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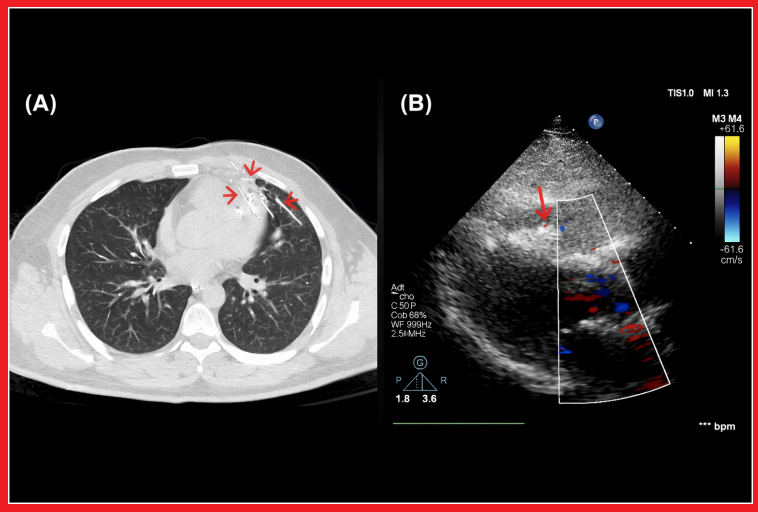
Original Investigations



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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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The Anatolian Journal of Cardiology aims to publish qualified and original clinical, experimental and basic research on cardiology at the international level. The journal's scope also covers editorial comments, reviews of innovations in medical education and practice, case reports, original images, scientific letters, educational articles, letters to the editor, articles on publication ethics, diagnostic puzzles, and issues in social cardiology.

The target readership includes academic members, specialists, residents, and general practitioners working in the fields of adult cardiology, pediatric cardiology, cardiovascular surgery and internal medicine.

The editorial and publication processes of the journal are conducted in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the European Association of Science Editors (EASE), the Committee on Publication Ethics (COPE) and the HEART Group.

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Ethics

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- An ethics committee report prepared in conformity with the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects and the Guide for the Care and Use of Laboratory Animals is required to be submitted with experimental and clinical studies, drug trial studies and some case reports. Authors may be asked by the Editor-in-Chief's Office for an ethics committee report or similar in other circumstances also. Manuscripts reporting the results of experimental studies must explain in detail all procedures which volunteer subjects and patients have undergone and a statement indicating that consent for the study has been obtained from all subjects should be included in the text. Animal studies should clearly specify how pain or discomfort has been relieved.

Artificial Intelligence (AI)–Assisted Technology

At submission, the journal should require authors to disclose whether they used artificial intelligence (AI)– assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of submitted work. Authors who use such technology should describe, in both the cover letter and the submitted work, how they used it. Use of AI for writing assistance should be reported in the acknowledgment section. Authors who used AI technology to conduct the study should describe its use in the methods section in sufficient detail to enable replication to the approach, including the tool used, version, and prompts where applicable. Chatbots (such as ChatGPT) should not be listed as authors because they cannot be responsible for the accuracy, integrity, and originality of the work, and these responsibilities are required for authorship. Therefore, humans are responsible for any submitted material that included the use of AI-assisted technologies. Authors should carefully review and edit the result because AI can generate authoritative-sounding output that can be incorrect, incomplete, or biased. Authors should not list AI and AIassisted technologies as an author or co-author, nor cite AI as an author. Authors should be able to assert that there is no plagiarism in their paper, including in text and images produced by the AI. Humans must ensure there is appropriate attribution of all quoted material, including full citations.

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1. Title Page
2. Main Text
3. Tables, Graphs and Figures
4. Copyright Transfer Form
5. Author Contribution Form
6. ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

1. Title Page

Information about the authors and their institutions should not be included in the main text, tables, figures and video documents. Since submitted manuscripts are evaluated by the reviewers through the online system, personal identification is excluded in the interests of unbiased interpretation. Thus, only information about the manuscript as specified below should be included on the title page. For each type of manuscript, it is mandatory to upload a title page as a separate Microsoft Word document through the online submission system. The title page should include the names of the authors with their latest academic degrees, and the name of the department and institution, city and country where the study was conducted. If the study was conducted in several institutions, the affiliation of each author must be specified with symbols. The correspondence address should contain the full name of the corresponding author, postal and e-mail addresses, phone and fax numbers. If the content of the manuscript has been presented before, the name, date and place of the meeting must be noted. Disclosure of conflict of interest, institutional and financial support, author contributions, acknowledgments, and ORCID iDs of the authors should be included on the title page.

2. Main Text

The manuscripts submitted to our journal are classified and evaluated according to the manuscript types stated below. During preliminary evaluation, the editors assess whether a manuscript's format and sub-headings are prepared in accordance with the journal's guidelines. Therefore, it is important that authors check the accuracy of the main text in terms of the following.

A. Manuscript types
- **Original investigation**
- **Editorial comment**
- **Review**
- **Education**
- **Scientific letter**
- **Case report**
- **Original image**
- **Letter to the editor**
- **Publication ethics**
- **Scientific puzzle**
- **Miscellaneous articles**

B. References

C. Special Terms and Conditions

A. Manuscript types

- **Original Research**
- Title
- Highlights: Each submission should be accompanied by 3 to 5 "highlight points" which should emphasize the most striking results of the study and highlight the message that is intended to be conveyed to the readers. It should be limited to 70 words.
- Structured Abstract: It should be structured with Objective, Methods, Results and Conclusion subheadings and should be limited to 250 words.
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- Main Text: It should consist of Introduction, Methods, Results, Discussion, Limitations of the Study and Conclusion sections and should not exceed 5000 words excluding the references.
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Statistical Analysis: Statistical analysis should be conducted in accordance with the guidelines on reporting statistical data in medical journals [Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93 and Lang T, Altman D. Basic statistical reporting for articles published in clinical medical journals: the SAMPL Guidelines. In: Smart P, Maisonneuve H, Polderman A (editors). Science Editors' Handbook, European Association of Science Editors, 2013.]. The software used for statistical analysis must be described. Data must be expressed as mean ± standard deviation when parametric tests are used to compare continuous variables. For nonparametric tests, data must be expressed as median (minimum-maximum) or percentiles (25th and 75th percentiles). In advanced and complex statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supported by confidence intervals and p values. The outcomes of statistical analyses and interpretation of the results must be in evidence-based scientific language (Editors of Heart Group journals. Statement on matching language to the type of evidence used in describing outcomes data. Anatolian Journal of Cardiology 2012;12:709).

- **Editorial Comment**

Authors are selected and invited by the Editor-in-Chief. This type of manuscript aims at providing a brief commentary on an article published in the journal by a researcher who is an authority in the relevant field or by the reviewer of the article.

- Title
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- **Review**

Reviews prepared by authors with extensive knowledge on a particular field, which has been reflected in international literature by a high number of publications and citations, are evaluated. The authors may be invited by the Editor-in-Chief. A review should be prepared in the format describing, discussing and evaluating the current level of knowledge or topic that is to be used in the clinical practice and it should guide further studies.

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- Keywords: This section should contain a minimum of three and a maximum of six items in accordance with Medical Subject Headings (MeSH) terms prepared by the National Library of Medicine (NLM) and should be provided just below the abstract.
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- **Education**
  Knowledge confirmed by the results of recent research studies, involved in education at academic level and used in clinical practices should be presented in detail in this type of manuscript.
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  Manuscripts which announce a new scientific invention, are clinically significant, and are in the form of a preliminary report are accepted for publication as scientific letters.
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- Abstract and Keywords should not be included.
- For scientific letters submitted by Turkish authors or from Türkiye, the Title should also be provided in Turkish. For letters submitted by foreign authors outside Türkiye, the translation of these sections will be carried out by Editor-in-Chief's Office.

- **Case Report**
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- Title
- Main Text: It should include Introduction, Case Report, Discussion and Conclusion sections and should not exceed 700 words excluding the references.
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NOTE 1: Case reports that include video images have a better chance of publication.

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  Impressive and rare images that reflect significant findings based on clinical science,
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  introduce new treatment methods are accepted for publication.
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- **Scientific Puzzle**

Images obtained directly or on operation, visuals revealed through EKG and/or imaging methods, and macroscopic-microscopic anatomical, pathological findings of attentiongrabbing and rare cases can be published. Unlike original images, the diagnosis and outcome of the case and image are hidden at the beginning in diagnostic puzzles. Four multiple-choice questions are prepared. In the following pages of the journal, the correct answer in terms of precise diagnosis and outcome is given with an explanation and didactic images and then discussed. The Editor-in-Chief will convert suitable images into the format of a diagnostic puzzle with the authors' permission.

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Journal: Muller C, Buttner HJ, Peterson J, Roskomun H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after placement of coronary artery stents. *Circulation*. 2000;101(6):590-593.

Book Chapter: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, eds. *Cardiovascular Medicine*. St Louis: Mosby; 1974:273-285.

Book with Single Author: Cohn PF. *Silent Myocardial Ischemia and Infarction*. 3rd ed. New York: Marcel Dekker; 1993.

Editor(s) as author: Norman IJ, Redfern SJ, eds. *Mental Health Care for Elderly People*. New York: Churchill Livingstone; 1996.

Conference Paper: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, eds. MEDINFO 92. Paper presented at the 7th World Congress on Medical Informatics; September 6-10 1992; Geneva, Switzerland. Amsterdam: North-Holland; 1992:1561-1565.

Scientific or Technical Report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: October 1994. Report No: HHSIGOE 169200860.

Thesis: Kaplan SI. *Post-hospital Home Health Care: Elderly Access and Utilization*. Dissertation. Washington University; 1995.

Manuscripts accepted for publication but not published yet: Leshner AI. *Molecular Mechanisms of Cocaine Addiction. N Engl J Med*. Forthcoming 1997.

Epub ahead of print articles: Aksu HU, Ertürk M, Gül M, Uslu N. Successful treatment of a patient with pulmonary embolism and biatrial thrombus. *Anatolian J Cardiol*. December 26, 2012. doi: 10.5152/akd.2013.062. [Epub ahead of print].

Manuscript published in electronic format: Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis (serial online)*. l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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- Tables should be prepared in a Microsoft Office Word document using the command 'Insert Table' and inserted at the end of the references in the main text.
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- All visuals should have a high resolution (minimum 300 dpi).
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Drawings should be performed by professionals. No grey colours should be used.
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- Roman numbers should be avoided in tables and figures within the text and their titles.
- Decimal numbers used in text, tables and figures should be separated by commas in Turkish sections and by dots in English sections.
- Tables should be easily understandable and should not repeat the data in the main text.
- In addition to the pictures included in case reports and original images, video and movie images are published on the journal's website. These images should be prepared in MPEG format with a maximum size of 2 MB. They should be submitted to the journal with the manuscript documents. The names of patients, doctors, institutions and places should be omitted from all documents.

NOTE: All visuals in the manuscripts are printed in black and white without charge. If color printing is required, Turkish authors must pay 300 TL, while foreign authors must pay 300 USD. For payment methods, please contact the Editor-in-Chief's Office of the Anatolian Journal of Cardiology.

EVALUATION AND PUBLICATION

- The main text submitted to the journal must be in English. Manuscripts written in other languages are not accepted. Citation potential is higher for manuscripts in English.
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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Official journal of the TURKISH SOCIETY OF CARDIOLOGY

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And a new case report, letters, e-page original...

I hope this new issue of our journal will be interest of our readers.

Çetin Erol

Editor-in-Chief, Ankara, Türkiye

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Managing Progressive Atherosclerotic Cardiovascular Disease in a Patient with Elevated Lipoprotein(a)

ABSTRACT

Lipoprotein(a) [Lp(a)] is a genetically determined, proatherogenic, and prothrombotic lipoprotein associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD). Elevated Lp(a) levels are associated with progressive ASCVD even when guideline-recommended low-density lipoprotein cholesterol (LDL-C) targets are achieved under optimal lipid-lowering therapy. There is currently no approved pharmacological therapy specifically targeting Lp(a) reduction in routine clinical practice; therefore, current management strategies for patients with elevated Lp(a) primarily focus on aggressive control of modifiable cardiovascular risk factors and intensive LDL-C lowering. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors provide a modest reduction in Lp(a) levels and have been associated with greater cardiovascular benefit in patients with high baseline Lp(a); however, this degree of reduction is often insufficient in individuals with markedly elevated Lp(a) levels and progressive ASCVD. At present, lipoprotein apheresis remains the only therapeutic option capable of achieving substantial and sustained reductions in Lp(a) concentrations and is recommended in selected high-risk patients with progressive ASCVD despite optimal medical therapy.

Meanwhile, Lp(a)-specific therapies, including antisense oligonucleotides and small interfering RNA agents, are in advanced clinical development and have shown marked reductions in Lp(a) levels in early phase trials. These emerging therapies are expected to significantly change future treatment strategies for patients with Lp(a)-driven residual cardiovascular risk.

Keywords: Atherosclerosis, cardiovascular events, cardiovascular risk factors, hyperlipidemia, lipoprotein, preventive cardiology

REVIEW

CASE

A 65-year-old man referred to a lipid clinic for progressive atherosclerotic cardiovascular disease (ASCVD) despite strict adherence to medical therapy. His cardiovascular history included left anterior descending artery stenting in 2010 and triple coronary artery bypass grafting (CABG) in 2024. Shortly after the CABG operation, he experienced a transient ischemic attack (TIA), although he reported no chest pain.

The patient did not smoke and had no history of hypertension or diabetes mellitus. His height was 177 cm and weight 85 kg, with a body mass index of 27 kg/m^2. His family history was remarkable: his father underwent CABG at age 51 years, his grandfather had a myocardial infarction at age 43 years, and his grandmother had a stroke at age 60 years.

Following the CABG, his low density lipoprotein cholesterol (LDL-C) level was 215 mg/dL (5.56 mmol/L), whereas Lipoprotein(a) [Lp(a)] had not been measured at that time. Based on his lipid profile, his treatment was re-adjusted, and he was started on rosuvastatin 40 mg, ezetimibe 10 mg, clopidogrel, and metoprolol. This treatment regimen was ongoing at the time of the TIA. At presentation with TIA, laboratory results under maximal lipid-lowering therapy were as follows: Total cholesterol: 111 mg/dL (2.8 mmol/L), triglycerides: 50 mg/dL (0.6 mmol/L), LDL-C: 54 mg/dL (1.4 mmol/L), HDL-C: 53 mg/dL (1.3 mmol/L), hs-CRP: <0.05 mg/dL,

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HbA1c: 5.5%, Lp(a): 214 mg/dL. Fibrinogen, D-dimer, Factor VIII, Protein C, and S levels were all within normal limits.

Despite achieving guideline-recommended lipid targets, markedly elevated Lp(a) levels and recurrent ASCVD events necessitated additional therapeutic interventions in this patient.

Treatment options, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition and lipoprotein apheresis, were discussed with the patient. Evolocumab 140 mg every 2 weeks was initiated. Following treatment, LDL-C decreased further to 31 mg/dL, and Lp(a) was reduced to 145 mg/dL. The addition of lipoprotein apheresis to his management is currently under consideration to further lower Lp(a) since he has recurrent events while we wait for the Lp(a)-specific therapies to be available.

Case Review

Lipoprotein(a) [Lp(a)] is a uniquely structured atherogenic lipoprotein similar to LDL particles, which differ by having a covalently bound apolipoprotein(a) via a disulfide bond. Lipoprotein(a) [Lp(a)] carries the majority of circulating oxidized phospholipids (OxPL), which induce a potent inflammatory response and enhance monocyte recruitment.[1] Moreover, the apo(a) component structurally resembles plasminogen and competitively inhibits fibrinolysis, thereby creating a pro-thrombotic environment that increases the risk of acute cardiovascular events. The level of Lp(a) is mostly determined by genetic factors, and environmental factors don't play a major role in its level.[2] The Apo(a) component contains multiple kringle IV type 2 repeats, whose number is genetically determined and inversely correlated with plasma Lp(a) concentration. Although Lp(a) levels remain relatively stable throughout a lifetime, it has been shown that Lp(a) levels increase in women after menopause, and studies have reported higher median Lp(a) levels in women compared with men.[3,4] Now it is proven that Lp(a) levels are related to ASCVD risk independent of and additive to traditional risk factors.[5,6] Importantly, this risk relationship is continuous and linear; increases in Lp(a) across its distribution associate with proportionally increasing risk of myocardial infarction, stroke, and aortic valve stenosis.[7] Because levels are genetically determined and stable throughout life, Lp(a) has unique value as a lifetime risk indicator.

According to European guidelines and atherosclerosis experts, Lp(a) should be measured at least once during adult life. [8–11] In women, a second Lp(a) measurement may be considered after menopause.[8] The value of Lp(a) measurement in both primary and secondary prevention is increasingly recognized, particularly by clinicians specialized in this field, and approximately 75% of clinicians working in lipid clinics across Europe measure Lp(a) levels in their patients.[12] Screening to detect elevated Lp(a) levels in individuals without known cardiovascular disease is recommended, and high Lp(a) should be regarded as a risk-enhancing factor, particularly in patients at intermediate risk or those near treatment thresholds. The presence of markedly elevated Lp(a), typically defined as ≥50 mg/dL (≈125 nmol/L), supports reclassification of individuals with intermediate risk into higher risk categories.[7] Moreover, Lp(a) measurement is recommended in patients with premature ASCVD, those with a family history of premature ASCVD or elevated Lp(a), and younger patients with familial hypercholesterolemia.[8] In secondary prevention, clinical trials have demonstrated that among patients with established coronary artery disease, elevated Lp(a) levels are associated with higher cardiovascular event rates even when LDL-C is well controlled, highlighting the concept of residual cardiovascular risk.[13]

Despite the increasing recognition of the importance of Lp(a) measurement, there is currently no approved pharmacological therapy specifically targeting Lp(a) reduction; therefore, cardiovascular risk management in patients with elevated Lp(a) primarily relies on optimal control of other modifiable risk factors, particularly LDL-C levels. The EPIC-Norfolk study demonstrated that, in individuals with elevated Lp(a), effective control of other cardiovascular risk factors and adherence to a healthy lifestyle are associated with a reduction in cardiovascular risk.[14] In individuals without known ASCVD but with intermediate cardiovascular risk, elevated Lp(a) may justify earlier initiation of lipid-lowering therapy and more ambitious LDL-C targets. In the setting of secondary prevention, close clinical follow-up and stricter LDL-C goals should be considered. Although statins may modestly increase Lp(a) levels, intensive LDL-C reduction mitigates the overall atherogenic burden.[15,16] However, despite strict LDL-C control, elevated Lp(a) remains a source of residual cardiovascular risk and is associated with recurrent cardiovascular events.

To address this residual risk, specific therapies targeting Lp(a) reduction have been developed; however, they remain under investigation in clinical trials and have not yet been approved for routine clinical use. Currently, PCSK9 inhibitors are the only approved pharmacological agents that provide

HIGHLIGHTS

- Elevated Lp(a) is an important cause of residual cardiovascular risk despite optimal low-density lipoprotein cholesterol (LDL-C) lowering and is associated with progressive ASCVD even when guideline-recommended lipid targets are achieved.
- In the presence of elevated Lp(a), more aggressive LDL-C reduction is recommended to minimize cardiovascular risk.
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors provide only modest reductions in Lp(a) levels and may be insufficient in patients with very high Lp(a) concentrations.
- Lipoprotein apheresis remains the most effective currently available option for substantial Lp(a) lowering in selected high-risk patients.
- Lp(a)-specific pharmacological therapies are close to completing clinical development, and their approval is expected to represent a major advance in preventive cardiology.

a moderate reduction in Lp(a) levels. In the ODYSSEY trials, alirocumab reduced Lp(a) levels by approximately 23% at 4 months, with a greater absolute reduction observed in patients in the highest Lp(a) quartile. Moreover, individuals in the upper Lp(a) quartile had a greater reduction in major adverse cardiovascular events (MACE) with PCSK9 inhibition.[17] Similarly, in the FOURIER trial, evolocumab reduced Lp(a) levels by 26.9% at 48 weeks. Importantly, in patients with baseline Lp(a) levels above the median, more coronary events were prevented compared with those with Lp(a) levels at or below the median (23% vs 7%, respectively).[18] When either LDL-C or Lp(a) levels were reduced below the median, the relative risk reduction was 15%, whereas reductions in both LDL-C and Lp(a) were associated with a 28% reduction in cardiovascular events, indicating an Lp(a)-dependent benefit independent of LDL-C lowering. Data from the ORION trials demonstrated that inclisiran treatment results in a 15-28% reduction in Lp(a) levels.[19]

Nevertheless, the degree of Lp(a) reduction achieved with PCSK9 inhibition is generally insufficient in patients with very high Lp(a) levels and progressive ASCVD. Currently, lipoprotein apheresis remains the only therapeutic option capable of producing large and immediate reductions in circulating Lp(a) concentrations, with acute reductions of 60-75% per session.[20] When performed weekly or biweekly, mean interval Lp(a) concentrations decline by approximately 30-40%, resulting in sustained reductions in atherogenic and inflammatory burden.[21] Although its availability is limited and it is reserved for highly selected patients, lipoprotein apheresis plays an important role in European lipid clinics, particularly in Germany, Austria, and Switzerland. It currently represents the most potent intervention available for lowering Lp(a).

Lipoprotein apheresis is indicated in patients with progressive ASCVD who fail to achieve LDL-C targets despite maximally tolerated lipid-lowering therapy, as well as in patients with LDL-C at target but elevated Lp(a) levels (>60 mg/dL) in the presence of ASCVD, or in those with both elevated LDL-C and Lp(a). The Pro(a)LiFe study enrolled patients with a history of ASCVD, LDL-C levels close to guideline-recommended targets, and Lp(a) concentrations >60 mg/dL.[22] Lipoprotein apheresis resulted in a 67% reduction in Lp(a) levels during the first year and 68% during the second year compared with pre-apheresis values. Low-density lipoprotein cholesterol (LDL-C) levels were reduced by 66% in the first year and 68% in the second year, and these reductions were sustained for up to 12 years. The rate of major cardiovascular events decreased by 78% at 5 years and by 75% at 12 years compared with the pre-apheresis period.

Although these findings suggest that Lp(a) reduction is associated with a substantial decrease in cardiovascular events, it remains difficult to disentangle the relative contributions of Lp(a) and LDL-C lowering to the observed risk reduction. Further insight is provided by data from the German Lipoprotein Apheresis Registry, in which patients were categorized into 3 groups: isolated LDL-C elevation, isolated Lp(a) elevation, and combined elevation of LDL-C and Lp(a).[23] Overall, lipoprotein apheresis reduced LDL-C levels by 68.1% and Lp(a) levels by 75.6%. In patients with isolated Lp(a) elevation, MACE were reduced by 83% in the first year and by 86% in the second year. In contrast, patients with isolated LDL-C elevation experienced MACE reductions of 42% and 61% in the first and second years, respectively. In patients with combined elevation of LDL-C and Lp(a), MACE rates were reduced by 71% in the first year and by 78% in the second year compared with the pre-apheresis period. These findings underscore that the benefit of lipoprotein apheresis is greater in patients with elevated Lp(a), with or without concomitant LDL-C elevation.

Consistent with these data, the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidance recognizes lipoprotein apheresis as a therapeutic option for patients with progressive ASCVD and markedly elevated Lp(a) levels despite optimal medical therapy.[9] Until the approval of Lp(a)-lowering specific therapies, lipoprotein apheresis represents the most potent currently available intervention for lowering Lp(a). However, apheresis has several limitations. It is resource-intensive, requiring specialized equipment, dedicated vascular access, and regular treatment sessions lasting 2 to 3 hours. These logistical, economic, and patient-related considerations restrict its use.

Meanwhile therapies specifically targeting Lp(a) are advancing rapidly through clinical trials and are likely to become available for clinical use in the near future. These therapies directly target hepatic production of apolipoprotein(a) using antisense oligonucleotides or small interfering ribonucleoic asid (siRNA).[24] They achieve marked Lp(a) reductions of approximately 80-98%. Antisense oligonucleotides are single-stranded nucleic acids designed to be complementary to a specific target messenger RNA (mRNA). They contain a DNA-like gap region that can be recognized by RNase H, leading to degradation of the target mRNA and subsequent reduction in protein synthesis. Pelacarsen is an antisense oligonucleotide conjugated with GalNAc to selectively target hepatocytes and reduce the production of apolipoprotein(a) in the liver. When administered by subcutaneous injection, pelacarsen has demonstrated dose-dependent reductions in Lp(a) levels of approximately 80-90% in phase II trials, with good tolerability and sustained efficacy.[25] Importantly, the Lp(a) HORIZON study, a large cardiovascular outcomes trial enrolling more than 8000 patients with established ASCVD and elevated Lp(a), is currently ongoing.[26] The results, expected in 2026, are anticipated to address whether selective Lp(a) lowering translates into a reduction in major adverse cardiovascular events.

Developments in siRNA therapeutics have also been impressive. siRNAs are double-stranded RNA molecules that are incorporated into the RNA-induced silencing complex (RISC) within the cell. The guide strand directs the RISC complex to the complementary target mRNA, which is subsequently cleaved by Argonaute-2, a key component of RNA-induced silencing complex (RISC), leading to degradation of the target mRNA and inhibition of protein synthesis. Olpasiran, a GalNAc-conjugated apo(a) siRNA, administered every 12 to 24 weeks, achieves Lp(a) reductions of 90-98%, with many patients reaching nearly undetectable

levels.[27] Early-phase trials have demonstrated a remarkable long-term effect, with reductions persisting for months after the last injection. A clinical outcomes trial in patients with ASCVD evaluating the effect of olpasiran on major adverse cardiovascular events is currently ongoing, with results expected in 2026.[28] Other siRNA agents, such as lepodisiran and zerlasiran, are in various stages of clinical development and appear capable of achieving similar reductions with very infrequent dosing intervals, which may support long-term adherence.

If clinical trials are successful, clinicians may, for the first time, be able to effectively neutralize a major genetic risk factor that has until now remained clinically unmodifiable. If outcome trials confirm a reduction in major cardiovascular events, these therapies are expected to reshape prevention strategies, screening practices, and treatment algorithms across Europe. The integration of Lp(a)-specific therapies into clinical practice will require careful consideration of risk thresholds, prioritization strategies, and cost-effectiveness. Individuals with very high Lp(a) levels and those with elevated Lp(a) and progressive ASCVD despite low LDL-C levels and the absence of other major risk factors, similar to the patient described here, are likely to derive the greatest benefit.

In summary, the case presented in this review highlights a clinically important and increasingly recognized scenario in contemporary cardiovascular medicine: a patient with excellent control of traditional risk factors, optimal adherence to therapy, and LDL-C levels well below guideline-recommended targets, yet ongoing progression of atherosclerotic disease and recurrent cerebrovascular events. In this setting, elevated Lp(a) emerged as the dominant residual risk factor. Although PCSK9 inhibition provided only modest Lp(a) reduction, further lowering of Lp(a) was critical for secondary prevention.

At present, lipoprotein apheresis remains the only effective therapeutic option to substantially reduce Lp(a) levels in such patients. However, the rapid development of Lp(a) specific therapies is expected to fundamentally change the management of patients with residual cardiovascular risk driven by elevated Lp(a) and to offer new preventive strategies for individuals similar to the case described here.

AI Disclosure

The authors declare that no generative AI tools (such as large language models, chatbots, or image creators) were used in any stage of the preparation or writing of this manuscript.

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Artificial Intelligence in Cardiovascular Disease Prevention: Current Applications and Future Perspectives

ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, emphasizing the ongoing need for effective and scalable primary and secondary prevention strategies. In this evolving landscape, artificial intelligence (AI) has emerged as a transformative force in preventive cardiology, with the potential to reshape risk assessment, early disease detection, and personalized preventive care. Artificial intelligence–driven models consistently outperform traditional risk scores by integrating large-scale, multidimensional, and longitudinal data derived from various platforms. These capabilities enable dynamic and time-adaptive cardiovascular risk prediction that more accurately reflects the evolving nature of individual risk profiles. Advances in machine learning and deep learning have facilitated the earlier identification of subclinical CVD often preceding clinical manifestation by several years. In parallel, AI-powered wearable devices and digital health (DH) solutions support continuous physiological monitoring, real-time feedback, and personalized lifestyle and behavioral interventions, thereby extending preventive care beyond traditional clinic-based settings. Such approaches appear particularly beneficial for high-risk populations by promoting sustained engagement, early intervention, and improved clinical outcomes. Looking ahead, emerging innovations such as multimodal AI systems, digital twin technologies, and AI-guided clinical guidelines signal a paradigm shift toward predictive, participatory, precision-based, and continuously learning prevention strategies. Nevertheless, the successful translation of AI into routine clinical practice will depend on increasing DH literacy, rigorous prospective validation, ethical and regulatory oversight, data transparency, and seamless integration into clinical workflows. When thoughtfully implemented, AI holds the promise to fundamentally advance preventive cardiology, enabling more patient-centered, participatory, and equitable cardiovascular care while reducing the global burden of CVD.

Keywords: Artifical intelligence, cardiovascular disease, prevention

REVIEW

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INTRODUCTION

In spite of all efforts, cardiovascular disease (CVD) still remains the leading cause of morbidity and mortality worldwide, representing a major public health challenge despite significant advances in diagnosis and treatment.[1]

In this context, prevention strategies, particularly primary and secondary prevention, are fundamental to reducing the overall burden of CVD. Preventive cardiology focuses on the early identification and modification of cardiovascular (CV) risk factors before disease onset (primary prevention) as well as on reducing recurrent events and slowing disease progression in individuals with established CVD (secondary prevention) in line with contemporary evidence and recent advances in CV prevention strategies.[2]

Artificial intelligence (AI) refers to the development of computational systems capable of performing tasks that typically require human intelligence, including pattern recognition, learning, and decision-making. In recent years, AI-based models have demonstrated substantial potential in the detection, screening, and risk stratification of various CVDs. By enabling the identification of novel phenotypes and complex risk patterns beyond traditional clinical approaches, AI has the

potential to augment personalized CV prevention and management strategies.[3,4]

Building on its supportive role in preventive care, AI has become particularly influential in CV risk prediction. AI-based systems integrate multidimensional data derived from lifestyle behaviors, clinical parameters, wearable devices, and digital health (DH) platforms to enable continuous risk assessment and personalized preventive strategies.[5]

By simultaneously addressing key determinants of CV care including nutrition, physical activity, weight management, sleep patterns, blood pressure, lipid profiles, smoking, substance use, and mental health, AI has the potential to prioritize individual risk factors, identify early deviations from optimal CV health, and support informed decision-making for both clinicians and patients.

This review provides an overview of current applications of AI in CV prevention, examines their potential clinical impact, and discusses the limitations and challenges associated with their implementation in both primary and secondary prevention of CVD.

ARTIFICIAL INTELLIGENCE–BASED CARDIOVASCULAR RISK PREDICTION

Artifical intelligence–based CV risk prediction models have consistently demonstrated superior predictive accuracy compared with traditional risk scores derived from linear or regression-based approaches representing a major advancement in both primary and secondary prevention of CVD.[6] Conventional risk models typically rely on a limited number of static variables measured at a single time point, which may inadequately capture the complex, dynamic, and evolving nature of CV risk.[5] In contrast, AI-driven models are capable of integrating large-scale, multidimensional, and longitudinal data including clinical characteristics, laboratory parameters, imaging findings, and sociodemographic factors.

Electronic health (EHR), wearable device data, retinal fundus images, electrocardiograms (ECG), and genetic information have all been utilized to train AI models capable of predicting incident CVD, hypertension, dyslipidemia, and atherosclerotic CVD events.[7-12]

HIGHLIGHTS

- Artifical intelligence (AI) enables dynamic and personalized cardiovascular risk prediction by integrating multimodal and longitudinal data beyond traditional risk models.
- Early identification of subclinical cardiovascular disease is enhanced by AI, supporting timely intervention before overt clinical manifestation.
- Artifical intelligence–powered wearables, digital health tools, and emerging technologies such as digital twins may transform preventive cardiology toward proactive, participatory, precision-based, and continuously learning care.

By integrating these heterogeneous data sources, AI-based clinical decision support systems can analyze large volumes of patient information to support accurate and informed clinical decision-making.[13]

Moreover, the ability of AI-based systems to continuously update risk estimates as new data become available enables dynamic and time-adaptive risk prediction, making them particularly valuable in preventive cardiology, where individual risk profiles evolve over time in response to aging, lifestyle modifications, and therapeutic interventions.

The major domains and key clinical contributions of AI across the spectrum of CV prevention are summarized in Table 1.

EARLY DETECTION OF SUBCLINICAL CARDIOVASCULAR DISEASE

The early detection of subclinical CVD is a cornerstone of effective preventive cardiology, as structural and functional abnormalities frequently precede the onset of clinical symptoms by several years.[14]

In this context, AI-based approaches have demonstrated substantial potential in identifying silent CV abnormalities, such as atrial fibrillation (AF), left ventricular (LV) dysfunction, and early coronary atherosclerosis, before overt disease manifestation.[15] By leveraging advanced pattern recognition capabilities, AI algorithms can detect subtle signals within routinely acquired diagnostic data that may not be readily apparent to human observers, thereby enabling earlier risk stratification and timely intervention.

Machine learning (ML) /Deep Learning (DL) models trained on standard 12-lead ECGs have shown high accuracy in identifying occult AF, asymptomatic LV systolic dysfunction, and other electrophysiological abnormalities, even in patients with normal sinus rhythm at the time of recording.[15] Similarly, AI-assisted echocardiographic analysis enables automated and reproducible assessment of cardiac structure and function, facilitating the early recognition of subclinical LV remodeling, diastolic dysfunction, and valvular abnormalities.[16,17]

Beyond functional assessment, AI has also enhanced the detection of early atherosclerotic disease through advanced imaging modalities such as computed tomography (CT). Artifical intelligence algorithms applied to coronary CT angiography and calcium scoring can identify high-risk plaque characteristics, accurately quantify coronary calcification, and refine CV risk prediction beyond traditional imaging metrics.[18]

WEARABLES AND DIGITAL HEALTH IN CARDIOVASCULAR PREVENTION

Artificial intelligence–powered wearable technologies enhance patient engagement by delivering personalized feedback, real-time alerts, and adaptive behavioral interventions tailored to individual CV risk profiles. Machine learning models can analyze longitudinal data collected from wearable devices to detect deviations from baseline physiological patterns, predict impending clinical

Table 1. Artificial Intelligence Applications Across the Spectrum of Cardiovascular Prevention

Domain	Data Sources	AI Approach	Clinical Contribution	Prevention Level
Cardiovascular risk prediction	Electronic health records, laboratory data, imaging, genomic information, sociodemographic variables, wearable devices	Machine learning/deep learning, multimodal data integration	Dynamic and time-adaptive risk estimation; individualized cardiovascular risk profiling	Primary and Secondary
Detection of subclinical CVD	Standard 12-lead ECG, echocardiography, coronary computed tomography	Deep learning–based signal and image analysis	Early identification of silent atrial fibrillation, subclinical left ventricular dysfunction, and early atherosclerosis	Primary
Wearables and digital health	Smartwatches, mobile sensors, remote monitoring systems	Continuous data analysis, anomaly detection	Real-time physiological monitoring, early warning signals, proactive risk management	Primary and Secondary
Lifestyle and behavioral prevention	Physical activity, sleep metrics, body weight, heart rate variability, patient-reported data	AI-supported digital coaching	Personalized lifestyle interventions and sustained behavioral change	Primary
High-risk populations (HF, DM, HT)	Wearables, mobile applications, longitudinal clinical data	Predictive machine learning models	Early detection of clinical deterioration and reduction of hospitalizations	Secondary

AI, artificial intelligence; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiogram; EHR, electronic health record; HF, heart failure; HT, hypertension.

deterioration, and support lifestyle modification strategies related to physical activity, weight management, and sleep hygiene.[19] These DH tools enable scalable, population-level prevention while simultaneously empowering individuals to take an active role in managing their CV health. The integration of AI-enabled wearables with telemedicine and remote monitoring platforms represents a pivotal advancement in preventive cardiology. By facilitating continuous data transmission from patients' homes to healthcare providers, these systems support timely clinical decision-making, early intervention, and proactive CV risk management.[19]

ARTIFICIAL INTELLIGENCE FOR LIFESTYLE MODIFICATION AND BEHAVIORAL PREVENTION

Lifestyle modification remains a cornerstone of CV prevention; however, sustained adherence to healthy behaviors continues to be a major challenge in routine clinical practice. Artificial intelligence–supported digital coaching systems offer a scalable and personalized solution to this problem by tailoring interventions to individual behavioral patterns, preferences, and CV risk profiles. By leveraging ML algorithms, these platforms can analyze real-time data from wearable devices, mobile applications, and self-reported inputs to deliver personalized recommendations aimed at improving physical activity, dietary habits, weight management, and smoking cessation, which facilitates primary and secondary prevention of CVD.[20]

Patients with heart failure (HF) and other high-risk cardiovascular populations also represent groups in whom lifestyle modification has a profound impact on clinical outcomes yet is often difficult to maintain over time.[21] In this context, AI-enabled digital coaching and remote monitoring systems have demonstrated particular promise by supporting individualized physical activity planning, promoting dietary adherence, facilitating symptom tracking, and enabling early detection of clinical decompensation. In patients with HF, ML models integrated into wearable devices and mobile platforms can continuously monitor daily activity levels, heart rate variability, sleep patterns, and weight fluctuations to identify early signs of clinical deterioration and prompt timely lifestyle or therapeutic adjustments.[22] Similarly, in other high-risk populations including older adults and individuals with diabetes, obesity, or hypertension, AI-driven behavioral interventions can dynamically adapt recommendations based on functional capacity, comorbid conditions, and real-world adherence patterns. By delivering tailored, context-aware feedback and reinforcing self-management behaviors, these systems may improve quality of life, reduce hospitalizations, and support sustained engagement in preventive strategies among vulnerable populations.[23]

ETHICAL, REGULATORY, AND PRACTICAL CHALLENGES

Despite the growing promise of AI in CV prevention, several ethical challenges must be addressed to ensure its responsible implementation. Data privacy and security remain central concerns, as AI systems depend on large volumes of sensitive personal and health-related information derived from EHRs, wearable devices, and digital platforms. Inadequate data governance frameworks or data breaches may undermine patient trust and compromise confidentiality. Moreover, algorithmic bias resulting from imbalanced or non-representative training datasets can lead to differential performance across sex, age, ethnicity, or socioeconomic groups, potentially exacerbating existing CV health disparities.

Regulatory and legal considerations represent additional barriers to the widespread adoption of AI-based preventive tools. Many AI algorithms function as adaptive systems that continuously evolve as new data become available, posing significant challenges for traditional regulatory

frameworks that were designed for static medical devices.[24] Ensuring transparency, explainability, and reproducibility is therefore essential for both regulatory approval and clinical acceptance. Clear and standardized requirements for model validation, performance reporting, and post-market surveillance are necessary to define accountability and liability when AI-driven recommendations influence preventive care decisions.[24]

From a practical standpoint, the successful integration of AI across the spectrum of CVD, interventional cardiology, and CV prevention relies on effective clinician oversight, seamless integration into existing clinical workflows, and robust prospective and external validation in representative cohorts.[25]

However, limited interoperability with current health information systems, insufficient DH literacy and clinician training, and the risk of alert fatigue may hinder real-world implementation.[26]

Therefore, future efforts should prioritize prospective trials, real-world effectiveness studies, and clinician-centered design to ensure that AI technologies function as safe, interpretable, and well-aligned decision support tools that complement rather than replace clinical judgment.[27,28]

FUTURE PERSPECTIVES

The future of preventive cardiology is poised to be fundamentally transformed by advanced multimodal AI systems capable of integrating and interpreting vast, heterogeneous data streams to generate clinically actionable insights. By combining longitudinal clinical records, advanced imaging data, wearable-derived physiological signals, genomic information, and social determinants of health, next-generation AI models may enable continuous, individualized CV risk profiling. This paradigm has the potential to shift preventive cardiology from a reactive model—focused on established risk—to a proactive, participatory, and precision-based approach that predicts disease trajectories before clinical manifestation.

Among the most transformative innovations in this evolving landscape is the emergence of digital twin technology. Digital twins are dynamic, virtual representations of individual patients that evolve in parallel with real-world clinical, physiological, and behavioral data.[29] In CV prevention, digital twins could enable the simulation of lifestyle interventions, pharmacological therapies, and risk factor modification strategies before their implementation in real life.[30] Such simulations may facilitate scenario-based decision-making, optimize preventive strategies for high-risk individuals, and enhance shared decision-making by allowing clinicians and patients to visualize potential future risk pathways and outcomes.

Looking forward, the integration of validated AI tools into clinical guidelines may redefine the practice of preventive cardiology. Artificial intelligence–guided guidelines can complement traditional evidence-based recommendations by incorporating real-time patient data and continuously updating individualized risk estimates, thereby enabling adaptive and context-aware prevention strategies.[31]

Realizing this vision will require close collaboration among clinicians, professional societies, regulators, and data scientists to ensure transparency, clinical validity, interpretability, and ethical oversight. Furthermore, increasing DH literacy among the population carries utmost importance as it constitutes a prerequisite for meaningful patient engagement, informed decision-making, and effective adoption of AI-driven DH Technologies.[32,33]

If successfully implemented, AI-driven and digital twin–informed frameworks may mark a paradigm shift from static, population-level prevention toward continuously learning, patient-centered, and participatory CV care empowering patients to actively engage in and comanage their own disease trajectories.

DISCUSSION

This review highlights the rapidly expanding role of AI across the full spectrum of CV prevention, ranging from individual-level risk prediction to population-based public health strategies. Artificial intelligence–driven approaches offer clear advantages over traditional methods by enabling the integration of multimodal data, dynamic risk assessment, and the early detection of subclinical CVD.[34] In particular, advances in ML and DL have enhanced CV risk prediction, facilitated earlier identification of silent pathologies such as AF and LV dysfunction, and supported the development of personalized preventive strategies that extend beyond conventional clinic-based care.[35]

The preventive potential of AI has been further amplified by the growing use of wearable technologies, DH platforms, and telemedicine, which enable continuous monitoring and real-time feedback in real-world settings.[36] These tools play a critical role in lifestyle modification and behavioral prevention, areas in which long-term adherence remains a major challenge.[37] Artifical intelligence–supported digital coaching systems and remote monitoring frameworks appear especially valuable for high-risk populations, including patients with HF, older adults, and individuals with multiple cardiometabolic comorbidities, by facilitating sustained engagement in preventive care and enabling early intervention.[38]

Looking ahead, emerging concepts such as multimodal AI models, digital twin technologies, and AI-guided clinical guidelines represent a potential paradigm shift in preventive cardiology. These innovations may enable more proactive and precision-based prevention by simulating disease trajectories and tailoring interventions to individual risk profiles. Nevertheless, their successful translation into clinical practice will depend on robust prospective validation, interdisciplinary collaboration, and thoughtful integration into existing healthcare systems. Importantly, AI should be viewed as a complement to, rather than a replacement for, clinical expertise, supporting shared decision-making and reinforcing evidence-based CV prevention.

CONCLUSION

Artificial intelligence represents a transformative opportunity for the prevention of CVD by enabling earlier detection of risk, personalized risk stratification, and scalable preventive interventions. Across multiple domains—including CV risk prediction, early identification of subclinical disease, and lifestyle modification—AI-driven approaches have demonstrated substantial potential to enhance preventive cardiology beyond the limitations of traditional models.

Despite these promising advances, widespread clinical implementation requires robust prospective validation, careful integration into healthcare systems, and sustained clinician engagement. Ethical governance, regulatory clarity, data transparency, and mitigation of algorithmic bias are essential to ensure equitable and responsible use of AI in CV prevention. Importantly, AI should function as a decision support tool that augments clinical expertise rather than replacing it.

Future developments in multimodal AI, digital twin technologies, and AI-guided clinical guidelines may further shift preventive cardiology toward a proactive, precision-based, and continuously learning paradigm. If thoughtfully developed and rigorously validated, AI has the potential to fundamentally reshape CV prevention, advancing patient-centered care while reducing the global burden of CVD.

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Electrophysiological Markers in Hypertrophic Cardiomyopathy: Enhancing Sudden Cardiac Death Risk Prediction with Index of Cardiac Electrophysiological Balance and Its Corrected Variant

ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is characterized by asymmetric left ventricular hypertrophy and myocardial fibrosis, which significantly increases the risk of sudden cardiac death (SCD). Existing risk stratification models are limited in predicting SCD risk in patients within the "gray zone"—those with intermediate risk. This study investigates the prognostic utility of the Index of Cardiac Electrophysiological Balance (ICEB) and its corrected variant (ICEBc) in predicting ventricular arrhythmias (VAs) in HCM. To evaluate the predictive value of ICEB and ICEBc for Life-Threatening Arrhythmias (LTA) and non-sustained ventricular tachycardia (NSVT) in HCM and compare their performance with traditional repolarization parameters and the European Society of Cardiology (ESC) SCD Risk Score.

Methods: A retrospective observational study was conducted at a single center, including 127 HCM patients categorized into 3 groups: LTA (n = 45), NSVT (n = 29), and control (n = 53). Electrocardiographic parameters, including ICEB, ICEBc, Tp-e interval, Tp-e/QTc ratio, and QRS-T angle were measured. Multiple logistic regression and receiver operating characteristic (ROC) curve analyses were performed to identify independent predictors of VAs.

Results: The ICEB and ICEBc were significantly lower in LTA and NSVT groups compared to the control group ($P < .001$), indicating increased arrhythmogenic risk. The ROC curve analysis showed that ICEB and ICEBc had superior predictive power for LTA and NSVT compared to traditional markers and the ESC SCD Risk Score, with the highest area under the curve (AUC) for the Base + ICEB Model (AUC = 0.79).

Conclusion: The ICEB and ICEBc are robust markers of repolarization heterogeneity and effective predictors of VAs in HCM patients. Their integration into existing risk stratification models could enhance predictive accuracy, particularly for gray zone patients.

Keywords: Hypertrophic cardiomyopathy, Index of Cardiac Electrophysiological Balance, life-threatening arrhythmias, risk stratification, sudden cardiac death, ventricular arrhythmias

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder characterized by asymmetric left ventricular hypertrophy and myocardial fibrosis, significantly increasing the risk of sudden cardiac death (SCD).[1] Although implantable cardioverter-defibrillators (ICDs) are recommended for SCD prevention, accurately identifying high-risk patients remains challenging.[2] Traditional risk stratification models, such as those recommended by the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA), primarily rely on structural parameters like maximal left ventricular wall thickness and family history of SCD.[3] However, these models inadequately account for electrical instabilities, particularly in patients within the "gray zone"—those with intermediate SCD risk who do not clearly meet ICD implantation criteria but may still be at significant risk.[4] This limitation contributes to clinical uncertainty,

ORIGINAL INVESTIGATION

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potentially leading to either unnecessary ICD placements or underestimation of SCD risk.[4]

Recent studies highlight the insufficiency of conventional models in stratifying patients in the gray zone, emphasizing the need for advanced tools that assess both structural and electrical heterogeneity in HCM.[5] Electrical instability, due to heterogeneous myocardial fibrosis and abnormal repolarization, plays a critical role in HCM's arrhythmogenic potential. Consequently, integrating advanced electrophysiological parameters could improve SCD risk prediction. The 2019 Enhanced ACC/AHA strategy incorporated additional clinical and electrocardiographic parameters, enhancing predictive accuracy.[6] However, even this advanced approach struggles to accurately assess gray zone patients, underscoring the need for innovative markers that more precisely evaluate electrophysiological stability.

New electrocardiographic markers, including the Index of Cardiac Electrophysiological Balance (ICEB) and its heart rate-corrected version (ICEBc), have been developed to address these limitations. The ICEB evaluates the balance between ventricular depolarization (QRS duration) and repolarization (QT interval), providing a more comprehensive assessment of electrical stability. The ICEBc offers improved risk prediction by adjusting for heart rate variability.[7,8] These parameters are particularly relevant in HCM, where myocardial fibrosis and electrical heterogeneity increase the risk of reentrant ventricular arrhythmias (VAs). Unlike traditional parameters, ICEB and ICEBc provide an integrated evaluation of depolarization and repolarization dynamics, offering a more accurate representation of myocardial electrical stability.

Traditional parameters like the Tp-e interval, Tp-e/QTc ratio, and QRS-T angle are widely used to assess repolarization heterogeneity but fail to provide a holistic view of electrophysiological balance.[9-11] In contrast, ICEB and ICEBc offer a more nuanced assessment by quantifying the dynamic interaction between ventricular depolarization and repolarization, thus more accurately reflecting myocardial electrical stability.

HIGHLIGHTS

- European Society of Cardiology (ESC) sudden cardiac death (SCD) risk score is insufficient to predict the SCD risk, particularly in patients within the "gray zone"—those with intermediate SCD risk.
- Index of Cardiac Electrophysiological Balance (ICEB) shows an inverse correlation with Life-Threatening Arrhythmias (LTA) risk, indicating that higher ICEB values are associated with lower LTA risk.
- The ICEB addition to ESC SCD risk score increases the area under the curve to 0.79, achieving the highest predictive power for SCD risk.
- The Base Model (SCD risk score) alone shows moderate predictive accuracy, whereas adding ICEB significantly improves SCD risk prediction, particularly enhancing risk assessment in gray zone patients.

This study aims to evaluate the prognostic utility of ICEB and ICEBc in predicting Life-Threatening Arrhythmias (LTA) and NSVT in HCM patients, comparing their predictive performance with conventional risk factors. It is hypothesized that ICEB and ICEBc will enhance SCD risk stratification, particularly for gray zone patients, by providing a more comprehensive assessment of electrical stability. This approach aims to improve the identification of high-risk HCM patients, ultimately guiding more precise ICD implantation decisions.

METHODS

Study Design and Patient Selection

This retrospective observational study was conducted at a tertiary cardiovascular center specializing in HCM, between 2017 and 2023. Patients were included if they were diagnosed with HCM according to the 2024 AHA/ACC guidelines, which define HCM as a left ventricular wall thickness of ≥15 mm in the absence of other identifiable causes of hypertrophy.[1] This criterion ensured accurate classification and risk stratification of HCM patients.

Patients were categorized into 3 groups based on the presence and severity of VAs:

- Life-Threatening Arrhythmias Group: Patients who experienced sudden cardiac arrest (SCA) or received appropriate ICD therapy for sustained ventricular tachycardia (VT) or ventricular fibrillation (VF).
- Non-sustained VT (NSVT) Group: Patients with at least 1 episode of NSVT detected on Holter monitoring or ICD interrogation.
- Control Group: The HCM patients without documented VAs throughout the follow-up period.

Exclusion Criteria

Patients were excluded if they had cardiac conditions affecting ventricular repolarization, including bundle branch block, pre-excitation syndromes, or significant coronary artery disease. Those with a history of cardiac surgery or septal reduction therapy, which could alter myocardial architecture and electrophysiological properties, were also excluded. Additionally, patients using antiarrhythmic drugs or medications known to influence ventricular repolarization were excluded to ensure accurate assessment of repolarization parameters. Finally, patients with incomplete medical records or poor-quality electrocardiograms (ECGs), which could compromise the accuracy of repolarization measurements, were excluded to maintain the study's reliability and validity.

Electrocardiographic Assessment

A standard 12-lead ECG was recorded at a paper speed of 25 mm/s and a voltage of 10 mm/mV. The following repolarization parameters were manually measured by 2 independent cardiologists who were blinded to clinical outcomes:

- Index of Cardiac Electrophysiological Balance: Calculated as the QT/QRS ratio, reflecting the balance between ventricular depolarization and repolarization. It was introduced as a biomarker for identifying patients at increased arrhythmic risk.[7,8]

- Corrected ICEB: A heart rate-adjusted variant of ICEB, proposed as a more reliable predictor of arrhythmic risk.[7,8]
- Tp-e/QTc Ratio: Calculated by normalizing the Tp-e interval to the heart rate-corrected QT (QTc) interval, assessing repolarization heterogeneity. It is considered a more stable parameter than the Tp-e interval alone.[10,11]
- Tp-e Interval: Defined as the duration between the peak and end of the T wave, reflecting transmural dispersion of repolarization. It was measured in leads V4, V5, or V6. Prolonged Tp-e interval is associated with increased risk of SCD.[12]
- QRS-T Angle: Representing the discrepancy between ventricular depolarization and repolarization, it was determined using digital ECG analysis. A QRS-T angle ≥90° is associated with an increased risk of VAs.[13,14]

To minimize measurement variability, each parameter was measured 3 times, and the average value was used for analysis.

Study Hypothesis and Outcomes

The primary hypothesis of this study was that repolarization parameters, including the Tp-e interval, Tp-e/QTc ratio, QRS-T angle, ICEB, and ICEBc, are associated with the occurrence of VAs in patients with HCM. The primary outcome was the occurrence of LTA, which included SCA and appropriate ICD therapy for sustained VT or VF. The secondary outcome was the occurrence of NSVT, defined as at least 1 episode of NSVT detected on Holter monitoring or ICD interrogation.

Statistical Analysis

All statistical analyses were conducted using SPSS software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation for normally distributed data or as median (interquartile range, IQR) for non-normally distributed data, while categorical variables were presented as frequencies and percentages. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. For group comparisons, 1-way ANOVA was applied for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Post-hoc pairwise comparisons were performed using Tukey's HSD test for parametric variables and Bonferroni-adjusted Dunn's test for nonparametric variables. Categorical variables were compared using the chi-square test or Fisher's exact test.

To evaluate the incremental predictive value of ECG parameters, multiple logistic regression models were constructed, including the Base Model (ESC SCD Risk Score alone) and Base + individual ECG parameters (ICEB, ICEBc, QTc interval, Tp-e interval, Tp-e/QT ratio). Comprehensive multiple regression models including all ECG parameters simultaneously were not performed due to the limited number of endpoints, which could lead to overfitting, and the high collinearity among ECG variables, which increases variance inflation factors. Model performance was assessed using the Area Under the Receiver Operating Characteristic Curve (AUC-ROC), Akaike Information Criterion (AIC), and McFadden's R^2 (R^2McF), with lower AIC and higher R^2McF indicating better model fit. DeLong's test was applied for formal comparison of ROC curves. A P value <.05 was considered statistically significant throughout all analyses.

Ethical Considerations

The study was approved by the local ethics committee with a decision dated April 08, 2025 and numbered 2025/05/1075. Written informed consent was obtained from all participants or their legal guardians, and the study was conducted in accordance with the Declaration of Helsinki. The confidentiality of patient data was maintained, and no identifiable personal information was disclosed in the study report.

RESULTS

This study evaluated the predictive utility of various ECG parameters, focusing on the ICEB and ICEBc, for predicting LTA and NSVT in patients with HCM. ICEB and ICEBc, as novel markers of repolarization heterogeneity, demonstrated superior predictive power compared to traditional parameters, including the SCD Risk Score, QTc interval, Tp-e interval, and Tp-e/QTc ratio, confirming their enhanced utility in risk stratification.

Baseline Characteristics of the Study Population

The study was conducted on 127 patients diagnosed with HCM between 2017 and 2023, divided into 3 groups: LTA group (n = 45), NSVT group (n = 29), and control group (n = 53) (Table 1). There were no significant differences in age, gender, hypertension, diabetes mellitus, smoking status, and ejection fraction among the groups. However, interventricular septum and posterior wall thickness were significantly greater in the LTA group, indicating increased ventricular hypertrophy ($P < .05$). Additionally, the maximum gradient was markedly higher in the LTA group ($P = .039$), suggesting left ventricular outflow tract obstruction. Notably, ICD implantation rates were significantly elevated in the LTA (80%) and NSVT (79.3%) groups compared to the control group (30.2%, $P < .001$), reflecting an increased arrhythmogenic risk (Table 1).

Electrocardiographic Parameters and Arrhythmogenic Risk

The QRS duration was significantly longer in the LTA and NSVT groups compared with the control group ($P < .001$, Table 1), indicating an association between ventricular conduction abnormalities and increased arrhythmogenicity. The Tp-e interval was also significantly prolonged in the LTA (86.8 ± 16.1 ms) and NSVT (85.3 ± 18.9 ms) groups compared with the control group (78.2 ± 11.7 ms, $P = .015$), reflecting greater transmural dispersion of repolarization. Both the Tp-e/QT ratio ($P = .006$) and the Tp-e/QTc ratio ($P = .046$) were significantly higher in the arrhythmic groups, indicating increased repolarization heterogeneity.

Despite these differences, the QRS–T angle did not show statistical significance among the groups ($P = .152$), although a widening trend was observed in the LTA group, suggesting potential repolarization instability that requires further validation. The QT and QTc intervals also did not show significant differences (QT interval: $P = .842$; QTc interval: $P = .295$), indicating limited predictive value for VAs in this population. Although a positive association between QTc interval and LTA risk was suggested (Figure 1), its predictive power

Table 1. Baseline Demographic and Clinical Characteristics of Study Groups

Variables	LTA (n = 45)	NSVT (n = 29)	No Arrhythmia (n = 53)	*P*
Gender, male (%)	28 (62.2)	20 (69.0)	31 (58.5)	.646
Age (mean ± SD)	46 ± 12.9	50.6 ± 11.9	48 ± 12.9	.320
Hypertension (%)	13 (28.9)	10 (34.5)	16 (30.2)	.873
Diabetes mellitus (%)	2 (4.4)	1 (3.4)	6 (11.3)	.366
Smoking (%)	4 (8.9)	5 (17.2)	5 (9.4)	.475
Surgery (marrow) (%)	2 (4.4)	1 (3.4)	0 (0)	.329
Family history of SCD (%)	10 (22.2)	5 (17.2)	14 (26.4)	.634
Syncope (%)	15 (33.3)	12 (41.4)	14 (26.4)	.376
Ejection fraction (EF, %)	63 ± 4.73	63.1 ± 3.89	62.8 ± 5.79	.965
Interventricular septum (IVS, mm)	26 ± 6.21	24.2 ± 4.20	22 ± 5.80	.009[c]
Posterior wall thickness (PW, mm)	15.3 ± 5.29	14.9 ± 3.31	13.2 ± 2.81	.028[c]
Left ventricular end-diastolic diameter (LVEDD, mm)	42.6 ± 4.56	43.2 ± 3.76	43.6 ± 3.71	.462
Left ventricular end-systolic diameter (LVESD, mm)	26.2 ± 5.75	25.8 ± 4.28	27.0 ± 2.53	.422
Left atrium (LA, mm)	40.0 ± 6.40	40.8 ± 6.65	40.9 ± 5.86	.756
Maximum gradient (max grad, mm Hg)	68.5 (45-90.5)	55 (22-72)	37 (16-80)	.039[b]
Mitral valve regurgitation (MVR, %)	1 (2.2)	0 (0)	0 (0)	.583
ICD implanted (%)	36 (80)	23 (79.3)	16 (30.2)	<.001[b, c]
Follow-up duration (months)	(64-96)	72 (64-84)	70 (56-80)	–
DCCV vs. ATP (%)	10 (30.3)	11 (73.3)	N/A	<.001
Number of shocks	0 (0-8)	0 (0-17)	N/A	.293
ASA (%)	12 (26.7)	5 (17.2)	5 (9.4)	.080
Beta-blocker use (%)	30 (66.7)	22 (75.9)	52 (98.1)	<.001[b, c]
Calcium channel blocker (%)	3 (6.7)	0 (0)	4 (7.5)	.422
ACEI/ARB use (%)	6 (13.3)	3 (10.3)	17 (32.1)	.022[b, c]
Heart rate (bpm)	69.9 ± 15.6	70.9 ± 16.0	68.8 ± 10.1	.790
QRS duration (ms)	119 ± 37.8	116 ± 29.7	94.3 ± 12.4	<.001[b, c]
QT interval (ms)	421 ± 48.6	416 ± 44.5	421 ± 35.1	.842
QTc interval (ms)	454 ± 43.3	450 ± 46.6	442 ± 25	.295
Tp-e interval (ms)	86.8 ± 16.1	85.3 ± 18.9	78.2 ± 11.7	.015[c]
Tp-e/QT ratio	0.207 ± 0.035	0.205 ± 0.038	0.187 ± 0.028	.006[b, c]
Tp-e/QTc ratio	0.192 ± 0.035	0.190 ± 0.041	0.177 ± 0.023	.046[c]
QT dispersion (ms)	10.2 (5.7-27.6)	17.6 (12-28.4)	9.1 (5.3-12.1)	<.001[b, c]
QRS-T angle (degrees)	122 ± 33.2	121 ± 43.2	107 ± 46.6	.152
ICEB	3.70 ± 0.71	3.76 ± 0.77	4.52 ± 0.56	<.001[b, c]
ICEBc	4.01 ± 0.8	4.07 ± 0.78	4.77 ± 0.65	<.001[b, c]
SCD risk score	8.04 (5.2-10.4)	9.6 (5.6-12.6)	2.4 (1.6-3.49)	<.001[b, c]
Mortality (%)	0 (0)	1 (3.4)	1 (1.9)	.702

Values are presented as n (%), mean ± SD, or median (IQR). $P < .05$ indicates statistical significance.
[a]LTA vs. NSVT.
[b]NSVT vs. control group.
[c]LTA vs. control group.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker, ASA, alcohol septal ablation; ATP, anti-tachycardia pacing; DCCV, direct current cardioversion; EF, ejection fraction; ICD, implantable cardioverter defibrillator; ICEB, Index of Cardiac Electrophysiological Balance; ICEBc, Corrected Index of Cardiac Electrophysiological Balance; IVS, interventricular septum; LA, left atrium; LTA, Life-Threatening Arrhythmias; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; Max Grad, maximum gradient; MVR, mitral valve regurgitation; NSVT, non-sustained ventricular tachycardia; PW, posterior wall thickness; QRS, QRS complex on ECG; QT, QT interval on ECG; QTc, corrected QT interval; SCD, sudden cardiac death; Tp-e, T-peak to T-end interval; Tpe/QT, ratio of Tpe interval to QT interval.

remains limited in this cohort. Heart rate likewise did not differ significantly between groups ($P = .790$).

Conversely, ICEB and ICEBc values were significantly lower in both the LTA (3.70 ± 0.71) and NSVT (3.76 ± 0.77) groups compared with the control group (4.52 ± 0.56, $P < .001$, Table 1). These findings indicate that reduced ICEB and ICEBc values are strongly associated with increased VA risk, reflecting enhanced repolarization heterogeneity and electrical instability (Figure 1).

Prediction of Life-Threatening Arrhythmias

The ROC analysis demonstrated the superior discriminatory power of ICEB and ICEBc compared to traditional ECG parameters (Table 2). The Base Model, which included only

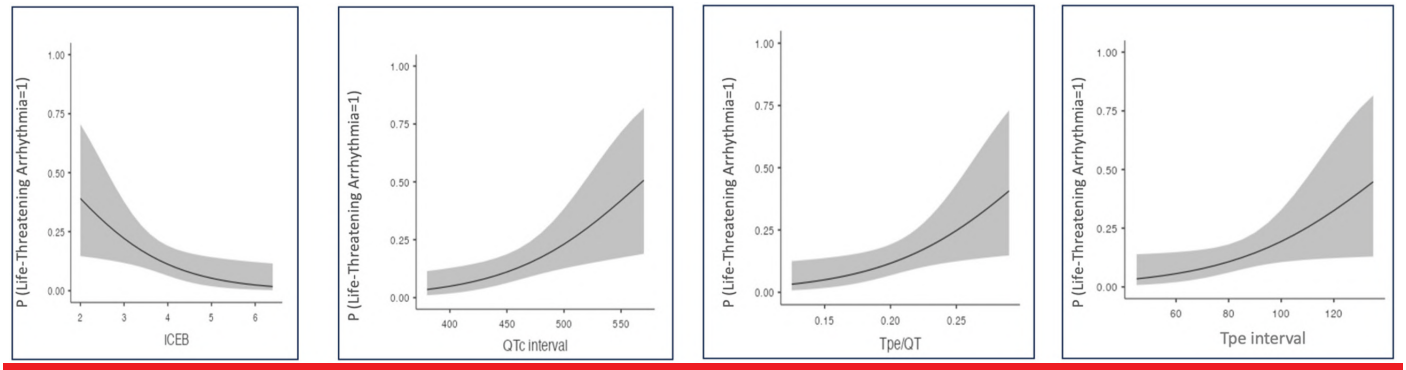

Figure 1. Partial effect plots for predicting Life-Threatening Arrhythmias (LTA) using ICEB, QTc interval, Tp-e/QT ratio, and Tp-e interval. These plots illustrate the relationship between ICEB, QTc Interval, Tp-e/QT Ratio, and Tp-e interval with the probability of Life-Threatening Arrhythmias (LTA); ICEB shows an inverse correlation with LTA risk, indicating that higher ICEB values are associated with lower LTA risk. This suggests that ICEB may reflect electrical stability. QTc Interval, Tp-e/QT Ratio, and Tp-e interval display positive associations with LTA risk, showing that higher values of these parameters are linked to an increased risk of LTA.

the ESC SCD Risk Score, showed moderate discriminatory capability (AUC = 0.74). In contrast, adding ICEB to the model significantly improved its predictive power, yielding the highest AUC of 0.79, confirming ICEB's effectiveness in predicting LTA risk (Figure 2). For LTA, an ICEB cut-off of 3.84 was identified (AUC = 0.707, sensitivity 76.8%, specificity 60%), while the corresponding cut-off for ICEBc was 4.08 (AUC = 0.668, sensitivity 76.8%, specificity 62.2%) (Supplementary Table 1).

Table 2. Incremental Predictive Value of ECG Parameters Added to the ESC SCD Risk Score for Life-Threatening Arrhythmias (LTA)

Model	AIC	BIC	R^2McF	AUC	Significant Predictors	Adjusted Odds Ratio (95% CI, *P*)
Base model	100	106	0.071	0.74	SCD risk score	OR = 1.15 (95% CI: 1.04-1.28, *P* = .006)
Base + QTc interval	95.4	104	0.138	0.75	QTc interval	OR = 1.02 (95% CI: 1.00-1.03, *P* = .047)
Base + Tp-e interval	98.0	107	0.113	0.74	Tp-e interval	OR = 1.04 (95% CI: 1.00-1.07, *P* = .039)
Base + Tp-e/QTc ratio	96.8	105	0.124	0.76	Tp-e/QTc ratio	OR = 9.27 (95% CI: 6.12-14.03, *P* < .001)
Base + ICEB	97.0	106	0.122	0.79	ICEB	OR = 0.44 (95% CI: 0.22-0.89, *P* = .021)
Base + ICEBc	96.2	105	0.128	0.77	ICEBc	OR = 0.47 (95% CI: 0.26-0.83, *P* = .011)

Values are presented as adjusted odds ratios (OR) with 95% CI and *P* values. A *P* value <.05 was considered statistically significant.

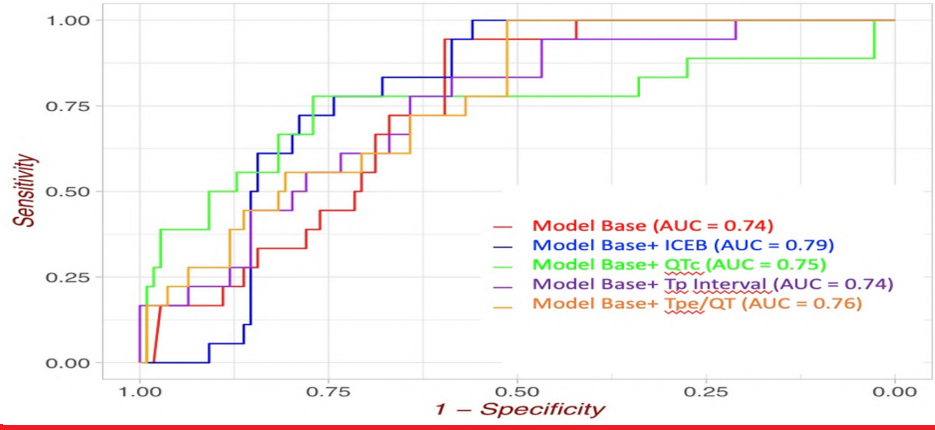

Figure 2. ROC curve for predicting Life-Threatening Arrhythmias using different models. The ROC curve compares the diagnostic performance of different repolarization parameters for predicting SCD risk in HCM patients: Base Model (AUC = 0.74): Includes only the ESC SCD Risk Score and shows moderate discriminatory power for predicting SCD risk. ICEB addition increases the AUC to 0.79, achieving the highest predictive power for SCD risk. Tp-e/QT ratio (AUC = 0.76) and QTc (AUC = 0.75) provide additional predictive value but are less effective than ICEB. Tp-e interval (AUC = 0.74) does not enhance the performance of the Base Model. The Base Model (SCD Risk score) alone shows moderate predictive accuracy, whereas adding ICEB significantly improves SCD risk prediction, particularly enhancing risk assessment in gray zone patients.

Traditional ECG parameters provided only minimal improvements in AUC values:

- Base + QTc Model: AUC = 0.75
- Base + Tp-e/QTc Ratio Model: AUC = 0.76
- Base + Tp-e interval Model: AUC = 0.74 (no improvement)

These findings illustrate the limited predictive value of conventional ECG markers in risk stratification, while ICEB emerged as the most effective predictor for LTA, highlighting ICEB's potential to enhance risk stratification and optimize preventive strategies in HCM patients.

Prediction of Non-Sustained Ventricular Tachycardia

ICEB and ICEBc emerged as the most powerful predictors of NSVT among all evaluated electrocardiographic parameters.

Figure 3 illustrates an inverse relationship between ICEB/ICEBc values and NSVT risk, indicating that higher ICEB or ICEBc values are associated with lower arrhythmic risk, emphasizing their role as markers of electrical stability. This inverse relationship remained consistent across all levels of the ESC SCD Risk Score, underscoring their robust predictive capacity.

As summarized in Table 3, adding ICEB or ICEBc to the Base Model (ESC SCD Risk Score alone) improved model performance, yielding the highest discriminative ability:

- Base + ICEB Model: AUC = 0.804
- Base + ICEBc Model: AUC = 0.801

For NSVT prediction, an ICEB cut-off of 4.09 (AUC = 0.696, sensitivity 65.4%, specificity 67.4%) and an ICEBc cut-off of

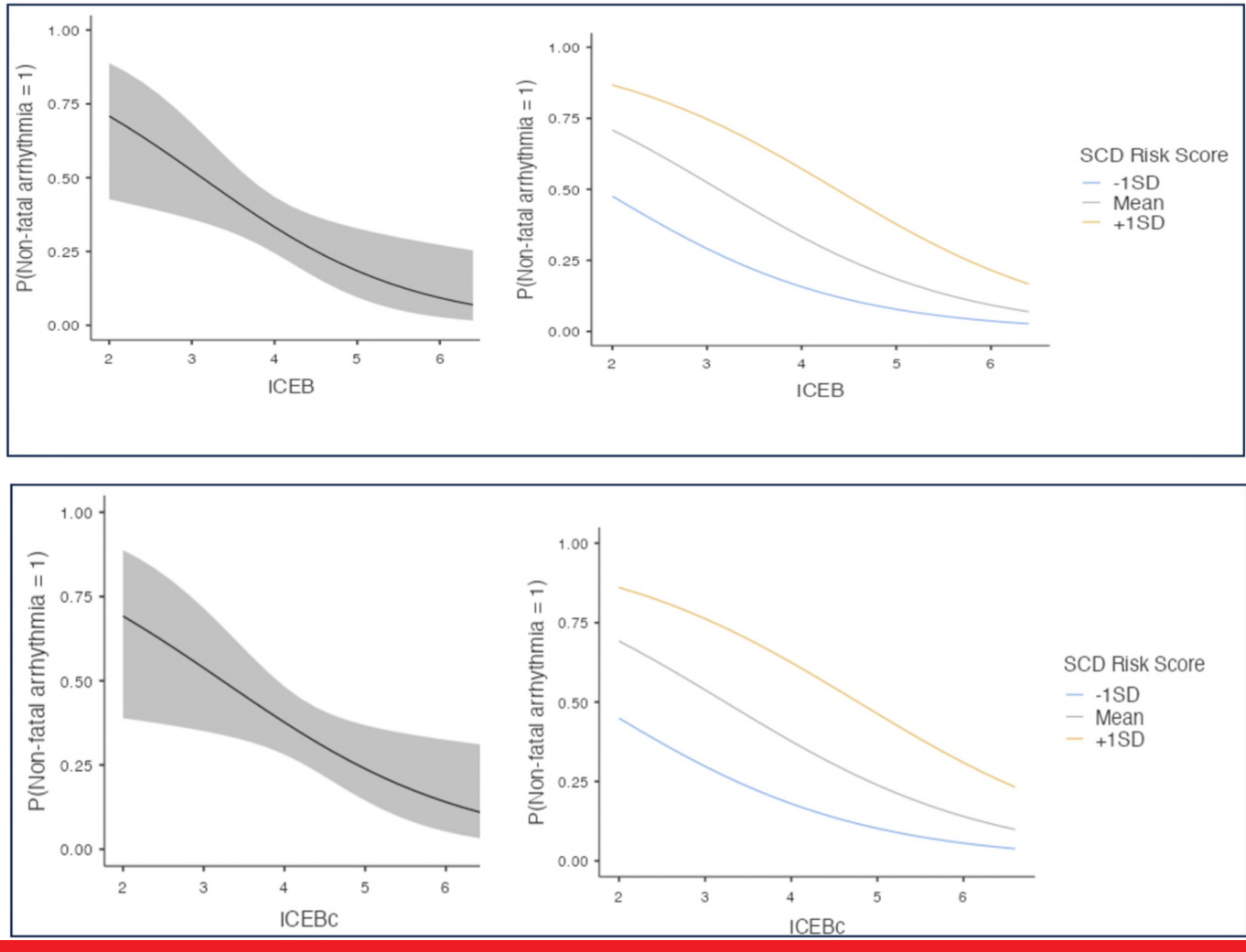

Figure 3. Prediction of NSVT using ICEB and ICEBc: interaction with ESC SCD Risk Score. This figure illustrates the relationship between ICEB and ICEBc with the probability of non-fatal arrhythmias, along with their interaction with the SCD Risk Score; Top Left (ICEB): Shows an inverse correlation with non-fatal arrhythmia risk, indicating that higher ICEB values are associated with lower arrhythmia risk. This suggests that ICEB may be a marker of electrical stability. Bottom Left (ICEBc): Similarly, higher ICEBc values correspond to reduced arrhythmia risk, consistent across both uncorrected and corrected versions. Top Right (ICEB with SCD Risk Score) and bottom right (ICEBc with SCD Risk Score): These plots display the interaction between ICEB/ICEBc and SCD Risk Score, with lines representing different levels of SCD Risk Score: −1SD (Blue): Represents patients with a lower-than-average SCD risk score, showing the lowest probability of arrhythmias. Mean (Gray): Shows a moderate risk profile, with a decreasing trend as ICEB/ICEBc increases. +1SD (Yellow): Represents high-risk patients with the highest probability of arrhythmias. However, increasing ICEB/ICEBc values are associated with a reduced risk, suggesting a potential protective effect even in high-risk groups.

Table 3. Incremental Predictive Value of ECG Parameters Added to the ESC SCD Risk Score for Non-Sustained Ventricular Tachycardia (NSVT)

Model	AIC	R^2McF	AUC	Significant Predictors	Adjusted Odds Ratio (95 % CI, *P*)
Base model	142	0.168	–	SCD Risk Score	OR = 1.267 (95% CI: 1.148-1.399, *P* < .001)
Base + QTc interval	144	0.168	–	SCD Risk Score	OR = 1.269 (95% CI: 1.148-1.400, *P* < .001)
Base + Tp-e interval	144	0.168	–	SCD Risk Score	OR = 1.269 (95% CI: 1.142-1.410, *P* < .001)
Base + Tp-e/QTc ratio	144	0.169	–	SCD Risk Score	OR = 1.258 (95% CI: 1.135-1.396, *P* < .001)
Base + ICEB	137	0.214	0.804	SCD Risk Score, ICEB	OR = 1.243 (95% CI: 1.124-1.374, *P* < .001) OR = 0.453 (95% CI: 0.253-0.810, *P* = .008)
Base + ICEBc	138	0.204	0.801	SCD Risk Score, ICEBc	OR = 1.250 (95% CI: 1.132-1.381, *P* < .001) OR = 0.519 (95% CI: 0.301-0.896, *P* = .011)

Values are presented as adjusted odds ratios (OR) with 95% CI and *P* values. A *P* <.05 was considered statistically significant. Both SCD Risk Score and ICEB/ICEBc were included in the same multiple logistic regression model; therefore, 2 odds ratios are reported for each model.

4.21 (AUC = 0.667, sensitivity 69.1%, specificity 60.1%) were identified (Supplementary Table 1).

These findings demonstrate that ICEB and ICEBc provide incremental predictive value beyond the ESC SCD Risk Score, supporting their potential integration into clinical risk-stratification frameworks for HCM.

Comparative Performance of Index of Cardiac Electrophysiological Balance and Its Corrected Variant in Predicting Non-Sustained Ventricular Tachycardia

The predictive utility of electrocardiographic parameters was assessed by comparing models incorporating ICEB, ICEBc, QTc interval, Tp-e interval, and Tp-e/QTc ratio with the Base Model, which included only the ESC SCD Risk Score. Figure 4 illustrates that ICEB and ICEBc provide higher sensitivity and specificity in predicting NSVT risk compared to conventional ECG parameters, with ROC curves positioned closer to the top-left corner, indicating superior discriminatory power. In contrast, traditional markers, including QTc interval, Tp-e interval, and Tp-e/QTc ratio, exhibited lower predictive ability, highlighting their limited utility for risk stratification in this cohort. Although DeLong's test revealed no statistically significant differences in discriminatory performance between the Base Model and any of the evaluated models for both LTA and NSVT endpoints, numerical trends toward improved model fit, along with lower AIC and BIC values when ICEB or ICEBc were added, suggest potential incremental predictive value. These findings indicate that, even in the absence of formal statistical significance, ICEB and ICEBc may provide clinically relevant information for risk stratification, particularly in gray zone patients.

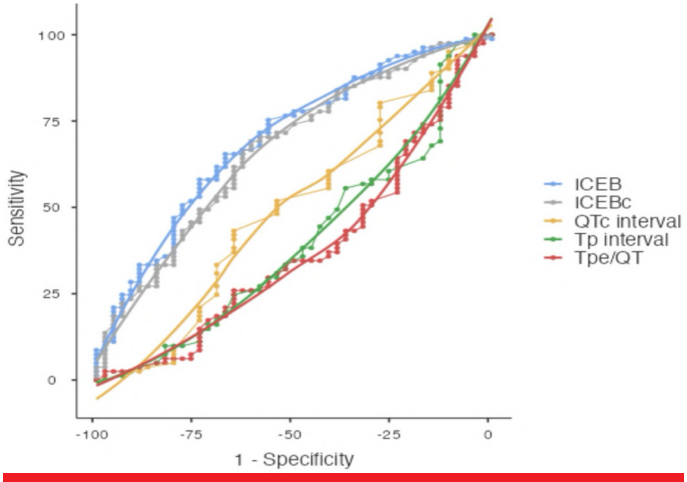

Figure 4. ROC curve: comparison of repolarization parameters in predicting NSVT. This ROC curve illustrates the performance of various repolarization parameters in predicting the risk of non-sustained ventricular tachycardia (NSVT) in patients with hypertrophic cardiomyopathy (HCM). The parameters compared are ICEB, ICEBc, QTc interval, Tp-e interval, and Tp-e/QT. The proximity of the curve to the top left corner indicates a higher combination of sensitivity and specificity. The results show that ICEB and ICEBc demonstrate the best performance in predicting NSVT, whereas Tp-e/QT and Tp-e interval exhibit lower predictive power.

Implications for Clinical Practice

These findings highlight the clinical utility of ICEB and ICEBc as robust markers of repolarization heterogeneity and effective risk stratification tools for predicting LTA and NSVT. Integrating ICEB and ICEBc into clinical practice could enable more accurate risk stratification and optimization of preventive strategies, particularly for HCM patients in the intermediate-risk (gray zone) category.

DISCUSSION

The findings indicate that the ICEB and its modified version may serve as effective predictors of LTA and NSVT in patients with HCM. Although further validation is required for definitive conclusions, these indices appear to provide a broader assessment of electrical stability by evaluating the dynamic interaction between ventricular depolarization and repolarization.[15]

The capacity of these indices to capture subtle electrical instabilities, such as repolarization heterogeneity and heart rate variability, may contribute to their prognostic value.[15] Specifically, in patients with an intermediate risk of SCD—those who cannot be clearly stratified by conventional models—these measures may allow for a more refined risk evaluation.[6] However, it is important to note that the observed association does not establish causality, and further prospective studies are needed to determine the impact of these parameters on clinical decision-making.

Traditional ECG parameters, including the Tp-e interval, Tp-e/QTc ratio, and QRS-T angle, are commonly used to evaluate repolarization heterogeneity and assess VA risk.[9,10] However, these conventional markers primarily reflect spatial repolarization dispersion and cannot adequately represent the complex interaction between depolarization and repolarization, which may limit their predictive performance.[12,13] Indeed, the current study, in line with prior evidence, demonstrated that conventional electrocardiographic indices have only limited predictive value.[14] Particularly in patients with borderline risk profiles, these parameters lead to ambiguous assessments, thereby complicating the clinical decision-making process. The ICEB and ICEBc, however, evaluate the dynamic interaction between ventricular depolarization and repolarization through a holistic approach, providing a more accurate representation of myocardial electrical stability. Given that heterogeneous myocardial fibrosis in HCM causes electrical instability and increases the risk of reentrant VAs, the ability of ICEB and ICEBc to sensitively measure this dynamic balance suggests that they may serve as more reliable electrophysiological stability indicators compared to traditional ECG parameters, particularly in gray zone patients.[16,17]

In HCM, late gadolinium enhancement (LGE) on cardiac magnetic resonance—a marker of myocardial fibrosis—may be associated with surface electrocardiographic abnormalities. It has been reported that patients with enhancement may exhibit substantially wider QRS-T angles, and a frontal QRS-T angle ≥90° may predict the presence of fibrosis.[18] These observations may support the concept that repolarization and conduction heterogeneity could reflect the underlying fibrotic substrate. Given that the ICEB is derived from the QT interval and QRS duration, it may have the potential to capture related electrophysiological imbalance; however, to the best of knowledge, a direct association between the index and LGE specifically in HCM has not yet been demonstrated and warrants further investigation.[19]

The study findings suggest that ICEB and ICEBc may have potential for improving risk stratification and guiding preventive strategies in HCM patients, particularly those in the gray zone. The gray zone represents a subgroup of patients with intermediate SCD risk, where risk stratification may remain ambiguous, potentially influencing clinical decision-making.[6] When current risk models fail to adequately classify gray zone patients as either high risk or low risk, unnecessary ICD implantations or risk underestimation may occur. The ability of ICEB and ICEBc to detect changes in electrophysiological stability suggests that risk assessment could be improved for gray zone patients, potentially enhancing clinical decision-making and allowing for more targeted preventive strategies.[15] However, for these parameters to be implemented in clinical practice, validation in larger populations using prospective study designs appears necessary.[4] Additionally, the establishment of standardized cutoff values and assessment of long-term prognostic value remain important.

By incorporating electrophysiological balance into assessment, ICEB and ICEBc may provide incremental value to current guideline-based risk models that mainly focus on structural and clinical features.[1,3] Through direct evaluation of electrophysiological stability, these indices may have the potential to address limitations of conventional models that account for repolarization heterogeneity and electrical instability to a limited extent.[15] For patients in the gray zone, integration of ICEB and ICEBc into current risk models may enhance predictive accuracy and contribute to more systematic approaches in ICD implantation decisions.[4,5] This approach may allow for individualized risk assessments and could support clinical decision-making processes in a manner that may reduce both undertreatment and over-treatment scenarios. Nevertheless, the clinical utility of ICEB and ICEBc in gray zone patients requires comprehensive validation through multicenter, prospective studies. Investigation of their integration with genetic testing and advanced imaging modalities may also contribute to the development of more comprehensive risk assessment frameworks.

Limitations and Future Directions

This study has several limitations. The retrospective, single-center design and relatively small sample size may limit the generalizability of the findings. Moreover, the study predominantly included patients from a Turkish population, which may restrict the applicability of the results to other ethnic groups. Selection bias and confounding factors should also be considered. Especially high rate of ICD implantation in the LTA and NSVT groups may introduce a selection bias and influence the observed associations between ICEB/ICEBc and arrhythmic events.

The absence of genetic testing limits the understanding of genotype-phenotype correlations, which could influence repolarization heterogeneity and arrhythmic risk.[20] Recent multicenter studies from diverse populations, such as the Turkish cohort analysis by Oktay et al,[21] have demonstrated the importance of comprehensive genetic screening in identifying both sarcomeric and non-sarcomeric mutations that may influence electrophysiological properties and arrhythmic risk stratification in HCM patients. Additionally, the lack of comparison with advanced imaging techniques, such as cardiac magnetic resonance imaging and LGE, restricts the comprehensive evaluation of myocardial fibrosis and its relationship with electrophysiological instability.[22] Another limitation of the study is the lack of intraobserver and interobserver reproducibility analyses for ICEB and ICEBc measurements, which might have further strengthened the reliability of the results.

Future studies should aim to validate ICEB and ICEBc in larger, more diverse populations using prospective, multicenter designs. Additionally, integrating genetic testing and advanced imaging modalities may provide a more comprehensive risk assessment. Investigating the utility of ICEB and ICEBc in other cardiovascular populations characterized by electrophysiological instability could further expand their clinical applicability.

CONCLUSION

The ICEB and ICEBc are powerful predictors of LTA and NSVT in HCM patients. Their integration into current SCD risk stratification models could enhance predictive accuracy, particularly for patients in the "gray zone." This approach would lead to more accurate identification of high-risk patients, optimizing preventive strategies and improving clinical decision-making. This study demonstrates the superior predictive power of ICEB and ICEBc compared to traditional ECG parameters, offering a novel approach to risk stratification in HCM. Future studies should validate these findings in larger, multicenter cohorts and explore the integration of ICEB and ICEBc with advanced imaging techniques and genetic testing to develop more comprehensive and robust risk prediction models for HCM.

Ethics Committee Approval: The study was approved by the Institutional Review Board of Kartal Koşuyolu Training and Research Hospital with the decision dated April 08, 2025 and numbered 2025/05/1075.

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Supplementary Table 1. ROC-derived cut-off values, area under the curve (AUC), sensitivity, and specificity of ICEB, ICEBc, and repolarization parameters (QTc, TP interval, Tpe/QT) for predicting life-threatening arrhythmia (LTA) and non-sustained ventricular tachycardia (NSVT)

Variables	Cut-off (LTA)	AUC (LTA)	Sens (%)	Spec (%)	Cut-off (NSVT)	AUC (NSVT)	Sens (%)	Spec (%)
ICEB	3.84	0.707	76.8	60	4.09	0.696	65.4	67.4
ICEBc	4.08	0.668	76.8	62.2	4.21	0.667	69.1	60.1
QTc	480	0.564	35.5	87.8	453	0.494	43.2	65.2
TP interval	73.2	0.612	93.3	34.1	82.8	0.599	52.1	64.2
Tpe/QT	0.194	0.626	60	64.6	0.193	0.621	60.9	62.9

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Early Urinary Sodium Levels May Predict the Extent of Myocardial Injury and Need for Decongestive Therapy in Non–ST-Elevation Myocardial Infarction

ABSTRACT

Background: Urinary sodium (UNa) has been increasingly studied in heart failure as a marker of diuretic response, but its prognostic role in acute myocardial infarction (MI) remains unclear. The aim was to evaluate whether admission UNa could provide prognostic information in patients with non–ST-elevation MI (NSTEMI).

Methods: This prospective observational study included 47 selected NSTEMI patients admitted to the coronary care unit. Spot urinary sodium was measured at admission and patients were stratified according to the median UNa value (92 mmol/L). Clinical outcomes, including peak troponin, Global Registry of Acute Coronary Events (GRACE) score, need for in-hospital diuretic therapy, and length of stay, were assessed.

Results: Patients with lower UNa (<92 mmol/L) had significantly higher peak troponin levels (median 1089 vs. 350 ng/L, $P = .004$) and a greater need for diuretic therapy during hospitalization (70.8% vs. 26.1%, $P = .002$). Urinary sodium was inversely correlated with peak troponin ($r = -0.37$, $P = .011$) and diuretic requirement ($r = -0.54$, $P < .001$). In multivariable regression, admission UNa remained an independent predictor of myocardial injury. Receiver operating characteristic analysis showed moderate discriminative ability of UNa for both troponin elevation (area under the curve [AUC]: 0.73) and need for diuretic use (AUC: 0.81).

Conclusion: Admission urinary sodium may serve as a simple, non-invasive adjunctive marker for risk stratification in NSTEMI, reflecting the neurohormonal activation. These findings suggest that UNa may complement established tools such as troponin and GRACE score in early evaluation.

Keywords: Neurohormonal activation, NSTEMI, urinary sodium

INTRODUCTION

Acute myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide, despite advances in early reperfusion strategies and pharmacological therapy. Reliable and easily accessible biomarkers that reflect both myocardial injury and systemic pathophysiology are essential to improve risk stratification in this high-risk population. While serum troponin remains the cornerstone biomarker for the diagnosis, quantification of myocardial necrosis and determining short- and long-term prognosis, recent research has suggested that indices of neurohormonal activation may provide complementary prognostic information by reflecting hemodynamic and inflammatory response to the acute coronary syndrome.[1-4]

Urinary sodium (UNa) has recently gained attention as a practical marker in both acute and chronic heart failure (HF), particularly for evaluating diuretic response, and is now recommended by guidelines.[5,6] Low UNa levels after loop diuretic administration consistently predict poor natriuretic response, insufficient decongestion, and adverse clinical outcomes including rehospitalization and mortality.[7,8] Similarly, lower admission UNa in acute HF has been associated with adverse short- and long-term outcomes, reflecting heightened neurohormonal activity,

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poor diuretic response, and increased risk of renal dysfunction.[9] These findings highlight impaired renal sodium excretion as a surrogate of systemic neurohormonal activation and cardiorenal dysfunction. Beyond HF, in the hypertensive population, it has been shown that low UNa excretion, often reflecting low dietary sodium intake, is independently associated with a higher risk of MI, particularly in men. This association is thought to be partly mediated by activation of the renin–angiotensin-aldosterone system (RAAS).[10] Taken together, these findings illustrate the lower limb of the well-described J-shaped relationship between urinary sodium excretion and cardiovascular outcomes, underscoring that low sodium excretion has been associated with increased cardiovascular risk.[11]

Neurohormonal activation, involving both sympathetic stimulation and the RAAS, is one of the key determinants of adverse outcomes in acute MI. In addition to worsening hemodynamic instability, this maladaptive response amplifies ischemic complications and increases the risk of arrhythmias, HF, and early mortality.[1,2,12] To date, no study has specifically investigated the impact of admission UNa levels on clinical outcomes in patients with acute MI. Several confounding factors may influence UNa in this setting, including the use of diuretics for congestion, contrast exposure during angiography, and the timing of urine sampling and the invasive management. In STEMI, the urgent need for reperfusion therapy usually precludes measuring baseline UNa. In contrast, in carefully selected NSTEMI patients, this assessment may be both feasible and informative. In this study, the prognostic significance of admission spot UNa was investigated in a carefully selected cohort of NSTEMI patients without prior diuretic use or overt decompensation. Specifically, the association of lower UNa levels with more severe myocardial injury, reflected by higher peak troponin concentrations, and with indicators of clinical risk, including Global Registry of Acute Coronary Events (GRACE) score, extent of coronary artery disease, signs of congestion, and length of hospital stay, was examined. By exploring these associations, this study provides preliminary evidence that early spot UNa measurement may serve as a simple, non-invasive marker of both disease severity and early prognosis in acute NSTEMI.

HIGHLIGHTS

- Admission urinary sodium was evaluated as a prognostic marker in non–ST-elevation myocardial infarction (NSTEMI) patients.
- Lower urinary sodium (UNa) was independently associated with greater myocardial injury (higher peak troponin).
- Patients with lower UNa had a significantly higher need for diuretic therapy during hospitalization.
- Urinary sodium demonstrated moderate discriminative ability in receiver operating characteristic analysis for both ischemic injury and congestion.
- Urinary sodium may provide complementary information to troponin and Global Registry of Acute Coronary Events score in early NSTEMI risk stratification.

METHODS

Study Design and Population

This prospective, observational study was conducted in the Cardiovascular Intensive Care Unit of Ankara University Hospital between September 2023 and April 2024. The study protocol was approved by the Ankara University Ethics Committee (approval date: January 30, 2023, approval code: 18-2023000018-2), conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. Consecutive patients aged ≥18 years with a confirmed diagnosis of NSTEMI with planned early coronary angiography established according to current European Society of Cardiology (ESC) guidelines were enrolled.[12] Patients were followed until discharge or in-hospital death.

Patients were excluded if they had active malignancy, severe liver disease, or chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation). Other exclusion criteria included a known history of chronic or decompensated HF at presentation, hemodynamic instability or cardiogenic shock, urgent indication for primary percutaneous coronary intervention (PCI), ongoing diuretic therapy at admission (including loop diuretics, thiazides, or mineralocorticoid receptor antagonists) or the need for diuretics before urine sampling. Patients receiving antihypertensive regimens that included diuretics were also excluded. Patients with dehydration or hypotension, severe infection, and non-ischemic causes of troponin elevation as judged by the attending physician, patients with MI with non-obstructive coronary arteries (MINOCA) on angiography, electrolyte disturbances (hyponatremia or hypernatremia), or known endocrine disorders affecting sodium balance were also excluded. Finally, patients with recent exposure to nephrotoxic drugs, intravenous contrast agents within the last 7 days, chronic corticosteroid or nonsteroidal anti-inflammatory drug (NSAID) use, or those unable to provide a urine sample before coronary angiography at admission were not eligible for inclusion.

Clinical and Laboratory Assessments

On admission, all patients underwent a comprehensive clinical evaluation including medical history, physical examination, and in-hospital risk was assessed using the GRACE 2.0 score, as recommended by current ESC guidelines.[12] The presence of hypertension, diabetes mellitus, and hyperlipidemia was determined based on established clinical criteria or ongoing treatment. Hypertension was defined as a documented history of elevated blood pressure (≥140/90 mm Hg) or the use of antihypertensive medications. Diabetes mellitus was diagnosed in patients with a prior clinical diagnosis, glycated hemoglobin (HbA1c) ≥6.5%, fasting plasma glucose ≥126 mg/dL, or those on antidiabetic therapy. Hyperlipidemia was identified by a documented history, elevated serum lipid levels according to guideline thresholds, or the use of lipid-lowering medications.

Transthoracic echocardiography was performed within 24 hours using a Vivid 9 ultrasound system (GE Medical Systems,

Milwaukee, WI, USA). Left ventricular ejection fraction (EF) was calculated with the modified Simpson's method according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations.[13]

Peripheral venous blood and spot urine samples were collected simultaneously on admission, before any intravenous or oral diuretic administration. Patients who required either oral or intravenous diuretic therapy at any point during hospitalization due to clinical signs of congestion were classified as having a need for diuretic treatment. All patients underwent routine coronary care unit laboratory testing at admission, including standard biochemistry, complete blood count, and baseline high-sensitivity cardiac troponin T (hs-cTnT) measurement. Hs-cTnT was measured using the Elecsys Troponin T hs assay (Roche Diagnostics, Mannheim, Germany). Measurements were obtained at admission and then at 24-hour intervals for 2 consecutive days. Both the admission value and the peak troponin level within 48 hours were included in analyses. All samples, including the spot urine, were promptly processed in a certified central laboratory. In patients with an indwelling urinary catheter, urine samples were obtained at the time of catheter insertion. Urinary sodium was analyzed in spot samples and the results were analyzed both as a continuous variable and stratified by the cohort median (92 mmol/L). Renal function was estimated using the CKD-EPI creatinine equation, in line with current recommendations.[14]

Coronary Angiography and Treatment

All included patients were considered high risk and were managed with an early invasive strategy in accordance with ESC guidelines.[12] The time interval from diagnosis to angiography was recorded in hours for each patient. Coronary angiography was performed within 24 hours of admission, and the revascularization strategy (PCI, coronary artery bypass grafting [CABG], or medical therapy) was determined by the Heart Team or the attending interventional cardiologist. Percutaneous coronary intervention was performed by experienced operators in the certified laboratory, with radial access preferred when feasible. All patients received guideline-directed pharmacological therapy.[12]

The number of diseased coronary arteries was determined by visual estimation of luminal stenosis. Significant coronary artery disease was defined as ≥70% diameter stenosis in an epicardial artery with a reference vessel diameter of ≥2.0 mm, or ≥50% stenosis of the left main coronary artery.

Data Collection

Clinical, laboratory, and procedural data were recorded, including baseline and peak troponin levels, echocardiographic parameters, GRACE score, number of diseased coronary vessels, length of hospital stay, and the requirement for decongestive therapy during hospitalization. All patients were monitored throughout their hospital stay until discharge or in-hospital death, and clinical events occurring during this period were systematically documented.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD or as median with interquartile range (IQR), depending on distribution assessed by the Shapiro–Wilk test. Due to the skewed distribution of troponin values, results were reported as median (IQR), and comparisons between groups were performed using the Mann–Whitney *U*-test. Categorical variables were summarized as counts and percentages.

Patients were stratified according to the median UNa concentration (92 mmol/L). Between-group comparisons were performed using the Mann–Whitney *U*-test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. Correlations between UNa (as a continuous variable) and clinical parameters, including peak troponin, length of hospital stay, left ventricular EF, GRACE score, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACE/ARB) were evaluated with Pearson's correlation coefficients. Correlation coefficients (r) and *P*-values were reported.

To identify independent predictors of clinical outcomes (peak troponin, hospital stay, EF, and the need for decongestive therapy), adjusted multiple regression analysis models were applied. Covariates included age, sex, diabetes mellitus, hypertension, eGFR, time to coronary angiography, number of diseased vessels, GRACE score, and UNa.

The prognostic value of UNa for categorical outcomes such as the requirement for diuretic therapy was further assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) and corresponding 95% confidence intervals were calculated. An optimal urinary sodium cutoff was determined using Youden's index, and sensitivity and specificity were reported.

A two-tailed *P*-value <.05 was considered statistically significant.

RESULTS

A total of 79 patients hospitalized with NSTEMI and planned for early coronary intervention were screened. After exclusions for early diuretic use prior to urine sampling (n = 7), inability to give urine samples before angiography (n = 7), refusal of angiography (n = 6), early transfer to surgery (n = 6), MINOCA as a result of the coronary angiography (n = 5), and 1 intraprocedural death, 47 patients completed the study protocol and were included in the final analysis. During hospitalization, 3 additional patients died—1 from fatal ventricular arrhythmia, 1 from ischemic stroke, and 1 from acute pulmonary edema refractory to therapy. These patients were not excluded from the analysis; however, given the small number of events, no statistical evaluation of mortality was performed.

The final study cohort had a mean age of 64.6 ± 10.5 years, and 36% were female. Hypertension was present in 81%, hyperlipidemia in 68%, diabetes mellitus in 49%, and 53% of patients were active smokers. The mean UNa concentration

on admission was 90.2 ± 32.7 mmol/L, with a median value of 92 mmol/L (IQR: 67.2-107.8). Patients were stratified into 2 groups according to this value: <92 mmol/L (n = 24) and ≥92 mmol/L (n = 23). Baseline demographics, cardiovascular risk factors, time to coronary angiography, and medication use were broadly similar between the groups. However, patients with lower UNa had significantly lower systolic and diastolic blood pressures, lower eGFR, and higher GRACE scores compared with those in the higher UNa group (Table 1).

Regarding clinical outcomes, patients with lower UNa had significantly higher baseline and peak troponin levels compared with those with higher UNa (baseline troponin: 169 vs. 78 ng/L, P = .012; peak troponin: 1089 vs. 350 ng/L, P = .004). They also required decongestive therapy more frequently during hospitalization (70.8% vs. 26.1%, P = .002) and had higher GRACE scores (138.4 ± 16.6 vs. 127.5 ± 18.4, P = .020). These differences are illustrated in Figure 1, showing significantly higher peak troponin concentrations and a greater proportion of patients requiring diuretic therapy in the low UNa group. In contrast, left ventricular EF, length of hospital stay, and the number of diseased coronary vessels did not differ significantly between the groups (Table 1).

Correlation analyses demonstrated that admission UNa was significantly associated with several clinical parameters. Lower UNa correlated strongly with the need for diuretic therapy during hospitalization (r = −0.54, P < .001) and with lower systolic blood pressure on admission (r = +0.71, P < .001). In addition, UNa was inversely related to both peak (r = −0.37, P = .011) and baseline troponin levels (r = −0.36, P = .014), as well as to length of hospital stay (r = −0.35, P = .015). By contrast, no significant correlations were observed between UNa and left ventricular EF or GRACE score (both P > .30). Ongoing use of ACE/ARB therapy, which may theoretically affect renal sodium handling, was not associated with admission UNa levels (P = .744). These relationships are summarized in Table 2 and correlation of UNa with troponin levels, diuretic need, and length of hospital stay are illustrated in Figure 2, which depicts the scatterplots and correlation lines for UNa against each of the examined parameters.

Table 1. Baseline Characteristics and Clinical Outcomes by Urinary Sodium Groups

Variables	Total (n = 47)	UNa < 92 mmol/L (n = 23)	UNa ≥ 92 mmol/L (n = 24)	*P*
Age (years)	64.6 ± 10.5	66.9 ± 9.6	62.2 ± 11.0	.140
Sex (Female/Male)	17/30	8/15	9/15	.540
Hypertension, n (%)	38 (80.9)	19 (82.6)	19 (79.2)	1.000
Diabetes mellitus, n (%)	23 (48.9)	12 (52.2)	11 (45.8)	.886
Hyperlipidemia, n (%)	32 (68.1)	19 (82.6)	13 (54.2)	.075
Smoking, n (%)	25 (53.2)	12 (52.2)	13 (54.2)	1.000
History of coronary artery disease, n (%)	16 (34.0)	7 (30.4)	9 (37.5)	.839
Statin use, n (%)	26 (55.3)	12 (52.2)	14 (58.3)	.896
Beta-blocker use, n (%)	25 (53.2)	15 (65.2)	10 (41.7)	.185
ACE/ARB use, n (%)	32 (68.1)	17 (73.9)	15 (62.5)	.599
Calcium channel blocker use, n (%)	19 (40.4)	7 (30.4)	12 (50.0)	.285
Systolic BP (mm Hg)	132.2 ± 21.0	118.7 ± 16.1	145.2 ± 16.7	<.001
Diastolic BP (mm Hg)	79.4 ± 12.8	71.8 ± 10.0	86.7 ± 11.0	<.001
eGFR (mL/min/1.73m^2)	75.4 ± 19.9	69.8 ± 19.6	80.8 ± 19.0	.059
Creatinine (mg/dL)	1.07 ± 0.29	1.12 ± 0.33	1.03 ± 0.24	.304
Serum sodium (mmol/L)	136.8 ± 2.9	136.7 ± 3.1	137.0 ± 2.8	.724
Baseline troponin* (ng/L)	Median 123 (IQR 41-214)	Median 169 (IQR 91-374)	Median 78 (IQR 32-147)	.012
Peak troponin* (ng/L)	Median 566 (IQR 238-1113)	Median 1089 (IQR 561-1412)	Median 350 (IQR 214-706)	.004
LVEF (%)	46.4 ± 8.6	46.5 ± 9.3	46.2 ± 8.0	.789
GRACE score	132.8 ± 18.2	138.4 ± 16.6	127.5 ± 18.4	.020
Length of stay (days)	4.5 ± 1.5	4.0 ± 1.0	4.9 ± 1.7	.073
Need for diuretic use, n (%)	23 (48.9)	6 (26.1%)	17 (70.8%)	.002
Time to angiography (hours)	9.3 ± 6.3	8.0 ± 5.5	10.7 ± 6.8	.138
No. of diseased coronary arteries	1.81 ± 0.68	1.75 ± 0.68	1.87 ± 0.69	.558

Values are presented as mean ± SD, median (IQR), or number (percentage). Categorical variables were compared using chi-square or Fisher's exact test.
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; UNa, urinary sodium.
*Troponin values are shown as median (IQR) due to skewed distribution and compared using the Mann–Whitney U-test.

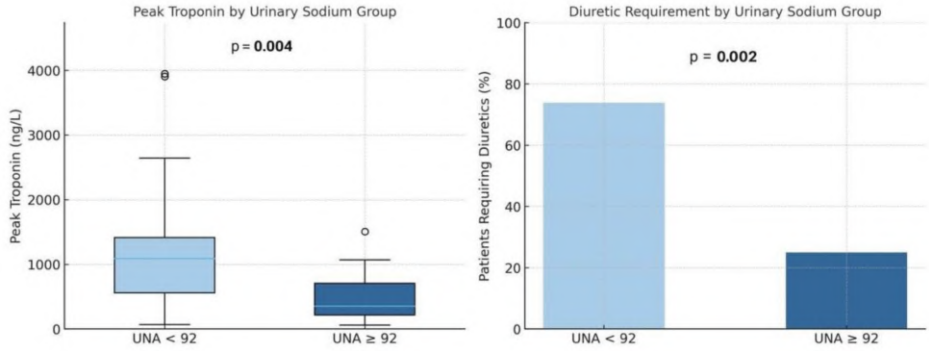

Figure 1. Comparison of clinical outcomes according to admission urinary sodium groups. At the left panel, patients with lower urinary sodium (<92 mmol/L) exhibited significantly higher peak troponin concentrations compared with those with higher urinary sodium (*P* = .004). At the right panel, the proportion of patients requiring diuretic therapy during hospitalization was also significantly greater in the low urinary sodium group (*P* = .002).

In adjusted multiple regression analysis according to age, sex, diabetes mellitus, hypertension, eGFR, time to angiography, number of diseased vessels, and GRACE score, admission UNa was independently and inversely associated with peak troponin levels (β = −11.6, *P* = .007). This indicates that each 1 mmol/L lower UNa corresponded to approximately 11.6 ng/L higher peak troponin. No other covariate reached statistical significance in the model.

Finally, ROC curve analyses were performed to evaluate the discriminatory performance of admission UNa. Urinary sodium demonstrated an AUC of 0.73 for predicting elevated peak troponin levels and an AUC of 0.81 for predicting the need for in-hospital diuretic therapy, indicating moderate prognostic ability (Figure 3). While these values do not reach thresholds typically considered diagnostic, they support a potential role for UNa as an adjunctive, easily obtainable marker in the early risk stratification of NSTEMI patients.

DISCUSSION

To the authors' knowledge, this is the first study to show that admission spot UNa provides clinically relevant information in patients presenting with NSTEMI. Lower UNa concentrations were independently associated with greater myocardial injury, reflected by higher peak troponin, and with an increased likelihood of requiring decongestive therapy during hospitalization. These associations were demonstrated in a carefully selected cohort without prior diuretic use or overt decompensated HF, minimizing confounding influences on UNa. In addition, UNa showed moderate discriminative ability in ROC analyses, supporting its potential role as a simple, non-invasive adjunct to early risk stratification in this setting.

Table 2. Correlation of Admission Urinary Sodium Concentration with Clinical and Laboratory Parameters

Parameters	Correlation Coefficient (*r*)	*P*
Need for diuretic use	−0.542	<.001
Systolic blood pressure	+0.705	<.001
Peak troponin	−0.367	.011
Baseline troponin	−0.356	.014
Length of hospital stay	−0.354	.015
Ejection fraction	+0.152	.309
GRACE score	−0.148	.320
ACE/ARB use	−0.049	.744

Correlation analyses were performed using Pearson correlation. *P* < .05 was considered statistically significant. UNa, urinary sodium; GRACE, Global Registry of Acute Coronary Events; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GRACE, Global Registry of Acute Coronary Events.

Urinary sodium has primarily been studied in HF, where it is recommended by the ESC Heart Failure Guidelines for early assessment of diuretic response, with values <50-70 mmol/L identifying insufficient natriuresis.[6] This approach is attractive because traditional metrics such as daily weight loss and urine volume often provide delayed or inaccurate feedback, potentially postponing timely adjustment of therapy. Studies suggest that spot UNa may be a useful marker of diuretic efficacy, allowing timely adjustment of therapy and proposed cutoff values to identify poor natriuretic response generally range between 50 and 100 mmol/L.[15,16] However, UNa must be interpreted with caution, as it is influenced by multiple factors, including kidney function, dietary sodium intake, prior diuretic therapy, and intravenous sodium administration. In this study, careful patient selection helped to minimize these potential confounders, although inter-individual variability can never be completely eliminated.

Peak troponin was used within the first 48 hours as a marker of myocardial injury. Troponin, a structural protein of the contractile apparatus, is released in a biphasic pattern after MI, with an initial peak at 24 hours. Reperfusion alters this kinetic profile, leading to variability in early values.[17] Ingkanisorn et al[18] were the first to investigate the relationship between early troponin values and infarct size measured by cardiac magnetic resonance imaging in patients with acute coronary syndromes. They reported that peak troponin-I strongly correlated with acute infarct mass in patients who underwent PCI within 6 hours of presentation ($r = 0.83$, $P < .001$).[18] In this study, NSTEMI patients underwent reperfusion on average

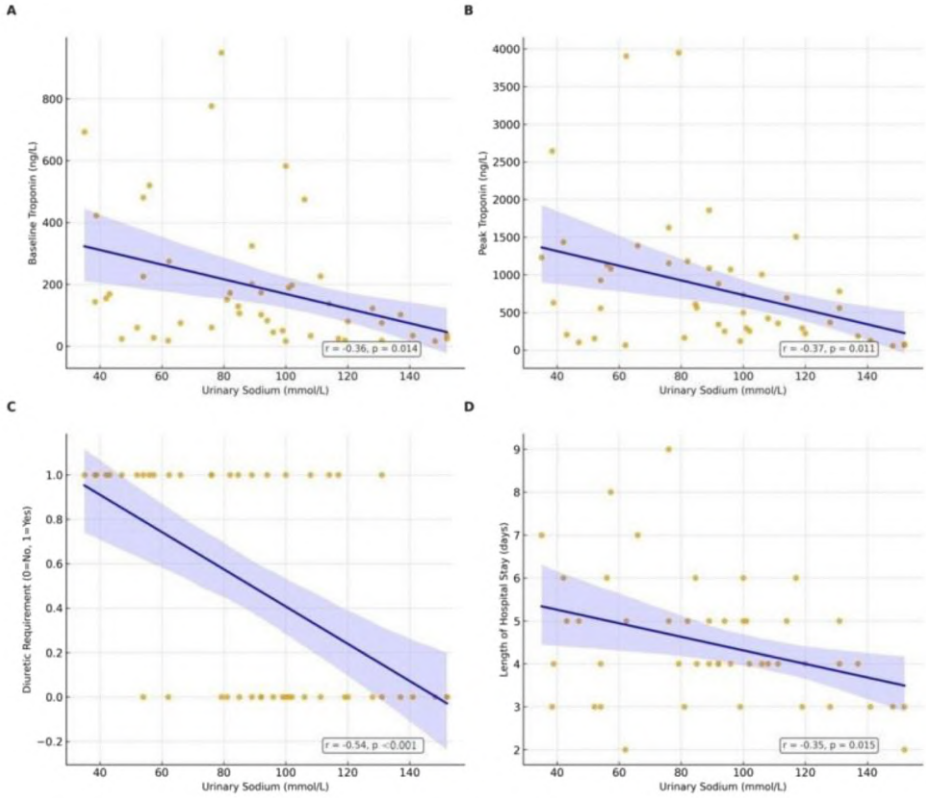

Figure 2. Correlations between admission urinary sodium concentration and (A) baseline troponin, (B) peak troponin, (C) diuretic requirement, and (D) length of hospital stay. Correlation coefficients (*r*) and *P*-values are shown in the panels.

within 9.3 ± 6.3 hours, and peak troponin levels measured within the first 48 hours were used as an indicator of myocardial injury. While not a precise quantification of infarct size, this approach, compatible with routine clinical practice, likely provides a meaningful estimate of the overall burden of myocardial necrosis.

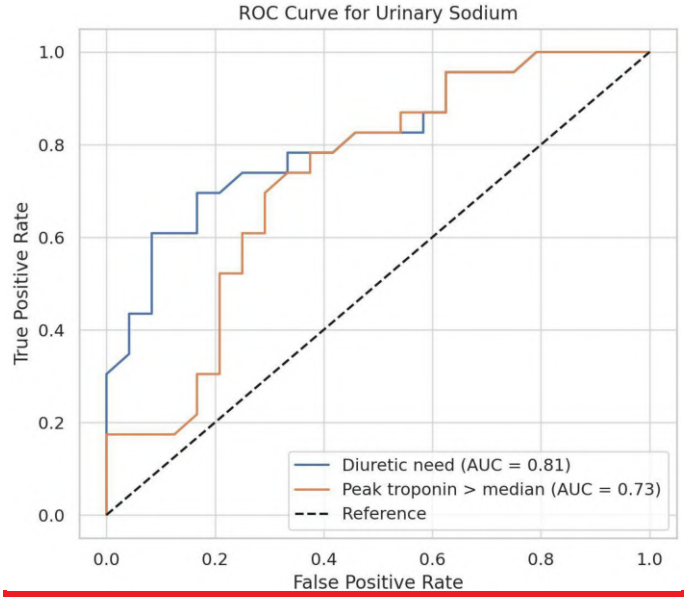

Figure 3. Receiver operating characteristic curve analysis of admission urinary sodium. Urinary sodium demonstrated moderate discriminative ability for predicting both (A) peak troponin levels above the median (AUC = 0.73) and (B) the in-hospital need for diuretic therapy (AUC = 0.81). The dashed line indicates the reference line of no discrimination.

The role of UNa in HF is well established, but its significance in acute MI has not been clearly defined. Myocardial infarction is characterized by a rapid neurohormonal surge, with activation of the sympathetic nervous system and RAAS. Excessive neurohormonal activity has been linked to arrhythmias, impaired ventricular function, and adverse ischemic complications.[19] Previous studies demonstrated that plasma catecholamines, angiotensin II, aldosterone, and atrial natriuretic peptide peak within the first 24 hours of infarction, and although they normalize in most patients, sustained elevations persist in those with left ventricular dysfunction or HF.[20] Neurohormonal activation is a hallmark of the acute phase of MI, and its persistence identifies patients at highest risk for complications and those most likely to benefit from therapies that attenuate these pathways.[21] In HF, impaired renal sodium excretion has been recognized as a surrogate of systemic neurohormonal activation and cardiorenal dysfunction.[7-9] Consistent with this framework, the finding that lower UNa was associated with greater myocardial necrosis and clinical congestion suggests that early disturbances in sodium handling may also reflect maladaptive neurohormonal responses in acute coronary syndromes. Using a median cutoff of 92 mmol/L, UNa demonstrated moderate discriminative ability in ROC analysis, supporting its potential role as a simple adjunctive marker for early risk stratification in NSTEMI. To the authors' knowledge, no studies

have specifically assessed the prognostic value of admission UNa in acute MI. Prior research has examined other markers of sympathetic activation, such as serum amylase, which has been associated with adverse in-hospital outcomes and GRACE score, or heart rate variability, an indirect measure of autonomic activity shown to predict adverse events after MI.[2,22] In this cohort, lower admission UNa was independently associated with greater myocardial injury, reflected by higher peak troponin concentrations, and with an increased likelihood of requiring decongestive therapy. These findings suggest that early sodium-handling abnormalities may mirror ischemic burden and neurohormonal activation in acute MI. Still, the single-center, limited sample design necessitates interpreting these results as hypothesis-generating pending external validation.

As a result, these findings suggest that admission UNa may provide complementary information in the management of acute MI. As a simple and readily available test, UNa could potentially help identify patients at greater ischemic risk and at higher likelihood of developing congestion during hospitalization. In this regard, UNa may serve as an adjunct to established tools such as troponin and the GRACE score, offering a broader perspective that integrates both myocardial injury and neurohormonal activation. While not diagnostic on its own, its ease of measurement makes it an attractive candidate for incorporation into early risk stratification strategies.

Study Limitations

Several limitations of this study should be acknowledged. First, this was a single-center study with a relatively small sample size, which limits the generalizability of the findings. Second, only selected NSTEMI patients without prior diuretic use, overt decompensated HF, or MINOCA were included, which restricts extrapolation to broader MI populations. Third, although UNa was measured at baseline before diuretic exposure, potential confounders such as dietary sodium intake, subclinical renal dysfunction, or prior non-reported outpatient therapies could not be fully excluded. Fourth, renal function was classified according to Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline criteria, based on eGFR alone, without assessment of albuminuria as recommended in the updated 2024 KDIGO guideline.[23] Another limitation is that patients presenting with low UNa at admission may have belonged to a subgroup with lower dietary sodium intake due to comorbid conditions or lifestyle factors, which could have influenced the present findings. There was no information on sodium consumption prior to admission, and therefore this potential confounding effect cannot be excluded. Also, detailed information on the duration and dosing of ACE/ARB therapy was not available; however, outpatient combined diuretic users were excluded and ACE/ARB exposure did not demonstrate a significant relationship with UNa. Another limitation was the evaluation of congestion and the subsequent need for diuretic therapy clinically by the attending physician, rather than by objective hemodynamic or imaging criteria. Although this reflects real-world practice and provides a pragmatic approach. Similarly, troponin was measured at baseline, 24 hours, and 48 hours in line with the routine NSTEMI practice; more frequent sampling might have provided a more precise definition of peak troponin. Finally, due to the small number of in-hospital deaths, mortality could not be analyzed as an outcome.

Ethics Committee Approval: Ethics committee approval was received from the Ankara University Ethics Committee (Approval date: January 30, 2023. Approval code: 2023/18-2023000018-2).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

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The Efficacy of Forest Therapy on Negative Emotions, Oxidative Stress, and Cardiovascular Disease Risk in Elderly Hypertensive Patients

ABSTRACT

Background: This study aims to explore the effects of forest therapy on negative emotional states, oxidative stress levels, and the risk of cardiovascular disease among elderly patients with hypertension.

Methods: A total of 120 eligible elderly hypertensive participants were randomly assigned to either a control group or an intervention group, utilizing a random number table, with each group comprising 60 individuals. The control group engaged in urban walking, while the intervention group underwent forest therapy. Following a 4-week intervention period, comparisons were made between the 2 groups regarding blood pressure, emotional well-being, and oxidative stress levels. Participants were subsequently followed for 12 months to evaluate the incidence of cardiovascular events.

Results: After the intervention, both groups exhibited significant reductions in systolic blood pressure and diastolic blood pressure, with the intervention group showing markedly greater improvements compared to the control group. Furthermore, the intervention group demonstrated a significantly greater increase in superoxide dismutase levels and a more pronounced decrease in malondialdehyde levels than the control group. Assessments of emotional health indicated that the intervention group had significantly lower scores in Tension-Anxiety, Anger-Hostility, Fatigue-Inertia, Depression-Dejection, and Confusion-Bewilderment, while scores for Vigor-Activity were significantly higher. The intervention group also exhibited a significantly reduced risk of cardiovascular events (hazard ratio = 0.340, $P = .018$, 95% CI: 0.120-0.950).

Conclusion: Forest therapy is an effective intervention for managing blood pressure, enhancing emotional well-being, and reducing oxidative stress levels in elderly hypertensive patients, ultimately contributing to a lower risk of cardiovascular events.

Keywords: Elderly hypertension, forest therapy, negative emotions, oxidative stress

ORIGINAL INVESTIGATION

INTRODUCTION

An estimated 7.5 million fatalities worldwide, or roughly 13% of yearly mortality rates, are attributed to hypertension, making it a significant risk factor for cardiovascular complications and mortality.[1,2] Apart from its high prevalence and multifaceted adverse effects, hypertension is also regarded as a preventable condition, underscoring the importance of blood pressure control in the prevention of disease and mortality.[3] The pathogenesis and progression of hypertension are influenced by a myriad of factors, including genetics, neuroendocrine mechanisms, organ dysfunction, lifestyle choices, and environmental factors.[4] Psychosocial stress is a prevalent modifiable risk factor contributing to the onset and exacerbation of hypertension. Stress-related alterations in blood pressure responses are mediated by changes in endothelial function, inflammation, and immune responses, which play a pivotal role in the progression of the disease.[5-7]

With an emphasis on the effects of forest settings on human health, forest therapy is a young multidisciplinary field that combines concepts from environmental medicine, alternative medicine, and preventive medicine.[8] This practice entails immersing individuals in natural settings and fostering connections through sensory engagement—sight, hearing, taste, smell, and touch—thereby bridging the

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divide between the human body and the natural world.[9] The serene ambiance, picturesque landscapes, mild climates, fresh air, and distinctive fragrances of forest environments are increasingly recognized for their ability to mitigate stress and promote relaxation.[10] Furthermore, volatile organic compounds emitted by plants, including alcohols, ketones, esters, and ethers, can alleviate stress and enhance mood by modulating parasympathetic nervous system activity, thereby improving both physical and mental well-being.[11] A systematic review has demonstrated that forest therapy significantly enhances cardiovascular function, immune response, and antioxidant activity, as well as markedly improving emotional well-being by alleviating anxiety and depression.[12]

In alignment with the Healthy China initiative, which has been established as a national strategic priority, the health industry in China is experiencing rapid growth. As an integral component of the health industry, forest therapy is garnering considerable attention for its potential applications in managing chronic diseases.[13] This study aims to investigate the efficacy of forest therapy in elderly patients with hypertension, providing robust evidence to support the broader implementation of this therapeutic approach.

METHODS

Study Design

This research was conducted as a prospective randomized controlled trial involving 120 elderly participants diagnosed with hypertension. Participants were randomly assigned to either a control group or an intervention group, with each group consisting of 60 individuals. The randomization process utilized a random number table to ensure unbiased allocation. Over a period of 4 weeks, both groups engaged in the intervention for 5 days each week, followed by 2 days of rest. The study protocol received ethical approval from the Institutional Ethics Committee, and all procedures were conducted in accordance with the ethical guidelines established in the Declaration of Helsinki for clinical research.

Study Population

Inclusion Criteria

1. Aged between 60 and 80 years, regardless of gender;
2. Systolic blood pressure (SBP) ranging from 140 to 159 mm Hg or diastolic blood pressure (DBP) between 90 and 99 mm Hg, or currently receiving antihypertensive medication;
3. New York Heart Association functional classification I-II; and
4. Capable of performing activities of daily living independently.

Exclusion Criteria

1. Presence of a cold or any acute illness within 2 weeks prior to enrollment or during the study;
2. History of cancer or chronic illnesses affecting the liver, kidneys, brain, heart, or lungs; and
3. Acute myocardial infarction or stroke within the 3 months preceding enrollment.

Intervention Methods

All participants were accommodated in a uniform hotel setting, where dietary intake and physical activity were closely monitored. Following randomization, the control group engaged in walking activities within urban areas, while the study group participated in a guided 2-hour forest walk that incorporated stimuli across the 5 senses: auditory, tactile, olfactory, visual, and gustatory.

To ensure standardization and participant safety, the forest therapy sessions were conducted under the supervision of 2 certified forest therapy guides who had completed accredited training programs in forest medicine and nature-based interventions. They were assisted by 1 physician and 1 nurse, who monitored participants' physiological status and ensured adherence to medical safety protocols.

A standardized forest therapy protocol, developed based on national forest health guidelines and previous research in forest medicine, was followed throughout the study. Each session began with a 5-minute orientation and breathing exercise, encouraging participants to focus on slow, deep breathing and relaxation. The guides provided structured verbal instructions to facilitate sensory engagement—for example: "Pay attention to the sound of leaves rustling and birdsong" (auditory); "Gently touch the surface of tree bark or leaves and notice the texture" (tactile); "Inhale deeply to perceive the scent of the forest air and nearby plants" (olfactory); "Observe changes in light, color, and movement around you" (visual); "If appropriate, taste approved edible leaves or flowers under supervision" (gustatory).

Throughout the walk, guides maintained a calm, reflective pace and encouraged participants to remain silent for parts of the session to deepen sensory perception and mindfulness. The same procedure was implemented for all intervention sessions to maintain consistency and reproducibility.

The total walking duration was approximately 60 minutes, covering about 3 kilometers. Throughout the study, participants were instructed to avoid strenuous exercise, smoking, and the consumption of alcoholic or caffeinated beverages, and to maintain their prescribed antihypertensive medications. The sensory stimulation components are detailed in Table 1.

HIGHLIGHTS

- Forest therapy is a multi-sensory nature-immersion intervention that integrates five sensory engagements to connect humans with natural environments.
- The intervention significantly reduces blood pressure and oxidative stress compared to urban walking in elderly hypertensive patients. It also markedly alleviates negative emotions and lowers the 12-month cardiovascular event risk.
- This work validates forest therapy as a valuable complementary clinical approach for elderly hypertension management and holistic health promotion.

Table 1. Sensory Stimulation Components

Sensory Modality	Main Content
Auditory	Listening to their breathing, the rustling of dry leaves, birdsong, and the sound of the wind.
Tactile	Experiencing the different textures of plants, leaves, rocks, wind, and soil through touch.
Olfactory	Appreciating the aromas provided by leaves, stems, and flowers.
Visual	Observing the landscape, including streams, small animals, rocks, large trees, and shrubs.
Gustatory	Tasting edible species of leaves and flowers.

Outcome Measures

Blood pressure and heart rate measurements, as well as fasting venous blood samples, were collected by qualified healthcare personnel between 7:00 and 7:30 AM, following an overnight fast, both before and after the intervention. After a 30-minute rest period, seated blood pressure was measured according to standardized operating procedures using a sphygmomanometer. All subjects were instructed to empty their bladders before measurement and were prohibited from consuming coffee or smoking. Blood pressure was measured 3 times consecutively, with a 30-second interval between measurements. If the differences between the readings exceeded 5 mm Hg, participants were asked to rest for an additional 5 minutes before repeating the measurements. The average of the 3 consecutive blood pressure readings was used. Concurrently, fasting venous blood samples were collected to assess oxidative stress markers, including superoxide dismutase (SOD) and malondialdehyde (MDA).

Post-intervention, the Profile of Mood States-Short Form (POMS-SF) was employed to evaluate emotional and mood states before and after the intervention. This assessment included 5 negative emotions: tension, anger, fatigue, depression, and confusion, as well as 2 positive emotions: vigor and self-esteem.

Following the intervention, all participants were followed up monthly for a total duration of 12 months to record the occurrence of cardiovascular adverse events, including angina pectoris, acute myocardial infarction, chronic heart failure, stroke, and cardiovascular mortality.

Statistical Methods

Statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data were first tested for normality using the Shapiro–Wilk test. Normally distributed continuous variables are presented as mean ± SD, while non-normally distributed variables are presented as median (interquartile range).

For blood pressure and oxidative stress indicators (SBP, DBP, SOD, and MDA), paired-sample t-tests were applied to assess within-group differences before and after the intervention, and independent-sample t-tests were used for between-group comparisons of changes. For the analysis of POMS subscale scores, a two-way repeated-measures analysis of variance (repeated-measures ANOVA) with 1 between-subject factor (group: control vs. study) and 1 within-subject factor (time: pre- vs. post-intervention) was conducted to evaluate both within-group (time) and between-group (group) differences, as well as their interaction. When significant interaction effects were observed, post hoc pairwise comparisons were performed to determine which specific between-group and within-group measurements differed. Categorical variables were expressed as frequencies and percentages, and analyzed using the chi-square (χ^2) test or Fisher's exact test.

For the analysis of cardiovascular event incidence, Kaplan–Meier survival curves were constructed and compared between groups using the log-rank test. Hazard ratios (HRs) with 95% CIs were calculated using the Cox proportional hazards model. A two-sided $P < .050$ was considered statistically significant. Graphical representations were generated using R packages ggplot2 and survminer.

RESULTS

Baseline Characteristics

Demographic data, including gender, age, body mass index, and duration of illness, as well as baseline clinical indicators such as SBP, DBP, MDA, and SOD, were well balanced (Table 2) (all P-values $>.050$).

Table 2. Baseline Characteristics

Characteristic	Control, n = 60	Study, n = 60	Statistic	*P*
Age (years)	66.57 ± 1.91	65.93 ± 2.35	1.62	.108
Gender			0.04	.850
Female	22 (36.7%)	23 (38.3%)		
Male	38 (63.3%)	37 (61.7%)		
BMI	23.68 ± 2.08	24.18 ± 2.35	−0.78	.439
Course of disease	7.62 ± 1.83	8.03 ± 1.84	−1.23	.222
Heart rate	74 ± 10	76 ± 11	−0.83	.411
Smoking, n (%)			0.03	.855
No	31 (51.7)	32 (53.3)		
Yes	29 (48.3)	28 (46.7)		
Drinking, n (%)			1.82	.178
No	43 (71.7)	36 (60.0)		
Yes	17 (28.3)	24 (40.0)		
SBP baseline	146 ± 10	166 ± 185	−0.82	.417
DBP baseline	86 ± 10	84 ± 11	0.67	.503
SOD baseline	44.9 ± 14.9	42.9 ± 15.1	0.73	.466
MDA baseline	10.04 ± 1.46	10.09 ± 1.50	−0.16	.871

BMI, body mass index; DBP diastolic blood pressure; MDA, malondialdehyde; SBP, systolic blood pressure; SOD superoxide dismutase.

Table 3. Blood Pressure

	SBP		DBP	
	Follow-Up	Mean Difference (95% CI)[a]	Follow-Up	Mean Difference (95% CI)[a]
Control group	142.2 ± 7.79	−13.94 (−16.80, −11.09)	82.3 (8.92)	−2.49 (−5.02, 0.04)
Study group	134.3 ± 13.83	−21.57 (−24.42, −18.72)	76.0 (10.69)	−8.83 (−11.36, −6.30)
Study - Control		−7.63 (−11.63, −3.63)		−6.34 (−9.89, −2.80)
P		<.001		<.001

DBP, diastolic blood pressure; SBP, systolic blood pressure. Note: "[a]" represents the change in the difference between post-intervention and pre-intervention values.

Blood Pressure

One month post-intervention, SBP and DBP were recorded and compared between the 2 groups, as detailed in Table 3. In the control group, the least squares mean change in SBP was −13.94 (−16.80, −11.09), and for DBP it was −2.49 (−5.02, 0.04). In the study group, the mean difference in SBP post-intervention was −21.57 (−24.42, −18.72), while for DBP it was −8.83 (−11.36, −6.30). Improvements in both SBP and DBP in the study group were more notable than in the control group.

Oxidative Stress

After 1 month of intervention, SOD and MDA levels were presented in Table 4. In the control group, the mean difference for SOD was 10.03 (7.20, 12.86), and for MDA it was −1.47 (−1.67, −1.27). In the study group, the mean difference for SOD was 21.12 (18.29, 23.95), while for MDA it was −1.95 (−2.15, −1.75). The increase in SOD and the decrease in MDA in the study group were both significantly greater than those in the control group.

Adverse Emotions

One month post-intervention, the POMS was employed to assess the emotional and mood states of the participants, with results depicted in Figure 1 and summarized in Table 5. A two-way repeated-measures ANOVA (group × time) demonstrated significant main effects of time and group, as well as significant group × time interaction effects for all POMS subscales (all *P*-values <.050). Compared with baseline, both groups showed reductions in negative emotion scores over time, but the study group exhibited markedly greater pre−post improvements in Tension-Anxiety, Anger-Hostility, Fatigue-Inertia, Depression-Dejection, and Confusion-Bewilderment. In contrast, Vigor-Activity increased to a significantly greater extent in the study group than in the control group. Post hoc comparisons further confirmed that, at post-intervention, all negative emotion scores were significantly lower and the Vigor-Activity score was significantly higher in the study group than in the control group.

Cardiovascular Events

All participants were followed up for 1 year post-intervention to document the occurrence of cardiovascular events. During the follow-up period, 16 individuals from the control group and 11 from the study group were lost to follow-up. By the end of the follow-up, 13 cardiovascular events were recorded in the control group, including 10 cases of angina pectoris, 2 strokes, and 1 myocardial infarction. In contrast, the study group reported 5 cardiovascular events, comprising 4 cases of angina pectoris and 1 stroke. In comparison to the control group, the study group saw a significantly decreased incidence of cardiovascular events ($\chi^2 = 5.557$, $P = .018$). The association between cardiovascular events and time was assessed using Kaplan−Meier analysis; the findings are shown in Figure 2. Cardiovascular events were considerably less likely to occur in the study group (HR = 0.340, $P = .018$, 95% CI: 0.120-0.950).

DISCUSSION

This study explored the effects of forest therapy on improving adverse emotional states, oxidative stress levels, and the prevention of cardiovascular events in elderly patients with hypertension. The findings substantiate that forest therapy is effective in enhancing blood pressure regulation, reducing oxidative stress, alleviating negative emotions, and decreasing the incidence of cardiovascular events. These results underscore the potential of forest therapy as a complementary approach for managing hypertension and promoting overall health in older adults.

Both groups demonstrated significant improvements in blood pressure. Previous research indicates that walking interventions lasting 20-40 minutes, conducted 3-5 times per week over a duration of approximately 15 weeks (in both indoor and outdoor environments), can lead to substantial reductions in blood pressure and heart rate.[14] Furthermore, walking offers numerous health benefits, including enhanced

Table 4. Oxidative Stress

	SOD		MDA	
	Follow-Up	Mean Difference (95% CI)[a]	Follow-Up	Mean Difference (95% CI)[a]
Control group	56.5 ± 6.46	10.03 (7.20, 12.86)	8.6 ± 0.64	−1.47 (−1.67, −1.27)
Study group	67.4 ± 13.80	21.12 (18.29, 23.95)	8.1 ± 0.91	−1.95 (−2.15, −1.75)
Study - Control		11.09 (7.05, 15.14)		−0.48 (−0.76, −0.20)
P		<.001		<.001

MDA, malondialdehyde; SOD superoxide dismutase. Note: "[a]" represents the change in the difference between post-intervention and pre-intervention values.

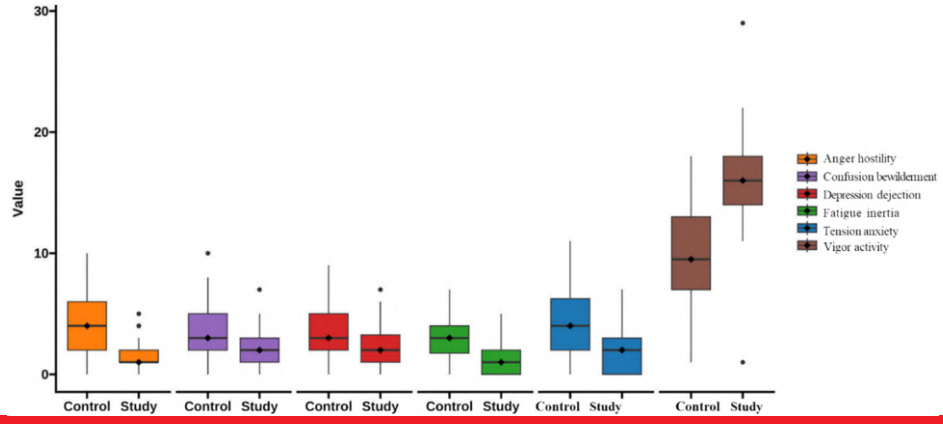

Figure 1. Changes in adverse emotions.

cardiovascular health, reduced risk of cardiovascular diseases, improved bone health, and effective weight management, all while posing a relatively low risk of adverse events.[15,16] The role of walking in mitigating negative emotional states has also been validated; a meta-analysis encompassing 75 randomized controlled trials revealed that various walking modalities effectively alleviate symptoms of depression and anxiety, with outcomes comparable to those of active therapeutic interventions.[17] Forest therapy may amplify the benefits associated with walking; for example, Ochiai et al[18] reported significant reductions in both systolic and DBP in middle-aged men with prehypertension following forest therapy. This study identifies similar effects in an elderly hypertensive cohort, suggesting that the beneficial impacts of forest environments on blood pressure regulation extend across different age demographics and levels of hypertension severity. The dual regulation of blood pressure by both the sympathetic and parasympathetic nervous systems may imply that forest therapy exerts its effects by attenuating sympathetic nervous system activity.[19,20]

In this investigation, serum MDA levels were significantly lower and SOD levels markedly higher in the study group compared to the control group. Oxidative stress is a critical factor in the pathophysiology of hypertension, and antioxidant therapies have demonstrated promise in both preventing and mitigating hypertension.[21,22] Ssuperoxide dismutase serves as a vital antioxidant enzyme that neutralizes superoxide anion radicals, thereby protecting cellular structures from oxidative damage.[23] Malondialdehyde, a product formed from the reaction between lipids and oxygen free radicals, serves as an indicator of lipid peroxidation levels.[24] Research conducted by Yamada et al[25] further corroborated that regular immersion in forest environments may help to attenuate oxidative modifications of proteins and lipids within the body. Additionally, Zhu et al[26] demonstrated that forest therapy positively influences immune function and overall well-being in patients with chronic fatigue, possibly through the modulation of the

nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4)/Reactive oxygen species (ROS)/ Nuclear factor kappa-B (NF-κB)

signaling pathway to mitigate chronic stress. According to the POMS questionnaire results, participants reported feeling more "comfortable," "natural," and "relaxed" following forest therapy, with a notable reduction in negative emotional states. Furthermore, when compared to urban walking, forest therapy emerged as an effective stress-reduction intervention, contributing to a decreased risk of psychosocial stress-related illnesses.[27] Importantly, this study included a 12-month follow-up period, thereby confirming the long-term cardiovascular benefits of forest therapy.

Table 5. Profile of Mood States Subscale Scores Before and After Intervention (Mean ± SD) and Between-Group Comparisons at Post-Intervention

Subscale	Control Group (Pre)	Control Group (Post)	Study Group (Pre)	Study Group (Post)	*P* (Between Groups at Post-Intervention)*
Tension-Anxiety	13.5 ± 2.8	11.2 ± 2.6	13.7 ± 2.9	8.6 ± 2.1	<.001
Anger-Hostility	12.8 ± 3.0	10.9 ± 2.5	13.1 ± 2.8	8.4 ± 2.0	<.001
Fatigue-Inertia	14.1 ± 3.1	12.3 ± 2.9	14.3 ± 3.2	9.1 ± 2.3	<.001
Depression-Dejection	15.0 ± 3.2	13.1 ± 3.0	15.3 ± 3.3	10.0 ± 2.4	<.001
Confusion-Bewilderment	12.6 ± 2.7	11.0 ± 2.5	12.8 ± 2.8	8.9 ± 2.2	<.001
Vigor-Activity	11.2 ± 2.6	12.5 ± 2.8	11.3 ± 2.7	15.8 ± 3.0	<.001

**P*-values are derived from post hoc between-group comparisons at post-intervention after a significant group × time interaction in the repeated-measures ANOVA.

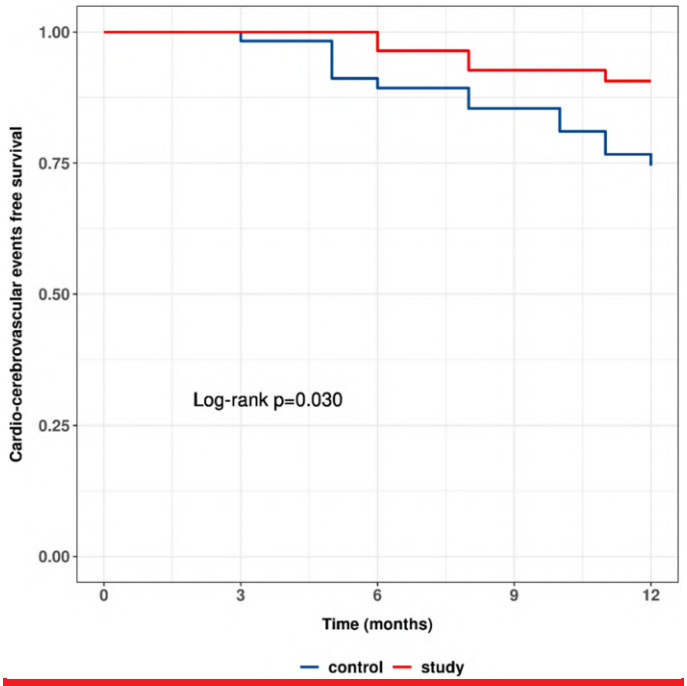

Figure 2. Kaplan–Meier curve of cardiovascular events.

The pronounced reduction in cardiovascular events observed in this study (HR = 0.340, *P* = .018, 95% CI: 0.120-0.950) likely reflects the cumulative physiological benefits of forest therapy across multiple interconnected domains. First, the significant decrease in both systolic and DBP reduces hemodynamic load on the vascular system, thereby lowering the risk of endothelial injury, a key precursor to atherosclerosis and thrombosis. Second, the observed enhancement of antioxidant capacity, reflected by higher SOD levels and reduced MDA concentrations, suggests attenuation of oxidative stress—a central mechanism in vascular inflammation, arterial stiffness, and plaque instability. Third, the improvement in negative emotional states such as tension, anger, and depression may indirectly contribute to cardiovascular protection by modulating autonomic nervous system balance and reducing sympathetic overactivity, which has been associated with elevated heart rate variability and reduced arrhythmic risk.

Taken together, these physiological and psychological adaptations form a synergistic mechanism that supports vascular homeostasis and reduces the likelihood of cardiovascular events. It is plausible that repeated exposure to restorative natural environments reinforces parasympathetic dominance, dampens systemic inflammation, and promotes endothelial nitric oxide production, collectively translating into tangible clinical benefits over time. Future mechanistic studies incorporating biomarkers of inflammation, autonomic function, and vascular reactivity are warranted to further elucidate these pathways.

Limitations

This study has several limitations that should be acknowledged. First, the sample size was relatively small, with 120 participants in total and only a limited number of cardiovascular events observed during the 12-month follow-up (13 in the control group and 5 in the study group). This small number of events reduces the statistical power of the HR estimation and leads to a wide CI (95% CI: 0.12-0.95). Second, the lack of blinding represents a potential source of bias. Because of the nature of the forest therapy intervention, it was not possible to blind either participants or researchers, which could have introduced expectancy bias, particularly in the subjective assessment of mood states using the POMS questionnaire. Third, this was a single-center study conducted within 1 geographical region, and therefore, the generalizability of the results to elderly populations in other cultural or environmental contexts may be limited. Finally, regarding intervention duration and sustainability, the study only evaluated short-term outcomes after a 4-week intervention. The long-term maintenance of behavioral or physiological benefits remains uncertain, as it is unclear whether participants continued similar activities following the study period. Future multi-center studies with larger sample sizes, longer follow-up durations, and more rigorous control of potential confounding factors are warranted to validate and expand upon these findings.

CONCLUSION

In elderly patients with hypertension, forest therapy effectively manages blood pressure, improves adverse emotional states, reduces oxidative stress levels, and diminishes the risk of cardiovascular events.

Data Availability Statement: The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: The study protocol was reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Zhejiang University School of Medicine (Acceptance Number: IIT20230086C-R1; Approval Document Number Reference Number: Zhejiang First Affiliated Hospital Lunshen 2023 Research No. 112 - Meeting. Ethical approval date: October 25, 2023).

Informed Consent: Written informed consent was obtained from all participants or their legal representatives prior to enrollment.

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Author Contributions: We declare that all the listed authors have participated actively in the study and all meet the requirements of authorship. Dr. SFL designed the study, performed research, managed the literature searches, and wrote the paper; Dr. HJL undertook the data acquisition and analysis; Dr. ZBC contributed to the correspondence and paper revision. All authors reviewed the manuscript.

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Phenotypic, Epidemiologic, and Imaging Features of Hypertrophic Cardiomyopathy: A Single-Center Experience

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is a complex myocardial disorder with heterogeneous clinical presentations and structural manifestations. This study aimed to assess the distribution, clinical characteristics, and diagnostic approaches in a regional cohort of patients with HCM.

Methods: Patients diagnosed with HCM at a tertiary cardiomyopathy clinic between October 2021 and November 2024 were retrospectively analyzed. Patients were classified into obstructive, latent obstructive, non-obstructive, or apical phenotypes based on clinical and imaging findings. Comprehensive demographic, clinical, and imaging data were collected for detailed analysis, providing valuable insights into the phenotypic diversity of HCM.

Results: The cohort included 701 patients with a median age of 53 years of whom 68% were male. The phenotypic distribution comprised 9.3% apical, 38.1% non-obstructive, 32.5% resting obstructive, and 20.1% latent obstructive HCM. Implantable cardioverter-defibrillator implantation was more common in obstructive phenotypes, particularly in the latent obstructive group. Although late gadolinium enhancement (LGE) was more frequently observed in apical HCM, post-hoc analysis showed no significant difference in prevalence across subgroups. In contrast, LGE extent was significantly greater in the apical group. Genetic testing, performed in 32% of patients, revealed a 44% positivity rate, with MYBPC3 and MYH7 being the most commonly detected mutations. The overall mortality rate was 2.8%, with heart failure identified as the leading cause of death.

Conclusion: In this large regional cohort of HCM patients, obstructive and non-obstructive phenotypes were predominant, with a notable burden of genetic mutations and a low overall mortality rate primarily driven by heart failure. These findings emphasize the clinical heterogeneity of HCM and highlight the importance of comprehensive diagnostic evaluation.

Keywords: Cardiac magnetic resonance imaging, echocardiography, epidemiology, genetic testing, hypertrophic cardiomyopathy

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disorder characterized by left ventricular hypertrophy (LVH) that cannot be fully explained by loading conditions. Over the past 3 decades, numerous studies have assessed the prevalence of HCM in the general population using echocardiography and cardiac magnetic resonance imaging (CMR), as well as clinical diagnoses derived from electronic health records and billing databases.[1]

Echocardiographic studies estimate its prevalence in the general population to range between 0.2% and 0.5%.[2] Recognized as one of the most common cardiomyopathies, HCM exhibits a broad spectrum of clinical presentations, ranging from asymptomatic individuals to those at significantly elevated risk of sudden cardiac death (SCD). The condition is primarily attributed to autosomal dominant mutations in genes encoding sarcomeric proteins, which account for the pronounced phenotypic and clinical heterogeneity observed in affected individuals.[3]

Hypertrophic cardiomyopathy demonstrates substantial phenotypic diversity, including obstructive, non-obstructive, and apical subtypes, with varying prevalence across different populations. This phenotypic variability arises from the interplay of genetic predispositions and environmental factors, influencing disease presentation, progression, and prognosis.[4,5] Although each phenotype has been associated with distinct patient-specific clinical and prognostic characteristics, the literature in this field continues to evolve, with new insights emerging regularly.[6]

Advances in cardiac imaging, particularly in echocardiography with the development of new techniques and the increased accessibility of CMR, have significantly facilitated the diagnostic process in HCM patients and enabled detailed phenotypic differentiation.[7] The multimodality approach has also improved the early detection of asymptomatic individuals, providing valuable insights into prognostic processes. Additionally, the widespread use of genetic analyses through family screening programs has further enhanced the identification of asymptomatic patients.[5] This progress has also allowed for the close monitoring of individuals described as genotype-positive but phenotype-negative, facilitating the identification of factors contributing to disease development in this population.[8] Despite these advancements, the underdiagnosis of HCM persists, emphasizing the need for broader application and accessibility of these technologies to improve patient outcomes.[9]

Considering the significant role of genetic factors in this patient population, the influence of environmental and geographical factors further underscores the importance of regional and population-specific data. Phenotypic characteristics, along with their clinical, imaging, and prognostic features, may vary across different regions. Given the limited data available in the country, the primary aim of this study is to investigate the epidemiological features, phenotypic profiles, and prognostic outcomes of the HCM population followed at the center.

METHODS

This retrospective observational study included patients aged 18 years and older who had been evaluated at the cardiomyopathy outpatient clinic of a tertiary referral center between October 2021 and November 2024. Patients with a confirmed diagnosis of HCM during this period were identified from institutional databases and electronic medical records, and their clinical, imaging, and laboratory data were subsequently analyzed. The inclusion criteria required a confirmed diagnosis of HCM based on clinical and imaging findings, in accordance with the 2023 European Society of Cardiology (ESC) guidelines. Although patient enrollment began in 2021, all diagnoses were retrospectively verified using the 2023 ESC criteria, which are consistent with the diagnostic definitions outlined in the 2014 version; therefore, no reclassification or classification bias was introduced.[2,10] The HCM was defined as a LV wall thickness of ≥15 mm in any myocardial segment, not attributable solely to loading conditions. Additionally, wall thickening of 13-14 mm was considered diagnostic when accompanied by features such as a family history of HCM, pathogenic genetic mutations, or abnormal electrocardiographic (ECG) findings.[2] Exclusion criteria included patients with other causes of;

1. LVH such as hypertensive heart disease and aortic stenosis,
2. Infiltrative/storage cardiomyopathies (e.g., amyloidosis, Anderson-Fabry disease, glycogen storage diseases),
3. Patients with incomplete clinical or imaging data were also excluded.

The 24-hour ambulatory blood pressure monitoring was performed on all hypertensive patients. The distinction between hypertensive LVH and HCM with concomitant hypertension was made using a comprehensive multimodality approach, including echocardiographic morphology, CMR characteristics, and, when available, genetic findings. In cases of clinical or laboratory suspicion of infiltrative or storage diseases, or when genetic mutations were identified, patients were referred to a metabolism specialist for further evaluation. Based on disease-specific red flags, α-GalA enzyme activity was evaluated, and lyso-Gb3 levels were measured in males for the diagnosis of Anderson-Fabry disease, while genetic testing was conducted in females to confirm the diagnosis.[11] For suspected amyloidosis, 99m-technetium-pyrophosphate (99mTc-PYP) cardiac scintigraphy was conducted. Furthermore, the exclusion of clonal dyscrasia was ensured through a comprehensive diagnostic assessment, including a serum-free light-chain assay, along with serum and urine protein electrophoresis with immunofixation.[2]

Cardiac Imaging Characteristics

Cardiac imaging was performed using transthoracic echocardiography (TTE) and CMR imaging to assess structural and functional parameters. The TTE was conducted for all participants using a Philips Epiq 7 echocardiography device (Philips Medical Systems, Andover, MA, USA).

Interventricular septal (IVS) and posterior wall (PW) thickness were measured in the parasternal long-axis view using TTE as recommended.[12] In accordance with current guidelines for the assessment of HCM, all LV wall segments were systematically evaluated from base to apex at end-diastole, preferably using the 2D parasternal short-axis view. Wall thickness measurements were obtained at the levels of the mitral valve, mid-ventricle, and apex. In cases with a sigmoid septum, IVS thickness was measured distal to the area of septal bulging. The highest

HIGHLIGHTS

- Obstructive and non-obstructive phenotypes were predominant in this large regional cohort of hypertrophic cardiomyopathy (HCM) patients.
- A notable burden of genetic mutations, particularly in MYBPC3 and MYH7, was observed.
- Overall mortality was relatively low and mainly driven by heart failure.
- Findings emphasize the clinical heterogeneity of HCM.
- The importance of comprehensive diagnostic evaluation in HCM is underscored.

wall thickness measured in any segment was recorded as the maximal wall thickness (MWT). These methodological principles were followed to ensure a comprehensive evaluation and accurate identification of hypertrophic segments.[12]

LV ejection fraction (LVEF) calculated using the biplane Simpson's method while left atrial diameter was evaluated in the parasternal long-axis view. The presence and severity of systolic anterior motion of the mitral valve were assessed in the parasternal long-axis and apical 3- and 5-chamber views using 2-dimensional and color Doppler imaging. Resting and provoked LV outflow tract (LVOT) gradients were assessed via continuous-wave Doppler under basal conditions and after maneuvers such as the Valsalva maneuver or exercise. Pulmonary artery systolic pressure was estimated based on the tricuspid regurgitation jet velocity, with the addition of right atrial pressure derived from inferior vena cava (IVC) assessment. Tricuspid annular plane systolic excursion (TAPSE) was measured from the apical four-chamber view using M-mode at the lateral tricuspid annulus. Right ventricular hypertrophy (RVH) was assessed by measuring RV free wall thickness in the subcostal view at end-diastole. A thickness ≥5 mm was considered indicative of RVH. The IVC diameter and its respiratory variation were evaluated in the subcostal long-axis view to estimate right atrial pressure, in line with guideline recommendations. Diastolic function was assessed in accordance with current guidelines.[12]

The CMR was performed using a 1.5 T scanner (Magnetom Aera; Siemens Medical Solutions, Erlangen, Germany) with phased-array body coils and prospective cardiac gating. The LVEF was calculated from short-axis cine images using the modified Simpson's method, and MWT was measured perpendicularly during end diastole. Apical aneurysms were assessed by carefully examining the apical segments in multiple long-axis and short-axis cine views for dyskinetic motion, thinning, and saccular outpouching of the myocardial wall. Myocardial fibrosis was identified through late gadolinium enhancement (LGE) imaging, performed 10-15 minutes after intravenous gadolinium administration. The presence of LGE was assessed by visual evaluation.[13] An experienced radiologist, blinded to clinical data, visually assessed and scored each segment for LGE distribution. Extensive LGE was defined as an LGE volume accounting for at least 15% of the LV mass.[14]

Phenotype Classification

Three distinct phenotypes of HCM were identified and analyzed in this study. Representative echocardiographic, ECG, and CMR findings across different HCM phenotypes are shown in Figure 1.

1. Obstructive HCM

This phenotype includes patients with a LVOT gradient ≥30 mmHg. The obstructive phenotype was evaluated in 2 distinct subgroups. Resting obstructive HCM is characterized by a persistent LVOT gradient of ≥30 mmHg at rest. In contrast, latent obstructive HCM refers to cases where the LVOT gradient is <30 mmHg at rest but increases to ≥30 mmHg during provocation, such as the Valsalva maneuver or exercise.[2,15] Provocation testing was routinely performed in all patients. The Valsalva maneuver was conducted by instructing patients to forcefully exhale against a closed airway (typically into a manometer) to maintain an intrathoracic pressure of approximately 40 mmHg for 10-15 seconds while in the supine position. This maneuver reduces preload and may enhance dynamic LVOT gradients in patients with obstructive physiology.[16] A standardized squat-to-stand maneuver was used as a physiologic provocation method. Patients were asked to perform rapid squatting followed by immediate standing, which transiently alters preload and afterload, thereby amplifying dynamic gradients in susceptible individuals.[16] In selected patients, a semi-supine bicycle exercise echocardiography was performed. The protocol involved progressive workload increments (usually 25 W every 2-3 minutes) while imaging was conducted in the left lateral decubitus position using continuous-wave Doppler to assess dynamic LVOT gradients during peak exertion. This method allows simultaneous assessment of exercise-induced gradients and symptoms.[17]

2. Non-Obstructive HCM

Patients classified as having non-obstructive HCM demonstrated no evidence of LVOT obstruction, either at rest or during physiologic provocation (e.g., Valsalva maneuver or exercise). To ensure a more homogeneous subgroup for analysis, only patients without apical involvement were included in the non-obstructive category. Specifically, individuals with isolated apical hypertrophy or mixed patterns involving the apex were excluded, thereby focusing this group on patients with asymmetric septal or concentric hypertrophy patterns that did not generate dynamic obstruction.

3. Apical HCM

This phenotype is characterized by predominant hypertrophy localized to the apex of the left ventricle. Apical HCM is identified by the presence of asymmetric LVH mainly localized to the LV apex, with an apical wall thickness of at least 15 mm and an apical-to-posterior wall thickness ratio greater than or equal to 1.5.[2]

Data Collection

Demographic and clinical data were recorded during patients' initial evaluations at the cardiomyopathy outpatient clinic. These included basic patient characteristics, comorbidities, family history of cardiomyopathy or SCD, and key clinical symptoms such as syncope, dyspnea, and palpitations. Functional capacity was assessed using the New York Heart Association (NYHA) classification to evaluate symptom severity and activity limitations.

Medication data were also collected, encompassing both treatments initiated prior to the first visit and those prescribed during follow-up. Baseline laboratory parameters were obtained at the time of the initial evaluation, including estimated glomerular filtration rate, creatine kinase-MB, troponin, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. These biomarkers were recorded to establish a biochemical and cardiac profile for each patient.

Electrocardiographic findings at the initial visit were also documented, including heart rhythm (e.g., sinus rhythm or

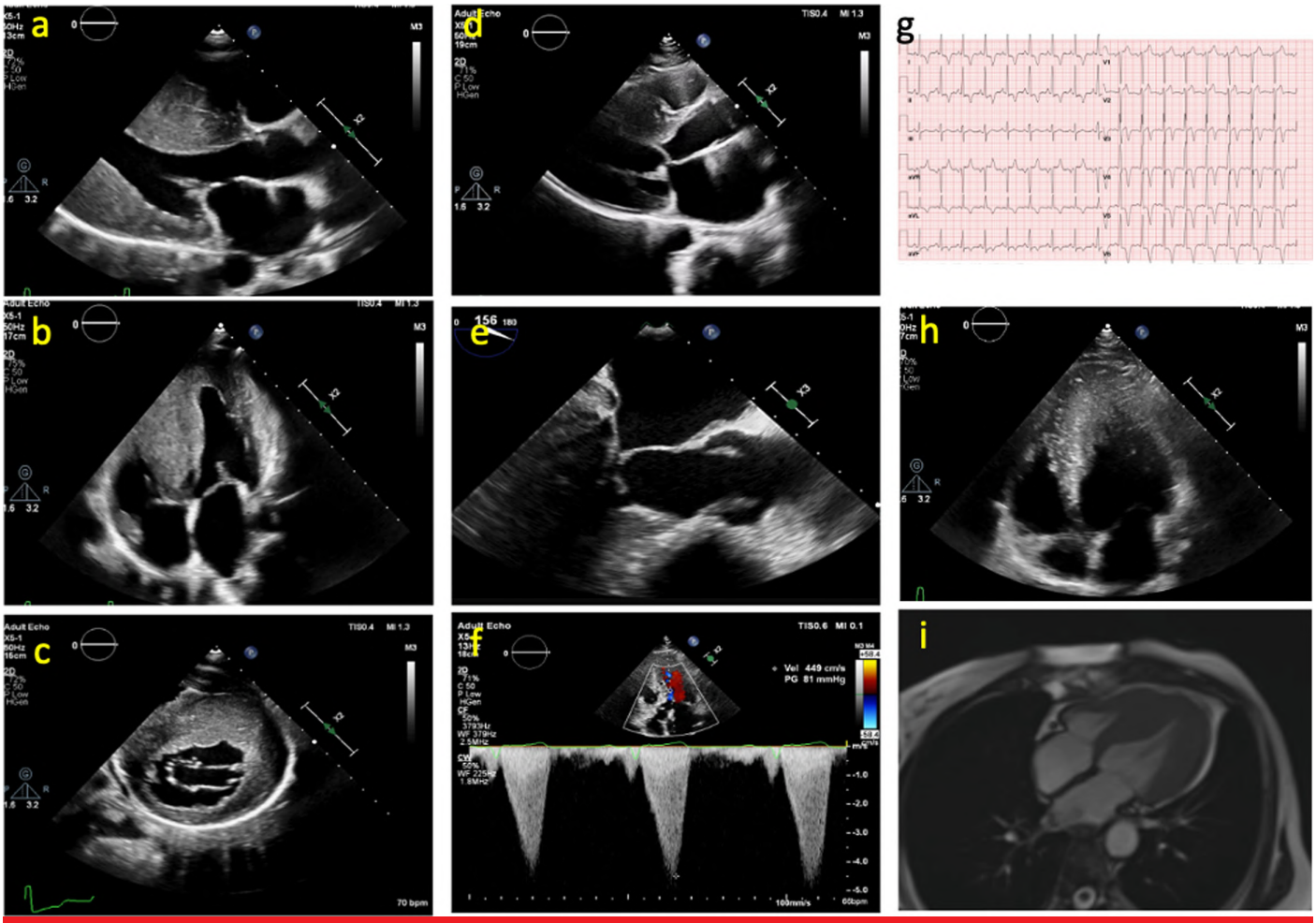

Figure 1. Multimodality imaging examples illustrating different hypertrophic cardiomyopathy (HCM) phenotypes. Parasternal long-axis view (a), apical 4-chamber view (b), and parasternal short-axis view (c) showing asymmetric septal hypertrophy without left ventricular outflow tract obstruction in a patient with non-obstructive HCM. Parasternal long-axis view showing systolic anterior motion (SAM) of the mitral valve and septal contact (d), transesophageal echocardiographic view of SAM at systole (e), and continuous-wave Doppler revealing a high LVOT gradient of 81 mmHg (f). Electrocardiogram showing giant negative T-waves, suggestive of apical involvement (g). Apical four-chamber view displaying marked apical hypertrophy with preserved basal dimensions (i). Cardiac magnetic resonance imaging confirming isolated apical hypertrophy.

atrial fibrillation), heart rate, PR interval, extreme hypertrophy, QRS duration, and corrected QT (QTc) interval.

The estimated 5-year risk of SCD was calculated using the ESC HCM Risk-SCD model, which includes clinical and echocardiographic parameters such as age, MWT, left atrial diameter, LVOT gradient, family history of SCD, unexplained syncope, and the presence of non-sustained ventricular tachycardia (NSVT).[18]

Data regarding the presence of implantable cardioverter-defibrillators (ICDs) and documented appropriate ICD shocks were retrospectively obtained from electronic medical records and device follow-up reports from the arrhythmia clinic. Information on previous septal reduction procedures, including alcohol septal ablation and surgical myectomy, was retrospectively obtained from hospital electronic records, catheterization laboratory reports, and surgical databases.

Clinical outcome data, including all-cause mortality, appropriate ICD shocks, NYHA functional class at last follow-up, and occurrence of septal reduction therapies, were retrospectively collected from electronic medical records and outpatient follow-up data.

Genetic Testing

Genetic testing was offered to all patients and performed in those who provided consent, using next-generation sequencing panels that included key sarcomeric and related genes known to be associated with HCM, such as MYH7, MYBPC3, and TNNT2. Variant classification followed the 2015 ACMG/AMP guidelines, and results were categorized as pathogenic, likely pathogenic, variants of uncertain significance (VUS), or benign/likely benign.[19] A result was considered positive if a pathogenic or likely pathogenic variant was identified. In cases where a VUS was detected—particularly in one of the core HCM-related genes and if supported by family history—segregation analysis was performed in

first-degree relatives. Genetic counseling was provided to all index cases before and after testing, and cascade screening was offered to families when clinically indicated. Variant interpretation was supported by multiple databases including ClinVar, gnomAD, HGMD, and in silico prediction tools (e.g., CADD, SIFT, MutationTaster). Pedigree analysis was also performed to assess inheritance patterns in families with multiple affected individuals.

Statistical Analysis

All statistical analyses were performed using R software (version 4.1.0 or later; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median with interquartile range (IQR). Categorical variables are reported as counts and percentages.

Comparisons between more than 2 groups were conducted using the Kruskal–Wallis test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. When overall group differences were significant, post hoc pairwise comparisons were performed using the Dunn–Bonferroni method.

A 2-tailed *P* value <.05 was considered statistically significant. Descriptive and comparative analyses were designed to characterize differences in clinical, imaging, and genetic features across HCM phenotypes.

RESULTS

Study Population

Among the 701 patients with HCM, 228 (32.5%) had resting obstruction, 141 (20.1%) had latent obstruction, 267 (38.1%) were classified as non-obstructive, and 65 (9.3%) had an apical phenotype. The median follow-up time was 13.0 months (IQR: 4.0-26.0 months). The mean follow-up duration was 16.5 months with a standard deviation of 12.8 months. The median age was similar across subgroups (53.0 years), and the majority of patients were male (68%), with a significantly higher male proportion in the non-obstructive group (75%, *P*=.028). Hypertension was present in 51% of the overall cohort. A statistically significant difference in hypertension prevalence was observed across subgroups, primarily driven by a higher prevalence in the non-obstructive group compared to the apical group (*P*=.003).

Regarding functional capacity, NYHA class II was the most common across all groups (51% overall). Symptoms such as dyspnea, syncope, angina, and palpitations were frequently reported, particularly dyspnea (43% overall), without statistically significant differences between subgroups.

The median SCD risk score differed significantly among groups (*P* < .001), being highest in the resting-obstructive

Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort According to Hypertrophic Cardiomyopathy Phenotypes

	Overall	Resting-Obstructive	Latent-Obstructive	Non-Obstructive	Apical	
Variables	**n=701**	**n=228**	**n=141**	**n=267**	**n=65**	***P*²**
Sex (female), n (%)	224 (32)	86 (38)	47 (33)	68 (25)	23 (35)	.028
Age, years	53.0 (45.0, 62.0)	55.0 (46.0, 63.0)	52.0 (44.0, 60.0)	53.0 (44.0, 62.0)	53.0 (44.0, 61.0)	.178
BMI	28.4 (25.7, 31.6)	28.5 (25.8, 31.6)	27.8 (26.2, 31.5)	28.5 (25.7, 31.2)	28.0 (25.6, 31.2)	.975
Family history of CM, n (%)	115 (17)	39 (17)	32 (23)	33 (13)	11 (17)	.055
Family history of SCD, n (%)	84 (12)	30 (13)	19 (14)	29 (11)	6 (9.4)	.688
Atrial fibrillation, n (%)	130 (19)	52 (23)	24 (17)	45 (17)	9 (14)	.220
HT, n (%)	355 (51)	101 (45)	79 (56)	151 (57)	24 (37)	.003
DM, n (%)	101 (15)	31 (14)	25 (18)	38 (14)	7 (11)	.547
CAD, n (%)	190 (27)	52 (23)	37 (27)	82 (31)	19 (29)	.248
Stroke, n (%)	19 (2.7)	4 (1.8)	4 (2.9)	11 (4.1)	0 (0)	.225
Smoking, n (%)	168 (25)	47 (21)	36 (27)	70 (27)	15 (23)	.427
NYHA, n (%)						.066
1	195 (29)	52 (24)	47 (35)	72 (29)	24 (39)	
2	337 (51)	110 (50)	63 (47)	139 (56)	25 (41)	
3	117 (18)	49 (22)	22 (16)	35 (14)	11 (18)	
4	13 (2.0)	7 (3.2)	2 (1.5)	3 (1.2)	1 (1.6)	
Syncope, n (%)	85 (12)	31 (14)	22 (16)	24 (9.1)	8 (13)	.196
Presyncope, n (%)	101 (15)	40 (18)	25 (18)	31 (12)	5 (7.8)	.059
Dyspnea, n (%)	298 (43)	107 (47)	65 (46)	102 (38)	24 (38)	.167
Angina, n (%)	139 (20)	42 (19)	27 (20)	62 (24)	8 (13)	.215
Palpitation, n (%)	143 (21)	51 (23)	28 (20)	54 (21)	10 (16)	.701
SCD score	2.2 (1.5, 3.4)	2.7 (2.0, 4.4)	2.2 (1.7, 3.7)	1.8 (1.3, 2.8)	1.9 (1.3, 3.0)	<.001

Values are expressed as median with interquartile range (IQR, 25th, 75th percentile).
BMI, body mass index; CAD, chronic artery disease; CM, cardiomyopathy; DM, diabetes mellitus; HT, hypertension; NYHA, New York Heart Association; SCD, sudden cardiac death.

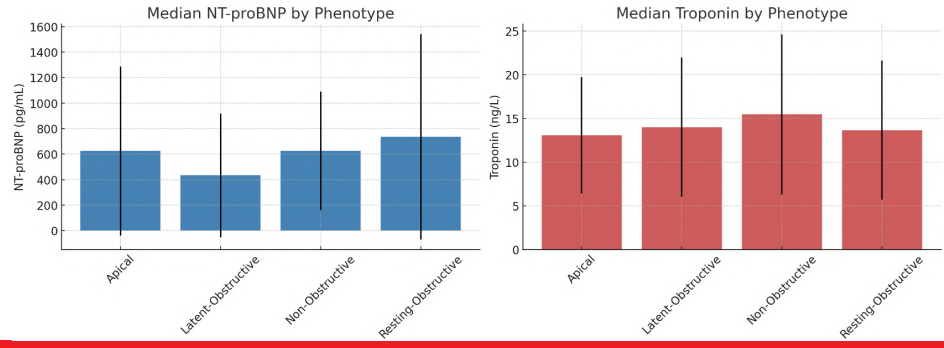

Figure 2. Median NT-proBNP and troponin levels across different hypertrophic cardiomyopathy (HCM) phenotypes. Error bars represent the interquartile range (IQR).

group (median 2.7, IQR 2.0-4.4) and lowest in the non-obstructive group (median 1.8, IQR 1.3-2.8). Table 1 summarizes the baseline demographic and clinical characteristics of the study group.

Implantable cardioverter-defibrillators were present in 11.8% of patients, with the highest prevalence observed in the latent-obstructive HCM subgroup. A statistically significant difference in ICD implantation rates was identified only between the latent-obstructive and non-obstructive subtypes (18% vs. 8.3%, $P=.022$); no significant differences were observed in other pairwise comparisons among the subgroups.

Beta-blockers were prescribed in 80.7% of the total cohort, with the highest usage in obstructive (83.8%) and latent-obstructive (82.3%) groups. Diuretics were prescribed in nearly one-third of patients (31.8%), with the highest use in the non-obstructive phenotype (37%). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were administered to 42% of patients overall, with significantly different usage across subgroups ($P=.004$), highest in the non-obstructive group (46%) and lowest in the apical group (31%). Oral anticoagulants were used in 15% of the cohort, with no statistically significant difference among subtypes ($P=.097$).

Regarding laboratory findings, NT-proBNP levels showed significant variation across HCM subtypes ($P=.006$). The highest median NT-proBNP level was observed in the resting-obstructive group (737.0 pg/mL [212.2-1820.0]), while the lowest was found in the latent-obstructive group (433.0 pg/mL [121.0-1091.0]). The NT-proBNP values in non-obstructive and apical groups were similar to the overall median level of

Table 2. Therapeutic Interventions, Medication Use, and Laboratory Findings According to Hypertrophic Cardiomyopathy Phenotypes

Characteristic	Overall n = 701	Resting-obstructive n = 228	Latent-obstructive n = 141	Non-obstructive n = 267	Apical n = 65	P[2]
Presence of ICD, n (%)	83 (11.8)	31 (14)	25 (18)	22 (8.3)	5 (7.7)	.022
Alcohol septal ablation, n (%)	37 (5.3)	28 (12)	9 (6.4)	0 (0)	0 (0)	<.001
Surgical myectomy, n (%)	17 (2.4)	9 (3.9)	5 (3.5)	3 (1.1)	0 (0)	.095
Disopyramide, n (%)	68 (9.9)	51 (22.3)	17 (12)	0 (0)	0 (0)	<.001
Beta blocker, n (%)	566 (80.7)	191 (83.8)	116 (82.3)	213 (79.8)	46 (70.8)	.030
Metoprolol	367 (54)	134 (58.7)	80 (56.7)	121 (45.3)	37 (56.9)	
Bisoprolol	114 (17)	41 (17.9)	22 (15.6)	44 (17)	6 (9.2)	
Calcium channel blockers, n (%)	139 (19.8)	41 (17.9)	30 (21.2)	59 (22)	9 (13.8)	.380
Diuretics, n (%)	223 (31.8)	64 (28)	46 (32.6)	99 (37)	14 (21.5)	.030
ACEi or ARBs, n (%)	284 (42)	76 (34)	68 (49)	120 (46)	20 (31)	.004
OACs, n (%)	103 (15)	44 (20)	20 (14)	31 (12)	8 (13)	.097
eGFR, mL/min/1.73 m^2	93.0 (74.3, 105.0)	92.0 (74.2, 105.0)	95.6 (78.0, 108.0)	92.0 (70.4, 103.5)	95.3 (83.1, 107.6)	.093
CKMB, ng/mL	2.9 (2.0, 4.2)	3.0 (2.0, 4.5)	2.8 (1.8, 4.5)	2.9 (2.0, 4.1)	2.4 (1.8, 3.2)	.285
Troponin, ng/L	14 (8, 24)	13 (9, 25)	15 (8, 26)	14 (9, 24)	14 (7, 23)	.553
NT-ProBNP, pg/mL	626.2 (206.9, 1,466.0)	737.0 (212.2, 1,820.0)	433.0 (121.0, 1,091.0)	625.0 (221.0, 1,162.0)	623.8 (302.4, 1,644.5)	.006

Values are expressed as median with interquartile range (IQR, 25th, 75th percentile).
ACE, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CKMB, creatine kinase-MB isoenzyme; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; NT-ProBNP, N-terminal pro B-type natriuretic peptide; OAC, oral anticoagulant.

626.2 pg/mL (206.9-1466.0). Differences in biomarker profiles among HCM phenotypes are depicted in Figure 2. Table 2 shows the medication use, therapeutic history, and the laboratory findings of the patients.

Imaging Characteristics and Genetics

Electrocardiographic parameters were largely similar among HCM subtypes. The QRS duration showed a statistically significant difference across groups ($P = .043$). The shortest median QRS duration was observed in the apical group (87 ms [80-97]), while the longest was in the resting- and latent-obstructive groups (94 ms in both) (Table 3).

Echocardiographic assessment revealed significant differences among HCM subtypes in multiple structural and functional parameters. Left ventricular ejection fraction was preserved in all groups but was significantly lower in the apical group compared to others ($P < .001$). Interventricular septal thickness, PW thickness, and MWT were all significantly lower in the apical group, while the highest values were observed in the resting- and latent-obstructive groups ($P < .001$ for all). Significant mitral regurgitation, which is defined as more than moderate, was present in 18.4% of the overall cohort, with a significantly higher prevalence in the resting-obstructive group (30.2%, $P < .001$). This was notably more frequent compared to latent-obstructive (12.7%), non-obstructive (12.3%), and apical (13.8%) groups. Left atrial diameter also varied significantly across subtypes, with larger dimensions in the obstructive phenotypes ($P < .001$). Pulmonary artery systolic pressure, TAPSE, and IVC diameter did not differ significantly among groups ($P = .208$, .064, and .406, respectively), suggesting similar RV function and filling pressures across phenotypes. Table 3 shows ECG and echocardiographic findings of the study group.

Cardiac magnetic resonance imaging was available in 84% of the overall cohort, with the highest utilization in the apical group (100%) and the lowest in the resting-obstructive group (79%) ($P = .001$). Although the overall median CMR-LVEF was 60.0% across subgroups, statistically significant differences were observed ($P < .001$). Specifically, LVEF values were significantly lower in the non-obstructive group compared to the obstructive, latent-obstructive, and apical subtypes. No significant differences were noted among the other groups.

Table 3. Electrocardiographic, Echocardiographic, and Cardiac Magnetic Resonance Imaging Findings Across Hypertrophic Cardiomyopathy Phenotypes

	Overall	Resting-obstructive	Latent-obstructive	Non-obstructive	Apical	
Characteristic	**n = 701**	**n = 228**	**n = 141**	**n = 267**	**n = 65**	***P*²**
Electrocardiography						
Heart rate, bpm	73.0 (65.0, 83.0)	73.0 (65.0, 82.5)	74.0 (65.0, 85.0)	72.0 (65.0, 82.0)	73.0 (65.5, 83.5)	.981
QRS duration, ms	92.0 (84.0, 102.0)	94.0 (85.0, 104.0)	94.0 (84.0, 102.0)	92.0 (84.0, 102.0)	87.0 (80.0, 97.0)	.043
QTc duration, ms	445 (426, 464)	448 (428, 466)	445 (429, 464)	442 (422, 463)	447 (433, 464)	.123
Echocardiography						
LVEF, %	60 (60, 65)	60 (60, 65)	60 (60, 65)	60 (55, 65)	60 (57, 60)	<.001
IVS, mm	17.0 (15.0, 20.0)	18.0 (16.0, 21.0)	17.0 (15.7, 20.8)	17.0 (15.0, 20.0)	13.0 (11.7, 15.0)	<.001
PW, mm	12.0 (11.0, 14.0)	12.5 (11.0, 14.0)	12.0 (10.5, 13.0)	13.0 (11.0, 14.0)	11.0 (10.0, 12.0)	<.001
MWT, mm	18.0 (16.0, 21.0)	18.0 (16.0, 21.9)	17.2 (16.0, 21.0)	17.0 (15.3, 20.5)	16.0 (14.0, 18.0)	<.001
E/e'	12.6 (10.0, 16.0)	12.5 (9.0, 15.7)	11.0 (9.2, 16.0)	12.6 (10.0, 16.5)	13.0 (10.5, 16.0)	.612
LA diameter, mm	41.0 (37.0, 46.0)	43.0 (38.5, 48.0)	41.0 (37.0, 45.0)	40.0 (37.0, 46.0)	39.0 (34.6, 42.0)	<.001
Rest gradient, mm Hg	31 (20, 48)	45 (35, 62)	17 (14, 22)	NA (NA, NA)	NA (NA, NA)	<.001
Provoked gradient, mmHg	60 (41, 86)	79 (62, 100)	40 (34, 51)	NA (NA, NA)	NA (NA, NA)	<.001
Mitral regurgitation, n (%)	129 (18.4)	69 (30.2)	18 (12.7)	33 (12.3)	9 (13.8)	<.001
PAPs , mm Hg	27.0 (23.0, 35.0)	29.0 (24.0, 35.0)	26.0 (21.0, 30.0)	26.0 (23.0, 37.0)	28.5 (23.5, 39.0)	.208
TAPSE, mm	21.1 (20.0, 23.2)	22.0 (20.0, 25.0)	21.0 (19.3, 23.0)	21.0 (20.0, 23.0)	20.0 (18.0, 22.0)	.064
IVC diameter, mm	15.3 (13.0, 19.0)	16.0 (13.0, 20.0)	15.0 (12.0, 18.0)	15.0 (12.8, 19.0)	14.5 (12.4, 18.0)	.406
Cardiac magnetic resonance imaging						
Presence of CMR, n (%)	587 (84)	179 (79)	120 (85)	223 (84)	65 (100)	.001
CMR-LVEF, %	60.0 (56.0, 62.0)	60.0 (57.0, 62.0)	60.0 (56.0, 62.0)	60.0 (55.0, 61.0)	60.0 (55.0, 63.0)	<.001
CMR-MWT, mm	18.5 (16.0, 22.0)	19.0 (16.7, 23.0)	18.7 (16.5, 22.0)	18.0 (15.3, 21.2)	18.0 (15.5, 21.7)	.039
CMR-RVEF, %	60.0 (56.0, 62.0)	60.0 (57.0, 62.0)	60.0 (56.0, 62.0)	60.0 (55.0, 61.0)	60.0 (55.0, 63.0)	.278
Presence of LGE, n (%)	502 (86)	146 (82)	100 (83)	194 (87)	62 (95)	.045
Extensive LGE, n (%)	146 (25)	32 (18)	24 (20)	66 (30)	24 (37)	.003
Apical aneurysm, n (%)	17 (3.0)	7 (4.1)	3 (2.7)	1 (0.5)	6 (9.7)	.001

Values are expressed as median with interquartile range (IQR, 25th, 75th percentile).
CMR, cardiac magnetic resonance; CMR-LVEF, cardiac magnetic resonance left ventricular ejection fraction; CMR-MWT, cardiac magnetic resonance-mean wall thickness; IVC, inferior vena cava; IVS, interventricular septum; LA, left atrium; LGE- late gadolinium enhancement; LVEF, left ventricular ejection fraction; MWT, mean wall thickness; PAPs, systolic pulmonary artery pressure; PW, posterior wall; TAPSE, Tricuspid annular plane systolic excursion.

Maximal wall thickness on CMR (CMR-MWT) differed significantly among subgroups ($P=.039$), with the highest values in the resting- and latent-obstructive groups and the lowest in the apical group. Late gadolinium enhancement was present in 86% of patients who underwent CMR. Although the prevalence appeared numerically higher in the apical group (95%, $P=.045$), post-hoc analysis revealed no statistically significant difference between subgroups. Extensive LGE was identified in 25% of the total cohort, again with the highest proportion in the apical group (37%) and lowest in the resting-obstructive group (18%) ($P=.003$). Apical aneurysms were detected in 3% of all patients, but were significantly more frequent in the apical group (9.7%) compared to other subtypes ($P=.001$). Table 3 reflects the imaging characteristics of the study group.

Genetic testing was performed in 221 patients (32% of the overall cohort), with similar proportions across HCM subtypes (range: 29%-38%, $P=.534$). Among those tested, 41% had a positive result, 37% were negative, and 22% carried a variant of uncertain significance (VUS), with no significant difference in distribution between subgroups ($P=.473$). The most frequently identified pathogenic or likely pathogenic mutations were in MYBPC3 (39% of positive cases) and MYH7 (26%), followed by MYL3 and TNNI3. Compound mutations were identified in 2.2% of genetically tested patients. No significant differences in gene distribution were observed among phenotypic subgroups ($P=.252$), although MYBPC3 mutations were numerically more common in obstructive and apical HCM, and compound mutations were only observed in the latent-obstructive group. Figure 3 shows the genetic results, distribution to the different phenotypes, and the specific gene results of the study population.

Clinical Outcomes

Implantable cardioverter-defibrillator shock was documented in 15% of patients with a device, with the highest rate observed in the apical group (40%), though this difference was not statistically significant ($P=.219$). Non-sustained ventricular tachycardia was identified in 17% of the overall cohort, with comparable rates across subgroups ($P=.906$).

Overall mortality was 2.9%, ranging from 1.4% in the latent-obstructive group to 4.8% in the resting-obstructive group ($P=.168$). Causes of death included heart failure (35%), SCD (25%), acute coronary syndrome (10%), surgical myectomy (10%), aortic dissection (5%), lung cancer (5%), respiratory failure (5%), and traffic accident (5%). No statistically significant difference in cause-specific mortality was observed among the subgroups ($P=.960$). Table 4 summarizes the clinical outcomes of the patients. Given the limited number of clinical events, performing a robust statistical comparison was not feasible. Nevertheless, for descriptive purposes, a comparison between patients with and without clinical outcomes is provided in the Supplementary Table 1. Pairwise

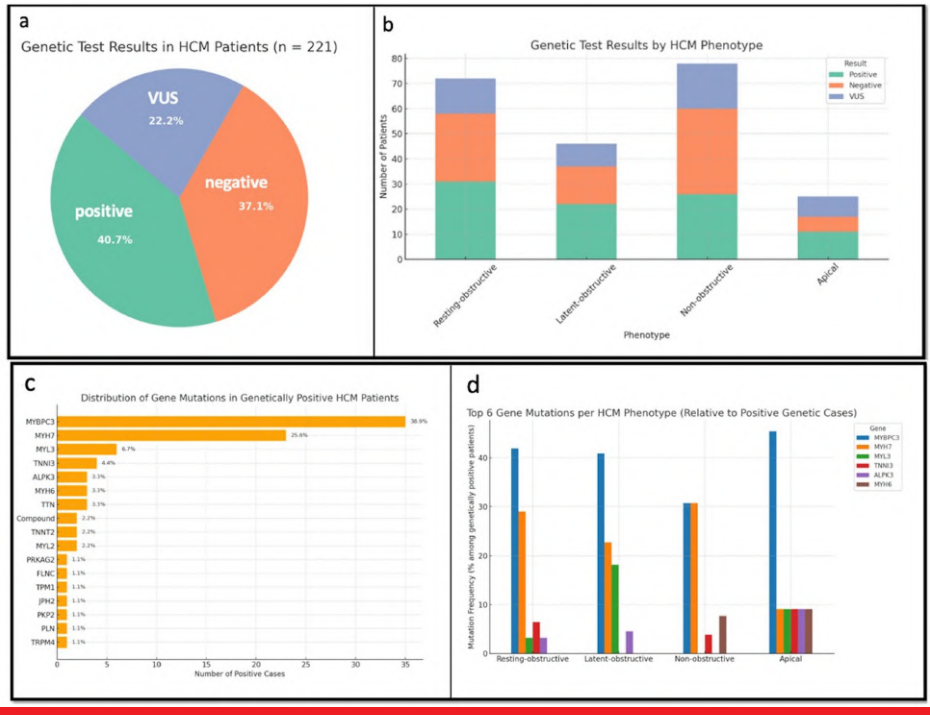

Figure 3. Genetic testing results in patients with HCM. (a) Distribution of genetic test results among 221 patients who underwent genetic testing. Results were categorized as positive (pathogenic or likely pathogenic variants), negative, or variant of uncertain significance (VUS). (b) Genetic test outcomes stratified by HCM phenotype, including resting-obstructive, latent-obstructive, non-obstructive, and apical subtypes. Distribution of gene mutations in genetically positive hypertrophic cardiomyopathy (HCM) patients. (c) Frequency of individual gene mutations among genetically positive cases. MYBPC3 and MYH7 were the most commonly detected mutations, followed by MYL3, TNNI3, ALPK3, and MYH6. (d) Distribution of the top 6 gene mutations stratified by HCM phenotype (resting-obstructive, latent-obstructive, non-obstructive, and apical), relative to genetically positive cases.

Table 4. Clinical Outcomes of the HCM Patients

	Overall	Resting-obstructive	Latent-obstructive	Non-obstructive	Apical	
Characteristic	**n = 701**	**n = 228**	**n = 141**	**n = 267**	**n = 65**	***P*²**
Follow-up, months	13.0 (4.0, 26.0)	13.0 (4.0, 28.3)	13.0 (3.0, 27.0)	13.0 (4.0, 24.0)	13.5 (3.7, 26.5)	.496
ICD shock, n (%)	12 (14.4)	4 (12.9)	2 (8)	4 (18.1)	2 (40)	.219
NSVT, n (%)	117 (17)	37 (16)	23 (16)	44 (16)	13 (20)	.906
Mortality, n (%)	20 (2.9)	11 (4.8)	2 (1.4)	5 (1.9)	2 (3.1)	.168
Mortality reasons, n (%)						.960
Heart failure, n (%)	7 (35)	3 (27)	0 (0)	3 (60)	1 (50)	
Sudden death, n (%)	5 (25)	2 (18)	1 (50)	1 (20)	1 (50)	
ACS, n (%)	2 (10)	0 (0)	1 (50)	1 (20)	0 (0)	
Aortic dissection, n (%)	1 (5.0)	1 (9.1)	0 (0)	0 (0)	0 (0)	
Surgical myectomy, n (%)	2 (10)	2 (18)	0 (0)	0 (0)	0 (0)	
Lung cancer, n (%)	1 (5.0)	1 (9.1)	0 (0)	0 (0)	0 (0)	
Respiratory failure, n (%)	1 (5.0)	1 (9.1)	0 (0)	0 (0)	0 (0)	
Traffic accident, n (%)	1 (5.0)	1 (9.1)	0 (0)	0 (0)	0 (0)	

Values are expressed as median with interquartile range (IQR, 25th, 75th percentile).
ACS, acute coronary syndrome; ICD, implantable cardioverter-defibrillator; NSVT, nonsustained ventricular tachycardia.

post-hoc comparisons using Dunn's test with Bonferroni correction were performed for variables showing significant overall differences in the tables, and the results are presented in Supplementary Table 2.

DISCUSSION

This study provides a comprehensive analysis of a large cohort of HCM patients, highlighting phenotypic variability and its clinical implications. The findings emphasize the importance of cardiac imaging, genetic testing, and clinical risk stratification in understanding the heterogeneity of HCM and guiding individualized patient management. Notably, data on HCM in Türkiye remains scarce, making this study a valuable contribution to understanding the disease within the region.

Although no gender differences in the prevalence of HCM are expected, a male predominance is evident in the study population, as observed in nearly all reports.[20,21] This disparity may be partly attributed to sex-related differences in symptom perception, pain threshold, and comorbid conditions such as obesity, which can influence the clinical presentation and timing of diagnosis in women.[22,23] However, evidence suggests that female HCM patients may have worse clinical outcomes, underscoring the critical importance of thorough diagnostic evaluations in this patient group.[24,25]

The study population includes 3 distinct phenotypes, with obstructive patients further categorized into rest and latent types to emphasize the importance of evaluating the latent subgroup. According to the literature, one-third of cases are obstructive at rest, one-third with provocation, and one-third non-obstructive.[26] The prevalence of apical HCM varies across studies, with rates reaching up to 25% in Asian populations and reported between 5% and 15% in Western societies.[27,28] In this cohort, the prevalence was 9.3%, which aligns with European data. However, with the increasing use of CMR, the diagnosis of apical HCM has become more frequent, and it is reasonable to predict that its prevalence will rise in the near future.[29,30] Latent-obstructive HCM prevalence in the cohort was 20.8%, slightly lower than reported, likely due to the possibility of limited use of provocation maneuvers. Accurate performance of the Valsalva maneuver, exercise echocardiography, or simple exercises during routine evaluations is essential for proper diagnosis.[31] To ensure optimal assessment, particularly in resource-limited settings, evaluations should be conducted in specialized centers with experienced clinicians.

Phenotypic comparisons in the study have yielded significant findings, particularly regarding patients with obstructive phenotype. Despite advances in treatment strategies, the resting-obstructive subtype remains the most common and clinically apparent form of HCM. In the study findings, although the comparison of functional capacity—which reflects heart failure symptoms—did not reach statistical significance, NYHA class III and IV patients were numerically more frequent in the resting-obstructive group. Consistent with this, and in a statistically significant manner, NT-proBNP levels were notably higher in the resting-obstructive subtype. Additionally, the presence of significant mitral regurgitation, which plays a role in both the pathophysiology and clinical presentation of these patients, was more prevalent in this group. It is also important to note that none of the patients in the cohort were treated with myosin inhibitors, which are increasingly used worldwide. Given the demonstrated benefits of these agents—such as improving clinical symptoms, enhancing functional capacity, and reducing NT-proBNP levels in obstructive HCM—it can be suggested that their wider adoption might help reverse these adverse findings in this specific patient population.

The use of CMR at a rate of approximately 84% in the study highlights its critical role in identifying phenotypic differences. The CMR is universally recommended by all guidelines as an indispensable tool for both the initial evaluation and

follow-up of cardiomyopathy patients.[2,15] Notably, CMR data revealed significant differences between groups, particularly in the assessment and frequency of LGE. The presence of LGE was observed in 95% of patients with apical HCM, a rate markedly higher compared to other phenotypes, but no statistical difference. Additionally, the extensive LGE observed in apical HCM patients, now recognized as a risk criterion for primary prevention ICD implantation, was significantly more prevalent in this phenotype. These findings not only underscore the potential inadequacy of current approaches in guiding primary prevention strategies for apical HCM but also highlight the need to reassess the clinical perspective and management algorithms. They emphasize the importance of developing dedicated risk stratification tools and ensuring closer follow-up and tailored care for this specific subgroup of patients. Furthermore, the presence of apical aneurysm, another well-known SCD risk factor, was also found to be more common in apical HCM patients. This observation aligns with previously reported data in the literature.[32,33]

The rate of genetic testing in the study was relatively low, reflecting the challenges of accessing genetic analysis in the country. However, recent regulatory changes aimed at improving access have enabled genetic testing to be performed in 221 patients, representing 32% of the study population. It is anticipated that these rates will increase over time, providing a more comprehensive understanding of the genetic basis of HCM in the population. Genetic analysis is particularly critical for population-specific characterizations, as environmental and geographic influences contribute to significant heterogeneity across different populations.[34,35] In the cohort, genetic positivity was identified in 41% of tested patients, a rate comparable to global reports.[3,5] Consistent with the literature, the MYBPC3 and MYH7 genes accounted for 70% of all positive results. While genotype-phenotype correlations were not statistically significant, the rate of genetic positivity was numerically lower in the non-obstructive subtype compared to the obstructive and apical phenotypes, which showed similar proportions of positive findings. This contrasts with the widely held view that genetic transmission in apical HCM is low, with positivity rates around 10%-30% reported in the literature.[36-38] The findings suggest the need for further investigation, as this discrepancy may be attributable to population-specific factors. A more definitive conclusion will require larger patient cohorts and increased rates of genetic testing to clarify these observations.

In the population, the proportion of patients with an implanted ICD was 11.8%, with 15% of these patients experiencing ICD shocks during follow-up. While ICD implantation rates were higher among patients with obstructive HCM, no clinical significance is claimed for this observation. Regarding ICD shocks, no significant differences were observed between groups, likely due to the limited number of events, which restricted meaningful statistical analysis. The overall mortality rate in the study cohort was 2.8%, with heart failure identified as the most common cause of death. Advances in treatment strategies and the use of ICDs have brought life expectancy in HCM patients closer to that of the general population. Notably, the prevention of SCD through ICD therapy has allowed for a more detailed observation of the natural progression of the disease.[39] Looking ahead, it can be hypothesized that the "burn-out" pattern in HCM will become increasingly prevalent, with disease outcomes progressively influenced by heart failure rather than SCD.[40,41] Consequently, identifying patients at risk of developing burn-out and implementing preventive measures will likely represent one of the major challenges in HCM management. Developing novel therapeutic strategies aimed at this subgroup will be essential for improving long-term outcomes in these patients. Although the current study provides valuable early insights into the demographic and clinical characteristics of patients with HCM, the median follow-up duration of approximately 13 months is relatively short for a chronic, slowly progressive condition such as HCM. Consequently, the mortality and ICD data reported here should be interpreted as preliminary and descriptive rather than prognostic. Longer-term follow-up from the institutional registry is ongoing and is expected to offer a more comprehensive evaluation of disease progression, arrhythmic risk, and survival outcomes in this population.

Study Limitations

The retrospective and single-center nature of the study may introduce selection bias, potentially overrepresenting more symptomatic or severe cases, and thus limiting the generalizability of the findings to broader HCM populations. Second, genetic testing was performed in 32% of the cohort, which restricts the exploration of genotype-phenotype correlations and limits insights into the genetic underpinnings of HCM in this population. This may also result in underestimating the role of specific genetic mutations in shaping phenotypic diversity. Also, the potential impact of specific genetic variants on clinical outcomes could not be assessed due to incomplete genetic data and the cross-sectional design of the study. Future longitudinal studies combining comprehensive genotyping with systematic follow-up are warranted to clarify genotype-driven differences in prognosis and adverse event risk. Third, while the study includes a relatively large and diverse cohort, it was conducted at a single tertiary center, which may limit the generalizability of the findings to other populations or healthcare systems. Additionally, the region-specific nature of the study provides valuable localized data but may not capture the full spectrum of HCM phenotypes observed globally. Furthermore, because this analysis was cross-sectional, longitudinal clinical outcomes such as mortality, arrhythmias, or other adverse cardiac events could not be systematically evaluated, and survival analyses were not feasible. Although CMR data were available for most patients, the study design and lack of uniform long-term follow-up precluded reliable assessment of the prognostic implications of LGE and other CMR-derived parameters. Lastly, the follow-up period, while reasonable, may not be sufficient to fully evaluate long-term outcomes, particularly regarding disease progression and mortality. The reliance on advanced imaging techniques like CMR, although beneficial, may not be feasible in all clinical settings,

potentially affecting the reproducibility of findings. Despite these limitations, this study provides significant insights into the phenotypic diversity and clinical management of HCM and lays the groundwork for future multicenter, prospective research.

CONCLUSION

This study provides valuable insight into the phenotypic spectrum and clinical characteristics of HCM within a regional cohort, representing the first epidemiological data from this population. Obstructive HCM—particularly the resting-obstructive subtype—emerged as the most prevalent and clinically dominant form, associated with more advanced heart failure symptoms, elevated NT-proBNP levels, and a higher prevalence of significant mitral regurgitation. The widespread use of cardiac MRI enhanced the detection of apical variants and LGE, both essential elements in contemporary risk stratification. Genetic testing was performed in approximately one-third of patients, with MYBPC3 and MYH7 mutations most commonly identified across phenotypes. These findings, grounded in a population-specific context, highlight the value of regional data in shaping individualized management strategies and enriching the global understanding of HCM phenotypes.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences, İstanbul MehmetAkif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital (Approval no: 2025.02-13; Date: 04.03.2025).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Supplementary Table 1. Comparison of baseline characteristics and imaging features according to clinical outcomes

Characteristic	Overall n = 701	Clinical outcome - n = 681	Clinical outcome + n = 20	*P*
Sex, n (%)	224 (32%)	215 (32%)	9 (45%)	0.204
Age, years	53.0 (45.0, 62.0)	53.0 (44.0, 62.0)	55.0 (48.0, 64.0)	0.211
Presence of ICD, n (%)	83 (12%)	81 (12%)	2 (10%)	1.000
Troponin, ng/L	14.0 (8.0, 24.3)	14.0 (8.0, 24.0)	25.7 (15.8, 80.0)	0.003
NT-ProBNP, pg/mL	626.2 (206.9, 1,466.0)	617.1 (194.0, 1,393.0)	1,759.0 (1,002.0, 4,888.0)	0.001
QRS duration, ms	92.0 (84.0, 102.0)	92.0 (84.0, 102.0)	95.0 (94.0, 116.0)	0.034
QTc duration, ms	445.0 (426.0, 464.0)	445.0 (426.0, 464.0)	468.0 (438.0, 485.0)	0.012
LVEF, %	60.0 (60.0, 65.0)	60.0 (60.0, 65.0)	50.0 (43.5, 65.0)	0.007
MWT, mm	18.0 (16.0, 21.0)	17.8 (16.0, 21.0)	19.1 (16.5, 22.1)	0.157
Type of HCM, n (%)				0.168
1	228 (33%)	217 (32%)	11 (55%)	
2	141 (20%)	139 (20%)	2 (10%)	
3	267 (38%)	262 (38%)	5 (25%)	
4	65 (9.3%)	63 (9.3%)	2 (10%)	
LA diameter, mm	41.0 (37.0, 46.0)	41.0 (37.0, 46.0)	43.0 (39.6, 50.4)	0.088
Rest gradient, mm Hg	13.0 (2.0, 35.0)	12.0 (2.0, 34.0)	36.0 (2.0, 56.5)	0.014
Provoked gradient, mm Hg	60.0 (41.0, 88.0)	60.0 (41.0, 86.0)	78.0 (56.0, 107.0)	0.180
Significant MR, n (%)	129 (20%)	118 (19%)	11 (58%)	0.001
TAPSE, mm	21.1 (20.0, 23.2)	21.9 (20.0, 23.3)	19.0 (17.0, 21.0)	0.047
RVH, n (%)	32 (6.3%)	29 (5.8%)	3 (25%)	0.033
PAPs, mm Hg	27.0 (23.0, 35.0)	27.0 (23.0, 34.0)	33.0 (26.0, 42.0)	0.075
IVC diameter, mm	15.3 (13.0, 19.0)	15.0 (13.0, 18.3)	19.2 (15.5, 20.8)	0.047
CMR LVEF, %	66.0 (63.0, 71.0)	66.0 (63.0, 71.0)	70.0 (53.0, 74.0)	0.620
CMR MWT, mm	18.5 (16.0, 22.0)	18.4 (16.0, 22.0)	22.3 (20.0, 26.0)	0.035
CMR RVEF, %	60.0 (56.0, 62.0)	60.0 (56.0, 62.0)	57.5 (52.0, 63.0)	0.413
LGE, n (%)	502 (86%)	490 (86%)	12 (86%)	1.000
Extensive LGE, n (%)	146 (25%)	143 (25%)	3 (21%)	1.000
NSVT, n (%)	117 (17%)	114 (17%)	3 (15%)	1.000

CMR- Cardiac magnetic resonance imaging, HCM- Hypertrophic cardiomyopathy, ICD - Implantable cardiac defibrillator, IVC- inferior vena cava, LA- Left atrium, LGE- late gadolinium enhancement, LVEF- Left ventricular ejection fraction, MR- mitral regurgitation, MWT- Mean wall thickness, NSVT- Nonsustanined ventricular tachycardia, NT-ProBNP- N-terminal pro B-type natriuretic peptide, PAPs- systolic pulmonary artery pressure, PW- posterior wall, RVEF – right ventricular ejection fraction, RVH: right ventricular hypertrophy, TAPSE- Tricuspid annular plane systolic excursion

Supplementary Table 2. Pairwise post-hoc comparisons of clinical, echocardiographic, and CMR characteristics across hypertrophic cardiomyopathy phenotypes

Variables	Comparison
LA diameter	Resting-obstructive vs Non-obstructive (p=0.038)
	Resting-obstructive vs Apical (p<0.001)
	Latent-obstructive vs Apical (p=0.007)
	Non-obstructive vs Apical (p=0.002)
Sex	Resting-obstructive vs Non-obstructive (p=0.011)
Hypertension	Resting-obstructive vs Non-obstructive (p=0.023)
	Latent-obstructive vs Apical (p=0.028)
	Non-obstructive vs Apical (p=0.012)
Diuretics	There were no statistically significant pairwise comparisons.
Beta-blockers	Non-obstructive vs Apical (p=0.009)
ICD	Latent-obstructive vs Non-obstructive (p=0.015)
Alcohol septal ablation	Resting-obstructive vs Non-obstructive (p<0.001)
	Latent-obstructive vs Non-obstructive (p=0.018)

	Resting-obstructive vs Apical (p<0.001)
Disopyramide	Resting-obstructive vs Latent-obstructive (p=0.004)
	Resting-obstructive vs Non-obstructive (p<0.001)
	Latent-obstructive vs Non-obstructive (p<0.001)
	Resting-obstructive vs Apical (p<0.001)
ACE/ARB use	Resting-obstructive vs Latent-obstructive (p=0.018)
	Resting-obstructive vs Non-obstructive (p=0.022)
NT-proBNP	Latent-obstructive vs Resting-obstructive (p=0.003)
QRS duration	Resting-obstructive vs Apical (p=0.019)
LVEF (Echocardiography)	Resting-obstructive vs Non-obstructive (p<0.001)
	Latent-obstructive vs Non-obstructive (p<0.001)
	Resting-obstructive vs Apical (p=0.001)
	Latent-obstructive vs Apical (p=0.019)
IVS thickness	Resting-obstructive vs Non-obstructive (p=0.001)
	Resting-obstructive vs Apical (p<0.001)
	Latent-obstructive vs Apical (p<0.001)
	Non-obstructive vs Apical (p<0.001)
Posterior wall thickness	Resting-obstructive vs Latent-obstructive (p=0.007)
	Latent-obstructive vs Non-obstructive (p=0.015)
	Resting-obstructive vs Apical (p<0.001)
	Non-obstructive vs Apical (p<0.001)
MWT (Echocardiography)	Resting-obstructive vs Non-obstructive (p=0.009)
	Resting-obstructive vs Apical (p<0.001)
	Latent-obstructive vs Apical (p<0.001)
	Non-obstructive vs Apical (p=0.004)
Rest gradient	All intergroup differences were statistically significant ($p < 0.001$), except for the comparison between the apical and non-obstructive groups ($p = 0.999$).
Provoked gradient	Resting-obstructive vs Latent-obstructive (p<0.001)
Mitral regurgitation	Resting-obstructive vs Non-obstructive (p<0.001)
Presence of CMR	Resting-obstructive vs Apical (p<0.001)
	Latent-obstructive vs Apical (p=0.021)
	Non-obstructive vs Apical (p=0.004)
CMR-LVEF	Resting-obstructive vs Non-obstructive (p<0.001)
	Latent-obstructive vs Non-obstructive (p<0.001)
CMR-MWT	Resting-obstructive vs Non-obstructive (p=0.039)
LGE presence	Resting-obstructive vs Apical (p=0.025)
Extensive LGE	Resting-obstructive vs Non-obstructive (p=0.019)
	Resting-obstructive vs Apical (p=0.008)
	Latent-obstructive vs Apical (p=0.034)
Apical aneurysm	Non-obstructive vs Apical (p<0.001)

ACE- Angiotensin-converting enzyme inhibitors, ARBs - Angiotensin receptor blockers, CMR- cardiac magnetic resonance imaging, ICD- Implantable cardioverter-defibrillator, IVS- interventricular septum, LA- left atrium, LGE- late gadolinium enhancement, LVEF- left ventciular ejection fraction, MWT- maximal wall thickness, NT-ProBNP- N-terminal pro B-type natriuretic peptide
Overall group differences were assessed using the Kruskal–Wallis test, followed by Dunn's post-hoc test with Bonferroni correction. Only statistically significant pairwise comparisons are reported.

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Transcatheter Closure of a Post-Surgical Left Atrial Appendage Ligation Leak Using a Patent Foramen Ovale Occluder

CASE REPORT

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INTRODUCTION

Incomplete surgical ligation of the left atrial appendage (LAA) is a well-recognized clinical challenge, with success rates reported as low as 40% when assessed by transesophageal echocardiography (TEE).[1] These residual post-surgical leaks are associated with blood stasis and an elevated risk of thromboembolic events, even in patients maintained on oral anticoagulation (OAC).[2] While dedicated LAA closure devices are engineered for native anatomies, post-surgical remnants often present with shallow depths and fibrotic borders, necessitating innovative transcatheter solutions.

CASE REPORT

A 74-year-old female with a history of hypertension, atrial fibrillation (AF), and prior bioprosthetic mitral valve replacement combined with surgical LAA ligation (performed 6 months earlier due to a documented LAA thrombus) presented with exertional dyspnea and palpitations. Despite strict adherence to apixaban (5 mg BID), she had suffered a cardioembolic cerebrovascular event 2 months prior to admission. Physical examination revealed an irregular pulse and bilateral pulmonary crackles. An electrocardiogram (ECG) confirmed AF with a ventricular rate of 118 bpm. Transthoracic echocardiography showed a left ventricular ejection fraction of 40%, a left ventricular end-diastolic diameter of 52 mm, a left atrial anteroposterior diameter of 46 mm, and a normally functioning bioprosthetic mitral valve. Catheter AF ablation was planned due to symptomatic arrhythmias.

Pre-procedural TEE identified a 6-mm post-surgical leak with significant flow on color Doppler (Video 1). Cardiac computed tomography (CT) confirmed the LAA leak with an internal diameter of 18 mm and a neck diameter of 8 mm (Figure 1A). Notably, CT imaging revealed that the LAA remnant was in close proximity to the pulmonary artery (PA) and the circumflex artery (Figure 1B and 1C).

Following successful radiofrequency AF ablation, percutaneous LAA leak closure was scheduled for a separate session. One month later, the procedure was performed under general anesthesia and uninterrupted OAC with TEE and fluoroscopic guidance. After an infero-posterior transseptal puncture, unfractionated heparin was administered to maintain an activated clotting time of 300-350 seconds. Due to the narrow and fibrotic nature of the leak site, conventional delivery sheaths lacked sufficient maneuverability. Consequently, a steerable radiofrequency (RF) ablation catheter (Marinr; Medtronic Inc., Minneapolis, MN, USA) was utilized to provide additional support and ensure coaxial alignment, facilitating the delivery sheath's entry into the LAA remnant (Video 2).

The choice of the occlusion device was guided by pre-procedural CT. To prevent potential mechanical trauma or perforation of the adjacent pulmonary and circumflex arteries by the anchoring hooks of conventional LAA devices, an Amplatzer Patent Foramen Ovale (PFO) Occluder (25/18 mm) (Abbott, USA) was selected. The 25-mm proximal disc ensured complete coverage of the ostium, while the 18-mm distal disc provided secure anchoring within the shallow 18-mm

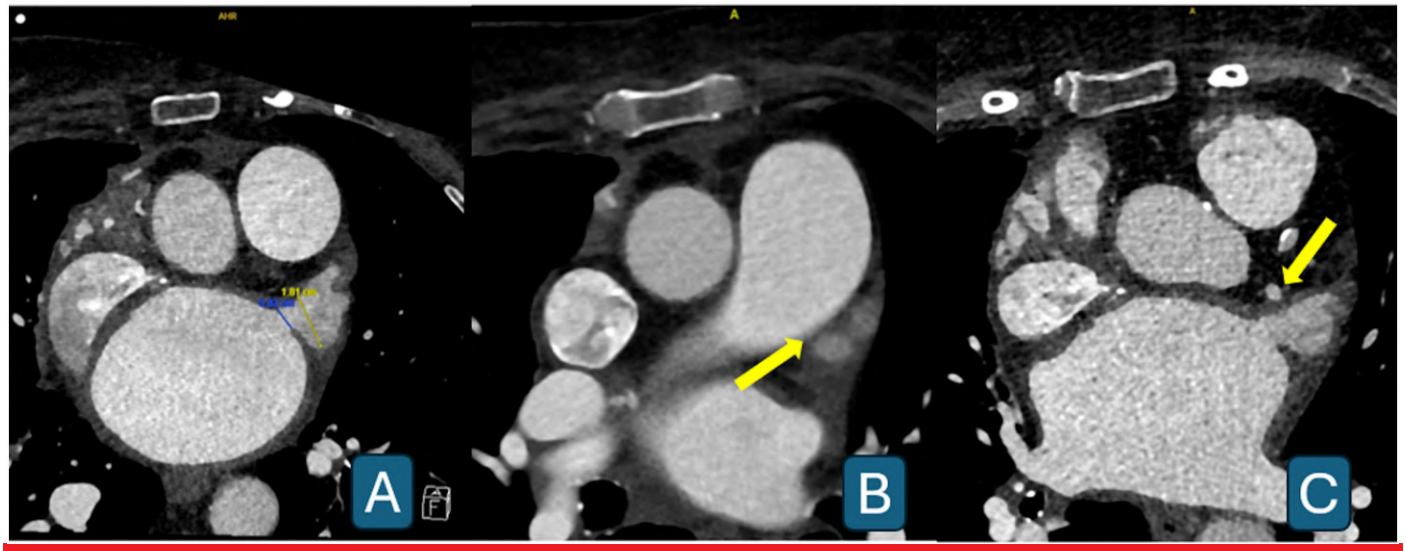

Figure 1. Pre-procedural Cardiac Computed Tomography (CT) Imaging. (A) Cardiac CT demonstrating the left atrial appendage (LAA) remnant with an internal diameter of 18 mm and a neck diameter of 8 mm. (B) CT image illustrating the close anatomical proximity of the leak site to the pulmonary artery. (C) CT image showing the proximity of the LAA remnant to the circumflex (Cx) artery.

internal cavity (Video 3). Stability was confirmed via a "tug test" (Video 4). Post-deployment TEE and angiography demonstrated complete occlusion without interference with the bioprosthetic mitral valve (Video 5). The patient was discharged on apixaban (5 mg BID) and aspirin (100 mg) for 1 month. At the 1-month follow-up, TEE confirmed stable device positioning with no residual leakage.

DISCUSSION

Currently, there is no definitive consensus or established algorithm in the literature regarding the management of leaks following percutaneous or surgical LAA closure. Although some studies provide evidence that leaks smaller than 3 mm can be managed conservatively, other research suggests that leaks of any size are associated with adverse thromboembolic events.[3,4] Furthermore, it has been demonstrated that leaks with visible flow on TEE have a stronger prognostic correlation with thromboembolic events compared to findings on CT.[3]

Despite the lack of a standardized algorithm, percutaneous leak closure should be strongly considered in patients—such as the one in the current case—who experience thromboembolic events despite prior surgical LAA ligation (performed due to the presence of an LAA thrombus during mitral valve surgery), especially when the surgical risk for re-intervention is high. Studies have shown that endocardial leak closure is an effective and safe procedure, with a complication rate of less than 3%.[5]

The selection of the appropriate technique and device is paramount for procedural success. Depending on the leak volume and anatomical characteristics, various techniques including device-based closure, RF ablation, coil embolization, and "stump space closure" have proven feasible.[4] Notably, RF ablation has been reported as an effective method for managing surgical leaks in certain cases.[6] Pre-procedural planning via CT is essential to evaluate the external, internal, and neck diameters of the leak site to guide device selection. For instance, in a case where a leak developed following a Lariat procedure, the Amplatzer Talisman PFO Occluder was successfully utilized due to its smaller distal disc and expandable waist.[7] Similarly, septal occluders have been effectively used in patients whose anatomy is not suitable for conventional closure devices.[8]

Furthermore, the anatomical proximity of the LAA to adjacent structures—such as the left superior pulmonary vein, the PA, and the circumflex (Cx) artery—must be carefully considered. Due to the anchoring mechanisms (hooks/barbs) of standard LAA closure (LAAC) devices, there is a rare but potential risk of perforation, particularly of the PA, which can lead to catastrophic outcomes.[9] In the current case, given the close proximity to both the PA and the Cx artery, a PFO closure device was used to minimize the risk of perforation. Additionally, in cases with a shallow appendage morphology where depth is insufficient, PFO devices may serve as a viable alternative for LAA leak closure.

CONCLUSION

Percutaneous closure of post-surgical LAA leak is an effective strategy to mitigate thromboembolic risk, but the procedure has technical challenges. A patient-centered approach is mandatory, requiring a comprehensive assessment of the LAA anatomy and its surrounding structures to determine the most appropriate device and technique. In cases involving shallow anatomy or proximity to vital adjacent vessels, PFO occluders may be safe and versatile alternatives. Success in these complex interventions requires meticulous pre-procedural imaging and a patient-specific approach to device selection.

Availability of data and materials: The data are presented in the manuscript files.

Informed Consent: Written and verbal informed consent was obtained from the patient for the publication of this case report, including all personal and clinical details and accompanying images.

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Video 1: Color Doppler TEE imaging showing significant flow through the 6-mm post-surgical LAA leak.

Video 2: Fluoroscopic guidance demonstrating the use of a steerable radiofrequency (RF) ablation catheter to provide support and coaxial alignment for the delivery sheath.

Video 3: Fluoroscopic sequence showing the deployment of the 25/18 mm Amplatzer PFO Occluder within the LAA remnant.

Video 4: The "tug test" is performed under fluoroscopy to confirm the stable positioning and secure anchoring of the PFO occluder.

Video 5: Post-procedural TEE assessment demonstrating complete occlusion of the leak with no residual flow and no interference with the bioprosthetic mitral valve.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Ventricular Fibrillation and Kounis Syndrome Can Result from a More Severe Delayed-Onset Allergic Reaction

LETTER TO THE EDITOR

To the Editor,

In the fascinating case report by Honggen Cui et al,[1] a 59-year-old woman, who had been treated with levofloxacin tablets for a urinary tract infection 2 days prior, developed itching on her limbs and chest along with sporadic urticaria. One day later, she started experiencing recurrent burning pain in her chest that radiated to her pharynx. Each episode lasted 2-3 minutes and was relieved on its own. The patient was administered aspirin and clopidogrel bisulfate in addition to other medications upon arrival. Thirty minutes later, the patient experienced severe chest pain and eventually lost consciousness while twitching. Ventricular fibrillation was detected and the patient was shocked with 200 Joules right away and regained consciousness.

According to emergency coronary angiography, there was no visible stenosis or blockage in the left main trunk, left anterior descending artery, left circumflex branch, or right coronary artery, and obstruction, and thrombolysis in myocardial infarction risk score blood flow grade 3.

This case highlights significant problems with the use of aspirin, clopidogrel, and the delayed allergic reactions. Paradoxically, these drugs, which are used to treat Kounis syndrome, thrombosis, and myocardial infarction,[2] may actually cause these conditions:

1. Instead of inducing a true immunoglobulin E-mediated allergy, aspirin causes allergic-type reactions by inhibiting the cyclooxygenase-1 enzyme, which diverts arachidonic acid metabolism to produce more leukotrienes. These extra leukotrienes directly cause symptoms including bronchospasm, urticaria (hives), and nasal obstruction. Although aspirin is good for cardiovascular conditions, it can cause Kounis syndrome. The Samter–Beer trio is a combination of asthma, nasal polyps, and aspirin allergy that causes myocardial infarction and vasospasm syndrome.[2-4] Treatment for this condition focuses on reducing the allergic reaction. Another article describes a case of Kounis syndrome brought on by asthma triggered by aspirin used to treat angina pectoris.[5] A case study of a patient with a history of aspirin allergy who experienced coronary vasospasm after taking aspirin is also presented in another article.[6]
2. There are currently 3 documented cases of Kounis syndrome brought on by clopidogrel. A 61-year-old man was admitted to the hospital in the initial report because of worsening chest discomfort that was accompanied by frequent episodes of severe chest pain during rest and regular activities, as well as excessive smoking. He also had a history of hypertension, atopic eczema, and allergic responses. Type I Kounis syndrome as a result of a clopidogrel allergic response was the ultimate diagnosis.[7] After receiving a loading dose of clopidogrel, a 56-year-old male patient with Kounis Syndrome suffered angioedema, respiratory distress, and vasospasm in the right coronary artery.[8] All of these instances have made desensitization to clopidogrel imperative. Desensitization is safe and highly effective for people who are sensitive

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to clopidogrel and require long-term dual antiplatelet therapy.[9]

3. Delayed allergic reactions can exacerbate subsequent rapid allergic reactions by increasing inflammation, attracting more immune cells, and perhaps causing chronic reactions—especially after repeated exposure. This can occur by causing a second, more severe wave of symptoms hours or even days later. Indeed, in severe delayed reactions or a biphasic reaction, the original anaphylactic symptoms recur without additional exposure to the allergen. Even while the majority of acute reactions are T-cell-mediated and antibody-independent, the immune system may still be primed, and further exposure to the allergen or its breakdown products may trigger a fresh, frequently more severe reaction.

Since it is frequently impossible to differentiate between hypersensitive reactions and the worsening of the basic inflammatory condition, diagnosing allergic reactions is difficult. Therefore, a high index of suspicion is required to determine the causal culprit and discover a safe substitute drug. By concentrating on the IgE pathway and the related inflammatory processes, there may be hope for lowering allergy-associated Kounis syndrome.[10]

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Comment on "Delayed-Onset Type 1 Kounis Syndrome Caused Ventricular Fibrillation: A Case Report"

LETTER TO THE EDITOR

To the Editor,

We read with interest the case by Cui et al. describing delayed-onset Type 1 Kounis syndrome triggered by levofloxacin and complicated by ventricular fibrillation (VF).[1] The report highlights the overlap between allergic activation and coronary vasoreactivity but raises several diagnostic and therapeutic concerns.

In this case, aspirin 300 mg and clopidogrel 300 mg were given before angiography despite normal cardiac biomarkers. The 2023 European Society of Cardiology guidelines advise against pretreatment with $P2Y_{12}$ inhibitors when an early invasive strategy is planned, recommending loading only after coronary anatomy is known.[2] Initial management of allergic coronary syndromes may focus on anti-allergic and vasodilator therapy. Observational evidence also discourages dual antiplatelet therapy (DAPT) in vasospastic settings. In the VA-Korea Registry of 1,838 patients with vasospastic angina, DAPT increased adverse outcomes compared with no antiplatelet therapy, whereas aspirin alone was neutral.[3]

A further issue is the unreported QTc interval. Fluoroquinolones, including levofloxacin, can prolong repolarization and provoke torsades de pointes or VF, especially with ischemia or electrolyte imbalance.[4] The electrocardiogram in this case suggests a QTc near 480 ms, yet QT or electrolyte data were absent. Levofloxacin-induced QT prolongation could thus have contributed to arrhythmogenesis. Serial QTc and electrolyte monitoring would help determine whether the arrhythmia was resulted from vasospasm, repolarization delay, or both.

Finally, vasospastic angina was presumed but not confirmed because no ergonovine provocation test was performed after stabilization. Such testing remains the diagnostic standard for coronary spasm in patients with non-obstructive angiography and compatible symptoms, improving diagnostic certainty and guiding treatment.[5]

In summary, early DAPT may worsen outcomes in allergic coronary syndromes, QT-active antibiotics can independently precipitate malignant arrhythmia, and provocation testing is essential for accurate diagnosis. Prompt anti-allergic and vasodilator therapy, QT monitoring, and anatomy-guided antiplatelet selection represent safer, evidence-based management.

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Reply to the Letter to the Editor: "Comment on 'Delayed-Onset Type 1 Kounis Syndrome Caused Ventricular Fibrillation: A Case Report'"

LETTER TO THE EDITOR
REPLY

To the Editor,

Carry out the following discussion and reply:

1. In this case,[1] aspirin 300 mg and clopidogrel 300 mg were given before angiography despite normal cardiac biomarkers. The 2023 European Society of Cardiology guidelines advise against pretreatment with $P2Y_{12}$ inhibitors when an early invasive strategy is planned, recommending loading only after coronary anatomy is known.

Re: It is reasonable to administer oral loading doses of aspirin and clopidogrel during the initial hospitalization of the patient when the coronary artery anatomy is unclear, especially when frequent chest pain occurs and thrombus formation cannot be ruled out, even in cases where allergy induction is also unclear.

2. A further issue is the unreported QTc interval. Fluoroquinolones, including levofloxacin, can prolong repolarization and provoke torsades de pointes or VF, especially with ischemia or electrolyte imbalance. The electrocardiogram in this case suggests a QTc near 480 ms, yet QT or electrolyte data were absent. Levofloxacin-induced QT prolongation could thus have contributed to arrhythmogenesis. Serial QTc and electrolyte monitoring would help determine whether the arrhythmia was resulted from vasospasm, repolarization delay, or both.

Re: The patient's electrocardiogram is not typical torsades de pointes. Upon admission, the blood potassium level was normal. The QT interval on the ECG was 480 ms, which was prolonged, and this may be related to levofloxacin. Our deficiency was that we did not follow up to check if the QT interval shortened after the patient stopped taking the medication.

3. **Re:** We inferred that the patient's acute myocardial infarction was caused by coronary spasm based on three aspects: negative coronary angiography, typical electrocardiogram of acute ST-segment elevation myocardial infarction, and elevated troponin. The evidence is sufficient; however, due to the limitations of our hospital's conditions, the ergonovine provocation test was not performed. Regarding treatment, we have been administering anti-allergic reaction medications to the patient since admission.

Finally, sincerely thank you for your comments[2] and attention.

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Is the Red Blood Cell Distribution Width-to-Albumin Ratio Sufficient to Predict Cardiovascular Risk?

LETTER TO THE EDITOR

To the Editor,

We read with interest the study by Li et al[1] demonstrating associations between red cell distribution width (RDW), RDW-to-albumin ratio (RAR), and cardiovascular disease (CVD) in 7619 postmenopausal women from NHANES 2003 to 2016.[1] The large sample and rigorous analysis are commendable, but several limitations constrain interpretation.

Key biomarkers were not included in the study. Low-density lipoprotein cholesterol (LDL-C), the primary lipid target in CVD prevention, was omitted despite adjustment for total cholesterol and high-density lipoprotein cholesterol (HDL-C).[2] The authors propose inflammation as the mechanistic link between RDW and CVD, yet no inflammatory markers such as C-reactive protein (CRP) or interleukin-6 were measured. Prior studies have shown RDW correlates strongly with CRP and other inflammatory indices, making these essential to validate the proposed pathway.[3] Without them, the inference that RDW serves as an "inflammatory surrogate" remains speculative. Medication use, particularly statins and anticoagulants, was also unaccounted for. Statins lower inflammation and affect albumin metabolism, while both drug classes are commonly used among older adults with CVD risk factors. Their omission may lead to residual confounding and overstate the independent effect of RDW and RAR.

The incomplete hematologic profile further limits interpretation. Elevated RDW may reflect iron deficiency or anemia of chronic disease, conditions with opposing clinical implications. Without hemoglobin, mean corpuscular volume, and ferritin levels, these mechanisms cannot be distinguished. Iron deficiency, common in postmenopausal women, independently increases cardiovascular risk.[4] The binary "anemia treatment history" variable cannot capture these differences, restricting clinical applicability.

Several subgroup results challenge the biological rationale. RDW was associated with CVD only in non-diabetic women and those with HDL-C ≥50 mg/dL, contrary to expectations if inflammation and oxidative stress are key mediators. The RAR showed broader associations, but whether this reflects greater statistical power or distinct mechanisms remains unclear.

The definition of CVD was narrow, limited to self-reported heart failure, coronary heart disease, angina, myocardial infarction, and stroke. It excluded atrial fibrillation, venous thromboembolism, and peripheral arterial disease, which are mechanistically linked to inflammation and thrombosis. The absence of an association with angina pectoris also raises concern about whether RDW and RAR capture true atherosclerotic burden or reflect more severe, memorable events prone to recall bias in self-reported data.[5]

The cross-sectional design precludes causal inference. Elevated RDW or RAR may be consequences rather than predictors of CVD. Heart failure, showing the strongest association (OR 3.06), can itself reduce albumin through hepatic congestion, suggesting possible reverse causation.

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Li et al[1] highlight accessible biomarkers with potential relevance for risk assessment, but clinical application requires caution. Future research should incorporate CRP, LDL-C, and full iron studies, adjust for medication use, include adjudicated endpoints such as atrial fibrillation and thromboembolic disease, and establish temporal and predictive validity.

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Risk Trajectory and Right Ventricular Adaptation in Selexipag-Based Triple Therapy for Pulmonary Arterial Hypertension

LETTER TO THE EDITOR

To the Editor,

We read with great interest the study by Tokgöz et al[1] evaluating the durability of selexipag-based sequential triple combination therapy in pulmonary arterial hypertension.[1] The authors should be acknowledged for their longitudinal design, extended follow-up, and the parallel application of multiple validated multiparametric risk frameworks. The integration of clinical status, echocardiography, invasive hemodynamics, and Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management–based tools allows a nuanced examination of risk evolution beyond isolated surrogate endpoints. However, certain aspects merit further discussion.

The longitudinal data reveal a pattern in which early improvements across functional class, 6-minute walk distance, echocardiographic indices, and composite risk scores are followed by gradual attenuation after the first year. This attenuation does not occur uniformly across physiological domains. Sustained reductions in N-terminal pro-brain natriuretic peptide levels and relative preservation of tricuspid annular plane systolic excursion suggest continued right ventricular adaptive capacity despite rising pulmonary arterial pressures. Such divergence implies that composite risk regression may reflect evolving ventricular–vascular uncoupling rather than simple loss of therapeutic effect.[2] Clinically, collapsing these trajectories into a single risk narrative may obscure opportunities for earlier phenotype-directed escalation.

Survival analyses further reinforce the primacy of baseline biological risk over treatment intensity. Outcomes tracked consistently with baseline Swedish Pulmonary Arterial Hypertension Registry, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management, and echocardiography-derived risk profiles, while achieved selexipag dose showed no independent association with mortality. This finding should be interpreted in the context of prostacyclin pathway pharmacology, where tolerability-driven dose ceilings do not reliably correspond to effective receptor engagement.[3] In practice, these data favor risk-guided strategy over dose-centric escalation and caution against equating higher nominal dosing with superior long-term benefit.

The limited prognostic separation afforded by early follow-up risk reassessment adds further complexity. Although several patients transitioned to lower-risk categories within the first year, this reclassification did not translate into sustained survival discrimination. Reliance on short-term risk improvement as evidence of disease stabilization may therefore delay recognition of ongoing pathobiological progression and postpone necessary therapeutic recalibration. The substantial representation of congenital heart disease–associated pulmonary arterial hypertension further contextualizes the findings. Differences in right ventricular remodeling and adaptive reserve across etiologies may contribute to the dissociation between functional gains and longer-term outcomes,[4] emphasizing the need for etiology-aware interpretation of aggregate risk metrics.

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Taken together, the data indicate that early improvements with selexipag-based triple therapy do not uniformly translate into durable risk modification and that baseline risk status remains the dominant determinant of prognosis. We commend the authors for their rigorous multiparametric evaluation and extended observation period. Incorporation of serial right ventricular–pulmonary arterial coupling metrics may help refine timing and selection of subsequent therapeutic strategies in pulmonary arterial hypertension.

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Reply to the Letter to the Editor: "Risk Trajectory and Right Ventricular Adaptation in Selexipag-Based Triple Therapy for Pulmonary Arterial Hypertension"

LETTER TO THE EDITOR REPLY

To the Editor,

We read with great interest the Letter to the Editor entitled "Risk Trajectory and Right Ventricular Adaptation in Selexipag-Based Triple Therapy for Pulmonary Arterial Hypertension"[1] on our manuscript published in the *Anatolian Journal of Cardiology* evaluating the durability of selexipag-based sequential triple combination therapy in pulmonary arterial hypertension (PAH).[2]

We thank the authors[1] for their thoughtful and constructive comments regarding our study on longitudinal evaluation of selexipag-based sequential triple therapy and their emphasis on right ventricular–pulmonary arterial (RV–PA) coupling dynamics.

We agree that signals suggesting a trend for attenuation of risk reduction after the first year deserve careful interpretation. Given the single-center data reflecting real-world longitudinal dynamics rather than randomized controlled trial conditions and decreasing sample size at later time points, attenuation should be interpreted cautiously. However, this pattern likely reflects the natural history of PAH rather than loss of therapeutic effect. Importantly, sustained reductions in N-terminal pro-brain natriuretic peptide levels and relative preservation of tricuspid annular plane systolic excursion (TAPSE) in our cohort suggest maintained RV adaptive reserve despite progressive pulmonary vascular load. This apparent divergence between RV performance markers and pulmonary arterial pressures may reflect dynamic alterations in RV-PA coupling rather than simple attenuation of therapeutic efficacy.[3,4]As discussed before, RV adaptation is not linearly related to afterload but depends on coupling efficiency and contractile reserve.[3] Accordingly, composite risk regression over time may capture evolving RV–pulmonary vascular interactions that are not fully represented by globally utilized multiparametric risk scores. Clinically, reliance on a single risk trajectory may obscure phenotype-specific signals that could inform earlier, individualized therapeutic escalation, suggesting ongoing RV compensation despite progressive vascular remodeling.

Our survival analyses further reinforce the primacy of baseline biological risk over treatment intensity, as stated by authors. Moreover, our observation that achieved selexipag dose was not independently associated with mortality should not be interpreted as a lack of dose relevance, but rather as a reflection of individualized titration strategies based on tolerability and clinical response in the context of prostacyclin pathway pharmacology, where tolerability-driven dose escalations may not reliably represent effective receptor occupation.[5]

While early risk reclassification did not yield strong long-term survival discrimination in our cohort, we believe early improvement remains clinically meaningful, particularly for symptom burden and functional status. We agree that

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lower risk status assessed by REVEAL Lite 2.0 at the time of selexipag initiation on the background double combination therapy predicted the risk status attained at final assessment. This finding aligns with the Prostacyclin (PGI) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study paradigm, suggesting that earlier escalation to triple therapy within 6 months, before progression to advanced risk strata, may allow more durable stabilization of disease course. [6] Thus, rather than contradicting the importance of baseline risk, our data reinforce the concept that risk at the time of therapeutic escalation is a modifiable determinant when intervention occurs sufficiently early.

We acknowledge that congenital heart disease–associated PAH represents a distinct adaptive phenotype. Subgroup analyses were limited by sample size; however, we agree that etiology-specific modeling represents an important direction for future investigation.

We appreciate the authors again for highlighting the importance of RV–PA coupling and phenotype-aware risk interpretation. We agree that tailored management strategies with the incorporation of serial coupling metrics for an extended observation period may enhance future longitudinal risk modeling strategies in this setting.

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Self-Inflicted Sewing Needles Penetrating the Interventricular Septum

A 34-year-old incarcerated male presented with left-sided chest pain. He reported deliberate self-harm by inserting sewing needles into his chest several months earlier. Physical examination and laboratory findings were unremarkable. Electrocardiography demonstrated normal sinus rhythm.

Posteroanterior chest radiography revealed multiple linear metallic foreign bodies projected over the cardiac silhouette (Figure 1). Thoracic computed tomography demonstrated several sewing needles within the thorax, including one penetrating the mid-interventricular septum (Figure 2A). Transthoracic echocardiography confirmed a hyperechoic linear structure embedded within the interventricular septum without pericardial effusion or ventricular dysfunction (Figure 2B).

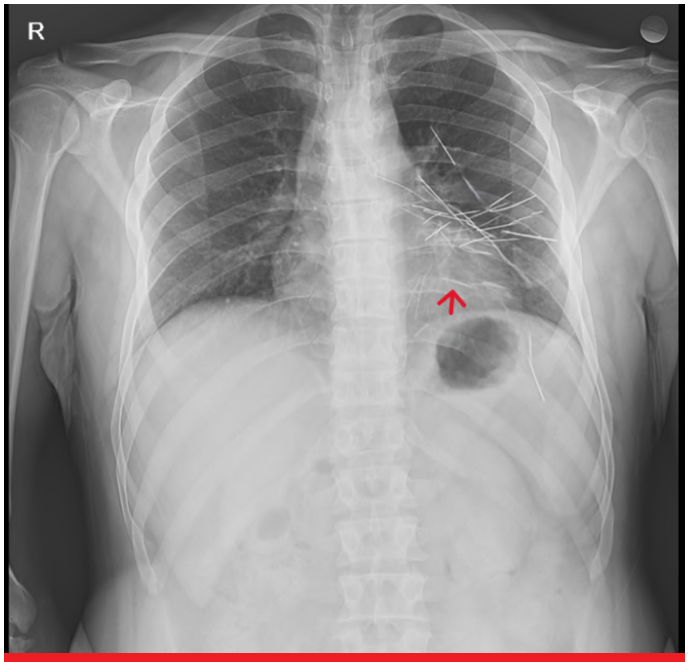

Figure 1. Chest radiograph showing multiple linear metallic foreign bodies over the cardiac silhouette.

Although the patient was hemodynamically stable, septal myocardial penetration raised concern for potential delayed complications such as arrhythmias, septal defect formation, or migration. Surgical removal was strongly recommended; however, the patient declined operative intervention and was discharged with follow-up advice.

E-PAGE ORIGINAL IMAGE

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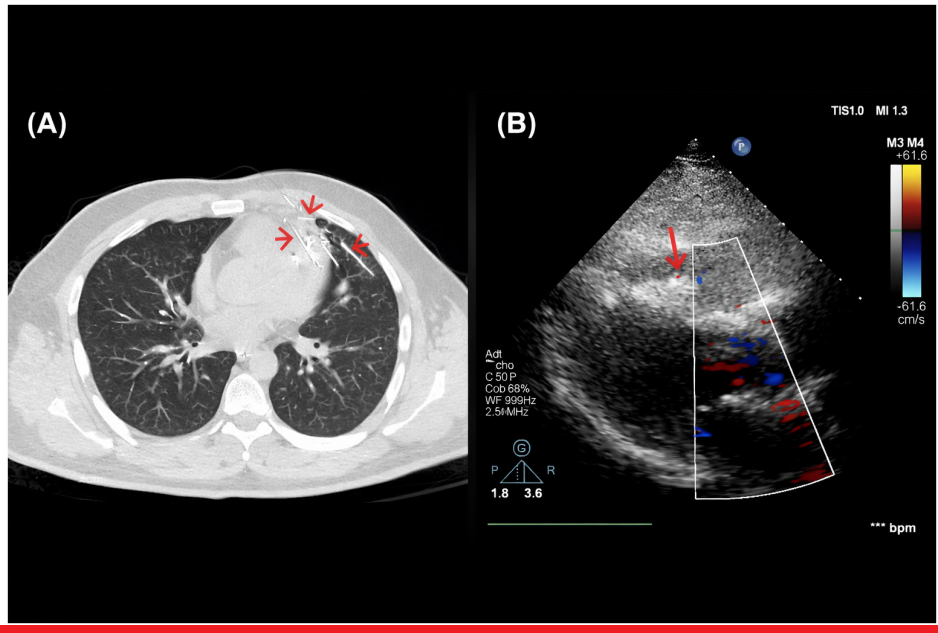

Figure 2. (A) Axial computed tomography demonstrating a sewing needle penetrating the interventricular septum. (B) Transthoracic echocardiography confirming septal myocardial involvement.

This case highlights the importance of multimodality imaging in identifying myocardial penetration and guiding management in patients with intracardiac sharp foreign bodies.

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