[8] Methylene blue, which acts as an artificial electron donor, remains the standard therapy in severe cases, while intravenous ascorbic acid has been used as an adjunct or alternative in patients with contraindications.[9,10]

The primary aim of this study was to characterize the biochemical behavior of methemoglobin levels following prilocaine-based local anesthesia during CIED implantation, rather than to establish clinical diagnostic thresholds for symptomatic methemoglobinemia.

Materials and Methods

This prospective observational study was approved by Necmettin Erbakan University Non-Drug and Non-Medical Device Research Ethics Committee (Approval Number: 2025/5879, Date: 27.06.2025), and all procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation.

The study included 126 patients who underwent CIED implantation between February 2024 and May 2025 at our hospital. The inclusion criteria were: age ≥ 18 years, undergoing de novo pacemaker, implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT) implantation, and provision of consent for blood sampling and follow-up. Exclusion criteria included known congenital methemoglobinemia, pre-existing anemia (hemoglobin < 10 g/dL), and severe hepatic dysfunction.

All patients received local anesthesia with 2% prilocaine hydrochloride. Laboratory evaluations included baseline and postoperative arterial blood gas analysis, pulse oximetry, complete blood count, serum creatinine, and liver function tests. Blood gas parameters, including SaO_2, pH, pCO_2, pO_2, and fractional methemoglobin (FMetHb), were recorded immediately after the procedure and at 60 and 120 minutes post-intervention. Arterial blood gas analyses, including fractional methemoglobin measurements, were performed using a co-oximetry–based blood gas analyzer (Radiometer ABL800 FLEX, Radiometer Medical, Denmark). A methemoglobin level > 1.5% was considered abnormal. Patients with mild elevations and no symptoms were monitored. All procedures were performed under room air, and no routine supplemental oxygen was administered unless clinically indicated. In symptomatic cases, intravenous vitamin C (1–2 g) and/or methylene blue (1–2 mg/kg) were administered according to clinical judgment. Baseline medication histories, including agents known to increase the risk of methemoglobinemia such as nitrates and oxidizing drugs, were reviewed using medical records and peri-procedural charts.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies and percentages for categorical variables and as mean ± standard deviation for continuous variables. Categorical variables were compared between groups using Pearson's chi-square test, Fisher's exact test, or the Fisher-Freeman-Halton test, as appropriate. The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, supported by visual methods, including histograms and Q-Q plots, as well as consideration of sample size. The independent samples t-test was used to compare continuous variables between two independent groups. For comparisons involving repeated measurements across more than two related groups, one-way and two-way repeated-measures analysis of variance (ANOVA) tests were applied. Univariate logistic regression analysis was performed to evaluate predictive factors associated with the presence of methemoglobinemia. The ability of variables to predict the presence of methemoglobinemia was further assessed using receiver operating characteristic (ROC) curve analysis. A p-value < 0.05 was considered statistically significant for all tests.

Results

The study included 126 patients undergoing CIED implantation, with a mean age of 69.04 ± 12.68 years, of whom 70 were male (Table 1). The majority of patients had methemoglobin levels above 1.5% (80.2%). Three patients developed clinically significant methemoglobinemia requiring treatment. Their peak

ABBREVIATIONS

ANOVA	Analysis of variance
BMI	Body Mass Index
CIED	Cardiac implantable electronic device
CRT	Cardiac resynchronization therapy
Fe^{2+}	Ferrous
Fe^{3+}	Ferric
FMetHb	Fractional methemoglobin
ICD	Implantable cardioverter-defibrillator
ROC	Receiver operating characteristic

Table 1. Demographic and clinical characteristics of patients

Variables	Results (n=126)
Age, years, Mean±SD	69.04±12.68
Gender, M/F	70/56
Weight, kg, Mean±SD	76.16±14.85
Comorbidities, n (%)	115 (91.3)
DM, n (%)	40 (31.7)
HT, n (%)	66 (52.4)
CAD, n (%)	49 (38.9)
HF, n (%)	94 (74.6)
AF, n (%)	12 (9.5)
COPD, n (%)	8 (6.3)
CKD, n (%)	8 (6.3)
EF, %, Mean±SD	42.58±15.17
Indication, n (%)	
CHB	61 (48.4)
CMP	51 (40.5)
SND	9 (7.1)
HOCM	5 (4.0)
Fluoroscopy time, min, Mean±SD	9.73±8.98
Drug amount, mg, Mean±SD	25.83±7.54
Mthb, n (%)	101 (80.2)
Treatment of Mthb, n (%)	3 (2.4)
Hospital stays, days, Median (min-max)	1 (1-11)

M, Male; F, Female; DM, Diabetes mellitus; HT, Hypertension; CAD, Coronary artery disease; HF, Heart failure; AF, Atrial fibrillation; COPD, Chronic obstructive pulmonary disease; CKD, Chronic kidney disease; EF, Ejection fraction; CHB, Complete heart block; CMP, Cardiomyopathy; SND, Sinus node dysfunction; HOCM, Hypertrophic obstructive cardiomyopathy; Mthb, Methemoglobinemia.

fractional methemoglobin levels were 2.9%, 11.7%, and 5.6%, respectively. At the time of symptom onset, arterial blood gas analysis revealed reduced SaO_2 values (83%, 86%, and 85%). All three patients had received higher prilocaine doses (20, 40, and 32 mg, respectively) compared with asymptomatic patients. Two patients with lower peak methemoglobin levels (2.9% and 5.6%) presented with mild symptoms, including fatigue and cyanosis, and were treated with intravenous vitamin C alone. The patient with the highest methemoglobin level (11.7%) developed dyspnea and required combined treatment with intravenous vitamin C and methylene blue, resulting in rapid symptomatic improvement within one hour and complete biochemical normalization within 24 hours. The median hospital stay was 1 day (1-11), and no patient required readmission or experienced adverse effects related to methemoglobinemia.

The changes in blood gas parameters over the course of the procedure are presented in Table 2 and Figure 1. Based on the fractional methemoglobin level measured at 60 minutes, patients were categorized into three groups: ≤ 1.5% (n = 20, 16%), 1.5–3% (n = 36, 28%), and > 3% (n = 70, 56%). The demographic and clinical characteristics of these groups are compared in Table 3. The distribution of drug dosage differed significantly between groups (P = 0.001), with lower doses

Table 2. Arterial blood gas samples

	0 min	60 min	120 min
SaO_2, %, Mean±SD	90.35±3.82	90.48±4.18	90.77±3.96
pH, Mean±SD	7.38±0.04	7.39±0.03	7.39±0.04
pCO2, Mean±SD	34.90±5.96	34.38±6.63	34.26±6.32
pO2, Mean±SD	63.66±21.04	66.87±18.46	66.54±22.29
FMtHb, %, Mean±SD	3.61±2.56	3.98±2.91	3.42±2.68

*Repeated Measure ANOVA test.

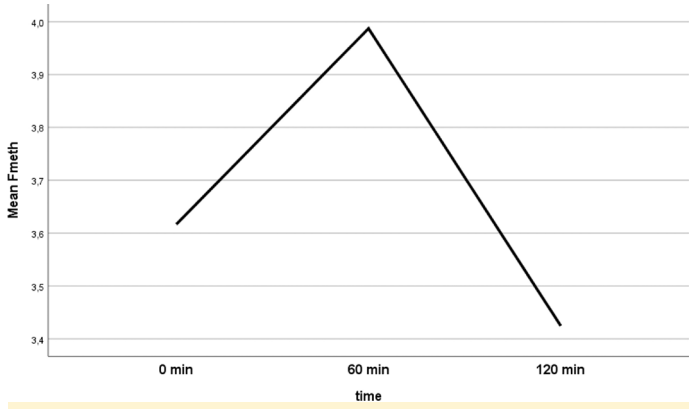

Figure 1. Time-dependent changes in mean methemoglobin (FmetHb) levels at baseline (0 min), 60 minutes, and 120 minutes. Mean FmetHb levels increased from baseline to 60 minutes, followed by a marked decrease at 120 minutes.

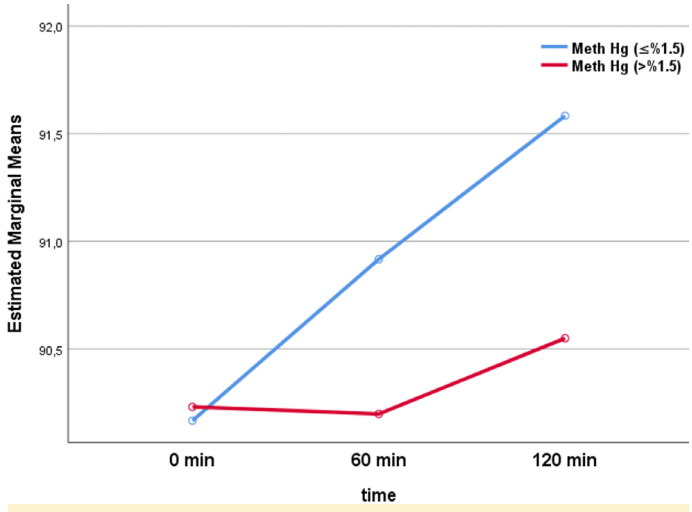

Figure 2. SpO_2 change over time according to methemoglobinemia groups.

observed in the group with FMetHb levels between 1.5% and 3% compared to the > 3% group (P < 0.001). A statistically significant difference was also found in pCO_2 levels at the 60-minute measurement (P = 0.031), driven by higher pCO_2 values in the group with FMetHb ≤ 1.5% compared to the group with FMetHb > 3% (P = 0.042). Although logistic regression analysis was performed to identify predictors of one-hour methemoglobinemia, none of the examined variables demonstrated a statistically significant association. Changes in

Table 3. Distribution of variables according to methemoglobin (1st hour) values

Variables	Meth Hg (≤%1.5) (n = 20)	Meth Hg (%1.5-3) (n = 36)	Meth Hg (>%3) (n = 70)	*P*
Age, years, Mean±SD	70.30±11.05	69.44±10.38	68.47±1.70	0.831*
Gender, M/F	12/8	17/19	41/29	0.498**
Weight, kg, Mean±SD	80.90±19.62	77.64±15.96	74.04±12.33	0.149*
Comorbidities, n (%)	19 (95.0)	30 (8.3)	66 (94.3)	0.144***
DM, n (%)	8 (40.0)	11 (30.6)	21 (30.0)	0.687**
HT, n (%)	7 (35.0)	17 (47.2)	42 (60.0)	0.109**
CAD, n (%)	10 (50.0)	14 (38.9)	25 (35.7)	0.513**
HF, n (%)	18 (90.0)	27 (75.0)	49 (70.0)	0.193**
AF, n (%)	4 (20.0)	4 (11.1)	4 (5.7)	0.126***
COPD, n (%)	1 (5.0)	4 (11.1)	3 (4.3)	0.352***
CKD, n (%)	1 (5.0)	1 (2.8)	6 (8.6)	0.687***
EF, %, Mean±SD	43.65±13.93	43.19±14.96	44.81±14.88	0.341*
Fluoroscopy time, min, Mean±SD	9.34±8.85	7.56±1.26	9.56±1.14	0.167*
Drug amount, mg, Mean±SD	24.35±6.98	22.33±6.10	28.04±7.66	**0.001***
Hospital stays, days, Mean±SD	1.60±1.04	1.69±1.30	1.84±1.92	0.811*
SaO_2 (0 min), %, Mean±SD	89.85±3.88	90.81±3.95	90.26±3.77	0.644*
pH (0 min), Mean±SD	7.37±0.05	7.39±0.04	7.39±0.04	0.150*
pCO_2 (0 min), Mean±SD	36.91±6.82	35.71±6.81	33.91±5.06	0.088*
pO_2 (0 min), Mean±SD	58.90±23.55	63.88±20.52	64.91±20.67	0.533*
SaO_2 (60 min), %, Mean±SD	90.70±4.26	91.17±3.08	90.06±4.63	0.423*
pH (60 min), Mean±SD	7.38±0.04	7.39±0.04	7.40±0.03	0.220*
pCO_2 (60 min), Mean±SD	36.38±7.03	35.95±7.12	32.98±5.98	**0.031***
pO_2 (60 min), Mean±SD	61.28±24.10	67.42±16.78	68.20±17.42	0.332*
SaO_2 (120 min), %, Mean±SD	90.89±3.58	91.73±3.15	90.22±4.37	0.208*
pH (120 min), Mean±SD	7.39±0.05	7.40±0.05	7.39±0.04	0.820*
pCO_2 (120 min), Mean±SD	35.95±6.72	35.63±6.32	33.02±6.02	0.068*
pO_2 (120 min), Mean±SD	59.45±22.57	67.40±16.86	68.22±24.50	0.315*

*: One Way ANOVA; **: Pearson Chi-Square Test; ***: Fisher Halton Freeman Test; M, Male; F, Female; DM, Diabetes mellitus; HT, Hypertension; CAD, Coronary artery disease; HF, Heart failure; AF, Atrial fibrillation; COPD, Chronic obstructive pulmonary disease; CKD, Chronic kidney disease; EF, Ejection fraction; CHB, Complete heart block; ICM, Ischemic cardiomyopathy; DCM, Dilated cardiomyopathy; SND, Sinus node dysfunction; HOCM, Hypertrophic obstructive cardiomyopathy; Mthb, Methemoglobinemia.

SaO_2 values at baseline, 60 minutes, and 120 minutes across the groups are illustrated in Figure 2. Receiver operating characteristic curve analysis was performed to identify the optimal cut-off value for predicting methemoglobinemia (FMetHb > 3%) at one hour. A prilocaine dose ≥ 24.50 predicted methemoglobinemia at one hour with 68.1% sensitivity and 58.9% specificity. The area under the curve was 0.693 (P < 0.001; 95% confidence interval [CI]: 0.601–0.785) (Figure 3).

Discussion

This study underscores the occurrence of methemoglobinemia as an underrecognized but clinically relevant complication following CIED procedures performed under local anesthesia. While the majority of patients with elevated methemoglobin levels remained asymptomatic, a small subset required pharmacologic intervention, and all responded well to treatment with methylene blue and/or intravenous vitamin C. Our findings are consistent with prior reports suggesting that the localized use of anesthetics, particularly prilocaine, can lead to dose-dependent oxidative stress and impaired oxygen transport, especially in susceptible populations.[11,12]

We acknowledge that most methemoglobin elevations observed in this study were biochemical and asymptomatic in nature. Percentage-based thresholds, such as 1.5% or 3%, should not be interpreted as definitive indicators of clinical toxicity, as the development of symptoms depends on the absolute methemoglobin burden, hemoglobin concentration, and underlying cardiopulmonary reserve. In patients with congestive heart failure, anemia, or chronic lung disease, even modest increases may theoretically have greater physiological impact; however, clinically meaningful methemoglobinemia remained rare in our cohort.

The stratification of patients into three methemoglobin level groups—≤ 1.5%, 1.5–3%, and > 3%—was based on the practical need for clinical clarity in the absence of definitive thresholds in the existing literature.[13] Although most studies

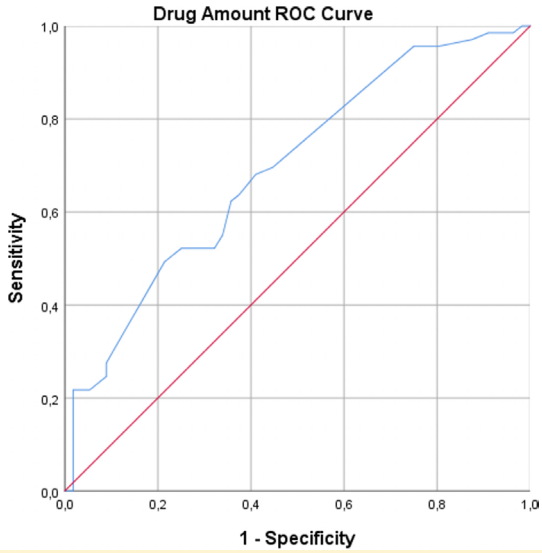

Figure 3. ROC curve analysis.

define symptomatic methemoglobinemia as levels exceeding 3–5%, lower levels may still produce clinically relevant effects in patients with comorbidities or reduced physiological reserve.[14,15] Our decision to consider > 3% as a threshold for more significant toxicity was informed by prior pharmacodynamic data and is consistent with other observational studies of local anesthetic-induced methemoglobinemia.

Differences in drug dosage between groups further reinforce the role of local anesthetics in methemoglobin formation. Patients with FMetHb > 3% received significantly higher anesthetic doses compared to those in the lower categories. This dose-dependent relationship supports previous findings suggesting that prilocaine and related agents may lead to methemoglobin accumulation, particularly when used at or above threshold concentrations required for effective nerve blockade.[16] In addition to this association, ROC curve analysis identified a prilocaine dose of ≥ 24.50 mg as the optimal threshold for predicting methemoglobinemia at one hour, with a sensitivity of 68.1% and a specificity of 58.9% (area under the curve [AUC]: 0.693, P < 0.001). Although the discriminative power was moderate, this cut-off provides a practical benchmark for clinicians when selecting anesthetic dosages during CIED implantation.

Another notable observation was the variation in pCO_2 levels at 60 minutes, which were significantly higher in patients with low FMetHb levels compared to those in the > 3% group. Although causality cannot be established, this inverse relationship may reflect a compensatory respiratory response or altered metabolic status, possibly influenced by underlying heart failure or oxygen transport dynamics. This finding raises the question of whether methemoglobin formation modifies carbon dioxide clearance, an area that remains largely unexplored in the clinical literature.

Although our study is limited by its observational design and single-center setting, the findings emphasize the importance of considering methemoglobinemia in patients receiving higher anesthetic doses or presenting with paradoxical desaturation. Future prospective studies should explore oxidative markers and patient-level predictors in a more systematic manner.

Limitations

This study has several limitations. First, the observational single-center design limits the generalizability of our findings to broader populations. Patient characteristics, local anesthetic protocols, and monitoring practices may differ significantly across institutions, potentially influencing the incidence and clinical profile of methemoglobinemia. In addition, although we categorized patients based on methemoglobin thresholds to explore clinical associations, these groupings were not derived from validated international guidelines due to the lack of consensus in the literature. Additionally, we did not evaluate oxidative stress biomarkers or enzymatic activities that could have helped elucidate individual susceptibility. Although medication histories were reviewed, the retrospective nature of peri-procedural chart documentation limited our ability to systematically quantify exposure to all potential oxidizing agents, such as nitrates, which may represent a source of residual confounding.

The ROC-derived prilocaine cut-off should be interpreted with caution, as it reflects the prediction of biochemical methemoglobin elevation rather than clinically significant methemoglobinemia. Given the limited number of symptomatic cases and the lack of weight-adjusted dosing, this threshold is not intended to guide direct clinical decision-making. Another important limitation is the absence of height and Body Mass Index (BMI) data, which precluded weight-adjusted analysis of local anesthetic dosing. Because symptoms related to methemoglobinemia correlate more closely with absolute methemoglobin mass and hemoglobin concentration rather than fractional values alone, percentage-based interpretation without full hematologic and anthropometric adjustment may be misleading. Therefore, the small number of clinically significant events limits any attempt at robust clinical risk prediction.

Conclusion

Methemoglobinemia is a relatively underrecognized yet clinically important complication following CIED implantation, particularly in patients receiving higher doses of local anesthetics. Stratifying methemoglobinemia using practical thresholds helped elucidate clinically relevant patterns despite the limited consensus in the literature. Vigilant perioperative surveillance and timely therapeutic intervention may help ensure optimal patient outcomes in this setting.

Ethics Committee Approval: Ethics committee approval was obtained from Necmettin Erbakan University Non-Drug and Non-Medical Device Research Ethics Committee (Approval Number: 2025/5879, Date: 27.06.2025).

Informed Consent: Written informed consent was obtained from all patients prior to participation.

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Residual Patent Ductus Arteriosus After Surgical and Transcatheter Closure: Anatomical Challenges and Transcatheter Re-Intervention Strategies

Cerrahi ve Transkateter Kapatma Sonrası Rezidüel Patent Duktus Arteriozus: Anatomik Zorluklar ve Transkateter Yeniden Girişim Stratejileri

ABSTRACT

Objective: The aim of this study was to present our single-center experience with transcatheter re-intervention for residual patent ductus arteriosus (rPDA), with particular emphasis on anatomical features and technical approaches.

Method: We retrospectively reviewed six patients (median age 2.9 years; range, 1.2–16) who underwent transcatheter closure of rPDA between January 2021 and May 2025. Re-intervention was performed for persistent residual shunting in the presence of previously implanted foreign material, based primarily on hemodynamic and anatomical considerations; infective endarteritis and hemolysis were considered additional potential risks. Procedural records, angiographic findings, device selection, and outcomes were analyzed.

Results: Five patients had undergone prior transcatheter patent ductus arteriosus (PDA) closure and one had surgical ligation. Among the transcatheter cases, persistent shunting was due to delayed malposition (n = 2), incomplete occlusion (n = 2), and a non-thrombosed coil (n = 1). In two patients, the original Amplatzer Duct Occluder II (ADO II) device was malpositioned toward the pulmonary artery; therefore, a second device was deployed encompassing the prior occluder. In one patient, a non-thrombosed coil with persistent central flow created a "stent-like" configuration, and closure was achieved by implanting a new device with its discs covering the coil. In the surgical case, both the residual ductus and an adjacent aortopulmonary collateral artery were successfully occluded with a single device. Complete closure was achieved in all patients without complications.

Conclusion: In this single-center case series, transcatheter re-intervention for residual PDA was feasible even in the presence of malpositioned prior devices. Careful anatomical evaluation and individualized procedural planning enabled successful closure of residual shunts.

Keywords: Coil occlusion, device closure, patent ductus arteriosus / complications, residual patent ductus arteriosus, transcatheter re-intervention

ÖZET

Amaç: Bu çalışmanın amacı, rezidüel patent duktus arteriozus (rPDA) nedeniyle yapılan transkateter yeniden girişimlere ilişkin tek merkez deneyimimizi, özellikle anatomik özellikler ve teknik yaklaşımlar açısından sunmaktır.

Yöntem: Ocak 2021 ile Mayıs 2025 arasında rPDA'nın transkateter kapatılması uygulanan altı hasta (medyan yaş 2,9 yıl; aralık 1,2–16) retrospektif olarak incelendi. Yeniden girişim, daha önce implante edilmiş yabancı materyal varlığında persistan rezidüel şant bulunması nedeniyle, öncelikle hemodinamik ve anatomik değerlendirmelere dayanılarak gerçekleştirildi. İnfektif endarterit ve hemoliz, ek potansiyel riskler olarak dikkate alındı. Prosedür kayıtları, anjiyografik bulgular, cihaz seçimi ve sonuçlar analiz edildi.

Bulgular: Beş hastaya daha önce transkateter PDA kapatılması, bir hastaya ise cerrahi ligasyon uygulanmıştı. Transkateter olgular arasında persistan şantın nedeni, iki hastada gecikmiş malpozisyon, iki hastada inkomplet oklüzyon ve bir hastada tromboze olmayan koil idi. İki hastada orijinal ADO II cihazı pulmoner artere doğru malpoze idi; bu nedenle, önceki oklüderi kapsayacak şekilde ikinci bir cihaz yerleştirildi. Bir hastada santral akımı devam eden tromboze olmayan koil, "stent benzeri" bir konfigürasyon oluşturmuş olup koili diskleriyle örten yeni bir cihaz implantasyonu ile kapatma sağlandı. Cerrahi olguda ise rezidüel duktus ve komşu aortopulmoner kollateral arter, tek bir cihazla başarıyla oklüde edildi. Tüm hastalarda komplikasyon gelişmeden tam kapanma elde edildi.

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

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Sonuç: Bu tek merkezli olgu serisinde, rezidüel PDA için transkateter yeniden girişimin, malpoze önceki cihaz varlığında dahi uygulanabilir olduğu gösterildi. Dikkatli anatomik değerlendirme ve bireyselleştirilmiş prosedürel planlama, rezidüel şantların başarılı şekilde kapatılmasını sağlamıştır.

Anahtar Kelimeler: Coil oklüzyonu, cihaz ile kapatma, patent duktus arteriozus / komplikasyonlar, rezidüel patent duktus arteriozus, transkateter yeniden girişim

Transcatheter closure of patent ductus arteriosus (PDA), first introduced in the 1980s, was initially reserved for hemodynamically significant lesions. However, with advancements in device technology and operator experience, complication rates have substantially decreased, and closure of even clinically silent rPDA has gained wider acceptance in many centers.[1] Despite high success rates, complications such as device embolization have been reported in other congenital defect closures, including atrial septal defect and ventricular septal defect, while rPDA may also persist after both surgical and transcatheter closure, often due to incomplete thrombosis, device malposition, or recanalization.[2-4] Although such residual lesions are frequently hemodynamically insignificant, persistent residual shunting in the presence of implanted foreign material carries a recognized risk of complications such as infective endarteritis and hemolysis. This risk has been highlighted in observational reports and in the current European Society of Cardiology (ESC) and American Heart Association (AHA) infective endocarditis guidelines, which may justify re-intervention in selected patients.[5-7]

With ongoing advancements in transcatheter occlusion techniques and newer-generation devices, effective solutions are now available for these challenging anatomical situations. In this single-center case series, we present six patients who underwent transcatheter re-intervention for rPDA following previous surgical or percutaneous closure, with a focus on anatomical substrates and technical considerations.

ABBREVIATIONS

ADO	Amplatzer Duct Occluder II
AHA	American Heart Association
APO	Amplatzer Piccolo Occluder
ESC	European Society of Cardiology
IE	Infective endocarditis
LV	Left ventricular
LVEDD	Left ventricular end-diastolic diameter
PDA	Patent ductus arteriosus
rPDA	Residual patent ductus arteriosus

Materials and Methods

This retrospective case series evaluated patients undergoing transcatheter re-intervention for residual PDA at our tertiary care center. Residual PDA was defined as the presence of persistent ductal flow detected by transthoracic echocardiography and/or angiography following the index closure procedure. Given that small residual shunts may close during the endothelialization period, persistence beyond 6 months was considered clinically relevant in our institutional practice.[8] The study included six patients who underwent transcatheter closure of rPDA between January 2021 and May 2025. During the same period, a total of 142 transcatheter PDA closure procedures were performed at our center. Among these, four patients (2.8%) developed persistent residual PDA requiring re-intervention beyond 6 months. One additional patient with a non-thrombosed coil referred from another center and one patient with residual PDA after surgical ligation performed at our institution were also included in this case series but were not part of the transcatheter PDA registry denominator. All cases demonstrated persistent residual ductal flow on follow-up imaging. In addition, patients in this series had isolated patent ductus arteriosus without associated structural congenital cardiac anomalies on baseline echocardiographic and angiographic evaluation. Antiplatelet therapy after the index procedure was not part of the standardized institutional protocol, and detailed medication data were unavailable for the patient referred from an external center.

Re-intervention was undertaken for persistent residual shunting beyond 6 months after the index procedure in the presence of previously implanted foreign material and was based on an individualized assessment incorporating hemodynamic parameters (pulmonary-to-systemic blood flow ratio [Qp/Qs] and evidence of left ventricular volume loading), together with anatomical and device-related considerations, including persistent flow across the implanted material.[5]

Inclusion criteria were: documented rPDA confirmed by transthoracic echocardiography and angiography, and transcatheter re-intervention performed at our center. This study was approved by Ankara Etlik City Hospital Medical Research Scientific and Ethical Review Board (Approval Number: TABED 1-25-1515, Date: 30.07.2025) and conducted in accordance with the Declaration of Helsinki.

Procedure Protocol

All procedures were performed under general anesthesia. Femoral arterial access was obtained in all patients. Intravenous heparin (50 U/kg) was administered following sheath placement. Aortic angiography was performed in straight lateral and right anterior oblique projections using a 4F pigtail catheter to evaluate the residual ductal anatomy. Measurements included the narrowest residual ductal diameter and the total ductal length.

Device type and size were selected based on the morphology of the residual ductus and the characteristics of the previously implanted device, when present. A retrograde approach was used in all patients. Occlusion was achieved using either the Amplatzer Duct Occluder II (ADO II) (Abbott, Plymouth, MN, USA) or the Amplatzer Piccolo Occluder (APO) (Abbott, Plymouth,

Table 1. Baseline demographic, hemodynamic, and angiographic characteristics of the study patients

Case	Age (years)	Sex	Weight (kg)	Mean PAP (mmHg)	Qp/Qs	LVEDD Z-score	Initial procedure	Initial device	Device used
1	6.6	F	19	22	1.9	2.4	Transcatheter	6/6 mm ADO II	6/6 mm ADO II
2	1.2	M	10.5	29	1.4	1.6	Transcatheter	5/4 mm ADO II	5/4 mm APO
3	2.4	M	6.6	21	1.5	1.7	Surgical	-	5/6 mm APO
4	16	F	48	11	1.7	2.1	Transcatheter	PFM coil	4/6 mm ADO II
5	3.4	M	14.6	22	1.5	1.5	Transcatheter	5/4 mm ADO II	5/4 mm ADO II
6	2.3	F	12.3	21	1.4	1.6	Transcatheter	4/4 mm ADO II	5/4 mm APO

ADO II, Amplatzer Duct Occluder II; APO, Amplatzer Piccolo Occluder; F, Female; LVEDD, Left ventricular end-diastolic diameter; M, Male; PAP, Pulmonary artery pressure; Qp/Qs, Pulmonary-to-systemic flow ratio.

MN, USA), ensuring complete coverage of the residual lumen. Device position and closure efficacy were confirmed by post-deployment angiography. All patients underwent transthoracic echocardiography at 24 hours, 2 weeks, and 1 and 6 months after the procedure to assess residual flow and device stability. No routine antiplatelet therapy was administered following the re-intervention procedures. Antiplatelet therapy after the index procedure was not part of the standardized protocol at our center, and medication data were unavailable for the patient referred from an external institution.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Data were summarized using descriptive statistics only. Categorical variables were expressed as frequencies (n) and percentages (%), and continuous variables were presented as median with range or interquartile range, as appropriate. No formal hypothesis testing was performed given the descriptive nature and small sample size of this case series.

Results

A total of six patients (three females, three males) with rPDA underwent transcatheter re-intervention. The median age at the time of re-intervention was 2.9 years (range, 1.2–16 years), and the median weight was 13.5 kg (range, 6.6–48 kg). The median time to re-intervention after the initial procedure was 11 months (interquartile range [IQR], 7–25 months). Residual lesions occurred following previous transcatheter PDA closure in five patients and surgical ligation in one patient. Based on angiographic records from the index procedure, PDA morphology was classified according to the Krichenko classification system. Among the six patients, two had type A (conical) morphology, two had type C (tubular) morphology (one following prior transcatheter closure and one after surgical ligation), and one had type E (elongated) morphology. In one patient referred with a previously implanted coil from another center, the index ductal morphology could not be reliably ascertained. Qp/Qs ratios ranged from 1.4 to 1.9, and left ventricular end-diastolic diameter (LVEDD) Z-scores ranged from 1.5 to 2.4. Two patients demonstrated left ventricular (LV) dilation (Z-score ≥ 2), while the remaining patients had borderline to mildly increased LVEDD Z-scores in the context of persistent residual shunting beyond 6 months and flow across previously implanted foreign material. Pulmonary artery pressure at the time of re-intervention demonstrated mildly elevated mean pulmonary artery pressure (≥ 20 mmHg) in five patients, whereas one patient had normal values (11 mmHg). No clinical signs of hemolysis were observed. Patient characteristics are summarized in Table 1.

All re-interventions were performed via a retrograde femoral arterial approach. Device selection was based on the morphology of the residual ductus as well as the type and position of the previously implanted device. In two cases, the prior occluder was malpositioned toward the pulmonary artery, with incomplete contact along the ductal wall and only partial alignment with the ductal trajectory (Figure 1A). In these patients, an ADO II was deployed within the ductus, encompassing the malpositioned occluder and redirecting it from the pulmonary artery toward the ductus to correct its orientation while achieving complete closure (Figure 1B).

In two patients, the previously implanted device was appropriately positioned but failed to achieve complete ductal closure, with persistent central flow through the device allowing residual shunting (Figure 1C). In these cases, the new device was implanted within the same ductal segment, either adjacent to, partially overlapping with, or fully nested within the previous device, depending on the anatomical configuration (Figure 1D).

Of the six patients, only one had previously undergone surgical PDA ligation. In this case, residual ductal flow was observed postoperatively. Angiography revealed not only a residual ductus but also a small aortopulmonary collateral artery adjacent to the ductus (Figure 1E). Both lesions were successfully occluded with a single APO device, achieving complete closure (Figure 1F).

In one patient, the residual ductus was associated with a previously implanted PFM coil (pfm medical ag, Germany) that had failed to thrombose and acted as a stent, maintaining a central flow channel (Figure 1G). However, the coil size was unknown because the procedure had been performed at another center and procedural records were unavailable. In this case, an ADO II was successfully deployed through the coil lumen. The waist of the device occluded the central flow channel, while both retention discs expanded beyond the coil margins, anchoring the device by bilaterally enveloping the coil (Figure 1H).

Angiographic closure was successful in all patients, and no complications such as embolization of either the newly implanted or previously placed device, hemolysis, vascular access injury, or rhythm abnormalities were observed during or after the procedures.

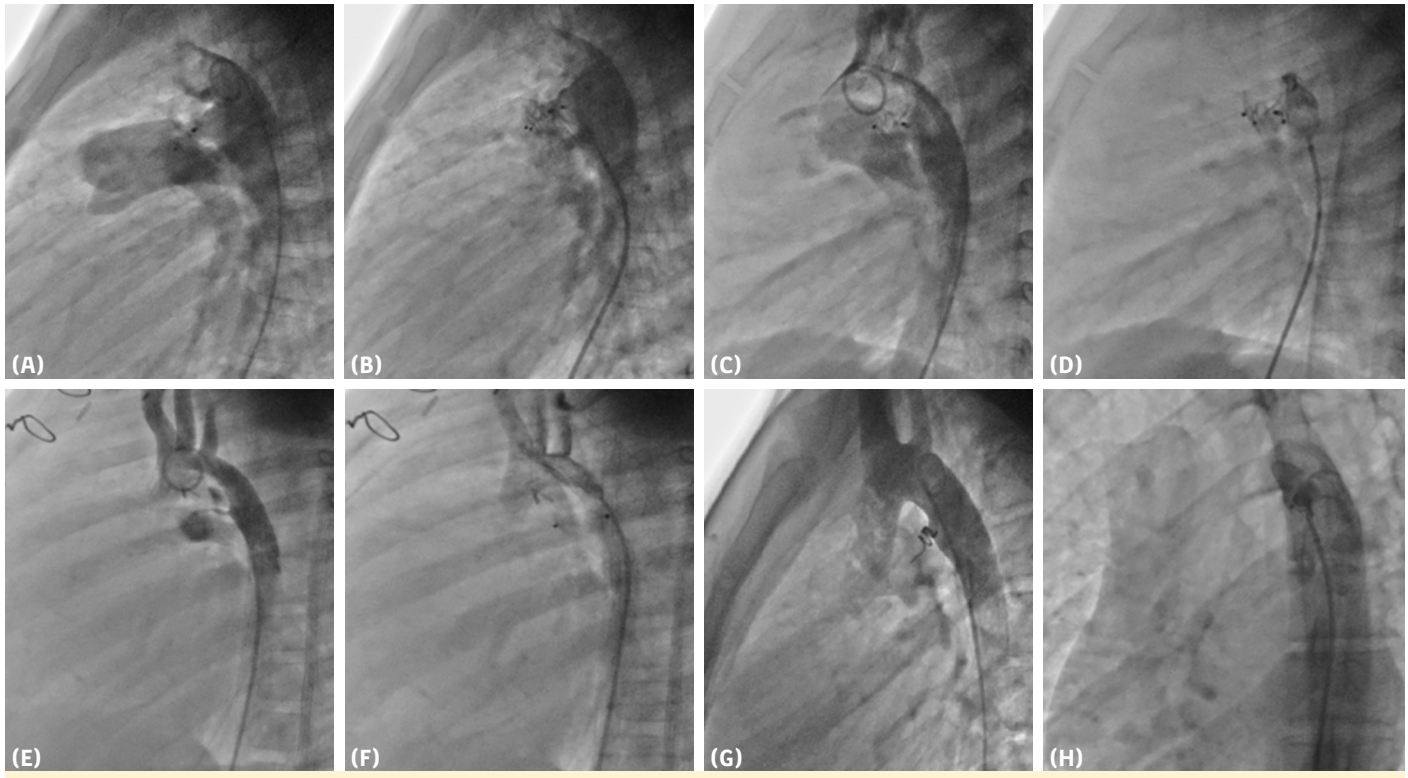

Figure 1. Angiographic images of the aorta in the 90° lateral projection from representative cases, demonstrating different clinical scenarios. (A) Malpositioned initial Amplatzer Duct Occluder II device failing to achieve proper ductal anchorage. (B) Successful closure of the residual ductus by placement of a second Amplatzer Duct Occluder II device, with the first device positioned between the discs of the second device. (C, D) Residual flow due to incomplete occlusion by the first Amplatzer Duct Occluder II device, with complete closure achieved using an Amplatzer Piccolo Occluder. (E, F) Residual ductus observed after surgical ligation, along with a small aortopulmonary collateral artery; both lesions successfully closed with a single Piccolo device. (G, H) Residual ductus associated with a previously implanted coil acting as a stent. An Amplatzer Duct Occluder II device was deployed through the coil lumen; the device waist occluded the central channel, while the discs bilaterally embraced the coil structure, resulting in complete closure.

Echocardiographic evaluation at 2 weeks demonstrated complete closure in five patients; in the remaining patient, minimal residual flow observed at 2 weeks had resolved by the 6-month follow-up.

Discussion

Residual patent ductus arteriosus after prior surgical or transcatheter closure is a well-recognized clinical entity. However, the anatomical substrates and technical challenges encountered during transcatheter re-intervention—particularly in the presence of previously implanted devices—remain incompletely characterized in the literature. Although such residual lesions are often asymptomatic or hemodynamically insignificant, persistent residual shunting in the presence of prosthetic material carries a recognized risk of complications such as infective endarteritis[6,7]. In the present series, mildly elevated mean pulmonary artery pressures were observed in the majority of patients at the time of re-intervention. Although closure of small, hemodynamically insignificant residual shunts solely for infective endocarditis (IE) prophylaxis remains controversial, re-intervention in our series was not performed on this basis alone. Qp/Qs ranged from 1.4 to 1.9, and two patients demonstrated LV dilation (Z-score ≥ 2), supporting ongoing volume loading. In the remaining patients, Qp/Qs values around 1.4 were considered borderline and were interpreted together with persistent shunting beyond 6 months and flow across previously implanted foreign material, rather than as an isolated trigger for re-intervention. When considered together with persistent residual shunting beyond 6 months and the presence of previously implanted foreign material, these findings indicate that re-intervention decisions were based on individualized clinical, hemodynamic (Qp/Qs and LV volume loading), and anatomical considerations rather than on angiographic appearance or theoretical IE risk alone.

In our series, the index PDA morphology was classified according to the Krichenko classification system. Residual shunting was observed across different ductal morphologies, including conical, tubular, and elongated types. However, the small sample size precludes any definitive association between ductal morphology and the risk of residual defects. Larger studies are needed to clarify whether specific anatomical subtypes predispose to persistent shunting after initial closure.

In patients with prior device closure, implanted devices may be partially anchored to the ductal wall rather than fully occluding the lumen, leading to altered ductal geometry and persistent residual flow. Specifically, in two patients the previously implanted ADO II device was malpositioned, resulting in only partial alignment with the ductal trajectory and incomplete contact with the ductal wall. Device malposition detected

during follow-up does not necessarily imply acute procedural maldeployment. In our ADO II cases, final angiography at the index procedure demonstrated satisfactory initial device positioning. The subsequent malalignment observed during follow-up may reflect time-dependent changes in ductal geometry, flow direction, and device–ductus interaction, as previously proposed. In particular, discrepancies between the ductal axis and device orientation, post-procedural ductal recoil, and altered flow patterns have been suggested as key contributors to delayed device malposition and persistent residual shunting.[9,10] These atypical configurations not only permit persistent shunting but may also complicate subsequent device placement.

In two of the five patients with prior transcatheter closure, the residual lesion was located within the same ductal segment as the previously implanted occluder. In these patients, the residual lesion was not due to gross device migration but rather to incomplete functional occlusion of the ductal lumen, with persistent residual flow occurring either through the central portion of the device or around the device waist despite appropriate initial device positioning. Depending on ductal anatomy and the orientation of the prior device, the second device was positioned adjacent to, overlapping with, or completely nested within the earlier one. These anatomical challenges highlight the need for individualized procedural planning and careful device selection. The use of ADO II and APO devices in our study proved effective even in the presence of altered ampullary anatomy and retained hardware. Given the limited number of cases and the preferential use of ADO II devices in larger ductal anatomies in our institutional practice, no definitive conclusions can be drawn regarding the association between device type and residual PDA.

The most likely causes of rPDA following surgical ligation include incomplete closure due to double-ligation techniques or recanalization.[11] In our surgical case, angiography demonstrated both a residual ductus and an adjacent aortopulmonary collateral artery, which were successfully occluded with a single APO. This finding highlights not only the feasibility of treating concomitant lesions in a single procedure but also the critical importance of comprehensive angiographic assessment, as such additional vascular connections may otherwise be overlooked.

Altered ampullary anatomy in rPDA may pose challenges for transcatheter closure. When deciding between antegrade or retrograde approaches, the anatomical configuration of the ductus is a key consideration.[12] Because a pre-existing device may increase the risk of embolization during subsequent procedures, we chose to delay re-intervention for at least six months in such cases. This strategy aimed to reduce procedural risks and ensure durable outcomes.

Another potential complication is hemolysis due to high-velocity jets across the residual lesion, which—although rare—may lead to significant anemia or renal injury.[13] No clinical or laboratory signs of hemolysis were observed in our series, supporting the procedural safety of transcatheter re-intervention. In our series, routine antiplatelet therapy was not administered after either the index procedure or the re-intervention. Although antiplatelet use varies across centers, no thrombotic or embolic events were observed during follow-up; however, larger studies are needed to clarify its role.

Conclusion

Residual lesions following surgical or transcatheter PDA closure may pose anatomical challenges, particularly in the presence of previously implanted devices. In this single-center case series, transcatheter re-intervention was feasible in selected patients and could be successfully performed with careful anatomical assessment and individualized procedural planning. Although limited by the small sample size, our experience highlights practical considerations and potential mechanisms underlying residual shunting and may help inform decision-making in similar complex cases.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara Etlik City Hospital Medical Research Scientific and Ethical Review Board (Approval Number: TABED 1-25-1515, Date: 30.07.2025).

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

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Transcatheter Mitral Valve Replacement in Mitral Annular Calcification Using the Novel Myval Valve: Contribution to the Growing Worldwide Experience

Mitral Anülüs Kalsifikasyonunda Yeni Myval Kapak Kullanılarak Transkateter Mitral Kapak Değişimi: Dünya Genelinde Artan Deneyime Katkı

ABSTRACT

Mitral annular calcification (MAC) is a complex structural abnormality often associated with severe mitral stenosis, regurgitation, or both. Mitral valve surgery carries greater risk especially in elderly patients with MAC, making transcatheter mitral valve replacement (TMVR) an emerging alternative. We report the case of an 84-year-old woman with a history of surgical bioprosthetic aortic valve replacement and recurrent hospitalizations due to severe MAC-related mitral valve disease. She was deemed inoperable by the heart team. Detailed multimodal imaging, including multidetector computed tomography (MDCT), revealed extensive MAC with acceptable neo-left ventricular outflow tract (neo-LVOT) dimensions and an acute aorto-mitral angle. Thus, TMVR was successfully performed via a transseptal approach using a 30.5 mm balloonexpandable Myval transcatheter heart valve (THV). Post-procedural imaging confirmed optimal valve position, no paravalvular leak, and no LVOT obstruction. The patient was discharged in stable condition. This is the first reported case from Türkiye of TMVR in MAC using the Myval THV, contributing to the growing worldwide experience. This report also emphasizes the role of advanced imaging in guiding patient selection and procedural planning and illustrates the feasibility of the Myval THV for valve-in-MAC in challenging mitral anatomy.

Keywords: Mitral annular calcification, myval, neo-LVOT, structural heart disease, transcatheter mitral valve replacement

ÖZET

Mitral annüler kalsifikasyon (MAC), genellikle şiddetli mitral darlığı, yetersizliği veya her ikisiyle birlikte görülen karmaşık bir yapısal anormalliktir. Mitral kapak cerrahisi, MAC'la birlikte ciddi mitral darlığı veya yetersizliği olan yaşlı hastalarda riskli olabilir. Seçilmiş hastalarda, transkateter mitral kapak replasmanı (TMVR) cerrahi'ye önemli bir alternatif olarak uygulanabilir. Bu yazıda, cerrahi biyoprotez aort kapak replasmanı öyküsü ve şiddetli MAC ile ilişkili mitral kapak hastalığı nedeniyle tekrarlayan hastaneye yatışları olan 84 yaşındaki bir kadın hasta sunulmuştur. Kalp takımı tarafından açık cerrahi için çok yüksek riskli olarak değerlendirilen hastaya yapılan ayrıntılı multimodal görüntülemede kabul edilebilir neo-LVOT alanı, akut aorto-mitral açı ile yaygın MAC saptanmış, hastaya 30,5 mm Myval transkateter kalp kapakçığı (THV) kullanılarak transseptal yaklaşımla başarılı bir TMVR işlemi gerçekleştirilmiştir. İşlem sonrası görüntüleme, optimal kapak pozisyonu ile birlikte paravalvüler kaçak veya akut LVOT tıkanıklığı olmadığını doğrulamış ve hasta klinik durumu stabil durumda taburcu edilmiştir. Bu vaka, Türkiye'den Myval THV kullanılarak ciddi MAC'de TMVR uygulanan ilk vaka olup, dünya genelinde artan TMVR deneyimine katkıda bulunmaktadır. Bu vaka sunumu, hasta seçimi ve prosedür planlamasında ileri görüntüleme yöntemlerinin rolünü ayrıntılı vurgulamakla birlikte; MAC ve zorlu anatomide TMVR uygulanması açısından Myval THV'nin kullanışlı olabileceğini göstermektedir.

Anahtar Kelimeler: Mitral anül kalcifikasyonu, myval, neo-LVOT, yapısal kalp hastalığı, transkateter mitral kapak replasmanı

CASE REPORT
OLGU SUNUMU

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Mitral annular calcification (MAC) is a progressive, degenerative disorder of the mitral valve (MV), commonly associated with mitral stenosis, regurgitation, or both.[1] Surgical treatment of severe MAC is technically challenging and carries high perioperative risk, making many patients unsuitable for conventional mitral valve surgery.[1,2] Transcatheter mitral valve replacement (TMVR) has emerged as a viable

alternative for these high-risk patients.[1,2] TMVR can be performed using balloon-expandable transcatheter aortic valves in a valve-in-MAC approach or with dedicated novel TMVR devices.[1,2] However, accurate anatomical evaluation is essential to avoid complications such as left ventricular outflow tract (LVOT) obstruction, valve migration, embolization, and paravalvular regurgitation.[1,3,4] The Myval (Meril Life Sciences Pvt. Ltd., Vapi, India) is a novel balloon-expandable transcatheter heart valve (THV) system featuring an innovative operator-friendly design that enhances deliverability and enables precise deployment.[5,6] In this report, we present the first transcatheter valve-in-MAC case in Türkiye performed using the novel balloon-expandable Myval THV, contributing to the growing worldwide experience.

ABBREVIATIONS

BATMAN	Balloon Assisted Translocation of the Mitral Anterior leaflet
IAS	Interatrial septum
LAMPOON	Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN
MAC	Mitral annular calcification
MDCT	Multidetector computed tomography
MV	Mitral valve
MVA	Mitral valve area
MVR	Mitral valve replacement
neo-LVOT	Neo-left ventricular outflow tract
NYHA	New York Heart Association
PHT	Pressure half-time
TEE	Transesophageal echocardiography
THV	Transcatheter heart valve
TMVR	Transcatheter mitral valve replacement

Case Report

An 84-year-old female with a history of degenerative severe aortic stenosis and severe degenerative mitral valve disease had previously undergone surgical aortic valve replacement with a bioprosthetic valve. She was referred to our center for percutaneous transcatheter mitral valve intervention due to recurrent episodes of acute heart failure secondary to advanced mitral valve disease. Over the past year, she had been hospitalized four times for pulmonary edema and pneumonia, two of which required intubation and mechanical ventilation.

Preprocedural Imaging

Transthoracic and transesophageal echocardiography confirmed a normally functioning bioprosthetic aortic valve and demonstrated severe MAC, with a mean transmitral gradient of 11 mmHg, planimetric mitral valve area (MVA) of 1.3 cm², pressure half-time (PHT)-derived MVA of 1.2 cm², and severe eccentric mitral regurgitation (Figure 1). Multidetector computed tomography (MDCT) confirmed heavy and circumferential MAC with a MAC score of 8 (Figure 2, Table 1). Annular dimensions were found suitable for a 30.5 mm Myval THV. Virtual valve modeling predicted a neo-LVOT area of 303.7 mm² at 40% systole and 217.2 mm² at 75% diastole. Additional findings included an aorto-mitral angle of 36.2°, an inverse angle of 143.8°, and septal bulging, which are well-known risk factors for LVOT obstruction (Figure 2). However, the calculated neo-LVOT and skirt-neo-LVOT areas remained above critical thresholds, and no other anatomical contraindications were identified (Figure 2). Thus, we decided to perform TMVR in this high-risk patient. Written informed consent was obtained from the patient before the procedure.

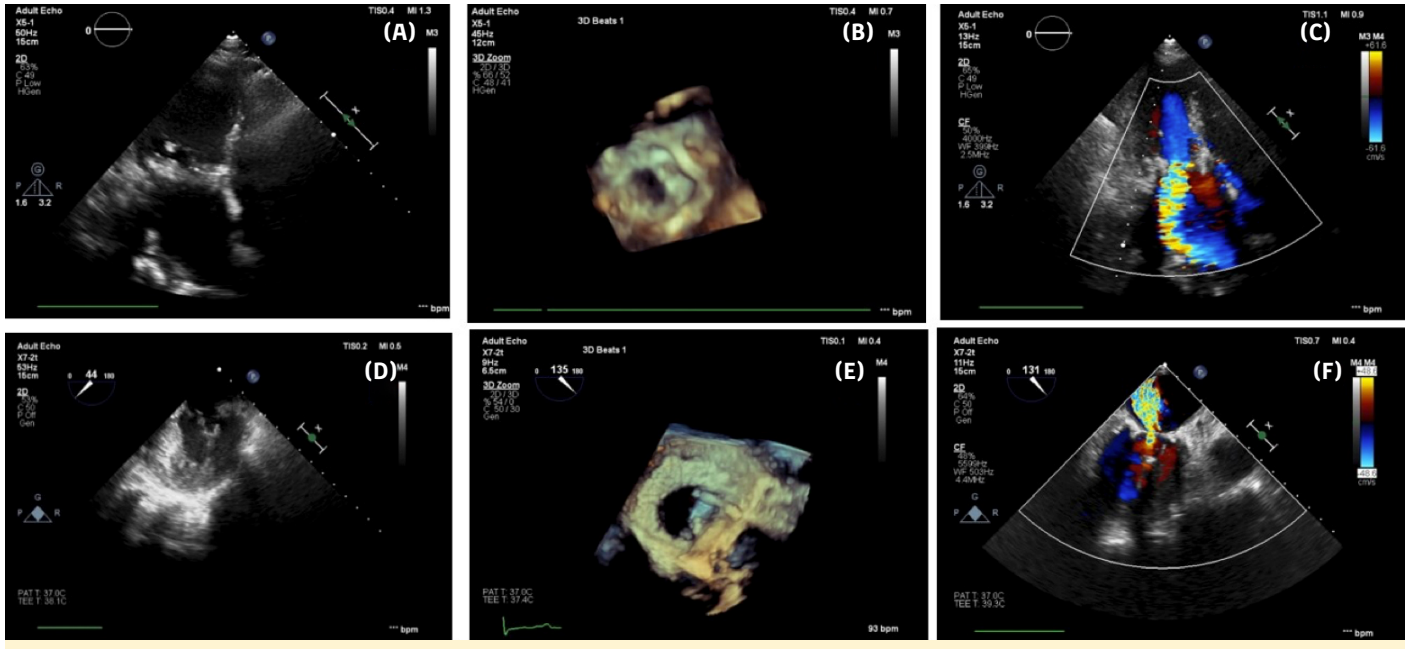

Figure 1. (A) Two-dimensional (2D) transthoracic echocardiography (TTE) image showing a calcific, degenerative mitral valve. (B) Three-dimensional (3D) TTE image showing severe circumferential calcification of the mitral valve. (C) Color Doppler TTE image showing severe mitral regurgitation. (D) Two-dimensional transesophageal echocardiography image showing calcific degenerative mitral valve disease. (E) Three-dimensional TEE image showing severe circumferential calcification of the mitral valve. (F) Two-dimensional TEE image showing severe mitral regurgitation.

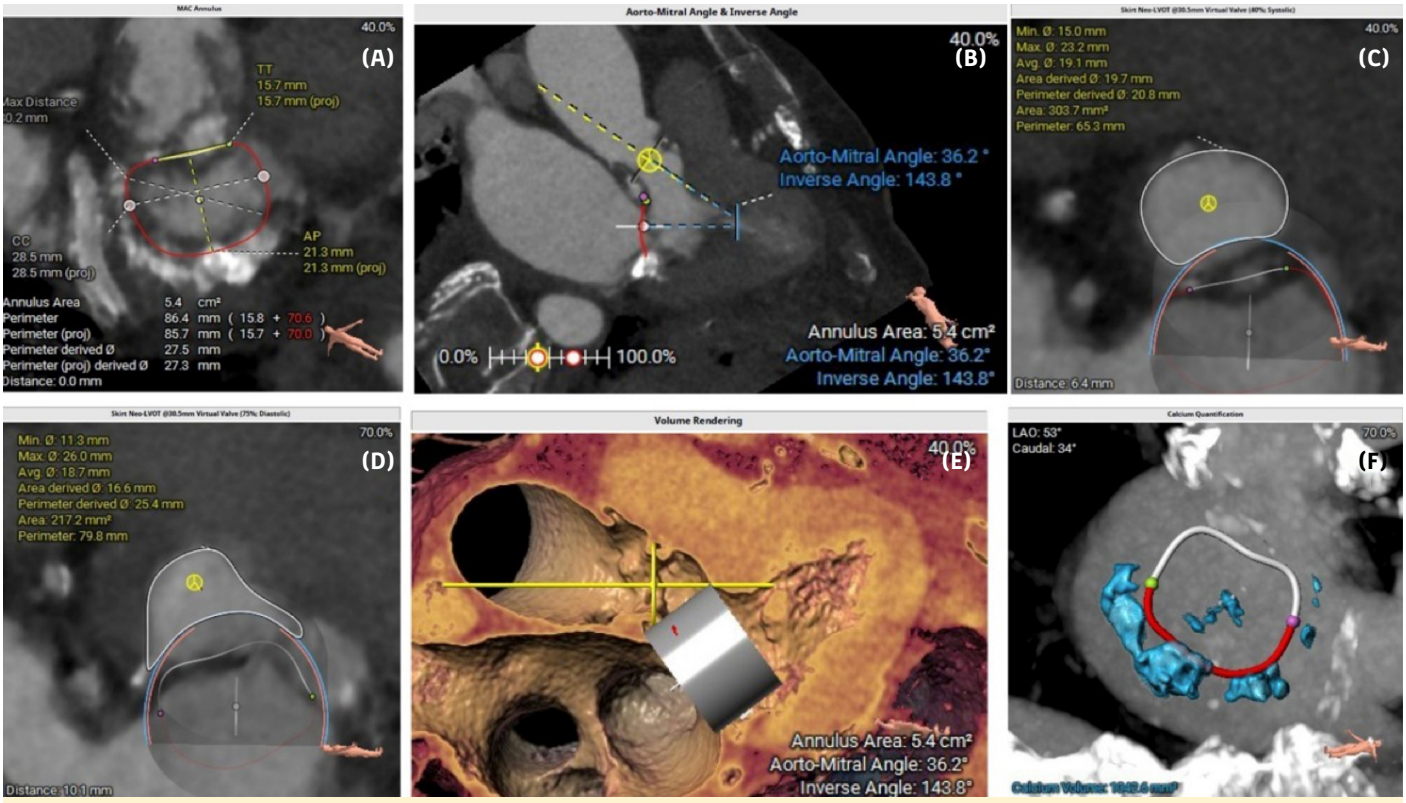

Figure 2. (A) Gated computed tomography (G-CT) image showing heavy and circumferential mitral annular calcification (MAC). (B) G-CT image showing an acute aorto-mitral angle (AMA). (C) G-CT image showing the predicted skirt neo-left ventricular outflow tract (LVOT) area using a virtual 30.5 mm Myval valve: 303.7 mm² (40% systole). (D) G-CT image showing the predicted skirt neo-LVOT area using a virtual 30.5 mm Myval valve: 217.7 mm2 (75% diastole). (E) G-CT image showing an acute AMA using a virtual 30.5 mm Myval. (F) G-CT image showing calcium quantification of MAC.

Table 1. CT-based MAC severity score calculation of the patient

CT-based MAC severity score*		
CT findings	**Points**	**Patient's points**
Ca thickness		
<5	1	
5-9.99	2	2
>10	3	
Ca distribution		
<180	1	
180-270	2	2
>270	3	
Trigone involvement		
None	0	
Anterolateral	1	1
Posteromedial	1	1
Leaflet involvement		
None	0	
Anterior	1	1
Posterior	1	1
Total points		8

CT, Computed tomography; MAC, Mitral annular calcification. *, MAC grade severity: mild: <3 points; moderate: 4-6 points; severe: >7 points.

Procedure

Under general anesthesia and transesophageal echocardiography (TEE) guidance, the patient underwent transseptal TMVR. Right femoral venous access was used for two venous sheaths and left femoral artery access for monitoring. An inferoposterior transseptal puncture was performed with a 0-1 Brockenbrough needle (BRK™, Abbott Vascular, IL, USA). A coiled-tip guidewire (Toray, Tokyo, Japan) was placed in the left atrium, followed by insertion of an 8.5F-Agilis™ NxT steerable sheath (Abbott Vascular, IL, USA). A 7F multipurpose guiding catheter was advanced through the mitral valve into the left ventricle, allowing placement of the first Safari (Boston Scientific, USA) guidewire. To enhance stability and facilitate device delivery, a second Safari wire was placed in the left ventricle alongside the first one.[7,8] Balloon atrial septostomy was performed to accommodate the delivery system. A 30.5 mm balloon-expandable Myval THV (Meril Life Sciences, Vapi, Gujarat, India) was deployed across the MAC under rapid pacing (Figure 3). Post-deployment imaging confirmed successful implantation with no paravalvular leak, no LVOT obstruction, and complete resolution of mitral stenosis and regurgitation (Figure 4). The patient was transferred to intensive care in stable condition.

Postoperative Status and Follow-up

The postoperative course was uneventful, with complete resolution of the initial signs of congestion. The patient was discharged after ten days on warfarin anticoagulation. At clinical

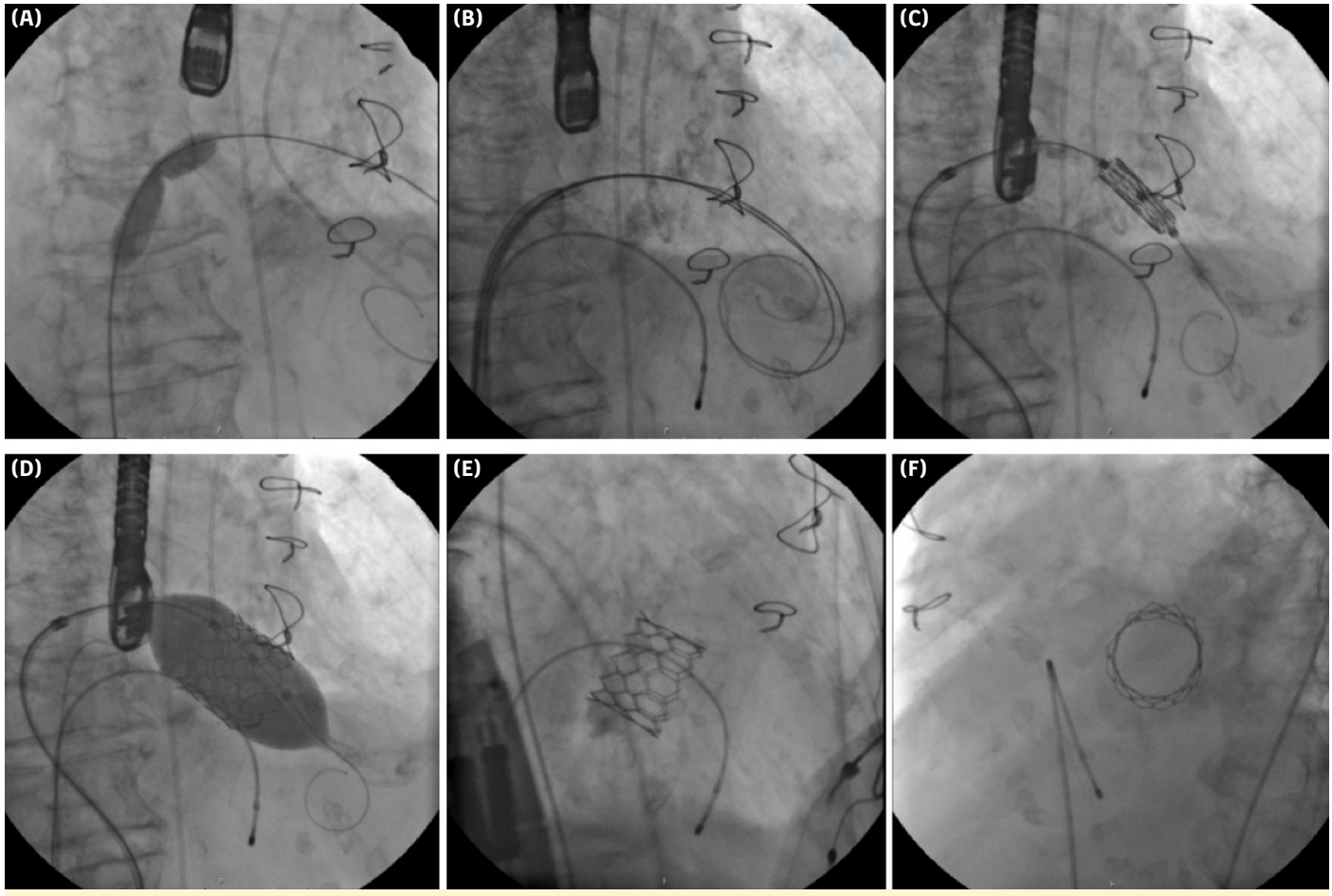

Figure 3. (A) Fluoroscopy image showing balloon dilation of the interatrial septum. (B) Fluoroscopy image showing the double-stiff wire technique. (C) Fluoroscopy image showing alignment of the 30.5 mm Myval valve. (D) Fluoroscopy image showing deployment of the 30.5 mm Myval valve. (E) Fluoroscopy image showing final position of the 30.5 mm Myval valve. (F) Fluoroscopy image showing the 30.5 mm Myval valve opened properly and symmetrically.

follow-ups performed at 1, 3, and 6 months, the patient remained in New York Heart Association (NYHA) functional class I, with a stable mean mitral diastolic gradient of 5 mmHg, a significant reduction in pulmonary artery systolic pressure, and no evidence of LVOT obstruction.

Discussion

Mitral annular calcification presents a particularly challenging clinical scenario in patients with mitral valve disease, especially when stenosis and regurgitation coexist. Conventional surgical mitral valve replacement (MVR) in the presence of extensive MAC is associated with increased perioperative morbidity and mortality due to technical difficulties such as annular debridement, risk of atrioventricular disruption, and challenges in prosthesis anchoring.[1,2] As a result, high-risk or inoperable patients with severe MAC have historically had limited treatment options.[1,2]

Transcatheter mitral valve replacement in MAC ("valve-in-MAC") has emerged as a less invasive alternative for this high-risk group. However, the procedure itself remains technically complex, with unique risks such as left ventricular outflow tract obstruction, valve embolization, and paravalvular leak. Careful pre-procedural imaging is essential to assess annular dimensions, calcification severity, aorto-mitral angle, and predicted neo-LVOT area.[1–4] In our patient, despite septal bulging and an acute aorto-mitral angle (36.2°) suggesting increased LVOT obstruction risk, the neo-LVOT area was above critical thresholds, suggesting safe device implantation. Thus, we proceeded with MAC without using the LAMPOON (Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN) or BATMAN (Balloon Assisted Translocation of the Mitral Anterior leaflet) techniques, which have been proposed as a preventive strategies in anatomies with high LVOT obstruction risk.[9–11]

Most previously reported valve-in-MAC procedures have used the Edwards Sapien 3 system.[1,2,12] One of the key challenges of TMVR with the Edwards Sapien 3 system is the inability to retrieve the valve into the sheath when it cannot be advanced through the native valve or a previously stiffened interatrial septum despite adequate balloon dilatation. In such cases, the entire assembly—including the sheath and valve—must be removed from the body and cannot be reimplanted.[5,6] In contrast, with the novel Myval THV system, if the valve cannot be advanced through the interatrial septum, it can be safely withdrawn into the 14F Python sheath, removed from the body, recrimped, and reimplanted.[5,6] Another disadvantage of the Edwards system is its limited ability

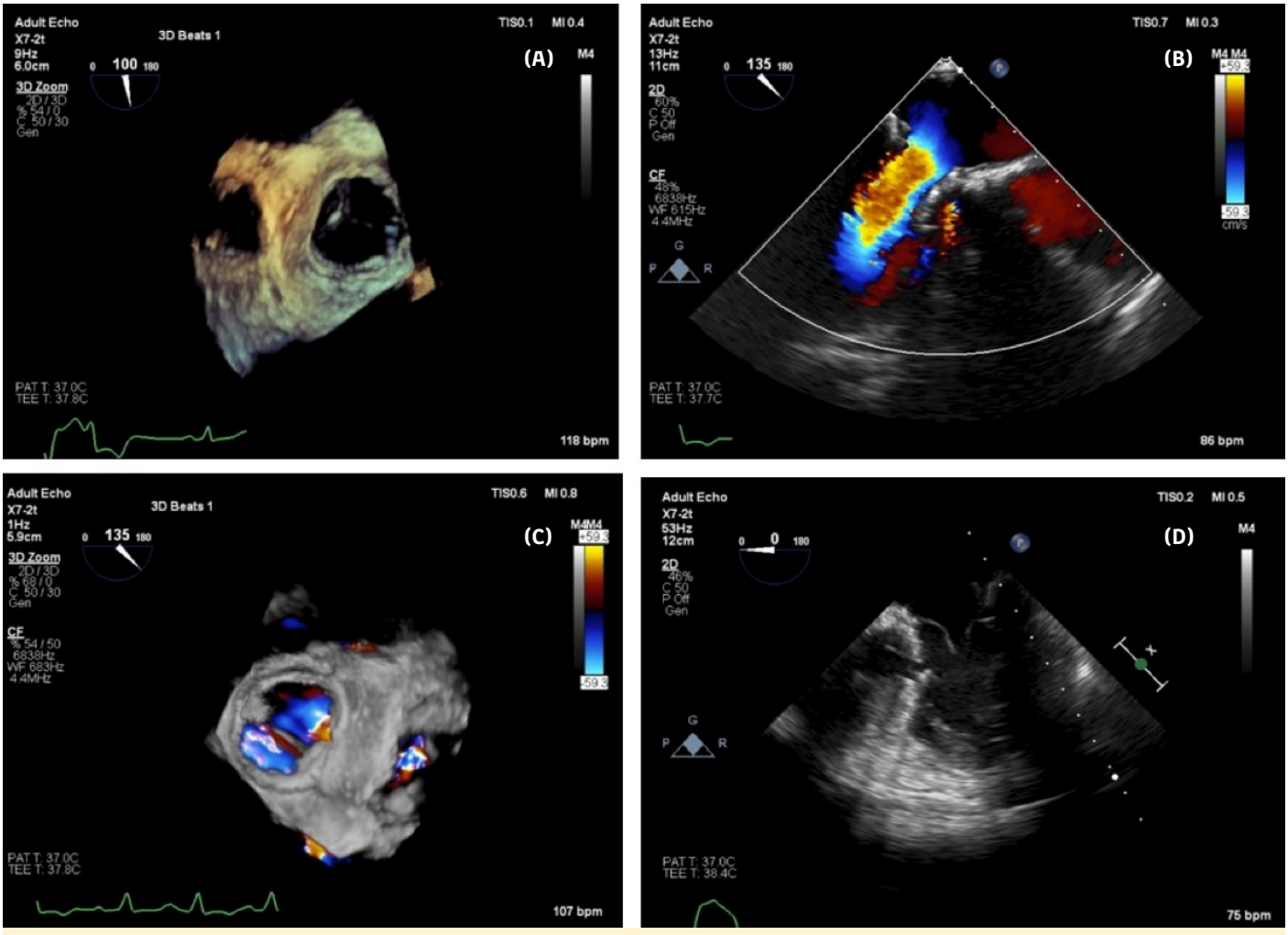

Figure 4. (A) Three-dimensional (3D) transesophageal echocardiography (TEE) image showing a well-functioning 30.5 mm Myval valve. (B) Color Doppler two-dimensional (2D) TEE image showing no paravalvular leak. (C) Color Doppler three-dimensional TEE image showing no paravalvular leak. (D) Two-dimensional TEE image showing a well-functioning 30.5 Myval valve.

to accommodate large annuli without overfilling, which may increase the risk of paravalvular leak and valve embolization.[5] In comparison with the Edwards Sapien 3 system's largest 29-mm prosthesis, the Myval THV provides extra-large options (30.5 mm and 32 mm), which may improve annular fit and reduce procedural risks of valve-in-MAC cases. In our patient, implantation of a 30.5 mm prosthesis successfully demonstrated the feasibility of the Myval THV system in anatomically complex settings with a large annulus.

In this case, we used a planned buddy guidewire technique to improve device stability during deployment. Crossing the interatrial septum (IAS) with a balloon-expandable THV may fail despite preparatory balloon septostomy. The use of a planned buddy guidewire placed in the left ventricle can facilitate crossing of the IAS and positioning of the mitral bioprosthesis.[8] We believe that this approach may facilitate the majority of TMVR and valve-in-MAC procedures.

Approximately 30%–40% of patients with severe MAC may be anatomically suitable for TMVR.[12,13] Despite this, the steep learning curve and risk of complications such as LVOT obstruction, valve migration, paravalvular leak, and valve thrombosis highlight the necessity of a multidisciplinary heart team approach. Our experience reinforces the value of collaborative decision-making, comprehensive imaging assessment, procedural planning, and the use of a novel Myval THV for successful outcomes during TMVR.

Conclusion

To the best of our knowledge, this report represents the first valve-in-MAC case in Türkiye using the Myval THV, contributing to the growing global experience. This case also highlights the successful application of a novel balloon-expandable Myval THV in a valve-in-MAC procedure, with favorable results achieved through meticulous imaging, accurate valve sizing, and the use of advanced procedural strategies. Further studies are required to confirm midterm and long-term results.

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

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

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

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Repeated Transcatheter Edge-to-Edge Repair Procedure of the Tricuspid Valve in a Patient with Mitral Valve Replacement

Mitral Kapak Replasmanlı Bir Hastada Triküspit Kapağın Tekrarlanan Transkateter Uçtan Uca Onarım Prosedürü

ABSTRACT

Tricuspid regurgitation (TR) is associated with poor prognosis and increased morbidity, especially in patients with high surgical risk and limited treatment options. We present the case of a 70-year-old male with a history of mitral valve replacement and prior tricuspid valve transcatheter edge-to-edge repair (TV-TEER), who underwent a successful redo TV-TEER due to torrential TR. Post-procedural evaluation revealed a significant reduction in TR severity and clinical improvement. Unfortunately, the patient succumbed to infectious complications and sepsis in the third week of follow-up. Due to the limited data on redo TV-TEER interventions, this case adds to the existing literature and suggests that redo TV-TEER may be a viable alternative to surgery in selected patients.

Keywords: Redo procedure, transcatheter edge-to-edge repair, tricuspid regurgitation

ÖZET

Triküspit yetmezliği (TR), kötü prognoz ve artmış morbidite ile ilişkili olup, yüksek cerrahi riske sahip hastalarda tedavi seçenekleri sınırlıdır. Bu olguda, mitral kapak replasmanı ve önceki triküspit kapak uç uca tamir TV-TEER öyküsü olan 70 yaşında erkek hastada, şiddetli TR nedeniyle redo triküspit kapak transkateter uç uca onarım başarıyla uygulanmış, işlem sonrası TR şiddeti azalmış ve klinik iyileşme sağlanmıştır. Ancak üçüncü haftada gelişen enfeksiyöz komplikasyonlar ve sepsis nedeniyle hasta kaybedilmiştir. Redo TV-TEER işlemlerine dair sınırlı veri bulunması bu olguyu literatürde özgün kılmakta olup, uygun hastalarda bu yöntem cerrahiye alternatif bir seçenek olarak değerlendirilebilir.

Anahtar Kelimeler: Redo işlem, transkateter uçtan uca onarım, triküspid yetersizliği

CASE REPORT
OLGU SUNUMU

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Tricuspid regurgitation (TR) is a common condition, with prevalence increasing with age.[1] Functional TR is the most frequent type, typically occurring in patients with left-sided valvular disease, pulmonary arterial hypertension, or atrial fibrillation (AF), in which annular dilation may develop independently.[1]

TR is associated with poor prognosis, with increased mortality and heart failure-related hospitalization. Surgical intervention is rarely performed in this population due to high comorbidity-related risk.[1] Despite advances in surgical techniques, valve repair, including annuloplasty for isolated TR, has not demonstrated a mortality benefit.[2] Interest in transcatheter approaches has grown for this high-risk group with controversial surgical outcomes. One such innovation, designed for severe TR management, is the TriClip system (Abbott, Chicago, IL, USA).[3] Recent studies indicate that transcatheter valve repair may surpass conventional methods.[4] Tricuspid valve transcatheter edge-to-edge repair (TV-TEER) reduces recurrent hospitalizations and improves quality of life in severe TR.[5] Advances in technology and access have increased both surgical and transcatheter interventions. Moreover, redo procedures are now considered when necessary.[6]

In our case, we highlight the feasibility and potential benefit of redo TV-TEER in a patient with prior mitral valve replacement and prior TV-TEER. Major studies on this topic excluded patients with previous tricuspid interventions, rendering our case particularly unique.[7]

Case Report

A 70-year-old male presented to our clinic with dyspnea, lower extremity edema, and abdominal distension. He had been hospitalized three times in the past six months. Twenty-five years earlier, he had undergone mitral valve replacement for primary valvular pathology. Three years earlier, he underwent TV-TEER for severe secondary TR. One XTW clip had been previously implanted between the septal and posterior leaflets, and another between the septal and anterior leaflets. TR decreased from massive to moderate severity. During the three-year follow-up period, his symptoms regressed and he remained hospitalization-free until the last six months. Congestion was managed with diuretics. In addition to known valvular heart disease, the patient had a history of AF and chronic obstructive pulmonary disease (COPD).

On admission, vital signs were stable. Physical examination revealed marked ascites and grade +3 pretibial edema in both legs. The patient's functional status was classified as New York Heart Association (NYHA) class IV. Electrocardiography demonstrated AF with a ventricular rate of 113 bpm. Transthoracic echocardiography demonstrated a left ventricular ejection fraction (LVEF) of 45%, a normofunctional mechanical mitral valve (gradient 10/5 mmHg), torrential TR, pulmonary artery systolic pressure (PASP) of 65 mmHg, right ventricular ejection fraction (RVEF) of 35%, tricuspid annular plane systolic excursion (TAPSE) of 2 cm, and right ventricular systolic tissue Doppler wave (Sm) of 10 cm/s.

The patient's medications included warfarin 5 mg once daily, sacubitril/valsartan 24/26 mg twice daily, carvedilol 6.25 mg twice daily, spironolactone 25 mg once daily, dapagliflozin 10 mg once daily, furosemide 40 mg three times daily, and inhaled ipratropium bromide plus levalbuterol 20/50 mcg. Blood tests revealed elevated creatinine, low hemoglobin levels, and raised acute phase reactants. International normalized ratio (INR) and liver function tests were within normal limits (Table 1).

The patient was admitted to the intensive care unit, where heart failure therapy was optimized and intravenous furosemide infusion initiated. Paracentesis and pleurocentesis were performed for third-space fluid management, and empirical antibiotic therapy was started per infectious disease team recommendations. Paracentesis fluid was transudative. TR progression over three years was attributed to annular dilatation secondary to chronic right ventricular volume overload from longstanding AF, along with progression of COPD and renal dysfunction. The patient had high surgical risk (European System for Cardiac Operative Risk Evaluation [EuroSCORE]: 49.48%). The Tricuspid Regurgitation Impact (TRI) score, used to estimate mortality risk after tricuspid valve surgery, was 9, indicating a 65% surgical mortality risk.

After transesophageal echocardiography (TEE) evaluation and in light of recurrent, prolonged hospitalizations despite high-dose diuretics, redo TV-TEER was performed for torrential TR (Figure 1). Two XTW clips were sequentially deployed between the septal-posterior and septal-anterior leaflets (Figure 2). Post-procedural echocardiography demonstrated a significant reduction in TR from torrential to severe. Vital signs remained stable. Over three weeks of follow-up, clinical improvement was observed, with decreased creatinine levels (Table 1). Congestion regressed, and the need for diuretics decreased to intravenous furosemide 20 mg twice daily.

ABBREVIATIONS

AF	Atrial fibrillation
CABG	Coronary artery bypass grafting
COPD	Chronic obstructive pulmonary disease
INR	International normalized ratio
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire–Overall Summary
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PASP	Pulmonary artery systolic pressure
RV	Right ventricular
RVEF	Right ventricular ejection fraction
STS	the Society of Thoracic Surgeons
TAPSE	Tricuspid annular plane systolic excursion
TEE	Transesophageal echocardiography
TR	Tricuspid regurgitation
TRI	Tricuspid Regurgitation Impact
TTVR	Transcatheter tricuspid valve replacement
TV-TEER	Tricuspid valve transcatheter edge-to-edge repair

In the second week, an increase in acute phase reactants and clinical deterioration prompted repeated blood cultures, which were positive for *Klebsiella pneumoniae*. The respiratory panel detected Coronavirus HKU1. The patient was treated with vancomycin, meropenem, polymyxin, and caspofungin. In the third week, liver function worsened and thrombocytopenia developed; hematology consultation attributed this to infection-related thrombocytopenia. The patient's condition deteriorated further, with impaired oral intake and hemodynamic instability. Despite inotropic support and appropriate antibiotic therapy, he developed cardiac arrest and was declared deceased after resuscitation attempts failed.

Discussion

TR is a common condition historically managed with diuretics or surgery and is associated with poor prognosis.[1] Repeat surgery for symptomatic TR in patients with prior coronary artery bypass grafting (CABG) or mitral valve surgery carries high risk.[2] Dreyfus et al.[8] reported that isolated tricuspid valve surgery was associated with high mortality rates. Standard risk scores, including the Society of Thoracic Surgeons (STS) and EuroSCORE/EuroSCORE II, are not designed for TV surgery, emphasizing the need for dedicated models. Dreyfus et al.[9] introduced the TRI-SCORE, comprising eight variables, with ≥ 6 indicating high surgical risk. Accurate TRI-SCORE assessment is essential for outcome optimization in TV surgery patients; in our case, scoring models indicated high risk.

The safety and efficacy of the TriClip procedure have been demonstrated in several studies. The TRILUMINATE trial (Tricuspid Regurgitation Repair with Transcatheter Edge-to-Edge Valve Repair Study) was a prospective, single-arm study involving 85 patients from 21 centers in the US and Europe.[7] Patients with severe pulmonary hypertension, LVEF < 20%, or prior TV procedures

Table 1. Laboratory findings at baseline and during follow-up

Parameter	Day 0	Week 1	Week 2	Week 3
WBC (10^3/μL)	8.23	8.56	7.56	14.99
Hemoglobin (g/dL)	8.3	9.8	9.4	9.7
Platelets (10^3/μL)	251	138	109	16
INR	3.65	2.9	3.19	3.05
Creatinine (mg/dL)	1.64	1.1	1.33	1.17
Sodium (mmol/L)	140	139	134	150
Potassium (mmol/L)	5.5	3.3	4.0	4.8
ALT (U/L)	15	15	10	1073
AST (U/L)	48	34	35	4000
Albumin (g/L)	19.8	24.5	23.3	22.3
Iron (mg/dL)	34	—	—	—
Total iron binding capacity (mg/dL)	80	—	—	—
Total bilirubin (mg/dL)	0.66	1.24	1.13	8.6
Direct bilirubin (mg/dL)	0.34	0.46	0.52	5.45
CRP (mg/L)	90	52	101	105
hs-Troponin	Negative	—	—	—
Microbiology	Blood culture: negative Respiratory panel: negative	—	Blood culture: *Klebsiella pneumoniae* Respiratory panel: Coronavirus HKU1	—

WBC, White blood cell; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein.

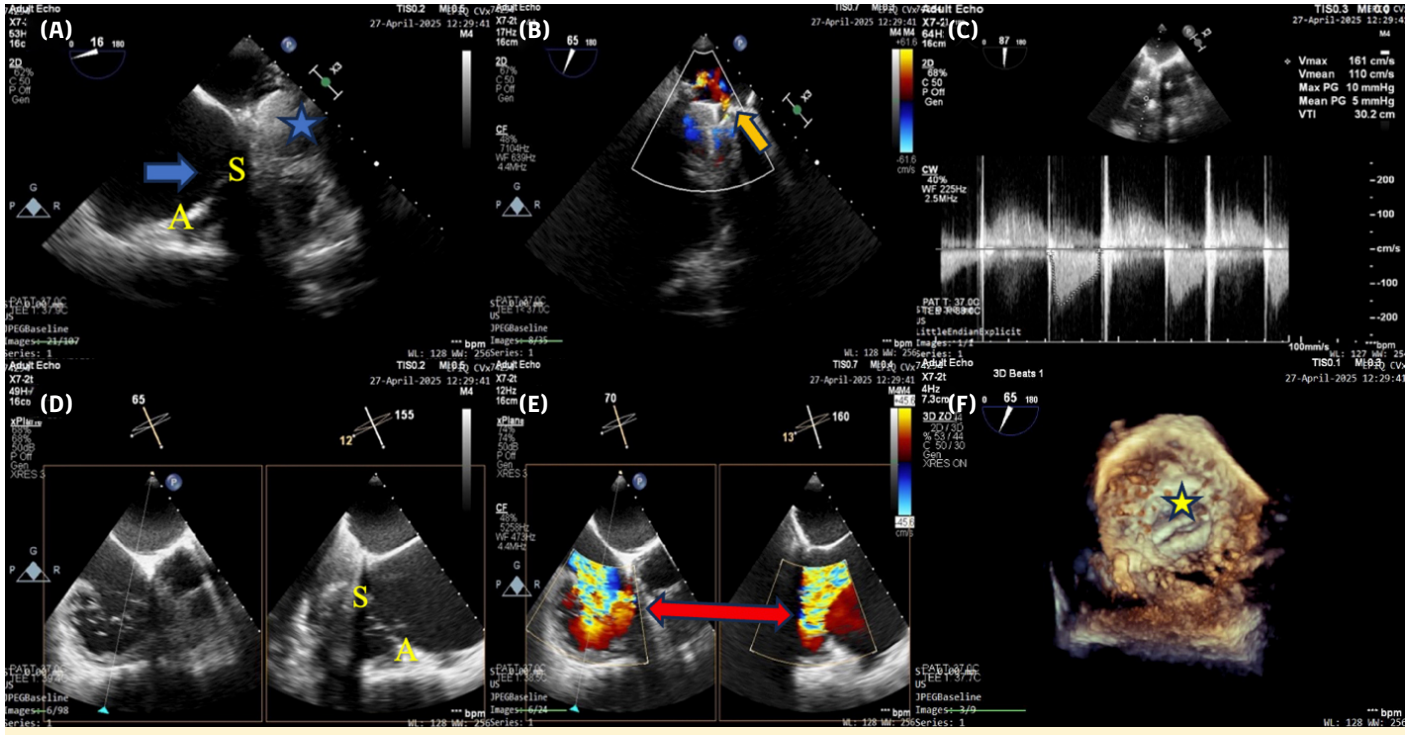

Figure 1. Pre-procedural transesophageal echocardiographic (TEE) images: (A) Mid-esophageal four-chamber view at 16° showing the mechanical mitral valve replacement (MVR) (blue star) and tricuspid valve leaflets (blue arrow; A: anterior leaflet, S: septal leaflet); (B) Mild paravalvular leak observed on MVR assessment (orange arrow); (C) MVR gradient measurement with a maximum/mean peak gradient of 10/5 mmHg; (D) X-plane view in the mid-esophageal right ventricular inflow-outflow window showing anterior (A), posterior, and septal (S) leaflets of the tricuspid valve; (E) Color Doppler imaging in the right ventricular inflow-outflow view demonstrating torrential tricuspid regurgitation (double-headed red arrow), with a vena contracta (VC) ≥ 21 mm; (F) 3D TEE view of the MVR (yellow star).

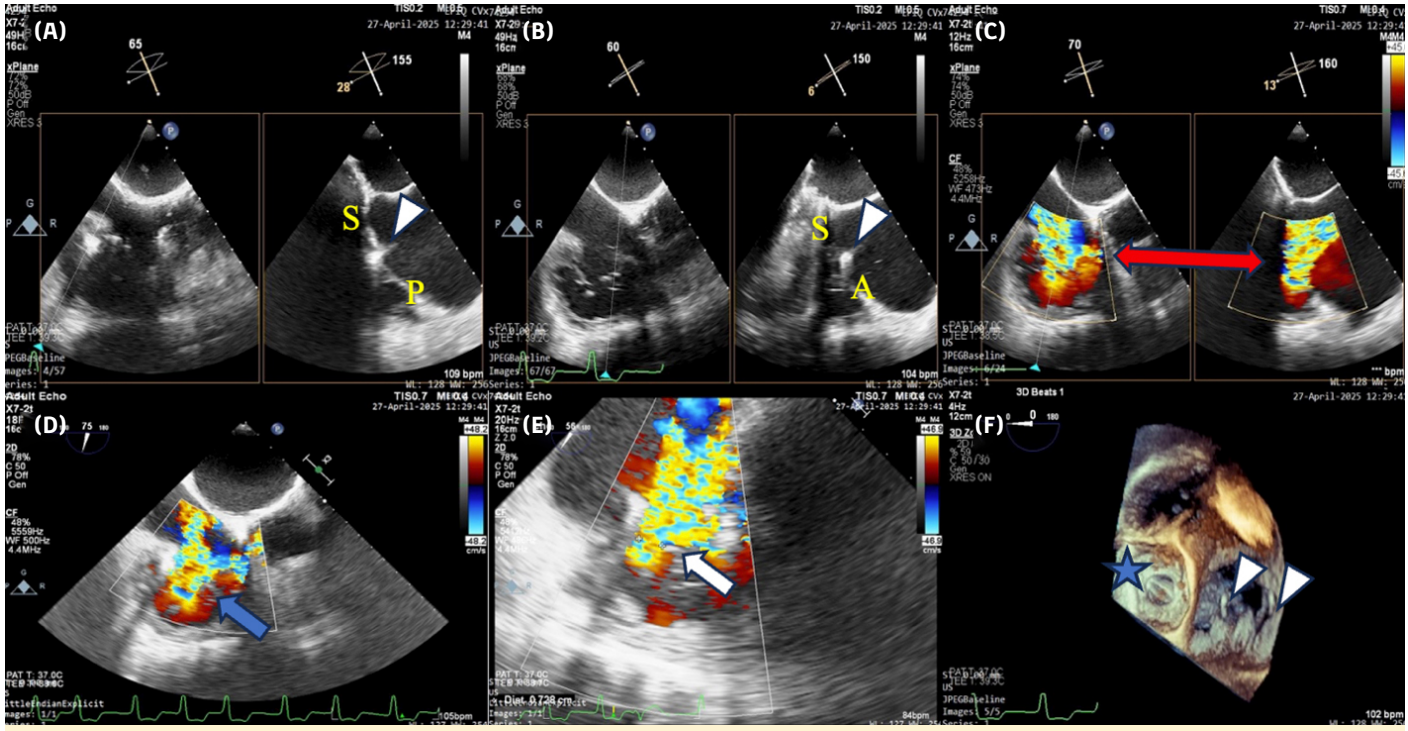

Figure 2. Intraprocedural and post-procedural transesophageal echocardiography (TEE) images: (A) X-plane view in the mid-esophageal right ventricular inflow-outflow window showing successful grasping of the septal (S) and posterior (P) leaflets of the tricuspid valve with a clip (white arrowhead); (B) X-plane view demonstrating grasping of the septal (S) and anterior (A) leaflets with a clip (white arrowhead); (C) Pre-procedural color Doppler imaging in the same view showing torrential tricuspid regurgitation (red arrow), with a vena contracta (VC) ≥ 21 mm; (D) Post-deployment of the first clip between the posterior and septal leaflets, a reduction in the regurgitant jet is observed (blue arrow, VC: 11 mm); (E) Following placement of a second clip between the prior clip and the septal-posterior leaflets, a further decrease in vena contracta is evident on color Doppler (white arrow, VC: 7 mm); (F) 3D TEE image showing the mechanical mitral valve replacement (MVR) (blue star) and implanted clips (white arrowheads).

were excluded. Of these patients, 75% were NYHA class III–IV, and 33% had a history of cardiac surgery. Procedural success (clip implantation) was 100%. At 30 days, 86.6% of patients showed ≥ 1-grade TR reduction. Echocardiographic assessments showed improved regurgitant volume, annular diameter, mean gradient, and cardiac output. Furthermore, 80% of patients were NYHA class I–II at 30 days. No deaths, myocardial infarctions, or strokes were reported, and no cases required conversion to open surgery. At two years, 85.4% of patients maintained at least a one-grade reduction in TR, and hospitalizations decreased by 49%. Quality-of-life improvements, measured by the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), were sustained over this period.[7]

Another important study by Polat et al.[10] evaluated 42 patients with symptomatic secondary TR (57.1% massive, 42.9% torrential, mean age 70.7 ± 14.0 years, 73.8% female). Exclusions included rheumatic valve disease, coaptation defect ≥ 10 mm, severe right ventricular (RV) dilation/dysfunction, PASP > 65 mmHg, pulmonary vascular resistance > 4 WU, or lead-induced TR. All patients were high surgical risk (EuroSCORE II, TRI-SCORE). The TriClip system was used in 69% of patients and MitraClip in 31%. Post-procedural TR severity was mild–moderate in 88.1% of patients, and only 11.9% had persistent severe TR. Within the first month, functional status improved (four patients remained in NYHA class III, while 28 improved to class II and eight to class I), with no significant change in hospital readmission rates.[10]

The need for a contemporary grading system to allow for a more objective and treatment-guiding assessment of TR has led to the introduction of a new classification that expands the severity scale to include the categories "massive" and "torrential." According to this scheme, TR is classified as mild, moderate, severe, massive, or torrential.[11]

Although TEER is a promising technique, it presents certain challenges, including the potential need for repeat procedures. Residual or recurrent TR is observed in approximately 14% of patients within the first month following all types of tricuspid annuloplasty. In annuloplasty using the De Vega technique, significant late worsening of TR has been reported in up to 30% of patients, likely due to gradual re-dilatation of the annulus.[12] In a case report published by Afzal et al.,[13] successful TEER was performed in a patient with a history of surgical tricuspid annuloplasty, resulting in a reduction of massive TR to mild. In our case, a history of prior surgical intervention on the TV did not constitute a barrier to performing TEER. Although the authors expressed concerns regarding the potential development of tricuspid stenosis, no post-procedural stenosis was observed. Consistent with the literature, the recurrence of torrential TR within three years after the initial TV-TEER in our patient was attributable to re-dilatation of the annulus. Furthermore, the feasibility of TV-TEER following annuloplasty in our case was encouraging.

Toggweiler et al.[14] reported the use of transcatheter tricuspid valve replacement (TTVR) with the EVOQUE valve in cases of severe TR following initially unsuccessful TV-TEER. In these cases, TR recurred after a transient improvement. Similarly, Ozdemir et al.[15] described TTVR in a patient with recurrent severe TR following prior TV-TEER. In our case, consistent with the literature, TR recurred, highlighting the need for alternative treatment strategies in the absence of a standardized approach. Our experience supports the consideration of redo TV-TEER, in addition to TTVR, as a viable therapeutic option in such complex scenarios.

Before considering redo TEER in patients with prior tricuspid annuloplasty or TV-TEER, several important factors should be taken into account. First, the underlying mechanism of recurrent TR must be understood, and the likelihood of successfully treating the regurgitation should be evaluated. In patients who previously underwent suture-based annuloplasty, annular re-dilatation, leaflet tethering, or suture loosening can often be effectively addressed with TV-TEER, whereas a tissue tear near the annuloplasty ring or ring dehiscence may be difficult or even impossible to treat percutaneously. The potential for worsening tricuspid stenosis following device deployment in a repeat TEER procedure should also be considered. Therefore, assessment of the transvalvular tricuspid valve gradient before and during the procedure is mandatory.[13]

According to the current literature, redo TV-TEER is feasible in patients with RVEF > 30%, coaptation gap < 7–8 mm, and no severe leaflet tethering, provided annular dilation is not excessive, though comprehensive clinical and imaging evaluation is needed.[10,13] Our patient presented with both a history of prior valve interventions and impaired right ventricular function (RVEF 35%, unexpectedly preserved TAPSE 2 cm, RV Sm 10 cm/s), in addition to pulmonary hypertension (PASP 65 mmHg), thus meeting exclusion criteria in most existing studies. This highlights the encouraging nature of the case and underscores the difficulty of defining clear procedural boundaries in light of current evidence.

TRILUMINATE's long-term results demonstrated sustained TR reduction in 85.4% of patients and a 49% reduction in hospitalizations over two years, highlighting the durability of the TriClip approach. Among the 84 patients followed, four (5%) died, with only one death considered possibly device-related.[7] In Polat et al.'s study,[10] 3 of 42 patients (7.1%) died—2 from heart failure and one from acute renal failure. In our case, TR reduction and improved cardiac output were maintained during the three-week follow-up period. Consistent with the literature, mortality in our case was unrelated to the procedure.

In our case, the TriClip system was used in a patient with NYHA class IV symptoms and torrential functional TR who had a high surgical risk profile. The patient also had AF and chronic kidney disease. Procedural success, defined as clip implantation and at least a one-grade TR reduction, was achieved without the need for emergency surgery. Notably, renal function improved significantly until the development of septic shock in the second week. Unlike the TRILUMINATE population, our patient had reduced LVEF, potentially increasing procedural risk and mortality.

Our case contributes to the growing body of evidence supporting TEER for tricuspid repair. The exclusion of patients with prior TV interventions from key studies further underscores the significance of this report. Although interest in TV-TEER has increased in recent years, the available studies remain limited in number, and key aspects such as procedural indications, predictors of procedural success, and anatomical eligibility criteria have not yet been standardized. There is a clear need for larger-scale studies in this field. Our case is particularly valuable in demonstrating procedural success in the context of the existing echocardiographic parameters. It offers valuable insights into the feasibility, safety, and outcomes of redo TV-TEER in high-risk patients with previous valve interventions.

Conclusion

In conclusion, this case contributes to the expanding body of evidence supporting TV-TEER as a feasible and effective alternative to conventional surgery, particularly in patients with limited treatment options and high surgical risks due to prior valve interventions. TV-TEER should therefore be considered a viable treatment option in carefully selected high-risk patients who are not suitable candidates for repeat surgery.

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

Informed Consent: Patient consent was obtained and is available upon request.

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

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Author Contributions: Concept – M.T., Z.K.; Design – Z.K.; Supervision – M.T., Y.K.; Resource – Y.K., İ.A.; Materials – Y.K.; Data Collection and/or Processing - M.T., İ.A.; Analysis and/or Interpretation - M.T., Z.K.; Literature Review – M.T.; Writing – M.T., Z.K.; Critical Review – Z.K., İ.A.

Peer-review: Externally peer-reviewed.

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Upgrade of a DF-1 Implantable Cardioverter Defibrillator Electrode with a Fractured Sensing-Pacing Cable for Left Bundle Branch Optimized Cardiac Resynchronization Therapy: A Practical Solution Without Lead Extraction

Kırık Algılama-Uyarım Kablosuna Sahip bir DF-1 İmplante Edilebilir Kardiyoverter Defibrilatör Elektrodunun Sol Dal Demeti Optimize Edilmiş Kardiyak Resenkronizasyon Tedavisine Yükseltilmesi: Elektrot Çıkarılmasına Gerek Kalmadan Pratik Çözüm

A 70-year-old male patient with a known history of hypertension, diabetes mellitus, and ischemic cardiomyopathy was admitted to another center after the alarm of an implantable cardioverter defibrillator (ICD) sounded. He had undergone right-sided ventricular demand pacing implantable cardioverter-defibrillator (VVI-ICD, DF-1) implantation five years earlier for primary prophylaxis, due to a skin lesion in the left pectoral region. On evaluation, there was high ventricular lead impedance, no ventricular capture during the threshold test, and a macrofracture of the electrode noted at the pacemaker pocket, as shown on chest X-ray (Figure 1). The patient was therefore referred to our institution. On admission, a 12-lead electrocardiogram (ECG) showed sinus rhythm with first-degree atrioventricular (AV) block (PR interval 360 ms) and intraventricular conduction delay (QRS duration 160 ms) (Figure 2). Transthoracic echocardiography revealed a left ventricular ejection fraction (LVEF) of 20%, akinesia of the septum and anterior wall, and moderate mitral and tricuspid regurgitation. ICD interrogation demonstrated that the DF-1 ICD electrode IS-1 cable impedance was greater than 3000 ohms, the shock impedance was normal, and no ventricular capture was observed with the IS-1 cable of the ICD lead. The arrhythmia logbook documented six non-sustained ventricular tachycardia episodes during the five-year follow-up. Thus, we planned a cardiac resynchronization therapy (CRT-D) upgrade procedure via left bundle branch area pacing (LBBaP) without extracting the existing DF-1 ICD lead. Venography revealed stenosis in the right subclavian vein, and venoplasty was performed using a 4.0 × 40 mm peripheral balloon. Despite left bundle branch (LBB) capture with an LBBaP lead (Solia S60, Biotronik) in the septum (R-wave sense amplitude: 10.2 mV), the V6 R-wave peak time was greater than 100 ms, so we switched to implanting an LBB-

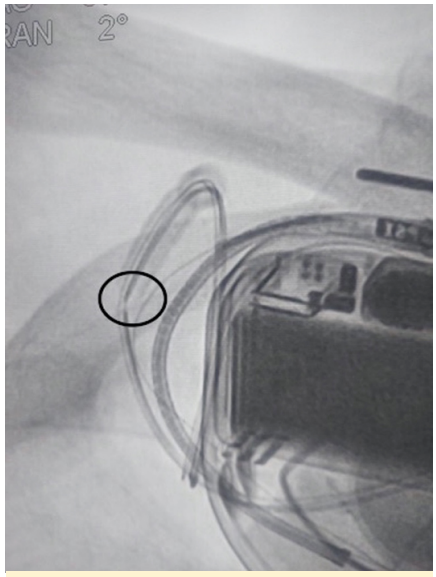

Figure 1. Macrofracture observed in the international standard-1 (IS-1) cable of the DF-1 connector implantable cardioverter-defibrillator (ICD) electrode.

CASE IMAGE
OLGU GÖRÜNTÜSÜ

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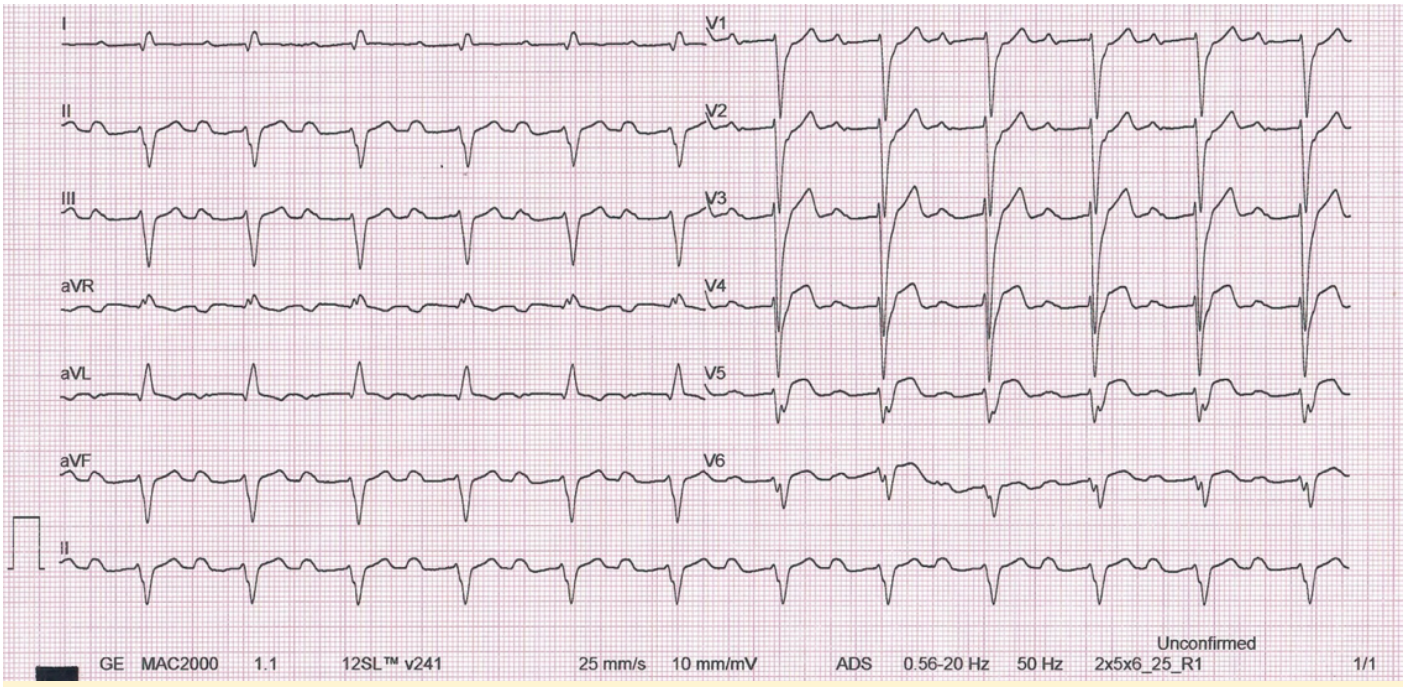

Figure 2. The 12-lead electrocardiogram (ECG) on admission.

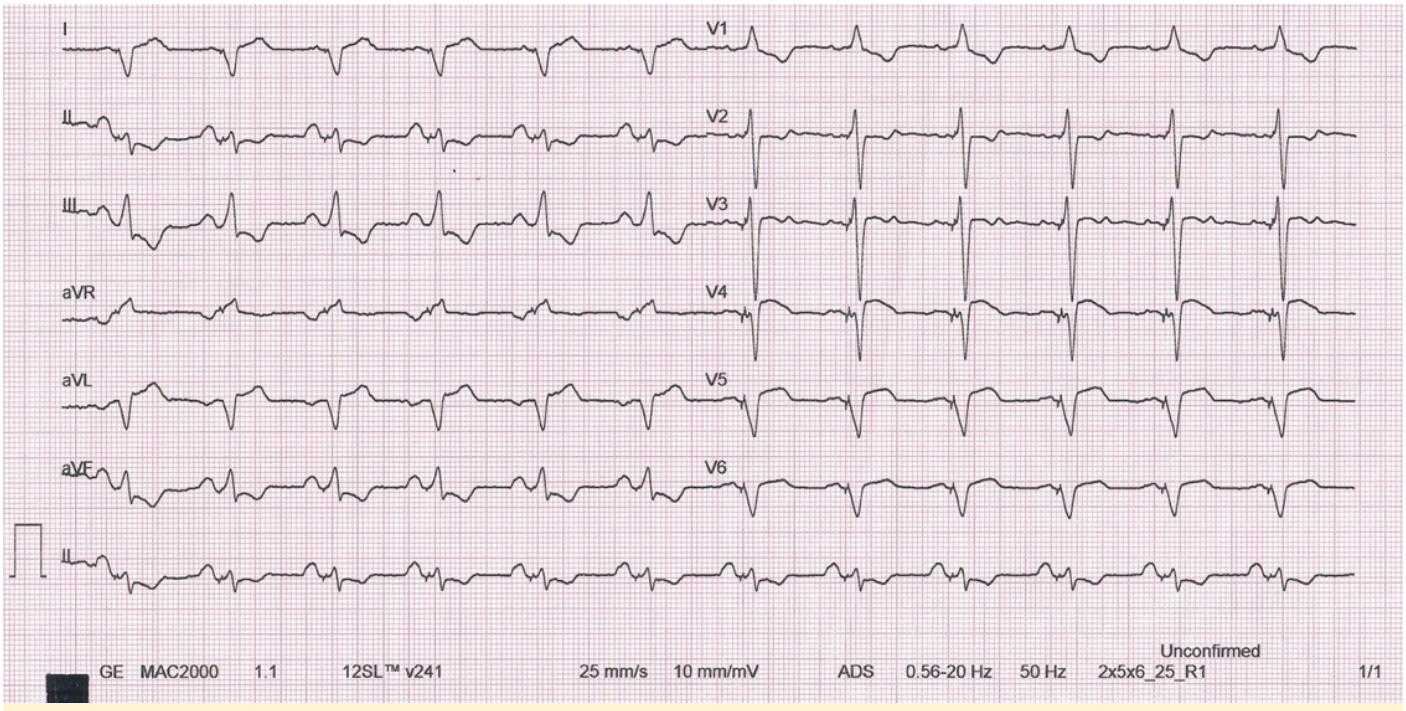

Figure 3. Final fluoroscopic image of the electrodes at the end of the left bundle branch-optimized cardiac resynchronization therapy defibrillator (LOT-CRT-D) upgrade procedure.

optimized CRT-D (LOT-CRT-D). An LV lead was placed into the lateral branch of the coronary sinus (qLV delay of 114 ms). The LBBaP lead was connected to the RV IS-1 port, and the coronary sinus lead was connected to the LV port of the DF-1 CRT-D battery (Figure 3). The fractured IS-1 cable of the DF-1 ICD lead was capped and placed in the pocket. The final ECG showed biventricular pacing with a QRS duration of 120 ms (Figure 4). For the safety of the abandoned ICD lead in the right pectoral region, a successful defibrillation test was performed. In addition, a skin biopsy for a malignant-looking lesion in the left pectoral region revealed basal cell carcinoma, and local excision with flap conversion by plastic surgery was performed one month later. The patient remained stable, and the electrical parameters were within normal limits at the 6- and 12-month follow-up visits.

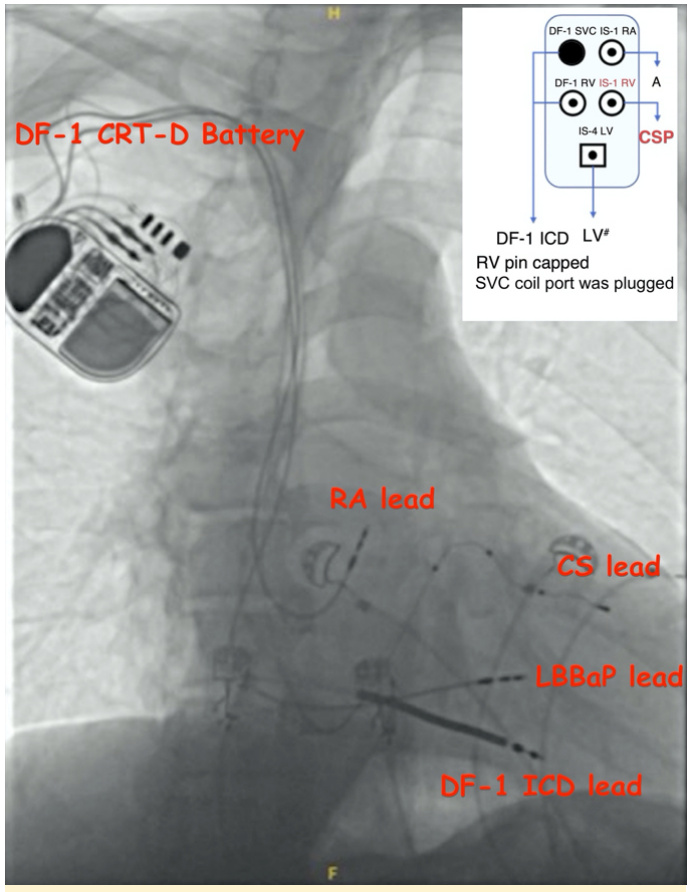

Figure 4. The 12-lead electrocardiogram (ECG) after the left bundle branch-optimized cardiac resynchronization therapy defibrillator (LOT-CRT-D) procedure.

With a DF-1 ICD connector, the addition of a separate pace-sense lead (a septal lead for LBBaP), along with abandonment of the IS-1 portion of the ICD lead, resolved the problem in this patient. This approach is an inexpensive, practical, and effective solution that avoids both extraction of the old ICD lead and the need for a second ICD lead.

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

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

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

Funding: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: Authors declare that this case image did not utilize AI-assisted technologies.

Author Contributions: Concept – S.C.K., U.C., A.H.A.; Design – S.C.K., U.C., S.Z., A.H.A.; Supervision – U.C., A.H.A., K.A.; Resource – U.C., A.H.A.; Data Collection and/or Processing – S.C.K., U.C., S.Z., A.H.A., K.A.; Analysis and/or Interpretation – S.C.K., U.C., S.Z., A.H.A., K.A.; Literature Review – S.C.K., U.C., S.Z., A.H.A., K.A.; Writing – S.C.K., U.C., S.Z., A.H.A.; Critical Review – S.C.K., U.C., S.Z., A.H.A., K.A.

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A Dual Catastrophe: Implantable Cardioverter-Defibrillator Lead Perforation Resulting in Right Ventricular Rupture and Pneumothorax

Çifte Felaket: ICD Elektrot Perforasyonuna Bağlı Sağ Ventrikül Rüptürü ve Pnömotoraks

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 64-year-old man with a history of nonischemic cardiomyopathy (ejection fraction: 20%) underwent implantation of an implantable cardioverter-defibrillator (ICD) three months earlier and presented to the emergency department with a three-day history of left-sided sharp chest pain. The pain was non-radiating and was not aggravated by inspiration. He denied shortness of breath or cough. Electrocardiography revealed normal sinus rhythm without ischemic changes (Supplementary Figure 1). His arterial blood pressure was 140/83 mmHg, heart rate was 73 beats per minute, and oxygen saturation was 96% on room air. High-sensitivity cardiac troponin T was 10.4 ng/L (n < 14 ng/L). Chest radiography demonstrated a left-sided basal pneumothorax and an abnormal position of the ICD lead. The lead tip was nearly in contact with the left lung (Figure 1A). Transthoracic echocardiography (TTE) revealed a small pericardial effusion surrounding the right ventricle (RV) (4 mm measured at end-diastole) without evidence of tamponade. ICD interrogation demonstrated loss of ventricular sensing and

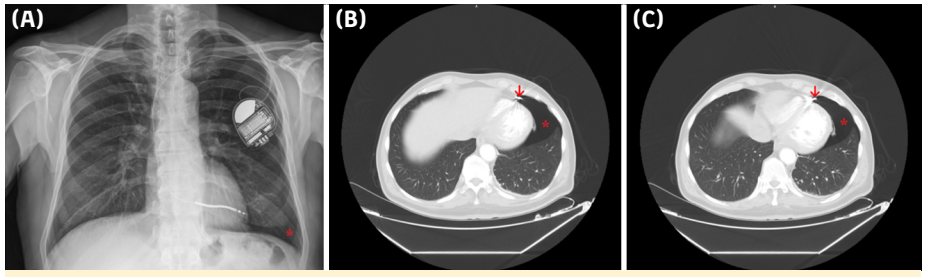

Figure 1. (A) Anteroposterior chest X-ray obtained at admission demonstrating a left-sided basal pneumothorax (red asterisk) and abnormal positioning of the implantable cardioverter-defibrillator (ICD) lead, with the lead tip nearly in contact with the left lung. (B, C) Chest computed tomography images demonstrating a left-sided pneumothorax (red asterisks) and a transvenous ICD lead (red arrows) that had perforated the apex of the right ventricle (RV) and migrated into the left pleural cavity.

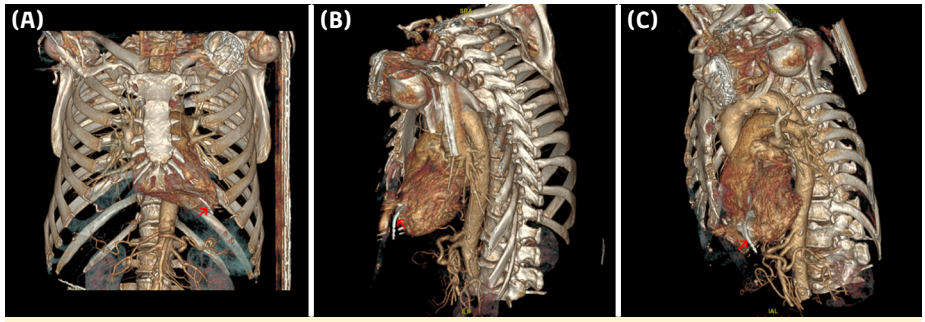

Figure 2. Three-dimensional volume-rendered computed tomography images (A–C) showing the implantable cardioverter-defibrillator (ICD) lead (red arrows) perforating the right ventricular apex.

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pacing, with markedly increased lead impedance (> 3000 Ω). A retrospective review of routine ICD interrogation performed one month earlier showed normal sensing, pacing, and impedance values. Computed tomography (CT) of the chest confirmed a left-sided pneumothorax. Additionally, the transvenous ICD lead had perforated the RV apex and migrated beyond the RV into the left pleural cavity (Figures 1B, C, 2). No history of trauma or other apparent precipitating factor was identified. An anteroposterior chest radiograph obtained three months earlier showed the ICD lead appropriately positioned at the RV apex (Supplementary Figure 2). The patient's condition was discussed with both the cardiac surgery and respiratory teams. Percutaneous ICD lead extraction under fluoroscopic and TTE guidance, with surgical backup available, was planned. A chest tube was inserted into the left chest to treat the pneumothorax. After informed consent was obtained, the patient was transferred to the hybrid catheterization laboratory, where successful percutaneous ICD lead extraction was performed. The active-fixation mechanism was retracted, and the lead was carefully withdrawn (Figure 3, Video 1). Serial TTE examinations demonstrated no significant increase in pericardial effusion (Supplementary Figure 3). The patient remained hemodynamically stable throughout the procedure. A new active-fixation lead was subsequently implanted in the lower interventricular septum. The remainder of the hospital course was uneventful. The chest tube was removed after four days, and the patient was discharged seven days later.

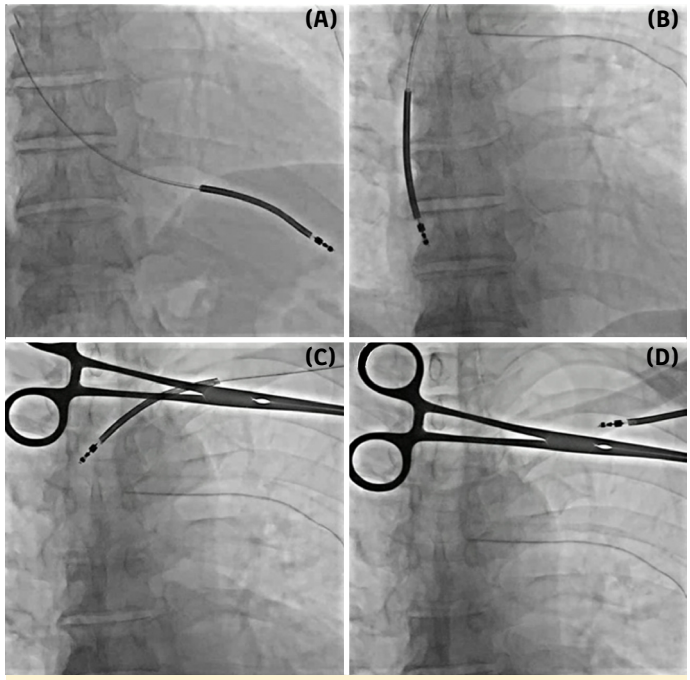

Figure 3. Fluoroscopic images (A–D) demonstrating successful percutaneous implantable cardioverter-defibrillator (ICD) lead extraction in the hybrid catheterization laboratory.

Lead perforation is an uncommon but potentially serious complication of cardiac implantable electronic devices. This case represents a rare and advanced presentation in which delayed RV lead perforation progressed to RV rupture, with extension into the pleural cavity resulting in pneumothorax. The underlying mechanism is likely multifactorial. Active-fixation leads may exert continuous focal stress on the myocardium, particularly at the thin-walled RV apex, predisposing to gradual penetration. Furthermore, delayed perforation has been associated with progressive myocardial remodeling, local inflammation, and fibrotic changes that may weaken tissue integrity over time. Several risk factors for lead perforation have been identified, including advanced age (> 80 years), female sex, active-fixation/screw-in leads, smaller lead diameter (5.7 French), stiffer insulation materials (silicone-polyurethane copolymer), and lead placement in thinner myocardial regions such as the right atrial appendage or RV apex. In contrast, septal positioning appears to be associated with a lower risk of perforation. In the present case, both the active-fixation lead design and apical placement likely contributed to the development of delayed perforation. The absence of significant pericardial effusion or tamponade suggests a gradual perforation process with decompression into the pleural space, thereby explaining the coexistence of pneumothorax without hemodynamic compromise and potentially masking the severity of the condition.

Clinically, lead perforation may present with nonspecific symptoms, while electrocardiographic (ECG) findings and cardiac biomarker levels may remain within normal limits, making the diagnosis easy to overlook. Therefore, a high index of suspicion is essential. Imaging, particularly CT, together with device interrogation, plays a critical role in establishing the diagnosis. Although surgical management is generally preferred in cases involving cardiac rupture or injury to adjacent structures, this case demonstrates that percutaneous lead extraction may represent a safe and effective alternative in carefully selected, hemodynamically stable patients when performed under close monitoring and with immediate surgical backup available.

What distinguishes this case is the simultaneous occurrence of right ventricular rupture and pneumothorax in the absence of typical diagnostic clues, along with successful percutaneous management despite concomitant visceral injury. This report highlights the importance of recognizing delayed lead perforation as a dynamic process and emphasizes the need for thorough evaluation of unexplained chest pain in patients with cardiac implantable electronic devices.

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

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

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

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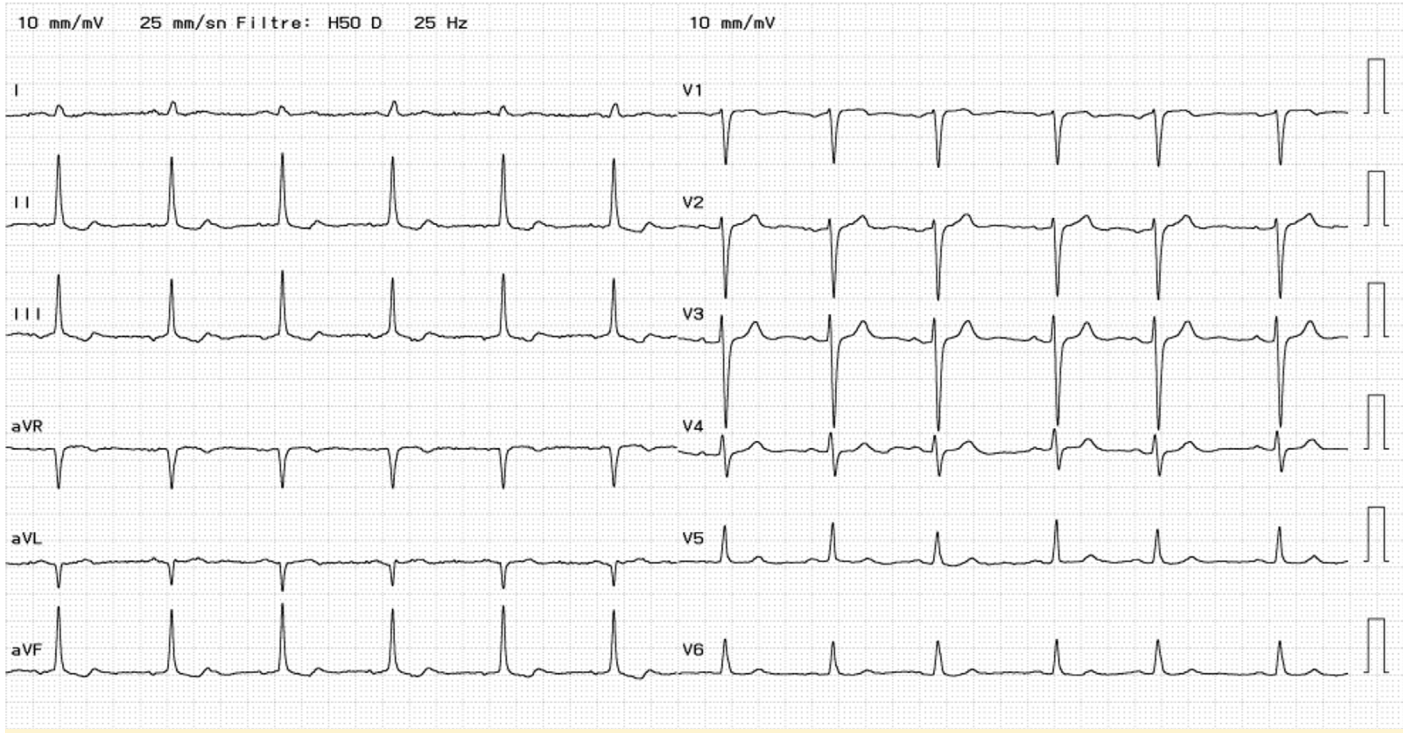
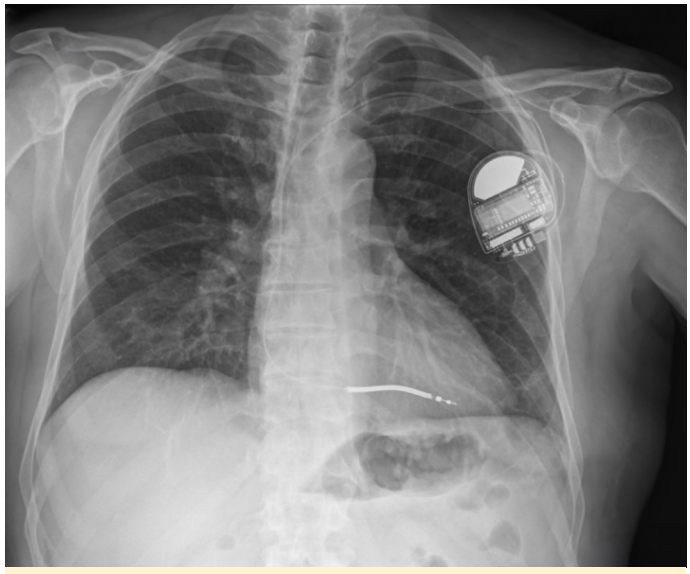
Author Contributions: Concept – Y.V.; Design – Y.V., E.K.; Supervision – Y.V., E.K.; Materials – O.Ş., M.Ç.B.; Data Collection and/or Processing – Y.V., O.Ş., M.Ç.B.; Literature Review – M.Ç.B., A.G.O.; Writing – Y.V.; Critical Review – Y.V., O.B.

Peer-review: Internally peer-reviewed.

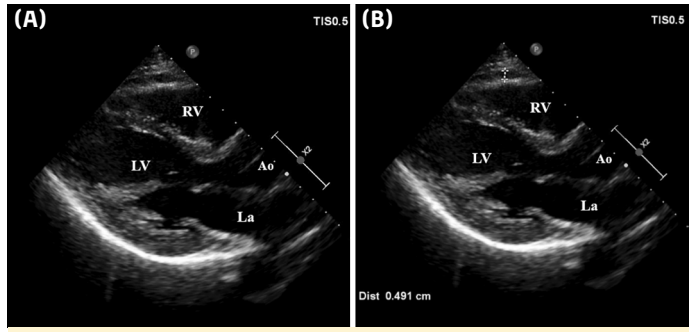
Video 1. Successful percutaneous implantable cardioverter-defibrillator (ICD) lead extraction procedure.



Supplementary Figure 1. Electrocardiogram obtained at admission demonstrating normal sinus rhythm without ischemic changes.



Supplementary Figure 2. Anteroposterior chest X-ray obtained three months earlier showing the implantable cardioverter-defibrillator (ICD) lead positioned at the right ventricular apex.



Supplementary Figure 3. Transthoracic echocardiographic images obtained after percutaneous implantable cardioverter-defibrillator (ICD) lead extraction from the parasternal long-axis view, demonstrating a small (~5 mm) pericardial effusion adjacent to the right ventricle (A, B).

LV, Left ventricle; LA, Left atrium; RV, Right ventricle; Ao, Aorta.

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Giant Right Atrial Appendage Aneurysm: An Unusual Cause of Right Ventricular Compression in a Retrovirus-Infected Patient

Dev Sağ Atriyal Apendiks Anevrizması: Retrovirüs Enfeksiyonu Olan Bir Hastada Sağ Ventrikül Sıkışmasının Nadir Görülen Bir Nedeni

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 39-year-old gentleman infected with human immunodeficiency virus (HIV) and receiving antiretroviral therapy for the last 13 years presented with nonspecific chest pain without features of right heart failure. His CD4 count was normal, and there were no opportunistic infections. Electrocardiography revealed an incomplete right bundle branch block. Echocardiographic evaluation demonstrated a large aneurysmal echolucent extension of the right atrial appendage causing compression of the right ventricle, without any hemodynamic effects (Figure 1A–C, Video 1). No other structural or functional cardiac abnormality was detected. Cardiac tomography confirmed the diagnosis of right atrial appendage aneurysm (RAAA) measuring 8.5 × 6.1 × 10.9 cm (Figure 1D–E, Video 2). Surgical repair was advised; however, the patient refused.

Retroviral infection is known to cause vascular aneurysms. Proposed mechanisms include weakening of the arterial wall due to the direct effects of HIV, immune

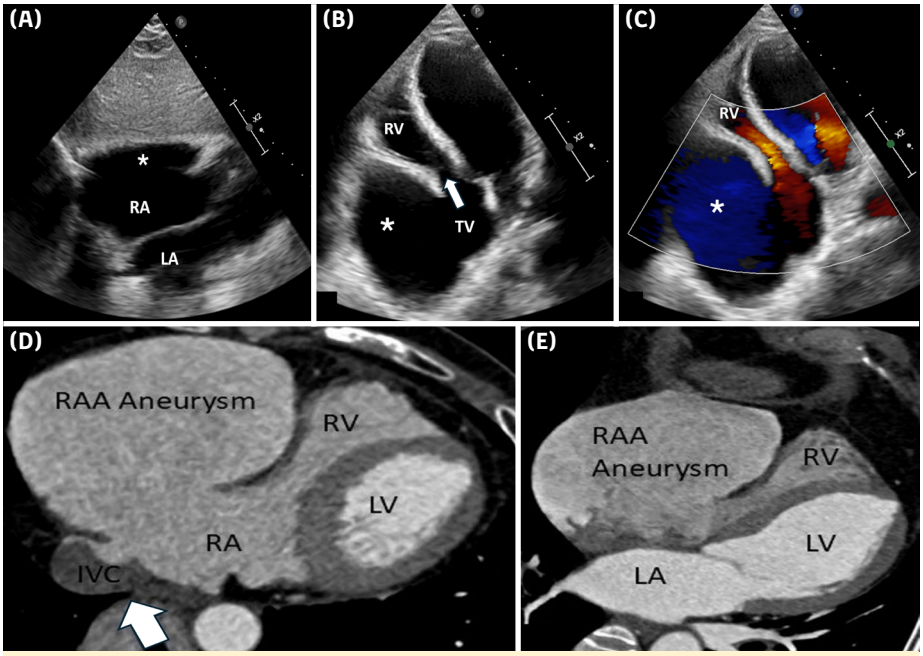

Figure 1. (A–C) Echocardiographic images of the aneurysm of the right atrial appendage (*) in the subcostal long-axis view (A) and apical four-chamber view without (B) and with (C) color Doppler. (D–E) Cardiac tomographic images corresponding to A and B. The aneurysm is seen compressing the right ventricle. The white arrow indicates the tricuspid valve in B and the inferior vena cava in D.

IVC, Inferior vena cava; LA, Left atrium; LV, Left ventricle; RA, Right atrium; RAA, Right atrial appendage aneurysm; RV, Right ventricle; TV, Tricuspid valve.

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complex formation, opportunistic infections, and antiretroviral therapy. Although it was difficult to establish HIV as the cause of the aneurysm in our case, its known pathophysiological role in vascular aneurysm formation suggests a possible etiological association. To the best of our knowledge, this is the first reported case of RAAA in an HIV-infected patient. Clinicians should remain vigilant for such abnormalities when performing echocardiography in these patients.

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

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

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

Funding: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: No use of AI-assisted technologies was declared by the authors.

Author Contributions: Concept – G.R.N., A.B., S.S.; Design – G.R.N., A.B.; Supervision – A.B.; Materials – G.R.N., A.B.; Data Collection and/or Processing - G.R.N., A.B., S.S.; Analysis and/or Interpretation - A.B., S.S.; Literature Review – G.R.N., A.B.; Writing – G.R.N., A.B., A.J.; Critical Review – G.R.N., A.B.

Peer-review: Internally peer-reviewed.

Video 1. 2D echocardiography in the apical four-chamber view demonstrating a large right atrial appendage aneurysm compressing the right ventricle.

Video 2. Cardiac tomographic axial section demonstrating a giant aneurysm arising from the right atrial appendage and compressing the right ventricle.

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High Discriminative Performance Without Clinical Readiness: Methodological Gaps in Machine Learning–Based Prediction of the No-Reflow Phenomenon in ST-Segment Elevation Myocardial Infarction

Klinik Kullanıma Hazır Olmadan Yüksek Ayırt Edici Performans: ST Segment Yükselmeli Miyokard İnfarktüsünde No-Reflow Fenomeninin Makine Öğrenmesine Dayalı Öngörüsündeki Metodolojik Eksiklikler

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

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To the Editor,

We read with great interest the study by Taşolar et al.,[1] a prospective, single-center, machine learning-based predictive study evaluating the performance of the Kolmogorov–Arnold Network (KAN) model in predicting the no-reflow phenomenon in patients with ST-segment elevation myocardial infarction (STEMI). This study represents an important contribution to the application of nonlinear machine learning (ML) models for capturing complex interactions among clinical, biomarker, and procedural variables involved in the pathophysiology of no-reflow. Quantitatively, the study demonstrated remarkably high discriminative performance, with both KAN and Extreme Gradient Boosting (XGBoost) models achieving an area under the curve (AUC) > 0.98 and an F1-score > 0.95, significantly outperforming conventional approaches such as logistic regression and decision tree models.

Furthermore, the use of analysis of variance (ANOVA)-based feature selection combined with variance inflation factor (VIF) analysis (< 5) reduced dimensionality and improved computational efficiency by 20–40% without compromising model performance.[1] From a biological perspective, SHapley Additive exPlanations (SHAP) analysis identified ejection fraction (EF) and B-type natriuretic peptide (BNP) as protective factors, whereas stent length and total ischemic time were associated with an increased risk of no-reflow, findings that are consistent with mechanisms of microvascular obstruction and reperfusion injury.[2]

Despite these strengths, the reported performance warrants cautious interpretation. An AUC approaching near-perfect discrimination in real-world clinical datasets raises concerns regarding potential overfitting, particularly because validation was limited to an internal dataset split (70/30) and cross-validation without a nested validation framework.[3] The absence of external and temporal validation substantially limits the generalizability of the findings. Additionally, the lack of calibration assessment, such as calibration plots or Brier scores, introduces uncertainty regarding the model's probabilistic accuracy in clinical settings.

Moreover, because the feature selection procedure was not explicitly incorporated within the validation loop, the possibility of data leakage cannot be excluded, potentially leading to inflated performance estimates.[3] The definition of the no-reflow phenomenon based solely on angiographic parameters, including Thrombolysis in Myocardial Infarction (TIMI) flow grade and myocardial blush grade (MBG), without confirmation by cardiac magnetic resonance imaging (CMR), the current gold standard, may also have introduced misclassification bias.[4] Furthermore, although SHAP analysis enhances model interpretability, its outputs are associative and cannot substitute for a causal inference framework.[5]

In light of these considerations, several methodological refinements and future research directions should be considered. First, external multicenter and temporal validation studies are essential to confirm model robustness across diverse patient populations and evolving clinical practices. Second, the incorporation of calibration analysis and decision-curve analysis is necessary to determine true clinical utility. Third, the use of nested cross-validation and a leakage-free analytical pipeline would improve model reliability. Fourth, integrating machine learning approaches with causal modeling frameworks may provide deeper mechanistic insights into the no-reflow phenomenon. Finally, prospective impact-analysis studies are required to determine whether implementation of these models can meaningfully improve clinical outcomes.

In conclusion, this study highlights the considerable potential of artificial intelligence for predicting cardiovascular outcomes. However, at present, it remains a high-performance predictive model rather than a clinically deployable decision-support system. Rigorous validation and comprehensive translational evaluation are necessary before widespread clinical implementation can be recommended.

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

Funding: The authors declared that this study received no financial support.

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Calibration and Validation Reporting for KAN-Based No-Reflow Prediction After Primary PCI

Primer PCI Sonrası KAN Temelli No-Reflow Tahmini için Kalibrasyon ve Doğrulama Raporlaması

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

Taşolar et al.[1] should be commended for evaluating the Kolmogorov-Arnold network (KAN) and comparator models for predicting angiographic no-reflow in 890 consecutive patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. KAN and XGBoost achieved area under the curve

Minimum validation sequence for KAN-based no-reflow prediction

Methodological steps required before bedside use in STEMI after primary PCI

1. Define the analytic cohort
Report the total number of patients and the number of no-reflow events in the training and test sets separately.
● Cohort definition ● Outcome prevalence ● Split-specific event counts

↓

2. Preserve a leakage-safe workflow
Perform oversampling, normalization, feature selection, and hyperparameter tuning only within the training process.
● Train-test split first ● No preprocessing on the test set ● Transparent pipeline description

↓

3. Report calibration with discrimination
Complement AUC with calibration-in-the-large, calibration slope, Brier score, and a calibration plot.
● Discrimination ● Calibration ● Overall accuracy

↓

4. Test clinical utility
Use decision-curve analysis to show whether the model improves pre-PCI planning across plausible risk thresholds.
● Net benefit ● Clinically relevant thresholds ● Comparison with simpler models

↓

5. Confirm transportability
Validate the model in a temporal or external STEMI cohort before clinical deployment.
● Temporal validation ● External validation ● Generalizability

Interpretation
High internal discrimination alone does not justify clinical implementation. A usable prediction model also requires leakage-safe development, calibration assessment, evaluation of net benefit, and independent validation.

Figure 1. Suggested validation sequence for clinical translation of a KAN-based no-reflow model. Internal discrimination should be followed by split-specific event reporting, leakage-safe preprocessing within training resamples, calibration assessment, decision-curve analysis, and temporal or external validation.

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values above 0.98, and the article states that cross-validation was restricted to the training set and that SMOTE was applied only within the training folds.[1] These findings support strong internal discrimination.

Several additions would make the model easier to interpret clinically. First, discrimination alone does not establish whether predicted probabilities are accurate. Because procedural decisions depend on absolute risk, calibration-in-the-large, calibration slope, a calibration plot, and the Brier score would complement the reported receiver operating characteristic analysis.[2] Second, split-specific no-reflow counts for the training and test partitions would help readers assess the precision of performance estimates in an imbalanced outcome setting. A concise pipeline diagram would also clarify the order of imputation, feature selection, oversampling, and hyperparameter tuning, making leakage control easier to verify. Figure 1 summarizes this sequence.

Third, decision-curve analysis would show whether the model provides net clinical benefit across plausible thresholds rather than statistical separation alone.[3] This distinction is important because the leading predictors included both baseline and procedural variables; therefore, the intended time point of use should be explicitly stated. Recent regional publications indicate growing interest in digital cardiology and artificial intelligence-enabled cardiovascular decision support, increasing the need for transparent reporting before clinical translation.[4,5]

The article already identifies the absence of full calibration analysis and external validation as limitations.[1] A temporally or externally validated analysis with complete calibration reporting, split-specific event counts, and decision-curve analysis would clarify whether KAN adds value beyond simpler no-reflow models.

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

Funding: The authors declared that this study received no financial support.

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Reply to the Letter to the Editor: Assessing the Predictive Value of Kolmogorov–Arnold Networks for the No-Reflow Phenomenon in ST-Segment Elevation Myocardial Infarction: A Comparative Machine Learning Study

Editöre Mektup Yanıtı: ST Segment Yükselmesi Miyokard Enfarktüsünde No-Reflow Fenomeni için Kolmogorov–Arnold Ağlarının Öngörü Değerinin Değerlendirilmesi: Karşılaştırmalı Makine Öğrenimi Çalışması

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

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DOI: 10.5543/tkda.2026.47680

To the Editor,

We would like to thank the authors of both Letters to the Editor[1,2] for their thoughtful and constructive comments on our article, "Assessing the Predictive Value of Kolmogorov–Arnold Networks for the No-Reflow Phenomenon in ST-Segment Elevation Myocardial Infarction: A Comparative Machine Learning Study."[3] We appreciate their interest in our work and agree that transparent reporting, calibration assessment, clinical utility analysis, leakage-safe validation, and external validation are essential before any machine learning model can be considered for clinical implementation.

However, we would like to emphasize that our study was designed primarily not to develop a ready-to-use clinical decision support system but to evaluate the comparative discriminative performance, variable contribution, and computational efficiency of the Kolmogorov–Arnold Network (KAN) model in a single-center STEMI cohort. Therefore, the main outcomes of the study were structured around ROC-AUC, F1-score, precision, recall, runtime, and SHAP-based explainability.[3] In this context, the study should be interpreted as a methodological and comparative machine learning investigation rather than a definitive clinical deployment study.

We agree with the authors that discrimination alone does not establish clinical readiness. Calibration-in-the-large, calibration slope, Brier score, and calibration plots would provide valuable complementary information regarding the agreement between predicted and observed probabilities.[4] Similarly, decision-curve analysis would be useful for determining whether the model provides a net clinical benefit across clinically relevant risk thresholds.[5] Reporting split-specific no-reflow event counts in the training and test datasets would also improve transparency, particularly in the setting of an imbalanced outcome. These analyses are important for future clinical translation; nevertheless, their absence does not invalidate the main findings of the present study, which focused on internal comparative discrimination and model interpretability.

The concern regarding potential overfitting is also important. In our study, the dataset was divided into a stratified 70% training set and a 30% independent test set, and five-fold cross-validation was restricted to the training data for hyperparameter optimization.[3] SMOTE was applied only during the training process to reduce the risk of data leakage. Final model performance was obtained from the independent test set, which was not used during model training. We acknowledge, however, that a more detailed pipeline diagram would improve reproducibility and make the sequence of imputation, feature selection, oversampling, hyperparameter tuning, and testing easier to verify. Future studies should report this workflow explicitly and, where possible, use nested cross-validation or external validation to further minimize optimism and strengthen reliability.[6]

We also agree that the intended time point of model use should be clarified. Because some of the strongest predictors included procedural variables such as stent length and total ischemic time, the current model should not be interpreted as a purely preprocedural decision-support tool. Rather, in its present form, it is more appropriately considered a periprocedural or early postprocedural risk stratification framework. Future models intended for pre-PCI decision support should be developed using only variables available before coronary intervention.

The comment regarding the definition of no-reflow is also well taken. Our study focused on angiographic no-reflow, defined using TIMI flow and Myocardial Blush Grade criteria, because these measures are immediately available in the catheterization laboratory and are widely used in interventional cardiology studies. Cardiac magnetic resonance imaging may provide a more detailed assessment of microvascular obstruction and infarct characteristics; however, it is not routinely available in the acute procedural setting and was beyond the scope of the present analysis. Future studies incorporating both angiographic and CMR-based endpoints would provide a more comprehensive evaluation of no-reflow and microvascular obstruction.[7,8]

We further agree that SHAP analysis should not be interpreted as a causal inference method. In our study, SHAP was used to improve transparency and evaluate whether model predictions were driven by clinically plausible variables, including ejection fraction, BNP, baseline troponin, total ischemic time, and stent length.[3,9] Therefore, SHAP-based findings should be considered explanatory and associative rather than causal. Combining machine learning with causal modeling frameworks may be a valuable direction for future research.

In summary, we agree that full calibration reporting, decision-curve analysis, split-specific event reporting, leakage-safe workflow visualization, nested or temporal validation, external multicenter validation, and prospective impact analyses would strengthen the clinical translation of KAN-based no-reflow prediction. At the same time, these additional requirements relate mainly to clinical implementation rather than to the primary objective of our study. Our findings support the potential value of KAN as a promising research framework for modeling complex nonlinear relationships in STEMI-related no-reflow; however, as stated in our original conclusion, KAN should currently be considered a research tool rather than a ready-to-use clinical decision support system.[3]

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A Critical Appraisal of Drug-Coated Balloon Use in STEMI: Biological Context, Cohort Heterogeneity, and Strategy Definition

STEMI'de İlaç Kaplı Balon Kullanımına İlişkin Eleştirel Bir Değerlendirme: Biyolojik Bağlam, Kohort Heterojenliği ve Strateji Tanımı

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

The role of drug-coated balloons (DCBs) in ST-elevation myocardial infarction (STEMI) remains incompletely defined, particularly given the unique thrombotic and microvascular milieu of the acute setting. The study by Darwish et al.[1] therefore addresses a clinically important and evolving area of interventional cardiology.

Several methodological and biological issues, however, merit consideration.

DCBs should be viewed not merely as devices but as a treatment strategy. The ESC-endorsed DCB-ARC consensus emphasizes the need to clearly distinguish among leave-nothing-behind, crossover, and blended strategies, each of which carries distinct clinical implications.[2] In the present study, the procedural approach is not sufficiently characterized within this framework, making it difficult to determine whether the reported outcomes reflect a true DCB-only strategy or a broader blended approach. Furthermore, the current DCB literature remains limited by heterogeneous endpoint definitions, inconsistent lesion preparation criteria, and variable definitions of procedural success, all of which complicate cross-study comparisons and outcome interpretation. Standardization of study design and endpoint adjudication according to DCB-ARC recommendations may therefore improve methodological consistency and enhance the interpretability and clinical relevance of future DCB trials.[2]

More importantly, DCB efficacy is highly dependent on the biological milieu. The STEMI setting, characterized by thrombus burden, vasoconstriction, and microvascular dysfunction, may impair drug transfer and distribution.[3] Thus, DCB performance should be viewed not solely as a function of the device but also in relation to the underlying biological substrate.

Importantly, the unfavorable outcomes reported in "in-stent culprit" lesions should not be interpreted as evidence against the established role of DCB therapy in conventional in-stent restenosis (ISR). On the contrary, DCBs represent one of the most widely accepted treatment options for ISR. The worse outcomes observed in the present study may instead reflect the thrombotic and biologically unstable STEMI milieu associated with culprit in-stent lesions, in which thrombus burden could impair effective drug transfer and tissue uptake during DCB angioplasty. This distinction is particularly relevant given the heterogeneous terminology used throughout the manuscript, including "in-stent culprit," "in-stent restenosis," and "in-stent thrombosis," which may represent biologically distinct entities with different implications for DCB performance.

Lesion preparation is another critical determinant of DCB efficacy. The predominant use of semi-compliant balloons suggests suboptimal lesion preparation, which may compromise drug delivery. The reported results may therefore reflect DCB performance under nonideal conditions rather than its full therapeutic potential.

Taken together, these findings should not be interpreted as evidence of universal equivalence between DCBs and drug-eluting stents (DESs) in STEMI. Rather, DCBs may

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represent a feasible option in carefully selected lesions when appropriate biological and procedural conditions are met. Future studies with homogeneous cohorts and clearly defined strategies are needed to better define their role.

Ultimately, in acute coronary syndromes, the success of DCBs appears to depend less on the device itself and more on appropriate lesion selection, biological context, and procedural precision.

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Reply to the Letter to the Editor: A Critical Appraisal of Drug-Coated Balloon Use in STEMI: Biological Context, Cohort Heterogeneity, and Strategy Definition

Editöre Mektup Yanıtı: STEMI'de İlaç Kaplı Balon Kullanımına İlişkin Eleştirel Bir Değerlendirme: Biyolojik Bağlam, Kohort Heterojenliği ve Strateji Tanımı

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

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To the Editor,

We appreciate the insightful comments and constructive critique provided by the authors.[1] regarding our manuscript.[2] "Clinical Outcomes of Using Drug-Coated Balloons During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Patients: Insights From High-Risk Groups." The letter raises important considerations regarding the use of drug-coated balloons (DCBs) in acute myocardial infarction settings, particularly emphasizing the complex interaction between the device and the biological substrate. Below, we address the specific points raised.

1. Regarding Strategy Definition and the DCB-ARC Consensus
Although we fully acknowledge the value of standardizing future trials according to DCB-ARC recommendations, our study represents a real-world, retrospective cohort reflecting immediate clinical practice during acute primary percutaneous coronary intervention (PPCI). We also agree that heterogeneity in endpoint definitions, lesion preparation techniques, and procedural success criteria remains a limitation across the current DCB literature. This variability complicates direct comparisons among studies and underscores the need for standardized methodologies and endpoint adjudication in future DCB trials.[3]

In our cohort, the primary intent was a "leave-nothing-behind" strategy. However, because of clinical necessity driven by acute flow-limiting dissections or major recoil, which are common in the highly volatile STEMI environment, crossover to a blended strategy involving rescue drug-eluting stent deployment was performed. In our study, procedural decisions were individualized according to lesion characteristics, thrombus burden, angiographic results after predilatation, and operator judgment in the acute STEMI setting. Although the DCB-ARC framework was published after our manuscript had been submitted for publication, we acknowledge that more detailed stratification of procedural strategies according to the DCB-ARC framework would further enhance interpretability and should be incorporated into future investigations.

2. Regarding the Biological Milieu and "In-Stent Culprit" Lesions
We completely agree with this important distinction. It was never our intention to challenge the established efficacy of DCBs in stable in-stent restenosis (ISR). Rather, our data highlight the unique risk posed by acute in-stent culprit lesions during STEMI. The presence of acute overlying thrombus within an already failed stent construct creates a compounding barrier. This not only impairs mechanical balloon expansion but also physically shields the vessel wall from appropriate paclitaxel/sirolimus transfer.[4] We appreciate the authors' observation regarding our varied terminology, including "in-stent culprit," "in-stent restenosis," and "in-stent thrombosis." We acknowledge that these represent biologically distinct entities, and future investigations should explicitly stratify these subsets.

3. Regarding Lesion Preparation and Balloon Compliance
In stable coronary artery disease (CAD) or standard ISR, aggressive lesion preparation using non-compliant (NC), scoring, or cutting balloons is necessary to achieve adequate

lumen gain before drug delivery. However, the primary PCI setting requires a delicate clinical balance. Aggressive predilatation with high-pressure NC or scoring balloons in an acutely thrombotic, fragile culprit vessel substantially increases the risk of distal embolization, no-reflow, and coronary dissection.[5]

Thus, the frequent reliance on semi-compliant balloons in our study reflects a cautious, real-world approach prioritized by operators to minimize microvascular plugging while establishing baseline antegrade flow. Nevertheless, we agree that more rigorous lesion preparation strategies may improve outcomes and warrant further study.

In summary, we agree with the letter's concluding sentiment: DCB use in STEMI should not be interpreted as universally equivalent to drug-eluting stents (DES). Instead, it represents a highly specialized and nuanced tool. Its success depends strongly on precise lesion selection, meticulous procedural execution, and a thorough understanding of the underlying biological substrate.

Our study provides an important view of the real-world challenges associated with introducing DCBs into the complex landscape of PPCI. It underscores exactly why standardized protocols, rigorous cohort homogeneity, and strict strategy definitions, as advocated by the DCB-ARC, are essential for the next generation of cardiovascular trials.

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