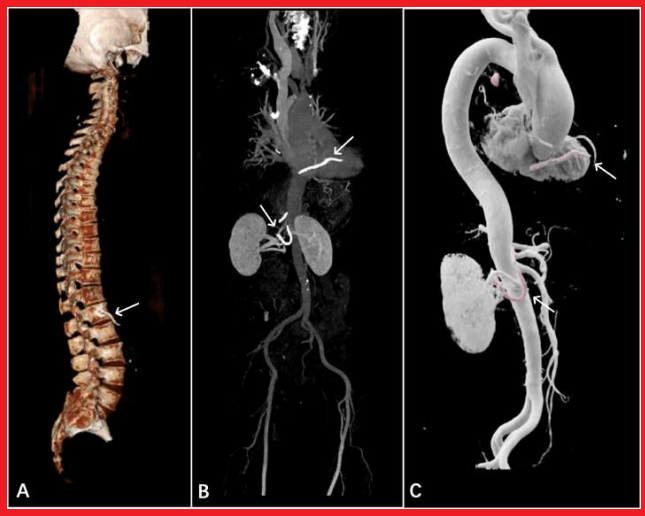
TURKISH SOCIETY OF CARDIOLOGY

March 2026
Volume 30, Issue 3

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Original Investigations



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ISSN - 2149-2263 eISSN 2149-2271
www.anatoljcardiol.com

THE ANATOLIAN JOURNAL OF CARDIOLOGY

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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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- 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 Alassisted 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.

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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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Headings (MeSH) terms prepared by the National Library of Medicine (NLM) and should be provided just below the abstract.
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- Abstract: It should not include subheadings and it should be limited to 250 words.
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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**
  Since a limited number of case reports is published, only reports which are related to rare cases and conditions that constitute challenges in diagnosis and treatment, offer new methods or suggest knowledge not included in books, and are interesting and educational are accepted for publication.
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- Main Text: It should include Introduction, Case Report, Discussion and Conclusion sections and should not exceed 700 words excluding the references.
- References: The reference list should follow the main text and the number of references should be limited to 10.
- Tables, Figures and Images: They should be provided after the reference list according to their order of appearance in the text and should be limited to two.
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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,
  shed light on fundamental mechanisms of diseases, emphasize abnormalities or
  introduce new treatment methods are accepted for publication.
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  Letters to the Editor aim to discuss the importance of a manuscript previously published in the journal. This type of manuscripts should also include a comment on the published manuscript. Moreover, articles on topics of interest to readers within the scope of the journal, especially on educational issues, can be published in the format of a Letter to the Editor.
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  These articles include current information on research and publication ethics and also cases of ethical violation.
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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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- Abbreviations should be explained in alphabetical order at the bottom of the tables, graphs and figures
- 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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EDITORIAL

Prior studies suggest that elevated The triglyceride–glucose (TyG) index is associated with poor collateral circulation, contrast-induced nephropathy (CIN), and major adverse cardiac and cerebrovascular events (MACCE) in CTO patients. In this review, Desai et al from USA synthesized current evidence linking the TyG index with CTO pathophysiology, PCI outcomes, and long-term prognosis. Is it a good marker?

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Comorbid insomnia and sleep apnea (COMISA) is a frequent but underrecognized condition in patients with obstructive sleep apnea (OSA). While OSA is strongly linked to hypertension, the independent contribution of COMISA to resistant hypertension remains unclear. Durak et al from Türkiye tried to make it clear this question.

Right ventriculo–pulmonary artery (RV–PA) coupling, commonly assessed by the ratio of tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP), has emerged as an important prognostic marker in various cardiovascular diseases. However, its predictive value after transcatheter aortic valve implantation (TAVI) remains insufficiently defined. Tanyeri et al from Türkiye studied this ratio after TAVI and found what?

And again 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

DOI: 10.14744/AnatolJCardiol.2026.3

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Pathophysiological Insights and Prognostic Value of the Triglyceride-Glucose Index in Patients with Chronic Total Occlusion

ABSTRACT

The triglyceride-glucose (TyG) index is a surrogate marker of insulin resistance (IR) associated with atherosclerosis, endothelial dysfunction, and cardiovascular disease (CVD). Chronic total occlusion (CTO) presents major clinical challenges, especially in patients undergoing percutaneous coronary intervention (PCI). This narrative review explores the role of the TyG index in predicting CTO development and adverse cardiovascular outcomes. A literature review of studies assessing the association between the TyG index and CTO, PCI outcomes, and contrast-induced nephropathy (CIN) was conducted. Pathophysiological mechanisms linking IR, TyG, and CTO progression were evaluated, and the predictive utility of the TyG index in risk stratification and post-PCI complications was analyzed. Multiple studies show that a higher TyG index is strongly associated with increased CTO risk, poor collateral circulation, CIN, and adverse outcomes after PCI. Elevated TyG values were independently predictive of impaired collateral formation in diabetic and non-diabetic patients, with stronger effects in metabolically vulnerable subgroups. Individuals with higher TyG levels had a greater likelihood of developing CIN, with analyses confirming its role as an independent predictor. Long-term prognosis in CTO patients was also worse with elevated TyG, with higher rates of major adverse cardiovascular events. The TyG index demonstrated consistent predictive capability compared with other metabolic markers, supporting its potential as a low-cost tool for risk stratification. The TyG index is a cost-effective biomarker for predicting adverse outcomes in CTO patients. Its incorporation into clinical assessment may improve early risk identification and support individualized PCI planning.

Keywords: Chronic total occlusion, insulin resistance, percutaneous coronary intervention, triglyceride-glucose index

INTRODUCTION

Coronary chronic total occlusions (CTOs) are defined as completely occluded coronary arteries with Thrombolysis in Myocardial Infarction grade 0 flow for ≥3 months.[1] The CTOs are encountered in up to 20% of patients undergoing coronary angiography and pose significant therapeutic challenges. The majority are managed with guideline-directed optimal medical therapy (OMT) targeting anginal relief and reduction of major adverse cardiovascular events.[1,2] While randomized clinical trials have not demonstrated mortality benefit with CTO-percutaneous coronary intervention (PCI) compared with OMT alone, evidence supports successful PCI is associated with improved symptoms, quality of life, and left ventricular function.[2-4]

Despite technological advances, CTO-PCI remains technically demanding, with lower procedural success rates and higher complication risks compared with non-CTO interventions.[5,6] Identifying high-risk patients is critical to optimizing outcomes. The triglyceride-glucose (TyG) index, calculated as ln [fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2], has emerged as a reliable surrogate of insulin resistance (IR).[2,6] The TyG index has demonstrated prognostic value in non-obstructive cardiovascular disease (CVD) populations across multiple observational studies, supporting its clinical utility as a cardiometabolic risk indicator.[8]

REVIEW

Rupak Desai[1]
Abhishek Prasad[2]
Jai Sivanandan Nagarajan[3]
Ananth Guddeti[4]
Navya Mandalapu[5]
Darsh Tusharbhai Patel[6]
Warda Shahnawaz[7]
Sourabh Khatri[8]
Abdul Aleem[9]
Adil Sarvar Mohammed[10]
Muhammad Usman Ghani[11]

[1]*Independent Researcher, Outcomes Research, Atlanta, GA, USA*
[2]*Department of Anesthesiology and Perioperative Medicine, MD Anderson Cancer Center, Houston, TX, USA*
[3]*Department of Medicine, SUNY Upstate Medical University, Syracuse, New York, USA*
[4]*Department of Internal Medicine, SUNY Upstate Medical University, Syracuse, NY, USA*
[5]*Department of Internal Medicine, Bronxcare Health Sciences, Bronx, NY, USA*
[6]*Department of Medicine, Mercy Catholic Medical Center, Darby, PA, USA*
[7]*Internal Medicine, Mobile Infirmary Medical Center, USA*
[8]*Department of Medicine, Independence Health System, Greensburg, PA, USA*
[9]*Department of Pulmonary and Critical Care Medicine, Henry Ford Genesys Hospital Grand Blanc, Michigan, USA*
[10]*Department of Internal Medicine, Central Michigan University, Mt. Pleasant, MI, USA*
[11]*Central Michigan University College of Medicine, Mt. Pleasant, MI, USA*

Corresponding author:
Muhammad Usman Ghani
✉ ghani1mu@cmich.edu

Received: November 21, 2025
Accepted: December 30, 2025
Available Online Date: February 10, 2026

Cite this article as: Desai R, Prasad A, Nagarajan JS, et al. Pathophysiological insights and prognostic value of the triglyceride-glucose index in patients with chronic total occlusion. *Anatol J Cardiol.* 2026;30(3):140-145.

DOI:10.14744/AnatolJCardiol.2025.6043

Insulin resistance promotes vascular injury through oxidative stress, endothelial dysfunction, and impaired collateral development, thereby exacerbating CAD progression.[18-20] Prior studies suggest that elevated TyG is associated with poor collateral circulation, contrast-induced nephropathy (CIN), and major adverse cardiac and cerebrovascular events (MACCE) in CTO patients.[11-16] In this review, we synthesize current evidence linking the TyG index with CTO pathophysiology, PCI outcomes, and long-term prognosis.

Methodology of Literature Review

A narrative review approach was used to synthesize current evidence addressing the relationship between the triglyceride–glucose (TyG) index and outcomes in patients undergoing PCI for CTO-PCI. A comprehensive literature search was performed using PubMed, Google Scholar, and Scopus to identify English-language studies published between January 2018 and January 2025, investigating the relationship between the TyG index and CTO-related outcomes. Search terms included "triglyceride–glucose index," "TyG," "chronic total occlusion," and "percutaneous coronary intervention." Studies were considered eligible if they examined associations between the TyG index and key CTO-related outcomes, including CIN, MACCE, collateral circulation, and mortality. Because this article serves as a narrative review rather than a systematic review, PRISMA-based procedures and formal risk-of-bias instruments were not utilized. Nonetheless, to enhance transparency, the databases searched, the key search terms, and the inclusion criteria for the studies were identified. Extracted data encompassed study design, sample size, TyG thresholds, outcome measures, and statistical indicators such as odds ratios (OR), hazard ratios (HR), and receiver operating characteristic area under the curve (ROC-AUC).

Across all included studies, the TyG index was derived using the standard formula: ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2]. Laboratory values for triglyceride and glucose were consistently reported in mg/dL and obtained after an overnight fast. The TyG index was analyzed either as a continuous variable (by tertiles or quartiles) or through predefined cutoffs (such as 8.65 for CIN; 9.10 for long-term cardiovascular risk), contributing to variability in reported optimal thresholds. Furthermore, differences in predefined cutoff thresholds (e.g., 8.65, 9.10, or tertile-based categorization) and variability in laboratory assay techniques likely contributed to the heterogeneity observed in reported findings. Given the heterogeneity of study designs and outcome definitions, findings were synthesized qualitatively to align with narrative methodology(Table 1).

HIGHLIGHTS

- In patients with chronic total occlusion (CTO), a higher triglyceride-glucose (TyG) index is associated with impaired coronary circulation.
- The TyG index serves as a reliable predictor for major adverse cardiac and cerebrovascular events and cerebrovascular accidents. For individuals undergoing CTO procedures, elevated TyG levels are independently associated with increased risk of developing contrast-induced nephropathy.
- As a practical and reproducible measure of insulin resistance, the TyG index offers superior clinical utility to the traditional Homeostatic Model Assessment of Insulin Resistance metric.
- The TyG is a cost-effective biomarker for pre-procedural risk stratification of CTO patients and adds strong prognostic ability.

RESULTS

Across the included studies, an elevated TyG index was consistently associated with adverse outcomes in patients with coronary CTO. In a 2025 cohort, Soner et al[13] reported that a TyG index ≥8.65 nearly doubled the risk of CIN (OR ≈2.17), although no independent association with mortality was observed. Zhu et al (2024)[11] and Gao et al (2021)[12] demonstrated a strong correlation between higher TyG values and impaired coronary collateral circulation, with ORs exceeding 5 and robust discrimination (AUC ~0.78). In terms of long-term prognosis, Yang et al[10], Song et al[9], Lin et al[15], and Li et al[14] consistently found that elevated TyG predicted MACCE. For example, Song et al[9] showed that patients with TyG >9.10 had a four-fold increased risk of cardiovascular death and a two-fold higher risk of MACCE. Xiao et al[16] also reported that higher TyG predicted increased likelihood of CTO presence in a large cross-sectional cohort. Collectively, these findings highlight that the TyG index provides strong predictive utility for CIN, impaired collateralization, and MACCE in CTO populations, with effect sizes generally larger in higher-risk subgroups such as diabetics and smokers.

DISCUSSION

Pathophysiological Insights

Insulin resistance, as reflected by the TyG index, plays a pivotal role in the cascade of pathophysiological changes that culminate in vascular dysfunction. Elevated TyG levels reflect a metabolic milieu of hyperglycemia and hypertriglyceridemia, which together promote vascular inflammation, oxidative stress, and endothelial injury.[7,18-20]

Insulin resistance, at the molecular level, disrupts PI3K/Akt signaling pathways responsible for activating endothelial nitric oxide (NO) synthase, leading to reduced NO production and impaired vasodilation.[18] In parallel, IR also increases endothelin-1 expression, further promoting vasoconstriction and exacerbating endothelial dysfunction.[18] Together, these alterations impair vascular homeostasis and contribute to early atherosclerotic changes.

Beyond these vasomotor effects, IR amplifies oxidative injury via the production of reactive oxygen species through activation of NADPH oxidase, leading to oxidative stress, lipid peroxidation, and progressive endothelial damage.[19] Consequently, this oxidative burden upregulates vascular adhesion molecules, including ICAM-1 (Intercellular Adhesion Molecule-1) and VCAM-1 (Vascular Cell Adhesion

Table 1. Association Between Triglyceride-Glucose Index and Clinical Outcomes in Chronic Total Occlusion: Summary of Observational Studies

Study	Sample Size	Study Population	Study Type	Follow-up	TyG Level	Main Results	Outcomes	Key Metrics
Soner et al, 2025	218	CTO patients undergoing PCI	Retrospective cohort	96 months	Cutoff ≥ 8.65	TyG index (Cutoff ≥ 8.65) was significantly associated with increased risk of CIN and mortality in CTO patients undergoing PCI.	CIN, Mortality	OR = 2.17
Zhu et al, 2024	681	CTO patients with varying glucose metabolism states	Cross-sectional	Cross-sectional—no follow-up	Continuous variable	Higher TyG index was associated with poor collateral circulation. ROC-AUC = 0.779 for prediction.	Collateral circulation	OR = 5.104, AUC = 0.779
Xiao et al, 2024	2691	General CTO patients	Cross-sectional	Cross-sectional – no follow-up	Quartiles (Q1-Q4)	Elevated TyG index was linked to a 2.09-fold increased risk of CTO. ROC-AUC = 0.643.	CTO Risk	OR = 2.09, AUC = 0.643
Yang et al, 2023	331	CTO patients post-successful PCI	Prospective cohort	44 months	Tertiles (T1-T3)	TyG index was an independent predictor of MACCE in CTO-PCI patients. ROC-AUC = 0.677.	MACCE	HR = 2.54, AUC = 0.677
Song et al, 2023	2740	CTO patients with angina	Prospective cohort	36 months	Cutoff >9.10	High TyG index (>9.10) predicted CV death/TVMI (HR = 4.23, $P < .001$) and MACCE (HR = 2.47, $P < .001$).	CV Death, TVMI, MACCE	HR = 4.23 (CV death), HR = 2.47 (MACCE), AUC = 0.623
Lin et al, 2023	681	CTO patients with type 2 diabetes mellitus	Retrospective cohort	24 months	Continuous	TyG index was significantly correlated with adverse events (HR = 1.699, $P = .001$). Adding TyG improved model AUC from 0.663 to 0.693.	Adverse Events	HR = 1.699, AUC = 0.693
Li et al, 2022	652	CTO patients undergoing revascularization	Retrospective cohort	22.8 ± 3.84 months	Tertile	TyG index (highest tertile) was associated with a 2.09-fold increase in MACCE risk.	MACCE	HR = 2.09
Gao et al, 2021	1093	CAD patients with CTO lesions	Cross-sectional	Cross-sectional—no follow-up	Tertile	High TyG index was strongly linked to impaired collateralization (OR = 5.72, $P < .001$). ROC-AUC demonstrated superior risk prediction.	Collateral circulation	OR = 5.72

CAD, coronary artery disease; CIN, contrast-induced nephropathy; CTO, chronic total occlusion; CV, cardiovascular; HR, hazard ratio; OR, odds ratio; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention; ROC-AUC, receiver operating characteristic-area under the curve; T2DM, type 2 diabetes mellitus; TVMI, target vessel myocardial infarction; TyG, triglyceride-glucose index.

Molecule-1), which facilitate monocyte adhesion and promote vascular inflammation.[20] These inflammatory and oxidative processes combined accelerate the formation and destabilization of atherosclerotic plaques—features that are characteristically pronounced in CTO lesions.

Furthermore, the development of collateral vessels, a key determinant of CTO prognosis, becomes severely limited in patients with IR. Diminished NO bioavailability, impaired macrophage-dependent arteriogenesis, and dysregulated angiogenic signaling collectively restrict the ability of collateral networks to mature fully.[18] These mechanistic impairments parallel clinical findings demonstrating that higher TyG index values correlate with poorer collateral vessel formation.

Finally, the CTO microenvironment exhibits persistent chronic hypoxia, which activates HIF-1α (Hypoxia-induced Factor 1 Alpha) and promotes inflammatory signaling, endothelial apoptosis, and microvascular rarefaction.[21] In the setting of IR, angiogenic responses are further compromised by attenuated VEGF signaling, making collateral development even more difficult.[21] The convergence of these mechanisms explains why CTO patients with elevated TyG index levels exhibit impaired collateralization, increased susceptibility to CIN, and worse cardiovascular outcomes.

Application in Special Populations

The TyG index shows variable relationships with cardiovascular risk across patients who have CTO. The metabolic characteristics of certain groups lead to a greater impact on these populations. For instance, individuals with type 2 diabetes mellitus (T2DM) typically present with more severe IR and endothelial dysfunction. These overlapping abnormalities may intensify the vascular pathways through which TyG influences CTO outcomes. Research findings from Lin et al. demonstrate that diabetic CTO patients with higher TyG values experience worse prognosis than non-diabetic patients with similar TyG levels.[15] A similar trend is seen in patients with pre-diabetes due to impaired regulation of glucose and lipid metabolism in this population. Even though these individuals have not developed overt diabetes, their metabolic profiles predispose them to poor collateral growth and higher post-PCI complications. In this context, the TyG index shows potential to function as an initial indicator of vascular vulnerability.[22]

Smoking and tobacco exposure promote oxidative stress and endothelial inflammation, further potentiating the metabolic disturbances reflected by the TyG index. When combined with IR, these smoking-related vascular insults contribute to impaired collateral development and accelerated atherosclerotic progression. Consistent with this, several studies have reported stronger associations between TyG and early signs of atherosclerosis among active smokers.[23]

Moreover, patients with obesity and metabolic syndrome—characterized by chronic low-grade inflammation, dyslipidemia, and visceral adiposity—cumulatively demonstrate elevated TyG values, which in turn promote vascular damage and accelerate atherosclerosis. Research by Guo et al[24] indicates that these factors may explain why CTO occurs more frequently in this subgroup and why revascularization success rates remain poor in these individuals.

Finally, older adults exhibit a distinct risk profile in which TyG may hold added prognostic relevance. The combination of diminished endothelial regenerative capacity and increased arterial stiffness predisposes this population to more pronounced TyG-related vascular injury. Research demonstrates that older adults with elevated TyG values show stronger correlations with cardiometabolic risk and microvascular damage.[25]

Taken together, these subgroup differences underscore the importance of interpreting TyG within a broader clinical context. The TyG index provides its best prognostic information when healthcare providers use it to make decisions about patient treatment based on their complete medical situation and metabolic health. The understanding of TyG performance in various patient populations will lead to better application of this test for CTO risk assessment and personalized treatment approaches.

Heterogeneity in Triglyceride-Glucose Thresholds Across Studies

The TyG thresholds which researchers measured in their studies displayed significant differences because their studies used different participant groups and research techniques. Among these influences, the most significant factor seems to be the characteristics of the population. Most existing research data originates from East Asian study groups, which show distinct metabolic patterns, visceral fat distribution, and IR rates compared to Western populations. As a result, the initial values between groups will affect how TyG values distribute and which threshold defines significant clinical risk.[26]

In addition to population differences, the way different conditions appear together in patients determines how their symptoms will reach the threshold for diagnosis. Research shows that people with diabetes, obesity, and metabolic syndrome often start with elevated TyG values, which makes it harder to distinguish between high-risk groups and requires separate risk threshold values for different studies. Furthermore, the risk of vascular disease which TyG measures becomes more complex because of how smoking and physical inactivity affect a person's lifestyle.

Methodologic differences also contribute to threshold variation. The research methods used in studies create additional variations between the groups investigated. Research studies about TyG used two different approaches—either treating the variable as a continuous value or dividing it into specific categories through tertiles, quartiles, and predefined cutoff points—which resulted in various threshold values. In turn, the reported effect sizes in studies become inconsistent because of different methods used to confirm fasting status, perform laboratory tests, and establish study endpoints, including collateral quality, CIN, and MACCE.

Given these variations, the present review uses study-defined TyG thresholds because the research methods and narrative approach of this review prevent us from creating standardized cutoff points. The evaluation of TyG results between different groups requires knowledge about all factors that affect test results. Looking ahead, future research should perform combined studies to create reference values that will work for different population groups.

Limitations of Triglyceride-Glucose Index

The TyG index provides convenient benefits as an easy-to-use indicator of IR, but healthcare providers need to understand its restrictions when using this test for CTO patients. The TyG values become unstable because of transient factors such as dietary changes, acute clinical conditions or infectious processes, and prescription medications. These factors create transient changes in blood glucose and triglyceride levels.[26] A single measurement becomes unreliable for the same reason, as these short-term influences cause TyG values to fluctuate. The TyG index reflects only hepatic IR and does not measure peripheral insulin sensitivity or β-cell function, which restricts its ability to represent the entire metabolic profile.[27]

The results of TyG tests between studies depend on differences in study populations. The metabolic health of patients, their comorbid conditions, and their abdominal fat distribution patterns influence their initial TyG test results, particularly because most research data originate from East Asian participants.[26] The available data from these cohorts create challenges for determining clinical risk thresholds, as different populations display varying metabolic characteristics. The research included observational studies and single-center investigations, which introduce potential risks from confounding factors and publication bias.

The TyG index operates as a standalone measurement, but researchers need to use it together with other variables to achieve its full potential. Research indicates that TyG measurements combined with additional metabolic indicators such as glycated hemoglobin, non-high-density lipoprotein cholesterol, and specific inflammatory markers enhance risk evaluation by detecting multiple metabolic dysfunction pathways.[24,28] However, current evidence does not provide sufficient data regarding the specific performance of these combination tests in patients with CTO.

The results from these studies demonstrate that healthcare providers need to approach TyG value interpretation with careful consideration in clinical practice. Research should further elucidate whether different population groups require their own specific TyG threshold values and should systematically evaluate the predictive value of TyG when combined with established cardiovascular risk indicators.

Clinical Utility of Triglyceride-Glucose

In CTO patients, metabolic dysfunction contributes to impaired collateral circulation, a vital compensatory mechanism.[11,12] Hyperglycemia and hypertriglyceridemia inhibit NO production and promote endothelial inflammation, thereby reducing collateral vessel development. This is clinically relevant, as robust collateral circulation is a major determinant of long-term outcomes in CTO. Moreover, renal microvascular injury and oxidative stress offer plausible explanations for the strong association between TyG and CIN in PCI patients.[13]

High TyG is consistently associated with adverse CTO outcomes, including CIN,[13] poor collateralization,[11,12] and MACCE.[9,10,14,15] Soner et al[13] (2025) showed that a TyG index ≥8.65 independently predicted CIN and was associated with worse clinical outcomes in CTO patients, while Yang et al (2023)[10] and Song et al[9] (2023) confirmed TyG as a strong predictor of MACCE and cardiovascular death. Zhu et al (2024)[11] demonstrated its value in identifying poor collateral circulation, and Lin et al (2023)[15] showed its incremental benefit in diabetics when added to conventional risk models. Collectively, these findings suggest that TyG may serve as an adjunct prognostic marker across diverse CTO outcomes. Its low cost, simplicity, and reproducibility make TyG a practical tool for pre-procedural evaluation. Elevated TyG may identify patients who require enhanced hydration, nephroprotective measures, and intensified metabolic management.

The TyG index compares favorably with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and stress hyperglycemia ratio. It avoids insulin measurement (HOMA-IR) and is less influenced by acute illness Stress Hyperglycemia Ratio (SHR).[7] Adding TyG to conventional models improves predictive accuracy, as demonstrated in diabetic CTO patients.[15]

Despite promising findings, important limitations remain. The included studies vary in design (retrospective vs prospective), TyG thresholds (≥8.65 vs. >9.10), and endpoint definitions, which introduces heterogeneity and complicates comparisons. Most studies were single-center and limited to Asian populations, raising concerns about external validity,[11,13] limiting generalizability. Furthermore, no interventional trial has confirmed that lowering TyG improves outcomes, reinforcing its role as a prognostic marker only at present.

Clinical and Public Health Implications

The TyG index's accessibility makes it appealing for integration into cardiovascular risk assessment, particularly in resource-limited settings.[7] An elevated TyG index is a significant predictor of increased heart failure risk in patients with H-type hypertension, with the effect being particularly pronounced among those with diabetes.[17] Large, multicenter prospective studies with standardized cut-offs and outcome definitions are needed. Interventional trials assessing whether lowering TyG through pharmacologic or lifestyle modification improves CTO outcomes are also warranted.

Future Directions

Future research should focus on three key areas: (1) standardization of TyG thresholds across populations; (2) validation in large, multicenter, prospective cohorts with diverse ethnic representation; and (3) interventional studies testing whether lowering TyG through pharmacologic (e.g., GLP-1 receptor agonists, SGLT2 inhibitors, statins) or lifestyle

interventions improves CTO and PCI outcomes. Additionally, subgroup analyses by sex, age, and comorbidity burden could provide more nuanced insights into TyG's role as a prognostic biomarker.

CONCLUSIONS

The TyG index is a cost-effective and reproducible biomarker with promising clinical relevance in CTO patients, although further validation is needed to establish its definitive role. Elevated TyG predicts impaired collateralization, CIN, and MACCE, highlighting its potential role in pre-procedural risk stratification and long-term prognosis. Future prospective validation and interventional studies are required before routine guideline integration.

Ethics Committee Approval: Ethics approval not required for this Narrative Review.

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.D., M.U.G.; Design – R.D., A.P., M.U.G.; Supervision – M.U.G., R.D.; Resources – R.D., A.P., J.S.N., M.U.G.; Materials – A.G., N.M., D.T.P., W.S.; Data Collection and/or Processing – A.P., J.S.N., A.G., N.M., D.T.P., W.S., S.K., A.A., A.S.M.; Analysis and/or Interpretation – R.D., A.P., J.S.N., S.K., A.A., M.U.G.; Literature Search – N.M., D.T.P., W.S., A.S.M.; Writing – R.D., A.P., J.S.N., M.U.G.; Critical Review – A.G., S.K., A.A., A.S.M., M.U.G.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

PCSK9 Inhibition Protects Against Myocardial Ischemia-Reperfusion Injury in Type 2 Diabetes Rats Via Suppressing Inflammation and Apoptosis

ABSTRACT

Background: Myocardial ischemia-reperfusion (I/R) injury is aggravated in type 2 diabetes mellitus (T2DM) due to metabolic dysfunction, inflammation, and apoptosis. This study investigated the cardioprotective role of alirocumab, a proprotein convertase subtilisin/kexin type 9 (*PCSK9*) inhibitor, compared with atorvastatin.

Methods: Type 2 diabetes mellitus was induced in rats by a high-fat/high-sugar diet plus streptozotocin injection, followed by myocardial I/R through transient ligation of the left anterior descending artery. Rats (n = 6/group) were randomized into Control, non-diabetic I/R, T2DM + I/R, T2DM + I/R + alirocumab, and T2DM + I/R + atorvastatin groups. Alirocumab (10 mg/kg/week, intraperitoneal injection) or atorvastatin (10 mg/kg/day, oral) was administered for 21 days. Outcomes included lipid deposition, myocardial fibrosis, metabolic parameters, inflammatory cytokines, apoptosis, and expression of *PCSK9*, nucleotide-binding oligomerization domain-like receptor protein 3 (*NLRP3*), and Caspase-3, assessed by histology, enzyme-linked immunosorbent assay, terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) assay, western blotting, and quantitative reverse transcription polymerase chain reaction.

Results: Non-diabetic I/R rats showed increased lipid accumulation, fibrosis, inflammation, and apoptosis compared with controls, while these effects were markedly exacerbated in T2DM + I/R, confirming the amplifying effect of diabetes. Both alirocumab and atorvastatin significantly reduced lipid accumulation, improved hepatic and renal function, lowered free fatty acids and HbA1c, and restored insulin and C-peptide levels ($P < .001$). Treatments also decreased pro-inflammatory cytokines (interleukin-1β [*IL-1β*], interleukin-6 [*IL-6*], tumor necrosis factor-α [*TNF-α*]), inhibited *NLRP3* inflammasome activation, reduced myocardial apoptosis and *caspase-3* activity, and downregulated myocardial *PCSK9*, *NLRP3*, and *caspase-3* expression. Protective effects were comparable between alirocumab and atorvastatin.

Conclusion: Alirocumab and atorvastatin effectively attenuated myocardial I/R injury in T2DM by modulating lipid metabolism, inflammation, and apoptosis. Diabetes substantially intensified I/R-induced cardiac injury, underscoring the importance of metabolic control in cardioprotection.

Keywords: Apoptosis, cardioprotection, inflammation, myocardial ischemia-reperfusion injury, PCSK9 inhibitor, statin, type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and pancreatic beta-cell dysfunction.[1,2] Type 2 diabetes mellitus is a major global health concern due to its increasing prevalence and association with significant morbidity and mortality, particularly related to cardiovascular complications.[3,4] Cardiovascular complications are the leading cause of mortality in individuals with T2DM, with a higher risk of developing conditions such as myocardial infarction, stroke, heart failure, and peripheral vascular disease compared to individuals without diabetes.[5,6]

ORIGINAL INVESTIGATION

Mengjuan Zhang[1,#]
Fu Liu[2,#]
Yanbo Gao[1]
Yi He[1]
Shouzheng Bian[1]
Bo Yang[1]
Peiqing Liu[1]
Yanan Zheng[3]
Yan Zhu[1]

[1]*Department of Endocrinology, Baotou Central Hospital, Baotou, China*
[2]*Department of Cardiology, Baotou Central Hospital, Baotou, China*
[3]*Department of Neurology, Baotou Central Hospital, Baotou, China*

Corresponding author:
Yan Zhu
✉ hr20072024@163.com

Received: June 17, 2025
Accepted: October 22, 2025
Available Online Date: November 12, 2025

Cite this article as: Zhang M, Liu F, Gao Y, et al. PCSK9 inhibition protects against myocardial ischemia-reperfusion injury in type 2 diabetes rats via suppressing inflammation and apoptosis. *Anatol J Cardiol.* 2026;30(3):146-156.

#Means they contributed equally to the article.

DOI:10.14744/AnatolJCardiol.2025.5523

Epidemiological studies have highlighted the substantial burden of cardiovascular complications in individuals with T2DM.[7] For example, a meta-analysis by Sarwar et al[8] reported that individuals with diabetes have a 2- to 4-fold increased risk of developing cardiovascular disease compared to non-diabetic individuals. Furthermore, the Framingham Heart Study demonstrated that individuals with T2DM have a 2- to 4-fold increased risk of coronary heart disease compared to those without diabetes.[9]

The association between T2DM and cardiovascular complications can be attributed to various factors, including the presence of other risk factors such as hypertension, dyslipidemia, and obesity, as well as the pro-inflammatory and prothrombotic state associated with diabetes.[10-12] In addition, dyslipidemia is a common feature of T2DM characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides, and decreased levels of high-density lipoprotein cholesterol (HDL-C).[13] Elevated LDL-C levels are particularly concerning as they are a major risk factor for atherosclerosis, the underlying cause of cardiovascular complications in diabetes.[14]

The development of novel therapeutic agents targeting dyslipidemia in individuals with T2DM has shown promise in reducing the risk of cardiovascular complications.[15] One such class of agents is proprotein convertase subtilisin/kexin type 9 (*PCSK9*) inhibitors, which have been shown to significantly lower LDL-C levels and reduce the risk of cardiovascular events in patients with atherosclerotic cardiovascular disease.[16]

Proprotein convertase subtilisin/kexin type 9 is a key regulator of low-density lipoprotein receptor (LDLR) levels and plays a crucial role in lipid metabolism and the development of cardiovascular disease.[17] Proprotein convertase subtilisin/kexin type 9 inhibitors have emerged as a promising therapeutic option for reducing LDL cholesterol levels and lowering the risk of cardiovascular events.[16] By inhibiting PCSK9, these drugs increase the expression of LDLR on the surface of hepatocytes, leading to enhanced clearance of circulating LDL cholesterol from the blood.

HIGHLIGHTS

- Alirocumab, a proprotein convertase subtilisin/kexin type 9 (*PCSK9*) inhibitor, significantly protects against myocardial ischemia-reperfusion injury in type 2 diabetic rats.
- Treatment with alirocumab reduced myocardial lipid accumulation and improved cardiac histology.
- Alirocumab suppressed inflammation by lowering *IL-1β*, *IL-6*, and *TNF-α* levels and inhibiting *NLRP3* inflammasome activation.
- Apoptosis was significantly reduced by alirocumab, as evidenced by decreased TUNEL-positive cells and *caspase-3* expression.
- *PCSK9* inhibition modulated key inflammatory and apoptotic pathways, highlighting its therapeutic potential in diabetic cardiovascular complications.

Despite the well-established benefits of PCSK9 inhibitors in reducing cardiovascular risk, their effects on diabetes-related cardiovascular complications remain less understood. Diabetes is a major risk factor for cardiovascular disease, with individuals experiencing diabetes being at a higher risk of developing adverse cardiovascular events such as myocardial infarction and stroke.[18] However, the specific impact of PCSK9 inhibitors on the incidence and progression of cardiovascular complications in individuals with diabetes is not fully elucidated, highlighting a gap in current research.

Several studies have suggested a potential role for PCSK9 inhibitors in modulating inflammation, oxidative stress, and endothelial dysfunction, which are key mechanisms involved in the pathogenesis of diabetic cardiovascular complications.[19,20] However, the exact mechanisms through which PCSK9 inhibitors may influence the development and progression of cardiovascular complications in individuals with diabetes remain to be elucidated.

In this study, the aim was to investigate the effects of PCSK9 inhibitors on the development of diabetes-related cardiovascular complications. By elucidating the mechanisms underlying the potential benefits of PCSK9 inhibition in individuals with diabetes, the hope is to provide valuable insights into the therapeutic potential of PCSK9 inhibitors in reducing the burden of cardiovascular disease in this high-risk population.

METHODS

Reagents and Animals

All experiments were approved by the Animal Ethics Committee of the hospital. Sprague-Dawley rats were used as experimental animals. The rats were acclimated for 1 week with free access to food and water under standard conditions with a 12-hour light-darkness cycle. Bedding was changed every 3 days, and water bottles and cages were cleaned regularly. Rats were randomly divided into 5 groups: (1) Control, (2) ischemia-reperfusion group without diabetes (I/R), (3) T2DM with ischemia-reperfusion (T2DM + I/R), (4) T2DM + I/R treated with alirocumab (alirocumab), and (5) T2DM + I/R treated with atorvastatin (atorvastatin). Control and I/R groups were fed a standard diet (60% carbohydrates, 10% fat primarily composed of soybean oil, 22% protein, and 8% other components including fiber) ad libitum. The T2DM + I/R, alirocumab, and atorvastatin groups were fed a high-sugar high-fat diet consisting of 50% carbohydrates, 30% fat primarily composed of animal fats, 13% protein, and 7% other components including fiber. The rats were fed for 6-8 weeks, and then streptozotocin (STZ) was administered at a dose of 150 mg/kg to induce diabetes in high-sugar high-fat diet groups. After 3 days, blood glucose levels were measured, and rats with blood glucose levels ≥16.7 mmol/L were considered successfully modeled. All surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

Myocardial Ischemia-Reperfusion Injury Model Establishment in Rats with Type 2 Diabetes Mellitus

After establishing the diabetic rat model, an I/R injury model was established in the diabetic rats. Anesthetized rats were

subjected to left anterior descending coronary artery ligation followed by reperfusion. After 2 hours of reperfusion, the rats were euthanized for further analysis. Successful induction of myocardial I/R injury was confirmed by visual observation of darkening of the distant myocardium, weakened contraction, ST segment (ST) elevation, and T wave heightening in the electrocardiogram. The non-diabetic I/R group underwent the same surgical procedure without STZ induction.

Drug Administration

The modeled diabetic rats were randomly assigned to the T2DM + I/R, alirocumab, or atorvastatin groups. Alirocumab was administered intraperitoneally at 10 mg/kg weekly, while Atorvastatin was given orally at 10 mg/kg/day. Control and I/R groups received equal volumes of distilled water. Treatments lasted for 21 days.

Sample Preparation

At the end of the 21-day intervention period and 24 hours after drug administration, rats from each group were euthanized, and their hearts were quickly harvested, rinsed with phosphate-buffered saline (PBS), and trimmed to remove the base and atrial tissues. The left ventricle was sectioned along the long axis, and the tissue located near the base of the left ventricle was immediately fixed in 4% paraformaldehyde and embedded in paraffin for sectioning (thickness: 4-5 μm).

Staining and Quantification of Lesions in Aortic Artery

The aortic artery was carefully dissected under a stereomicroscope and fixed in 4% paraformaldehyde for 24 hours. The lesions were stained with Oil Red O. The images were obtained by stereomicroscopy and analyzed with Fiji. Considering individual differences in arterial plaque as well as the aortic artery, the percentage of atherosclerotic lesions was determined by dividing the area of red area plaques stained by Oil Red O by the area of the overall aortic artery after microdissection.

Histomorphological Analysis

Histomorphological analysis was performed using hematoxylin and eosin (H&E) staining and Masson staining on myocardial tissue samples. Sections were dewaxed and rehydrated by immersion in eluent and ethanol. For H&E staining, sections were stained with hematoxylin for 5 minutes and eosin for 15 seconds, washed in 1% hydrochloric acid alcohol, dehydrated, and fixed. All sections were observed by microscopy and photographed with ToupView digital software. The distribution and extent of myocardial interstitial fibrosis were observed using the horsetail pine staining method. Analysis was performed using 400 × 3 fields of view. The average percentage of fibrous tissue area to total area was measured and calculated using Image-Pro Plus software.

Immunofluorescence

The TUNEL assay was performed to detect apoptotic cells in the myocardial tissue. Specific steps were followed for the TUNEL assay.

Measurement of Inflammatory Markers

Serum and myocardial levels of inflammatory markers including IL-1β, IL-6, TNF-α, NLRP3, and C-reactive protein (CRP) were assessed using enzyme-linked immunosorbent assay (ELISA). Additionally, ELISA was used to measure PCSK9 levels in the myocardium.

Quantitative Real-Time Polymerase Chain Reaction

Total RNA was extracted from myocardial tissue of rats using the TRIzol reagent (Tiangen Biotech; China; DP424) and then reverse-transcribed to complementary DNA using the RevertAid First Strand cDNA Synthesis Kit (Thermo, K1622). Quantification was performed using the SYBR Green qPCR Master Mix (Selleck, B21203). Each sample was analyzed in triplicate using the real-time fluorescence quantitative polymerase chain reaction instrument (Applied Biosystems, ABI). The relative expression levels of RNA were calculated using the $2^{-\Delta\Delta Ct}$ method. Primers for PCSK9, NLRP3, Caspase3, or β-actin were used (Table 1).

Western Blot Analysis

Western blotting was performed to detect the protein expression levels of PCSK9, NLRP3, caspase-3, and cleaved caspase-3, using glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) as a loading control. Myocardial tissues were homogenized and lysed in radio-immunoprecipitation assay (RIPA) buffer containing protease inhibitors. Protein concentration was determined using the bicinchoninic acid (BCA) assay, and equal amounts of protein (30-50 μg) were separated on 10%-12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), followed by transfer onto polyvinylidene fluoride (PVDF) membranes. Membranes were blocked with 5% nonfat milk in Tris-Buffered Saline with Tween-20 (TBST) for 1 hour at room temperature and incubated overnight at 4°C with primary antibodies. The following primary antibodies were used: *cleaved caspase-3* (Rabbit, Proteintech, 25128-1-AP), *caspase-3* (Rabbit, Affinity, AF6311), *NLRP3* (Rabbit, Affinity, DF15549), *PCSK9* (Rabbit, Affinity, DF12687), and *GAPDH* (Mouse, Servicebio, GB12002). After washing, membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies for 1 hour at room temperature: goat anti-rabbit

Table 1. Primer Sequences Used for Quantitative Reverse Transcription Polymerase Chain Reaction

	Primer Sequences		
Gene	**Forward**	**Reverse**	**Fragment (bp)**
PCSK9	GGGTGAGGGTGTCTATGCTGTCG	GCTGCTGGGCTCTAAGGTTTTCC	179
NLRP3	TTGTGTGAAAAAATGAAGGACCC	CTGAGCAGCACAGTGAAGTAAGG	85
Caspase3	GTATGCTTACTCTACCGCACCCG	AAAGTGGCGTCCAGGGAGAAG	186
β-actin	GTCGTACCACTGGCATTGTG	TCTCAGCTGTGGTGGTGAAG	180

bp, base pairs.

IgG-HRP (Servicebio, GB23303) and goat anti-mouse IgG-HRP (Servicebio, GB23301). Protein bands were visualized using enhanced chemiluminescence reagents and quantified with ImageJ software.

Sample Size Calculation

A priori power analysis was performed using G*Power 3.1 software to determine the minimum number of animals required per group. Based on preliminary pilot experiments and previous reports of myocardial ischemia-reperfusion injury in diabetic rats, the expected effect size (f) for primary outcomes such as myocardial fibrosis and inflammatory cytokines was set at 0.65 (large effect). With an α error probability of 0.05 and a power (1-β) of 0.80, one-way ANOVA indicated that a minimum of 5 animals per group was necessary to detect statistically significant differences. To account for potential dropouts or unsuccessful modeling, 6 rats were included in each group (n = 6).

Statistical Analysis

All data are expressed as mean ± standard error of the mean. Statistical analyses were performed using GraphPad Prism version 10.1.2 (GraphPad Software, San Diego, CA, USA). Differences among groups were analyzed using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons. A P value < .05 was considered statistically significant.

RESULTS

Effects of Alirocumab and Atorvastatin on Lipid Accumulation and Myocardial Fibrosis

As shown in Figure 1, Oil Red O staining revealed marked lipid accumulation in the aortic artery of the T2DM + I/R group compared with controls. Both alirocumab and atorvastatin significantly reduced lipid deposition, as indicated by a decreased Oil Red O-positive area (P < .0001), with no difference between the 2 treatments. Hematoxylin and eosin staining showed extensive myocardial disorganization and cellular damage in the T2DM + I/R group, which were markedly improved by either treatment, restoring near-normal myocardial structure. Masson's trichrome staining further demonstrated substantial fibrosis in the T2DM + I/R group, while both alirocumab and atorvastatin significantly reduced fibrotic area (P < .0001), with levels approaching those of the controls. These findings indicate that both treatments effectively protect against lipid accumulation and myocardial fibrosis following ischemia-reperfusion injury in T2DM.

Importantly, the non-diabetic I/R group also exhibited significant lipid accumulation and fibrosis compared with controls, though to a lesser extent than the T2DM + I/R group. This observation suggests that diabetes aggravates I/R-induced lipid deposition and fibrotic remodeling.

Given that lipid accumulation and fibrosis were profoundly aggravated in diabetic I/R rats, the next investigation is whether these pathological changes were accompanied by systemic metabolic disturbances.

Effects of Alirocumab and Atorvastatin on Metabolic Parameters

Table 2 summarizes the metabolic and biochemical parameters in the 5 groups (n = 6 each). Compared with controls, the I/R group displayed moderate increases in liver injury markers (alanine aminotransferase [ALT], aspartate

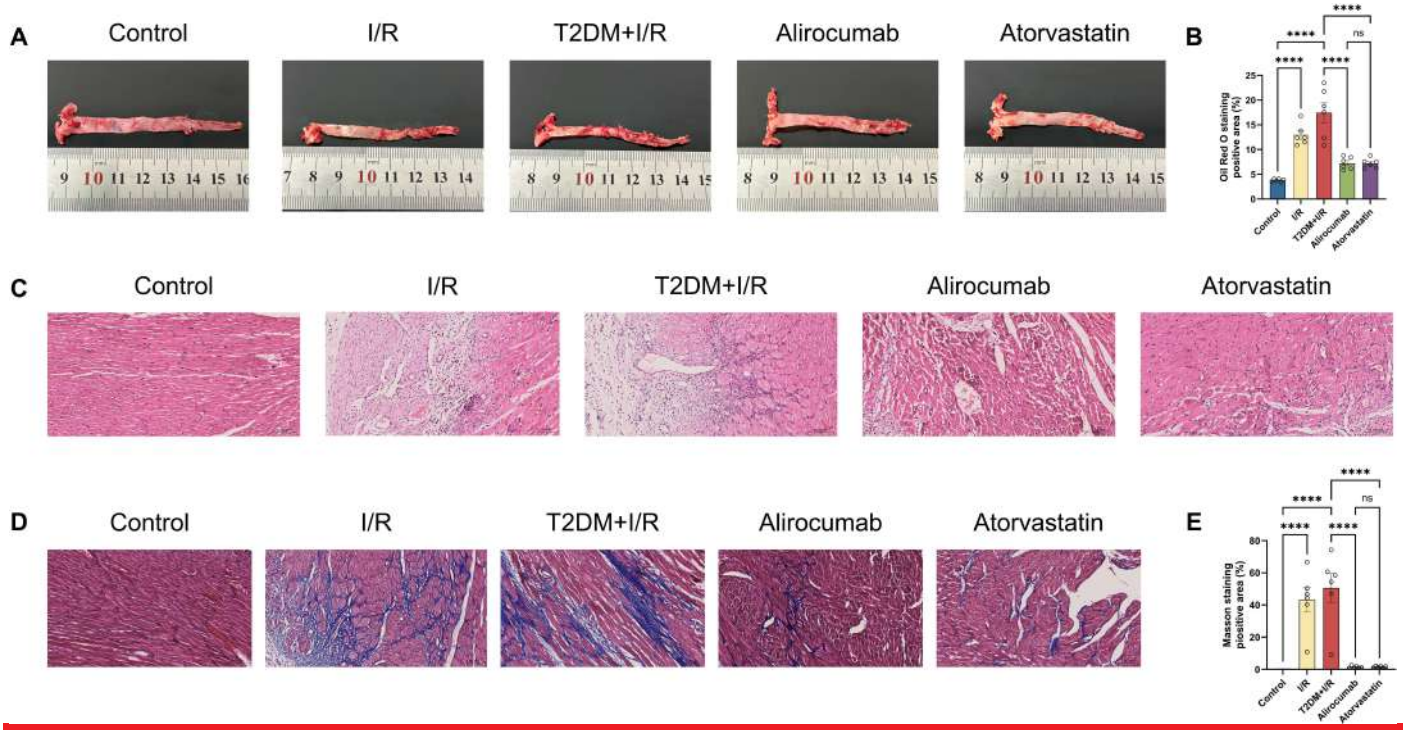

Figure 1. Protective effects of alirocumab and atorvastatin on myocardial ischemia-reperfusion injury in rats (n = 6 per group). (A) Macroscopic images of Oil Red O staining of hearts from Control, I/R, T2DM + I/R, alirocumab, and atorvastatin groups. (B) Quantification of the Oil Red O-positive area (%). (C) Representative hematoxylin and eosin staining images of myocardial tissue. (D) Masson's trichrome staining of myocardial tissue. (E) Quantification of fibrosis area (%). ns, not significant; ****P < .0001.

aminotransferase [AST]), renal markers (urea, creatinine), and dyslipidemia (triacylglycerol [TG], total cholesterol [CHO], LDL), along with reduced HDL. These abnormalities were more pronounced in the T2DM + I/R group, underscoring the amplifying effect of diabetes on I/R-induced organ dysfunction. Both alirocumab and atorvastatin significantly improved these parameters compared with untreated T2DM + I/R rats, lowering ALT, AST, TG, CHO, LDL, urea, and creatinine, while partially restoring HDL. Blood glucose was markedly higher in the T2DM + I/R group than in controls, whereas the I/R group showed intermediate values. Alirocumab and atorvastatin significantly reduced glucose levels compared with untreated T2DM + I/R rats, although values remained above those of controls. Collectively, these results indicate that both therapies alleviate metabolic disturbances and organ injury associated with I/R in the diabetic state. All values in Table 2 are presented as fasting measurements with standard units.

To further delineate these systemic metabolic alterations, specific markers in both serum and myocardial tissue were analyzed.

Effects of Alirocumab and Atorvastatin on Metabolic Markers in Serum and Myocardium

Figure 2 presents serum and myocardial levels of free fatty acids (FFAs), glycosylated hemoglobin (GHb), insulin, and C-peptide. In T2DM + I/R rats, FFAs and GHb levels were markedly elevated ($P < .0001$), reflecting severe metabolic dysregulation, while both treatments significantly reduced these values toward control levels. Serum and myocardial insulin and C-peptide were significantly decreased in T2DM + I/R rats, consistent with impaired pancreatic function. Both alirocumab and atorvastatin significantly restored insulin and C-peptide ($P < .0001$), though levels did not fully normalize. No significant differences were observed between the 2 treatment groups.

The I/R group also showed higher FFAs and GHb and lower insulin and C-peptide than controls, though changes were less pronounced than in T2DM + I/R rats. These results again suggest that diabetes amplifies I/R-induced metabolic disturbances.

Since metabolic dysfunction is closely linked to inflammatory activation, inflammatory cytokines and NLRP3 inflammasome activity were examined.

Effects of Alirocumab and Atorvastatin on Inflammatory Markers and NLRP3 Inflammasome

Figure 3 shows that pro-inflammatory cytokines (*IL-1β*, *IL-6*, *TNF-α*) and *NLRP3* inflammasome activity were significantly increased in both serum and myocardial tissue of T2DM + I/R rats compared with controls ($P < .0001$). Both treatments significantly reduced cytokine levels and *NLRP3* expression ($P < .0001$), confirming strong anti-inflammatory effects. Notably, reduction of *NLRP3* activation is particularly relevant, as this inflammasome plays a pivotal role in regulating myocardial inflammatory responses. There was no significant difference between alirocumab and atorvastatin.

The I/R group also displayed elevated inflammatory cytokines compared with controls, but the levels were consistently lower than those in T2DM + I/R rats, indicating that diabetes worsens the inflammatory response to I/R.

Given the interplay between inflammation and apoptosis in myocardial injury, the extent of cardiomyocyte apoptosis was assessed next.

Effects of Alirocumab and Atorvastatin on Myocardial Apoptosis

Figure 4 demonstrates apoptotic changes in myocardial tissue. The T2DM + I/R group showed a marked increase in apoptosis, with significantly more TUNEL-positive cells compared with controls ($P < .0001$). Both alirocumab and atorvastatin substantially reduced apoptotic cell numbers, restoring them closer to control values, with no significant difference between the 2.

In addition, serum and myocardial *caspase-3* levels were markedly elevated in T2DM + I/R rats, further supporting

Table 2. Comparison of Metabolic Characteristics Among Control, I/R, T2DM + I/R, Alirocumab, and Atorvastatin Rats

	Control (n = 6)	T2DM (n = 6)	I/R (n = 6)	Alirocumab (n = 6)	Atorvastatin (n = 6)
ALT (U/L)	77 ± 5	112 ± 7	157 ± 9	96 ± 6	96 ± 7
AST (U/L)	105 ± 6	148 ± 9	207 ± 13	133 ± 6	134 ± 10
GGT (U/L)	0.38 ± 0.09	0.64 ± 0.10	1.26 ± 0.18	0.79 ± 0.10	0.78 ± 0.09
TBA (umol/L)	1.86 ± 0.21	3.55 ± 0.42	10.09 ± 0.72	5.13 ± 0.47	5.25 ± 0.54
Urea (mmol/L)	1.64 ± 0.31	2.34 ± 0.28	5.58 ± 0.37	3.03 ± 0.29	3.08 ± 0.46
CRE (umol/L)	0.80 ± 0.22	1.85 ± 0.33	6.47 ± 0.53	2.50 ± 0.39	2.47 ± 0.52
UA (mmol/L)	0.16 ± 0.05	0.38 ± 0.06	1.09 ± 0.22	0.56 ± 0.05	0.56 ± 0.06
TG (mmol/L)	0.24 ± 0.05	0.41 ± 0.07	0.87 ± 0.10	0.52 ± 0.07	0.51 ± 0.01
CHO (mmol/L)	2.08 ± 0.14	2.56 ± 0.23	4.87 ± 0.45	3.02 ± 0.26	3.07 ± 0.36
HDL (mmol/L)	0.50 ± 0.05	0.39 ± 0.04	0.16 ± 0.05	0.31 ± 0.03	0.30 ± 0.05
LDL (mmol/L)	0.15 ± 0.04	0.26 ± 0.05	0.57 ± 0.03	0.35 ± 0.05	0.33 ± 0.02
BG (mmol/L)	10.5 ± 0.5	12.8 ± 0.7	20.0 ± 0.8	14.4 ± 0.5	14.4 ± 1.5

Data are expressed as mean ± SEM.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BG, blood glucose; CHO, total cholesterol; CRE, creatinine; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TBA, total bile acid; TG, triacylglycerol; UA, uric acid.

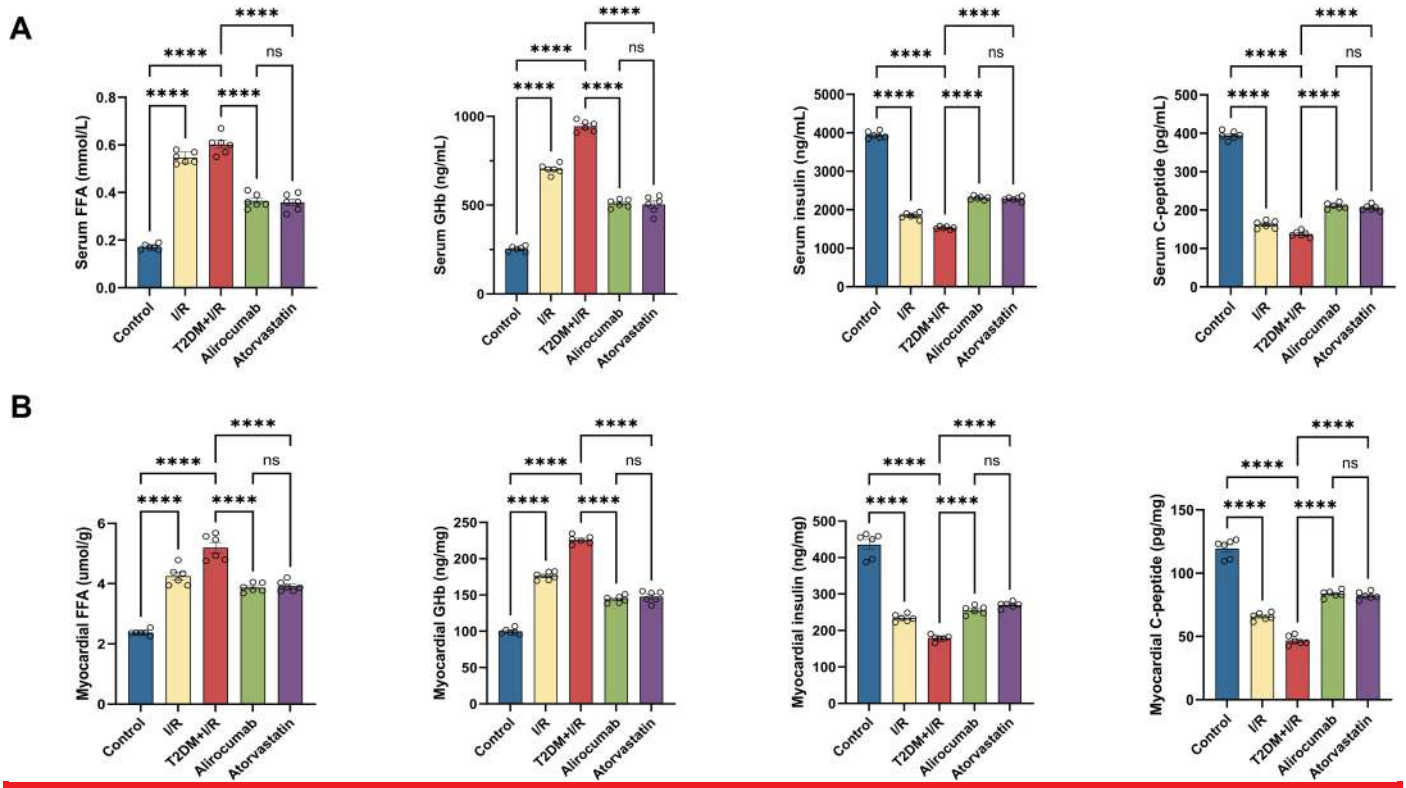

Figure 2. Effects of alirocumab and atorvastatin on serum and myocardial metabolic markers in rats (n = 6 per group). (A) Serum levels of free fatty acids (FFAs), glycosylated hemoglobin (GHb), insulin, and C-peptide in Control, I/R, T2DM + I/R, alirocumab, and atorvastatin groups. (B) Myocardial levels of FFAs, GHb, insulin, and C-peptide. ns, not significant; ****$P < .0001$.

enhanced apoptotic activity. Both treatments significantly reduced *caspase-3* ($P < .0001$), confirming their anti-apoptotic effects. The I/R group also exhibited increased apoptosis and caspase-3 compared with controls, though the magnitude was less than in T2DM + I/R rats. These results highlight the aggravating effect of diabetes on I/R-induced apoptosis.

To further clarify the molecular basis of these pathological processes, the expression of PCSK9, NLRP3, and Caspase-3 was finally examined at both the protein and gene levels.

Effects of Alirocumab and Atorvastatin on Proprotein Convertase Subtilisin/Kexin Type 9, *NLRP3*, and *Caspase-3* Gene Expression

Figure 5 shows the expression of *PCSK9*, *NLRP3*, and *Caspase-3* in myocardial tissues. In T2DM + I/R rats, expression of all 3 genes was significantly upregulated compared with controls ($P < .0001$), reflecting activation of inflammatory (*NLRP3*), apoptotic (*Caspase-3*), and *PCSK9*-mediated pathways. Both alirocumab and atorvastatin significantly downregulated these genes compared with T2DM + I/R ($P < .0001$), with comparable efficacy.

The I/R group also showed increased expression of *PCSK9*, *NLRP3*, and *Caspase-3* relative to controls, but the levels were consistently lower than in T2DM + I/R rats. These findings support the conclusion that diabetes intensifies I/R-induced activation of inflammatory and apoptotic pathways and that both treatments exert cardioprotective effects by suppressing these signals.

DISCUSSION

In this study, it was revealed that both alirocumab and atorvastatin provide significant cardioprotective effects in a rat model of T2DM subjected to myocardial I/R injury. Our major findings indicate that both treatments effectively reduced lipid accumulation, fibrosis, inflammation, and apoptosis in the myocardium. Specifically, alirocumab and atorvastatin improved lipid and glucose metabolism, as reflected by reductions in FFAs, HbA1c, and dyslipidemia. Moreover, both therapies decreased pro-inflammatory cytokines and suppressed *NLRP3* inflammasome activation in serum and myocardial tissues, underscoring their anti-inflammatory potential. Apoptosis was also markedly reduced, as shown by lower levels of TUNEL-positive cells and *caspase-3* expression. At the molecular level, both treatments downregulated the expression of genes involved in inflammation and apoptosis, including *PCSK9*, *NLRP3*, and *caspase-3*. Taken together, these findings suggest that alirocumab and atorvastatin confer significant protection against myocardial I/R injury in T2DM by mitigating metabolic dysfunction, inflammation, and apoptosis.

Our results are largely consistent with prior studies on the cardioprotective effects of *PCSK9* inhibitors and statins. Wu et al[21] demonstrated that *PCSK9* inhibition reduces inflammation and fibrosis in myocardial infarction via the *Notch1* signaling pathway, which aligns with our observation of reduced fibrosis and inflammatory cytokines following alirocumab treatment. Additionally, Huang et al[22] highlighted

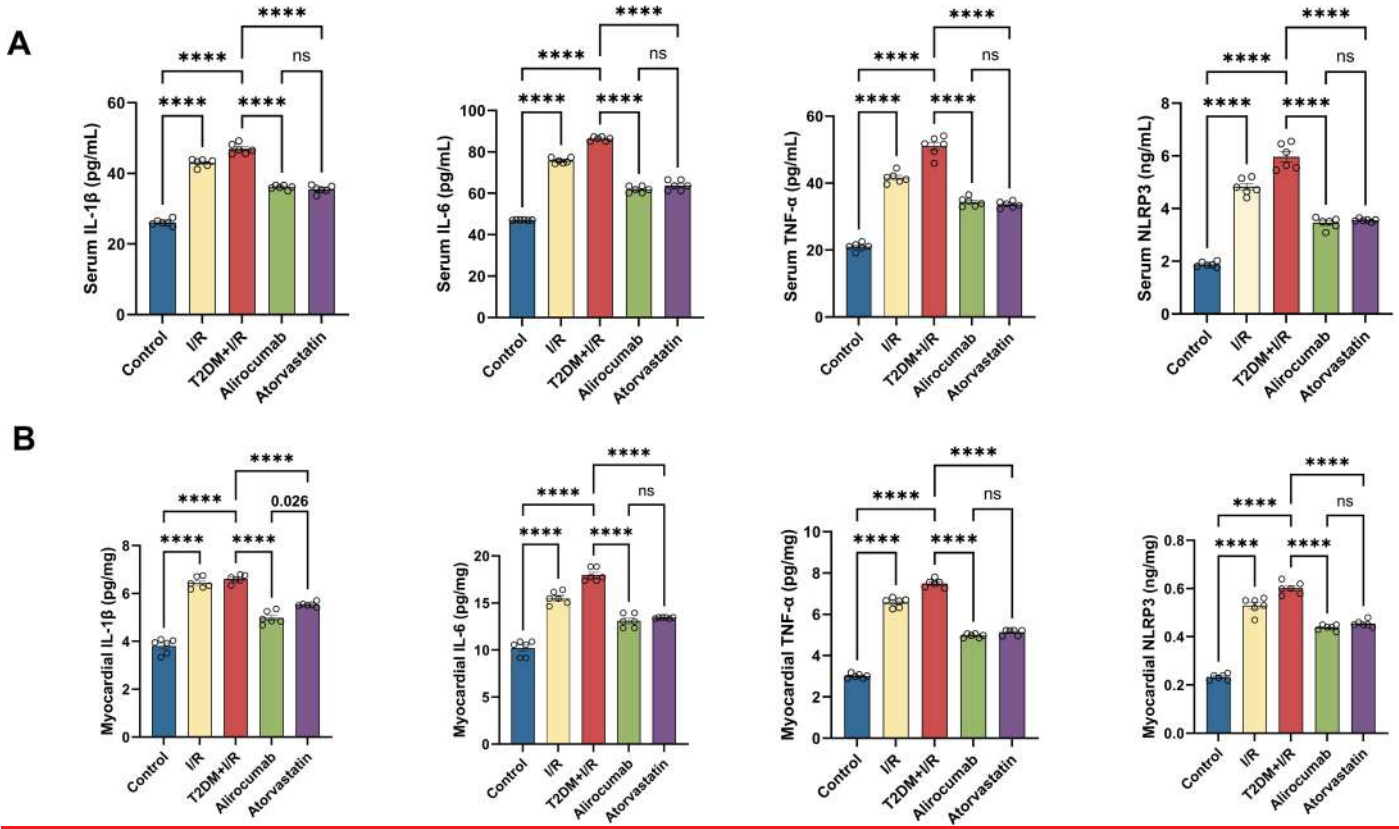

Figure 3. Effects of alirocumab and atorvastatin on pro-inflammatory cytokines and *NLRP3* inflammasome activation (n = 6 per group). (A) Serum levels of *IL-1β*, *IL-6*, *TNF-α*, and *NLRP3* in Control, I/R, T2DM + I/R, alirocumab, and atorvastatin groups. (B) Myocardial levels of *IL-1β*, *IL-6*, *TNF-α*, and *NLRP3*. ns, not significant; ****$P < .0001$.

the protective effects of *PCSK9* inhibition against ischemia-reperfusion injury by modulating autophagy, consistent with our finding that alirocumab alleviates apoptosis and metabolic disturbances. Atorvastatin's ability to reduce inflammation and lipid accumulation in diabetic models has also been widely reported,[23] and our study corroborates these findings by showing improvements in lipid metabolism and inflammatory status in myocardial tissue.

Importantly, our study extends previous research by directly comparing alirocumab and atorvastatin within the same diabetic I/R model. While prior work has primarily focused on either *PCSK9* inhibitors or statins in isolation, our study provides a comparative perspective, demonstrating that both therapies are equally effective in attenuating myocardial injury. Furthermore, novel evidence that both treatments downregulate *PCSK9*, *NLRP3*, and *Caspase-3* gene expression has been provided, linking their protective effects not only to systemic improvements but also to regulation of key molecular pathways.

Growing evidence suggests that *PCSK9* plays an important role in inflammation.[24-26] Elevated *PCSK9* has been positively correlated with circulating CRP levels and shown to be a stronger predictor of cardiovascular disease than LDL-C.[27] Oxidized LDL can upregulate *PCSK9* expression and promote the secretion of *IL-1α*, *IL-6*, and *TNF-α* in a dose-dependent manner.[28] Tang et al[29] reported that *PCSK9* silencing in hyperlipidemic knockout mice reduced TLR pathway activity, thereby decreasing cytokine secretion and atherosclerosis independently of cholesterol levels. Ricci et al[30] further demonstrated that *PCSK9* directly activates *NF-κB* signaling in macrophages. These studies support our findings and suggest that targeting *PCSK9* may suppress inflammatory pathways during myocardial I/R injury.

Another strength of this study is the comprehensive evaluation of gene expression alongside histological and biochemical assessments. Both alirocumab and atorvastatin downregulated *PCSK9*, *NLRP3*, and *Caspase-3* mRNA expression, providing molecular evidence for their cardioprotective actions. This highlights that these therapies not only reduce circulating inflammatory markers but also regulate intracellular signaling pathways central to myocardial injury. In addition, the combined use of TUNEL assays and *caspase-3* activity measurements offered a robust assessment of apoptosis, reinforcing the observed anti-apoptotic effects. This integrative approach strengthens our conclusion that both treatments confer multifaceted protection against I/R injury in T2DM.

The inclusion of a non-diabetic I/R group provided new insights into the interaction between diabetes and ischemia. Our results showed that I/R alone induced lipid accumulation, metabolic disturbances, inflammation, and apoptosis, but these alterations were consistently more severe in the

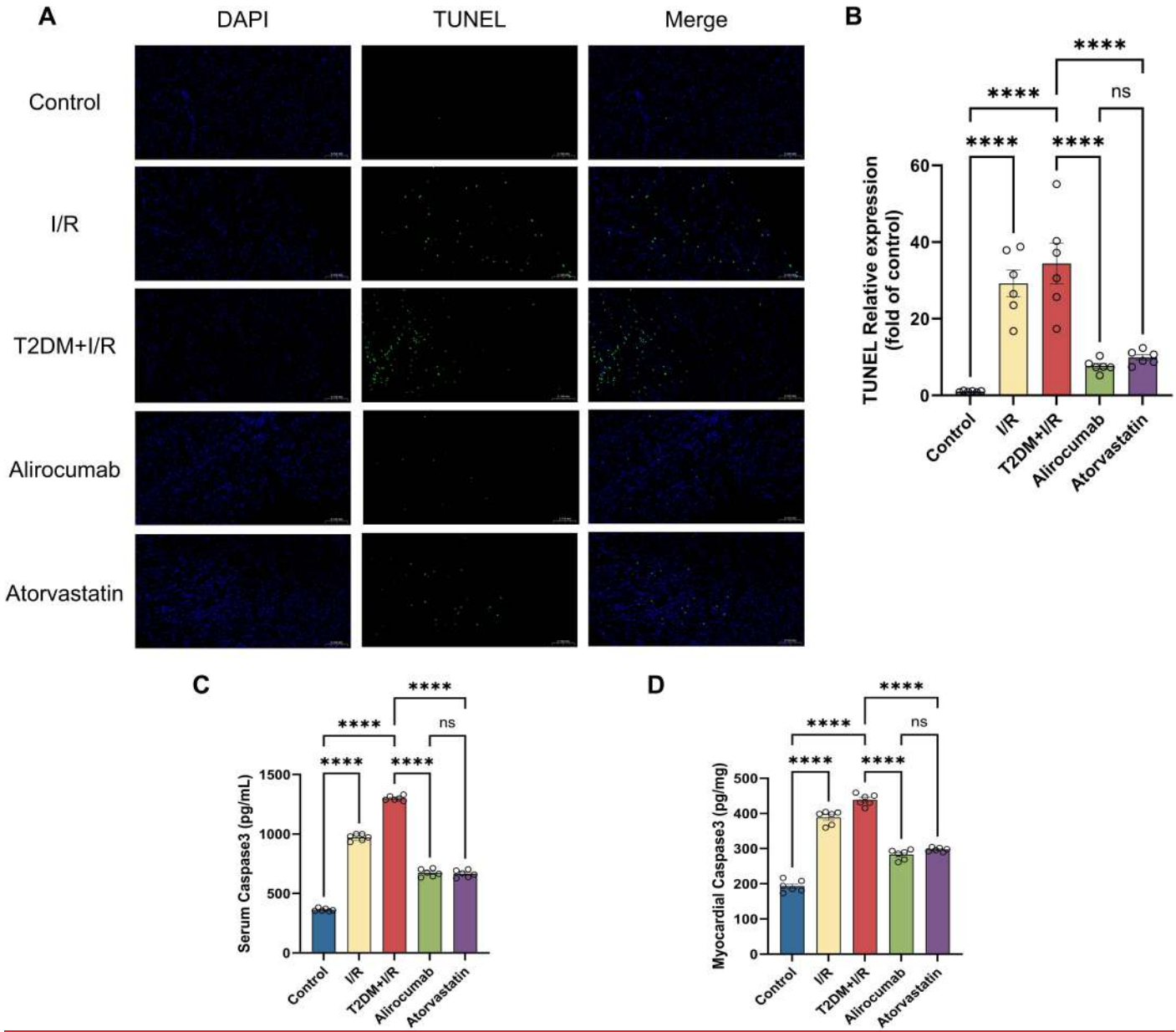

Figure 4. Effects of alirocumab and atorvastatin on myocardial apoptosis and *caspase-3* activity (n = 6 per group). (A) TUNEL assay images (DAPI staining for nuclei and TUNEL for apoptotic cells) in myocardial tissue from Control, I/R, T2DM + I/R, alirocumab, and atorvastatin groups. (B) Quantification of TUNEL-positive cells (fold change relative to control). (C) Serum levels of *caspase-3*. (D) Myocardial levels of *caspase-3*. ns, not significant; ****$P < .0001$. DAPI, 4′,6-diamidino-2-phenylindole.

diabetic setting. This confirms that diabetes amplifies myocardial vulnerability to I/R injury, likely through mechanisms involving oxidative stress, mitochondrial dysfunction, and enhanced *NLRP3* activation.[31,32]

Although both treatments were equally effective in our model, their mechanisms may differ. Statins exert pleiotropic actions beyond lipid lowering, including improving endothelial function, reducing oxidative stress, and modulating inflammatory signaling.[33] Proprotein convertase subtilisin/kexin type 9 inhibitors, while primarily targeting cholesterol metabolism, are increasingly recognized for their direct anti-inflammatory and anti-apoptotic effects. Miettinen et al[34] showed that *PCSK9* activates *TLR4* signaling and promotes cytokine release, linking *PCSK9* activity to vascular and myocardial inflammation.[34] Our observation that *PCSK9* expression was elevated in both I/R and T2DM + I/R groups supports this dual role in lipid metabolism and inflammation.

The TUNEL and caspase-3 data further highlight that apoptosis occurs in both non-diabetic and diabetic I/R settings but is significantly amplified by diabetes. This is consistent with Dai et al,[35] who reported that hyperglycemia enhances I/R-induced apoptosis via *caspase-3* activation.[35] These findings highlight the synergistic impact of hyperglycemia and ischemia and underscore the need for therapeutic approaches addressing both metabolic and ischemic stress.

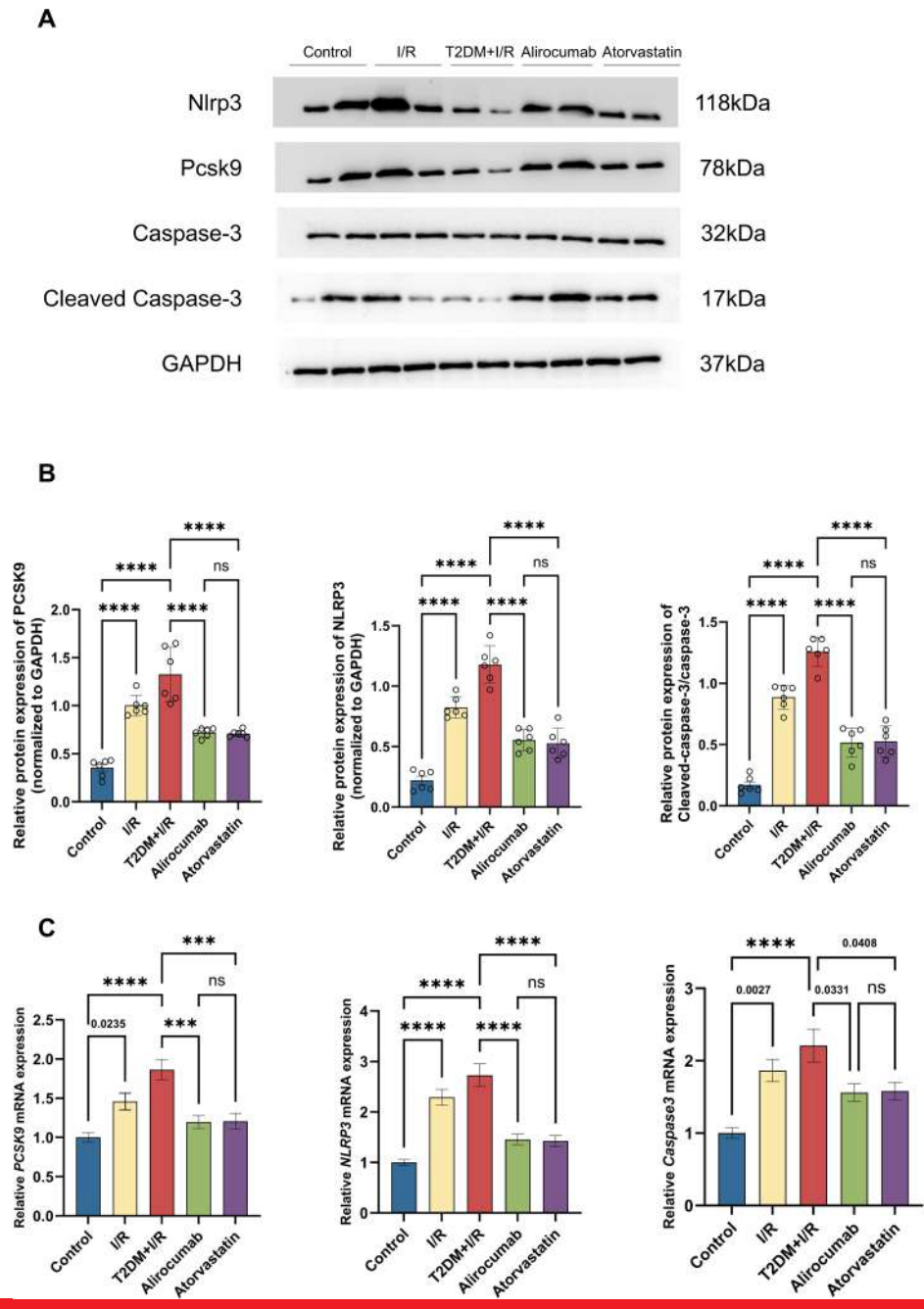

Figure 5. Effects of alirocumab and atorvastatin on mRNA expression of *PCSK9*, *NLRP3*, and *caspase-3* in myocardial tissues (n=6 per group). (A) Western blot analysis of *PCSK9*, *NLRP3*, and *caspase-3* protein levels in control, I/R, T2DM + I/R, alirocumab, and atorvastatin groups. (B) Quantification of Western blot protein expression levels. (C) Quantitative reverse transcription polymerase chain reaction analysis of mRNA expression for *PCSK9*, *NLRP3*, and *caspase-3*. ns, not significant; ***$P < .001$; ****$P < .0001$.

Despite its strengths, this study has several limitations. First, the long-term effects of alirocumab and atorvastatin were not investigated, which limits understanding of sustained efficacy. Second, while *PCSK9*, *NLRP3*, and *Caspase-3* were examined, other critical mechanisms such as autophagy, oxidative stress, and mitochondrial dynamics were not assessed. Finally, the use of a rodent model, while informative, limits direct extrapolation to humans, particularly regarding dosage and treatment response.

Future studies should include larger sample sizes and longer follow-up periods to evaluate sustained cardioprotective effects. Investigating additional pathways such as autophagy, oxidative stress, and mitochondrial function will further clarify underlying mechanisms. Most importantly, clinical trials in human populations are essential to confirm the translational potential of alirocumab and atorvastatin in preventing cardiovascular complications in T2DM, ensuring that preclinical findings can be effectively applied in clinical practice.[36]

CONCLUSION

In conclusion, the present study provides evidence that both statins and *PCSK9* inhibition can attenuate myocardial I/R injury, particularly in the context of T2DM, by reducing inflammation, apoptosis, and metabolic dysfunction. The inclusion of the non-diabetic I/R group highlights that diabetes amplifies I/R-induced damage, providing mechanistic insight into the heightened cardiovascular risk in diabetic patients. Together, these findings underscore the translational potential of *PCSK9* inhibition and statin therapy as complementary strategies in managing diabetes-related cardiovascular complications.

Ethics Committee Approval: This study was approved by the Animal Ethics Committee of Baotou Central Hospital (Approval No.: KYLL2024-099; Date: 2024-08).

Informed Consent: This study did not involve human subjects; therefore, informed consent is not applicable.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Z., F.L.; Design – M.Z., F.L.; Supervision – Y.Z.; Resources – Y.Z., M.Z.; Materials – B.Y., P.L.; Data Collection and/or Processing – Y.G., Y.H.; Analysis and/or Interpretation – S.B., B.Y.; Literature Search – S.B., B.Y.; Writing – M.Z., F.L.; Critical Review – Y.Z., Y.Z.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This study was supported by the Baotou City Health Commission Science and Technology Plan Project (grant No. YKD2022LH058, 2024wsjkkj18) and the Science and Technology Program of the Joint Fund of Scientific Research for the Public Hospitals of Inner Mongolia Academy of Medical Sciences (grant No. 2024GLLH0461). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Integrating Thyroid Function with Body Composition: The BRITSH Ratio and Cardiovascular Risk – A Pilot Study

ABSTRACT

Background: Hypothyroidism is a known risk factor for cardiovascular diseases, affecting metabolic pathways such as dyslipidemia, insulin resistance, and visceral fat accumulation. This study aimed to investigate the value of the Body Roundness Index (BRI) and the newly defined BRI/TSH (thyroid-stimulating hormone) ratio (BRITSH) in predicting coronary artery disease (CAD) in patients with hypothyroidism.

Methods: This cross-sectional study included 152 hypothyroid patients, of whom 55 had CAD and 97 served as controls. Data collected included age, sex, body mass index (BMI), waist circumference, BRI, lipid profiles, and TSH levels. Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis and logistic regression. A new ratio, BRITSH, was also evaluated.

Results: Patients with CAD had significantly higher BRI values ($P < .001$). The BRI/TSH ratio was significantly lower in the CAD group ($P = .005$). Non–high-density lipoprotein (non-HDL) cholesterol levels were also elevated in the CAD group ($P < .001$). Receiver operating characteristic analysis showed a strong predictive value for BRI (area under the curve [AUC] = 0.86). BRITSH ratio demonstrated a moderate predictive capacity (AUC = 0.67). In multiple logistic regression analysis, BRITSH, age, diabetes mellitus, high-sensitivity C-reactive protein, and non-HDL cholesterol remained independent predictors of CAD, whereas male sex, BMI, and smoking were not.

Conclusion: The new BRITSH ratio, combining body fat and thyroid function, was an independent predictor of CAD. The BRI also showed good ability to identify CAD risk in patients with hypothyroidism. These simple measures may help improve heart risk assessment and could be incorporated into routine care for patients with hypothyroidism.

Keywords: Body roundness index, BRITSH ratio, cardiovascular risk, coronary artery disease, hypothyroidism

ORIGINAL INVESTIGATION

INTRODUCTION

Hypothyroidism contributes significantly to cardiovascular disease (CVD) risk by disrupting metabolic homeostasis, leading to dyslipidemia, insulin resistance, and visceral adiposity, key drivers of atherosclerosis progression, particularly in subclinical hypothyroidism.[1] While traditional risk factors remain central to CVD assessment, emerging evidence supports the utility of novel anthropometric and biochemical indices in refining risk stratification. The Body Roundness Index (BRI) has been proposed as a more accurate measure for assessing central obesity and visceral fat distribution, outperforming conventional measures such as body mass index (BMI).[2] In this study, the BRITSH ratio (BRI/TSH), a novel index integrating adiposity and thyroid function, is also introduced to assess its potential role in cardiovascular risk stratification. This is the first study to examine the relationship between the BRI/TSH ratio and CAD, highlighting a novel anthropometric-endocrine marker for CAD risk. The aim was to evaluate the predictive value of BRI, BRITSH for coronary artery disease (CAD) in patients with hypothyroidism and highlight their potential clinical utility.

Çağlar Kaya[1]
Servet Altay[1]
Meral Kayıkçıoğlu[2]

[1]*Department of Cardiology, Faculty of Medicine, Trakya University, Edirne, Türkiye*
[2]*Department of Cardiology, Faculty of Medicine, Ege University, İzmir, Türkiye*

Corresponding author:
Çağlar Kaya
caglarkaya2626@gmail.com

Received: September 11, 2025
Accepted: November 14, 2025
Available Online Date: December 15, 2025

Cite this article as: Kaya Ç, Altay S, Kayıkçıoğlu M. Integrating thyroid function with body composition: The BRITSH ratio and cardiovascular risk – A pilot study. *Anatol J Cardiol.* 2026;30(3):157-164.

DOI:10.14744/AnatolJCardiol.2025.5793

METHODS

This pilot study included 152 consecutive patients with previously diagnosed hypothyroidism (subclinical or previously treated) who presented to the cardiology outpatient clinic. Patients in the CAD group had angiographically confirmed disease (>50% stenosis) or a documented history of revascularization, whereas controls were those without any evidence or history of coronary events. Indications for angiography included standard clinical reasons such as angina, ischemic electrocardiography (ECG) changes, or a positive stress test.

They were stratified into 2 main groups based on the presence or absence of CAD: 55 patients comprised the CAD group, and 97 served as controls. CAD was defined as the presence of greater than 50% stenosis in any coronary artery and/or documented history of coronary revascularization.

Patients with overt hypothyroidism, acute infection, malignancy, chronic renal, or hepatic failure were excluded. Only patients with a prior diagnosis of hypothyroidism (subclinical or previously treated) who were receiving levothyroxine replacement therapy at the time of enrollment were included. Detailed information regarding the initiation protocols, dosing strategies, and monitoring intervals of levothyroxine therapy was not available due to the retrospective design. However, all patients were on treatment at the time of enrollment.

Use of lipid-lowering therapies, statins, or statin-ezetimibe combinations was recorded as a single variable. The study adhered to the principles of the Declaration of Helsinki and was approved by the Trakya University Ethics Committee (approval no.: TUTF-GOBAEK 2025/73).

Biochemical Analyses and Anthropometric Measurements

Laboratory analyses included total cholesterol, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol (total cholesterol minus HDL-C), thyroid-stimulating hormone (TSH), HbA1c, fasting glucose, high-sensitivity C-reactive protein (hs-CRP), neutrophil, and lymphocyte counts.

Anthropometric parameters, including BMI, waist circumference (WC), height, and weight, were obtained from hospital records. Waist-to-height ratio (WHtR) was calculated as WC (cm) / height (cm), while BMI was calculated as weight (kg) / height^2 (m^2). BRI was calculated using the validated formula: $BRI = 364.2 - 365.5 \times \sqrt{[1 - (WC / 2\pi)^2 / (0.5 \times height^2)]}$.[3] A novel index, the BRITSH ratio, was derived by dividing BRI by TSH, hypothesizing a functional interaction between adiposity and thyroid activity.

Statistical Analysis

All statistical analyses were conducted using SPSS version 25.0 (SPSS, Chicago, IL, USA). The Shapiro–Wilk test assessed the normality of continuous variables. Normally distributed data were compared using the independent t-test, while nonparametric data were analyzed using the Mann–Whitney U test. Categorical variables were assessed using the Pearson chi-square test.

Descriptive statistics were reported as mean ± SD for continuous variables and frequencies (percentages) for categorical variables. Non-normally distributed variables were summarized using median and interquartile range (IQR). The diagnostic performance of BRI and BRITSH ratio was evaluated using receiver operating characteristic (ROC) curve analysis, with area under the curve (AUC) values and optimal cutoff points reported. Independent predictors of CAD were evaluated by both univariate and multiple regression analyses using known risk factors (age, sex, diabetes, smoking, hypertension). A two-tailed *P*-value < .05 was considered statistically significant. To minimize multiplicity and potential overfitting, exploratory variables not central to the study aim were excluded from the main analysis; relevant summaries are provided in the Supplementary Material.

RESULTS

A total of 152 hypothyroid patients were included, with 97 (63.80%) in the control group and 55 (36.20%) in the CAD group. The overall population was predominantly female (78.9%, *P* = .025) (Table 1). Patients with CAD were significantly older than controls (57 (40-64) vs. 45 (36-57) years, *P* = .001). Smoking (50.9% vs. 36.1%), diabetes mellitus (34.5% vs. 11.3%, *P* < .001), and hypertension (30.9% vs. 17.5%) were more prevalent in the CAD group, although the difference for hypertension did not reach statistical significance (*P* = .072).

Lipid analysis showed lower LDL-C and HDL-C levels in the CAD group, whereas non-HDL cholesterol was significantly elevated (*P* < .001) (Table 1). Total cholesterol and TG levels did not differ between the groups. The use of lipid-lowering therapy was more common in CAD patients. TSH levels at inclusion were significantly higher in the CAD group compared to the control group (5.98 ± 2.29 mIU/L vs. 3.91 ± 2.31 mIU/L, *P* < .001).

No significant difference was observed in BMI between groups (*P* = .099), while WC, WHtR, BRI were significantly higher in the CAD group (*P* < .001 for both). The distribution of BRI within the study population is illustrated in Figure 1A. The BRITSH ratio was significantly lower in CAD patients (*P* = .005).

Correlation analyses revealed a positive correlation between BRI and TSH (*r* = 0.3798, *P* < .001) (Figure 1B). BRI was also

HIGHLIGHTS

- Although body mass index (BMI) is a widely used measurement, it is limited in cardiovascular risk assessment as it does not adequately reflect visceral adiposity.
- The Body Roundness Index (BRI) reflects central adiposity better than BMI and shows strong discrimination for coronary artery disease in hypothyroid patients.
- The BRITSH ratio (BRI/TSH) ratio may serve as a novel parameter for improving cardiovascular risk stratification in hypothyroid populations by incorporating both adiposity and thyroid function.

Table 1. Clinical Characteristics of Patients of the Study Population

Variables	Control (n = 97)	CAD (n = 55)	*P*
Age (years)	48.87 ± 14.14	54.12 ± 16.03	.001
Sex, n (%)			.025
Male	15 (15.46)	17 (30.91)	
Female	82 (84.54)	38 (69.09)	
BMI, kg/m^2	26.67 (23.05-30.29)	27.89 (25.95-30.48)	.141
Waist (cm)	109.76 ± 5.54	116.18 ± 5.64	<.001
BRI/TSH ratio	1.83 (1.27-2.71)	1.3 (1.11-1.91)	.005
DM, n (%)	11 (11.34)	19 (34.54)	<.001
HT, n (%)	17 (17.53)	17 (30.90)	.072
Smoker, n (%)	35 (36.08)	28 (50.91)	.075
Anti-lipid medication	30 (30.92)	43 (78.18)	<.001
TSH, mIU/L	3.91 ± 2.31	5.98 ± 2.29	<.001
fT4, ng/dL	0.91 ± 0.59	0.89 ± 0.44	.957
fT3, pg/mL	2.65 ± 0.78	2.83 ± 0.81	.179
Blood glucose	97.12 ± 16.70	107.47 ± 24.75	.003
Neutrophile (×10^9/L)	3.30 ± 1.16	4.48 ± 1.26	<.001
Lymphocyte (×10^9/L)	2.22 ± 0.51	2.24 ± 0.50	.575
hs-CRP, mg/mL	2.95 ± 1.32	3.84 ± 1.68	<.001
Hba1C, %	6.1 (5.8-6.7)	6.9 (6.1-7.2)	.001
TG, mg/dL	181.32 ± 50.94	168.25 ± 40.56	.084
LDL-C, mg/dL	157 (121-188)	121 (104-142)	<.001
HDL-C, mg/dL	58 (52-62)	38 (34-50)	<.001
Non-HDL-C, mg/dL	116.04 ± 46.49	147.92 ± 47.56	<.001
Total cholesterol, mg/dL	168 (137-188)	171 (147-190)	.061

BMI, body mass index; BRI, Body Roundness Index; CAD, coronary artery disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TSH, thyroid-stimulating hormone.

moderately correlated with WHtR ($r = 0.3112$, $P < .001$), HbA1c ($r = 0.2901$, $P < .001$), and non-HDL cholesterol ($r = 0.2775$, $P < .001$) (Figure 2). The BRITSH ratio showed a weak negative correlation with non-HDL cholesterol ($r = -0.2405$, $P = .003$) (Figure 3). Finally, WHtR was weak but significantly correlated with non-HDL-C ($r = 0.2697$, $P < .001$).

The cutoff values and predictive power of BRI and BRITSH ratio for CAD prediction are presented in Table 2. ROC curve analysis demonstrated strong predictive performance for BRI (AUC = 0.86, 95% CI: 0.80-0.91) and BRITSH (AUC = 0.67, 95% CI: 0.52-0.68). The ROC curves for BRI and BRITSH ratio are depicted in Figure 4.

In the univariate analysis, older age, male sex, diabetes mellitus, BRI, BRITSH, hs-CRP, and non-HDL cholesterol were significantly associated with CAD, whereas BMI and smoking were not. In the multiple binary logistic regression analyses, age (OR = 1.041, $P = .008$, 95% CI: 1.01-1.07), diabetes mellitus (OR = 5.31, $P = .001$, 95% CI: 1.94-14.51), BRITSH (OR = 0.64, $P = .024$, 95% CI: 0.43-0.94), hs-CRP (OR = 1.58, $P = .003$, 95% CI: 1.17-2.13), and non-HDL cholesterol (OR = 1.018, $P < .001$, 95% CI: 1.01-1.03) remained independent predictors of CAD, whereas male sex, BMI, and smoking were not (Table 3).

DISCUSSION

Main findings of this study are as follows: 1) BRI demonstrated a strong predictive value for CAD, with a threshold of 7.61, yielding 70% sensitivity and 90% specificity; 2) BRITISH ratio was identified as an independent predictor of CAD, with significantly high odds ratios (BRITISH: OR = 0.64, $P = .024$); 3) TSH levels showed a positive correlation with both BRI, suggesting a potential link between thyroid function and body fat distribution (adiposity) (Figure 1); 4) The BRITSH ratio demonstrated significant diagnostic performance for CAD, with a cutoff value of 1.34 (AUC = 0.67, $P \leq .001$); and 5) The non-HDL-cholesterol levels were significantly higher in the CAD group and identified as an independent predictor. As expected, CAD patients receiving statin therapy had lower LDL-C levels compared to the control group. Moreover, non-HDL-cholesterol was positively correlated with BRI, indicating that individuals with greater adiposity and altered fat distribution exhibit a more atherogenic lipid profile**.** Additionally, a significant negative association was observed between non-HDL cholesterol and the BRITSH index, suggesting that higher BRITSH values may coincide with a less atherogenic lipid profile."

Elevated TSH levels are known to increase ApoB-containing lipoproteins. Mechanistically, TSH exerts regulatory effects on lipid metabolism through its receptors on adipocytes and hepatocytes. Triiodothyronine (T3) stimulates cholesterol synthesis by upregulating hepatic HMG-CoA reductase and may enhance intestinal cholesterol absorption via the Niemann-Pick C1-like 1 (NPC1L1) transporter.[4] T3 also upregulates hepatic LDL receptors, promoting LDL clearance, a mechanism impaired in hypothyroidism. Moreover, reduced activity of lipoprotein lipase and hepatic lipase in hypothyroid states impairs TG-rich lipoprotein catabolism.[5] Thyroid hormones downregulate proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of LDL receptor degradation; thus, elevated PCSK9 levels in hypothyroidism exacerbate LDL-C accumulation. T3 also stimulates cholesterol 7 alpha-hydroxylase (CYP7A1), promoting bile acid synthesis from cholesterol—another pathway attenuated in thyroid hormone deficiency.[6] These effects are mediated through nuclear thyroid hormone receptors, THR-α and THR-β, with THR-α primarily regulating cardiac and adipose tissue function, while THR-β modulates hepatic lipid metabolism and TSH secretion. Consequently, thyroid hormones regulate lipid regulation in a tissue-specific manner, influencing fatty acid oxidation, lipogenesis, and systemic lipid homeostasis.[7] Although all the patients had a prior diagnosis of hypothyroidism and were on levothyroxine therapy, TSH levels at inclusion (CAD group: 5.98 ± 2.29 mIU/L; Control group: 3.91 ± 2.31 mIU/L) may suggest incomplete hormonal control,

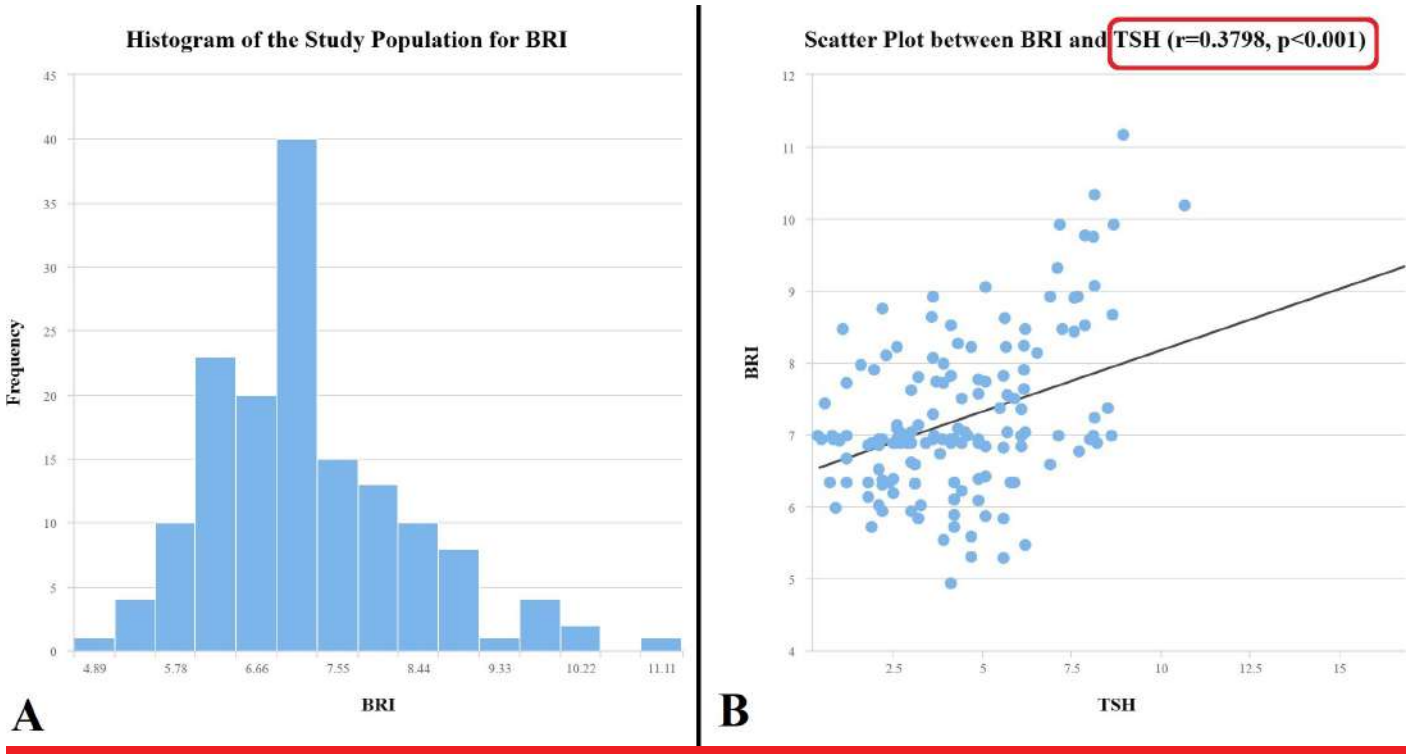

Figure 1. Histogram of the study population for the Body Roundness Index and scatter plot between BRI and thyroid-stimulating hormone.

which may have contributed to the observed metabolic abnormalities. This finding may be explained by real-world factors such as cautious low-dose initiation of levothyroxine in cardiac patients, variable adherence, concomitant medications affecting absorption (e.g., calcium or iron), and the possibility that residual TSH elevation itself reflects cardiovascular risk. Importantly, in daily practice patients with CAD are typically started on lower levothyroxine doses (25-50 µg/day) with gradual titration, in line with international guideline recommendations, to avoid ischemic complications. This conservative approach may result in transiently higher TSH values. Additionally, medication interactions and adherence issues may contribute to suboptimal biochemical control. Finally, it is also plausible that higher TSH represents not only treatment variability but also an intrinsic marker of cardiovascular risk, consistent with prior studies linking subclinical hypothyroidism to adverse outcomes.

This study underscores the clinical relevance of BRI in predicting CAD among patients with hypothyroidism. BRI, a

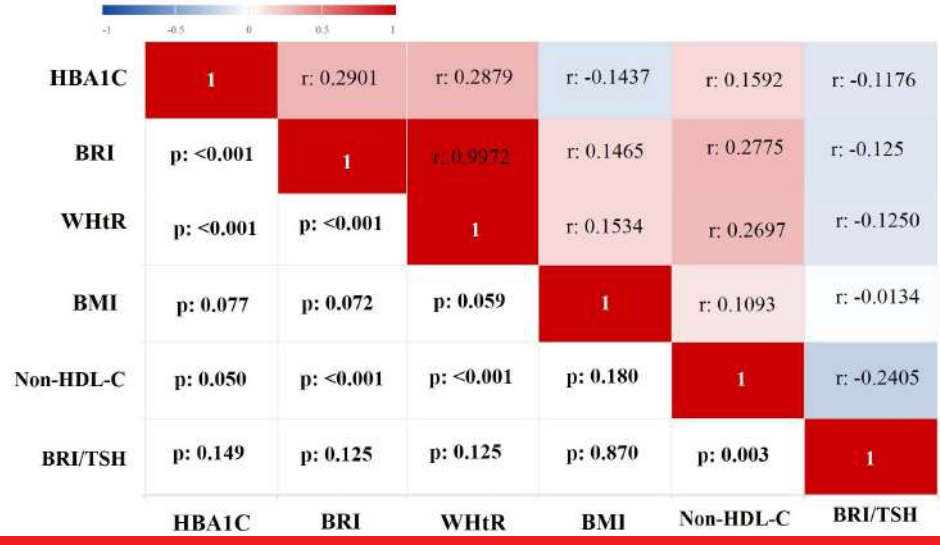

Figure 2. Correlogram with some indexes and parameters.

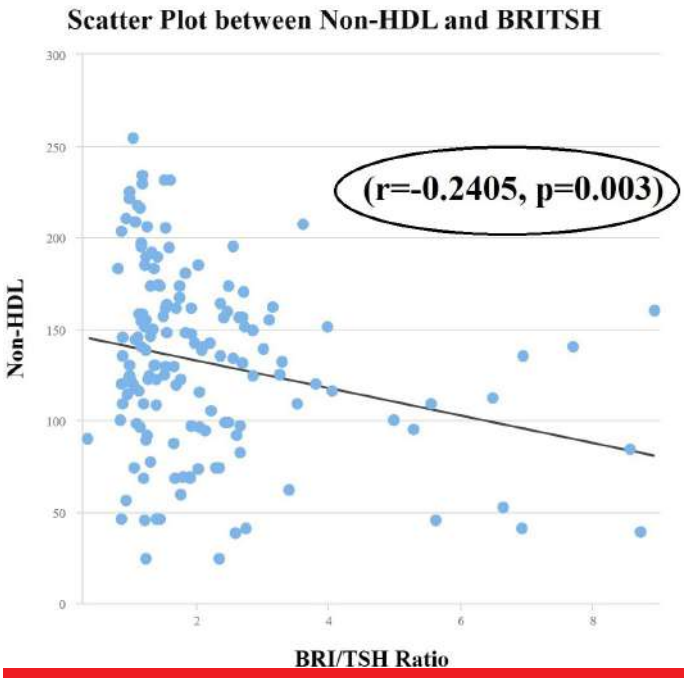

Figure 3. Scatter plot between non–high-density lipoprotein and BRITSH.

geometry-based anthropometric measure, more accurately reflects visceral fat distribution than traditional indices such as WC or BMI.[8] Prior research has demonstrated BRI's utility in identifying cardiovascular-kidney-metabolic (CKM) syndrome (formerly metabolic syndrome) and in predicting cardiovascular events.[9] Given that CKM syndrome components including abdominal adiposity and insulin resistance are frequently present in hypothyroid individuals, particularly those with elevated TSH levels, increased BRI may serve as an early indicator of cardiometabolic risk.[10] Hypothyroidism facilitates fat accumulation by reducing basal metabolic rate and altering lipid metabolism, thereby enhancing cardiovascular vulnerability. As a marker of central obesity, BRI has been associated with metabolic dysfunction, systemic inflammation, vascular dysfunction, and oxidative stress, all of which contribute to atherogenesis.[11] Emerging evidence suggests that BRI outperforms BMI and WC in identifying CKM syndrome and insulin resistance, supporting its use in cardiovascular risk stratification in hypothyroid individuals.[12]

BMI is a convenient measure of overall body size but lacks sensitivity to body fat distribution, limiting its utility in cardiovascular risk assessment. Unlike visceral adiposity indices, it does not distinguish fat from lean mass. Evidence shows that abdominal obesity measures, such as WC and waist-to-height ratio, better predict CVD mortality than BMI.[13] In line with these findings, BMI was not significantly different between groups in this study, underscoring its limited value in CAD risk assessment. These findings agree with growing evidence that body-shape measures like BRI show heart disease risk better than BMI. For patients with hypothyroidism, BRI could be an easy, non-invasive method of identifying those at a higher risk of CAD during routine care. However, this requires confirmation in future studies. Yamashita et al[14] reported that BMI alone was not a reliable prognostic marker in patients undergoing transcatheter aortic valve replacement (TAVR), as the obesity paradox was not confirmed and obesity was associated with worse outcomes in the presence of comorbidities. These findings highlight the limitations of BMI and support the use of novel anthropometric-endocrine indices such as BRI, and the BRITSH ratio for improved cardiovascular risk prediction.

This study population consisted of treated hypothyroid patients on levothyroxine therapy, among whom serum TSH levels showed interindividual variability, reflecting differences in treatment duration, adherence, or dose titration. Elevated TSH levels, even within the high-normal range, have been associated with increased cardiovascular mortality.[15] Gönülalan et al[16] reported higher BRI values in hypothyroid patients compared to euthyroid controls yet found no significant correlation between BRI and TSH. This discrepancy may stem from demographic and clinical differences; this cohort had a higher mean age, a confirmed hypothyroidism diagnosis under treatment, and greater comorbidity burden. In contrast, this study demonstrated a positive correlation between BRI and TSH levels, suggesting that monitoring TSH levels in individuals with thyroid dysfunction may aid in cardiovascular risk management.

Non-HDL cholesterol has emerged as a strong predictor of atherosclerotic risk and is closely associated with CKM syndrome, obesity, and diabetes.[17,18] It has been suggested that non-HDL cholesterol may be a better risk indicator than LDL-C, especially in those with cardiometabolic disturbances and insulin resistance. Notably, its predictive capacity persists even when LDL-C levels are within normal limits.[19] In this study, non-HDL cholesterol was significantly higher in the CAD group, despite lower LDL-C levels, likely reflecting statin use. These findings emphasize the utility of non-HDL cholesterol in assessing residual risk, particularly in hypothyroid populations where lipid-lowering response may be attenuated.

The BRITSH ratio was developed to reflect how body fat and thyroid function work together to affect heart health. BRI

Table 2. Diagnostic Performance of the Body Roundness Index and BRI/TSH Ratio in the Group of Coronary Artery Disease

Diagnostic Performance of BRI and BRI/TSH Ratio					
	Cutoff	AUC (95% CI)	Sensitivity	Specificity	*P*
BRI	7.61	0.86 (0.80-0.91)	0.70 (0.57-0.81)	0.90 (0.85-0.96)	<.001
BRITSH	1.34	0.67 (0.52-0.68)	0.56(0.43-0.68)	0.73 (0.63-0.81)	<.001

AUC, area under the curve; BRI, Body Roundness Index; BRISTH, BRI/TSH ratio; TSH, thyroid-stimulating hormone.

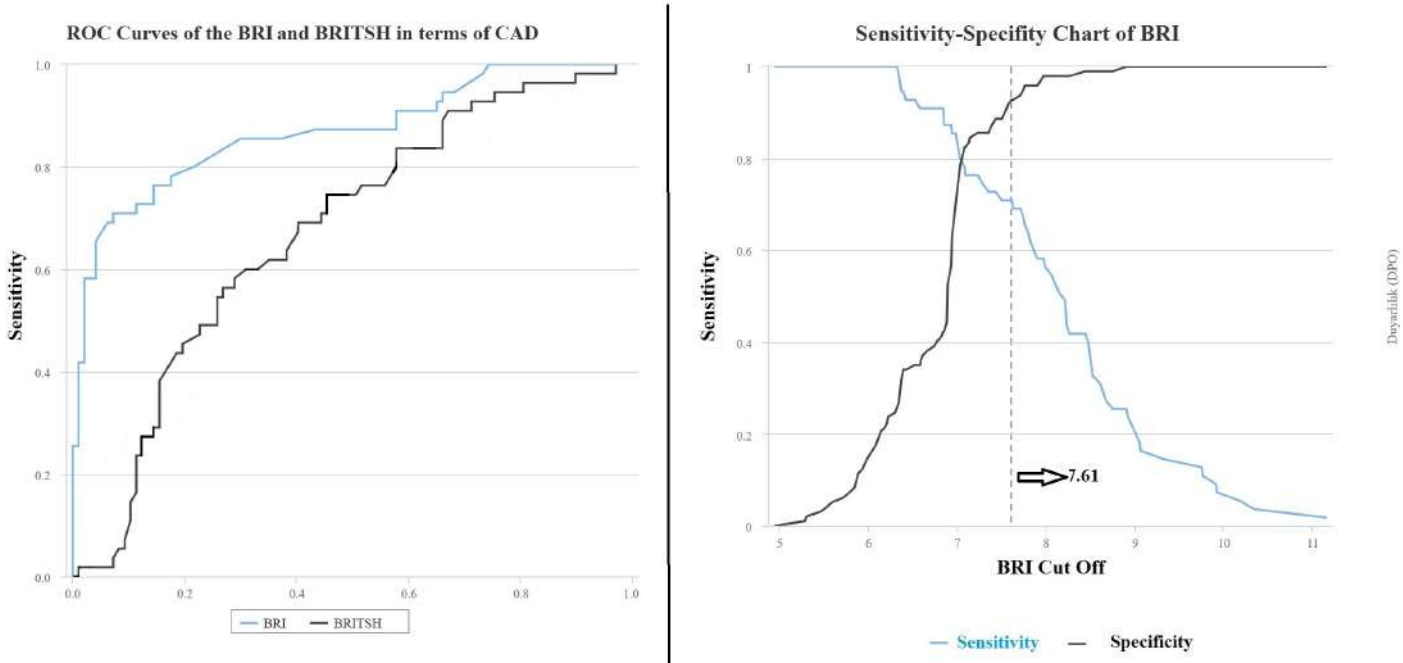

Figure 4. Receiver operating characteristic curves of the Body Roundness Index (BRI) and BRI/TSH ratio in terms of coronary artery disease and sensitivity–specificity chart of BRI.

shows the amount of central or abdominal fat, while TSH indicates how well the thyroid regulates metabolism and cholesterol balance. Because both excess fat and low thyroid activity can cause inflammation, abnormal lipids, and damage to blood vessels, combining them in 1 measure may give a clearer view of heart disease risk in people with hypothyroidism. In this way, the BRITSH ratio may offer a simple and practical way to connect both hormonal and metabolic factors related to CAD.

Additionally, the BRITSH ratio, which integrates visceral adiposity and thyroid function, may serve as a complementary metric to albumin-based nutritional indices such as prognostic nutritional index (PNI) and controlling nutritional status (CONUT). Given that serum albumin reflects systemic inflammation, oxidative stress, and vascular dysfunction in acute coronary syndrome (ACS), as highlighted by Hayıroğlu and Altay,[20] combining BRITSH with albumin-centered scores may provide a more comprehensive cardiometabolic risk assessment in hypothyroid patients.

Inflammatory burden, as reflected by hs-CRP in this model, remained independently associated with CAD, aligning with the inflammatory component of hypothyroidism-related cardiometabolic risk. In the literature, Christ-Crain et al[21] reported that CRP rises with worsening thyroid failure, potentially serving as "an additional risk factor for the development of coronary heart disease in hypothyroid patients.

The BRITSH ratio, by integrating visceral adiposity with the thyroid axis, may complement traditional lipid-lowering strategies in high-risk patients such as those with ACS. In the context of Özdoğan et al's[22] country-specific algorithm for ACS management in Türkiye, incorporating novel indices like BRITSH could enhance the precision of cardiometabolic risk stratification, moving beyond LDL-centric models to include cardiometabolic interplay.

Table 3. Univariate and Multiple Binary Logistic Regression Analysis for the Coronary Artery Disease

	Univariate Model			Multiple Model		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age (years)	1.031	1.01-1.06	.002	1.041	1.01-1.07	.008
Sex (Male)	2.460	1.10-5.40	.027	1.72	0.62-4.76	.292
DM	4.121	1.78-9.54	<.001	5.31	1.94-14.51	.001
Smoking	1.834	0.93-3.62	.079	1.68	0.70-3.99	.238
BMI kg/m^2	1.071	0.98-1.16	.120	1.04	0.93-1.15	.476
BRITSH	0.633	0.44-0.89	.010	0.64	0.43-0.94	.024
hs-CRP mg/mL	1.49	1.18-1.89	<.001	1.58	1.17-2.13	.003
Non-HDL-c	1.022	1.012-1.029	<.001	1.018	1.01-1.03	<.001

BMI, body mass index; BRISTH, BRI/TSH ratio; CAD, coronary artery disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; OR, odds ratio.

A novel index, the BRITSH ratio (BRI/TSH), was introduced to assess the interplay between thyroid function and body composition in relation to cardiovascular risk. This ratio differed significantly between groups and emerged as an independent predictor of CAD in regression analysis. These findings suggest that integrating TSH into adiposity-based indices may improve cardiovascular risk stratification in hypothyroid patients. Further validation in prospective cohorts is warranted to establish its clinical applicability.

Limitations and Strengths of the Study

Strengths of this study include its focus on a specific and clinically relevant patient population with hypothyroidism, who are often underrepresented in cardiovascular risk research. The investigation of novel indices such as BRI, and the BRITSH ratio provides new insights into the interplay between thyroid function, adiposity, and cardiovascular risk. The use of comprehensive anthropometric, biochemical, and statistical analyses, including ROC curve and multiple regression, strengthens the robustness of the findings.

However, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference. Second, the relatively small sample size and single-center setting limit the generalizability of the results. Because this was a cardiology outpatient-based cohort, patients who underwent angiography did so for standard clinical indications (such as angina or ischemic ECG findings) rather than population screening, which may limit the generalizability of the results. Third, the predominance of female participants may have influenced sex-specific associations, potentially overestimating the odds ratio for male sex. Fourth, residual confounding from unmeasured variables such as dietary habits, physical activity, genetic predisposition, or medication adherence cannot be excluded. Moreover, detailed data on levothyroxine dosing history, titration intervals, or treatment adherence were not available, which may partly explain the higher TSH levels observed in the CAD group. Finally, the absence of long-term follow-up prevents assessment of the prognostic utility of the proposed indices over time.

CONCLUSION

The BRITSH ratio, introduced in this study, demonstrated significant potential as an independent predictor of CAD risk in hypothyroid patients. By integrating thyroid function and adiposity into a single metric, it may offer a more precise assessment of cardiovascular risk, potentially enhancing risk stratification and personalized management in clinical practice.

The current findings also highlight the utility of BRI as an easily obtainable anthropometric index and underscore the independent association of the BRITSH ratio with CAD in hypothyroid patients. Incorporating BRITSH alongside established clinical and biochemical markers (e.g., non-HDL cholesterol and hs-CRP) may refine cardiovascular risk stratification in this population.

Together, these parameters provide a more nuanced understanding of cardiometabolic risk, reinforcing the interrelationship between adiposity, thyroid dysfunction, and dyslipidemia. These results underscore the need to incorporate assessments of thyroid function and lipid metabolism into cardiovascular risk models, particularly in patients with increased central adiposity. Future large-scale, prospective studies are warranted to validate these indices and determine their long-term clinical applicability.

Ethics Committee Approval: The Trakya University Ethics Committee approved this study (approval no.: TUTF-GOBAEK 2025/73, Date: 03.03.2025).

Informed Consent: Individual patient consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Ç.K., S.A., M.K.; Design – Ç.K., S.A., M.K.; Supervision – Ç.K., S.A., M.K.; Fundings – Ç.K., S.A., M.K.; Materials – Ç.K., S.A., M.K.; Data collection and/or processing – Ç.K., S.A., M.K.; Analysis and/or interpretation – Ç.K., S.A., M.K.; Literature review – Ç.K., S.A., M.K.; Writing – Ç.K., S.A., M.K.; Critical review – Ç.K., S.A., M.K.

Declaration of Interests: Ç.K. reports honoraria (for lectures or consultancy) from Humanis, Novartis, and NovoNordisk. Research funding from NovoNordisk and Lilly for the past 3 years.

S.A. serves as the Editor-in-Chief of the Balkan Medical Journal. S.A. reports honoraria (for lectures or consultancy) from Novartis, Abdi Ibrahim, Novo Nordisk, and Pfizer, and research funding from NovoNordisk and Lilly for the past 3 years.

M.K. serves as an Associate Editor for the Archives of the Turkish Society of Cardiology. M.K. reports honoraria (for lectures or consultancy) from Abbott, Abdi Ibrahim, Amgen, LIB Therapeutics, MSD, Novartis, Novo Nordisk, Pfizer, Recordati, and Ultragenix and research funding from Amgen, Ionis, LIB Therapeutics, Lilly, MSD, and Novartis for the past 3 years.

Funding: This research received no external funding. All costs associated with the study were covered by the authors.

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SUPPLEMENTARY FILE

Supplementary Introduction

In our study, we compiled additional analyses, tables, and figures for parameters that, although not included in the main regression models due to potential multicollinearity, were considered valuable for exploratory assessment. The supplementary indices and their formulas are presented below:

- **Plasma Atherogenicity Index (PAI):** calculated as log (TG / HDL-C), representing the relationship between lipid profile and cardiovascular risk.
- **Lipid Accumulation Product (LAP):** calculated as (WC – 65) × TG (mmol/L) for men and (WC – 58) × TG (mmol/L) for women.
- **Neutrophil-to-Lymphocyte Ratio (NLR):** calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Supplementary Discussion

PAI, calculated as log (TG/HDL-C), is a well-recognized indicator of atherogenic dyslipidemia and endothelial dysfunction, particularly in thyroid disorders. In hypothyroidism, reduced thyroid hormone activity elevates TGs, lowers HDL-C, and increases PAI. Its utility in risk stratification has been demonstrated across various conditions, including liver disease, stroke, and thyroid dysfunction. A recent meta-analysis by Assempoor et al. confirmed elevated PAI in CAD patients. Consistently, our study found significantly higher PAI levels in the CAD group, supporting the relevance of this finding in hypothyroid populations.[1] Although PAI showed a strong association, the wide confidence interval suggests some statistical uncertainty, likely due to the sample size and the scale of the index. This finding should therefore be interpreted with caution and validated in larger cohorts.

The strong correlation between PAI and LAP ($r = 0.7162$, $p < 0.001$) highlights the link between visceral adiposity and atherogenic lipid profiles. The moderate correlation between BRI and LAP ($r = 0.4711$, $p < 0.001$) further supports the role of central fat accumulation in CAD risk. These findings align with prior studies associating elevated BRI and LAP with CKM syndrome and cardiovascular events, emphasizing their utility in cardiometabolic risk assessment.[2]

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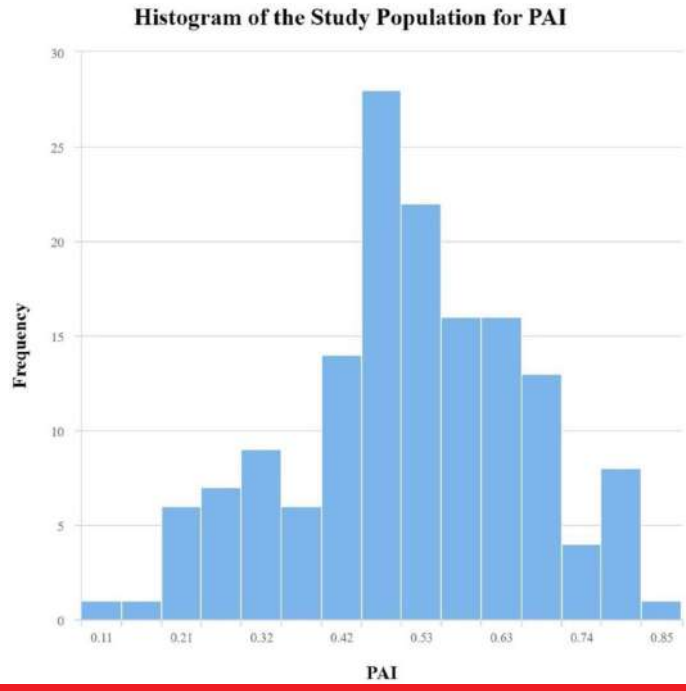
Supplementary Table 1. Other Parameters of the study population

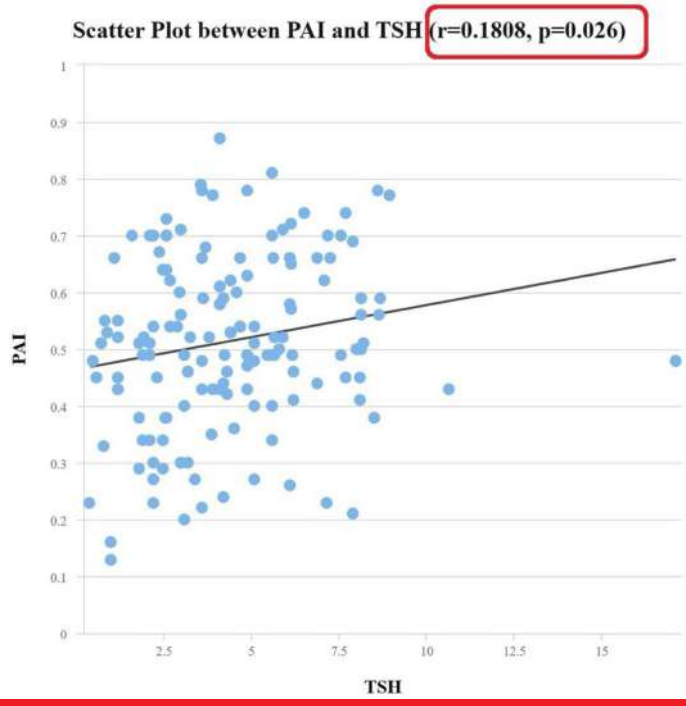
Variables	Control (n=97)	CAD (n=55)	*P*
LAP cm × mmol/L	474.39±133.20	567.63±183.09	<0.001
PAI	0.46±0.12	0.60±0.15	<0.001
NLR	1.54±0.65	2.10±0.76	<0.001

Supplementary Table 2. Diagnostic Performance of PAI in ROC Analyses

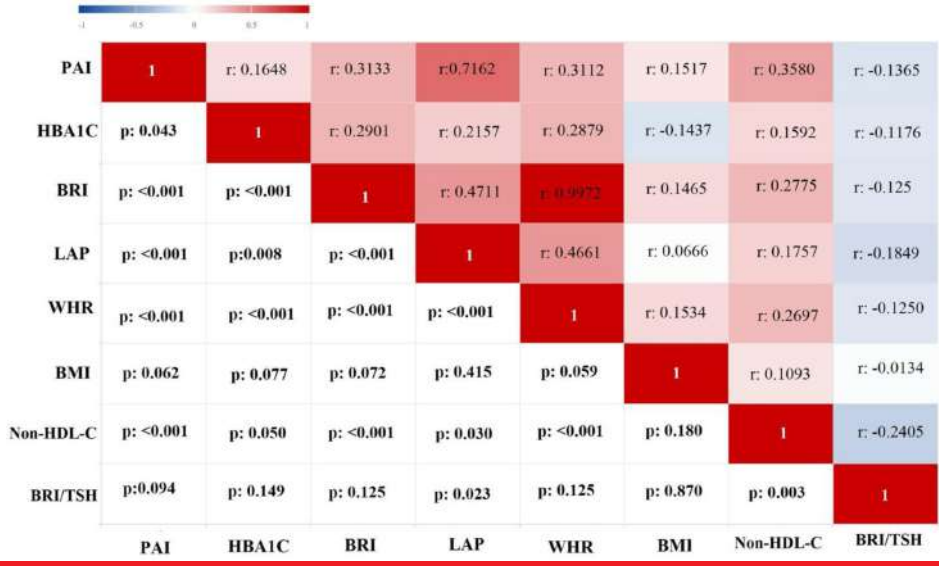
	Diagnostic Performance of BRI, and BRI/TSH ratio				
	Cut off	AUC (95% CI)	Sensitivity	Specificity	*P*
PAI	0.61	0.76 (0.69-0.83)	0.60 (0.46-0.71)	0.90 (0.83-0.95)	<0.001



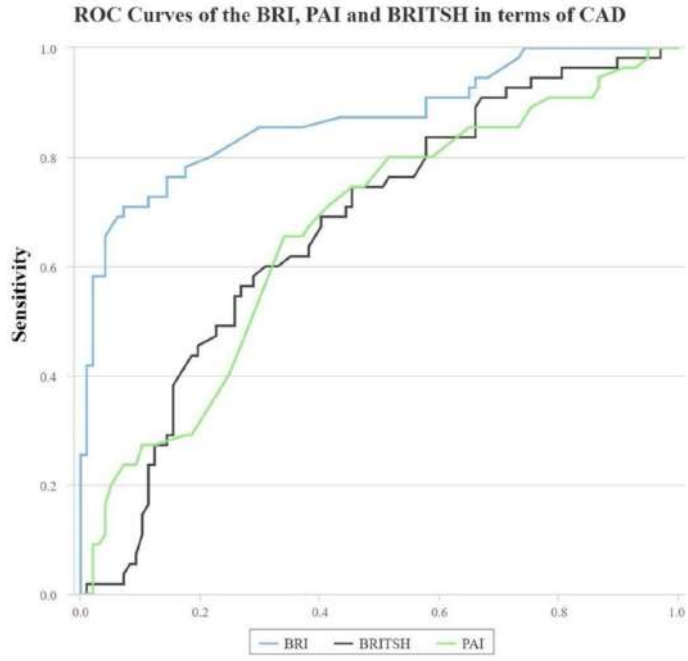
Supplementary Figure 1. Histogram of PAI.



Supplementary Figure 2. Supp: Scatter plot between PAI and TSH.



Supplementary Figure 3. Supp: Correlogram of all indices and parameters with PAI and LAP



Supplementary Figure 4. Supp: ROC Curves of the BRI, PAI and BRITSH in terms of CAD

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Thrombotic and Hemorrhagic Adverse Events of Direct Oral Anticoagulants: An Analysis of Sex-Related Differences Using Food and Drug Administration Adverse Event Reporting System

ABSTRACT

Background: Sex-related differences in the safety profiles of direct oral anticoagulants (DOACs) remain insufficiently understood. This study aimed to evaluate sex-specific differences in the most frequently reported hemorrhagic and thrombotic adverse events (AEs) associated with DOAC therapy using data from the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: A retrospective pharmacovigilance analysis was conducted using FAERS reports from each DOAC's approval date through 2024. Only cases in which a single DOAC was designated as the primary suspect and the report was submitted by a healthcare professional were included. Six major AEs were evaluated: gastrointestinal hemorrhage, intracerebral hemorrhage, pulmonary embolism (PE), deep vein thrombosis, ischemic stroke, and myocardial infarction (MI). Dabigatran served as the reference comparator. Reporting odds ratios (RORs) with 95% CIs were calculated to identify disproportionate reporting signals.

Results: Hemorrhagic and thrombotic AE patterns demonstrated notable sex differences. Gastrointestinal hemorrhage risk was higher with apixaban (ROR = 2.32, $P < .001$, 95% CI: 2.20-2.45) and edoxaban (ROR = 2.95, $P < .001$, 95% CI: 2.54-3.42) compared with dabigatran, while female dabigatran users reported these events more frequently ($P < .001$). Intracranial hemorrhage was reported more often among males using dabigatran and rivaroxaban ($P = .003$ and $P = .004$). All DOACs were associated with increased MI reports (e.g., apixaban ROR = 2.37, $P < .001$, 95% CI: 2.08-2.71), particularly among males. Conversely, PE and ischemic stroke were more frequently reported in female rivaroxaban users ($P < .001$ and $P = .018$).

Conclusions: Significant sex-specific differences exist in DOAC safety profiles. Recognizing these patterns may inform individualized anticoagulant selection and enhance pharmacovigilance-driven personalized medicine.

Keywords: Adverse Drug Reaction Reporting Systems, anticoagulants, hemorrhage, sex differences, thrombosis

INTRODUCTION

Anticoagulants play a critical role in the prevention and treatment of thromboembolic disorders. Over the past decade, a new generation of direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban, has gained widespread use in clinical practice owing to their unique pharmacological advantages. Their fixed dosing, lack of routine laboratory monitoring, and broad clinical indications make them appealing alternatives to traditional vitamin K antagonists (VKAs).[1,2] However, serious bleeding events and thrombotic complications remain important safety concerns.[3,4]

Most of the available safety data on DOACs have been derived from clinical trial populations. Randomized trials typically involve selected and homogeneous patient groups. As a result, the findings may not fully reflect sex-related safety differences in real-world settings.[3] The reflection of biological and clinical factors related to sex (e.g. hormone levels, thrombotic and hemorrhagic tendencies,

ORIGINAL INVESTIGATION

Mehmet Şahinbaş[1]
Burcu Şahinbaş[2]
Ezgi Ağadayı[3]

[1]*Department of Cardiology, Sivas Numune Hospital, Sivas, Türkiye*
[2]*Department of Pharmacology, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye*
[3]*Department of Medical Education, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye*

Corresponding author:
Ezgi Ağadayı
✉ drezgiagadayi@hotmail.com

Received: September 19, 2025
Accepted: December 23, 2025
Available Online Date: February 10, 2026

Cite this article as: Şahinbaş M, Şahinbaş B, Ağadayı E. Thrombotic and hemorrhagic adverse events of direct oral anticoagulants: An analysis of sex-related differences using FDA Adverse Event Reporting System. *Anatol J Cardiol.* 2026;30(3):165-173.

DOI:10.14744/AnatolJCardiol.2025.5827

pharmacokinetic properties) in adverse event (AE) profiles has not been comprehensively explored.[4] Despite this gap, growing evidence suggests that there may be significant sex differences in the efficacy and safety profiles of DOACs.[5] Overall, the available data for sex-specific differences remain fragmentary and are often restricted to subgroup analyses, which limits statistical power and complicates clinical interpretation. In addition to sex-related differences, elderly patients with multiple comorbidities or polypharmacy are often excluded from randomized trials, further contributing to uncertainties about the safety of DOACs in complex clinical populations.[6]

Large-scale pharmacovigilance databases such as the Food and Drug Administration Adverse Event Reporting System (FAERS) involving heterogeneous populations have the potential to reveal sex-specific AE differences with respect to DOACs that may not be noticed in controlled clinical trials.[7,8] Therefore, this study analyzed FAERS data to evaluate the most commonly reported hemorrhagic and thrombotic AEs associated with DOAC use and to investigate potential sex-related differences. The findings provide clinicians with insights that support more individualized anticoagulant selection and contribute to the growing body of pharmacovigilance research in this field.

METHODS

Data Source and Study Design

This retrospective, descriptive data analysis was performed using FAERS data.[9] The FAERS is an open-access database to which patients, pharmaceutical companies, and healthcare professionals voluntarily submit reports of drug-related AEs and product quality issues. The database includes case-level information including the year of reporting, type of reaction, product/generic name, patient age and sex, reporter type/region, event outcome, severity classification, and therapeutic indication. Reported reactions in FAERS represent suspected AEs at the Preferred Term level according to the Dictionary of Medical Regulatory Activities.[10]

HIGHLIGHTS

- Reports from healthcare professionals in the United States Food and Drug Administration Adverse Event Reporting System between 2010 and 2024 were analyzed.
- Direct oral anticoagulants were compared with dabigatran using disproportionality analysis.
- Gastrointestinal hemorrhage was more frequently associated with apixaban and edoxaban, while rivaroxaban showed fewer reports; edoxaban had the highest signal for intracranial hemorrhage.
- Pulmonary embolism and deep vein thrombosis were less common with rivaroxaban, whereas myocardial infarction (MI) and ischemic stroke were more frequent with all agents.
- Gastrointestinal hemorrhage was more often reported in female patients, whereas intracranial hemorrhage and MI were more frequently reported in male patients.

For hemorrhagic events, the terms "cerebral hemorrhage" and "intracranial hemorrhage" were used to describe intracranial bleeding, and "gastrointestinal hemorrhage" was used to define gastrointestinal bleeding. Thrombotic events consisted of deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, and myocardial infarction (MI); only the terms "myocardial infarction" and "acute myocardial infarction" were used to define MI. The AE records were retrieved by querying the database using the relevant generic name: "dabigatran," "dabigatran etexilate," "dabigatran etexilate mesylate," "rivaroxaban," "apixaban," "edoxaban," "edoxaban tosylate," and "edoxaban tosylate monohydrate."

In this study, predefined inclusion and exclusion criteria were applied. The AEs reports associated with DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) were evaluated for the period from each drug's FDA approval date to the end of 2024. Betrixaban was excluded from the study due to its limited number of reports (n = 35). Only records in which the DOAC was designated as the primary suspect were included; concomitant medications were not considered in this analysis. Records in which the DOAC was coded as a secondary suspect or concomitant agent were excluded. Only AEs submitted by healthcare professionals were included (Figure 1). Cases with missing sex information were included in the overall analysis but excluded from sex-specific subgroup assessments. Duplicate reports were addressed according to the FDA-recommended procedures.[11] Among entries sharing the same case identifiers (CASEID), the version with the latest FDA receipt date (FDA_DT) was retained.

Disproportionality Analysis and Statistical Analysis

Annual AE reporting rates were calculated by dividing the total number of AEs by the number of years each drug had been listed in the FAERS database. Demographic characteristics were summarized descriptively. For comparative analyses, each Factor Xa inhibitor (rivaroxaban, apixaban, and edoxaban) was compared with dabigatran. Reporting odds ratios (RORs) for each AE were calculated using a 2 × 2 contingency table. A potential safety signal indicating a disproportionate association between a drug and a specific AE was identified by an ROR exceeding 1.[12] The chi-square test was used to evaluate sex-based differences for each of the 6 AEs. All statistical analyses and graphical visualizations were conducted using SPSS versions 23.0 and GraphPad Prism version 10.4.1. A *P* value of <.05 was considered statistically significant.

RESULTS

After applying the inclusion and exclusion criteria to 30 179 725 AE reports in the FAERS database through 2024, a total of 37 537 dabigatran, 61 983 rivaroxaban, 43 930 apixaban, and 5040 edoxaban cases were included in the final analysis (Figure 1). Among DOACs, apixaban accounted for the highest number of primary-suspect AE reports, whereas rivaroxaban had the highest number of AEs reported specifically by healthcare professionals. Annual AE counts, thrombotic and hemorrhagic events, annual death totals, and the study periods for each DOAC are shown in Figure 2. Apixaban

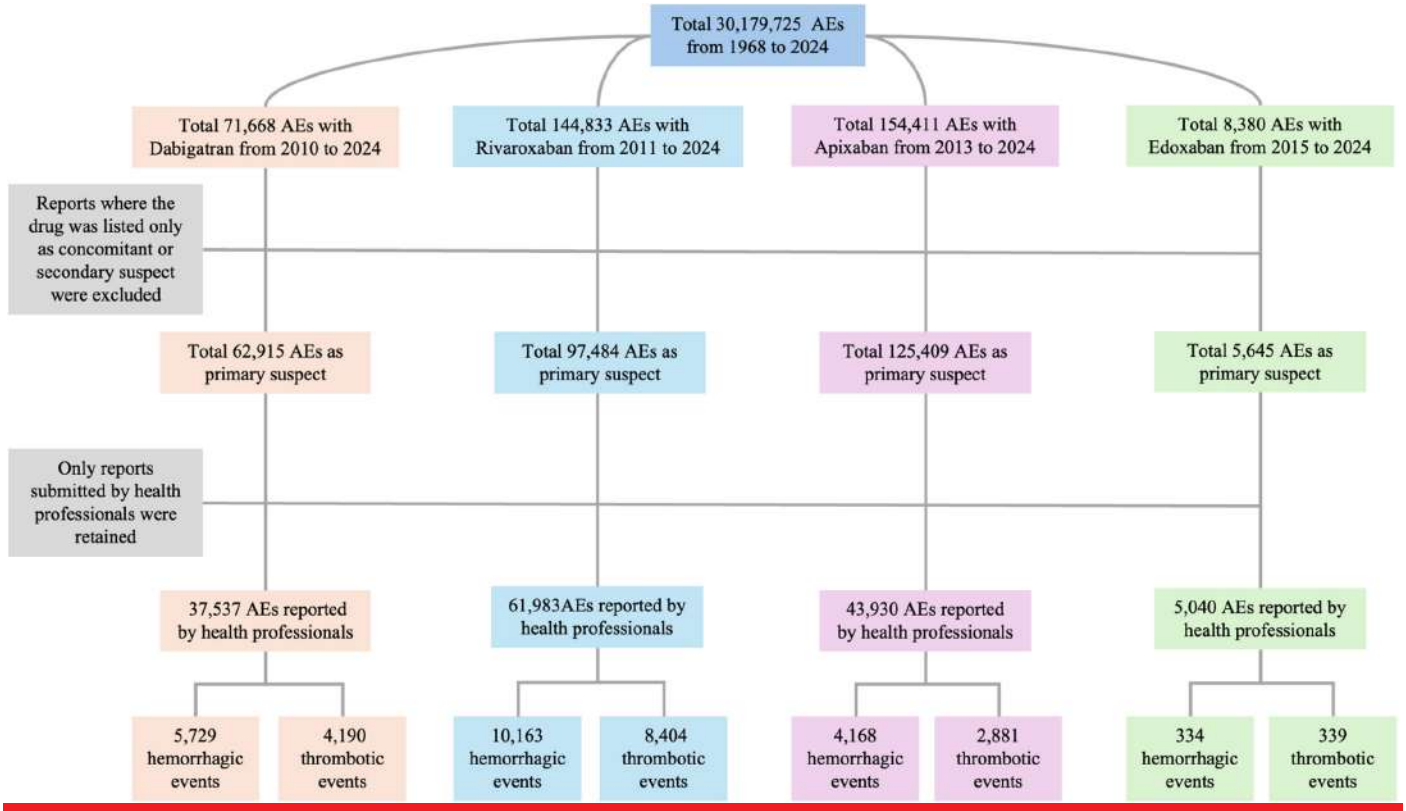


Figure 1. Flowchart of adverse events reported to the FAERS with DOACs. AEs, Adverse events.

exhibited the highest annual number of reported deaths, while edoxaban showed the lowest annual AE counts, reflecting its comparatively lower usage. Demographic characteristics of patients experiencing hemorrhagic and thrombotic disorders related to DOAC use are presented in Table 1. For all DOACs, these AEs were most reported in individuals aged 65-85 years. When overall hemorrhagic and thrombotic AEs were evaluated, male patients receiving dabigatran and apixaban demonstrated a significantly higher reporting frequency ($P < .001$; Figure 3).

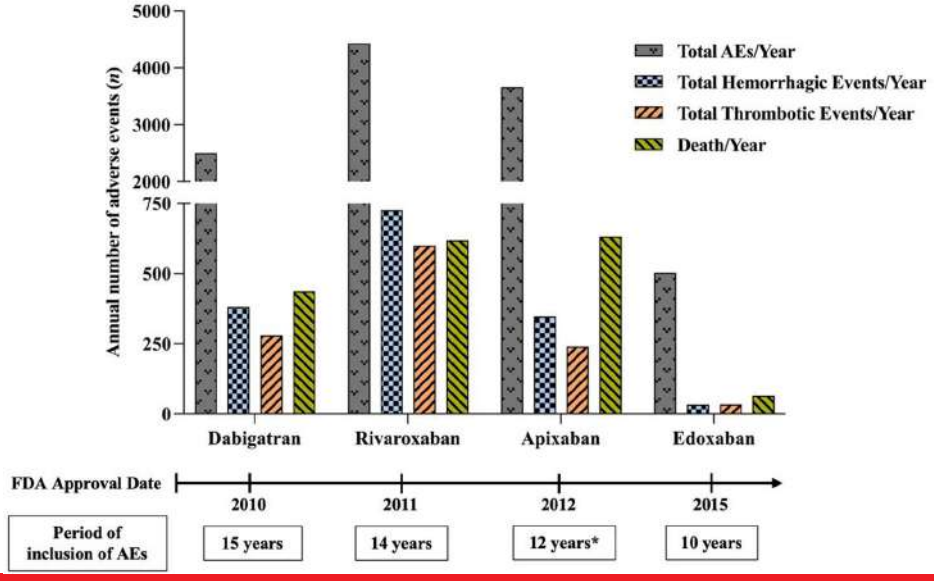


Figure 2. Annual number of adverse events reported with DOACs as the primary suspect. Hemorrhagic, thrombotic, and death-related events are shown on the graph together with annualized total AE numbers. Each drug's FDA approval date served as the basis for calculating the inclusion period (in years). *Apixaban was approved on December 28, 2012; hence, the year 2012 was excluded from the period used to calculate annual averages. AEs, Adverse events.

Table 1. Demographics of Reported Selected Thrombotic and Hemorrhagic AEs with DOACs

Characteristics	Dabigatran (n = 9619)	Rivaroxaban (n = 17806)	Apixaban (n = 6844)	Edoxaban (n = 657)
Serious type				
Serious, n (%)	9530 (99.07)	17755 (99.71)	6755 (98.69)	626 (95.28)
Non-serious, n (%)	89 (0.92)	51 (0.28)	89 (1.30)	31 (4.71)
Sex				
Female, n (%)	3829 (39.80)	7867 (44.18)	2649 (38.70)	160 (24.35)
Male, n (%)	4366 (45.38)	7677 (43.11)	3072 (44.88)	155 (23.59)
Not specified, n (%)	1424 (14.80)	2262 (12.70)	1123 (16.40)	342 (52.05)
Age group				
<18, n (%)	9 (0.09)	18 (0.10)	3 (0.04)	1 (0.15)
18-64, n (%)	1041 (10.82)	3808 (21.38)	833 (12.17)	33 (5.02)
65-85, n (%)	4500 (46.78)	7568 (42.50)	2866 (41.87)	165 (25.11)
>85, n (%)	1030 (10.70)	1396 (7.84)	918 (13.41)	67 (10.19)
Not specified, n (%)	3039 (31.59)	5016 (28.17)	2222 (32.46)	391 (59.51)
Outcome of event				
Died, n (%)	2271 (23.60)	3522 (19.77)	1184 (17.29)	120 (18.26)
Life-threatening, n (%)	1379 (14.33)	1301 (7.30)	887 (12.96)	92 (14.00)
Hospitalized, n (%)	6515 (67.73)	11172 (62.74)	3129 (45.71)	424 (64.53)
Disabled, n (%)	354 (3.68)	388 (2.17)	194 (2.83)	26 (3.95)
Congenital anomaly, n (%)	2 (0.02)	1 (0.00)	2 (0.02)	0 (0.00)
Required intervention, n (%)	52 (0.54)	54 (0.30)	136 (1.98)	2 (0.30)
Other, n (%)	3273 (34.02)	7784 (43.71)	5774 (84.36)	311 (47.33)
Case priority				
Direct, n (%)	572 (5.94)	741 (4.16)	842 (12.30)	11 (1.67)
Expedited, n (%)	7192 (74.76)	11404 (64.04)	5305 (77.51)	615 (93.60)
Non-expedited, n (%)	1855 (19.28)	5661 (31.79)	693 (10.12)	31 (4.71)

Events include gastrointestinal hemorrhage, intracranial hemorrhage, pulmonary embolism, deep vein thrombosis, myocardial infarction, and ischemic stroke.

Hemorrhagic Adverse Events

For gastrointestinal hemorrhage, apixaban (ROR = 2.32, $P < .001$, 95% CI: 2.20-2.45) and edoxaban (ROR = 2.95, $P < .001$, 95% CI: 2.54-3.42) were associated with significantly higher reporting risk compared with dabigatran. In contrast, rivaroxaban demonstrated a significantly lower risk of gastrointestinal hemorrhage (ROR = 0.86, $P < .001$, 95% CI: 0.82-0.89; Table 2). In the sex-based assessment, reports of gastrointestinal hemorrhage were more frequent in females receiving rivaroxaban and edoxaban, although these differences did not reach statistical significance ($P = .949$ and $P = .908$, respectively). However, this difference was significantly in favor of females for dabigatran ($P < .001$; Figure 4).

For intracranial hemorrhage, edoxaban (ROR = 1.76, $P < .001$, 95% CI: 1.49-2.09) and rivaroxaban (ROR = 1.09, $P = .007$, 95% CI: 1.02-1.15) were associated with significantly increased risks compared with dabigatran. The modest increase

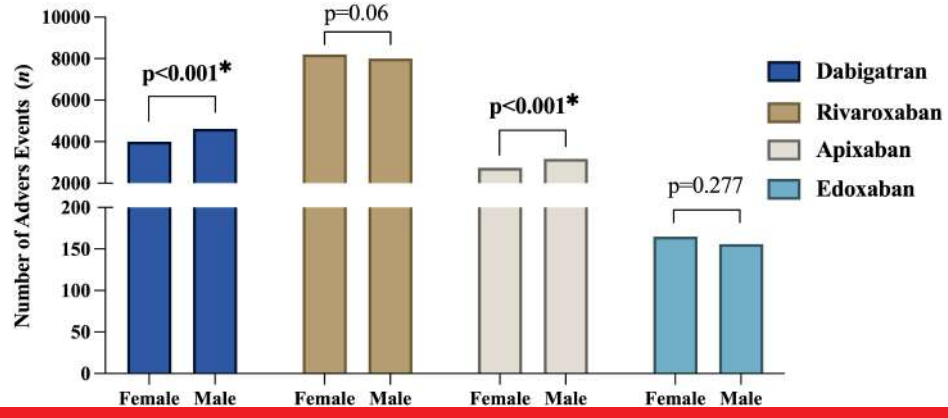


Figure 3. Sex differences of total hemorrhagic and thrombotic adverse events with DOACs. *$P < .05$.

observed with apixaban was not statistically significant ($P = .186$). In sex-stratified analyses, intracranial hemorrhage was reported significantly more frequently in males receiving dabigatran and rivaroxaban ($P = .003$ and $P = .004$, respectively).

Thrombotic Adverse Events

For PE, rivaroxaban (ROR = 0.40, $P < .001$, 95% CI: 0.38-0.44) and apixaban (ROR = 0.91, $P = .039$, 95% CI: 0.83-0.99) were associated with significantly fewer reports than dabigatran. No significant difference was observed for edoxaban ($P = .996$; Table 2). In sex-stratified analyses, PE was reported significantly more often in females receiving rivaroxaban ($P < .001$; Figure 4).

For DVT, rivaroxaban demonstrated a significantly lower reporting risk (ROR = 0.41, $P < .001$, 95% CI: 0.38-0.44), whereas edoxaban was associated with a higher risk (ROR = 1.63, $P < .001$, 95% CI: 1.27-2.09). The difference for apixaban did not exceed the statistical limit ($P = .066$). In sex-based assessments, DVT was reported more frequently in male patients receiving dabigatran, rivaroxaban, and apixaban; however, this difference was statistically significant only for rivaroxaban ($P = .019$).

With respect to MI, all DOACs showed a significantly higher reporting risk than dabigatran: rivaroxaban (ROR = 1.92, $P < .001$, 95% CI: 1.71-2.14), apixaban (ROR = 2.37, $P < .001$, 95% CI: 2.08-2.71), and edoxaban (ROR = 2.51, $P < .001$, 95% CI: 1.81-3.54). When stratified by sex, MI AEs were more frequently reported in male patients for all DOACs. This difference was statistically significant for dabigatran ($P < .001$), rivaroxaban ($P < .001$), and apixaban ($P = .001$) but not significant for edoxaban ($P = .481$).

For ischemic stroke, all DOACs were associated with higher AE reporting compared with dabigatran: apixaban (ROR = 5.12, $P < .001$, 95% CI: 4.62-5.69), rivaroxaban (ROR = 2.35, $P < .001$, 95% CI: 2.19-2.53), and edoxaban (ROR = 2.09, $P < .001$, 95% CI: 1.74-2.51). In sex-based analyses, ischemic stroke was reported significantly more frequently in female patients using rivaroxaban ($P = .018$).

DISCUSSION

This study comprehensively evaluated sex-based differences in hemorrhagic and thrombotic AEs associated with DOACs by analyzing data from the FAERS database. Among DOACs, rivaroxaban accounted for the highest overall number of

Table 2. The Comparison Between Hemorrhagic and Thrombotic Disorder Adverse Events of DOACs as a Primary Suspect Medication

Type of Reaction	DOACs	Cases	Non-cases	ROR (95% CI)	*P*
Gastrointestinal hemorrhage	*Dabigatran*	*3856*	*33681*		
	Rivaroxaban	7305	54678	0.86 (0.82-0.89)	<.001***
	Apixaban	2064	41866	2.32 (2.20-2.45)	<.001***
	Edoxaban	188	4852	2.95 (2.54-3.42)	<.001***
Intracranial hemorrhage	*Dabigatran*	*1873*	*35664*		
	Rivaroxaban	2858	59125	1.09 (1.02-1.15)	.007**
	Apixaban	2104	41826	1.04 (0.98-1.11)	.186
	Edoxaban	146	4894	1.76 (1.49-2.09)	<.001***
Pulmonary embolism	*Dabigatran*	*842*	*36695*		
	Rivaroxaban	3324	58659	0.40 (0.38-0.44)	<.001***
	Apixaban	1082	42848	0.91 (0.83-0.99)	.039*
	Edoxaban	113	4927	1.00 (0.82-1.22)	.996
Deep vein thrombosis	*Dabigatran*	*799*	*36738*		
	Rivaroxaban	3140	58843	0.41 (0.38-0.44)	<.001***
	Apixaban	1019	42911	0.92 (0.83-1.01)	.066
	Edoxaban	66	4974	1.63 (1.27-2.09)	<.001***
Myocardial infarction	*Dabigatran*	*665*	*36872*		
	Rivaroxaban	578	61405	1.92 (1.71-2.14)	<.001***
	Apixaban	332	43598	2.37 (2.08-2.71)	<.001***
	Edoxaban	36	5004	2.51 (1.81-3.54)	<.001***
Ischemic stroke	*Dabigatran*	*1884*	*35653*		
	Rivaroxaban	1362	60621	2.35 (2.19-2.53)	<.001***
	Apixaban	448	43482	5.12 (4.62-5.69)	<.001***
	Edoxaban	124	4916	2.09 (1.74-2.51)	<.001***

*$P < .05$ **$P < .01$ ***$P < .001$; *Dabigatran* was used as the reference among DOACs. Other medications include all non-DOAC primary suspect reports within the same adverse event category. RORs were calculated with 95% CI.
DOAC, direct oral anticoagulant; ROR, reporting odds ratio.
*$P < .05$.
**$P < .01$.
***$P < .001$.

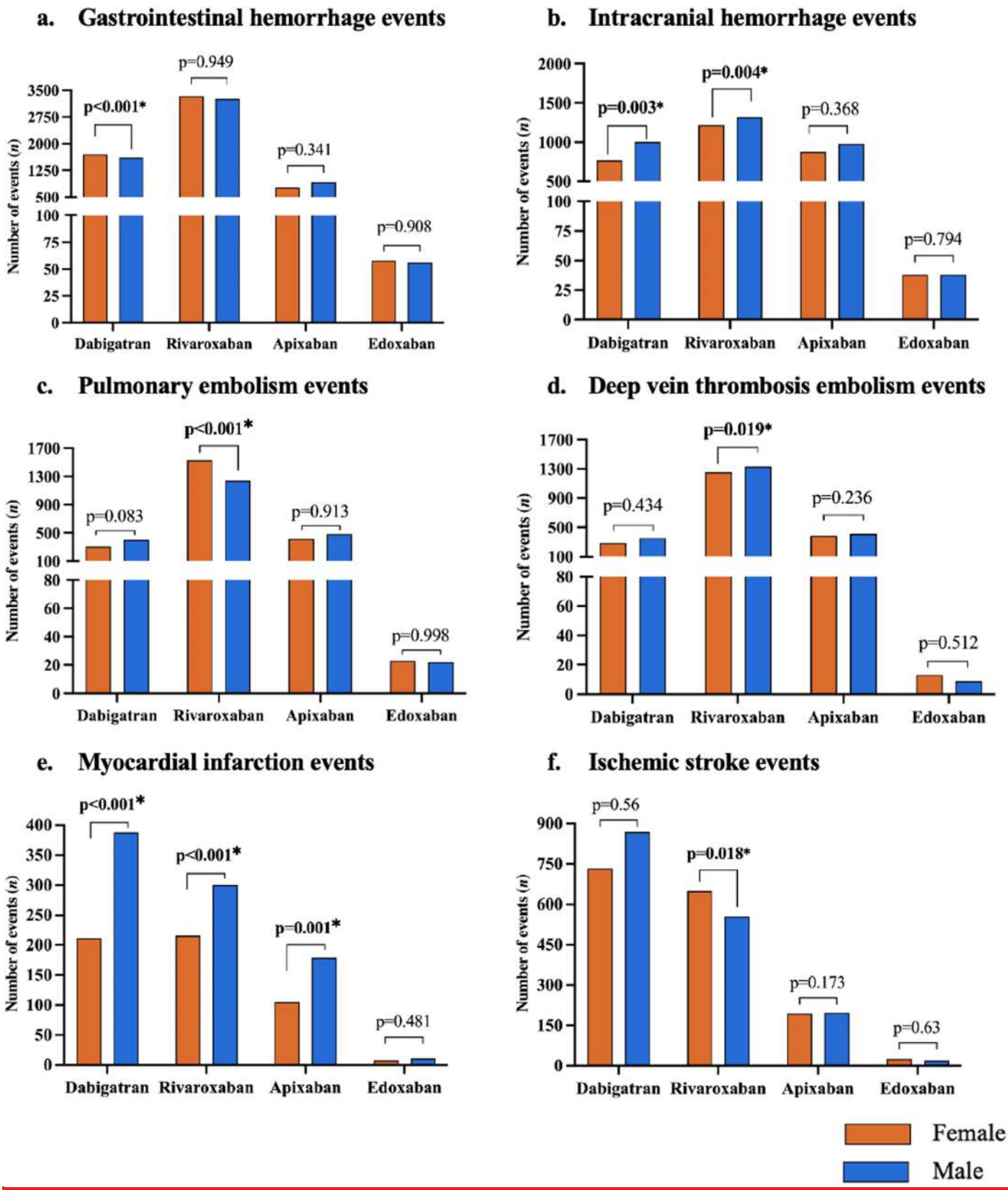


Figure 4. Sex-based differences in hemorrhagic and thrombotic adverse events reported with DOACs. a. Gastrointestinal hemorrhage events, b. Intracranial hemorrhage events, c. Pulmonary embolism events, d. Deep vein thrombosis events, e. Myocardial infarction events, f. Ischemic stroke events. *P < .05.

AE reports, whereas apixaban was most frequently associated with fatal outcomes. The most notable finding of this study is the clear sex-specific divergence in AE patterns. Hemorrhagic events were more commonly reported in females, whereas thrombotic events predominated in males. Gastrointestinal hemorrhage was dominant in females, while intracranial hemorrhage was more prominent in males. Additionally, MI and DVT were more frequently observed in males, whereas PE and rivaroxaban-associated ischemic stroke were more prominent in females. These findings suggest that DOAC-related AEs may exhibit sex-specific patterns, potentially influenced by biological differences or pharmacokinetic variability between males and females.

Dabigatran was selected as the reference drug based on its distinct mechanism of action, its status as the first approved drug in this class, and the high number of AE reports available. This approach enabled a structured comparison of the safety profiles of Factor Xa inhibitors versus Factor IIa inhibitor dabigatran. The VKAs were not included due to their longstanding use and well-characterized safety profiles, as well as the increased likelihood of underreporting due to their frequent use.

In the study, rivaroxaban was the DOAC most frequently associated with hemorrhagic AEs, particularly gastrointestinal and intracranial hemorrhages. However, its risk of gastrointestinal hemorrhage was significantly lower compared with dabigatran. This finding contradicts several FAERS-based analyses but aligns more closely with data from the EudraVigilance system.[13,14] Additionally, recent data from Türkiye suggests that low-dose rivaroxaban may be associated with adverse outcomes, highlighting the importance of individualized dosing strategies.[15] Edoxaban demonstrated higher reporting rates for both gastrointestinal and intracranial hemorrhages, consistent with previously published DOAC studies.[16] However, this increase may partly reflect its relatively recent introduction and the greater sensitivity associated with drugs prescribed at lower volumes.[1,17] The frequency of gastrointestinal hemorrhage was significantly increased for apixaban compared to dabigatran, but no significant difference was found regarding intracranial hemorrhage. This result contradicts retrospective studies and pharmacovigilance analyses, in which apixaban was typically associated with a lower risk of bleeding.[14,17] Declining prescription rates and dose adjustments for dabigatran in recent years may partially account for this discrepancy.[18]

Sex-stratified analyses revealed that gastrointestinal hemorrhage was more frequently reported in females, whereas intracranial hemorrhage was significantly more common in males. This suggests that bleeding patterns may be influenced by biological sex. Females exhibit higher rates of gastrointestinal comorbidities such as irritable bowel syndrome and more frequent use of gastro-toxic medications, including SSRIs and NSAIDs, and hormonal differences in mucosal integrity may increase susceptibility to gastrointestinal hemorrhage.[19,20] In addition, slower gastric emptying in females and differences in anticoagulant absorption or metabolism may further increase local gastrointestinal exposure, potentiating the risk.[21] In contrast, intracranial hemorrhage in males may be attributable to a higher prevalence of cerebrovascular risk modifiers such as hypertension, smoking, and alcohol consumption, as well as sex-specific differences in vascular structure and cerebral autoregulation.[22] Clinically, these observations highlight the importance of tailoring anticoagulation management not only according to overall bleeding risk but also to sex-specific bleeding patterns. Enhanced vigilance for gastrointestinal hemorrhage, particularly in older, multimorbid, or polypharmacy-exposed female patients, and stricter monitoring for intracranial complications in males may meaningfully improve the safety of DOAC therapy.

In the study, PE reports were most frequently observed among individuals using dabigatran. The use of dabigatran at lower doses in clinical practice due to bleeding concerns suggests that this finding may be related to relatively reduced anticoagulant efficacy.[18] Among the DOACs, edoxaban had the highest reporting rate for MI. Comparative studies in the literature indicate that edoxaban carries an MI risk similar to warfarin.[23] All DOACs demonstrated an increased signal for MI AEs compared with dabigatran, a finding that is inconsistent with clinical trials conducted in atrial fibrillation (AF) populations.[24] This discrepancy may stem from the fact that the study, unlike clinical trials, evaluated all AEs without any distinction of age, indication, or comorbidity. National registry studies such as the TRAFFIC registry from Türkiye are expected to contribute to the interpretation of these findings, providing more contemporary insights into AF management and anticoagulant safety.[25] Ischemic stroke was most reported in patients using apixaban and rivaroxaban. However, previous clinical trials suggest that both drugs reduce the risk of ischemic stroke and improve prognosis compared to warfarin.[26]

Sex-based assessments revealed that DVT was reported significantly more often in males, whereas PE was more commonly reported in females among patients using rivaroxaban. Males have a greater disposition to DVT, while females exhibit a comparatively higher incidence of PE due to hormonal factors. Furthermore, the elevated PE reporting rate among females may be partially related to suboptimal anticoagulation, given the tendency in clinical practice to prescribe lower anticoagulant doses to females.[27] There were no significant sex differences for PE and DVT reporting with the other DOACs. Across all DOACs, MI AEs were reported more frequently in male patients, a trend consistent with overall clinical observations in the literature.[28] In contrast, it is noteworthy that ischemic stroke was more frequently reported in female patients using rivaroxaban. Rivaroxaban is largely excreted by the renal route, suggesting that pharmacokinetic differences between the sexes may contribute to this pattern. Reduced creatinine clearance, particularly common in older females, may impair drug elimination, potentially leading to subtherapeutic anticoagulation and an increased risk of thromboembolic events.[29] These findings suggest that sex-specific differences should be considered in anticoagulant therapy and dosage adjustments should be based on an individualized approach.

It is important to recognize that the sex-related differences in AE reporting observed in this study may reflect not only underlying biological mechanisms but also variations in prescribing practices, dose selection, treatment intensity, or comorbidity patterns across sexes. Such clinical practice-related trends may influence the apparent dominance of certain AEs in 1 sex. By examining sex-based safety patterns among DOACs using FAERS data up to 2024, this study provides a novel and timely contribution to the literature.

Study Limitations

This study has several limitations inherent to disproportionality analyses based on ROR methodology. Such analyses are subject to reporting biases, incomplete or missing data, exclusion of healthy populations, lack of denominator information, and potential confounding factors. Although reliance on healthcare professional reports may reduce bias, indication-specific information for DOAC use was missing in many cases. Moreover, because prescription data were not available, AE reports could not be normalized to the actual number of drug users. Furthermore, the sex of patients was not specified in more than 50% of edoxaban reports, a limitation that substantially restricted sex-based subgroup analyses for this agent. Finally, the ROR provides only an approximate estimate of disproportionality intended to generate hypotheses regarding potential safety signals; it does not allow for causal interference or direct comparison of risk between drugs.

CONCLUSION

In this study, gastrointestinal hemorrhage emerged as the most frequently reported hemorrhagic AE, particularly among females using dabigatran, whereas intracranial hemorrhage was more commonly reported in males, especially those treated with dabigatran and rivaroxaban. Among thrombotic events, MI and DVT were reported more often in males, while PE and ischemic stroke were reported at higher rates in females, particularly those receiving rivaroxaban. These findings indicate that the evaluation of AE profiles associated with DOACs by sex, organ systems, and other factors may enhance the clinical decision-making process. When developing individualized anticoagulant therapy regimens, physicians may benefit from considering the relationship between sex and system-specific AEs.

Data Availability Statement: The data underlying this article are publicly available from the FDA Adverse Event Reporting System (FAERS): https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard (Accessed August 31, 2025)

Ethics Committee Approval: Not applicable. This study was based on publicly available, de-identified data from a spontaneous reporting system and did not involve human or animal research requiring ethical approval.

Informed Consent: As this research is based on publicly available, de-identified data obtained from the FAERS spontaneous reporting system, it does not involve direct patient participation. Therefore, obtaining verbal or written informed consent from patients is not required.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Ş., E.A.; Design – M.Ş., B.Ş.; Supervision – E.A., M.Ş.; Resources – B.Ş., E.A.; Materials – M.Ş., B.Ş.; Data Collection and/or Processing – M.Ş., B.Ş.; Analysis and/or Interpretation – M.Ş., E.A.; Literature Search – M.Ş., B.Ş.; Writing – M.Ş., E.A.; Critical Review – E.A., B.Ş.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

Statement on Use of AI-Assisted Technologies: Artificial intelligence tools (ChatGPT, OpenAI) were used solely for grammar and language editing. All content was reviewed and verified by the authors, who take full responsibility for the manuscript.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Neutrophil Percentage-to-Albumin Ratio as a Novel Predictor of Diuretic Resistance and Mortality in Patients with Heart Failure with Preserved Ejection Fraction

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as a systemic inflammatory and metabolic disorder. Diuretic resistance remains a major therapeutic challenge in this population. The neutrophil percentage-to-albumin ratio (NPAR), a novel marker of systemic inflammation, may serve as a predictor of diuretic resistance and adverse outcomes in HFpEF.

Methods: This retrospective cohort study included 1487 HFpEF patients treated between January 2017 and August 2022. Patients were divided into 2 groups: those with and without diuretic resistance. Clinical, laboratory, and echocardiographic parameters were compared between groups. Receiver-operating characteristic (ROC) analysis, logistic regression, and Kaplan–Meier survival analyses were used to determine predictive and prognostic factors.

Results: Patients with diuretic resistance exhibited significantly higher NPAR values, H_2FPEF scores, NT-proBNP levels, and echocardiographic indices of diastolic dysfunction. ROC analysis identified an NPAR cut-off of 13.98 for predicting diuretic resistance (AUC = 0.892, 95% CI: 0.741-0.993, $P < .01$). Multiple Cox's proportional hazard regression analysis revealed that NPAR, hs-C-reactive protein, sodium, NT-proBNP, left atrial volume index, and E/e′ were independent predictors of diuretic resistance. Kaplan–Meier analysis demonstrated increased mid-term mortality in patients with NPAR > 13.98 (log-rank $P < .001$). Elevated NPAR independently predicted mortality in the diuretic-resistant HFpEF subgroup (OR = 1.95, 95% CI: 1.80-2.22, $P < .001$).

Conclusion: NPAR is a simple and accessible inflammatory biomarker that independently predicts diuretic resistance and mortality in HFpEF. The findings underscore the role of systemic inflammation in HFpEF pathophysiology and highlight NPAR as a potential tool for early risk stratification and therapeutic decision-making.

Keywords: Diuretic resistance, heart failure with preserved ejection fraction, neutrophil-to-albumin ratio, systemic inflammation

ORIGINAL INVESTIGATION

INTRODUCTION

Heart failure (HF) is a common clinical syndrome with rising prevalence, particularly in older adults.[1] In contemporary cohorts, heart failure with preserved ejection fraction (HFpEF) constitutes a substantial proportion of HF presentations[2] and is diagnosed according to current European Society of Cardiology (ESC) criteria.[3]

Congestion is the leading cause of hospitalization in acute decompensated HF, and diuretics remain the cornerstone of symptomatic relief.[4] However, epidemiological studies indicate that diuretic resistance develops in approximately 20-35% of HF patients.[5] Although HFpEF has historically been considered to have a better prognosis than HFrEF, most observational studies suggest that this difference is not significant.[6]

Beyond hemodynamic impairment, HFpEF is increasingly viewed as a systemic inflammatory state in which comorbidity-driven microvascular endothelial inflammation contributes to myocardial dysfunction and progression of

Sefa Erdi Ömür
Kayıhan Karaman
Çağrı Zorlu
Gülşen Genç Tapar

Department of Cardiology, Tokat Gaziosmanpaşa University, Tokat, Türkiye

Corresponding author:
Sefa Erdi Ömür
✉ sefaerdi61@gmail.com

Received: October 10, 2025
Accepted: January 12, 2026
Available Online Date: February 20, 2026

Cite this article as: Ömür SE, Karaman K, Zorlu Ç, Tapar Genç G. Neutrophil percentage-to-albumin ratio as a novel predictor of diuretic resistance and mortality in patients with heart failure with preserved ejection fraction. *Anatol J Cardiol.* 2026;30(3):174-183.

10.14744/AnatolJCardiol.2026.5893

symptoms. In line with this concept, readily available hemogram-derived inflammatory indices—such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio—have been proposed as practical markers of subclinical inflammation and have shown prognostic value in HF.[7,8]

More recently, the neutrophil percentage-to-albumin ratio (NPAR) has emerged as a simple composite biomarker integrating an inflammatory component and a negative acute-phase reactant and has been associated with adverse outcomes across cardiovascular conditions.[9-12] However, data regarding the value of NPAR for identifying diuretic resistance and related prognosis specifically in HFpEF are limited. Therefore, this study was designed to investigate the relationship between systemic inflammation and diuretic resistance in HFpEF using NPAR as an inflammatory marker.

METHODS

A total of 1927 HFpEF patients receiving regular HF maintenance treatment in the cardiology department of the local cardiology hospital between January 2017 and August 2022 were included in the study. A total of 440 patients were excluded from the study due to missing data (Flowchart, Supplementary Material). This was a single-center retrospective cohort study conducted in the cardiology department of a tertiary referral cardiology hospital. The study complies with the principles outlined in the Declaration of Helsinki. No funding was received for the study from any institution or organization. The study was approved by the Ethics Committee of the local university hospital (25-MOBAEK-144, Date: 22.04.2025). The study did not receive financial support (no funding) from any institution or organization. Artificial intelligence–supported technologies [such as Large Language Models (LLM), chatbots, or image generators] were not used in the production of the study.

HIGHLIGHTS

- The neutrophil percentage-to-albumin ratio (NPAR) was significantly higher in heart failure with preserved ejection fraction (HFpEF) patients with diuretic resistance, indicating a strong link between systemic inflammation and poor diuretic response.
- The NPAR ≥13.98 predicted diuretic resistance with 86% sensitivity and 85% specificity (AUC = 0.892, $P < .01$), demonstrating its potential as a reliable clinical marker.
- Elevated NPAR levels were independently associated with increased all-cause mortality in HFpEF, even after adjustment for NT-proBNP, hs-CRP, and echocardiographic parameters.
- Multiple Cox's proportional hazard regression analysis confirmed that NPAR remained an independent predictor of mid-term mortality (HR = 1.62, $P < .001$, 95% CI = 1.31-1.94).
- The NPAR may serve as a simple, inexpensive, and accessible biomarker for identifying high-risk HFpEF patients and guiding early management strategies.

Patients were included in the study by searching the local hospital system database. Data were determined from institutional electronic health records, including laboratory results (serum sodium, creatinine/estimated glomerular filtration rate (eGFR), spot urine sodium), medication administration records (loop diuretic dose increases, metolazone use, IV inotropes), and inpatient clinical documentation. For each potentially eligible case, the diagnosis of HFpEF was confirmed by reviewing echocardiography reports and relevant clinical data. Patients with missing baseline variables were excluded as shown in the study flowchart. The inclusion period corresponded to the entire database search interval (January 2017-August 2022). The authors included consecutive adult patients hospitalized for worsening HF (index hospitalization) who met diagnostic criteria for HFpEF (LVEF ≥50%) according to contemporary ESC (3). Outpatient clinic visits were not used as an index event; outpatient data were considered only for baseline history and for routine post-discharge follow-up documentation when available. Patients with HFpEF were classified into diuretic-resistant and non–diuretic-resistant groups based on predefined criteria, and all-cause mortality was assessed retrospectively from existing records. Diuretic resistance was defined as the presence of one or more (≥1) of the following during the index hospitalization: hyponatremia, requirement to increase the daily furosemide-equivalent dose to >160 mg/day and/or add metolazone, spot urine sodium <50 to 70 mmol/L measured after diuretic administration (when available), worsening renal function (creatinine increase ≥0.3 mg/dL within 48-72 h or ≥25% from baseline), and need for IV inotropic therapy.[13,14]

Acute infection or sepsis, pulmonary embolism, severe valve disease (moderate mitral stenosis and all other severe valve diseases and prosthetic valve disease), malignancy, coagulation disorder, patients under 18 years of age, acute or chronic stroke, storage diseases (glycogen, lipid, lysosomal, etc.), acute kidney disease, mechanical valve, end-stage renal disease, severe anemia, patients with recent acute coronary syndrome (first 6 months) were excluded from the study.

Laboratory and Demographic Examination

All blood samples were obtained from peripheral venous blood after patients were hospitalized with worsening HF. Lipid panel, fasting plasma glucose, creatine kinase myocardial band (CK-MB), troponin-I, NT-proBNP (ng/mL), hs-C-reactive protein (CRP), and other routine parameters were obtained from the blood samples. Complete blood count (CBC) was evaluated with an automatic blood cell counter (Coulter LH 780 Hematology Analyzer, Beckman Coulter Corp, Hileh, Florida, USA). Patients with fasting plasma glucose level >125 mg/dL, HbA1c level >6.5%, or using antidiabetic drugs (oral/insulin) were considered as diabetes mellitus (DM) patients. Patients with low-density lipoprotein cholesterol (LDL-C) level above 100 mg/dL or using antilipidemic drugs were considered as hyperlipidemia (HL) patients. Use of antihypertensive drugs or systolic and diastolic blood pressures above 140-90 mm Hg were considered as hypertension (HT). Patients who had smoked for the last 6 months were considered as smokers.

Echocardiographic Evaluation

Echocardiographic evaluations were performed in the ECHO unit of the center with the Vivid S5 ECHO device (General Electric, Milwaukee, WI, USA) using a 2.5-3.5 MHz transducer in the left decubitus position for all participants. All Doppler ECHO and Tissue Doppler Imaging (TDI) ECHO measurements were performed during normal breathing. Data obtained with 2-dimensional, color Doppler, continuous wave (CW)/pulsed wave (PW) Doppler ECHO were examined and recorded by 3 experienced echocardiographers who were unaware of the participants. The left ventricular ejection fractions (LVEF) of all participants were calculated using the modified Simpson's method.

From the parasternal long axis view; left atrium (LA), left ventricular end diastolic diameter (LVDD), left ventricular end systolic diameter (LVSD), left ventricular posterior wall thickness (LVPWT), interventricular septum in diastole (IVSD) measurements were performed. LA volume was measured by planimetrically drawing the left atrium borders from standard apical 2- and 4-chamber views at the end of systole. Left atrium (LA) volume was divided by body surface area to obtain left atrial volume index (LAVI). Estimated systolic pulmonary artery pressure (sPAP) was calculated based on the tricuspid regurgitation pressure gradient calculated from the peak tricuspid regurgitation flow velocity using the Bernoulli equation. Transmitral early diastolic flow velocity (E) was measured in the apical 4-chamber view by pulsed-wave Doppler with the sample volume placed at the tips of the mitral leaflets. Early diastolic mitral annular velocity (e′) was assessed using TDI in the apical 4-chamber view, positioning the sample volume at the septal or lateral mitral annulus. The E/e′ ratio was calculated as an estimate of left ventricular filling pressure.

Follow-Up

Patients were followed for a mean duration of 8.3 ± 2.1 months. Two investigators abstracted baseline characteristics and in-hospital endpoints from electronic records using a standardized data collection form. Follow-up duration was calculated from the date of index admission/discharge. Post-discharge information at approximately 1, 3, 6, and 12 months was ascertained retrospectively from documentation available in the electronic medical record, including routine outpatient clinic visits and telephone contacts performed as part of standard clinical care. Mortality status and dates were obtained from institutional records (and linked registries when available). No study-driven follow-up contact was performed. All clinical endpoints were independently adjudicated in a blinded manner by 2 members of the event adjudication committee.

Statistical Analysis

The data obtained from the study were evaluated with SPSS 25.0 (SPSS, Inc., Chicago, IL, USA) program. For statistical significance, $P \leq .05$ was taken as the test. Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were summarized as mean ± standard deviation and compared with *t*-test. Those without normal distribution were presented as median (interquartile range) and compared with Mann-Whitney U-test. Categorical variables were presented as frequency (percentage) and compared using χ^2 test and Fisher's exact tests. The best cut-off values of NPAR were calculated using the ROC curve analysis. The best cut-off value obtained from the ROC curve of NPAR was taken as the cut-off value for categorizing NPAR values as high and low. Univariate logistic regression analysis was performed to determine the predictors of mortality in HFpEF patients with diuretic resistance. Variables that were significant in the univariate logistic regression analysis ($P < .05$) were included in the Multiple Cox's regression analysis. The results of the logistic analysis were presented as Odds Ratio (OR) and 95% CI. Kaplan-Meier survival curve was used to examine the difference in event-free survival rates between the groups and statistical significance was determined using the log-rank test. The proportional hazards assumption was assessed using Schoenfeld residuals and was not violated. A Multiple Cox's proportional hazard regression analysis was performed to assess the independent prognostic significance of the NPAR on mid-term mortality. Time to event was defined from the index admission date until death or last follow-up, and survivors were censored at last contact. A modeling system was constructed for this purpose. The modeling was constructed in 3 separate hierarchical steps to allow parsimonious adjustment for potential confounders. Model 1 included demographic variables (age and sex). Model 2 further adjusted for major prognostic comorbidities and laboratory parameters, including HT, DM, estimated glomerular filtration rate (eGFR), serum sodium, serum albumin, and atrial fibrillation. Model 3, the fully adjusted model, included cardiac and inflammatory markers (NT-proBNP, hs-CRP, LAVI, E/e′ ratio, sPAP, H_2FPEF score, and diuretic resistance status). NPAR was analyzed both as a continuous variable and as a dichotomous variable using the receiver operating characteristic (ROC)-derived cutoff of 13.98. Hazard ratios (HR) and 95% cCI were calculated. Nonlinear associations between NPAR and mortality risk were further explored using restricted cubic spline analysis. A 2-sided $P < .05$ was considered statistically significant.

RESULTS

During the study period (January 2017-August 2022), 1927 HFpEF patients were screened. After excluding 440 patients due to missing data, 1487 patients constituted the final study cohort. Among these, 248 patients met the definition of diuretic resistance, whereas 1239 did not. Basic demographic, clinical, and laboratory characteristics, echocardiographic results, and medications used by the patients included in the study are detailed in Table 1. H_2FPEF score and NPAR were found to be statistically higher in the diuretic resistant group. Routine blood tests; neutrophil percentage, ALT, AST, hs-CRP, troponin, NT-proBNP; echocardiographic parameters; sPAP, LVDD, LA, LAVI, LVPWT, IVSD, E/e′, and medication; carbonic anhydrase inhibitors use were found to be significantly higher in the diuretic resistant group compared to the other group. Albumin, sodium level, and LVEF were significantly higher in the non-diuretic resistant group compared to the other group.

Table 1. Baseline Demographic, Clinical, Laboratory, and Echocardiographic Characteristics of HFpEF Patients According to Diuretic Resistance Status

Variables	Diuretic Resistant (n = 248)	No Diuretic Resistant (n = 1239)	*P*
Age (mean ± SD)	62.34 ± 11.30	61.91 ± 10.87	.552
Gender (female, n%)	144 (58.06)	720 (58.11)	.794
BMI (mean ± SD)	33.25 ± 4.80	31.29±3.44	.053
DM n (%)	63 (25.40)	312 (25.18)	.530
HT n (%)	148 (59.67)	743 (59.96)	.188
HL n (%)	61 (24.5)	310 (25.02)	.804
COPD n (%)	37 (14.9)	165 (13.31)	.637
AF n (%)	122 (49.19)	609 (49.15)	.997
Current Smoker n (%)	38 (15.32)	186 (15.01)	.883
Previous myocardial infarction n (%)	92 (37.09)	459 (37.04)	.795
H_2FPEF score	7.01 ± 0.88	6.05 ± 0.91	.035
NPAR	16.83 ± 2.08	14.92 ± 2.13	< .001
Hematological results			
Creatinine (mg/dL)	1.35 ± 0.71	1.33 ± 0.69	.559
eGFR (mL/dk/1.73 m^2)	58.41 ± 12.47	59.18 ± 12.09	.473
Hemoglobin (g/dL)	10.30 ± 1.33	10.82 ± 1.20	.704
Hematocrit value	35.52 ± 9.57	35.79 ± 8.93	.507
Platelet (X10^3/μL)	258.36 ± 12.33	259.51 ± 11.34	.768
Neutrophil percentage (%)	68.66 ± 10.52	55.41 ± 10.79	< .001
TSH (ng/dL)	2.13 ± 0.51	2.09 ± 0.48	.617
T4 (ng/dL)	1.55 ± 0.21	1.59 ± 0.32	.580
Albumin (g/dL)	2.10 ± 0.92	4.33 ± 0.91	< .001
Total cholesterol (mg/dL)	219.17 ± 32.17	222.89 ± 30.71	.594
LDL cholesterol(mg/dL)	122.31 ± 20.12	125.03 ± 19.94	.761
ALT (U/L)	62.31 ± 10.71	55.13 ± 9.83	< .001
AST (U/L)	51.39 ± 9.71	45.12 ± 8.09	< .001
Sodium (mmol/L)	128.31 ± 13.70	134.88 ± 12.73	< .001
Potassium(mmol/L)	4.92 ± 1.37	4.53 ± 1.06	.052
Magnesium (mg/dL)	2.14 ± 0.78	2.11 ± 0.66	.329
hs-CRP (mg/L)	35.57 ± 12.70	28.32 ± 10.34	< .001
Troponin (ng/mL)	62.72 ± 13.61	42.52 ± 11.13	< .001
NT-proBNP (ng/mL)	2471 ± 357.46	1539 ± 210.41	< .001
Echocardiographic findings			
LVEF (%)	53.14 ± 2.17	55.22 ± 3.41	.031
LVDD (mm)	51.26 ± 2.36	50.51 ± 2.29	.018
LVSD (mm)	36.47 ± 3.28	35.51 ± 2.79	.059
LA size (mm)	5.29 ± 1.06	4.52 ± 0.41	< .001
LAVI (ml/m^2)	48.91 ± 2.13	46.81 ± 1.85	< .001
LVPWT (mm)	12.21 ± 1.31	11.13 ± 0.84	.029
IVSD (mm)	13.09 ± 1.11	11.29 ± 0.79	.017
E/e'	14.52 ± 1.37	13.05 ± 1.28	.022
sPAP (mm Hg)	45.21 ± 3.70	42.32 ± 2.89	< .001
Medication			
ACE, ARB n (%)	138 (55.64)	682 (55.04)	.664
B blocker n (%)	152 (61.29)	756 (61.01)	.537
Furosemid n (%)	232 (93.54)	1155 (93.22)	.834
Spironolactone/eplerenone n (%)	103 (41.53)	508 (41.00)	.758
Thiazides n (%)	130 (52.41)	645 (52.05)	.349

(*Continued*)

Table 1. Baseline Demographic, Clinical, Laboratory, and Echocardiographic Characteristics of HFpEF Patients According to Diuretic Resistance Status (*Continued*)

Variables	Diuretic Resistant (n = 248)	No Diuretic Resistant (n = 1239)	*P*
Thiazide-like agents n (%)	28 (11.29)	138 (11.13)	.618
Carbonic anhydrase inhibitors n (%)	155 (62.50)	21 (1.69)	< .001
SGLT2 inhibitors n (%)	54 (21.77)	262 (21.14)	.553
Anticoagulant n (%)	126 (50.80)	622 (50.20)	.827
Digoksin n (%)	49 (19.75)	237 (19.12)	.223
ASA n (%)	40 (16.80)	201 (16.22)	.307
Ultrafiltration therapy, n (%)	148 (59.67)	39 (3.14)	< .001
IV inotropic therapy, n (%)	152 (61.29)	35 (2.82)	< .001

Values are presented as mean ± SD for continuous variables and n (%) for categorical variables. Percentages are column percentages.
ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; dL, deciliter; dk, minute; DM, diabetes mellitus; g, gram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HL, hyperlipidemia; HPL, hyperlipidemia; HT, hypertension; IVSD, interventricular septal diameter; LA, left atrium; LAVI, left atrial volume index; LDL, low-density lipoprotein; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVPWT, left ventricular posterior wall thickness; LVSD, left ventricular end-systolic diameter; m, meter; mg, milligram; mmol, millimole; mm, millimeter; mm Hg, millimeters of mercury; mL, milliliter; µL, microliter; NPAR, neutrophil percentage-to-albumin ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; TSH, thyroid-stimulating hormone; U, unit; WBC, white blood cell count.

In ROC analysis, the cut-off value of NPAR score for diuretic resistance in HFpEF was determined as 13.98 with 86% sensitivity and 85% specificity (AUC = 0.892, 95% CI = 0.741–0.993, $P < .01$) (Figure 1). Multiple Cox's regression analysis revealed that H_2FPEF score, LA size, LAVI, E/e', Sodium, hs-CRP, NT-proBNP, and NPAR were independent potential predictors of HFpEF diuretic resistance (Table 2).

Kaplan–Meier cumulative survival curves showed that the risk of mortality was increased in patients with HEpEF and NPAR > 13.98 compared to patients with NPAR < 13.98 (log-rank test: $P < .001$) (Figure 2). Multiple Cox's proportional hazard regression analysis for NPAR levels associated with mid-term mortality is presented in Table 3. NPAR was found to be an independent predictor of mid-term mortality in HFpEF patients with diuretic resistance [Odds ratio (OR) = 1.952, $P < .001$, 95% CI: 1.803-2.224].

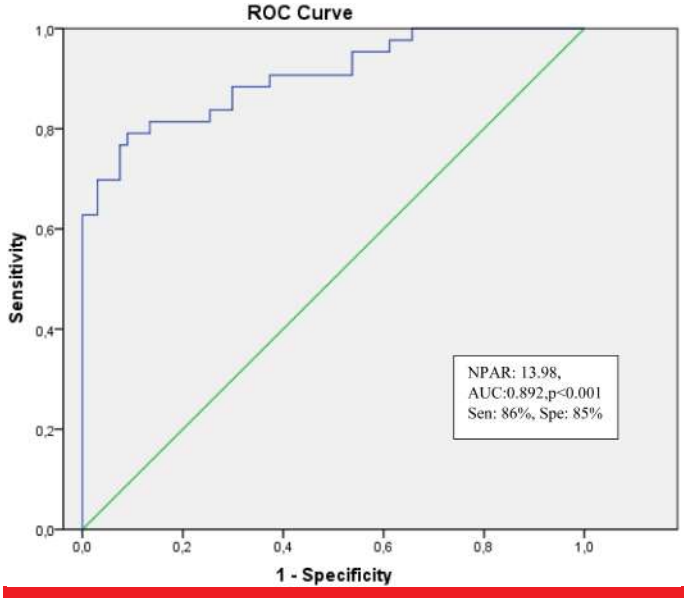

Figure 1. ROC curve of NPAR in predicting diuretic resistance in patients with HF

Multiple Cox's regression analysis was conducted to determine the independent predictors of all-cause mortality in patients with HFpEF (Table 4). In univariate analysis, higher NPAR levels were significantly associated with increased risk of mortality (HR = 1.93, $P < .001$, 95% CI: 1.68-2.20). After adjusting for demographic and clinical parameters in Model 2, the association remained robust (HR = 1.71, $P < .001$, 95% CI: 1.45-2.01). In the fully adjusted Model 3, which incorporated echocardiographic and laboratory parameters, NPAR persisted as an independent predictor of mortality (HR = 1.62, $P < .001$, 95% CI: 1.31-1.94). Among other variables, higher NT-proBNP, elevated hs-CRP, increased LAVI, higher E/e' ratio, and presence of diuretic resistance were also significantly associated with increased mortality. Conversely, higher serum sodium and albumin levels were found to be protective factors. This Figure 3 demonstrates the adjusted hazard ratios and 95% confidence intervals for the variables included in the Multiple Cox's proportional hazard regression analysis model.

Among the 248 patients classified as diuretic-resistant, the frequency of each component criterion is summarized in Table 5. The most common components were hyponatremia (Na <135 mmol/L; 92/248, 37.1%) and loop diuretic escalation to >160 mg/day furosemide-equivalent (71/248, 28.6%), whereas post-diuretic spot urine sodium was available in 120 patients.

DISCUSSION

In this study, it was aimed to demonstrate the association between diuretic-resistance and systemic inflammation in patients with HFpEF using NPAR. NPAR was found to be significantly higher in the group with diuretic-resistance. The findings suggest that the risk of developing diuretic-resistance increases in parallel with rising NPAR levels. Therefore, the authors conclude that heightened systemic

Table 2. Univariate and Multiple Cox Regression to Identify Independent Predictors in Heart Failure Patients

Variables	Univariate Analysis OR (95% CI)	*P*	Multiple Analysis OR (95% CI)	*P*
H_2FPEF score	1.128 (1.012-1.259)	.030	1.104 (1.018-1.231)	.021
LVEF (%)	0.879 (0.759-0.987)	.034	0.861 (0.751-0.963)	.041
LVDD (mm)	1.089 (1.012-1.178)	.024	1.057 (1.009-1.132)	.038
LA size (mm)	1.351 (1.141-1.451)	< .001	1.228 (1.097-1.341)	.026
LAVI (mL/m^2)	1.293 (1.112-1.412)	< .001	1.182 (1.045-1.263)	.029
E/e′	1.187 (1.092-1.341)	.018	1.123 (1.044-1.219)	.036
sPAP (mm Hg)	1.271 (1.149-1.418)	< .001	1.134 (1.052-1.301)	.020
Sodium (mmol/L)	1.257 (1.097-1.340)	< .001	1.127 (1.043-1.249)	.018
hs-CRP (mg/L)	1.371 (1.207-1.501)	< .001	1.201 (1.081-1.327)	.042
NT-proBNP (ng/mL)	1.288 (1.121-1.396)	< .001	1.158 (1.043-1.271)	.025
NPAR	2.544 (1.982-3.216)	< .001	2.236 (1.812-2.962)	< .001
ALT (U/L)	1.021 (0.971-1.064)	.338	1.015 (0.956-1.078)	.462
AST (U/L)	1.028 (0.982-1.071)	.212	1.019 (0.962-1.082)	.295
Troponin (L)	1.094 (0.918-1.281)	.286	1.068 (0.911-1.245)	.341
IVSD (mm)	1.048 (0.974-1.123)	.214	1.029 (0.948-1.117)	.311
LVPWT (mm)	1.052 (0.991-1.141)	.072	1.036 (0.961-1.124)	.198
Hemoglobin (g/dL)	0.973 (0.927-1.018)	.216	0.982 (0.931-1.027)	.283
Age (years)	1.014 (0.994-1.036)	.164	1.008 (0.981-1.032)	.372

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; IVSD, interventricular septal diameter; LA, left atrial; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVPWT, left ventricular posterior wall thickness; NPAR, neutrophil percentage-to-albumin ratio; OR, odds ratio; sPAP, systolic pulmonary artery pressure.

inflammation may pave the way for the development of diuretic-resistance.

Beyond its relationship with diuretic resistance, the extended analysis revealed that elevated NPAR independently predicted all-cause mortality in patients with HFpEF. Multiple Cox's proportional hazard regression analysis modeling demonstrated that NPAR remained a strong and independent prognostic factor even after adjusting for age, comorbidities,

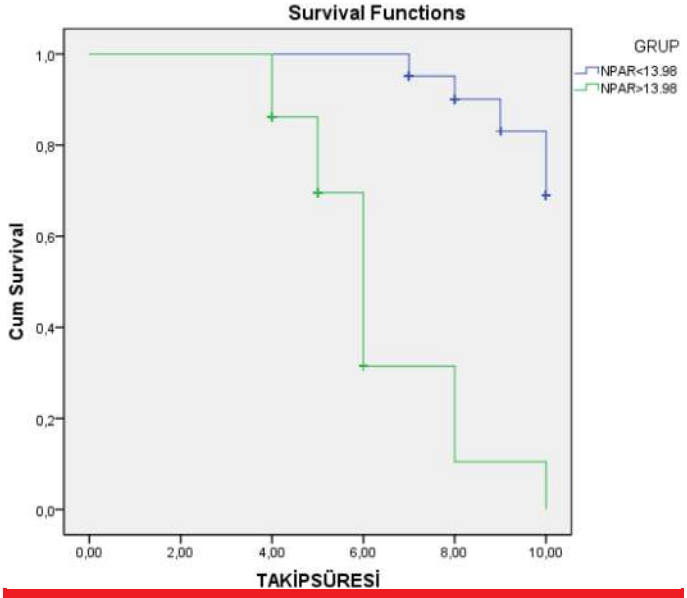

Figure 2. Kaplan–Meier survival curve analysis showing the association between NAPR and mortality in patients with diuretic resistance

NT-proBNP, hs-CRP, echocardiographic parameters (LAVI, E/e′, sPAP), and diuretic resistance status. This indicates that the systemic inflammatory burden quantified by NPAR not only contributes to treatment resistance but also carries mid-term prognostic significance. Importantly, NPAR values above the identified cut-off (13.98) were associated with almost a 2-fold increase in mortality risk, underscoring its clinical relevance in the risk stratification of HFpEF.

HFpEF accounts for more than half of all HF cases in individuals aged over 65 years.[15] Comorbid conditions such as advanced age, HT, DM, obesity, and atrial fibrillation contribute to the pathophysiology of HFpEF by promoting low-grade systemic inflammation.[16,17] Consequently, HFpEF is now regarded not only as a disease characterized by diastolic dysfunction but also as a multisystem syndrome underpinned by inflammation.[17]

Systemic inflammation plays an increasingly recognized role in the pathophysiology of both HFrEF and HFpEF. Neutrophils, one of the key cellular markers of inflammation,

Table 3. Hazard Ratios Based on Cox Regression Models to Estimate the Effects of NPAR, NT-proBNP, E/e′, and LA Size on Mid-Term Mortality in Patients with HFpEF and Diuretic Resistance

Variables	Hazard Ratio (95% CI)	*P*
NPAR	1.952 (1.403-2.224)	< .001
NT-proBNP	1.213 (1.052-1.552)	.008
E/e′	1.139 (0.893-1.213)	.117
LA size (mm)	1.104 (0.937-1.217)	.204

NPAR, neutrophil percentage-to-albumin ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide; LA, left atrium.

Table 4. Multiple Cox Proportional Hazards Models for All-Cause Mortality

Variables	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Model 3 HR (95% CI)	*P*
NPAR (per 1 unit)	1.93 (1.68-2.20)	< .001	1.71 (1.45-2.01)	< .001	1.62 (1.31-1.94)	< .001
Age (per year)	1.03 (1.01-1.06)	.004	1.02 (1.00-1.04)	.021	1.01 (0.99-1.03)	.162
Male sex	1.12 (0.82-1.54)	.459	1.07 (0.79-1.47)	.639	1.09 (0.78-1.52)	.612
Hypertension	—	—	1.18 (0.87-1.59)	.283	1.11 (0.80-1.54)	.537
Diabetes mellitus	—	—	1.34 (1.02-1.78)	.039	1.29 (0.97-1.73)	.081
Sodium (per 1 mmol/L)	—	—	0.96 (0.94-0.98)	.001	0.97 (0.95-0.99)	.004
Albumin (per 1 g/dL)	—	—	0.81 (0.69-0.95)	.009	0.84 (0.72-0.98)	.026
NT-proBNP (per 100 ng/mL)	—	—	—	—	1.12 (1.04-1.21)	.002
hs-CRP (per mg/L)	—	—	—	—	1.05 (1.02—-1.09)	.003
LAVI (per mL/m^2)	—	—	—	—	1.03 (1.01-1.05)	.018
E/e′ ratio (per unit)	—	—	—	—	1.04 (1.01-1.07)	.012
sPAP (per mm Hg)	—	—	—	—	1.02 (1.00-1.04)	.046
H_2FPEF score	—	—	—	—	1.09 (1.02-1.16)	.008
Diuretic resistance	—	—	—	—	1.78 (1.21-2.61)	.004

CI, Confidence interval; CRP, C-reactive protein; E/e′, mitral inflow to annular velocity ratio; HR, Hazard ratio; LAVI, Left atrial volume index; sPAP, systolic pulmonary artery pressure.

are associated with coronary artery disease, HF, and stroke. They contribute to myocardial injury through proteolytic enzymes such as elastase and myeloperoxidase.[18-20] Neutrophil activation promotes the release of proinflammatory cytokines including CRP, TNF-α, IL-1, and IL-6, leading to impaired cardiac function and increased cardiovascular mortality.[21,22]

Our results support this mechanistic link, demonstrating that higher hs-CRP and NT-proBNP levels, alongside elevated NPAR, were significant predictors of mortality. This finding aligns with previous evidence that inflammatory and neurohormonal activation synergistically contribute to disease progression and poor outcomes in HFpEF. The inclusion of echocardiographic parameters such as LAVI and E/e′ in the model further confirms that both structural and inflammatory factors interact to influence mid-term prognosis.

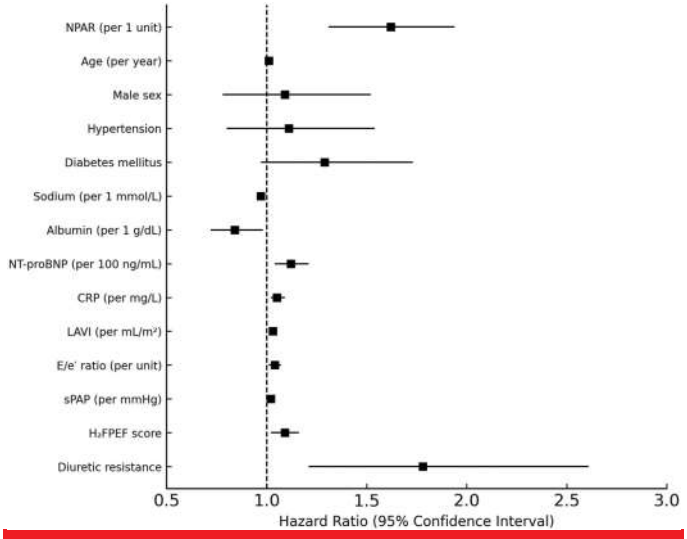

Figure 3. Forest plot of adjusted hazard ratios (HR) and 95% CI for all-cause mortality in HFpEF patients

Diuretic-resistance in HFrEF is a multifactorial process that often reflects disease progression. Previous studies have shown that a high diuretic requirement due to diuretic-resistance is associated with increased mortality and sudden death in HFrEF patients.[23,24] Impaired renal perfusion, secondary to reduced cardiac output and elevated central venous pressure, diminishes the pressure gradient across the kidneys and limits natriuresis. Additionally, activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system enhances sodium reabsorption in the distal tubules, reducing diuretic efficacy and necessitating dose escalation.[25-27] Although diuretic resistance has been extensively described in HFrEF, it is also highly relevant in HFpEF, where congestion-driven admissions are common and impaired natriuresis may be observed despite high-dose loop diuretics, particularly in patients with concomitant chronic kidney disease. Contemporary reports indicate that resistance to high-dose loop diuretics can be frequent in hospitalized HFpEF populations, underscoring the need for practical markers that capture treatment non-response early during decongestion.[28]

While many causes can explain diuretic resistance in HFrEF patients, it has been reported that comorbid conditions play a role in HFpEF patients.[25] In obesity and metabolic syndrome, adipokines released from adipose tissue trigger proinflammatory cytokine production, while hypertension brings about vascular inflammation and decreased nitric oxide bioavailability. In diabetes, advanced glycation end products initiate vascular and myocardial inflammatory processes.[16,17] For these reasons, HFpEF has recently begun to be considered a systemic inflammatory and metabolic syndrome.[29]

Many studies have shown an increased proinflammatory state in patients with HFpEF.[17] Some inflammatory markers have been suggested to have predictive and prognostic value for HF. Pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 released from inflammatory cells activate inflammatory

Table 5. Components of the Diuretic-Resistance Definition Among Patients Classified as Diuretic-Resistant (n = 248)

Component Criterion (Index Hospitalization)	Data Source (Retrospective Ascertainment)	n / 248	%
Hyponatremia (Na <135 mmol/L)	Lab (serum sodium)	92 / 248	37.1
Loop diuretic escalation (>160 mg/day furosemide)	Medication orders + MAR	71 / 248	28.6
Additional metolazone use	Medication orders + MAR	54 / 248	21.8
Low post-diuretic spot urine sodium (<50 to 70 mmol/L)*	Lab (spot urine sodium after diuretic)	33 / 120	27.5
Worsening renal function (Cr ↑ ≥0.3 mg/dL within 48-72 hour)	Serial creatinine/eGFR	65 / 248	26.2
Need for IV inotropic therapy	MAR/ICU-ward orders	18 / 248	7.3

*Due to the retrospective cohort study design, spot urine sodium was not available in all patients; percentages for this component were calculated among patients with available measurements (n = 120).
Diuretic resistance was defined as the presence of ≥1 component criterion.
eGFR, estimated glomerular filtration rate; ICU, intensive care unit; MAR, Medication Administration Record.

signaling pathways in both cardiomyocytes and endothelium. This process leads to cellular apoptosis, fibrosis, and ventricular remodeling.[18,21] Progressive inflammatory activation results in ventricular diastolic dysfunction and contributes to the progression of HFpEF. Thus, in HFpEF, inflammation plays a central role in the disease's underlying pathophysiology and diuretic resistance by causing endothelial dysfunction.[29]

Proinflammatory cytokines (TNF-α, IL-1, IL-6) can impair renal microcirculation, reducing glomerular filtration, increasing vascular permeability, and triggering distal tubular sodium reabsorption. These processes weaken the natriuretic response and contribute to diuretic resistance.[30] Inflammation also triggers neurohormonal activation, leading to increased RAAS and sympathetic system activity, causing renal vasoconstriction and sodium retention. Therefore, inflammation can be considered an essential pathophysiological link that exacerbates diuretic resistance in HFpEF.[25,27] From a clinical standpoint, early assessment of natriuretic response using urinary sodium has emerged as a pragmatic approach to detect inadequate diuretic response, and low post-diuretic urinary sodium has been associated with poorer decongestion and more intensive diuretic regimens in acute HF. These observations align with the concept that inflammation and endothelial dysfunction—central features of HFpEF—may impair renal microcirculation and sodium handling, thereby contributing to diuretic resistance and worse outcomes.[31] Taken together, recent evidence supporting an inflammatory/oxidative HFpEF phenotype suggests that systemic oxidative stress may also contribute to impaired natriuretic response and predispose to diuretic resistance; accordingly, antioxidant protection and signaling homeostasis have been reported to be altered in HFpEF, supporting the biological plausibility of the findings.[32]

Serum albumin (SA) has anti-inflammatory and antioxidant activity.[26] SA inhibits the release of proinflammatory cytokines by regulating signaling systems between inflammatory cells, such as neutrophils. Studies have shown that low serum albumin levels are independently associated with both short- and long-term mortality in patients with acute coronary syndrome and myocardial infarction.[30,33,34]

The neutrophil-to-albumin ratio has recently been defined as a new biomarker reflecting systemic inflammatory load.[27] The neutrophil percentage indicates acute inflammatory response and immune activation, while serum albumin level is a negative acute phase reactant reflecting inflammation.[30,33] Combining these 2 parameters more strongly represents the severity of inflammatory processes.[27,33] Elevated NPAR indicates predominant inflammatory activity and insufficient albumin reserves, thus signifying a worsened prognosis. Clinical studies have shown that high NPAR levels are closely associated with the prognosis of HF, coronary artery disease, atrial fibrillation, severe sepsis, and acute kidney injury.

In this context, the findings extend the existing evidence and confirm that NPAR not only reflects systemic inflammation but also independently predicts both diuretic resistance and mortality risk in HFpEF, consistent with previous data.[35] Therefore, NPAR may serve as a simple, inexpensive, and accessible marker to assess systemic inflammation and identify high-risk HFpEF patients in clinical practice.

Clinical implementation of NPAR may aid in early identification of patients at high risk of poor outcomes, facilitating timely optimization of therapy and closer follow-up. Future large-scale prospective studies are warranted to validate NPAR as a prognostic biomarker and to explore whether interventions targeting systemic inflammation can improve outcomes in this patient population.

Study Limitations

This study has several limitations that should be acknowledged.

First, it was a single-center and retrospective study, which may limit the generalizability of the findings. Second, although the authors adjusted for multiple confounding variables, residual confounding cannot be fully excluded. Third, inflammatory markers such as interleukin-6, TNF-α, and other cytokines were not routinely measured, which may have limited the assessment of the complete inflammatory profile. Fourth, the mean follow-up duration was relatively short (8.3 ± 2.1 months), which may limit the assessment of true long-term outcomes and could lead to underestimation of late events. Therefore, the prognostic value of NPAR should be interpreted as reflecting mid-term risk and requires confirmation in multicenter studies with longer follow-up. Finally, the study design does not allow for establishing a causal relationship between elevated NPAR and adverse outcomes. Future multicenter, prospective studies with longer follow-up and a broader inflammatory marker panel are required to confirm these results.

CONCLUSION

In conclusion, elevated NPAR levels were significantly associated with both diuretic resistance and increased all-cause mortality in patients with HFpEF.

NPAR reflects the combined effect of systemic inflammation and nutritional status, providing an accessible and inexpensive biomarker for risk stratification.

The findings indicate that NPAR can serve as a valuable tool for identifying high-risk HFpEF patients and guiding early management strategies.

Further large-scale studies are needed to confirm its prognostic value and to explore potential therapeutic approaches targeting inflammation in this population.

Artificial Intelligence (AI) Disclosure: The authors declare that no artificial intelligence (AI)–assisted technologies (such as LLMs, chatbots, or image generation tools) were used in the preparation, writing, analysis, or production of this manuscript.

Ethics Committee Approval: This study was approved by the Tokat Gaziosmanpaşa University Faculty of Medicine, Non-Interventional Scientific Research Ethics Committee (Approval No.: 25-MOBAEK-144; Date: April 22, 2025).

Informed Consent: Since the study was conducted retrospectively, informed consent was not obtained from the patients. Information was received from the ethics committee of the hospital due to the current situation.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.E.Ö., K.K.; Design – S.E.Ö., K.K.; Supervision – S.E.Ö., Ç.Z.; Resources – S.E.Ö., G.G.T.; Materials – S.E.Ö., Ç.Z.; Data Collection and/or Processing – S.E.Ö., K.K.; Analysis and/or Interpretation – S.E.Ö., K.K.; Literature Search – S.E.Ö., Ç.Z.; Writing – S.E.Ö., K.K.; Critical Review – S.E.Ö., K.K.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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SUPPLEMENTARY MATERIAL

Initial screening (January 2017 – August 2022)

HFpEF patients identified from institutional database: n = 1927

↓

Exclusion criteria applied

Missing clinical or echocardiographic data (n = 440)

Acute infection, sepsis, or malignancy

Severe valvular disease or prosthetic valve

Acute coronary syndrome (<6 months)

End-stage renal disease, severe anemia, age < 18 years

↓

Eligible HFpEF patients included in final analysis

n = 1487

↓

Grouping according to diuretic resistance

Diuretic-resistant group: n = 248

Non–diuretic-resistant group: n = 1239

↓

Statistical analyses performed

ROC curve → NPAR cut-off (13.98) for diuretic resistance prediction

Logistic regression → Independent predictors of diuretic resistance

Cox regression → Predictors of all-cause mortality

Kaplan–Meier survival analysis → Mortality according to NPAR level

↓

Main outcomes

Elevated NPAR (>13.98) predicted both diuretic resistance and higher mortality risk in HFpEF patients.

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Hidden Burden of COMISA in Hypertensive Obstructive Sleep Apnea Patients

ABSTRACT

Background: Comorbid insomnia and sleep apnea (COMISA) is a frequent but underrecognized condition in patients with obstructive sleep apnea (OSA). While OSA is strongly linked to hypertension, the independent contribution of COMISA to resistant hypertension (RH) remains unclear. This study aimed to investigate the association between COMISA and RH in hypertensive OSA patients and to identify independent predictors of RH.

Methods: This retrospective cross-sectional study included 131 patients diagnosed with both OSA and hypertension who underwent full-night polysomnography (PSG) at a tertiary sleep center. The Insomnia Severity Index (ISI) was used to define COMISA (ISI ≥15). Resistant hypertension (RH) was defined as uncontrolled blood pressure despite the use of at least 3 antihypertensive agents of different classes, including a diuretic. Demographic, clinical, and polysomnographic data were analyzed using multiple logistic regression to determine independent predictors of RH.

Results: Of 131 hypertensive OSA patients, 39 (29.8%) met criteria for COMISA. The prevalence of RH was 43.5%. COMISA was significantly more frequent in the RH group (66.7% vs. 33.3%, $P = .006$). In the multiple logistic regression analysis, COMISA (OR = 5.26, $P < .001$, 95% CI: 2.04-13.57) and male sex (OR = 3.24, $P = .010$, 95% CI: 1.36-7.72) were identified as independent predictors of RH, while age, apnea–hypopnea index (AHI), and body mass index (BMI) were not significantly associated.

Conclusion: Comorbid insomnia and sleep apnea (COMISA) markedly increases the risk of RH in hypertensive OSA patients, independent of apnea severity and obesity. These findings highlight COMISA as a distinct cardiovascular phenotype within the OSA spectrum. Routine screening and targeted treatment of insomnia in OSA may represent a critical approach to improving blood pressure control and cardiovascular outcomes.

Keywords: Cardiovascular risk, COMISA, Insomnia, Obstructive sleep apnea, Resistant hypertension

ORIGINAL INVESTIGATION

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by recurrent upper airway collapse during sleep, resulting in intermittent hypoxemia and sleep fragmentation.[1,2] It affects up to 20% of middle-aged adults and is strongly associated with hypertension and other cardiovascular diseases.[3-6]

The relationship between OSA and hypertension has been well recognized over the past 2 decades. The pathogenesis of OSA-related hypertension is multifactorial. Intermittent hypoxemia, recurrent arousals, and intrathoracic pressure swings contribute to chronic sympathetic activation, oxidative stress, and endothelial dysfunction. These mechanisms promote a non-dipping nocturnal blood pressure pattern and exaggerated morning surges, both of which worsen cardiovascular outcomes.[4,7] Resistant hypertension (RH), defined as the failure to achieve target blood pressure despite the use of at least 3 antihypertensive agents of different classes, including a diuretic, all at optimal doses, is one of the most clinically significant cardiovascular complications of OSA.[3,5] Among all hypertensive phenotypes, the estimated prevalence of RH ranges from 12% to 15%.[5] Ahmad et al,[8] in their review, reported that the prevalence of hypertension

Büşra Durak[1]
Duygu Özol[2]
Sema Saraç[2]
İbrahim Durak[3]
Azra Tanrıkulu[4]

[1]*Department of Pulmonology, Hitit University Faculty of Medicine, Çorum, Türkiye*
[2]*Department of Pulmonology, Süreyyapasa Training and Research Hospital, İstanbul, Türkiye*
[3]*Department of Gastroenterology, Hitit University Faculty of Medicine, Çorum, Türkiye*
[4]*Clinic of Cardiology, Maltepe State Hospital, İstanbul, Türkiye*

Corresponding author:
Büşra Durak
✉ drbusradurak@gmail.com

Received: November 17, 2025
Accepted: January 22, 2026
Available Online Date: February 20, 2026

Cite this article as: Durak B, Özol D, Saraç S, Durak İ, Tanrıkulu A. The hidden burden of COMISA in hypertensive obstructive sleep apnea patients. *Anatol J Cardiol.* 2026;30(3):184-189.

DOI:10.14744/AnatolJCardiol.2026.6025

among OSA patients ranges between 30% and 70%, with the highest rates observed in those with severe OSA.[8] On the other hand, Shiina et al,[9] in their recent review, summarized that 70-80% of patients with RH have coexisting OSA.[9]

The coexistence of insomnia and OSA, known as comorbid insomnia and sleep apnea (COMISA), has gained attention as a distinct clinical phenotype. Comorbid insomnia and sleep apnea (COMISA) affects 30%-50% of OSA patients and has been linked to increased cardiovascular and metabolic risk, poor CPAP adherence, and reduced quality of life.[10,11] Although the relationship between OSA and hypertension is well established, the effects of this COMISA phenotype on hypertension and RH remain limited.[12-14] Comparing OSA in regular hypertensives vs those with RH helps to identify factors that worsen BP control and may guide screening and treatment. Therefore, this study aimed to evaluate the relationship between COMISA and RH in patients with hypertensive OSA and to identify independent predictors of RH within this population.

METHODS

Study Design and Participants

This cross-sectional, retrospective study included 131 patients diagnosed with OSA and hypertension. Data were obtained from the medical records of patients who had undergone full-night diagnostic polysomnography (PSG) at the Sleep Disorders Center.

Inclusion and Exclusion Criteria

Eligible participants were adults aged between 30 and 75 years with a confirmed diagnosis of OSA by PSG and a diagnosis of hypertension receiving antihypertensive treatment by a cardiologist or internal medicine. Patients with a history of central sleep apnea, chronic kidney failure, congestive heart failure, chronic liver disease, inflammatory bowel disease, electrolyte imbalance, or major psychiatric disorders were excluded from the study. Only patients undergoing their first diagnostic PSG were included; therefore, all participants were CPAP-naive at baseline, and no patient had received prior CPAP therapy before the assessment.

Data Collection and Measurements

Demographic (age, sex, body mass index (BMI)) and clinical data were retrieved from the hospital database. All patients underwent overnight PSG, and the following parameters were recorded: apnea–hypopnea index (AHI), oxygen desaturation index (ODI), minimum oxygen saturation (min O_2), mean oxygen saturation (mean O_2), and time spent with oxygen saturation <90% (T90).

Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), while insomnia symptoms were evaluated with the Insomnia Severity Index (ISI). A cutoff value of ISI ≥15 was used to define COMISA (comorbid insomnia and sleep apnea).

Definition of Resistant Hypertension

All patients were evaluated, and additional differential diagnostic assessments were conducted by both cardiology and internal medicine specialists. Office blood pressure was measured according to current guidelines as the mean of 3 readings taken at 5-minute intervals after the participant had been seated for at least 5 minutes. Resistant hypertension (RH) was defined as uncontrolled BP despite optimal doses of 3 antihypertensive drug classes, including a diuretic. Patients who achieved blood pressure control or were on ≤2 antihypertensive agents were classified as having non-resistant hypertension.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA) and Python (statsmodels, scipy) software. The normality of data distribution was tested using the Shapiro–Wilk test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median (interquartile range, IQR). Group comparisons were made using the student's *t*-test or Mann–Whitney *U*-test, and categorical variables were analyzed with the chi-square or Fisher's exact test. Independent predictors of RH were determined using multiple logistic regression analysis (Enter method). A *P* value < .05 was considered statistically significant. To reduce the risk of overfitting, multiple logistic regression was performed following the events-per-variable (EPV ≥10) principle. Only clinically meaningful covariates supported by previous literature were included in the final model.

HIGHLIGHTS

- Comorbid insomnia and sleep apnea (COMISA) was significantly more common in patients with resistant hypertension (RH) than in those with controlled hypertension.
- COMISA independently increased the risk of RH by more than fivefold (OR = 5.3), regardless of apnea severity or obesity.
- Male sex was identified as another independent predictor of RH in hypertensive obstructive sleep apnea (OSA) patients.
- Polysomnographic parameters such as apnea–hypopnea index (AHI), oxygen desaturation index (ODI), and nocturnal desaturation were not associated with RH.
- Early identification and management of insomnia symptoms in OSA patients may improve blood pressure control and reduce cardiovascular risk.

RESULTS

A total of 131 patients diagnosed with PSG as OSA and hypertension were included in the study. The mean age of the participants was approximately 57 years, and the mean BMI was 33 kg/m^2. Among all patients, 47% were female and 53% were male.

According to the ISI score, 39 patients (29.8%) were classified in the COMISA group (ISI ≥15), while 92 patients (70.2%) were in the OSA-only group (ISI <15).

Table 1. Baseline Characteristics of the Study Population According to Resistant Hypertension Status

	RH (-) n = 74 (56.5%)	RH (+) n = 57 (43.5%)	*P*
Age*	55.0 (50.5-61.0)	60.0 (47.0-67.0)	.362
BMI*	31.9 (28.4-35.2)	33.0 (29.2-37.2)	.335
Insomnia Severity Index (ISI)*	5.0 (2.8-10.0)	8.0 (3.0-16.2)	.019
Epworth*	9.0 (5.0-12.0)	7.0 (6.0-11.0)	.427
AHI*	33.5 (17.6-51.8)	39.0 (22.3-62.0)	.355
ODI*	35.5 (20.0-56.6)	36.5 (23.2-60.8)	.736
Min O_2*	75.0 (68.0-81.0)	74.0 (64.2-80.0)	.452
Mean O_2*	93.0 (92.0-95.0)	92.0 (91.0-95.0)	.439
T90 (%) *	12.0 (3.9-34.2)	19.9 (8.2-35.8)	.132
Gender (Female) **	33 (67.4%)	16 (32.6%)	.024
COMISA (ISI≥15) **	13 (33.3%)	26 (66.7%)	.006
Smoke (1 = Non-Smoker, 2 = Ex-Smoker, 3 = Smoker) **	1:50.0%/ 2:45.7%/ 3:63.6%	1:50.0%/ 2:54.3%/3:36.4%	.164

AHI, apnea–hypopnea index; BMI, body mass index; ISI, insomnia severity index; Min O_2, minimum oxygen saturation; Mean O_2, mean oxygen saturation; ODI, oxygen desaturation index; RH, resistant hypertension; T90, time spent with oxygen saturation <90%.
*Mann–Whitney *U*-test, Median (Q1-Q3), **chi-square test, %.

When patients with and without RH were compared, no significant differences were observed in terms of age, BMI, ESS, AHI, ODI, mean or minimum oxygen saturation, or T90 percentage ($P > .05$). However, the ISI score was significantly higher in the RH group [8.0 (3.0-16.2) vs. 5.0 (2.8-10.0); $P = .019$]. The proportion of women was lower, and the prevalence of male sex was significantly higher among patients with RH ($P = .024$). In addition, the frequency of COMISA (ISI ≥15) was significantly greater in patients with RH (67.7% vs. 32.3%, $P = .006$). No significant differences were found between the two groups regarding smoking status ($P = 0.164$) (Table 1).

When patients were grouped according to the presence of COMISA, no significant differences were found between the COMISA (ISI ≥15) and OSA-only (ISI <15) groups in terms of age, BMI, ESS, AHI, ODI, minimum or mean oxygen saturation, or T90 percentage (all $P > .05$). However, the prevalence of RH (grades 1-2) was significantly higher in the COMISA group compared to the OSA-only group (67.7% vs. 38.1%, $P = .006$). This finding supports that the presence of insomnia symptoms in OSA patients is associated with an increased risk of RH (Table 2).

When stratified by sex, male patients demonstrated a significantly higher prevalence of RH compared to females (54.9% vs. 32.6%, $P < .001$). Age was slightly lower in men, and ODI values were significantly higher in males ($P = .030$), whereas no significant differences were observed in BMI, ISI, ESS, AHI, mean SpO_2, or T90 between groups (Table 3).

In the multiple logistic regression analysis, COMISA (ISI ≥15) and male sex were identified as significant independent predictors of RH. The presence of COMISA increased the likelihood of RH by approximately 5.3-fold (OR = 5.26, $P < .001$, 95% CI = 2.04-13.57), while male sex increased the risk by approximately 3.2-fold (OR = 3.24, $P = .010$, 95% CI = 1.36-7.72). Age, AHI, and BMI were included in the final model as clinically relevant covariates, selected based on prior evidence and maintaining an acceptable events-per-variable threshold to avoid model overfitting. However, these variables were not statistically significant predictors in the adjusted analysis (all $P > .05$) (Table 4, Figure 1).

DISCUSSION

The present study revealed that COMISA and male sex were independent predictors of RH among hypertensive OSA

Table 2. Comparison of Clinical and Polysomnographic Parameters Between COMISA (ISI ≥ 15) and OSAS (ISI < 15) Groups

Variables	OSAS (ISI<15) n = 92	COMISA (ISI ≥ 15) n = 39	*P*
Age (Years)*	57.13 ± 10.79	56.61 ± 13.41	.843
BMI (kg/m^2)**	32.7 (28.7–37.5)	32.5 (28.9-35.8)	.998
Epworth Sleepiness Scale**	8.0 (6.0–12.0)	8.0 (6.0-11.0)	.896
Apnea–Hypopnea Index (events/h)**	37.0 (21.5–57.0)	34.0 (15.0-60.2)	.594
Oxygen Desaturation Index (events/h)**	38.0 (21.4–59.8)	30.0 (17.5-51.4)	.262
Minimum O_2 saturation (%)**	74.0 (66.0–80.0)	77.5 (69.5-81.0)	.131
Mean O_2 saturation (%)**	93.0 (91.0–95.0)	92.0 (91.0-94.0)	.790
Time with O_2 <90% (T90, %)**	15.0 (5.0–37.0)	11.9 (3.9-30.4)	.540
Resistant hypertension, n (%) ***	20 (38.1%)	37 (67.7%)	0.006

AHI, apnea–hypopnea index; BMI, body mass index; ISI, insomnia severity index; ODI, oxygen desaturation index; Min O_2, minimum oxygen saturation; Mean O_2, mean oxygen saturation; T90, time spent with oxygen saturation <90%; RH, resistant hypertension.
* *t*-Test, mean ± SD; ** Mann–Whitney *U*-test, median (Q1-Q3); ***chi-square test.

Table 3. Comparison of Clinical and Polysomnographic Parameters Between Female and Male Patients

Variables	Female (n = 49)	Male (n = 82)	*P*
Age (years)*	58.0 (12.0)	55.0 (15.0)	.036
BMI (kg/m^2)*	31.22 (6.32)	32.32 (7.31)	.524
Insomnia Severity Index (ISI)*	8.00 (12.00)	6.50 (7.00)	.282
Epworth Sleepiness Scale*	8.0 (6.0)	8.0 (6.0)	.954
Apnea–Hypopnea Index (events/h)*	28.00 (32.80)	39.50 (35.88)	.069
Oxygen Desaturation Index (events/h)*	29.50 (34.50)	38.08 (39.00)	.030
Minimum O_2 saturation (%)*	74.50 (14.75)	76.00 (12.25)	.422
Mean O_2 saturation (%)*	92.0 (3.25)	93.0 (4.00)	.486
Time with O_2 <90% (T90, %)*	14.00 (28.32)	12.00 (31.75)	.441
Resistant hypertension, n (%)**	16 (32.6%)	45 (54.9%)	< .001

AHI, apnea–hypopnea index; BMI, body mass index; ISI, insomnia severity index; ODI: oxygen desaturation index; Min O_2, minimum oxygen saturation; Mean O_2, mean oxygen saturation; RH, resistant hypertension; T90, time spent with O_2 <90%.
*Mann–Whitney *U* test, median (IQR); **chi-square.

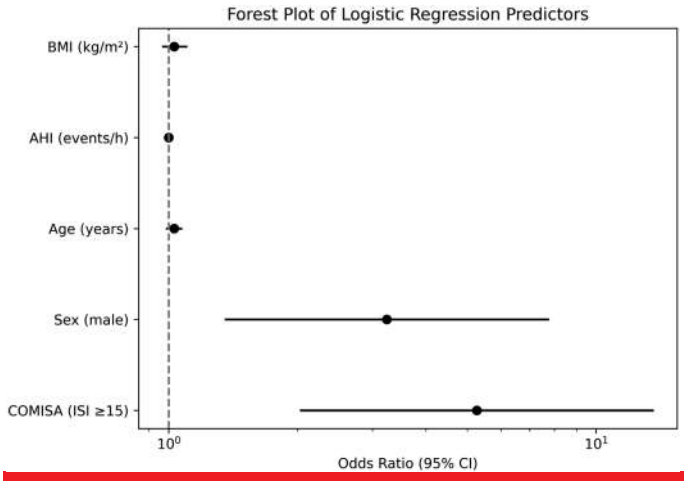

Figure 1. Forest plot displaying odds ratios (OR) and 95% confidence intervals for predictors of resistant hypertension in hypertensive OSA patients.

patients. The presence of insomnia increased the likelihood of RH by more than fivefold, even after adjusting for apnea severity and obesity. These results support the growing evidence that COMISA represents a distinct phenotype associated with an additive cardiovascular burden.[12-17]

The prevalence of OSA among middle-aged adults ranges from 24%-26% in men and 17%-28% in women.[1,18] This rate is substantially higher in individuals with hypertension, reaching 30%-80%, and may rise to as high as 64%-83% in those with RH.[5,19,20] In our study, the prevalence of RH was 43.5%. Given this strong overlap, identifying reliable predictors is crucial for early screening and management. Accurate assessment of blood pressure and adherence to recommended monitoring strategies are also essential components of adequate hypertension control, as demonstrated in recent studies.[21]

AHI values above 30 events per hour have been particularly associated with uncontrolled or non-dipping blood pressure patterns. Another significant predictor is ODI and minimum nocturnal oxygen saturation. Persistent nocturnal hypoxemia triggers sympathetic overactivation, oxidative stress, and endothelial dysfunction, all of which perpetuate

Table 4. Multiple Logistic Regression Analysis for Predictors of Resistant Hypertension

Variables	B	Odds Ratio (Exp B)	*P*	95% Confidence Interval for OR
COMISA	1.662	5.26	< .001	2.04-13.57
Age (years)	0.030	1.03	.114	0.99-1.07
AHI (events/h)	0.002	1.00	.786	0.98-1.02
Sex (male)	1.176	3.24	.010	1.36-7.72
BMI (kg/m^2)	0.035	1.03	.279	0.97-1.10

AHI, apnea–hypopnea index; BMI, body mass index; Exp(B), exponentiated B coefficient; OR, odds ratio; RH, resistant hypertension.

RH. Several studies have demonstrated that an ODI >15 or a mean SpO_2 below 90% independently predicts RH in OSA patients.[5,20]

The relationship between COMISA and RH appears multifactorial and synergistic.
OSA-related intermittent hypoxemia contributes to oxidative stress, inflammation, endothelial dysfunction, and activation of the renin–angiotensin–aldosterone system, all of which promote sustained hypertension.[4,7,22] Conversely, insomnia induces chronic inflammation by arousals and hypothalamic–pituitary–adrenal axis activation, leading to elevated nocturnal cortisol and increased sympathetic tone.[10,11,23] The coexistence of both disorders may therefore amplify autonomic and neuroendocrine stress, resulting in greater cardiovascular strain. Recent studies using heart rate variability have shown marked autonomic imbalance in COMISA compared to OSA alone,[24] supporting this synergistic mechanism. Persistent sleep fragmentation may also blunt nocturnal dipping and sustain 24-hour hypertension by impairing baroreflex sensitivity.[16,22]

Our findings are consistent with recent longitudinal studies. Wu[13] demonstrated that insomnia independently predicted the development of RH in OSA patients, while Draelants[12] reported that COMISA was associated with a higher 10-year cardiovascular risk.[12-14] These observations align with previous systematic reviews and meta-analyses, including Ahmed et al,[25] which confirmed that OSA significantly increases the risk of RH and poor antihypertensive response. In a population-based cohort, Frisk et al. found that COMISA correlated with uncontrolled hypertension, reinforcing the clinical relevance of this interaction.[26] Furthermore, Quan et al[16] and Pejovic[17] observed that insomnia symptoms were linked to sustained sympathetic activation and increased incidence of hypertension, even in non-OSA populations. Recent cardiovascular studies have also demonstrated that inadequately controlled or treatment-RH is associated with a higher risk of adverse clinical outcomes, underscoring the need for early identification of high-risk hypertensive phenotypes.[27] Taken

together, these studies indicate that insomnia is not a coincidental comorbidity but a major modifier of OSA's cardiovascular consequences.

From a practical standpoint, these results underscore the importance of screening for insomnia symptoms in all OSA patients, particularly those with suboptimal blood pressure control despite adequate pharmacologic therapy. In clinical workflow, administering a brief tool such as the ISI at the initial sleep clinic visit or hypertension evaluation may help identify COMISA early. Insomnia has been shown to impair adherence to continuous positive airway pressure (CPAP) treatment,[15,28] reducing its antihypertensive efficacy. Combined management approaches integrating cognitive behavioral therapy for insomnia (CBT-I) with CPAP have been shown to improve sleep continuity, therapy adherence, and blood pressure outcomes.[16,29,30] Moreover, the incorporation of COMISA status into risk prediction models, such as the nomogram developed by Lin,[31] could enable early identification of high-risk patients and personalized management strategies. Clinicians should recognize COMISA as a high-risk cardiovascular phenotype requiring multidisciplinary management, including pulmonology, cardiology, and behavioral sleep medicine.

One of the limitations of our study was the inability to perform 24-hour ambulatory blood pressure monitoring; therefore, we could not evaluate the distinction between dipper and non-dipper patterns. However, all medications used by the patients were verified through the pharmacy records, and additional differential diagnostic assessments were conducted by both cardiology and internal medicine specialists. The main strengths of this study include objective polysomnographic assessment, validated evaluation of ISI, and robust multiple modeling. However, the retrospective and single-center design limits generalizability, and unmeasured confounders such as sodium intake, medication adherence, and secondary hypertension causes cannot be excluded. The study was conducted in a tertiary referral sleep center, which may have led to a selection of patients with more severe symptoms or comorbidities compared with the general population. Therefore, the generalizability of our findings to primary care or community-based OSA cohorts may be limited. The use of self-reported scales (ESS, ISI) may introduce recall bias. Another limitation of our study is the absence of objective sleep fragmentation parameters such as arousal index. Although ISI provided a subjective assessment of insomnia symptoms, integrating arousal-based PSG markers could further clarify the physiological interaction between COMISA and RH. In addition, the cross-sectional design precludes establishing causality between COMISA and RH. Whether insomnia contributes to RH, whether the hypertensive burden worsens sleep quality, or whether both share common autonomic and neuroendocrine pathways remains uncertain; therefore, our findings should be interpreted as associative. Future multicenter prospective studies incorporating arousal scoring, continuous blood pressure monitoring, and mechanistic biomarkers (e.g., catecholamines, endothelin-1) are warranted. Moreover, advanced analytical approaches such as machine learning models may enhance individualized risk prediction in OSA and COMISA populations.[32]

CONCLUSION

In conclusion, the coexistence of insomnia and OSA significantly increases the risk of RH, independent of apnea severity and obesity. COMISA appears to represent a distinct cardiovascular phenotype within the OSA spectrum.

Routine assessment and targeted treatment of insomnia in OSA patients through behavioral and pharmacologic interventions may represent a critical yet underutilized approach to improving blood pressure control and reducing long-term cardiovascular risk.

AI Disclosure: Artificial intelligence–assisted technologies (including large language models and text-based editing tools) were used solely for language editing, formatting assistance, and improving the clarity of the manuscript. All scientific content, study design, data analysis, and conclusions were produced entirely by the authors.

Ethics Committee Approval: This study was approved by the Hitit University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Approval No.: 2025-135; Date: July 2, 2025).

Informed Consent: Since this study was designed as a retrospective chart review, the requirement for informed consent was waived by the ethics committee.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.D., D.Ö., S.S.; Design – B.D., D.Ö., S.S.; Supervision – B.D., D.Ö., S.S., İ.D.; Resources – B.D., D.Ö.; Materials – B.D., D.Ö., İ.D.; Data Collection and/or Processing – B.D., İ.D., A.T.; Analysis and/or Interpretation – B.D., D.Ö., İ.D.; Literature Search – B.D., D.Ö., S.S., İ.D., A.T.; Writing – B.D., İ.D.; Critical Review – D.Ö., S.S.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Postoperative Right Ventriculo-Pulmonary Artery Coupling Assessed by TAPSE/PASP as a Predictor of Long-Term Outcomes After TAVI

ABSTRACT

Background: Right ventriculo-pulmonary artery (RV–PA) coupling, commonly assessed by the ratio of tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP), has emerged as an important prognostic marker in various cardiovascular diseases. However, its predictive value after transcatheter aortic valve implantation (TAVI) remains insufficiently defined. This study aimed to evaluate whether postoperative TAPSE/PASP is independently associated with long-term all-cause mortality in patients undergoing transfemoral TAVI.

Methods: We retrospectively analyzed 786 consecutive patients who underwent transfemoral TAVI between June 2020 and March 2025. Postoperative TAPSE/PASP was measured within the first week after the procedure. Receiver-operating characteristic (ROC) curve analysis determined the optimal TAPSE/PASP cut-off for predicting long-term mortality. Survival analyses were performed using the Kaplan–Meier method and Cox proportional hazards regression.

Results: During a median follow-up of 509 days (interquartile range: 283-847), 61 patients (9.0%) died. Receiver-operating characteristic (ROC) analysis identified 0.52 mm/mmHg as the optimal postoperative TAPSE/PASP cut-off (AUC = 0.626, $P < .001$, 95% CI: 0.57-0.68). Patients with TAPSE/PASP <0.52 (n = 278) had worse clinical, echocardiographic, and laboratory profiles than those with TAPSE/PASP ≥0.52 (n = 508). Kaplan–Meier analysis demonstrated significantly reduced survival in the lower TAPSE/PASP group (12.6% vs. 5.1% mortality, log-rank $P < .001$). In multiple Cox regression, age (HR = 1.044, $P = .044$, 95% CI: 1.001-1.089), chronic obstructive pulmonary disease (COPD) (HR = 2.261, $P = .012$, 95% CI: 1.192-4.290), and postoperative TAPSE/PASP (HR = 0.856 per 0.1 mm/mm Hg increase, $P = .033$, 95% CI: 0.743-0.988) remained independent predictors of long-term mortality.

Conclusions: Lower postoperative TAPSE/PASP (<0.52 mm/mmHg) is independently associated with increased long-term mortality after TAVI, supporting its use for early postoperative risk stratification.

Keywords: Right ventricular function, right ventriculo, prognosis, pulmonary artery coupling, transcatheter aortic valve implantation

ORIGINAL INVESTIGATION

Seda Tanyeri Uzel[1]
Berhan Keskin[2]
İsmail Balaban[1]
Halit Eminoğlu[1]
Barkın Kültürsay[3]
Baver Bozan[1]
Tezel Kovancı[1]
Doğan Şen[1]
Murat Karaçam[4]
Ferhat Keten[1]
Büşra Güvendi Şengör[1]
Rezzan Deniz Acar[1]
Ali Karagöz[1]
Elnur Alizade[1]

[1]*Department of Cardiology, Kartal Koşuyolu High Specialization Education and Research Hospital, İstanbul, Türkiye*
[2]*Department of Cardiology, Bağcılar Medipol Mega University Hospital, İstanbul, Türkiye*
[3]*Department of Cardiology, Tunceli State Hospital, Tunceli, Türkiye*
[4]*Department of Cardiology, Bitlis State Hospital, Bitlis, Türkiye*

Corresponding author:
Seda Tanyeri Uzel
✉ sedatanyeri@hotmail.com

Received: August 8, 2025
Accepted: January 29, 2026
Available Online Date: February 25, 2026

Cite this article as: Tanyeri Uzel S, Keskin B, Balaban İ, et al. Postoperative right ventriculo-pulmonary artery coupling assessed by TAPSE/PASP as a predictor of long-term outcomes after TAVI. *Anatol J Cardiol.* 2026;30(3):190-199.

DOI: 10.14744/AnatolJCardiol.2026.5716

INTRODUCTION

Severe aortic stenosis (AS) is a common and progressive valvular disease among the elderly, often remaining undiagnosed until advanced stages.[1,2] Despite the substantial clinical burden, risk stratification remains challenging. Transcatheter aortic valve implantation (TAVI) has become the standard treatment across all surgical risk categories; however, long-term outcomes after the procedure remain heterogeneous, with reported 5-year survival rates of 40-60%.[3] This variability indicates that conventional risk models may not fully capture patient heterogeneity, underscoring the need for novel prognostic markers that reflect cardiac and hemodynamic adaptation beyond left-sided parameters.

Right ventricular (RV) function has gained increasing recognition as an important determinant of outcomes in left-sided valvular diseases. The RV–pulmonary circulation unit is functionally interconnected with left heart hemodynamics through

ventricular interdependence and shared loading conditions.[4] In severe AS, chronic left ventricular pressure overload frequently leads to elevated left atrial pressures, secondary pulmonary hypertension, and progressive RV dysfunction. All these conditions have been associated with adverse clinical outcomes.

The ratio of tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP) has been proposed as a simple and reproducible echocardiographic index of RV–pulmonary artery (PA) coupling.[5] By incorporating both RV contractile function (TAPSE) and afterload (PASP), this ratio provides a more comprehensive assessment of RV performance within its hemodynamic environment compared to isolated measurements. Lower TAPSE/PASP values have been associated with unfavorable prognosis in several cardiovascular conditions, including pulmonary hypertension, heart failure, and valvular heart disease.[6-10]

In patients undergoing TAVI, TAPSE/PASP has recently been explored as a potential prognostic marker. While some studies have demonstrated an association between lower TAPSE/PASP and increased mortality,[11] others have reported inconsistent findings, likely influenced by differences in study design, patient characteristics, and timing of measurement.[12] Notably, most previous studies have predominantly focused on preoperative TAPSE/PASP, aiming to characterize baseline RV–PA uncoupling and its impact on procedural or short-term outcomes. However, preprocedural measurements may not reflect the dynamic changes that occur after relief of valvular obstruction. Given that TAVI itself can substantially alter RV function and pulmonary pressures, postoperative assessments may provide incremental prognostic insights beyond preoperative values. Nevertheless, the prognostic value of postoperative TAPSE/PASP, particularly beyond the early recovery phase, remains insufficiently defined.

Given that TAVI markedly modifies RV loading conditions and pulmonary pressures, postoperative RV–PA coupling may carry distinct prognostic information, integrating both the degree of RV recovery and the residual hemodynamic burden after intervention. The change in coupling (ΔTAPSE/PASP) may further differentiate patients with reversible dysfunction from those with persistent uncoupling. Accordingly, postoperative assessment of RV–PA coupling may represent an early window into right ventricular adaptive capacity following TAVI, allowing identification of patients with persistent hemodynamic vulnerability despite technically successful valve implantation.

The aim of this study was to evaluate the prognostic significance of postoperative right ventriculo–pulmonary artery (RV–PA) coupling, assessed by the TAPSE/PASP ratio, in patients undergoing TAVI. We further sought to examine the perioperative change in TAPSE/PASP (ΔTAPSE/PASP) to determine whether improvement or persistence of RV–PA uncoupling after valve implantation carries prognostic implications for long-term mortality. We hypothesized that postoperative RV–PA coupling reflects the ability of the right ventricle to recover after relief of left-sided pressure overload and therefore provides incremental prognostic information beyond preoperative measurements.

HIGHLIGHTS

- Postoperative tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP) ratio <0.52 mm/mmHg independently predicts long-term mortality after transcatheter aortic valve implantation (TAVI).
- Impaired right ventriculo-pulmonary artery (RV–PA) coupling reflects persistent hemodynamic stress and right ventricular dysfunction despite valve intervention.
- Tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP) offers a simple, non-invasive echocardiographic parameter for postoperative risk stratification in TAVI patients.
- Routine assessment of RV–PA coupling may help identify high-risk individuals who could benefit from closer follow-up and tailored therapies.

METHODS

Study Design and Population

This was a single-center, retrospective observational study including consecutive patients who underwent transfemoral TAVI at our institution between June 1, 2020, and March 1, 2025. Of the total cohort, patients who experienced in-hospital death (n = 73) or had incomplete echocardiographic or clinical data (n = 35) were excluded prior to the outcome analyses. The final study cohort consisted of 786 patients with available postoperative TAPSE/PASP measurements. The study was approved by the institutional ethics committee, and the need for written informed consent was waived owing to the retrospective design. All procedures were performed in accordance with the Declaration of Helsinki.

Data Collection

Baseline demographic characteristics, comorbidities, and laboratory values at admission were obtained from electronic medical records. Pre-procedural coronary calcium burden was quantified by the Agatston score derived from computed tomography scans. Clinical endpoints and follow-up data were collected through hospital records and the national mortality registry.

Echocardiographic Assessment

Transthoracic echocardiographyTTE was performed by experienced sonographers using commercially available ultrasound systems in accordance with American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) recommendations.[13,14] Postoperative echocardiographic examinations were routinely performed between postoperative days 3 and 7 (median 4 [IQR 3-6]), depending on patient stability and discharge timing.

- Tricuspid annular plane systolic excursion (TAPSE) was measured in the apical 4-chamber view with M-mode, aligning the cursor with the lateral tricuspid annulus.

- Pulmonary artery systolic pressure (PASP) was estimated using the peak tricuspid regurgitation velocity and the simplified Bernoulli equation, with right atrial pressure estimated from inferior vena cava size and respiratory variability.
- The TAPSE/PASP ratio was calculated as TAPSE (in mm) divided by PASP (in mm Hg), expressed in mm/mmHg.

Intra- and inter-observer reproducibility were assessed in a randomly selected subset of 30 patients, yielding intraclass correlation coefficients of 0.92 and 0.89, respectively, for TAPSE measurements.

Outcome Measures

The primary outcome was long-term all-cause mortality. The follow-up period was calculated from the date of the procedure to the date of death or last contact, with a median follow-up of 509 (IQR: 283-847) days.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), depending on data distribution, and categorical variables are presented as counts and percentages. Normality of continuous variables was assessed using the Shapiro–Wilk test. Group comparisons were performed using the Student's *t*-test for normally distributed variables or the Mann–Whitney *U*-test for non-normally distributed variables, and the chi-square test for categorical variables. Within-group pre- and postoperative comparisons of echocardiographic parameters, including TAPSE/PASP, were performed using paired statistical tests (paired Student's *t*-test or Wilcoxon signed-rank test, as appropriate). Between-group differences in periprocedural change (ΔTAPSE/PASP) were assessed using independent group comparisons.

Receiver-operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value of postoperative TAPSE/PASP for predicting long-term mortality. Based on this analysis, patients were stratified into 2 groups according to the identified cut-off. Survival curves were constructed using the Kaplan–Meier method and compared with the log-rank test.

Univariate Cox proportional hazards regression was conducted to identify variables potentially associated with long-term mortality, including baseline characteristics, comorbidities, postoperative echocardiographic parameters, laboratory findings, and Agatston score. Variables with $P < .10$ in univariate analysis and those deemed clinically relevant were entered into the multiple Cox regression model. Backward stepwise elimination was applied to retain independent predictors of mortality. Hazard ratios (HR) and 95% confidence intervals (CIs) were reported. A 2-tailed *P*-value < .05 was considered statistically significant. All statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 786 patients undergoing transfemoral TAVI were included in the analysis after exclusion criteria were applied. The median follow-up duration was 509 days (IQR: 283-847), during which 61 patients (9.0%) died from all causes.

Receiver operating characteristic (ROC) curve analysis was first performed to determine the prognostic threshold for postoperative TAPSE/PASP. The analysis identified 0.52 mm/mm Hg as the optimal cut-off for predicting long-term mortality, with AUC = 0.626, $P < .001$, 95% CI: 0.57-0.68, sensitivity of 62.1%, and specificity of 60.4%. This cut-off demonstrated modest but statistically significant discriminatory ability and was therefore used to stratify patients for outcome analyses (Figure 1).

Baseline characteristics differed substantially between groups defined by this cut-off. As summarized in Table 1,

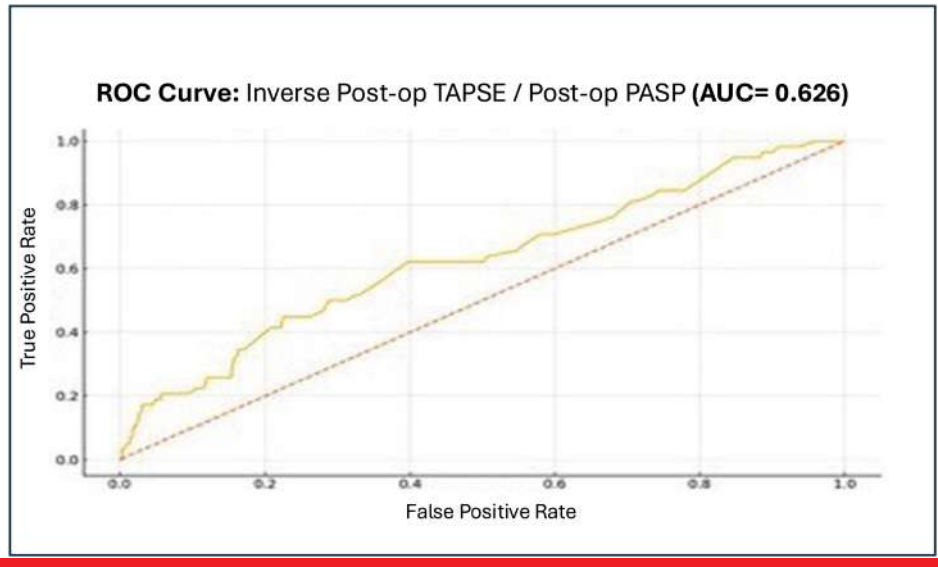

Figure 1. Receiver-operating characteristic (ROC) curve for postoperative tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP). Receiver-operating characteristic curve illustrating the predictive value of postoperative TAPSE/PASP for long-term mortality after transfemoral transcatheter aortic valve implantation (TAVI). The optimal cut-off value of 0.52 mm/mmHg yielded AUC = 0.626, *P* < .001, 95% CI: 0.57-0.68, with sensitivity of 62.1% and specificity of 60.4%.

Table 1. Baseline Clinical, Laboratory, Echocardiographic Characteristics, and Outcomes of Patients Stratified by Post-operative TAPSE/PASP Ratio (<0.52 vs. ≥0.52)

Variables	<0.52 (n = 278)	≥ 0.52 (n = 508)	*P*
Baseline clinical characteristics			
Age (years)	78.40 ± 6.64	77.64 ± 6.30	.116
Sex (1 = Female, 2 = Male)			.008
1	109 (39%)	251 (49%)	
2	169 (61%)	257 (51%)	
HT (0/1)			.943
0	49 (18%)	92 (18%)	
1	229 (82%)	416 (82%)	
CAD (0/1)			.311
0	125 (45%)	249 (49%)	
1	153 (55%)	259 (51%)	
DM (0/1)			.772
0	183 (66%)	341 (67%)	
1	95 (34%)	167 (33%)	
CHF (0/1)			< .001
0	192 (69%)	436 (86%)	
1	86 (31%)	72 (14%)	
COPD (0/1)			1.000
0	238 (86%)	435 (86%)	
1	40 (14%)	73 (14%)	
CVA (0/1)			.047
0	248 (89%)	475 (94%)	
1	30 (11%)	33 (6%)	
AF (0/1)			< .001
0	151 (54%)	405 (80%)	
1	127 (46%)	103 (20%)	
CKD (0/1)			.126
0	219 (79%)	424 (83%)	
1	59 (21%)	84 (17%)	
Agatston Score	2775.00 (1952.00-4123.00)	3076.50 (2124.25-4315.00)	.062
Laboratory findings			
Hgb (g/dL)	11.48 ± 1.91	11.97 ± 1.90	.001
Plt (10^3/μL)	236.44 ± 75.08	231.14 ± 78.99	.288
Wbc (10^3/μL)	7.79 ± 2.90	7.98 ± 5.49	.968
Cre (mg/dL)	1.18 ± 0.74	1.11 ± 0.76	.012
AST (U/L)	27.86 ± 34.59	24.79 ± 37.01	.060
ALT (U/L)	20.31 ± 22.08	18.20 ± 34.91	.209
Albumin (g/dL)	3.88 ± 0.41	3.93 ± 0.42	.017
CRP (mg/L)	15.76 ± 28.58	13.14 ± 25.03	.029
BNP (pg/mL)	1085.00 (476.00-2928.00)	432.00 (182.00-1080.00)	< .001
Post-op platelet (10^3/μL)	194.25 ± 76.55	192.54±75.74	.737
Post-op Cre (mg/dL)	1.16 ± 0.76	1.07 ± 0.70	.132
Post-op AKF (1 = Yes)	24 (8.7%)	24 (4.8%)	.043
Post-op BNP (pg/mL)	481.00 (183.00-1462.00)	227.50 (74.25-580.00)	< .001
Echocardiographic parameters (preoperative)			
LVEF (%)	53.45 ± 13.09	58.27 ± 10.44	< .001
LVEDD (cm)	4.87 ± 0.65	4.72 ± 0.59	< .001
LVESD (cm)	3.29 ± 0.83	3.00 ± 0.71	< .001
PASP (mm Hg)	50.12 ± 15.74	33.90 ± 11.68	< .001
Ao Max Grad (mm Hg)	70.75 ± 22.12	73.94 ± 20.00	.030
Ao Mean Grad (mm Hg)	43.44 ± 14.36	45.91 ± 13.03	.019
AVA (cm^2)	0.64 ± 0.21	0.69 ± 0.18	< .001
Ao Vmax (m/s)	4.14 ± 0.67	4.26 ± 0.61	.031

(*Continued*)

Table 1. Baseline Clinical, Laboratory, Echocardiographic Characteristics, and Outcomes of Patients Stratified by Post-operative TAPSE/PASP Ratio (<0.52 vs. ≥0.52) (Continued)

Variables	<0.52 (n = 278)	≥ 0.52 (n = 508)	*P*
LVOT diameter (cm)	1.93 ± 0.19	1.96 ± 0.20	.066
Ao VTI (cm)	96.20 ± 22.37	97.43 ± 21.10	.393
Lvot VTI (cm)	20.41 ± 6.10	22.91 ± 7.53	< .001
TAPSE (mm)	1.81 ± 0.35	2.07 ± 0.32	< .001
MR (Grade 0-4)			< .001
0	22 (8%)	35 (7%)	
1	81 (29%)	280 (55%)	
2	121 (44%)	165 (32%)	
3	52 (19%)	26 (5%)	
4	2 (1%)	1 (0%)	
AR (Grade 0-4)			.016
0	59 (21%)	135 (27%)	
1	123 (44%)	253 (50%)	
2	77 (28%)	101 (20%)	
3	17 (6%)	16 (3%)	
4	2 (1%)	2 (0%)	
TR (Grade 0-4)			< .001
0	4 (1%)	67 (13%)	
1	72 (26%)	326 (64%)	
2	126 (45%)	99 (19%)	
3	65 (23%)	13 (3%)	
4	11 (4%)	2 (0%)	
LFLGAS (1 = yes)	53 (19%)	46 (9%)	< .001
Echocardiographic parameters (post-operative)			
Post-op LVEF (%)	54.44 ± 12.33	59.43 ± 9.08	< .001
Post-op TAPSE (mm)	1.77 ± 0.29	2.04 ± 0.31	< .001
Post-op PASP (mm Hg)	47.88 ± 12.02	28.51 ± 5.74	< .001
Post-op Ao Max Grad (mm Hg)	16.42 ± 7.31	17.51 ± 7.03	.016
Post-op Ao Mean Grad (mm Hg)	8.64 ± 4.69	9.19 ± 4.37	.032
Post-op Ao Vmax (m/s)	1.54 ± 0.52	1.60 ± 0.54	.228
Post-op MR (Grade 0-4)			< .001
0	27 (10%)	71 (14%)	
1	109 (39%)	342 (67%)	
2	111 (40%)	73 (14%)	
3	30 (11%)	11 (2%)	
4	1 (0%)	0 (0%)	
Post-op AR (Grade 0-4)			.002
0	121 (44%)	284 (56%)	
1	126 (45%)	183 (36%)	
2	28 (10%)	28 (6%)	
3	3 (1%)	3 (1%)	
4	0 (0%)	0 (0%)	
Post-op TR (Grade 0-4)			< .001
0	1 (0%)	110 (22%)	
1	86 (31%)	335 (66%)	
2	133 (48%)	44 (9%)	
3	49 (18%)	7 (1%)	
4	9 (3%)	1 (0%)	
Operative outcomes and clinical endpoints			
Long-term mortality (1 = yes)	35 (12.6%)	26 (5.1%)	< .001
Follow-up duration (days)	506 (274-847.75)	511 (289-843.25)	.814
Moderate/severe PVL (1 = yes)	32 (12%)	36 (7%)	.059

AF, Atrial fibrillation; AKF, acute kidney failure; ALT, alanine aminotransferase; AR, aortic regurgitation; AST, aspartate aminotransferase; AVA, aortic valve area; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary sisease; CRP, C-reactive protein; Cre, creatinine; CVA, cerebrovascular accident; DM, diabetes mellitus; Hgb, hemoglobin; HT, hypertension; LFLGAS, low-flow; low-gradient aortic stenosis; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVOT, left ventricular outflow tract; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; Plt, platelet; Post-op, postoperative; PVL, paravalvular leak; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VTI, velocity time integral; Wbc, white blood cell.

patients with postoperative TAPSE/PASP <0.52 (n = 278) were older (78.4 ± 6.6 vs. 77.6 ± 6.3 years, *P* = .116), although this difference was not statistically significant. Clinically, patients with postoperative TAPSE/PASP <0.52 exhibited a higher prevalence of congestive heart failure (31% vs. 14%, *P* < .001), atrial fibrillation (46% vs. 20%, *P* < .001), and cerebrovascular disease (11% vs. 6%, *P* = .047). They also showed evidence of more advanced systemic congestion and neurohormonal activation, with significantly higher CRP (15.7 ± 28.6 vs. 13.1 ± 25.0 mg/L, *P* = .029) and BNP levels (1085 vs. 432 pg/mL, *P* < .001). Although serum albumin was slightly lower in this group (3.88 ± 0.41 vs. 3.93 ± 0.42 g/dL, *P* = .017), this difference is likely of limited clinical relevance. Echocardiographic assessment showed that these patients had worse preoperative cardiac function, characterized by lower LVEF (53.4 ± 13.1% vs. 58.3 ± 10.4%, *P* < .001) and higher PASP (50.1 ± 15.7 vs. 33.9 ± 11.7 mm Hg, *P* < .001). Postoperatively, impaired RV–PA coupling persisted, with significantly elevated pulmonary pressures (47.9 ± 12.0 vs. 28.5 ± 5.7 mm Hg, *P* < .001) and reduced TAPSE (17.7 ± 2.9 vs. 20.4 ± 3.1 mm, *P* < .001).

During follow-up, patients with TAPSE/PASP <0.52 experienced markedly higher mortality compared with those with preserved RV–PA coupling (≥0.52) (12.6% vs. 5.1%, *P* < .001). The Kaplan–Meier survival curve (Figure 2) demonstrated an early and persistent divergence in survival trajectories, indicating that impaired postoperative RV–PA coupling was associated with sustained adverse outcomes. The log-rank test confirmed that this difference was statistically significant (*P* < .001).

In the univariate Cox regression analysis (Table 2), several factors were significantly associated with increased long-term mortality, including age, chronic obstructive pulmonary disease (COPD), atrial fibrillation, renal dysfunction (creatinine), hypoalbuminemia, elevated C-reactive protein, reduced postoperative left ventricular ejection fraction, and lower postoperative TAPSE/PASP. Notably, postoperative TAPSE/PASP was strongly associated with outcome, with HR = 0.808, *P* = .002, 95% CI: 0.708-0.922 per 0.1 mm/mmHg increase.

In the multiple Cox regression analysis (Table 3), after adjustment for potential confounders, only age (HR = 1.044, *P* = .044, 95% CI: 1.001-1.089), COPD (HR = 2.261, *P* = .012, 95% CI: 1.192-4.290), and postoperative TAPSE/PASP (HR = 0.856 per 0.1 mm/mm Hg increase, *P* = .033, 95% CI: 0.743-0.988) remained independent predictors of long-term mortality. These associations and their relative strengths are illustrated in the forest plot (Figure 3), which highlights the prognostic significance of postoperative RV–PA coupling.

Paired pre- and postoperative echocardiographic data were available in a subset of patients (n = 723). When stratified according to postoperative TAPSE/PASP category, the ratio increased from 0.36 ± 0.09 to 0.37 ± 0.10 in the <0.52 group and from 0.61 ± 0.12 to 0.72 ± 0.13 in the ≥0.52 group (*P* < .001 for both). The mean change (ΔTAPSE/PASP) was +0.01 ± 0.11 and +0.11 ± 0.12, respectively (*P* < .001 between groups). These findings, summarized in Table 4, demonstrate that RV–PA coupling improved significantly only in patients with preserved postoperative TAPSE/PASP, supporting the concept of persistent uncoupling in those with lower postoperative ratios.

Overall, the identified threshold of 0.52 mm/mm Hg effectively discriminated patients at higher risk of adverse outcomes. Those with impaired postoperative RV–PA coupling not only presented with a worse clinical and echocardiographic profile but also experienced significantly higher long-term mortality. Importantly, postoperative TAPSE/PASP preserved its prognostic value even after adjusting for

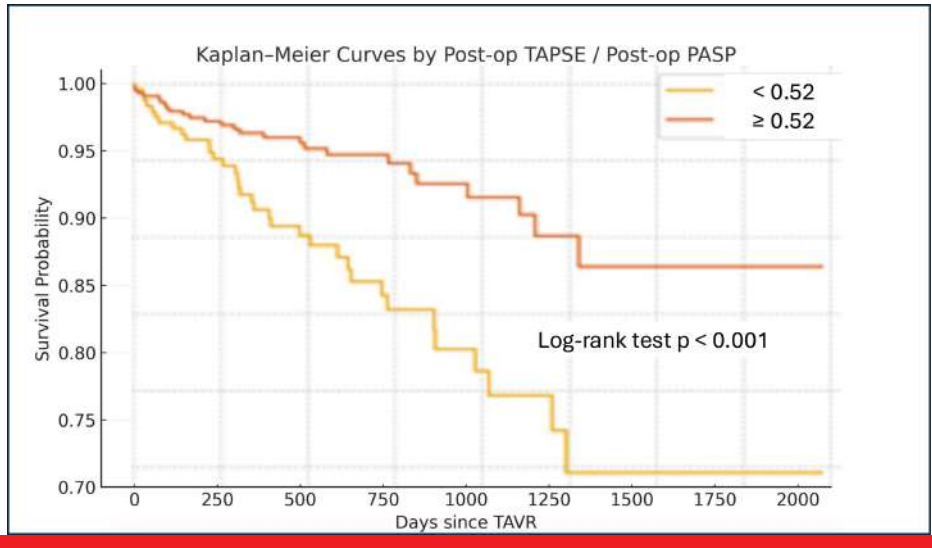

Figure 2. Kaplan–Meier survival curves stratified by postoperative tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP). Kaplan–Meier survival analysis comparing patients with postoperative TAPSE/PASP <0.52 versus ≥0.52 mm/mmHg. Patients with impaired right ventriculo-pulmonary artery (RV–PA) coupling (<0.52) exhibited significantly reduced survival during follow-up. The log-rank test confirmed a statistically significant difference between groups (*P* < .001).

Table 2. Univariate Cox Regression Analysis for the Prediction of Long-term Mortality

Variables	Hazard Ratio	95% Confidence Interval	*P*
Baseline clinical characteristics			
Age (per 1-year increase)	1.044	1.002-1.087	.037
Sex (male)	0.936	0.566-1.548	.797
Hypertension	0.861	0.466-1.589	.632
Coronary artery disease	1.573	0.932-2.653	.089
Diabetes mellitus	1.260	0.751-2.117	.380
Chronic obstructive pulmonary disease	2.024	1.114-3.680	.020
History of cerebrovascular accident	1.629	0.739-3.588	.225
Atrial fibrillation	2.034	1.229-3.366	.005
Laboratory parameters at admission			
Hemoglobin (per 1 g/dL increase)	0.891	0.781-1.016	.087
Creatinine (per 1 mg/dL increase)	1.274	1.023-1.588	.030
Aspartate aminotransferase (per 1 IU/L increase)	1.003	1.000-1.006	.047
Alanine aminotransferase (per 1 IU/L increase)	1.002	0.997-1.006	.385
Albumin (per 1 g/dL increase)	0.601	0.401-0.902	.014
C-reactive protein (per 1 mg/L increase)	1.008	1.003-1.014	.001
Post-operative echocardiographic parameters			
Left ventricular ejection fraction (per 1% increase)	0.969	0.950-0.988	.002
TAPSE/PASP ratio (per 0.01 mm/mm Hg increase)	0.808	0.708-0.922	.002
Maximal aortic gradient (per 1 mm Hg increase)	0.954	0.913-0.997	.036
Moderate-to-severe paravalvular leak	1.658	0.815-3.374	.163
Pre-operative computed tomography			
Agatston Score	0.745	0.469-1.182	.211

other risk factors, confirming its role as an independent and clinically relevant marker for risk stratification in the TAVI population.

DISCUSSION

In this retrospective analysis of patients undergoing transfemoral TAVI, we observed that a lower postoperative TAPSE/PASP ratio (<0.52 mm/mm Hg) revealed an independent association with increased risk of long-term mortality. Notably, this parameter remained an independent predictor after adjustment for established clinical and echocardiographic risk factors. These findings suggest that RV–PA coupling, as assessed by TAPSE/PASP, retains prognostic relevance beyond procedural success and conventional determinants of outcome. Importantly, our additional analysis of ΔTAPSE/PASP demonstrated that RV–PA coupling improved significantly only in patients with preserved postoperative ratios, suggesting the persistence of RV–PA uncoupling among those with lower postoperative TAPSE/PASP values. This observation highlights the concept that the extent of RV functional recovery after TAVI, rather than

Table 3. Multivariate Cox Regression Analysis for the Prediction of Long-Term Mortality

Variables	Hazard Ratio	95% Confidence Interval	*P*
Age (per 1-year increase)	1.044	1.001-1.089	.044
Sex (male)	1.001	0.564-1.776	.997
Chronic obstructive pulmonary disease	2.261	1.192-4.290	.012
Atrial fibrillation	1.311	0.752-2.287	.339
Hemoglobin (per 1 g/dL increase)	0.947	0.817-1.098	.471
Creatinine (per 1 mg/dL increase)	1.218	0.920-1.614	.167
Aspartate aminotransferase (per 1 IU/L increase)	1.001	0.997-1.006	.459
Albumin (per 1 g/dL increase)	0.884	0.447-1.747	.723
C-reactive protein (per 1 mg/L increase)	1.003	0.995-1.010	.473
Post-op left ventricular ejection fraction (per 1% increase)	0.983	0.961-1.007	.162
Post-op TAPSE/PASP ratio (per 0.01 mm/mm Hg increase)	0.856	0.743-0.988	**.033**
Post-op maximal aortic gradient (per 1 mm Hg increase)	0.962	0.917-1.008	.108

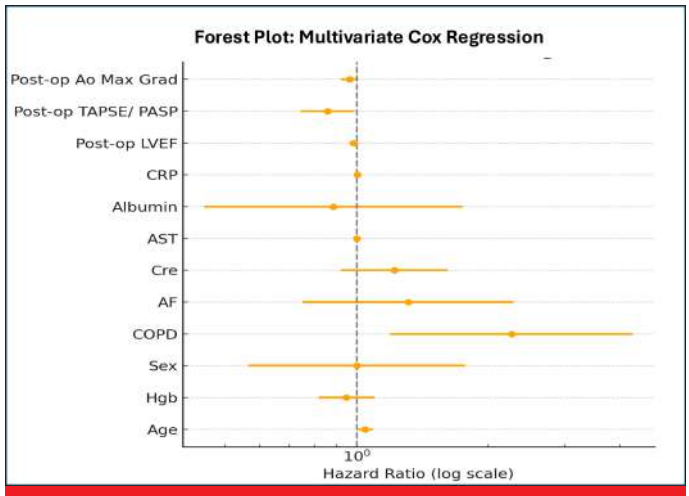

Figure 3. Forest plot of multiple Cox regression analysis. Forest plot depicting the independent predictors of long-term mortality after transcatheter aortic valve implantation (TAVI) identified in the multiple Cox regression model. Age, chronic obstructive pulmonary disease (COPD), and postoperative tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP) were retained as significant predictors, with postoperative TAPSE/PASP demonstrating an independent protective effect (per 0.1 mm/mm Hg increase; HR 0.856, 95% CI: 0.743-0.988, *P* = .033).

the preprocedural status alone, may be a critical determinant of long-term prognosis.

Our findings are consistent with and extend previous evidence regarding the prognostic significance of RV–PA coupling in patients undergoing TAVI. Sultan et al[11] (2019) demonstrated that a lower baseline TAPSE/PASP ratio was independently associated with increased mortality following the procedure. In a subsequent study, Adamo and colleagues (2022) confirmed that impaired RV–PA coupling identified patients at higher risk, irrespective of traditional surgical risk scores.[15] However, the majority of earlier studies primarily focused on preoperative assessments, which characterize chronic RV–PA uncoupling but not the dynamic hemodynamic recovery that follows TAVI.[11,15,16] More recently, Mendes et al[12] (2024) reported that postoperative TAPSE/PASP measurements offered superior prognostic discrimination compared with preprocedural values, highlighting the importance of RV functional adaptation and pulmonary pressure reduction after valve intervention. Our findings reinforce and extend these observations, demonstrating that early postoperative TAPSE/PASP not only reflects residual hemodynamic burden but also encapsulates the degree of RV recovery, thereby serving as an integrative marker of both structural and functional remodeling.

Table 4. Pre- and Postoperative TAPSE/PASP Ratio and its Change (Δ) According to Postoperative Coupling Group

Variables	<0.52 (n = 278)	≥ 0.52 (n = 508)	*P*
Pre-op TAPSE/PASP, cm/mm Hg	0.36 ± 0.09	0.61 ± 0.12	< .001
Post-op TAPSE/PASP, cm/mm Hg	0.37 ± 0.10	0.72 ± 0.13	< .001
Δ TAPSE/PASP, cm/ mm Hg	+ 0.01 ± 0.11	+ 0.11 ± 0.12	< .001

PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Lillo et al[17] (2022) investigated RV systolic function and RV–PA coupling in patients with severe AS, focusing on early changes after TAVI. They reported that while early postoperative RV systolic function did not show significant improvement, a reduction in pulmonary artery systolic pressure led to an increase in TAPSE/PASP, indicating partial restoration of RV–PA coupling. In our cohort, the prognostic association of postoperative TAPSE/PASP beyond the early phase suggests that long-term outcomes are influenced by the persistence or reversal of uncoupling, supporting the hypothesis that early hemodynamic unloading does not uniformly translate into sustained myocardial recovery. Future prospective studies incorporating serial echocardiographic follow-up could clarify whether normalization of TAPSE/PASP over time confers durable prognostic benefit.

Furthermore, recent meta-analytic data support the broader prognostic role of TAPSE/PASP across cardiovascular conditions. In a systematic review and meta-analysis including nearly 9,000 patients with heart failure, Anastasiou et al[18] (2023) reported that lower TAPSE/PASP values were strongly associated with increased all-cause mortality, with patients below the commonly reported threshold of 0.36 mm/mmHg experiencing a nearly threefold higher risk of death. Although this meta-analysis focused primarily on heart failure cohorts, the consistent prognostic signal across different patient populations reinforces the clinical relevance of RV–PA coupling assessment. Taken together, these findings suggest that TAPSE/PASP integrates the hemodynamic and functional dimensions of RV performance, providing incremental prognostic value not only in heart failure but also in the post-TAVI setting examined in our study.

The mechanisms underlying this association are likely multifactorial. Severe aortic stenosis is characterized by chronic left ventricular pressure overload leading to secondary pulmonary hypertension, increased RV afterload, and progressive structural remodeling with fibrosis and impaired contractile reserve.[19] Although TAVI reduces left-sided pressures, the pulmonary vasculature may exhibit fixed remodeling, limiting afterload reduction for the RV. Consequently, persistent RV–PA uncoupling after TAVI may reflect advanced myocardial and vascular remodeling rather than technical procedural failure. The observed associations between lower TAPSE/PASP, higher BNP levels, and a greater prevalence of atrial fibrillation in our cohort support the concept of ongoing myocardial stress and impaired reverse remodeling in these patients.

The threshold identified in our analysis (0.52 mm/mm Hg) lies toward the upper range of those previously reported, which have varied from 0.32 to 0.55 mm/mmHg.[12,15] Differences in patient selection, procedural techniques, and timing of assessments may account for this variability. Nevertheless,

the consistent direction of findings across studies supports the clinical relevance of impaired RV–PA coupling as a marker of increased risk.

The ΔTAPSE/PASP analysis further underscores that only patients demonstrating postoperative RV–PA recoupling achieved significant hemodynamic improvement, highlighting the prognostic importance of early RV adaptation after TAVI. From a clinical perspective, TAPSE/PASP is an easily obtainable, reproducible parameter that can be incorporated into routine postoperative echocardiographic evaluations without additional resource requirements. Identification of patients with impaired postoperative RV–PA coupling may guide closer follow-up, tailored heart failure management, and targeted therapies aimed at reducing pulmonary pressures or improving RV contractile performance. However, given the moderate discriminatory ability observed in our cohort, TAPSE/PASP should be used as part of a multiparametric risk assessment strategy—in conjunction with clinical variables, biomarkers, and advanced imaging indices—rather than as a standalone prognostic tool. Future studies integrating TAPSE/PASP into comprehensive risk models or machine-learning frameworks could refine patient stratification and optimize post-TAVI care.

Limitations

Several limitations should be acknowledged. First, this was a single-center, retrospective study, which may limit generalizability and introduce selection bias. Second, echocardiographic evaluations were performed between postoperative days 3 and 7 (median 4 [IQR 3-6]); although this reflects real-world practice, the lack of serial imaging beyond this period precluded assessment of long-term temporal trends in RV–PA coupling. Third, advanced imaging modalities such as right ventricular strain analysis and quantitative assessment of tricuspid regurgitation were not systematically available, limiting comprehensive evaluation of RV function. Fourth, the primary endpoint was all-cause mortality; differentiation between cardiovascular and non-cardiovascular deaths was not feasible because of incomplete adjudication data. Fifth, the study period overlapped with the COVID-19 pandemic, which may have influenced patient selection and follow-up patterns. Finally, although multivariable adjustments were performed, the potential for residual confounding due to unmeasured variables—such as medication optimization or heart failure management—cannot be excluded. Despite these limitations, the study provides novel, hypothesis-generating evidence that warrants prospective multicenter validation.

CONCLUSION

In summary, this study demonstrates that a lower postoperative TAPSE/PASP ratio (<0.52 mm/mm Hg) is independently associated with increased long-term mortality, reflecting persistent right ventriculo–pulmonary artery (RV–PA) uncoupling despite technically successful TAVI. These findings emphasize the clinical value of postoperative RV–PA coupling as an integrative marker of residual pulmonary load and right ventricular recovery, suggesting that its routine assessment may enhance early post-TAVI risk reclassification and guide closer clinical follow-up or targeted therapy in high-risk patients. Prospective multicenter studies incorporating serial echocardiographic and advanced imaging assessments are needed to validate these observations, determine optimal timing and thresholds for TAPSE/PASP evaluation, and clarify whether interventions aimed at improving RV–PA coupling can translate into better long-term outcomes after TAVI.

Ethics Committee Approval: This study was approved by the Ethics Committee of Koşuyolu High Specialization Training and Research Hospital (Approval No: 2025/12/1198, Date: 22/07/2025).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.T.U., A.K., E.A.; Design – S.T.U., İ.B., A.K.; Supervision – A.K., E.A.; Resources – H.E., B.B., T.K., D.Ş.; Materials – H.E., F.K., B.G.Ş.; Data Collection and/or Processing – S.T.U., B.K., H.E., B.B., T.K., D.Ş., M.K., F.K.; Analysis and/or Interpretation – S.T.U., İ.B., R.D.A., E.A.; Literature Search – S.T.U., B.K., İ.B.; Writing – S.T.U., İ.B.; Critical Review – A.K., E.A., R.D.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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Comments on Nonsustained Atrial Fibrillation and Stroke Risk: Methodological and Interpretive Considerations

LETTER TO THE EDITOR

To the Editor,

We read with interest the study by Yurtseven et al,[1] which investigates the association between nonsustained atrial fibrillation (NS-AF) episodes lasting less than 30 seconds and ischemic stroke risk.[1] While the study addresses a clinically relevant question, we identified several issues that warrant discussion, including inconsistencies within the manuscript, discrepancies with existing literature, and methodological limitations.

The study reports a significant association between NS-AF episodes (<30 seconds) and stroke risk (OR = 3.930, 95% CI: 1.235-12.510, $P = .021$), with a CHA2DS2-VA score ≥2 showing high sensitivity (85.7%) for predicting stroke. However, a discrepancy in the reported sample size raises concerns. The methods section states that 133 patients with NS-AF and 113 controls were included (totaling 246), but the results section references 163 NS-AF patients (Table 1). This inconsistency questions the accuracy of patient inclusion and statistical analyses. Could the authors clarify the correct sample size and its impact on the study's findings?

The conclusion that NS-AF episodes <30 seconds independently increase stroke risk contrasts with studies suggesting that brief AF episodes carry minimal risk unless prolonged. The ASSERT trial found that subclinical AF episodes >24 hours were strongly associated with stroke, while shorter episodes (<6 minutes) showed weaker links.[2] Similarly, the RATE Registry reported no significant stroke risk for AF episodes of 10-20 seconds.[3] Although cited, these studies are not reconciled with the current findings. How do the authors explain this divergence, particularly given the limitations of 24-hour Holter monitoring in capturing AF burden?

Methodologically, the retrospective design and reliance on 24-hour Holter monitoring may underestimate AF burden, as longer monitoring (e.g., implantable devices) is more sensitive. The authors acknowledge this but do not discuss its impact. Additionally, excluding patients with paroxysmal or persistent AF during follow-up relied on hospital records and phone interviews, which may miss subclinical AF, potentially confounding results. Propensity score matching failed to eliminate age differences ($P = .045$ post-matching), a critical confounder given age's association with stroke risk.[4] Why did age remain unmatched, and how does this affect the reported odds ratio for NS-AF? Furthermore, the definition of NS-AF as "more than 3 consecutive irregular atrial contractions without visible P waves" lacks specificity, risking inclusion of non-specific atrial ectopy.[5] How was this definition validated and were inter-observer agreement metrics assessed?

We pose the following questions: (1) Can the authors resolve the sample size discrepancy (133 vs. 163)? (2) What mechanistic insights explain the elevated stroke risk in this cohort compared to conflicting literature? (3) Why was 24-hour Holter monitoring chosen over longer-term monitoring, and how was subclinical AF accounted for? (4) Why was CHA2DS2-VA used instead of CHA2DS2-VASc, and how does this affect generalizability?

Çağrı Zorlu
Sefa Erdi Ömür

Department of Cardiology, Tokat Gaziosmanpaşa University Hospital, Tokat, Türkiye

Corresponding author:
Çağrı Zorlu
✉ zorlufb@hotmail.com

Cite this article as: Zorlu Ç, Ömür SE. Comments on nonsustained atrial fibrillation and stroke risk: methodological and interpretive considerations. *Anatol J Cardiol.* 2026;30(3):200-201.

DOI:10.14744/AnatolJCardiol.2025.5722

While the study highlights a potential stroke risk in brief NS-AF episodes, these issues limit the robustness of the findings. We encourage the authors to address these concerns and suggest larger prospective studies with extended monitoring to guide anticoagulation strategies.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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Reply to Letter to the Editor: "Comments on Nonsustained Atrial Fibrillation and Stroke Risk: Methodological and Interpretive Considerations"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the authors[1] for their thoughtful comments on our article.[2]

First, we would like to clarify that the figure "163" in the first sentence of the Results section was a typographical error. The correct number of patients with NS-AF at inclusion was 133, and this has been corrected in the published version. After propensity score matching, 20 cases were excluded, yielding 113 patients in the NS-AF group and 113 controls for all subsequent analyses.

Regarding the authors' questions:

In both the ASSERT and RATE trials, patients with cardiac devices were enrolled; these individuals had a higher risk of cardiovascular events and closer follow-up.[3,4] In contrast, our cohort comprised symptomatic patients referred for palpitations, with visually adjudicated clinical AF episodes rather than device-detected atrial high-rate episodes. In those trials, AF was detected by device algorithms, which may sometimes be confused with atrial tachyarrhythmias. In our study, we did not consider regular rhythms as atrial fibrillation during Holter evaluation and excluded them from analysis. There are also notable differences between the study populations. The ASSERT trial included hypertensive patients aged ≥65 years, and aspirin use was around 60%, whereas in the RATE trial, approximately 15% of patients were receiving anticoagulant therapy. We acknowledge the limitations of 24-hour Holter monitoring and the potential underestimation of AF burden. Our patient population who documented episodes of an AF episode (even very short) in only 24-hour Holter monitoring is also quite different from the patient population who had short episodes of AF in continuous rhythm monitoring in the ASSERT and RATE registry. To be able to document AF in patients in only 24-hour Holter monitoring probably indicates that those patients either already had longer episodes of AF/higher AF load or would develop it.

In our study, all brief AF episodes were verified by 2 independent observers using 3-channel ECG recordings, and age was adjusted for in multivariable models, in which NS-AF remained an independent predictor of ischemic stroke. While extended monitoring and long-term prospective follow-up are indeed important, our primary aim was to highlight a common problem in everyday clinical practice, brief AF episodes detected on routine Holter monitoring, and to help clinicians avoid overlooking the increased stroke risk, particularly among patients with higher CHA_2DS_2-VA scores. Moreover, in previous studies, even the presence of short atrial runs on 48-hour Holter monitoring has been shown to be associated with an increased risk of stroke and adverse cardiovascular outcomes.[5] For such individuals, closer follow-up and individualized risk assessment may be warranted. We did not claim that these patients never experienced longer episodes;

Ece Yurtseven[1]
Dilek Ural[1]
Kurtuluş Karaüzüm[2]
İrem Yılmaz[2]
Yengi Umut Çelikyurt[2]
Kaan Hancı[2]
Müjdat Aktaş[2]
Ümit Yaşar Sinan[3]
Serdar Küçükoğlu[3]
Ayşen Ağaçdiken Ağır[2]

[1]*Department of Cardiology, Faculty of Medicine, Koç University, İstanbul, Türkiye*
[2]*Department of Cardiology, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye*
[3]*Department of Cardiology, İstanbul University-Cerrahpaşa, Institute of Cardiology, İstanbul, Türkiye*

Corresponding author:
Ece Yurtseven
✉ eyurtseven@ku.edu.tr

Cite this article as: Yurtseven E, Ural D, Karaüzüm K, et al. Reply to letter to the editor: "Comments on nonsustained atrial fibrillation and stroke risk: methodological and interpretive considerations". *Anatol J Cardiol.* 2026;30(3):202-203.

DOI:10.14744/AnatolJCardiol.2025.5725

Table 1. Independent Predictors of Ischemic Stroke in Multivariable Model Incorparating the CHA_2DS_2-VASc Score

Variables	OR [Exp(B)]	95% CI (Lower–Upper)	*P*
eGFR	0.997	0.975-1.018	.752
Pulmonary artery systolic pressure	1.018	0.981-1.056	.357
Left atrium enlargement	0.978	0.872-1.097	.707
Left ventricle hypertrophy	1.920	0.755-4.881	.171
CHA_2DS_2-VASc score	1.603	1.210-2.123	<.001
Paroxysmal atrial fibrillation	3.623	1.231-10.665	.019

eGFR, estimated glomerular filtration rate; NS-AF, non-sustained atrial fibrillation.

rather, our key message is that when short AF episodes are observed on Holter monitoring, clinicians should recognize the elevated stroke risk, especially when the CHA_2DS_2-VA score is ≥2.

We used the CHA_2DS_2-VA score because the latest European Society of Cardiology guidelines recommend its use.[6] The ASSERT trial applied the CHA_2DS_2-VASc score, whereas the RATE trial used the CHA_2DS_2 score. To eliminate any confusion, we also reanalyzed our cohort using the CHA_2DS_2-VASc score, and the independent predictive value of short AF episodes remained unchanged (Table 1).

We appreciate the opportunity to provide these clarifications and thank the reviewers for their valuable insights.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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Commentary on the Prognostic Interpretation of the Triglyceride-Glucose Index in Patients with HCM and HFpEF

LETTER TO THE EDITOR

To the Editor,

I read with great interest the article by Liu et al,[1] titled "Association Between Triglyceride–Glucose Index and Prognosis of Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction," recently published in the *Anatolian Journal of Cardiology*. The authors should be congratulated for addressing the prognostic relevance of the triglyceride–glucose (TyG) index in a challenging and understudied clinical population. Several methodological and pathophysiological considerations, however, merit further discussion.

The proposed physiological explanation for the "protective effect" of higher TyG levels appears insufficient. Elevated TyG is widely recognized as a marker of insulin resistance, metabolic impairment, and proarrhythmogenic electrical abnormalities.[2-4] In high-risk populations such as hypertrophic cardiomyopathy (HCM) with heart failure with preserved ejection fraction (HFpEF)—where electrical instability and myocardial remodeling are prominent—an increase in TyG would typically be expected to worsen, rather than improve, mortality. The hypothesis of "adaptive glucose oxidation" in hypertrophied myocardium remains speculative and lacks mechanistic evidence. More plausible explanations, including residual confounding, selection bias, metabolic reverse epidemiology, and unmeasured clinical variables, should be considered. Clarifying this paradox requires prospectively designed and phenotypically more homogeneous studies.

The markedly unequal distribution of diabetes across TyG quartiles introduces additional confounding. Diabetes prevalence increases from 7.3% to 21.3% across quartiles, and patients in the upper quartile are more likely to receive cardioprotective agents—particularly sodium-glucose co-transporter 2 (SGLT2) inhibitors—that independently reduce mortality and hospitalization.[5] Such therapeutic effects may obscure or distort the true association between TyG and outcomes. Adjustment or stratification by antidiabetic therapy would help disentangle these overlapping effects.

Further limitations include substantial heterogeneity within the HCM/HFpEF population—comprising obstructive, non-obstructive, apical, and restrictive phenotypes—which may mask phenotype-specific associations. The retrospective design also precludes causal inference, and residual confounding related to nutritional status, body composition, metabolic comorbidities, and hemodynamic parameters cannot be excluded. Moreover, the lack of external validation limits generalizability, particularly given inter-population differences in TyG distribution. Finally, only 56 cases of sudden cardiac death (SCD) were recorded, rendering the study underpowered to draw firm conclusions regarding the absence of a TyG–SCD relationship.

In conclusion, while this study provides valuable preliminary insight, the paradoxical direction of the associations, the potential for metabolic and therapeutic confounding, the phenotypic heterogeneity of the cohort, and the limited power for SCD outcomes warrant cautious interpretation. Future prospective studies with standardized metabolic profiling, adequate adjustment for medical therapies,

Ahmet Yılmaz

Department of Cardiology, Faculty of Medicine, Karamanoğlu Mehmetbey University, Karaman, Türkiye

Corresponding author:
Ahmet Yılmaz
✉ dr.ahmetyilmaz@gmail.com

Cite this article as: Yılmaz A. Commentary on the prognostic interpretation of the triglyceride-glucose index in patients with HCM and HFpEF. *Anatol J Cardiol.* 2026;30(3):204-205.

DOI:10.14744/AnatolJCardiol.2025.6029

and external validation are essential to determine whether TyG truly carries prognostic significance in patients with HCM-HFpEF.

Declaration of Interests: The author has no conflicts of interest to declare.

Funding: The author declare that this study received no financial support.

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Reply to the Letter to the Editor: "Commentary on the Prognostic Interpretation of the Triglyceride-Glucose Index in Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the reader[1] for their thoughtful commentary and for engaging with our study[2] on the triglyceride-glucose (TyG) index in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF). We appreciate the opportunity to address the methodological and pathophysiological points raised.

The reader rightly notes that an elevated TyG index is conventionally associated with insulin resistance and adverse outcomes in the general population. However, we propose that the observed protective association in HCM-HFpEF may reflect a context-dependent metabolic phenotype unique to this population. In HCM, chronic pressure overload induces a shift in myocardial substrate utilization from fatty acid oxidation toward glucose oxidation, a well-documented adaptive response to maintain energetic efficiency.[3] This metabolic remodeling is supported by positron emission tomography studies showing increased glucose uptake in hypertrophied myocardium.[4] Thus, a higher TyG index in this specific setting may not solely reflect systemic insulin resistance but could also indicate enhanced myocardial glucose availability. While we acknowledge the observed protective effect requires further mechanistic validation, it is consistent with prior evidence in HCM populations.[5]

We agree that the unequal distribution of diabetes and related treatments across TyG quartiles is an important consideration. However, our multivariable models are adjusted for diabetes status and key comorbidities.[2] Furthermore, during the study period, the use of sodium-glucose cotransporter 2 inhibitors in this multicenter Chinese HCM-HFpEF cohort was not widespread, minimizing their potential confounding effect. Nevertheless, we recognize that unmeasured or residual confounding, including detailed antidiabetic therapy, cannot be entirely excluded in a retrospective design.

Regarding phenotypic heterogeneity, our cohort indeed included varied HCM subtypes. However, this reflects real-world clinical diversity, and our models adjusted for relevant echocardiographic parameters, including left ventricular diameter, left atrial diameter, right atrial diameter, maximum wall thickness, and left ventricular outflow tract gradient to mitigate confounding.[2] We agree that future studies with deeper phenotyping are needed to explore subtype-specific associations.

We also acknowledge the limitation regarding sudden cardiac death. With only 56 events, the analysis was underpowered to detect modest associations, a point explicitly stated in the Study Limitations part of our study.[2] This does not

Yi Zheng[1,#]
Lei Liu[2,#]
Xiaoping Li[3,*]
Tong Liu[1,*]

[1]*Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China*
[2]*Department of Cardiology, Suining Central Hospital, Suining, China*
[3]*Institute of Cardiovascular Diseases & Department of Cardiology, Ultrasound in Cardiac Electrophysiology and Biomechanics Key Laboratory of Sichuan Province, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*

Corresponding author:
Tong Liu
✉ liutongdoc@126.com

Cite this article as: Zheng Y, Liu L, Li X, Liu T. Reply to the letter to the editor: "Commentary on the prognostic interpretation of the triglyceride-glucose index in patients with hypertrophic cardiomyopathy and heart failure with preserved ejection fraction." *Anatol J Cardiol.* 2026;30(3):206-207.

#These authors contributed equally.
*joint senior authors.

DOI:10.14744/AnatolJCardiol.2025.6052

negate the robust associations observed for all-cause and cardiovascular mortality in a large, well-characterized cohort.

In conclusion, while the paradoxical association challenges conventional interpretations, it underscores the importance of contextualizing biomarkers within specific disease pathophysiology. We agree that prospective studies with detailed metabolic profiling, standardized therapies, and external validation are essential. Our findings highlight a potentially unique role of TyG in HCM-HFpEF that warrants further investigation.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Comment on "Association Between Triglyceride-Glucose Index and Prognosis of Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction"

LETTER TO THE EDITOR

To the Editor,

I read with great interest the article by Liu et al[1] entitled "Association Between Triglyceride-Glucose Index and Prognosis of Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction," recently published in the *Anatolian Journal of Cardiology* [2025;29(11):619-629]. The authors deserve credit for addressing an underexplored intersection between metabolic dysregulation and myocardial structural disease.

Their observation that a higher triglyceride-glucose (TyG) index was associated with lower all-cause and cardiovascular mortality in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF) challenges the conventional view that elevated TyG reflects adverse cardiometabolic risk. This intriguing "metabolic paradox" warrants deeper consideration.

In my opinion, the unexpected inverse relationship may reflect adaptive metabolic remodeling rather than a true protective effect of insulin resistance. In hypertrophied myocardium, a shift from fatty acid oxidation toward glucose utilization is an established compensatory mechanism to maintain energy efficiency. Enhanced glycolytic flux in this setting could theoretically translate into higher TyG values, yet indicate more active glucose metabolism rather than systemic insulin resistance. This interpretation aligns with positron emission tomography studies showing increased glucose uptake in hypertrophic segments of HCM hearts.

Furthermore, the study excluded patients with reduced left ventricular ejection fraction and low N-terminal pro–B-type natriuretic peptide levels, potentially enriching the cohort with metabolically stable individuals. Consequently, the higher TyG index might simply mark better metabolic reserve rather than protection against adverse outcomes. It would be informative to analyze whether this relationship persists after adjusting for body composition, nutritional parameters, and inflammatory status, which are known to influence both TyG and survival in chronic heart failure.

Another aspect worth exploring is the sex-specific metabolic adaptation observed in the subgroup analysis. The inverse association between TyG and mortality was significant only in males. This finding may reflect sex-related differences in myocardial substrate preference, mitochondrial function, and hormonal modulation of insulin signaling. Investigating these mechanisms in future studies could illuminate the biological basis of this disparity.

Finally, this work opens an important discussion about whether metabolic indices such as TyG should be interpreted uniformly across different cardiac phenotypes. While TyG is a reliable surrogate of insulin resistance in metabolic syndrome and atherosclerosis, its prognostic meaning may diverge in structural heart diseases characterized by altered myocardial energetics. Clarifying this distinction could substantially refine the use of TyG as a clinical biomarker in cardiomyopathies.

Gamze Yeter Arslan

Department of Cardiology, Kepez State Hospital, Antalya, Türkiye

Corresponding author:
Gamze Yeter Arslan
✉ dr.gamzeyeterarslan@gmail.com

Cite this article as: Arslan GY. Comment on "Association between triglyceride-glucose index and prognosis of patients with hypertrophic cardiomyopathy and heart failure with preserved ejection fraction." *Anatol J Cardiol.* 2026;30(3):208-209.

DOI:10.14744/AnatolJCardiol.2025.5988

We sincerely congratulate Liu et al for stimulating a new line of thought in cardio-metabolic research and hope that future prospective and mechanistic studies will further elucidate whether the "protective" TyG signal in HCM-HFpEF reflects a compensatory phenomenon or a true prognostic advantage.[2-5]

Declaration of Interests: The author has no conflicts of interest to declare.

Funding: The author declare that this study received no financial support.

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Reply to the Letter to the Editor: "Comment on 'Association Between Triglyceride-Glucose Index and Prognosis of Patients with Hypertrophic Cardiomyopathy and Heart Failure with Preserved Ejection Fraction'"

LETTER TO THE EDITOR REPLY

To the Editor,

We sincerely thank the reader[1] for their thoughtful and constructive comments regarding our study[2] on the triglyceride-glucose (TyG) index in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF). We appreciate the opportunity to further discuss the potential mechanisms and implications of our findings.

The reader aptly characterizes the observed inverse relationship between the TyG index and mortality as a "metabolic paradox." We agree that this finding challenges the conventional view of the TyG index as a marker of adverse cardiometabolic risk. As the reader suggests, this paradox may indeed reflect adaptive metabolic remodeling in the context of HCM. In the hypertrophied myocardium, energy substrate preference shifts from fatty acid oxidation toward glucose utilization to maintain ATP production under pressure overload. This compensatory increase in glycolytic flux may contribute to higher TyG values, which in this specific setting could indicate a more favorable metabolic phenotype rather than systemic insulin resistance.

Regarding the potential influence of cohort selection, we acknowledge that our exclusion of patients with reduced left ventricular ejection fraction and low N-terminal pro-B-type natriuretic peptide may have enriched the study with a more metabolically stable population. However, our multivariable models extensively adjusted for key clinical, biochemical, and echocardiographic confounders, including N-terminal pro-B-type natriuretic peptide, left ventricular ejection fraction, renal function, and inflammatory markers.[2] While we did not have data on body composition or detailed nutritional parameters, the consistency of the association across multiple models and subgroup analyses supports the robustness of the findings. We agree that future studies incorporating these additional parameters would be valuable.

The sex-specific association, where the protective relationship was significant only in males, is indeed intriguing and warrants further investigation. As noted, this may reflect underlying differences in myocardial substrate metabolism, mitochondrial efficiency, or hormonal regulation. Our subgroup analysis was exploratory, and we emphasize the need for dedicated studies to dissect the sex-specific metabolic adaptations in patients with HCM and HFpEF.

Finally, we fully concur with the reader's concluding insight: the interpretation of the TyG index must be contextualized within the specific cardiac phenotype. While it reliably indicates insulin resistance in general populations, its prognostic significance appears to be reversed in patients with HCM and HFpEF, a population

Yi Zheng[1,#]
Lei Liu[2,#]
Xiaoping Li[3,*]
Tong Liu[1,*]

[1]*Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China*
[2]*Department of Cardiology, Suining Central Hospital, Suining, China*
[3]*Institute of Cardiovascular Diseases & Department of Cardiology, Ultrasound in Cardiac Electrophysiology and Biomechanics Key Laboratory of Sichuan Province, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*

Corresponding author:
Tong Liu
✉ liutongdoc@126.com

Cite this article as: Zheng Y, Liu L, Li X, Liu T. Reply to the letter to the editor: "Comment on 'association between triglyceride-glucose index and prognosis of patients with hypertrophic cardiomyopathy and heart failure with preserved ejection fraction'". *Anatol J Cardiol.* 2026;30(3):210-211.

#These authors contributed equally.
*joint senior authors.

DOI:10.14744/AnatolJCardiol.2025.5903

with distinct myocardial energetics. This underscores the importance of disease-specific biomarker validation.

We thank the reader for their insightful critique and for highlighting the need to explore whether the TyG index reflects compensatory metabolism or a true prognostic advantage. Further prospective studies will be essential to clarify these mechanisms.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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A Fishbone-Like Bone Cement Fragment Crossing the Tricuspid Valve and Penetrating the Septum: Rare Sequela of Percutaneous Vertebroplasty

E-PAGE ORIGINAL IMAGE

Percutaneous vertebroplasty is a commonly used minimally invasive procedure for osteoporotic or metastatic vertebral compression fractures, but cement leakage is frequent and, in rare cases, may enter the paravertebral venous system, migrate to the azygos vein and inferior vena cava, and finally reach the right atrium or ventricle, leading to severe complications such as arrhythmia, cardiac perforation, or pulmonary embolism. We report a case of delayed intracardiac cement embolism occurring 1 year after vertebroplasty. A 77-year-old woman presented with recurrent dizziness, palpitations, and precordial stabbing pain. Echocardiography and computed tomography revealed a linear high-density fragment extending across the tricuspid valve into the right heart chambers (Figure 1). Open-heart surgery under cardiopulmonary bypass removed a 7-cm fishbone-shaped cement

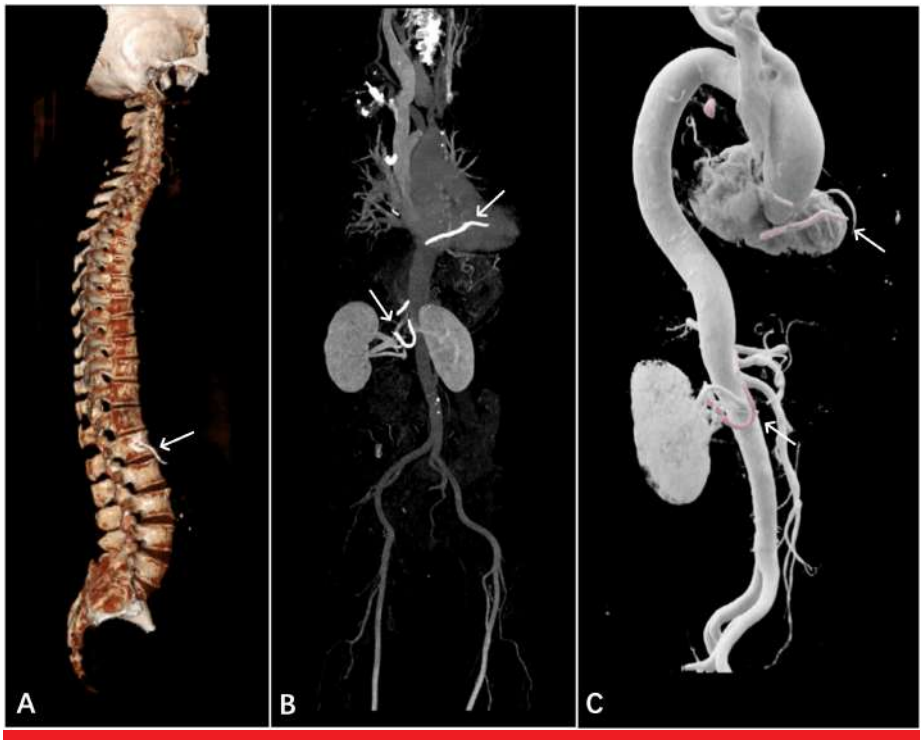

Figure 1. Contrast-enhanced CT with 3D reconstruction. Figure A shows a strip-like, fishbone-shaped bone cement fragment originating from the right anterolateral aspect of the T12 vertebral body. Figure B demonstrates the presence of bone cement adjacent to the T12 vertebra and within the heart. Figure C presents a 3D reconstruction of the fishbone-shaped bone cement fragment and its anatomical relationship to surrounding structures; the pink strip in the image represents the bone cement.

Xin Xie

Yibing Fang

Department of Cardiac Surgery, First Affiliated Hospital, Army Medical University (Third Military Medical University), Chongqing, China

Corresponding author:
Yibing Fang
✉ fybohyes@163.com

Cite this article as: Xie X, Fang Y. A fishbone-like bone cement fragment crossing the tricuspid valve and penetrating the septum: rare sequela of percutaneous vertebroplasty. *Anatol J Cardiol.* 2026;30(3):E-9-E-10.

DOI:10.14744/AnatolJCardiol.2025.6015

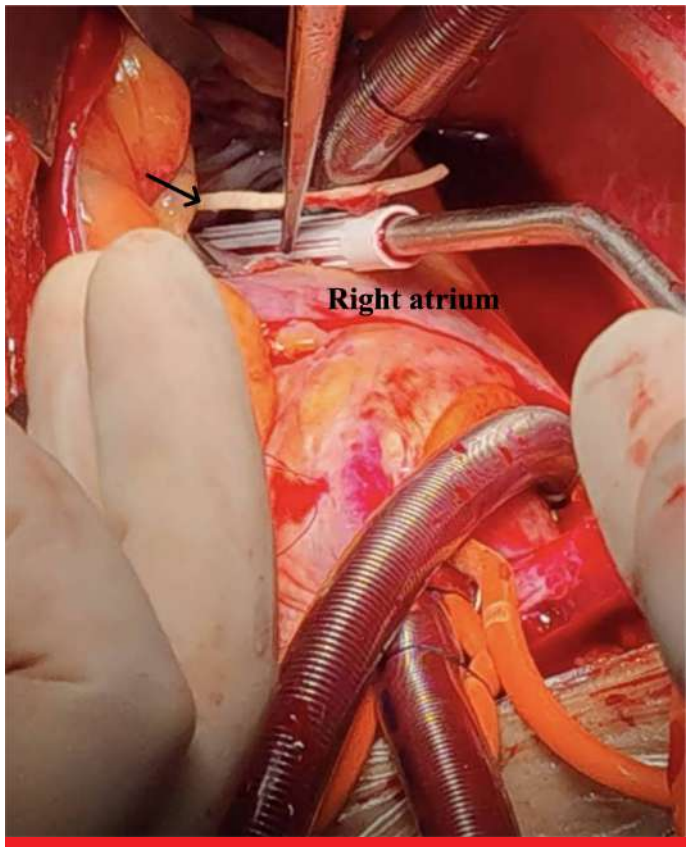

Figure 2. Intraoperative view of the intracardiac bone cement fragment. The surgical plan involved cardiopulmonary bypass with a beating heart. The right atrium was incised to expose the bone cement fragment, which was then completely removed.

fragment (Figure 2), and no major myocardial injury was observed. The patient recovered uneventfully.

Cement leakage is related to osteoporosis severity, vertebral integrity, injection pressure, and cement viscosity; venous leakage is most likely to cause distant embolization. Intracardiac cement fragments may induce serious cardiovascular events, and asymptomatic cases can delay diagnosis. Management should be individualized according to symptoms, fragment location, and mobility; surgery is recommended when there is cardiac involvement or high risk of complications. Prevention relies on thorough preoperative assessment, meticulous injection technique, and vigilant postoperative monitoring. Nonspecific symptoms such as palpitations, chest pain, or dyspnea after vertebroplasty warrant timely imaging to detect potential embolism and reduce adverse outcomes.

Informed Consent: Written informed consent was obtained from the patient for participation in the study.

Declaration of Interests: The authors have no conflicts of interest to declare.

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