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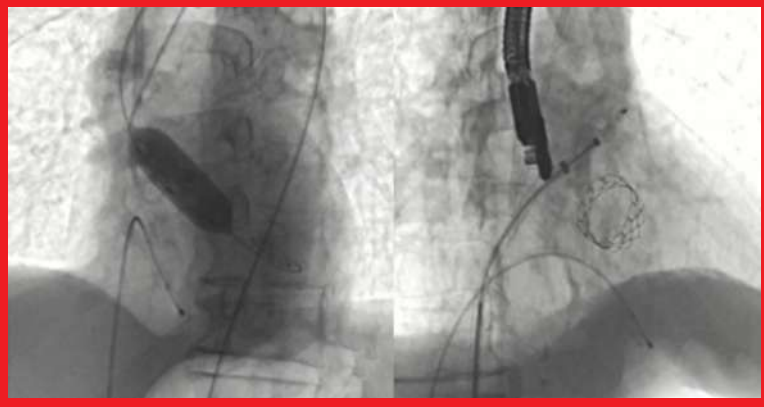
Original Investigations



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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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

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

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

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Ethics

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

Artificial Intelligence (AI)–Assisted Technology

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

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

1. Title Page

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

2. Main Text

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

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

B. References

C. Special Terms and Conditions

A. Manuscript types

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

- **Editorial Comment**

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

- Title
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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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  Knowledge confirmed by the results of recent research studies, involved in education at academic level and used in clinical practices should be presented in detail in this type of manuscript.
- Title
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  Manuscripts which announce a new scientific invention, are clinically significant, and are in the form of a preliminary report are accepted for publication as scientific letters.
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- Abstract and Keywords should not be included.
- For scientific letters submitted by Turkish authors or from Türkiye, the Title should also be provided in Turkish. For letters submitted by foreign authors outside Türkiye, the translation of these sections will be carried out by Editor-in-Chief's Office.

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

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  Impressive and rare images that reflect significant findings based on clinical science,
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- **Scientific Puzzle**

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

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

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

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

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

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

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

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

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

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

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

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

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

EVALUATION AND PUBLICATION

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

CONTENTS

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Selexipag for Pulmonary Hypertension, TAVI and more

EDITORIAL

Atrial septal defect closure can be performed surgically or via transcatheter intervention, yet comparative outcomes remain inconsistent between children and adults. Kannady et al from Indonesia in their meta-analysis synthesized observational evidence to evaluate procedural success, complications, and peri-procedural characteristics across both populations.

Transcatheter aortic valve replacement (TAVR) is the standard therapy for severe aortic stenosis, particularly in elderly patients with comorbidities. Simple biomarkers to predict mid-term mortality are still needed. Aslan et al from Türkiye evaluated the prognostic value of the preprocedural neutrophil percentage-to-albumin ratio for 2-year all-cause mortality after TAVR.

Serum miR-107 may have significant potential in diagnosing cardiac hypertrophy in maintenance hemodialysis (MHD) patients and is a potential biological indicator for cardiac hypertrophy in MHD patients. Li et al from China found this result in their study.

Patients with atrial fibrillation (AF) undergoing transcatheter aortic valve implantation (TAVI) often require long-term oral anticoagulation, which may not be appropriate for those at high bleeding risk. Performing left atrial appendage closure (LAAC) during TAVI can reduce the risk of thromboembolism while avoiding the need for prolonged anticoagulation. Kıvrak et al from Türkiye did same-session TAVI and LAAC in AF patients with high bleeding risk and found that it was technically feasible and showed an acceptable short-term safety profile.

Tokgöz et al from Türkiye assessed the efficacy and tolerability of the oral IP receptor agonist selexipag as part of sequential triple combination therapy in patients with pulmonary arterial hypertension. This is such an important study that two well known expert in this topic Roberto Badagliacca and Khodr Tello wrote an editorial on this sudy. Thanks all the contributors.

Najafov and Alekberov from Azerbaijan aimed to assess the prognostic significance of clinical, biochemical, and duplex ultrasound parameters in predicting ASCVD, and to determine the prevalence and predictors of preclinical atherosclerosis in dyslipidemic patients without clinically evident CAD.

And a case report, letters, e-page originals...

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

Çetin Erol

Editor-in-Chief, Ankara, Türkiye

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Transcatheter Versus Surgical Closure of Atrial Septal Defect in Children and Adults: A Systematic Review and Meta-Analysis of Observational Studies

ABSTRACT

Background: Atrial septal defect closure can be performed surgically or via transcatheter intervention, yet comparative outcomes remain inconsistent between children and adults. This review synthesizes observational evidence to evaluate procedural success, complications, and peri-procedural characteristics across both populations.

Methods: A systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines was conducted, including 36 observational studies published through 2024. Study quality was assessed using the Newcastle–Ottawa Scale. Random effects models were applied, with subgroup analyses by age and procedure type. Publication bias was examined using funnel plots and Egger's test.

Results: The pooled procedural success rate was 95% (95% CI: 92%-97%; I^2 = 90.2%). Among children, raw procedural success was 87% (1445/1656) for transcatheter closure and 99% (505/510) with surgery. In adults, transcatheter closure achieved 97% (95% CI: 90%-99%), whereas surgery reached 98% (95% CI: 70%-100%). Transcatheter closure resulted in shorter hospitalization (mean difference: −3.86 days, 95% CI: −6.03 to −1.69; P = .0004) and fewer major complications (risk ratio: 0.58, 95% CI: 0.39-0.86; P = .006). Sensitivity analysis restricted to high-quality studies (n = 12) remained consistent. Egger's regression did not indicate significant publication bias (P = .069).

Conclusion: Both approaches provide high closure success, yet transcatheter intervention offers lower complication rates and faster recovery, particularly in anatomically suitable patients. These findings support individualized treatment selection based on age, anatomy, and institutional experience.

Keywords: Atrial septal defect, complications, meta-analysis, procedural outcomes, surgical repair, transcatheter closure

META-ANALYSIS

INTRODUCTION

Atrial septal defect (ASD) is one of the most common congenital heart diseases, accounting for 10%-15% of cases in both children and adults. The secundum subtype predominates and, when left untreated, may lead to progressive right-sided volume overload, arrhythmia, pulmonary hypertension, and early mortality.[1-3] Closure is therefore recommended in symptomatic patients and in those with evidence of right ventricular dilation regardless of age.[3]

Surgical repair has long been the definitive treatment for ASD, achieving excellent long-term outcomes and near-complete defect closure. However, since the 1990s, transcatheter closure has emerged as a less invasive alternative for anatomically suitable patients, offering shorter recovery, reduced postoperative morbidity, and superior cosmetic results.[4,5] Current guidelines increasingly support transcatheter closure as first-line therapy when feasible.[4-6]

Despite these advantages, comparative evidence remains inconsistent. Most available data originate from observational studies rather than randomized trials, and reported outcomes vary considerably across age groups and clinical settings.

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Some studies suggest that transcatheter closure provides comparable or even superior safety profiles with fewer complications, while others emphasize the procedural durability of surgery, particularly in cases with complex or unfavorable anatomy.[6-9] Additionally, children and adults exhibit distinct technical challenges and comorbidity profiles that influence procedural success and complication risk, complicating comparative interpretation.[9]

Given these uncertainties, an updated synthesis is needed to clarify outcome differences between transcatheter and surgical closure across age groups. A systematic review and meta-analysis of observational studies comparing both approaches was conducted, focusing on procedural success, complication patterns, and peri-procedural characteristics in children and adults.

METHODS

Study Design

We conducted a systematic review and meta-analysis of observational studies comparing transcatheter and surgical ASD closure. This review adhered to PRISMA 2020 guidelines.[10] The protocol was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO;CRD420251052612). Because the published data was analyzed and did not include new patient contact, no ethical approval or consent was required.

Eligibility Criteria

We included observational studies such as prospective cohort studies, retrospective cohort studies, case-control studies, and national registries that reported outcomes of transcatheter or surgical ASD closure in children or adults. A study was eligible if it reported at least one of the following outcomes: procedural success, procedural characteristics including procedure duration, fluoroscopy duration, radiation exposure, length of stay, or complications during the procedure or follow-up period. Case reports, review articles, conference abstracts, and studies without extractable quantifiable outcome data were excluded.

Search Strategy

We conducted a comprehensive search of PubMed, Embase, Scopus, and Web of Science up to December 2024. Search terms included "atrial septal defect," "ASD," "transcatheter closure," "device closure," "surgical repair," and "outcomes" combined with Boolean operators. Reference lists from eligible studies were manually screened to identify additional publications.

Study Selection

Three reviewers independently screened titles and abstracts. Full text review followed for studies that met preliminary criteria. Disagreements were resolved through discussion with a fourth reviewer. The selection process is summarized in the PRISMA flow diagram.[10]

Data Extraction

Three reviewers extracted data independently using a structured data form. Extracted variables included study design, publication year, country, sample size, patient demographics including age, sex, and weight, anatomical characteristics of the defect, type of intervention, success rates, intra-procedural and follow-up complications, procedure duration, fluoroscopy duration, and length of hospital stay. Device type and device diameter for transcatheter closure were recorded when available and are presented in Supplementary Tables 1 and 2.

Procedural success was defined in this review as successful closure confirmed by imaging without major complications during the same admission. The included studies did not use a uniform definition because some investigators defined success based on device deployment alone, while others required the absence of complications or complete closure on follow-up imaging. To address these differences, a single operational definition was applied and the data elements that matched this definition as closely as possible were extracted. Only a limited number of studies used identical criteria; therefore, a sensitivity analysis restricted to studies with fully consistent definitions could not be performed.

Risk of Bias Assessment

We assessed methodological quality using the Newcastle–Ottawa Scale (NOS).[11] This tool evaluates 3 domains: patient selection, comparability of groups, and outcome assessment. Studies with a score of 7 or higher were classified as high quality.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Assessment

We assessed certainty of evidence using the GRADE framework. A summary of grading for each outcome is provided in Supplementary Table 3.

Outcomes of Interest

The primary outcome was procedural success, defined according to the standardized operational definition applied in this review. Secondary outcomes included procedure duration, fluoroscopy duration, radiation exposure, length of stay, and peri-procedural or follow-up complications. Variation in follow-up duration across studies limited time-specific outcome comparison.

Statistical Analysis

Meta analyses were performed using random effects models (DerSimonian–Laird). All analyses were conducted in

HIGHLIGHTS

- Transcatheter closure of atrial septal defect significantly reduces hospital stay and procedural complications compared to surgery.
- Both transcatheter and surgical approaches achieve high procedural success (>95%) across children and adult patients.
- Surgery remains indispensable for complex anatomy and large defects not amenable to device closure.
- Age-specific differences suggest that transcatheter closure is especially advantageous in pediatric patients.

RStudio (RStudio version 2024.12.0).[12] Risk ratios for dichotomous outcomes and mean differences for continuous outcomes were reported, each with 95% CIs. Data distribution for continuous outcomes including procedure duration and fluoroscopy duration was visually inspected and demonstrated right skew patterns in several studies. However, because most publications reported only mean and standard deviation without providing median or interquartile range values, transformation into nonparametric effect measures was not possible. Mean difference was therefore retained for consistency in pooled synthesis.

For outcomes that included 1 or more 0 event cells, a continuity correction of 0.5 was applied to enable computation of risk ratios. Peto or modified Mantel–Haenszel estimators were not applied because several outcomes contained studies with unbalanced sample distribution, and risk ratios provided a more clinically interpretable measure for comparison.

Statistical heterogeneity was quantified using the I^2 statistic.[13] Follow-up duration varied substantially across the included studies and ranged from early in-hospital assessments to long-term evaluations. Because the studies did not provide a consistent prespecified follow-up window, the outcome that most closely reflected the first systematic evaluation after the intervention was extracted. The analysis was not restricted to a single follow-up length because too few studies reported outcomes at identical time points. Stratified pooling based on short-term or long-term follow-up could not be performed for the same reason. The pooled estimates for late complications should therefore be interpreted as summaries of heterogeneous follow-up intervals rather than strictly comparable time-matched outcomes. Prespecified subgroup analyses were performed according to procedure type (transcatheter versus surgical) and age group (children versus adults). Sensitivity analyses restricted to high-quality studies with Newcastle Ottawa Scale score 7 or greater were conducted to assess the robustness of the pooled estimates. Publication bias was evaluated by funnel plot assessment and Egger regression.[14]

RESULTS

Study Selection

The initial search retrieved 1683 records. After duplicate removal and screening of titles and abstracts, 36 observational studies met the eligibility criteria and were included in the quantitative synthesis. The study selection process is presented in the PRISMA 2020 flow diagram (Figure 1).

Study Characteristics

The 36 included studies comprised a total of 12 739 patients undergoing transcatheter or surgical ASD closure (7014 transcatheter; 5725 surgical). Study designs consisted of prospective and retrospective cohorts, case-control studies, and 1 nationwide registry. Mean age in adult cohorts ranged from 28 to 42 years, while pediatric cohorts ranged from 1.5 to 7 years. Baseline characteristics including age, sex, weight, and defect size on echocardiography or angiography are summarized in Table 1.

Detailed baseline patient demographics and peri-procedural characteristics stratified by closure approach are presented in Table 2.

Most studies reported the type of device used for transcatheter closure.

Amplatzer devices predominated (78.9% of all transcatheter implants), with much smaller contributions from Starflex (4.7%), Occlutech (3.7%), CardioSEAL (2.6%), Helex (2.9%), and Angelwing (2.3%). Use of other devices was uncommon or not reported.

Risk of Bias Assessment

Newcastle–Ottawa Scale scores ranged from 6 to 9. Twelve studies (33%) achieved high quality (≥7 points), while the remainder were of moderate quality. The most common limitation was lack of a concurrent control group, which affected comparability. A detailed summary of NOS assessment is provided in Supplementary Table 4.

Procedural Success

The pooled procedural success rate for ASD closure without major complications was 95% (95% CI: 92%-97%; I^2 = 90.2%). To better quantify expected effect variability across future studies, a prediction interval (0.55-1.00) was calculated, indicating a wide range of possible true effects and reflecting substantial clinical heterogeneity among included cohorts. Leave-one-out sensitivity analysis (sequential exclusion of each study) demonstrated stability of the pooled procedural success estimate. Sequential removal of individual studies produced changes of ≤0.85% in the pooled estimate, with no single study altering the direction or magnitude meaningfully. These results are reported in Supplementary Table 5.

Baujat analysis identified 2 studies, Meyer et al[9] and Marini et al[34], as the largest contributors to statistical heterogeneity while also exerting notable influence on the pooled success estimate. Several other studies, including Esraa, Formigari, and Martins, contributed moderate variability, whereas most remaining cohorts showed minimal impact on heterogeneity or the overall pooled effect. These findings are shown in Supplementary Figure 1.

In children, the raw procedural success rates were 87.3% (1445/1656) for transcatheter closure and 99.0% (505/510) for surgical closure (Table 3). The pooled meta-analytic model estimated success at 93% and 97%, respectively; differences reflect study weighting and between-study variance.

Device generation likely contributed to outcome variability. Early cohorts predominantly used first-generation Amplatzer/AGA devices, while more recent studies increasingly employed Occlutech and CERA systems, which may offer improved deployment control and stability. In the surgical group, outcomes represented a combination of sternotomy and minimally invasive approaches, although most studies did not report these separately, limiting direct comparison of technique-specific morbidity.

Cumulative meta-analysis of transcatheter procedures (studies added chronologically by publication year) showed

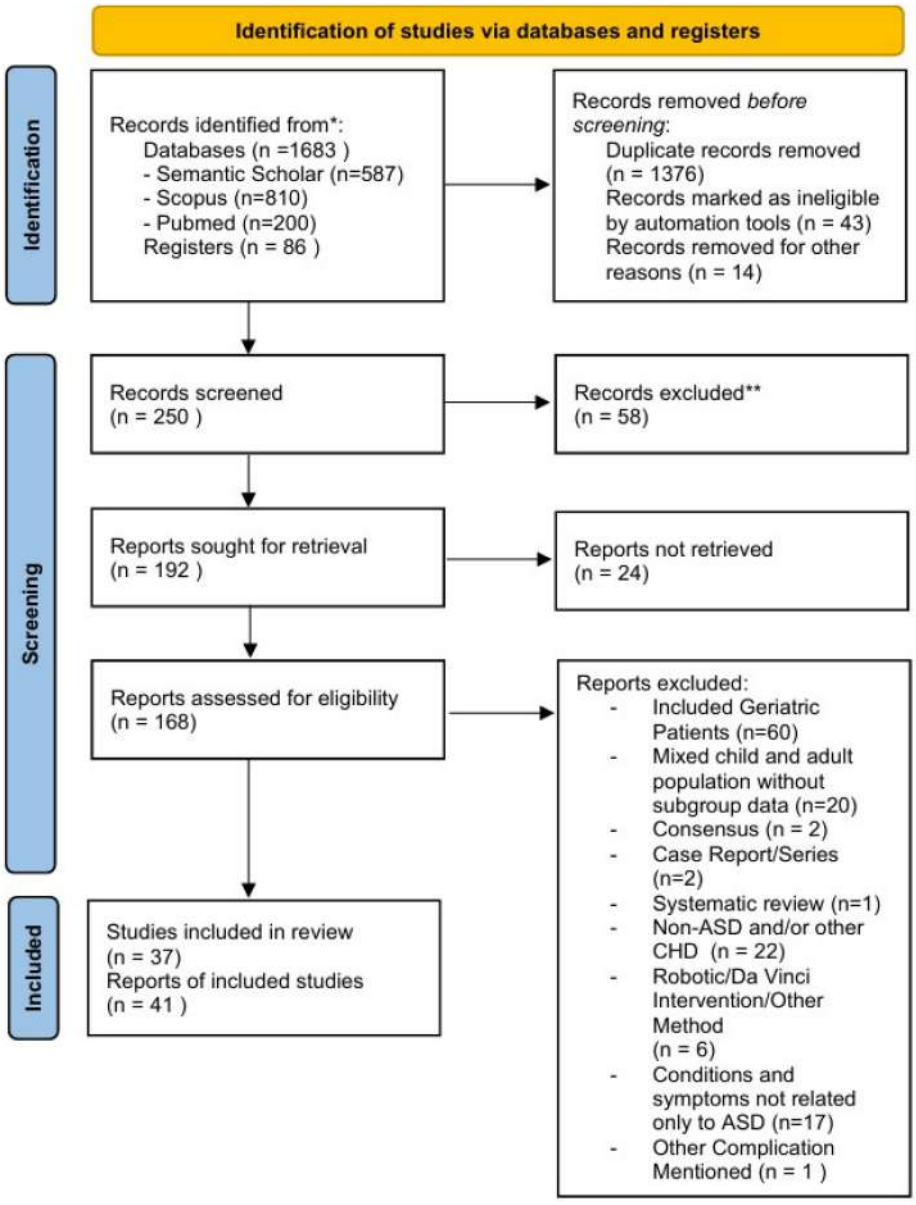

Figure 1. PRISMA 2020 flow diagram of study selection.

early variability in pooled success rates with progressive stabilization after 2008. At the most recent cumulative step (including studies up to 2022), the pooled transcatheter success proportion was 0.788 (95% CI: 0.771-0.805). Supplementary Figure 2 provide the full cumulative plot.

Procedural Characteristics

Transcatheter closure demonstrated shorter procedure duration compared with surgery (adults: 43.2 ± 11.9 minutes vs 89.8 ± 32.6 minutes; children: 70.7 ± 37.2 minutes vs 83.2 ± 55.0 minutes; both $P < .001$). Hospital stay was also significantly shorter (mean difference: −3.86 days; 95% CI: −6.03 to −1.69; $P = .0004$). Fluoroscopy time averaged 12.0 ± 3.6 minutes in adults and 19.3 ± 34.5 minutes in children, although pediatric comparison was limited due to fewer surgical comparators. These findings are displayed in Figure 2.

Complications During Procedure

Transcatheter closure had lower intra-procedural complication rates.

Among children, the most frequent events were residual shunt (1.8%), arrhythmia (1.2%), and device embolization (1.0%). In adults, device embolization (1.3%) and arrhythmia (1.6%) were most commonly reported. Surgical closure was associated with higher rates of pleural effusion (0.7%), pericardial effusion (2.1%), pulmonary edema (1.1%), and shock (3.9%). Full complication distribution is summarized in Table 3 and visualized in Figure 3.

Complications on Follow-Up

During follow-up, residual shunt was observed in 4.6% of children and 7.2% of adults following transcatheter closure, compared with 1.7% in surgically treated children. Arrhythmia was lower after transcatheter closure versus surgery (0.7%

Table 1. Characteristics of Included Studies

Author	Year	Country	Design	Transcatheter (n)	Surgical/Open thoracostomy (n)	Population	Age Population
Yew et al	2004	Auckland, New Zealand	Retrospective cohort	25	NA	25	Children
Rossi et al	2007	Porto Alegre-RS, Brazil	Retrospective cohort	27	NA	27	Children
Gildein et al	1997	Freiburg, Germany	Prospective cohort	3	NA	7	Children
Çeliker et al	2005	Ankara, Türkiye	Retrospective cohort	80	NA	99	Children
Fraisse et al	2008	France	Retrospective cohort	35	NA	35	Children
Russell et al	2002	Canada	Retrospective cohort	NA	43	44	Children
Han et al	2020	China	Comparative cohort	86	NA	186	Children
Ammar et al	2013	Egypt	Prospective cohort	17	NA	17	Children
Smith et al	2008	English	Retrospective cohort	33	NA	33	Children
Zhang et al	2007	China	Comparative cohort	NA	10	12	Children
Tuzcu et al	2004	Germany	Retrospective cohort	65	NA	129	Children
Esraa et al	2020	Egypt	Retrospective cohort	65	NA	67	Children
Lu et al	2022	China	Prospective cohort	11	NA	11	Children
Liao et al	2023	China	Retrospective cohort	NA	NA	24	Children
Costa et al	2013	Brazil	Comparative cohort	75	105	180	Children
Sharfi et al	2018	Saudi Arabia	Case - control	44	NA	44	Children
Ali et al	2014	Egypt	Retrospective cohort	24	NA	24	Children
Formigari et al	2001	Dallas, USA	Comparative cohort	54	NA	57	Children
Marini et al	2012	Paris, France	Prospective cohort	47	NA	50	Children
Bolz et al	2005	Basel, Switzerland	Retrospective cohort	NA	135	135	Children
Fischer et al	1999	Germany	Prospective cohort	30	50	80	Children
Thomson et al	2002	UK	Prospective cohort	24	19	46	Children
Hughes et al	2002	Australia	Prospective cohort	43	19	62	Children
Vida et al	2006	Guatemala	Comparative cohort	72	28	111	Children
Cardenas et al	2007	Belgia	Retrospective cohort	49	NA	52	Children
Huang et al	2008	China	Prospective cohort	58	NA	63	Children
Sahin et al	2011	NA	Prospective cohort	40	NA	40	Children
Yuan et al	2012	China	Prospective cohort	61	NA	61	Children
Sagar et al	2022	India	Comparative cohort	25	NA	25	Adult
Doğan et al	2024	Türkiye	Retrospective cohort	319	NA	323	Children
Marini et al	2007	Paris, France	Prospective cohort	51	NA	51	Children
Zheng et al	2014	China	Comparative cohort	NA	507	508	Adult
Lee et al	2017	South Korea	Prospective cohort	52	14	66	Adult
Meyer et al	2016	Switzerland	Comparative cohort	99	NA	107	Adult
Świątkiewicz et al	2022	Poland	Comparative cohort	182	NA	184	Adult
English et al	2025	England	National cohort	NA	1181	1346	Adult

NA = data not available (information not reported or not retrievable from the original study).

Table 2. Baseline Demographics and Defect Characteristics of Patients Undergoing Transcatheter and Surgical Closure

Age (Years)	Transcatheter (Mean ± SD)	Surgical (Mean ± SD)	*P*
Adult	33.67 ± 6.14 (n = 5625)	31.36 ± 10.6 (n = 2632)	<.001
Child	3.69 ± 3.73 (n = 1389)	4.03 ± 1.99 (n = 603)	.035
Gender (male)			
Adult	n = 1939	n = 1865	<.001
Child	n = 1298	n = 588	.056
Weight (kg)			
Adult	45.70 ± 15.7 (n = 254)	52.4 ± 13.85 (n = 508)	<.001
Child	22.57 ± 8.74 (n = 1352)	14.6 ± 3.8 (n = 416)	<.001

vs. 5.8% in children). Late device-related complications such as embolization were rare (0.2%-0.8%). Surgical follow-up complications included heart failure (1.9%) and renal failure (0.5%). Complete outcome data are provided in Table 4 and Figure 4.

Sensitivity Analysis

Sensitivity analysis restricted to 12 high-quality studies (NOS ≥ 7) yielded similar results to the primary analysis, reinforcing robustness. Corresponding forest plots are shown in Supplementary Figure 3.

Publication Bias

Funnel plot distribution appeared largely symmetrical, and Egger's regression test showed no significant small study effects ($P = .069$), although minor asymmetry suggests publication bias cannot be fully excluded.

DISCUSSION

Principal Findings

This systematic review and meta-analysis of 36 observational studies involving more than 12 thousand patients provides updated comparative evidence for transcatheter and surgical ASD closure. Both approaches demonstrated very high procedural success, consistently above 95%. Transcatheter closure resulted in shorter hospital stays, shorter procedure duration, and lower complication rates, particularly in children. Surgical closure remained effective and continues to be the preferred option for patients with large defects, deficient rims, or anatomical variants that are not suitable for device placement.

Many factors caused the wide differences between studies. Centers used different device generations, starting from early Amplatzer and AGA devices and later moving to Occlutech and CERA models. Operators also became more skilled over time, so older studies often reflect early learning periods while newer studies show more stable practice. Each center also used different rules for choosing which patients were suitable for device closure, which changed the types of defects included. The length of follow-up and the way outcomes were defined also varied a lot. Some studies reported only events during the hospital stay, while others followed patients for months or years. Practice patterns also differed across countries, including the type of device used, the style of care, and whether surgeons preferred a small chest cut or a full chest opening. All these differences created the large variation seen in the results, and readers should keep this in mind when interpreting the pooled findings. Cumulative meta-analysis suggests that pooled transcatheter success rates became more consistent after 2008, supporting the hypothesis that improvements in device generation and growing operator experience contributed to more reliable procedural outcomes.

Prediction intervals are wider than CIs and reflect the expected range of effects in a new study; the wide prediction intervals that were observed indicate that effects may differ substantially between settings, underscoring caution when applying pooled estimates to individual centers.

Baujat influence analysis further demonstrated that heterogeneity in transcatheter success was disproportionately driven by a small subset of studies, particularly Meyer and Marini (2007), which deviated more prominently from the pooled effect relative to the larger evidence base. These cohorts likely reflect differences in operator experience, device era, anatomical case selection, or institutional technical protocol during earlier adoption phases. The concentration of heterogeneity within only a few influential studies indicates that the majority of included cohorts cluster closely around the pooled effect, supporting the robustness of the overall estimate despite substantial I^2.

These variations collectively contribute to the high heterogeneity, and they should be considered carefully when interpreting the pooled effect estimates. Leave-one-out analysis confirmed that the pooled procedural success estimate was robust; no individual study exerted a dominant influence on the overall result.

This finding increases confidence that the observed heterogeneity reflects between-study clinical and methodological variation rather than outlier-driven distortion. In addition to high I^2 values, prediction interval analysis further supported

Table 3. Procedural Success Rates Stratified by Age Group and Closure Type

General Characteristic Associated with Surgical and Transcatheter Defect Closure

	Children		Adults		
	Transcatheter, n (%)	Surgical, n (%)	Transcatheter, n (%)	Surgical, n (%)	*P*
Procedural success* rate, n/total (%)	1445/1656 (87.25)	505/510 (99.0)	351/361 (97.2)	1702/1868 (91.1)	<.001
Devices used in successful procedures, n	1445	505	351	1702	

*Success was defined as complete closure without major peri-procedural complications, based on the standardized operational definition applied in this review.

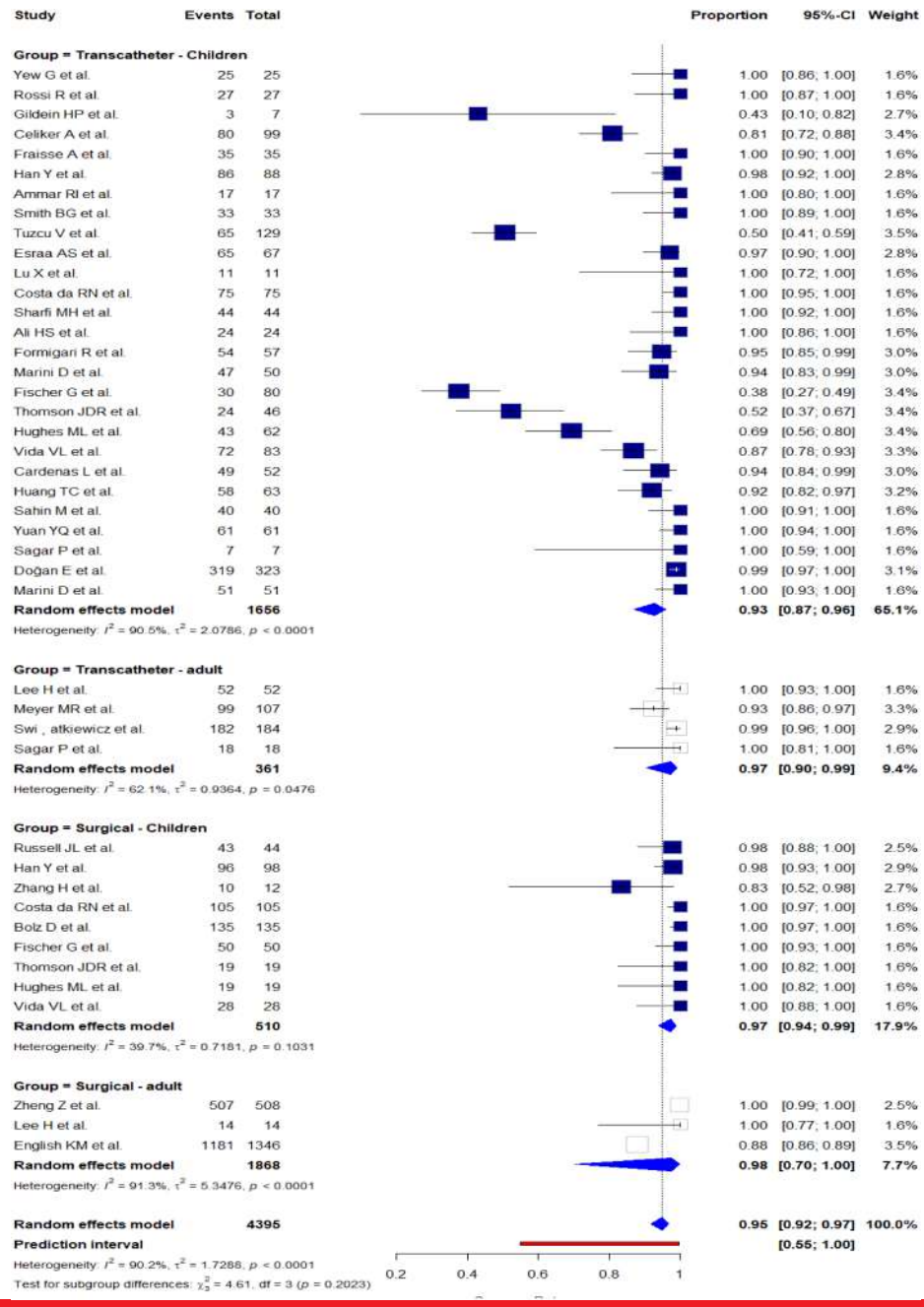

Figure 2. Forest plot of procedural success rate by subgroup (children vs. adults).

the presence of real-world variability. For procedural success, the prediction interval ranged from 0.55 to 1.00, indicating that while the pooled success rate was high, true effects in future clinical settings may lie anywhere within this broader distribution.

This implies that although most centers achieve excellent results, outcomes may differ depending on device generation, operator familiarity, anatomical complexity, and periprocedural protocol differences, consistent with the clinical heterogeneity described above. Incorporating prediction intervals therefore improves interpretability and provides a more clinically realistic expectation range beyond the conventional pooled estimate.

Variation in the definition of procedural success across studies also contributes to inconsistency in the pooled estimates. Some investigators defined success based solely on successful device placement, while others required the absence of complications or complete closure on imaging. A single operational definition was applied to harmonize reporting, but the lack of uniform criteria across studies limits the ability to perform sensitivity analyses with consistent definitions. This limitation should be considered when the results are interpreted.

Variation in follow-up duration across studies also affects the interpretation of late outcomes such as arrhythmia and residual shunt. Some investigators reported outcomes

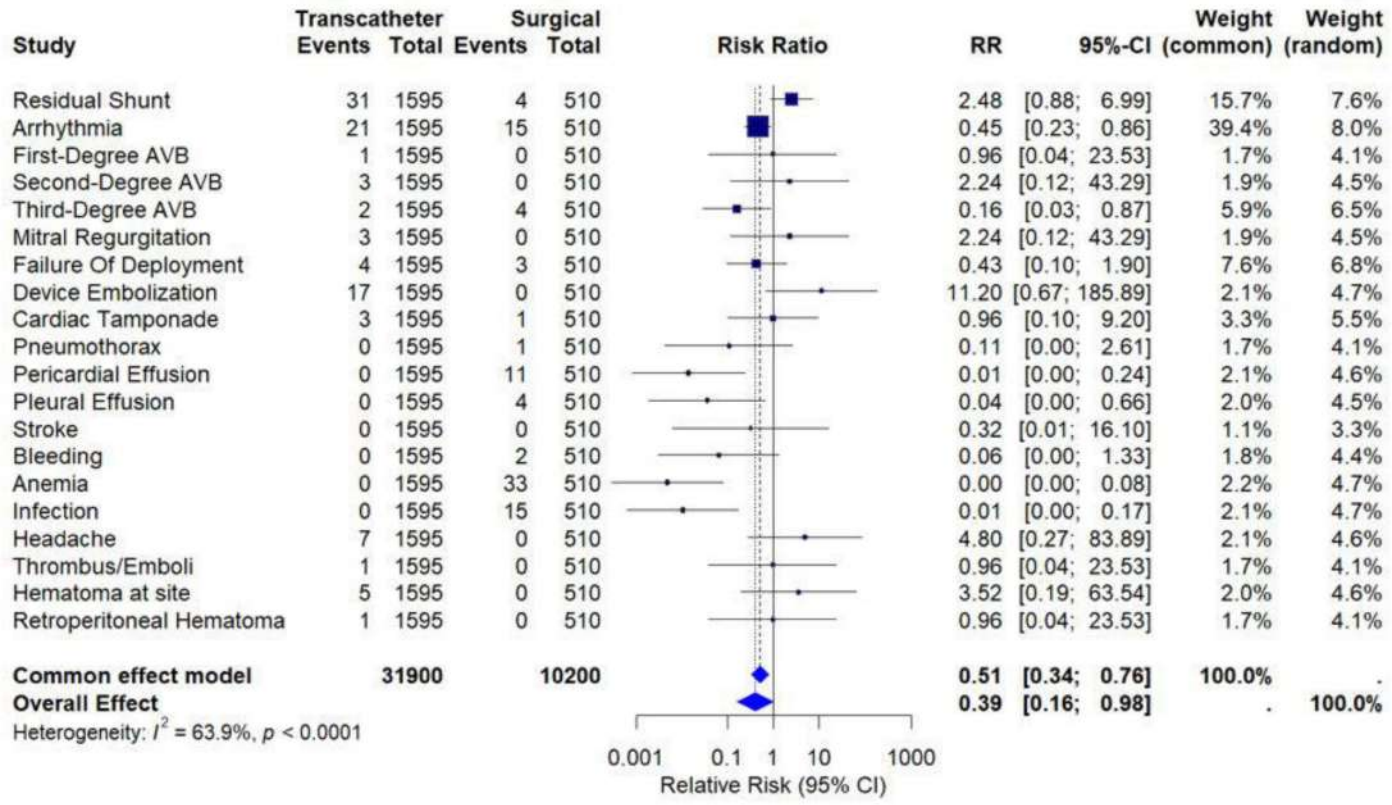

Figure 3. Forest plot of complications during procedure (transcatheter vs. surgical). Squares represent the effect size of each study; horizontal lines represent 95% CI; diamond indicates pooled effect. Complications include arrhythmia, pericardial effusion, pleural effusion, pulmonary edema, device embolization, and procedure-related shock. RR, risk ratio.

within the first year while others included longer-term evaluations, which introduces inconsistency in the time frames represented in the pooled estimates. Because only a small number of studies reported outcomes at uniform intervals, stratified analyses could not be performed based on predefined follow-up lengths. As a result, the pooled findings reflect aggregated data from heterogeneous follow-up periods, and this should be considered when comparing late outcomes between transcatheter and surgical closure.

Assessment of publication bias showed no statistical evidence of small study effects because the Egger regression test did not demonstrate significant asymmetry. However, the test had limited power because several pooled outcomes included a small number of studies. Funnel plots for the major outcomes are provided in the supplementary material to enhance transparency and allow visual inspection of plot symmetry.

Differences in device design may also contribute to variation in procedural complexity and clinical outcomes. Most transcatheter studies used the Amplatzer septal occluder while others used Occlutech, CERA, or related double disk devices. Earlier generation devices tended to be stiffer or bulkier, whereas newer systems provide improved flexibility and more controlled deployment, which may reduce complications in anatomically challenging defects. Although the present analysis was not powered to compare individual device types, variation in device characteristics and generational improvements should be considered when interpreting pooled estimates from transcatheter closure cohorts. In the surgical group, several studies combined conventional sternotomy with minimally invasive thoracotomy approaches. Because the number of studies reporting minimally invasive techniques was limited and reporting formats were inconsistent, these approaches were pooled with standard surgery for quantitative analysis. This pooling may shorten length of stay or influence complication rates in some cohorts and represents an additional source of clinical variation across studies.

Comparison with Previous Evidence

Our findings align with earlier systematic reviews that demonstrated the non-inferiority of transcatheter closure compared with surgery in terms of success rates and safety.[6] Xu et al[1] confirmed the superiority of transcatheter closure for children secundum ASDs with fewer complications and faster recovery. Similarly, national registry data demonstrated favorable long-term outcomes with transcatheter techniques, though residual shunts occurred more frequently compared with surgery.[7] In contrast, surgical closure continues to show excellent durability and remains the preferred approach in complex anatomy or large defects not amenable to transcatheter closure.[9] Furthermore, a recent *Anatolian Journal of Cardiology* case report highlighted successful transcatheter ASD closure in patients with challenging

Table 4. Complications During Procedure and Follow-Up (Transcatheter vs. Surgical)

Complications During Procedure Associated with Surgical and Transcatheter closure

	Children		Adults	
Complication	**Transcatheter, n (%)**	**Surgical, n (%)**	**Transcatheter, n (%)**	**Surgical, n (%)**
Residual shunt	31 (1.8)	4 (0.7)	NR	NR
Arrhythmia*	21 (1.2)	15 (2.9)	6 (1.6)	NR
First-degree Atrioventricular Block	1 (0.0)	NR	NR	NR
Second-degree Atrioventricular Block	3 (0.1)	NR	NR	NR
Third-degree Atrioventricular Block	2 (0.1)	4 (0.7)	NR	NR
Mitral regurgitation	3 (0.1)	NR	NR	NR
Tricuspid regurgitation	NR	NR	NR	NR
Failure of deployment †	4 (0.2)	3 (0.5)	2 (0.5)	2 (0.1)
Device embolization	17 (1.0)	NR	5 (1.3)	NR
SVC stenosis	NR	1 (0.1)	NR	NR
Stroke	NR	NR	NR	NR
Transient ischemic attack	NR	NR	NR	NR
Pericardial effusion	NR	11 (2.1)	NR	NR
Pleural effusion	NR	4 (0.7)	NR	NR
Cardiac tamponade	3 (0.1)	1 (0.1)	NR	NR
Pneumothorax	NR	1 (0.1)	NR	2 (0.1)
Pulmonary edema	NR	6 (1.1)	NR	NR
Pneumonia	NR	NR	NR	NR
AV fistula	NR	NR	NR	NR
Thrombus/Emboli	1 (0.0)	NR	NR	NR
Hematoma at site	5 (0.3)	NR	NR	NR
Retroperitoneal Hematoma	1 (0.0)	NR	NR	NR
Bleeding	NR	2 (0.3)	3 (0.8)	NR
Anemia	NR	33 (6.4)	NR	NR
Fever	NR	NR	NR	NR
Headache	7 (0.4)	NR	NR	NR
Hypertension	NR	NR	NR	NR
Infection	NR	15 (2.9)	NR	NR
Reintubation	NR	NR	NR	2 (0.1)
Reoperation	NR	NR	NR	2 (0.1)
Shock	NR	20 (3.9)	NR	NR
Acute kidney injury	NR	NR	NR	NR
Acute decompensated heart failure	NR	NR	1 (0.2)	NR
Increase length of stay	NR	NR	NR	NR
Cosmesis	NR	NR	NR	1 (0.0)
Death	NR	NR	1 (0.2)	5 (0.2)

NR, not reported. Absence of reporting does not indicate absence of events; cells with NR reflect studies that did not provide data for that specific outcome.
*Arrhythmia includes atrial fibrillation, supraventricular tachycardia, and non-specific conduction abnormalities as reported in individual studies.
†Failure of deployment refers to unsuccessful device positioning requiring retrieval or conversion to surgery.

venous anatomy, illustrating the expanding applicability of transcatheter closure in complex clinical scenarios.[15,16]

Children Versus Adult Considerations

Age subgroup analyses revealed clinically meaningful differences. In children, transcatheter closure reduced arrhythmia, bleeding, and pleural complications compared with surgical closure, supporting its role as first-line therapy when anatomy is favorable.[1,4] In adults, both approaches achieved high success, but surgery was more often associated with pulmonary edema and longer recovery. Conversely, adults undergoing transcatheter closure faced slightly higher risks of late residual shunt, which requires long-term echocardiographic monitoring.[7,9]

Clinical Implications

These findings emphasize that treatment strategy should be individualized. Transcatheter closure offers clear

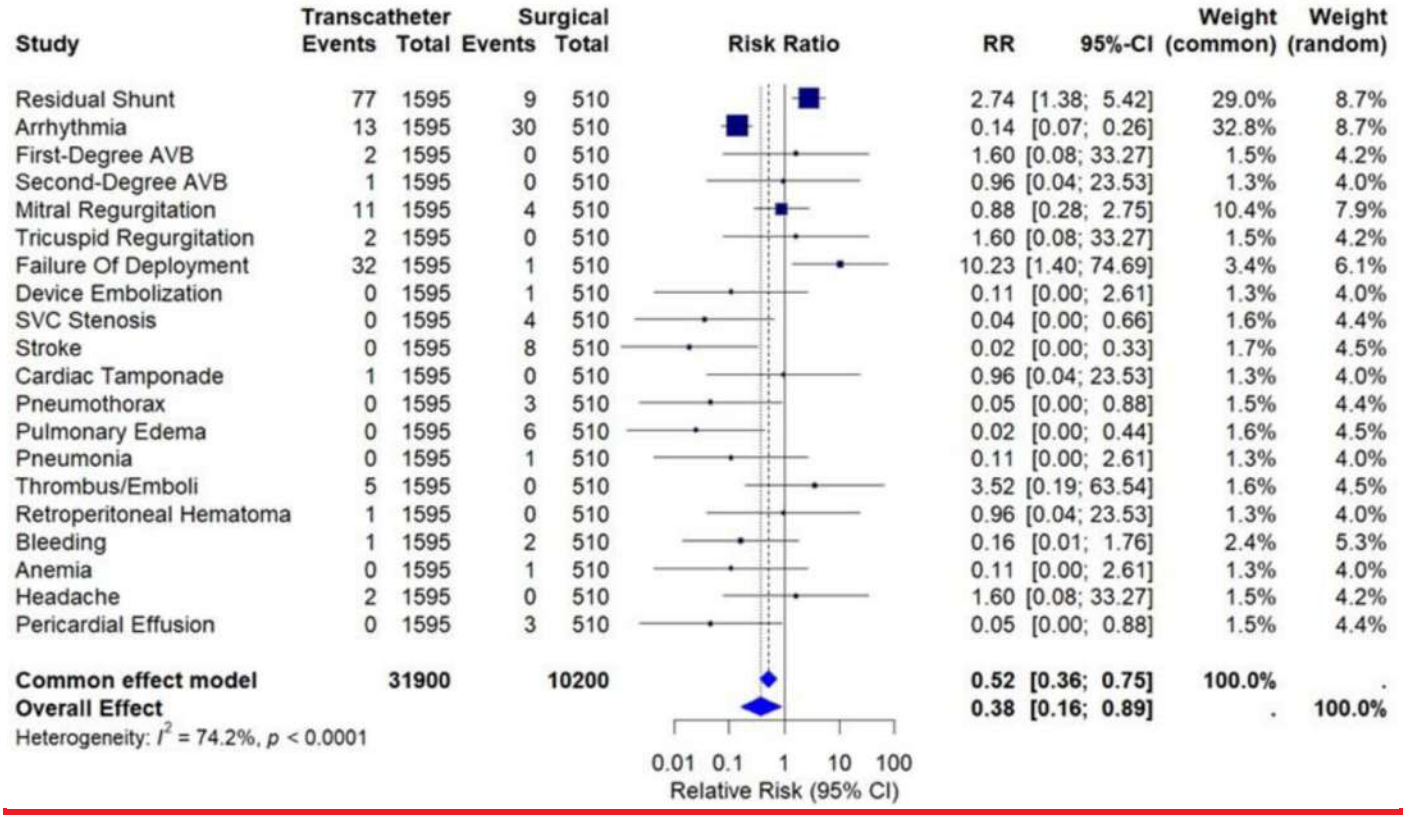

Figure 4. Forest plot of complications during follow-up (transcatheter vs surgical). Squares represent the effect size of each study; horizontal lines represent 95% CI; diamond indicates pooled effect. RR, risk ratio.

advantages in terms of safety, recovery, and patient quality of life, particularly in younger patients. However, surgical closure remains critical for patients with very large defects, deficient septal rims, or concomitant cardiac anomalies requiring repair. The procedural decision should therefore integrate patient age, anatomy, comorbidities, and institutional expertise.

Strengths and Limitations

The main strengths of this meta-analysis include a large pooled sample size, adherence to PRISMA 2020 guidelines,[10] a prospectively registered protocol in PROSPERO (CRD420251052612) that reduces the risk of selective reporting bias, and comprehensive subgroup analyses stratified by age and procedure type. Sensitivity analysis restricted to high-quality studies further confirmed the robustness of the findings. To enhance transparency, the certainty of evidence was assessed using the GRADE approach, which demonstrated moderate certainty for procedural success, peri-procedural complications, hospital stay, and procedure time, whereas outcomes with low event rates or inconsistent follow-up yielded lower certainty ratings.

However, several limitations should be acknowledged. All included studies were observational, which may introduce confounding. Heterogeneity across studies was substantial, reflecting differences in patient selection, operator experience, and device evolution. Because surgical cohorts frequently reported longer follow-up than transcatheter cohorts, the higher rate of some late complications after surgery may partly reflect longer observation time rather than a true difference in per-time risk. Long-term data beyond 10 years remain limited, particularly for device closure, which precludes definitive conclusions on durability. Outcomes between minimally invasive thoracotomy and conventional sternotomy could not be differentiated because most surgical studies did not stratify results by operative technique, which restricts interpretation of the relative morbidity of modern surgical approaches. Egger's regression did not show statistically significant small study effects (P = .069), although the borderline value and asymmetry on visual inspection suggest that publication bias cannot be entirely excluded.

Future Directions

Future research should prioritize high-quality prospective comparative studies, particularly in adults with complex anatomy. Long-term durability data for transcatheter device closure remain limited, particularly regarding late adverse events such as device erosion, arrhythmia, and right ventricular dysfunction. Future work should therefore include long-duration registries and surveillance to better characterize late risk profiles.

Both transcatheter and surgical closure of ASDs are highly effective. Transcatheter closure offers advantages of shorter recovery and fewer complications, supporting its preferential use in anatomically suitable patients, whereas surgery remains essential for complex cases. Individualized treatment planning that incorporates patient-specific and anatomical factors is paramount to optimize outcomes.

Ethics Committee Approval: This study was approved by the Health Research Ethics Committee of Universitas Sumatera Utara, Ministry of Education, Culture, Research, and Technology, Indonesia (Approval No.: 157/KEPK/USU/2024; Date: July 6, 2025).

Informed Consent: Informed consent was not required as this study was a systematic review and meta-analysis based exclusively on previously published data and did not involve direct patient contact.

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REFERENCES

1. Xu M, He R, Jiang J, Yan L, Li Y, Su J. Complications and efficacies of surgical versus transcatheter closure for children ostium secundum atrial septal defect: a meta-analysis. *Front Cardiovasc Med*. 2023;10:1201358. [CrossRef]
2. Stout KK, Daniels CJ, Aboulhosn JA, et al. AHA/ACC guideline for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2018;73(12):e81-e192. [CrossRef]
3. Baumgartner H, De Backer J, Babu-Narayan SV, et al. 2020 ESC guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42(6):563-645. [CrossRef]
4. Hussein A, Hamdan R, Ghali A, Osman A. Outcome comparison between transcatheter closure and surgical closure of atrial septum defect. *Acta Med Marisiensis*. 2025;71(2):81-87. [CrossRef]
5. English KM, Lockhart CJ, Allen D, et al. Secundum atrial septal defects: transcatheter closure versus surgery in adulthood, 2000-2020. *Cardiol Young*. 2024;34(5):689-698. [CrossRef]
6. Harmouch F, Assaidi A, Moutakiallah Y, et al. Transcatheter versus surgical closure of atrial septal defects: a systematic review and meta-analysis of clinical outcomes. *Heart Surg Forum*. 2021;24(6):E1038-E1046. [CrossRef]
7. Chen CC, Hsiao FC, Chiu SN, et al. In-hospital and long-term outcomes after transcatheter versus surgical closure of atrial septal defect: analysis of a nationwide cohort. *Heart*. 2015;101(9):702-708. [CrossRef]
8. Costa RN, Ribeiro MS, Silva AG, et al. Transcatheter closure of atrial septal defect in children: a multicenter experience. *Rev Port Cardiol (Engl Ed)*. 2019;38(4):279-286. [CrossRef]
9. Meyer S, Hofbeck M, Singer H, Rüffer A. Interventional versus surgical closure of atrial septal defects in adults: comparison of short- and long-term results. *Clin Res Cardiol*. 2016;105(7):566-573. [CrossRef]
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. [CrossRef]
11. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute website. Published 2011. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 2, 2025.
12. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45(Pt A):139-145. [CrossRef]
13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. [CrossRef]
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. [CrossRef]
15. Yücel İK, Aslan Çınar A, Sürücü M, Çelebi A. Successful transjugular percutaneous atrial septal defect closure in a dextrocardia patient with Kartagener's syndrome, situs inversus, interrupted inferior vena cava, and bilateral superior vena cava. *Anatol J Cardiol*. 2023;27(1):47-49. [CrossRef]
16. Toprak MHH, Öztürk E, Hatemi AC, Güzeltaş A, Tanıdır İC. Does transcatheter therapy replace surgery? Transcatheter closure of sinus venosus atrial septal defect and partial pulmonary venous return. *Anatol J Cardiol*. 2023;27(11):673-674. [CrossRef]
17. Yew G, Wilson NJ. Transcatheter atrial septal defect closure with the Amplatzer septal occluder: five-year follow-up. *Catheter Cardiovasc Interv*. 2005;64(2):193-196. [CrossRef]
18. Rossi RI, Cardoso CO, Machado PR, Francois LG, Horowitz ESK, Sarmento-Leite R. Transcatheter closure of atrial septal defect with Amplatzer device in children aged less than 10 years old: immediate and late follow-up. *Catheter Cardiovasc Interv*. 2008;71(2):231-236. [CrossRef]
19. Gildein HP, Däbritz S, Geibel A, et al. Transcatheter closure of atrial septal defects by the "buttoned" device: complications and need for surgical revision. *Pediatr Cardiol*. 1997;18(5):328-331. [CrossRef]
20. Çeliker A, Ozkutlu S, Karagöz T, Ayabakan C, Bilgiç A. Transcatheter closure of interatrial communications with Amplatzer device: results, unfulfilled attempts and special considerations in children and adolescents. *Anatol J Cardiol*. 2005;5(3):159-164.
21. Fraisse A, Losay J, Bourlon F, et al. Efficiency of transcatheter closure of atrial septal defects in small and symptomatic children. *Cardiol Young*. 2008;18(3):343-347. [CrossRef]
22. Russell JL, LeBlanc JG, Deagle ML, Potts JE. Outcome following repair of sinus venosus atrial septal defects in children. *Asian Cardiovasc Thorac Ann*. 2002;10(3):231-234. [CrossRef]
23. Han Y, Zhang X, Zhang F. Transcatheter and intraoperative device closure of atrial septal defect in infants under three years of age. *J Cardiothorac Surg*. 2020;15(1):9. [CrossRef]
24. Ammar RI, Hegazy RA. Transcatheter closure of secundum atrial septal defect using Occlutech Figulla-N device in symptomatic children younger than two years of age. *J Invasive Cardiol*. 2013;25(2):76-79.
25. Smith BG, Wilson N, Richens T, Knight WB. Midterm follow-up of percutaneous closure of secundum atrial septal defect with Helex Septal Occluder. *J Interv Cardiol*. 2008;21(4):363-368. [CrossRef]
26. Zhang H, Li SJ, Li YQ, Wang H, Hu SS. Open-chest device closure for the minimally invasive management of atrial septal defect in young children. *Heart Surg Forum*. 2007;10(2):E125–E128.
27. Tuzcu V, Michel-Behnke I, Schranz D. Transcatheter closure of atrial septal defects: experience of a pediatric heart center. *Pediatr Cardiol*. 2004;25(3):241–247.
28. Sorour EA, Elatafy EE, Lotfy WN, Zoair AM. Changes of cardiac rhythm after closure of secundum atrial septal defect in children. *J Adv Med Med Res*. 2020;32(10):84-96. [CrossRef]

29. Lu X, Wen P, Liu Y, Zhu Q, Wang N. Simultaneous percutaneous interventional treatment of atrial septal defects and pulmonary valve stenosis in children under the guidance of transoesophageal echocardiography alone: preliminary experiences. *Front Cardiovasc Med*. 2022;9:771281. [CrossRef]
30. Liao LC, Jan SL, Lin MC, Lee HH, Fu YC. Novel technique to reduce prolapsed device in atrial septal defect closure. *Front Cardiovasc Med*. 2023;10:1164061.
31. Sharfi MH, Al-Ata J, Al-Kouatli A, Baho H, Al-Ghamdi L, Galal MO. Safety and efficacy of transcatheter closure of atrial septal defect type II under transthoracic echocardiographic guidance: a case control study. *J Saudi Heart Assoc*. 2019;31(1):2-8. [CrossRef]
32. Ali SH, Abdalla SES. Percutaneous transcatheter Closure of atrial septal defect in Children younger than 5 years: initial experience of Sohag University. *Life Sci J*. 2014;11(8):954-959. [CrossRef]
33. Formigari R, Di Donato RM, Mazzera E, et al. Minimally invasive or interventional repair of atrial septal defects in children: experience in 171 cases and comparison with conventional strategies. *J Am Coll Cardiol*. 2001;37(6):1707-1712. [CrossRef]
34. Marini D, Ou P, Boudjemline Y, Kenny D, Bonnet D, Agnoletti G. Midterm results of percutaneous closure of very large atrial septal defects in children: role of multislice computed tomography. *EuroIntervention*. 2012;7(12):1428-1434. [CrossRef]
35. Fischer G, Masura J, Kramer HH, Gavora P. Transcatheter occlusion of secundum atrial septal defects with the self-centering Amplatzer septal occluder. *Prog Pediatr Cardiol*. 1998;9(2):119–124.
36. Bolz D, Lacina T, Buser P, Buser M, Guenthard J. Long-term outcome after surgical closure of atrial septal defect in childhood with extensive assessment including MRI measurement of the ventricles. *Pediatr Cardiol*. 2005;26(5):614-621. [CrossRef]
37. Thomson JD, Aburawi EH, Watterson KG, Van Doorn C, Gibbs JL. Surgical and transcatheter (Amplatzer) closure of atrial septal defects: a prospective comparison of results and cost. *Heart*. 2002;87(5):466-469. [CrossRef]
38. Hughes ML, Maskell G, Goh TH, Wilkinson JL. Prospective comparison of costs and short term health outcomes of surgical versus device closure of atrial septal defect in children. *Heart*. 2002;88(1):67-70. [CrossRef]
39. Vida VL, Barnoya J, O'Connell M, Leon-Wyss J, Larrazabal LA, Castañeda AR. Surgical versus percutaneous occlusion of ostium secundum atrial septal defects: results and cost-effective considerations in a low-income country. *J Am Coll Cardiol*. 2006;47(2):326-331. [CrossRef]
40. Cardenas L, Panzer J, Boshoff D, Malekzadeh-Milani S, Ovaert C. Transcatheter closure of secundum atrial defect in small children. *Catheter Cardiovasc Interv*. 2007;69(3):447-452. [CrossRef]
41. Huang TC, Hsieh KS, Lin CC, Lee CL. Clinical results of percutaneous closure of large secundum atrial septal defects in children using the Amplatzer septal occluder. *Heart Vessels*. 2008;23(3):187-192. [CrossRef]
42. Sahin M, Ozkutlu S, Yıldırım I, Karagöz T, Celiker A. Transcatheter closure of atrial septal defects with transthoracic echocardiography. *Cardiol Young*. 2011;21(2):204-208. [CrossRef]
43. Yuan YQ, Huang Q, Yu L, et al. Long-term follow up of interventional therapy of secundum atrial septal defect. *Chin Med J (Engl)*. 2012;125(1):149-152.
44. Sagar P, Sivakumar K, Chandrasekaran R, Pavithran S, Thejaswi P, Monica R. Transcatheter closure of multiple secundum atrial septal defects using multiple occluder devices: a comparative experience between pediatric and adult patients. *Ann Pediatr Cardiol*. 2022;15(2):128-137. [CrossRef]
45. Doğan E, Levent E. Transcatheter closure of secundum atrial septal defects in pediatric patients: A 15-year single-center experience. *Cureus*. 2024;16(3):e57150. [CrossRef]
46. Zhe Z, Kun H, Xuezeng X, et al. Totally thoracoscopic versus open surgery for closure of atrial septal defect: propensity-score matched comparison. *Heart Surg Forum*. 2014;17(4):E227-E231. [CrossRef]
47. Lee H, Yang JH, Jun TG, et al. The mid-term results of thoracoscopic closure of atrial septal defects. *Korean Circ J*. 2017;47(5):769-775. [CrossRef]
48. Świątkiewicz I, Bednarczyk Ł, Kasprzak M, Laskowska E, Woźnicki M. Effectiveness and safety of transcatheter atrial septal defect closure in adults with systemic essential hypertension. *J Clin Med*. 2022;11(4):973. [CrossRef]

Supplementary Table 1. Device type distribution in transcatheter closure

Device type used in successful procedures, n (%)

	Children		Adults	
	Transcatheter, n(%)	**Surgical, n(%)**	**Transcatheter, n(%)**	**Surgical, n(%)**
AGA	1268	NR	104	NR
CARDIOSEAL / CARDIO-O-FIX	46	12	NR	NR
STARFLEX	82	NR	NR	NR
Buttoned	7	NR	NR	NR
ANGELWING	40	NR	NR	NR
HELEX	50	NR	1	NR
OCCLUTECH / FIGGULA	53	NR	12	NR
MEMOPART	NR	NR	NR	NR
CERA / CSO	NR	NR	NR	NR
CRIBIFORM	2	NR	9	NR
BIOSTAR	NR	NR	NR	NR
COCOON	NR	NR	NR	NR
CARDIASTAR	NR	NR	NR	NR
LIFETECH	NR	NR	NR	NR
LONGZHOUFEDU	NR	NR	NR	NR
SOLYSAFE	2	NR	11	NR
PERICARDIAL PATCH (DACRON & BOVINE)	NR	70	52	NR
DIRECT SURTURE	NR	18	NR	522
SHANGHAI SHAPE MEMORY	NR	98	NR	NR

NR = not reported. Absence of reporting does not indicate absence of events; cells with NR reflect studies that did not provide data for that specific outcome. Device abbreviations: AGA = Amplatzer/AGA septal occlude, CERA = CeraFlex septal occlude, HELEX = Gore HELEX septal occlude, Occlutech = Occlutech Figulla septal occlude

Supplementary Table 2. Device size/diameter used across studies

Device diameter used in successful procedures, mm

Children			Adults		
Transcatheter, n(%)	**Surgical, n(%)**	**P-value**	**Transcatheter, n(%)**	**Surgical, n(%)**	***P*-value**
20.09 (11.4-40.0)	21.73 (12.0-35.0)	0.839	24.1 (16.3-30.0)	25.8*	>0.99

*Device diameter for adults in the surgical group corresponds to intraoperative patch sizing, not device implantation.

Supplementary Table 3. GRADE Summary of Findings: Transcatheter versus Surgical ASD Closure

Outcome	**Effect (Summary)**	**No of Studies**	**Certainty of Evidence (GRADE)**	**Rationale**
Procedural success	Both procedures showed very high success (>95%). TC 93–97%; Surgery 97–98%.	36	●●●◯ **Moderate**	Observational evidence; large consistent effect; downgraded for study design.
Major procedural complications	TC reduces complications compared with surgery (RR ≈ 0.58).	28	●●◯◯ **Low**	Observational studies, heterogeneity, risk of confounding.
Hospital stay	TC reduces length of stay by ~3.9 days (MD −3.86 days).	16	●●●◯ **Moderate**	Consistent direction of effect; downgraded due to inconsistency.
Procedure time	TC significantly shorter procedure time (adults: −46 mins; children: −12 mins).	12	●●●◯ **Moderate**	Observational studies; moderate heterogeneity.
Arrhythmia (procedural)	Lower in TC group (children 1.2% vs surgery higher).	20	●●◯◯ **Low**	Event rates low; risk of underreporting; observational.
Residual shunt (follow-up)	More common in TC (adults: 7.2%) than surgery.	22	●●◯◯ **Low**	Outcome definitions vary; follow-up duration inconsistent.
Device embolization	Rare in TC (0.2–1.3%).	18	●●◯◯ **Low**	Very low event rate; imprecision; observational.
Mortality (short-term/ long-term)	Extremely low in both groups (<1%).	10	●●◯◯ **Low**	Rare events; imprecision; observational data only.

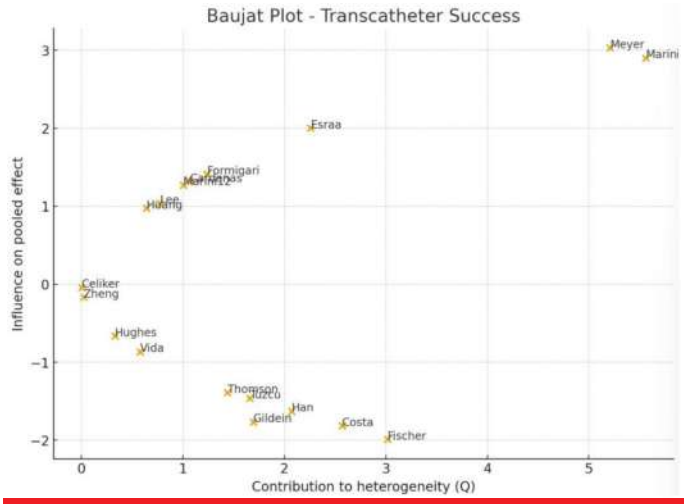
Supplementary Table 4. Newcastle–Ottawa Scale (NOS) risk of bias assessment of included studies

No	Study (Author, Year)	Study Design	Selection (4)	Comparability (2)	Outcome (3)	Total Score
1	Fraisse 2008	Retrospective cohort	3	0	3	6
2	Çeliker 2005	Retrospective cohort	3	0	3	6
3	Gildein 1997	Prospective cohort	3	0	3	6
4	Rossi 2008	Retrospective cohort	3	0	3	6
5	Yew 2005	Retrospective cohort	3	0	3	6
6	Russell 2002	Retrospective cohort	3	0	3	6
7	Han 2020	Comparative cohort	4	2	3	9
8	Ammar 2013	Prospective cohort	3	0	3	6
9	Zhang 2007	Comparative cohort	4	2	3	9
10	Smith 2008	Retrospective cohort	3	0	3	6
11	Tuzcu 2004	Retrospective cohort	3	0	3	6
12	Lu 2022	Prospective cohort	3	0	3	6
13	Liao 2023	Retrospective cohort	3	0	3	6
14	Costa 2013	Comparative cohort	4	2	3	9
15	Sharfi 2019	Case Control	4	2	3	9
16	Ali 2014	Restrospective cohort	3	0	3	6
17	Formigari 2001	Comparative cohort	4	2	3	9
18	Marini 2012 (MSCT)	Prospective cohort	3	0	3	6
19	Bolz 2005	Restrospective cohort	3	0	3	6
20	Fischer 1999	Prospective cohort	3	0	3	6
21	Thomson 2002	Comparative cohort	4	2	3	9
22	Hughes 2002	Comparative cohort	4	2	3	9
23	Vida 2006	Comparative cohort	4	2	3	9
24	Cardenas 2007	Restrospective cohort	3	0	3	6
25	Huang 2008	Prospective cohort	3	0	3	6
26	Sahin 2011	Prospective cohort	3	0	3	6
27	Yuan 2012	Prospective cohort	3	0	3	6
28	Sagar 2022	Comparative cohort	4	2	3	9
29	Doğan 2024	Restrospective cohort	3	0	3	6
30	Marini 2012 (echo)	Prospective cohort	3	0	3	6
31	Zheng 2014	Comparative cohort	4	2	3	9
32	Esraa 2020	Prospective cohort	3	0	3	6
33	Lee 2017	Prospective cohort	3	0	3	6
34	Świątkiewicz 2022	Comparative cohort	4	2	3	9
35	English 2024	National Cohort	4	2	3	9
36	Meyer 2016	Comparative cohort	4	2	3	9

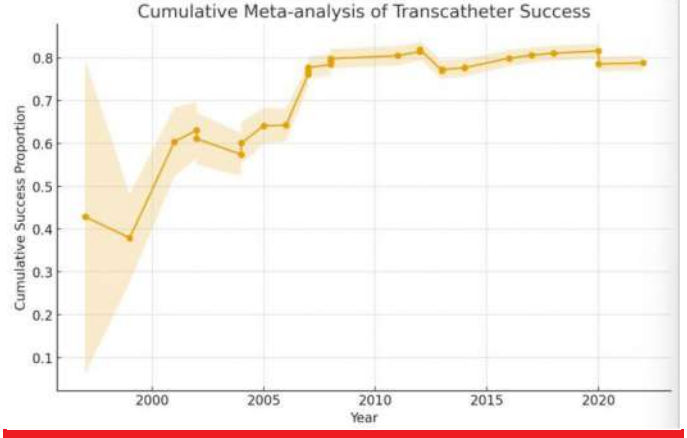
Supplementary Table 5. Leave-one-out sensitivity analysis for pooled procedural success rates comparing transcatheter versus surgical ASD closure

Study removed	Pooled proportion	95% CI	Δ change	Tau^2	Q
Yew G et al.	0.894	0.849–0.940	−0.003	2.044	805.41
Rossi R et al.	0.891	0.845–0.938	−0.006	2.036	799.72
Gildein HP et al.	0.892	0.847–0.939	−0.005	2.039	802.11
Çeliker A et al.	0.894	0.849–0.940	−0.003	2.042	803.98
Fraisse A et al.	0.896	0.851–0.941	−0.001	2.047	807.61
Russell JL (surg)	0.892	0.847–0.940	−0.005	2.039	801.35
Russell JL (TC)	0.892	0.847–0.938	−0.005	2.038	801.87
Han Y et al.	0.895	0.850–0.940	−0.002	2.041	802.99
Ammar RI et al.	0.893	0.848–0.939	−0.004	2.041	802.51
Smith BG et al.	0.894	0.849–0.940	−0.003	2.044	805.41
Zhang H et al.	0.893	0.847–0.938	−0.004	2.037	800.72
Tuzcu V et al.	0.893	0.847–0.938	−0.004	2.038	801.26
Esraa AS et al.	0.893	0.848–0.939	−0.004	2.040	803.07
Lu X et al.	0.893	0.848–0.939	−0.004	2.041	804.55
Liao LC (TC)	0.894	0.849–0.940	−0.003	2.044	806.79
Liao LC (surg)	0.894	0.849–0.940	−0.003	2.044	806.97
Costa RN (TC)	0.894	0.849–0.939	−0.003	2.042	804.50
Costa RN (surg)	0.895	0.850–0.940	−0.002	2.039	802.10
Sharfi MH et al.	0.894	0.848–0.939	−0.003	2.040	802.94
Ali HS et al.	0.894	0.849–0.940	−0.003	2.043	805.94
Formigari R et al.	0.894	0.849–0.940	−0.003	2.043	805.88
Marini D (child)	0.893	0.848–0.939	−0.004	2.041	804.39
Bolz D et al.	0.893	0.848–0.939	−0.004	2.041	804.43
Fischer (TC)	0.894	0.849–0.939	−0.003	2.042	804.91
Fischer (Surg)	0.894	0.849–0.940	−0.003	2.043	805.52
Thomson (TC)	0.893	0.848–0.939	−0.004	2.041	804.39
Thomson (Surg)	0.894	0.849–0.940	−0.003	2.042	804.83
Hughes (TC)	0.894	0.849–0.940	−0.003	2.043	806.20
Hughes (Surg)	0.894	0.849–0.940	−0.003	2.042	805.15
Vida (TC)	0.894	0.849–0.940	−0.003	2.043	806.01
Vida (Surg)	0.894	0.849–0.939	−0.003	2.042	805.15
Cardenas L et al.	0.894	0.849–0.940	−0.003	2.043	804.88
Huang TC et al.	0.894	0.849–0.940	−0.003	2.043	805.41
Sahin M et al.	0.893	0.848–0.938	−0.004	2.042	805.07
Yuan YQ et al.	0.893	0.848–0.939	−0.004	2.041	804.66
Sagar P et al.	0.896	0.851–0.941	−0.001	2.047	807.91
Doğan	0.893	0.847–0.939	−0.004	2.037	800.57
Marini D (adult surg)	0.892	0.846–0.938	−0.005	2.035	799.09
Zheng Z (TC)	0.895	0.850–0.940	−0.002	2.041	804.28
Zheng Z (surg)	0.895	0.850–0.940	−0.002	2.041	804.10
Lee H (TC)	0.895	0.850–0.940	−0.002	2.040	803.99
Lee H (surg)	0.894	0.849–0.939	−0.003	2.039	803.26
Meyer MR et al.	0.894	0.849–0.940	−0.003	2.044	806.77
Świątkiewicz	0.893	0.847–0.939	−0.004	2.037	801.69
English	0.892	0.846–0.938	−0.005	2.034	799.40

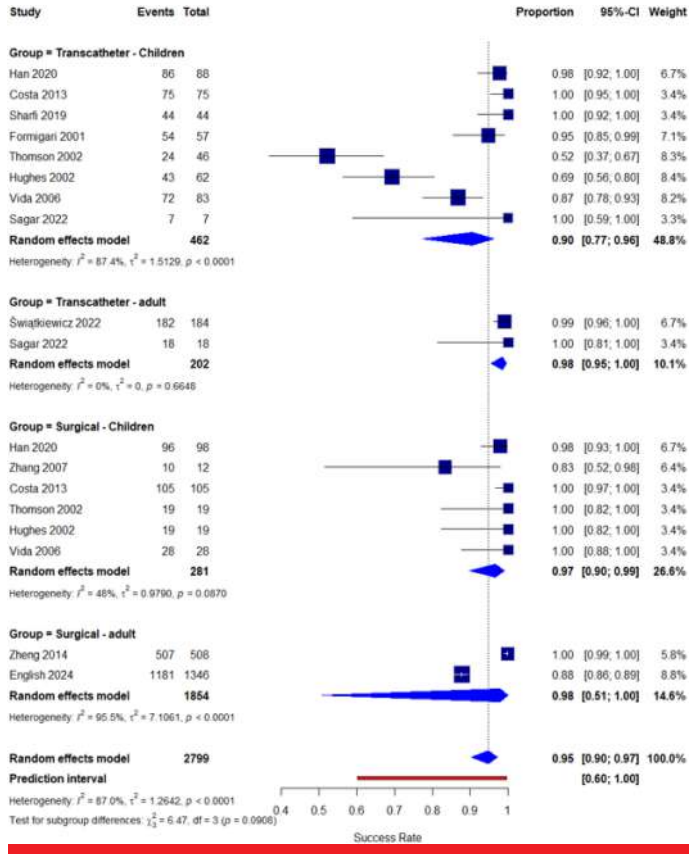
Each iteration reflects the pooled proportional success rate after removing 1 study at a time. Minimal variation was observed across all iterations (Δ ≤ 0.85%), indicating that no individual study exerted disproportionate influence on the summary effect estimate.



Supplementary Figure 1. Baujat plot showing each study's contribution to heterogeneity (x-axis, Q statistic) and influence on the pooled transcatheter success estimate (y-axis). Meyer and Marini were the most influential studies, contributing disproportionately to between-study variability, while most other cohorts showed minimal impact on heterogeneity and pooled effect size.



Supplementary Figure 2. Cumulative meta-analysis of transcatheter procedural success. Pooled proportion (points) and 95% CI (vertical bars) after sequential addition of studies by publication year. Stabilization of estimates is apparent after 2008.



Supplementary Figure 3. Sensitivity analysis restricted to high-quality studies (NOS ≥7).

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Association Between Neutrophil Percentage-to-Albumin Ratio and 2-Year Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement

ABSTRACT

Background: Transcatheter aortic valve replacement (TAVR) is the standard therapy for severe aortic stenosis, particularly in elderly patients with comorbidities. Simple biomarkers to predict mid-term mortality are still needed. This study evaluated the prognostic value of the preprocedural neutrophil percentage-to-albumin ratio (NPAR) for 2-year all-cause mortality after TAVR.

Methods: A total of 618 patients undergoing TAVR between 2013 and 2023 were retrospectively analyzed. NPAR was calculated as neutrophil percentage × 100 / albumin (g/dL), and patients were classified into tertiles. The prognostic role of NPAR was assessed using Cox regression, Kaplan–Meier survival analysis, and receiver operating characteristic curves.

Results: Baseline characteristics were similar across tertiles, but higher NPAR was associated with elevated inflammation and lower albumin levels. In multivariable Cox analysis, high NPAR independently predicted 2-year mortality (T3 vs. T1: hazard ratio [HR] 2.75, 95% CI 1.77-4.28; $P < .001$). In a model including both categorical NPAR and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), tertile 3 of NPAR (HR 2.49, 95% CI 1.61-3.85; $P < .001$) and STS-PROM (HR 1.31, 95% CI 1.12-1.53; $P = .001$) remained independent predictors, indicating incremental prognostic value of NPAR beyond established surgical risk scores. Kaplan–Meier curves showed the lowest survival in the highest tertile (35.9% mortality at 2 years). Receiver operating characteristic analysis confirmed NPAR had the best discriminatory ability (area under the curve = 0.703).

Conclusion: Preprocedural NPAR is an independent, low-cost, and readily available biomarker for predicting mid-term mortality after TAVR. Its integration into risk models may improve prediction accuracy and help guide patient management.

Keywords: Inflammation, mortality, neutrophils, prognostic value, serum albumin, transcatheter aortic valve replacement

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly being used as an alternative to surgery in patients with severe symptomatic aortic stenosis. While current guidelines recommend TAVR for intermediate- and high-risk patients, studies demonstrating similar efficacy to surgery in low-risk groups have made it applicable to all risk groups.[1-4] While short-term procedural success rates are high thanks to increasing clinical experience and technological advancements, the observed mortality risk in the mid- and long-term remains a clinically significant problem.[5-9] In this context, predicting mortality risk with readily available, inexpensive, and reliable biomarkers before the procedure can contribute to personalized medical decisions in patient management.

In recent years, hematological and biochemical markers reflecting the relationship between systemic inflammation, nutritional status, and mortality have attracted attention.[10-12] Neutrophil percentage and serum albumin are 2 important parameters that provide information about inflammatory burden and nutritional reserve,

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respectively. The neutrophil percentage-to-albumin ratio (NPAR), combining these markers, has been proposed as a holistic indicator of inflammation and general health status, and has been associated with poor prognosis in cardiovascular conditions such as acute myocardial infarction, heart failure, and cardiogenic shock.[13-15] In contrast to the neutrophil-to-albumin ratio (NAR), which relies on the absolute neutrophil count, NPAR incorporates neutrophil percentage together with serum albumin. This distinct calculation may yield different prognostic insights. To the authors' knowledge, its prognostic relevance has never been explored in TAVR populations, positioning this study as the first to investigate this relationship.

Therefore, this study aimed to investigate the relationship between NPAR and 2-year all-cause mortality, and to evaluate the clinical utility of NPAR in predicting mortality after TAVR.

METHODS

Study Design and Population

A retrospective analysis was performed on consecutive patients who underwent TAVR at this institution, a tertiary cardiac center, from February 2013 to June 2023. The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee (Date: August 19, 2025; Decision No.: 2025.07-75). Inclusion criteria were as follows: (1) TAVR was performed with a diagnosis of symptomatic severe aortic stenosis, (2) preprocedural complete blood count (CBC) and biochemistry data were available, and (3) at least 2 years of follow-up data were available. Exclusion criteria included active infection, malignancy, autoimmune disease, hematological malignancy, or use of immunosuppressive therapy, chronic liver disease, and patients referred to another center during follow-up or missing mortality data. Finally, a total of 618 eligible patients were included in the study (Figure 1).

Data Collection and Definitions

Study data were collected retrospectively through the hospital information system and patient follow-up files. Demographic characteristics (age, gender), comorbidities (hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, atrial fibrillation, stroke history), echocardiographic parameters (left ventricular ejection fraction [LVEF], aortic valve area, systolic pulmonary artery pressure [sPAP]), and preprocedure laboratory data (CBC, biochemistry, inflammatory markers) were systematically recorded.

Laboratory Analysis and Neutrophil Percentage-to-Albumin Ratio Calculation

All blood samples were collected within 24 hours before the TAVR procedure. Neutrophil percentage and serum albumin levels were measured from the same sample. Neutrophil percentage-to-albumin ratio, the ratio of these 2 variables, was calculated using the following formula: NPAR = Neutrophil percentage (%) × 100 / Albumin (g/dL). Neutrophil percentage-to-albumin ratio values were divided into 3 tertiles for use in statistical analyses in the study: low NPAR (Tertile 1), medium NPAR (Tertile 2), and high NPAR (Tertile 3).

Transcatheter Aortic Valve Replacement Procedure

All patients were thoroughly evaluated by a multidisciplinary cardiac team and considered candidates for TAVR after being determined to be at high risk for valve surgery. All TAVR procedures were performed in a fully equipped hybrid operating room using a transfemoral approach. The method of anesthesia (local or general) was made at the discretion of the operator and the anesthesiologist, considering the clinical indications. Valve type and size were determined according to manufacturer recommendations based on computed tomography and echocardiography findings. The following transcatheter valve designs were used: CoreValve Evolut R (Medtronic, Minneapolis, Minn, USA), Portico (St. Jude Medical, St. Paul, Minneapolis, Minn, USA), Acurate neo2 (Boston Scientific, Marlborough, MA, USA), Sapien XT/Sapien 3 (Edwards Lifesciences, Irvine, California, USA), and Myval (Meril Life Sciences Private Ltd., Gujarat, India). Predilation of the native aortic valve was performed at the operator's discretion. Postdilation under rapid pacing was considered in cases of moderate or severe paravalvular aortic regurgitation and/or underdilatation of the prosthesis. A percutaneous closure system (Perclose ProGlide; Abbott Laboratories, Abbott Park, Illinois) was used to close the vascular access site. A temporary pacemaker was placed as a backup for high-degree atrioventricular (AV) block when necessary. Postprocedural care was conducted in accordance with current guidelines.[1,2]

Follow-Up and Clinical Endpoints

Patients were followed up at outpatient clinic visits and by telephone when necessary. Death information was verified with the National Death Notification System and hospital records. All clinical endpoints were defined according to Valve Academic Research Consortium-3 (VARC-3) criteria.[16] The primary endpoint was 2-year all-cause mortality after TAVR. Secondary endpoints included 30-day stroke, major vascular complications, bleeding, acute kidney injury, myocardial infarction, and new permanent pacemaker implantation.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 24 software

HIGHLIGHTS

- Neutrophil percentage-to-albumin ratio (NPAR) provides a simple and low-cost biomarker for risk stratification in transcatheter aortic valve replacement (TAVR) patients.
- Higher NPAR levels are independently associated with increased all-cause mortality over 2 years.
- This study is the first to demonstrate the prognostic utility of NPAR in the TAVR population.
- Neutrophil percentage-to-albumin ratio offers incremental prognostic value beyond STS-PROM, supporting its integration into existing risk models.

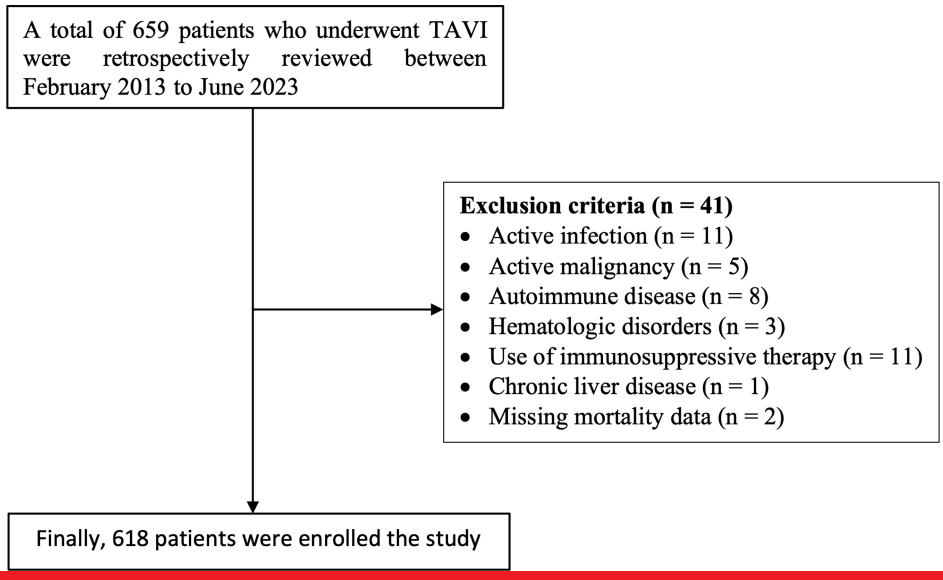

Figure 1. Flowchart of the study population.

package (SPSS Inc., Chicago, Illinois, USA). The normality of distribution of continuous variables was evaluated using both graphical (histograms) and numerical methods. Among numerical tests, both Kolmogorov–Smirnov and Shapiro–Wilk tests were performed to ensure robustness. As each group included more than 200 patients, the Kolmogorov–Smirnov test was considered more appropriate for evaluating normality. One-way ANOVA was used for normally distributed data, and the Kruskal–Wallis test was used for non-normally distributed data. Comparisons between categorical data were made using the Chi-square or Fisher's exact test. Continuous variables are presented as mean ± SD or median and interquartile range. Categorical variables are expressed as numbers (percentages). The predictive power of NPAR, neutrophil percentage, and albumin levels for mortality was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) for each parameter was calculated and reported with its 95% CI. The optimal cut-off value of NPAR for predicting 2-year all-cause mortality was determined using the Youden index. Comparisons between ROC curves were performed using the DeLong test. All-cause survival time was analyzed using the Kaplan–Meier method, and survival curves were plotted for the 3 NPAR groups. The difference between the groups was assessed using the log-rank test. Median survival time and event incidence rates were calculated separately for 30 days, 1 year, and 2 years. Cox proportional hazards regression analyses were performed to identify independent risk factors associated with 2-year mortality. Analyses were performed as follows: Univariable analysis for all available variables; Multivariable Model 1, including demographic, clinical, and laboratory variables with $P < .10$ in univariable analysis; and Multivariable Model 2, including Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and categorical NPAR simultaneously to avoid multicollinearity with individual variables incorporated within STS-PROM. The model results are presented with hazard ratio (HR) and 95% CI. Statistical significance was set at $P < .05$.

RESULTS

Demographic and Clinical Characteristics

A total of 618 patients were included in this study. Demographic characteristics, comorbidities, laboratory, and echocardiographic parameters were compared among the 3 tertiles established according to NPAR (Table 1). The mean age was 78.5 ± 7.0 years, and 41.9% of the patients were male. The most common comorbidities were hypertension (76.4%), coronary artery disease (69.1%), and diabetes mellitus (45.1%). Demographic data and comorbidities were similar between the groups ($P > .05$). However, laboratory findings revealed that as NPAR increased, the neutrophil percentage increased, while albumin levels decreased ($P < .001$ for both). White blood cell and neutrophil counts were highest in the T3 group ($P = .032$ and $P < .001$), while the lymphocyte count was inversely proportional ($P < .001$). Hemoglobin levels were lowest in the T3 group ($P < .001$). The difference between groups for C-reactive protein (CRP) and creatinine was not statistically significant. Left ventricular ejection fraction and sPAP differed significantly with NPAR ($P = .001$ and $P = .041$).

Procedural Characteristics and Clinical Outcomes

A total of 66.8% of patients underwent TAVR under conscious sedation, and these rates were similar between the groups. There were no significant differences in procedure time, contrast amount, or the intensive care unit stay ($P > .05$). However, the length of hospitalization was longer in the high NPAR group (median 9 days; $P = .024$). No differences were observed between the groups in terms of valve type, size, or gradients. Clinical outcome data are summarized in Table 2. Significant increases in 30-day, 1-year, and 2-year mortality rates were observed with increasing NPAR levels ($P = .006$, $P < .001$, $P < .001$, respectively). Cardiovascular mortality was similarly associated with NPAR ($P = .006$). There were no significant differences in secondary endpoints.

Predictors of Mortality

In the multivariable Cox proportional hazards regression analysis, 2 separate models were constructed (Table 3): Model

Table 1. Baseline Characteristics According to Neutrophil Percentage-to-Albumin Ratio Tertiles

Variables	Total (n = 618)	Neutrophil Percentage-to-Albumin Ratio			P
		Tertile 1 ≤14 (n = 206)	Tertile 2 14-20 (n = 206)	Tertile 3 ≥20 (n = 206)	
Age (years)	78.50 ± 7.03	78.05 ± 7.46	78.39 ± 7.01	79.05 ± 6.61	.342
Sex (male), n (%)	259 (41.9)	87 (42.2)	83 (40.3)	89 (43.2)	.830
Comorbidities, n (%)					
Hypertension	472 (76.4)	165 (80.1)	154 (74.8)	153 (74.3)	.303
Diabetes mellitus	279 (45.1)	94 (45.6)	85 (41.3)	100 (48.5)	.327
Coronary artery disease	427 (69.1)	149 (72.3)	138 (67.0)	140 (68.0)	.458
Previous CABG	127 (20.6)	50 (24.3)	38 (18.4)	39 (18.9)	.268
Peripheral artery disease	114 (18.4)	37 (18.0)	35 (17.0)	42 (20.4)	.657
Chronic lung disease	196 (31.7)	59 (28.6)	66 (32.0)	71 (34.5)	.443
Chronic kidney disease	169 (27.3)	50 (24.3)	55 (26.7)	64 (31.1)	.292
Previous Stroke/TIA	35 (5.7)	13 (6.3)	9 (4.4)	13 (6.3)	.616
Paroxysmal or persistent atrial fibrillation	118 (19.1)	31 (15.0)	39 (18.9)	48 (23.3)	.103
Prior pacemaker	20 (3.2)	5 (2.4)	9 (4.4)	6 (2.9)	.511
STS-PROM score: mortality (%)	6.22 ± 0.80	6.12 ± 0.76	6.18 ± 0.90	6.35 ± 0.71	.010
Laboratory parameters					
Neutrophil percentage, %	63.1 ± 10.4	53.1 ± 7.2	63.5 ± 5.7	72.6 ± 7.1	<.001
Albumin, g/dL	3.90 ± 0.41	4.14 ± 0.33	3.96 ± 0.33	3.61 ± 0.38	<.001
NPAR	16.38 ± 3.51	12.83 ± 1.54	16.04 ± 0.75	20.28 ± 2.51	<.001
White blood cell, 10^9/L	7.54 ± 3.31	7.31 ± 2.52	7.28 ± 2.23	8.04 ± 4.62	.032
Hemoglobin, g/dL	11.35 ± 1.64	11.60 ± 1.57	11.54 ± 1.61	10.90 ± 1.66	<.001
Neutrophil, 10^9/L	4.87 ± 2.98	4.28 ± 1.89	4.63 ± 1.49	5.69 ± 4.45	<.001
Lymphocyte, 10^9/L	1.82 ± 1.23	2.17 ± 1.50	1.79 ± 1.28	1.49 ± 0.65	<.001
CRP, mg/L	6.5 (16.2)	4.0 (8.1)	6.0 (17.1)	11 (17.1)	.314
Creatine, mg/dL	1.14 ± 0.65	1.10 ± 0.60	1.11 ± 0.77	1.21 ± 0.54	.138
Total cholesterol, mg/dL	156 ± 73	160 ± 73	150 ± 76	156 ± 69	.467
Echocardiographic parameters					
LVEF (%)	60 (14)	60 (10)	60 (10)	55 (20)	.001
Aortic valve area (cm^2)	0.72 ± 0.16	0.73 ± 0.18	0.72 ± 0.14	0.70 ± 0.15	.268
Maximum aortic gradient (mm Hg)	77.27 ± 32.94	80.76 ± 47.60	76.71 ± 23.53	74.39 ± 20.74	.147
Mean aortic gradient (mm Hg)	48.12 ± 13.38	49.21 ± 13.49	47.73 ± 13.37	47.41 ± 13.27	.357
Aortic peak systolic velocity (m/s)	4.33 ± 0.61	4.37 ± 0.48	4.35 ± 0.68	4.27 ± 0.64	.362
Systolic pulmonary arterial pressure	42 ± 13.82	42.67 ± 14.25	40.72 ± 13.81	44.67 ± 13.26	.041

Continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are presented as number (percentage).
CABG, coronary artery bypass grafting; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NPAR, neutrophil-percentage-to-albumin ratio; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack.

1: including demographic, clinical, and laboratory variables with $P < .10$ in univariable analysis (excluding STS-PROM). In this model, categorical NPAR remained an independent predictor of 2-year all-cause mortality. The risk of mortality was significantly higher in individuals in Tertile 3 compared to Tertile 1 (HR: 2.75; 95% CI: 1.77-4.28; $P < .001$). The increase in Tertile 2 showed borderline significance (HR: 1.59; 95% CI: 0.99-2.55; $P = .055$). Peripheral arterial disease (HR: 1.52; 95% CI: 1.03-2.25; $P = .034$) and serum creatinine level (HR: 1.26; 95% CI: 1.05-1.50; $P = .011$) were also independent factors increasing the risk of mortality. In contrast, previous CABG history was identified as an independent protective factor reducing mortality risk (HR: 0.52; 95% CI: 0.32-0.84; $P = .009$).

Model 2: including both categorical NPAR and STS-PROM. In this model, STS-PROM was independently associated with 2-year mortality (HR: 1.31; 95% CI: 1.12-1.53; $P = .001$). Among the NPAR categories, patients in Tertile 3 had a significantly higher risk of 2-year mortality compared with Tertile 1 (HR: 2.49; 95% CI: 1.61-3.85; $P < .001$), while Tertile 2 showed only a borderline association (HR: 1.55; 95% CI: 0.96-2.49; $P = .068$). These findings indicate that NPAR provides incremental prognostic value beyond STS-PROM, primarily driven by the highest NPAR tertile.

Survival Analysis

Kaplan–Meier survival curves for 2-year all-cause mortality showed a significant difference in survival between

Table 2. Procedural Characteristics and Primary/Secondary Clinical Outcomes According to Neutrophil Percentage-to-Albumin Ratio Tertiles

Variables	Total (n = 618)	Neutrophil Percentage-to-Albumin Ratio			*P*
		Tertile 1 ≤14 (n = 206)	Tertile 2 14-20 (n = 206)	Tertile 3 ≥20 (n = 206)	
Procedural characteristics, n (%)					
Conscious sedation	413 (66.8)	136 (66.0)	143 (69.4)	134 (65.0)	.613
Procedure time*, min	71 (35)	73 (39)	72 (36)	70 (34)	.573
Total contrast used (mL)	150 (90)	150 (88)	150 (94)	150 (90)	.386
ICU stay, days	2 (3)	2 (3)	2 (3)	2 (4)	.357
Discharge time, days	8 (7)	7 (5)	7 (6)	9 (5)	.024
Valve type, self	273 (44.2)	91 (44.2)	82 (39.8)	100 (48.5)	.203
Valve size	26.36 ± 2.82	26.41 ± 2.68	26.13 ± 2.83	26.56 ± 2.82	.283
Primary outcomes, n (%)					
30-day mortality	46 (7.4)	9 (4.4)	12 (5.8)	25 (12.1)	.006
1-year mortality	107 (17.3)	17 (8.3)	35 (17.0)	55 (26.7)	<.001
2-year mortality	147 (23.8)	28 (13.6)	45 (21.8)	74 (35.9)	<.001
Secondary outcomes, n (%)					
Cardiovascular mortality	76 (12.3)	16 (7.8)	23 (11.2)	37 (18.0)	.006
All stroke	18 (2.9)	4 (1.9)	5 (2.4)	9 (4.4)	.143
Bleeding and transfusions (≥Type 2)	138 (22.3)	51 (24.8)	47 (22.8)	40 (19.4)	.420
Major vascular and access-related complications	48 (7.8)	21 (10.2)	13 (6.3)	14 (6.8)	.276
Moderate or severe aortic regurgitation	20 (3.3)	7 (3.4)	5 (2.5)	8 (3.9)	.708
Acute kidney injury stage 3 or 4	24 (3.9)	4 (1.9)	7 (3.4)	13 (6.3)	.065
Myocardial infarction	6 (1.0)	2 (1.0)	1 (0.5)	3 (1.5)	.616
New permanent pacemaker	105 (17.0)	36 (17.5)	38 (18.4)	31 (15.0)	.639

Continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are presented as number (percentage).
ICU, intensive care unit.

NPAR tertiles (Figure 2). Patients in the highest tertile (Tertile 3) had the lowest cumulative survival, while those in the lowest tertile (Tertile 1) had the highest probability of survival. Event rates at the end of follow-up were 13.6%, 21.8%, and 35.9% for Tertiles 1, 2, and 3, respectively. Median survival time decreased to 666.0 days (95% CI: 640.5-691.5) in Tertile 1, 617.2 days (95% CI: 584.7-649.7) in Tertile 2, and 535.5 days (95% CI: 495.4-575.5) in Tertile 3. According to the log-rank test, there was a statistically significant difference in survival distributions between NPAR tertiles ($P < .001$).

Receiver Operating Characteristic Curve Analysis

The predictive power of NPAR, albumin, and neutrophil percentage for all-cause mortality was evaluated using ROC analyses. The ROC curves of the 3 variables are presented together in Figure 3. Receiver operating characteristic analysis yielded an AUC of 0.703, with an optimal cut-off value of NPAR = 16.07 (sensitivity 75.5%, specificity 58.2%) for predicting 2-year all-cause mortality ($P < .001$). The AUC for neutrophil percentage and albumin was 0.634 and 0.668, respectively, while NPAR showed the highest AUC (0.703) and was superior to both markers in predicting mortality (DeLong test, $P < .05$). These results indicate that NPAR provides moderate but superior discriminatory ability compared with traditional parameters.

DISCUSSION

This is the first study to evaluate the relationship between preprocedural NPAR and all-cause mortality in patients undergoing TAVR. Mortality rates were observed to gradually increase with increasing NPAR values. Receiver operating characteristic curve analysis demonstrated that NPAR had a higher predictive value than albumin levels and neutrophil percentage. Multivariable Cox regression analysis demonstrated that elevated NPAR was independently associated with mortality. These results suggest that NPAR can be used as a simple, inexpensive, and accessible prognostic marker in TAVR patients.

Neutrophil percentage is one of the main cellular components involved in the acute phase response to inflammation. Neutrophils are known to play a central role in the triggering of cardiovascular events and contribute to endothelial dysfunction and atherothrombotic processes.[17-20] A strong correlation has been demonstrated between elevated neutrophil percentage and mortality, particularly in conditions such as acute myocardial infarction, cardiogenic shock, and heart failure.[13-15,21,22] Excessive activation of neutrophils can increase myocardial damage through the release of inflammatory cytokines and procoagulant effects. On the other hand, serum albumin level is an important indicator

Table 3. Univariable and Multivariable Cox Proportional Hazards Regression Analyses of 2-Year All-Cause Mortality

	Univariable analysis	
Variables	**HR (95% CI)**	***P***
Age (years)	1.01 (0.99-1.04)	.131
Sex (male)	1.29 (0.93-1.78)	.119
Hypertension	0.80 (0.55-1.15)	.231
Diabetes mellitus	1.23 (0.89-1.70)	.199
Coronary artery disease	0.83 (0.59-1.17)	.304
Previous CABG	0.56 (0.35-0.90)	.018
Peripheral artery disease	1.39 (0.94-2.04)	.091
Chronic lung disease	1.17 (0.83-1.64)	.365
Chronic kidney disease	1.84 (1.32-2.56)	<.001
Previous Stroke/TIA	1.48 (0.82-2.68)	.188
Paroxysmal or persistent atrial fibrillation	1.01 (0.67-1.52)	.959
Prior pacemaker	0.37 (0.09-1.50)	.164
STS-PROM score	1.33 (1.15-1.54)	<.001
LVEF	0.98 (0.97-0.99)	.007
Systolic pulmonary arterial pressure	1.01 (0.99-1.02)	.137
Neutrophil percentage	1.04 (1.02-1.05)	<.001
Albumin	0.27 (0.19-0.40)	<.001
NPAR		<.001
Tertile 1	1.0 (reference)	
Tertile 2	1.68 (1.05-2.70)	.030
Tertile 3	3.08 (1.99-4.76)	<.001
White blood cell	1.00 (0.95-1.05)	.902
Hemoglobin	0.92 (0.83-1.01)	.106
CRP	1.00 (1.00-1.01)	.067
Creatine	1.32 (1.12-1.55)	.001
Total cholesterol	1.00 (0.99-1.00)	.946
Valve type, self	1.17 (0.85-1.62)	.331
Conscious sedation	0.79 (0.56-1.10)	.171

	Multivariable analysis			
	Model 1 for NPAR and clinical variables		**Model 2 for NPAR and STS-PROM**	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Previous CABG	0.52 (0.32-0.84)	.009		
Peripheral artery disease	1.52 (1.03-2.25)	.034		
LVEF	0.98 (0.97-1.00)	.080		
CRP	1.00 (0.99-1.01)	.335		
Creatine	1.26 (1.05-1.50)	.011		
NPAR, categorical		<.001		<.001
Tertile 1	1.0 (reference)			
Tertile 2	1.59 (0.99-2.55)	.055	1.55 (0.96-2.49)	.068
Tertile 3	2.75 (1.77-4.28)	<.001	2.49 (1.61-13.85)	<.001
STS-PROM score			1.31 (1.12-1.53)	.001

CABG, coronary artery bypass grafting; CRP, C-reactive protein; HR, hazard ratio; LVEF, left ventricular ejection fraction; NPAR, neutrophil-percentage-to-albumin ratio; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack.

of chronic inflammation, malnutrition, and liver function. Hypoalbuminemia has been associated with an increased risk of mortality in elderly patients and has been used as an independent prognostic marker in various cardiovascular conditions.[23-25] The antioxidant and anti-inflammatory properties of albumin play an important role in maintaining vascular integrity. Therefore, a decrease in albumin level may indicate advanced systemic inflammation and decreased physiological reserve. Neutrophil percentage-to-albumin ratio is the combination of these 2 parameters and is a composite biomarker that simultaneously reflects systemic inflammation, as indicated by neutrophil

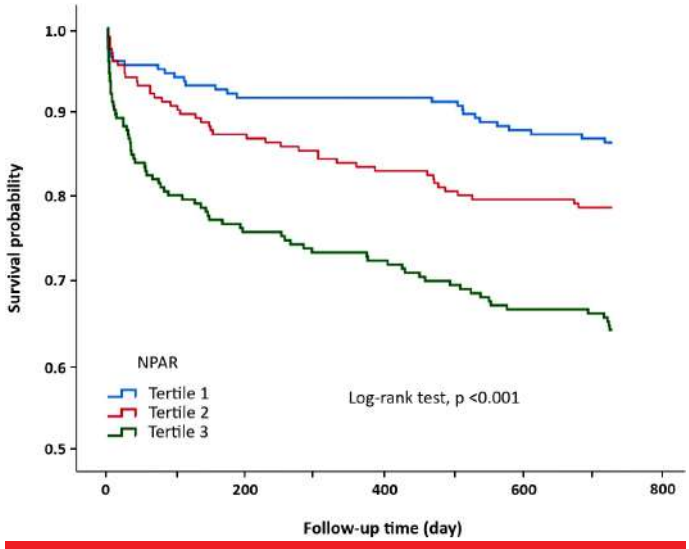

Figure 2. Kaplan–Meier curves of 2-year all-cause mortality according to NPAR tertiles. NPAR, neutrophil percentage-to-albumin ratio.

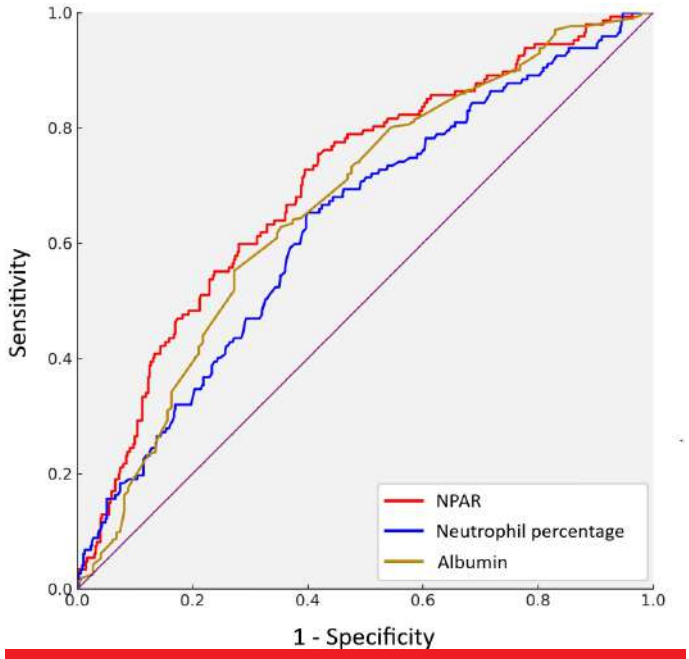

Figure 3. Receiver operating characteristic curves showing the predictive value of NPAR, neutrophil percentage, and albumin for the prediction of 2-year all-cause mortality. AUC for NPAR = 0.703, 95% CI 0.655-0.751, $P < .001$; AUC for neutrophil percentage = 0.634, 95% CI 0.582-0.685, $P < .001$; AUC for albumin = 0.668, 95% CI 0.616-0.719, $P < .001$. AUC, area under the curve; NPAR, neutrophil percentage-to-albumin ratio.

percentage, and nutritional/immune reserve, as indicated by albumin level.

The patient group undergoing TAVR generally consists of individuals with advanced age, a high comorbidity burden, and increased frailty. In this patient group, postoperative outcomes and prognosis are closely related not only to the correction of valvular pathology but also to parameters such as systemic inflammatory burden and nutritional status. Previous studies have investigated the prognostic role of other inflammation-based indices in TAVR populations. For example, both the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio have been associated with increased mortality and adverse cardiovascular events after TAVR, suggesting that systemic inflammation plays a central role in determining outcomes.[10,26] Similarly, the C-reactive protein/albumin ratio has been linked with poor prognosis, emphasizing the combined importance of inflammatory burden and nutritional reserve.[27] Taken together, these findings support the utility of composite biomarkers that integrate different biological dimensions. The current results with NPAR are consistent with this line of evidence, reinforcing the prognostic significance of systemic inflammation and nutritional status in TAVR patients.

It is important to distinguish NPAR from the NAR. While NAR uses the absolute neutrophil count, NPAR is derived from neutrophil percentage in combination with serum albumin.[28] This methodological difference may influence its prognostic implications, as percentage-based indices may better capture relative leukocyte distribution in systemic inflammation. To date, no study has evaluated NPAR in TAVR patients, making this work the first to address this gap in the literature. Importantly, in a dedicated model including both STS-PROM and NPAR, each variable remained independently associated with mortality, suggesting that NPAR provides incremental prognostic information beyond established surgical risk scores.

This study showed that as NPAR levels increased, 30-day, 1-year, and 2-year mortality rates increased significantly. Furthermore, Kaplan–Meier survival analysis revealed significantly shorter survival in the higher NPAR tertile. These findings suggest that NPAR is a strong predictor of clinical outcomes after TAVR. Kaplan–Meier survival analysis further confirmed that high NPAR levels were associated with significantly increased 2-year all-cause mortality. The approximately 22% difference in mortality rates across tertiles and the median survival time exceeding 130 days suggest that NPAR is a strong predictor of clinical outcome after TAVR.

In this study, patients with elevated NPAR experienced longer hospital stays following TAVR. This observation may reflect underlying biological mechanisms linking inflammation and frailty to adverse perioperative outcomes. Elevated systemic inflammation can impair wound healing and increase vulnerability to complications, while low albumin levels may signal impaired nutritional reserve and reduced physiological resilience.[23-25] Furthermore, frailty—a common feature in elderly TAVR candidates—may exacerbate these effects, contributing to delayed convalescence and extended hospitalization. Taken together, these findings suggest that NPAR not only predicts long-term mortality but may also be associated with short-term clinical trajectories, underscoring its potential relevance for perioperative management.

In the ROC analysis, the AUC value for NPAR (0.703) indicates moderate predictive power, which is higher than its

individual components, such as albumin (0.668) and neutrophil percentage (0.634). This finding suggests that composite markers such as NPAR may have stronger prognostic capacity than individual laboratory parameters, consistent with previous reports in patients with coronary artery disease and heart failure.[13,15,29] The ROC-derived threshold further supports the potential clinical applicability of NPAR, although its discriminatory ability remains moderate and should be interpreted with caution. While tertile-based categorization enabled exploratory risk stratification, the ROC cut-off provides a more practical benchmark for potential clinical use.

In multivariable Cox regression analysis, elevated NPAR remained an independent predictor of 2-year all-cause mortality, even after adjusting for classical risk factors such as age, LVEF, creatinine, and peripheral artery disease. Patients in the Tertile 3 group, in particular, had a 2.75-fold higher risk of mortality compared to the reference group (HR: 2.75; 95% CI: 1.77-4.28; $P < .001$). This finding highlights the robustness of NPAR as a prognostic marker and supports its potential integration into existing risk scoring systems. Additionally, high creatinine levels and peripheral artery disease negatively impacted survival, indicating that systemic vascular health plays a decisive role in prognosis after TAVR. Interestingly, prior CABG has been identified as a protective factor in terms of mortality. This suggests that myocardial perfusion achieved through revascularization may have a favorable contribution to mid-term prognosis. Importantly, in the current analysis, STS-PROM emerged as a significant predictor of mortality, consistent with prior literature.[30] To account for potential multicollinearity, a dedicated model including both STS-PROM and categorical NPAR was constructed. In this model, each variable remained independently associated with 2-year mortality, suggesting that NPAR provides incremental prognostic information beyond STS-PROM. This finding highlights the potential value of incorporating NPAR alongside established surgical risk scores in clinical decision-making.

Risk assessment in TAVR patients has traditionally relied on scores such as STS-PROM and EuroSCORE II, developed for surgical populations and currently widely used.[31-33] The STS-PROM score does include measurements of Hb, WBC, and platelet count in addition to a myriad of clinical characteristics, highlighting that these blood markers are important prognostic tools in the preoperative workup. In recent years, it has been demonstrated that inflammation-based indices such as NLR and platelet-to-lymphocyte ratio (PLR) can provide prognostic value equivalent to or even superior to established risk scores.[10,26,34] Consistent with these findings, the current study demonstrated that NPAR, which reflects both systemic inflammation and nutritional reserve, has prognostic value independent of STS-PROM. Neutrophil percentage-to-albumin ratio is an easily accessible and cost-effective indicator that can be calculated using standard biochemical parameters, providing an additional advantage in clinical practice. Integrating this parameter into risk models may contribute to more accurate identification and close monitoring of patients, particularly those with frailty or a high inflammatory burden. The prognostic value of NPAR has been previously demonstrated in acute myocardial infarction, congestive heart failure, cardiogenic shock, and intensive care populations, and the current study extends this knowledge specifically to TAVR patients.[14,21,22,35,36] In conclusion, these findings suggest that NPAR is an independent marker and may enhance the accuracy of prognostication in TAVR populations by complementing existing risk scores and clinical variables.

Study Limitations

This study has several limitations. First, due to its retrospective design, a causal relationship cannot be established. Second, it was conducted at a single center with a limited patient population, which may affect the generalizability of the results. In addition, the long inclusion period (2013-2023) coincided with significant advances in TAVR technology and practice that could have influenced outcomes. Moreover, other markers of inflammation [e.g., CRP, interleukin (IL)-6, tumor necrosis factor-α (TNF-α)] were not included, preventing a comprehensive evaluation of inflammatory processes. Finally, patients with malignancy or autoimmune disease were excluded, although they constituted only a relatively small subgroup. This exclusion was necessary to minimize potential confounding effects of systemic inflammation or cachexia on NPAR values and is therefore unlikely to have significantly impacted the overall findings. Nevertheless, the large patient number, mid-term follow-up period, and adjustment for numerous potential confounding factors represent important strengths of this study.

Future Directions

Future studies should aim to further evaluate the prognostic value of NPAR and support its integration into clinical decision-making. In particular, temporal changes in NPAR should be monitored, and their association with short- and mid-term outcomes after TAVR should be clarified. Moreover, randomized controlled trials assessing the impact of preoperative interventions targeting inflammation and nutritional optimization on survival in patients with high NPAR levels are warranted. Combining NPAR with existing risk scoring systems to develop novel prognostic models could further enhance individualized patient management.

In conclusion, this study demonstrates that NPAR is an independent, accessible, and low-cost biomarker for predicting mid-term all-cause mortality in patients undergoing TAVR. Incorporating NPAR into routine clinical assessment could help refine risk stratification and guide postprocedural management in this growing patient population.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics (Committee date: August 19, 2025; Decision no: 2025.07-75).

Informed Consent: As this was a retrospective study, no informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

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Statement on Use of AI-Assisted Technologies: Artificial intelligence assisted technologies, such as large language models, chatbots, or image creators, were not used in the production of submitted work in this study.

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632. [CrossRef]. Erratum in: *Eur Heart J*. 2022;43(21):2022-2022. (https://doi.org/10.1093/eurheartj/ehac051)
2. Otto CM, Nishimura RA, Bonow RO, et al. ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2020;77(4):e25-e197. [CrossRef]. Erratum in: *J Am Coll Cardiol*. 2021;77(4):509. (https://doi.org/10.1016/j.jacc.2020.12.040). Erratum in: *J Am Coll Cardiol*. 2021;77(9):1275. (https://doi.org/10.1016/j.jacc.2021.02.007). Erratum in: *J Am Coll Cardiol*. 2023;82(9):969. (https://doi.org/10.1016/j.jacc.2023.07.010). Erratum in: *J Am Coll Cardiol*. 2024;84(18):1772. (https://doi.org/10.1016/j.jacc.2024.09.025).
3. UK TAVI Trial Investigators, Toff WD, Hildick-Smith D, Kovac J, et al. Effect of transcatheter aortic valve implantation vs surgical aortic valve replacement on all-cause mortality in patients with aortic stenosis: a randomized clinical trial. *JAMA*. 2022;327(19):1875-1887. [CrossRef]
4. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380(18):1706-1715. [CrossRef]
5. Blankenberg S, Seiffert M, Vonthein R, et al. Transcatheter or surgical treatment of aortic-valve stenosis. *N Engl J Med*. 2024;390(17):1572-1583. [CrossRef]
6. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement in low-risk patients at five years. *N Engl J Med*. 2023;389(21):1949-1960. [CrossRef]
7. Van Mieghem NM, Deeb GM, Søndergaard L, et al. Self-expanding transcatheter vs surgical aortic valve replacement in intermediate-risk patients: 5-year outcomes of the SURTAVI randomized clinical trial. *JAMA Cardiol*. 2022;7(10):1000-1008. [CrossRef]
8. Yamashita Y, Baudo M, Sicouri S, et al. Effect of elevated body mass index on outcomes of transcatheter aortic valve replacement for severe aortic stenosis. *Anatol J Cardiol*. 2024;28(12):565-574. [CrossRef]
9. Kılıç R, Güzel T, Aktan A, et al. Comparison of evolut-R 34 mm valve and smaller evolut-R valves in patients undergoing transcatheter aortic valve implantation and determination of mild paravalvular leak predictors. *Anatol J Cardiol*. 2024;28(2):109-117. [CrossRef]
10. Abushouk A, Agrawal A, Hariri E, et al. Association between haematological parameters and outcomes following transcatheter aortic valve implantation at mid-term follow-up. *Open Heart*. 2022;9(2):e002108. [CrossRef]
11. Seoudy H, Shamekhi J, Voigtländer L, et al. C-reactive protein to albumin ratio in patients undergoing transcatheter aortic valve replacement. *Mayo Clin Proc*. 2022;97(5):931-940. [CrossRef]
12. Stan A, Călburean PA, Drinkal RK, et al. Inflammatory status assessment by machine learning techniques to predict outcomes in patients with symptomatic aortic stenosis treated by transcatheter aortic valve replacement. *Diagnostics (Basel)*. 2023;13(18):2907. [CrossRef]
13. Cui H, Ding X, Li W, Chen H, Li H. The neutrophil percentage to albumin ratio as a new predictor of in-hospital mortality in patients with ST-segment elevation myocardial infarction. *Med Sci Monit*. 2019;25:7845-7852. [CrossRef]
14. Yu Y, Liu Y, Ling X, et al. The neutrophil percentage-to-albumin ratio as a new predictor of all-cause mortality in patients with cardiogenic shock. *BioMed Res Int*. 2020;2020:7458451. [CrossRef]
15. Wang X, Zhang Y, Wang Y, et al. The neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with chronic heart failure. *BMC Cardiovasc Disord*. 2023;23(1):568. [CrossRef]
16. VARC-3 Writing Committee, Généreux P, Piazza N, Alu MC, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77(21):2717-2746. [CrossRef]
17. Della Bona R, Cardillo MT, Leo M, et al. Polymorphonuclear neutrophils and instability of the atherosclerotic plaque: a causative role? *Inflamm Res*. 2013;62(6):537-550. [CrossRef]
18. Carbone F, Mach F, Montecucco F. Update on the role of neutrophils in atherosclerotic plaque vulnerability. *Curr Drug Targets*. 2015;16(4):321-333. [CrossRef]
19. Bonaventura A, Montecucco F, Dallegri F, et al. Novel findings in neutrophil biology and their impact on cardiovascular disease. *Cardiovasc Res*. 2019;115(8):1266-1285. [CrossRef]
20. Pende A, Artom N, Bertolotto M, Montecucco F, Dallegri F. Role of neutrophils in atherogenesis: an update. *Eur J Clin Investig*. 2016;46(3):252-263. [CrossRef]
21. Lin Y, Lin Y, Yue J, Zou Q. The neutrophil percentage-to-albumin ratio is associated with all-cause mortality in critically ill patients with acute myocardial infarction. *BMC Cardiovasc Disord*. 2022;22(1):115. [CrossRef]
22. Cai C, Zhang B, Sun T, et al. Neutrophil percentage to albumin ratio was associated with clinical outcomes in coronary care unit patients. *Rev Cardiovasc Med*. 2022;23(10):333. [CrossRef]
23. Plakht Y, Gilutz H, Shiyovich A. Decreased admission serum albumin level is an independent predictor of long-term mortality in hospital survivors of acute myocardial infarction. Soroka acute myocardial infarction II (SAMI-II) project. *Int J Cardiol*. 2016;219:20-24. [CrossRef]
24. Wada H, Dohi T, Miyauchi K, et al. Impact of serum albumin levels on long-term outcomes in patients undergoing percutaneous coronary intervention. *Heart Vessels*. 2017;32(9):1085-1092. [CrossRef]
25. Cheng CW, Lee CW, Chien SC, Yeh HI, Chen CY. Serum albumin was associated with a long term cardiovascular mortality among elderly patients with stable coronary artery disease. *Acta Cardiol Sin*. 2024;40(1):87-96. [CrossRef]
26. Shahim B, Redfors B, Lindman BR, et al. Neutrophil-to-lymphocyte ratios in patients undergoing aortic valve replacement: the PARTNER trials and registries. *J Am Heart Assoc*. 2022;11(11):e024091. [CrossRef]

27. Avci Y, Demir AR, Duran M, et al. The prognostic value of C-reactive protein to albumin ratio in patients undergoing transcatheter aortic valve implantation. *Acta Cardiol*. 2022;77(10):930-936. [CrossRef]
28. Peng Y, Xue Y, Wang J, et al. Association between neutrophil-to-albumin ratio and mortality in patients with cardiogenic shock: a retrospective cohort study. *BMJ Open*. 2020;10(10):e039860. [CrossRef]
29. Yin R, Zhu W, Chen W, Shen J, Wu Y, Wang Z. The relationship between neutrophil percentage-to-albumin ratio and slow and normal coronary flow phenomenon. *BMC Cardiovasc Disord*. 2025;25(1):64. [CrossRef]
30. Nair S, Ha FJ, Baradi A, et al. The use of the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in predicting transcatheter aortic valve implantation mortality. *Heart Lung Circ*. 2024;33(12):1680-1687. [CrossRef]
31. Shahian DM, Jacobs JP, Badhwar V, et al. The society of thoracic surgeons 2018 adult cardiac surgery risk models: Part 1-background, design considerations, and model development. *Ann Thorac Surg*. 2018;105(5):1411-1418. [CrossRef]
32. O'Brien SM, Feng L, He X, et al. Adult cardiac surgery risk models: Part 2-Statistical Methods and Results. *Ann Thorac Surg*. 2018;105(5):1419-1428. [CrossRef]
33. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41(4):734-745. [CrossRef]
34. Condado JF, Junpaparp P, Binongo JN, et al. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) can risk stratify patients in transcatheter aortic-valve replacement (TAVR). *Int J Cardiol*. 2016;223:444-449. [CrossRef]
35. Karaca M, Gumusdag A. Prognostic role of neutrophil percentage-to-albumin ratio in patients with non-ST-elevation myocardial infarction. *Medicina (Kaunas)*. 2024;60(12):2101. [CrossRef]
36. Sun T, Shen H, Guo Q, et al. Association between neutrophil percentage-to-albumin ratio and all-cause mortality in critically ill patients with coronary artery disease. *BioMed Res Int*. 2020;2020:8137576. [CrossRef]

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MiR-107 as a Biomarker Predicts Cardiac Hypertrophy in Chronic Hemodialysis Patients

ABSTRACT

Background: Maintenance hemodialysis (MHD) can lead to hypertrophy of myocardial cells and interstitial fibrosis in patients, which can ultimately culminate in left ventricular hypertrophy (LVH). The objective of this study is to examine the expression of miR-107 in patients undergoing MHD who also present with LVH and to evaluate its predictive value.

Methods: A total of 135 patients with end-stage renal disease who were undergoing MHD were included as the research subjects. Patients were grouped based on left ventricular mass index. Real-time quantitative polymerase chain reaction was used to detect the expression of miR-107 in the serum of the patients. The receiver operating characteristic curve was used to evaluate the diagnostic value of miR-107 in MHD with LVH patients. The Pearson's method was used for correlation analysis. Logistic regression model was used to analyze the risk factors for cardiac hypertrophy in MHD patients.

Results: Serum miR-107 is highly expressed in patients with MHD and LVH, and it may be a potential diagnostic biomarker. miR-107 has relatively high sensitivity and specificity in predicting LVH in patients with MHD. Serum miR-107 is closely related to the serum high-sensitivity C-reactive protein level and echocardiographic characteristics of patients with MHD combined with LVH. MiR-107 correlates with echocardiographic characteristics of MHD patients with LVH. Finally, logistic regression analysis indicated that miR-107 was a risk factor for LVH in MHD patients.

Conclusion: Serum miR-107 may have significant potential in diagnosing cardiac hypertrophy in MHD patients and is a potential biological indicator for cardiac hypertrophy in MHD patients.

Keywords: Diagnosis, left ventricular hypertrophy, maintenance hemodialysis, miR-107

ORIGINAL INVESTIGATION

INTRODUCTION

Chronic kidney disease (CKD) constitutes a significant global public health challenge.[1] Hemodialysis (HD) stands as the cornerstone of renal replacement therapy, playing a critical role in extending survival and enhancing the quality of life for patients.[2] End-stage renal disease (ESRD) represents a severe and irreversible deterioration of kidney function, necessitating long-term maintenance hemodialysis (MHD) as the disease progresses.[3] Patients undergoing MHD frequently contend with a myriad of complications, including hypertension, volume overload, the accumulation of uremic toxins, and disorders of mineral metabolism. These conditions can precipitate myocardial cell hypertrophy and interstitial fibrosis, leading to the development of left ventricular hypertrophy (LVH).[4] Cardiac hypertrophy frequently arises due to sustained pressure overload or underlying pathological conditions and can ultimately progress to deleterious heart failure, which is a notable clinical risk factor for mortality.[5] Consequently, it is of paramount importance to investigate the onset and progression of LVH in MHD patients, as well as to identify innovative, cost-effective, and clinically relevant biomarkers for early detection.

In recent years, a growing body of evidence has elucidated the role of microRNA (miRNA) molecules in the regulation of various diseases, including cardiac hypertrophy.[6-8] MiR-590-5p has been implicated in the pathological hypertrophy associated with heart failure.[9] Research has identified serum miR-27b as a promising

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biomarker for the screening of LVH.[10] Furthermore, it has been demonstrated that miR-133a is expressed at diminished levels in the hearts of patients with maintenance hemodialysis (MHD) who exhibit cardiac hypertrophy.[11] Among the members of the miRNA family, miR-107 has garnered attention for its involvement in a diverse array of pathological and physiological processes, including cell proliferation, apoptosis, metabolism, and fibrosis.[12] Recent studies have revealed that miR-107 is aberrantly expressed in cardiovascular diseases, such as myocardial hypertrophy and heart failure.[13]

Previous studies have indicated a potential role for miR-107 in the development of cardiac hypertrophy. However, the specific expression and association of miR-107 in MHD-induced cardiac hypertrophy remain largely uncharted. Therefore, this research endeavor seeks to investigate the expression levels and predictive significance of miR-107 in MHD with LVH patients.

METHODS

General Information

A total of 135 patients with ESRD who underwent MHD treatment at The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine between February 2023 and February 2024 were selected for this study. The criteria for inclusion encompassed: a confirmed diagnosis of ESRD; a minimum of 3 months of MHD treatment; willingness to participate in the study, with a duly signed informed consent form. The exclusion criteria included: irregularities in dialysis or inadequate volume management; unstable medical conditions such as malignant hypertension or acute infections; coexisting malignant tumors; presence of active systemic infections; recent cardiovascular events occurring within the past 3 months; and cases of chronic inflammation, hematological disorders, or significant hepatic dysfunction. Furthermore, all patients were excluded from special types of LVH, such as cardiac amyloidosis and Fabry disease, through clinical evaluation, laboratory tests, and imaging examinations. This research has received ethical approval from the Medical Ethics Committee of The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (Date: June 8, 2022; No. 20220101). This article did not use artificial intelligence–assisted technology.

Treatment and Nursing

The Prirnus1350 dialyzer, manufactured in the USA, is designed as a disposable device. It features a membrane composed of polysulfone, with a membrane area ranging from 1.2 to 1.6 m^2. The dialysate water is sourced from a reverse osmosis system, utilizing standard bicarbonate dialysate. The dialysate flow rate is maintained at 500 mL/min, while the blood flow rate is set between 200 and 300 mL/min. Patients typically undergo HD 3 times a week, with each session lasting 4 hours. During this process, anticoagulation therapy is administered, employing either unfractionated heparin or low molecular weight heparin.

The patient receives consistent and comprehensive care, with a strong emphasis on dietary management. Hemodialysis treatments are meticulously conducted in adherence to established medical protocols, which encompass the determination of dialysis frequency, the careful selection of dialysate, and the vigilant maintenance of vascular access. General nursing practices involve the routine monitoring of patients' physiological parameters to detect any changes in renal function, allowing for timely adjustments to treatment plans. In the realm of health education, nursing staff provide patients with essential knowledge regarding HD, ensuring they are equipped with a fundamental understanding of their condition. Dietary guidance is tailored to restrict high-potassium and high-phosphorus foods, as well as managing fluid intake, thereby alleviating discomfort and minimizing potential risks during the inter-dialytic period. Management of pharmacotherapy is equally critical and involves the careful control of hypertension, the management of anemia, and the regulation of phosphate levels, ensuring that all medications administered do not exacerbate renal impairment. Complementing these medical and dietary interventions, psychological support is an integral component of care, wherein nursing staff offer personalized explanations of self-management strategies, tailored to each patient's psychological state.

Survey Indicators

Basic information such as sex, age, body mass index (BMI), medical history, MHD duration, and drug use were recorded. Diagnosis of diabetes was established based on criteria that included recent utilization of hypoglycemic agents, fasting blood glucose levels exceeding 126 mg/dL, random blood glucose levels surpassing 200 mg/dL, and/or a glycosylated hemoglobin (HbA1c) percentage of 6.5% or higher. The most important biochemical indicators of the patients were collected as well. A fasting blood specimen was collected from each patient, and serum was subsequently separated for future analyses.

Grouping of Patients

All patients underwent comprehensive transthoracic echocardiography, which was employed to assess key cardiac parameters, including interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular diastolic dimension (LVDD), and left ventricular systolic diameter. Patients were categorized into 2 distinct groups based on their left ventricular mass index (LVMI) values: those exhibiting LVH during MHD (MHD with LVH group) and those who did not exhibit LVH (MHD without LVH group). Left ventricular hypertrophy was defined according to sex-specific criteria, with LVMI values exceeding 125 g/m^2 for male

HIGHLIGHTS

- Serum miR-17-5p expression is upregulated in maintenance hemodialysis (MHD) patients with left ventricular hypertrophy (LVH).
- MiR-107 has a high sensitivity and specificity in predicting MHD patients with LVH.
- MiR-107 is closely related to the inflammation and echocardiographic features of patients with MHD and LVH.
- MiR-107 was a risk factor for LVH in MHD patients.

patients and 115 g/m^2 for female patients.[14,15] The Devereux formula was employed to compute LVMI,[16] with left ventricular mass (LVM) calculated as follows: LVM (g) = 0.8 × [1.04 × (LVDD + IVST + LVPWT)^3 – (LVDD)^3] + 0.6. Subsequently, LVMI is derived from the patient's measured body surface area (BSA) using the equation: LVMI (g/m^2) = LVM/BSA. The BSA is calculated using the following formula: BSA (m^2) = [0.0061 × height (cm) + 0.0128 × weight (kg)] – 0.1529.

Real-Time Quantitative Polymerase Chain Reaction

Total RNA was meticulously extracted from serum utilizing TRIzol RNA Extraction Reagent (Life Technologies). Subsequently, complementary DNA (cDNA) was synthesized employing the Swe-Script RT II First Strand cDNA Synthesis Reagent Kit (Service Bio). Real-time quantitative polymerase chain reaction (RT-qPCR) was performed with the 2 × SYBR Green qPCR Master Mix (Service Bio) on the Step One Real-Time PCR System (Life Technologies). Each assay was conducted in triplicate, and the final results were calculated based on U6 as the internal reference for determining the relative expression levels of miR-107.

Statistical Methods

Data analysis was conducted using SPSS version 26.0 software. To assess differences between groups, independent samples analysis of variance was employed for normally distributed measurement data, while the Kruskal–Wallis test was utilized for non-normally distributed data. For categorical data, the chi-squared test was implemented. Correlation analysis was performed using Pearson's method. The diagnostic value of miR-107 in patients with cardiac hypertrophy undergoing MHD was evaluated through receiver operating characteristic (ROC) curve analysis. A multivariate logistic regression model was applied to examine the risk factors associated with cardiac hypertrophy in MHD patients. All statistical analyses were executed with a two-tailed test, and a significance level of $P < .05$ was established.

RESULTS

Comparative Clinical Data Between the Two Groups

In a cohort of 135 patients undergoing MHD, a notable 62.2% (84 patients) were found to have developed LVH. The study encompassed a total of 135 MHD patients, categorized into 2 distinct groups: MHD without LVH group (n = 51) and MHD with LVH group (n = 84). There was no statistically significant difference in age, gender, BMI, underlying diseases, MHD duration, and information on medication use between the 2 groups ($P > .05$) (Table 1).

However, the levels of parathyroid hormone (PTH), total serum cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were significantly elevated in the MHD patients with LVH compared to those without LVH, with the differences reaching statistical significance ($P < .05$) (Table 2).

Expression and Diagnostic Significance of MiR-107 in Maintenance Hemodialysis with Left Ventricular Hypertrophy Patients

The results of the RT-qPCR analysis revealed no significant differences in serum miR-107 expression pre- and post-first dialysis in the patient cohort ($t = 1.570$, $P = .118$) (Figure 1A).

Table 1. General Information on Chronic Hemodialysis Patients

Variables	MHD Without LVH (n = 51)	MHD with LVH (n = 84)	*t*	*P*
Age (years)	53.25 ± 9.89	55.05 ± 12.27	0.883	.379
Sex (male/female)	21/30	43/41	1.127	.262
BMI (kg/m^2)	20.50 ± 1.44	21.07 ± 3.29	1.161	.248
Hypertension (yes/no)	19/32	38/46	0.907	.366
Diabetes (yes/no)	12/39	29/65	1.346	.181
MHD duration (months)	83.84 ± 37.49	96.70 ± 52.80	1.521	.131
Drug [n (%)]			0.585	.560
Calcium inhibitors	18 (35.3)	33 (39.3)		
ACE inhibitors	11 (21.6)	20 (22.6)		
AT IIr inhibitors	8 (15.7)	10 (13.1)		
β-Blockers	14 (27.4)	21 (25.0)		

ACE, angiotensin-converting enzyme; AT IIr, angiotensin II receptor; BMI, body mass index; LVH, left ventricular hypertrophy; MHD, maintenance hemodialysis; β-Blockers, β receptor blocker.

Notably, the serum miR-107 levels were significantly elevated in the MHD with LVH group compared to those without LVH ($t = 10.500$, $P < .001$) (Figure 1B). Furthermore, the ROC curve analysis demonstrated that miR-107 serves as an effective predictor for MHD with LVH. The optimal diagnostic cut-off value of miR-107 in predicting LVH in MHD patients was 1.15, with a sensitivity of 86.9%, a specificity of 82.4%, and an area under the curve of 0.905 (95% CI: 0.855-0.954, $P < .001$) (Figure 1C).

Analysis of the Correlation Between MiR-107 and the Inflammatory Marker High-Sensitivity C-Reactive Protein

The serum level of high-sensitivity C-reactive protein (hs-CRP) in MHD patients with LVH was significantly higher

Table 2. Biochemical Characteristics of Chronic Hemodialysis Patients

Variables	MHD Without LVH (n = 51)	MHD with LVH (n = 84)	*t*	*P*
Hemoglobin (g/dL)	9.12 ± 0.67	9.29 ± 0.76	1.341	.182
Albumin (g/dL)	4.21 ± 0.46	4.31 ± 0.58	1.019	.310
PTH (pg/mL)	185.71 ± 63.41	223.05 ± 87.08	2.662	.009**
TC (mmol/L)	6.73 ± 0.79	7.09 ± 0.62	2.909	.004**
TG (mmol/L)	6.78 ± 0.71	7.25 ± 2.14	1.489	.139
HDL-C (mmol/L)	2.22 ± 0.56	2.12 ± 0.37	1.292	.199
LDL-C (mmol/L)	4.28 ± 0.98	4.84 ± 0.95	3.277	.001**

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MHD, maintenance hemodialysis; PTH, parathyroid hormone; TC, serum total cholesterol; TG, triglycerides.
**$P < .01$.

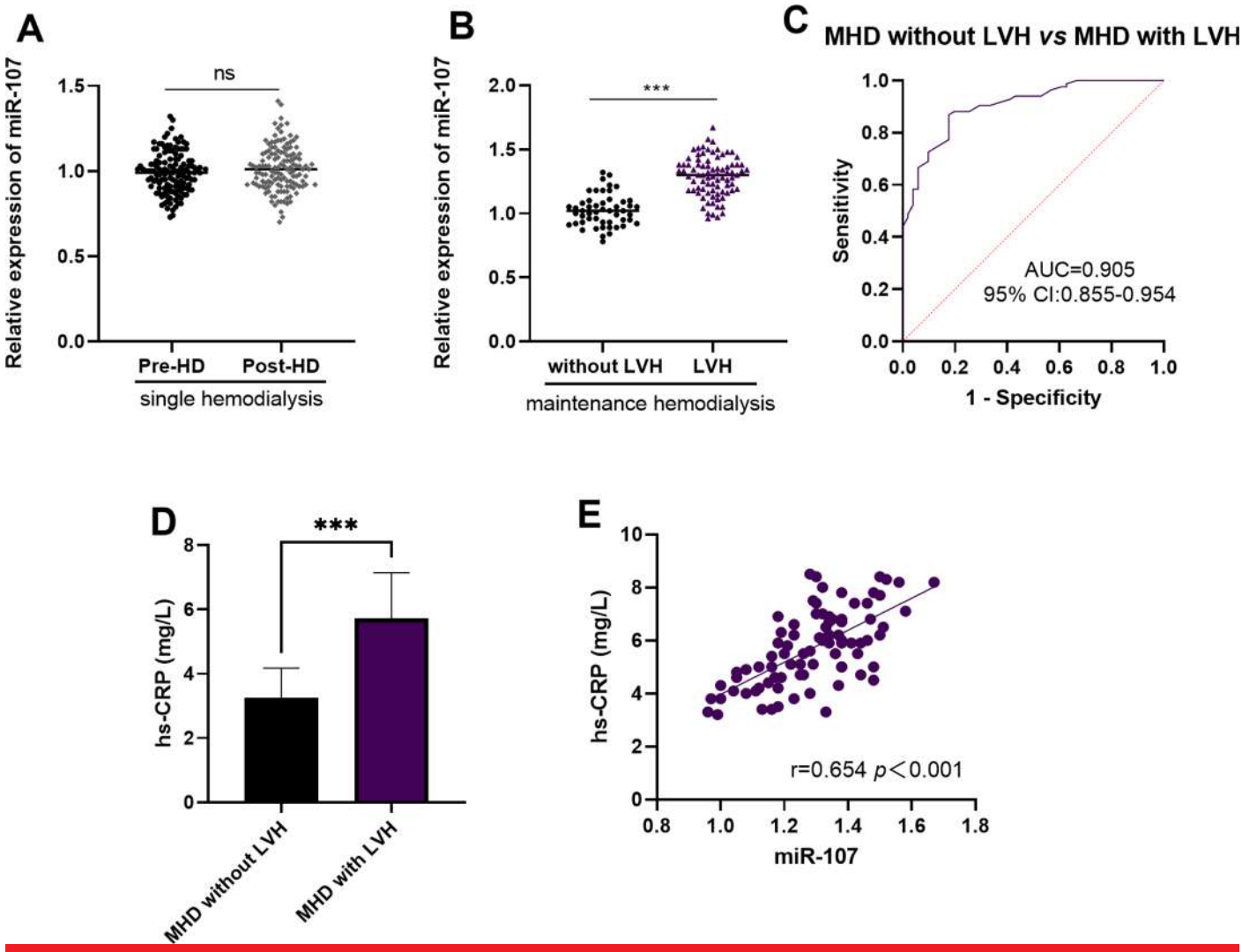

Figure 1. Expression and diagnostic significance of miR-107 in MHD with LVH patients. There was no significant difference in the expression of serum miR-107 before and after the first dialysis in the patients ($P > .05$) (A). The serum miR-107 level in the MHD with LVH group was higher than that in the MHD without LVH group ($P < .001$) (B). The ROC curve was used to evaluate the diagnostic value of miR-107 in MHD patients with LVH (C). The serum level of hs-CRP in MHD patients with LVH was significantly higher than that in the non-LVH group (D). A moderate positive correlation between the serum levels of miR-107 and hs-CRP in MHD patients with LVH ($r = 0.654$, $P < .001$) (E). ns, $P > .05$; *** $P < .001$.

than that in the non-LVH group (5.72 ± 1.42 mg/L vs. 2.87 ± 0.85 mg/L, $t = 12.94$, $P < .001$) (Figure 1D). Pearson correlation analysis showed a moderate positive correlation between the serum levels of miR-107 and hs-CRP in MHD patients with LVH ($r = 0.654$, 95% CI = 0.511-0.762, $P < .001$) (Figure 1E), suggesting that miR-107 may synergistically interact with the inflammatory response during the progression of LVH in MHD patients.

Correlation Between MiR-107 and Echocardiographic Features of Cardiac Hypertrophy in Maintenance Hemodialysis Patients

In the MHD with LVH group, IVST ($t = 15.45$), LVPWT ($t = 16.68$) and LVMI ($t = 15.04$) were significantly higher than those in the MHD without LVH group ($P < .001$) (Figure 2A-C). Furthermore, the results of the Pearson correlation analysis revealed a positive association between serum levels of miR-107 and IVST ($r = 0.619$, 95% CI = 0.466-0.736), LVPWT ($r = 0.662$, 95% CI = 0.521-0.767), and LVMI ($r = 0.528$, 95% CI = 0.354-0.667) in MHD patients with LVH ($P < .001$) (Figure 2D-F).

Analysis of Risk Factors for Cardiac Hypertrophy in Patients with Maintenance Hemodialysis

The findings from the logistic regression analysis revealed that miR-107 (odds ratio [OR] = 2.764, 95% CI = 1.229-6.219, $P = .014$), alongside hypertension (OR = 2.517, 95% CI = 1.097-5.777, $P = .029$) and diabetes (OR = 2.417, 95% CI = 1.031-5.664, $P = .042$) were identified as significant risk factors for MHD patients experiencing LVH (Table 3). The results of further multivariate logistic regression analysis showed that the OR of miR-107 was 2.459 (95% CI = 1.168-5.180, $P = .018$), suggesting that it is an independent risk factor for LVH (Table 4).

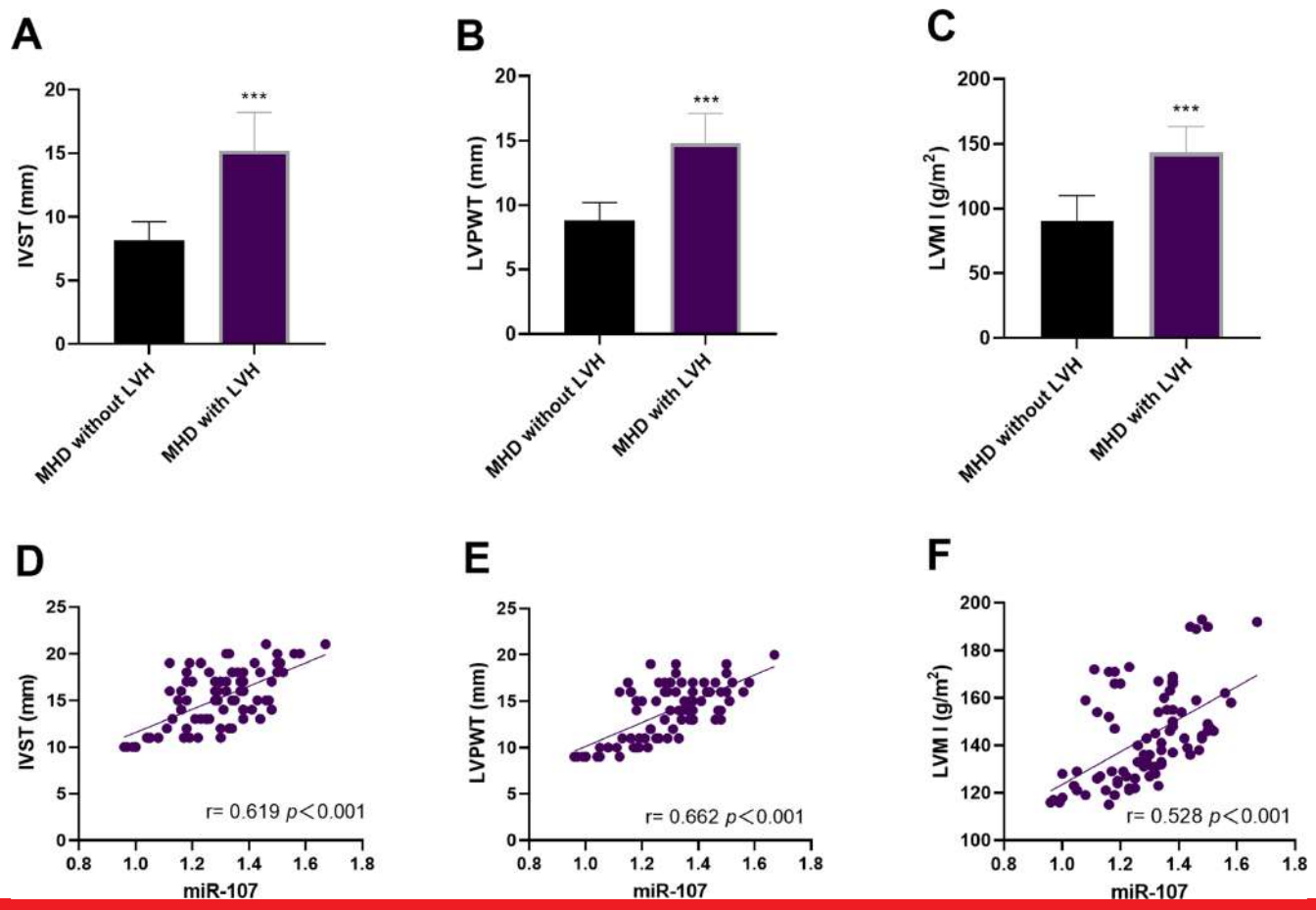

Figure 2. Correlation analysis of miR-107 with echocardiographic characteristics. In the MHD with LVH group, IVST, LVPWT and LVMI were significantly higher than those in the MHD without LVH group ($P < .001$) (A-C). The serum miR-107 level in MHD patients with LVH was positively correlated with IVST ($r = 0.619$), LVPWT ($r = 0.662$) and LVMI ($r = 0.528$) ($P < .001$) (D-F). *** $P < .001$

Table 3. Logistics Regression Analysis of the Risk Factors of Cardiac Hypertrophy in Chronic Hemodialysis Patient

		95% CI for HR		
Variables	**OR**	**Lower**	**Upper**	***P***
MiR-107	2.764	1.229	6.219	.014*
Age (years)	1.268	0.574	2.804	.557
Sex	1.827	0.786	4.248	.161
BMI	0.477	0.215	1.062	.070
Hypertension	2.517	1.097	5.777	.029*
Diabetes	2.417	1.031	5.664	.042*
MHD duration	1.291	0.584	2.851	.528
Hemoglobin	1.258	0.552	2.865	.585
Albumin	0.555	0.243	1.267	.162
PTH	1.476	0.655	3.324	.347
TC	1.591	0.703	3.600	.265
TG	1.190	0.542	2.613	.664
HDL-C	0.883	0.390	1.998	.765
LDL-C	1.320	0.595	2.927	.495

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HR, hazards ratio; LDL-C, low-density lipoprotein cholesterol; MHD, maintenance hemodialysis; OR, odds ratio; PTH, parathyroid hormone; TC, serum total cholesterol; TG, triglycerides.
*$P < .05$.

DISCUSSION

To address the hemodynamic stresses encountered during loading, the left ventricle adapts through physiological myocardial hypertrophy in the early stages, thereby preserving normal cardiac output in patients with MHD.[17] Left ventricular hypertrophy serves as a significant precursor to cardiovascular diseases, markedly influencing individuals' physical well-being and overall quality of life.[18] Emerging research increasingly elucidates the intricate relationship between miRNA and the development of cardiac hypertrophy in MHD patients.[19] Studies have shown that miR-217 promotes cardiac hypertrophy and dysfunction by targeting PTEN.[20] Concurrent findings suggest that miR-337-5p also plays a substantial role in the onset of cardiac hypertrophy.[21] Furthermore, elevated expression of miR-100-5p has been documented in the context of cardiac hypertrophy.[22] Similarly, the current results showed that the serum level of miR-107 was significantly upregulated in MHD patients with LVH, with a sensitivity of 86.9% and a specificity of 82.4% in diagnosing LVH. This finding is consistent with the previously reported elevated trend of miR-107 in hypertensive cardiomyopathy and diabetic cardiomyopathy,[23,24] suggesting that it may be involved in the common pathological processes of LVH caused by different etiologies.

Table 4. Multivariate Logistic Regression Analysis Results of Myocardial Hypertrophy in Patients Undergoing Chronic Hemodialysis

Variables	β	SE	Wald χ^2	*P*	OR	95% CI
MiR-107	0.900	0.380	5.608	.018*	2.459	1.168-5.180
Hypertension	0.914	0.394	5.387	.020*	2.494	1.153-5.394
Diabetes	0.733	0.398	3.397	.065	2.081	0.955-4.539

OR, odds ratio; SE, standard error.
*$P < .05$.

Chronic inflammation constitutes one of the core pathological features in patients undergoing MHD. C-reactive protein and particularly hs-CRP serve as a pivotal marker reflecting the state of chronic inflammation.[25] The present study revealed a significant positive correlation between miR-107 levels and hs-CRP in MHD patients with LVH, implying that inflammatory responses may represent a crucial mediating pathway through which miR-107 participates in the initiation and progression of LVH. This result supports miR-107 as a molecular marker for inflammation-cardiac remodeling coupling, providing a basis for the combined monitoring of miR-107 and hs-CRP in assessing the risk of LVH. Future research could target miR-107 to delve into its regulatory role in the inflammatory factor network, thereby providing novel targets and strategies for anti-inflammatory therapy of LVH in MHD patients.

Currently, the diagnosis of LVH relies on various techniques, including electrocardiogram (ECG), echocardiography, and cardiac magnetic resonance imaging (cMRI).[26] Left ventricular hypertrophy can be detected by echocardiography through the display of hypertrophy or other abnormalities typically associated with hypertrophic phenotypes.[27] The current study further establishes a close association between miR-107 and echocardiographic features in patients with MHD and LVH, identifying it as a critical risk factor for LVH in this patient population. These findings underscore the potential of miR-107 as a diagnostic or complementary diagnostic marker for MHD with LVH. Nonetheless, further investigation into its combined diagnostic efficacy is warranted.

Furthermore, it is important to underscore the significant impact of nursing interventions in mitigating complications and enhancing the therapeutic efficacy of HD throughout the MHD process.[28] End-stage renal disease is a critical pathological condition that arises when CKD progresses to an advanced stage, ultimately leading to partial or complete loss of renal function. This deterioration often results in the retention of metabolic waste products, as well as disturbances in water, electrolyte, and acid-base balance.[29] Maintenance hemodialysis has emerged as a widely adopted therapeutic approach for managing ESRD, effectively improving patients' quality of life and extending their longevity.[30] Additionally, the protracted nature of chronic renal failure leaves patients susceptible to negative emotional states such as anxiety and depression, which can adversely influence treatment outcomes.[31] Consequently, the implementation of effective and standardized nursing measures during HD for patients with chronic renal failure is paramount. The findings from this study indicate that, under targeted nursing interventions, the incidence of LVH was observed to be 62.2%. Previous studies have established that LVH is notably prevalent among patients with ESRD, with roughly 75% of MHD patients being affected.[32,33] Although the current data suggest a reduction in incidence compared to earlier research, further validation is required to substantiate this specific effect.

This investigation was conducted as a retrospective clinical study. However, it did not delve into the molecular mechanisms through which serum miR-107 influences cardiac hypertrophy and facilitates disease progression. Consequently, further in-depth research is warranted in this area. Additionally, the establishment of multi-center and large-scale studies is essential for both internal and external validation, which will ultimately enhance the predictive performance and clinical applicability of the model.

CONCLUSION

Serum miR-107 may have significant potential in diagnosing cardiac hypertrophy in MHD patients and is a potential biological indicator for cardiac hypertrophy in MHD patients.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (Date: June 8, 2022; No. 20220101).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Conceptualization: J.H.Z.; Methodology: L.L.; Formal analysis and investigation: J.C., Y.M.X.; Writing - original draft preparation: L.L.; Writing - review and editing: W.Y., S.W.; Funding acquisition: L.L.

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REFERENCES

1. Morales Palomares S, Parozzi M, Ferrara G, et al. Olfactory dysfunctions and chronic kidney disease: a scoping review. *J Ren Nutr*. 2025;35(1):4-14. [CrossRef]
2. Makkar V, Kumar M, Mahajan R, Khaira NS. Comparison of outcomes and quality of life between hemodialysis and peritoneal

dialysis patients in Indian ESRD population. *J Clin Diagn Res*. 2015;9(3):OC28-OC31. [CrossRef]
3. Wu TC, Hsu BG, Kuo CH, Wang CH, Tsai JP. Serum angiopoietin-like Protein 3 levels are associated with endothelial function in patients with maintenance hemodialysis. *Life (Basel, Switzerland)*. 2023;14(1):18. [CrossRef]
4. Junho CVC, Frisch J, Soppert J, Wollenhaupt J, Noels H. Cardiomyopathy in chronic kidney disease: clinical features, biomarkers and the contribution of murine models in understanding pathophysiology. *Clin Kidney J*. 2023;16(11):1786-1803. [CrossRef]
5. Hu H, Wang X, Yu H, Wang Z. Extracellular vesicular microRNAs and cardiac hypertrophy. *Front Endocrinol*. 2024;15:1444940. [CrossRef]
6. Derda AA, Thum S, Lorenzen JM, et al. Blood-based microRNA signatures differentiate various forms of cardiac hypertrophy. *Int J Cardiol*. 2015;196:115-122. [CrossRef]
7. Osmak G, Baulina N, Kiselev I, Favorova O. MiRNA-regulated pathways for hypertrophic cardiomyopathy: network-based approach to insight into pathogenesis. *Genes*. 2021;12(12):2016. [CrossRef]
8. Scolari FL, Faganello LS, Garbin HI, Piva E Mattos B, Biolo A. A systematic review of microRNAs in patients with hypertrophic cardiomyopathy. *Int J Cardiol*. 2021;327:146-154. [CrossRef]
9. Fan P, Zhang L, Cheng T, et al. MiR-590-5p inhibits pathological hypertrophy mediated heart failure by targeting RTN4. *J Mol Histol*. 2021;52(5):955-964. [CrossRef]
10. Wang Y, Chen S, Gao Y, Zhang S. Serum MicroRNA-27b as a screening biomarker for left ventricular hypertrophy. *Tex Heart Inst J*. 2017;44(6):385-389. [CrossRef]
11. Wen P, Song D, Ye H, et al. Circulating MiR-133a as a biomarker predicts cardiac hypertrophy in chronic hemodialysis patients. *PLoS One*. 2014;9(10):e103079. [CrossRef]
12. Zhang L, Jin G, Zhang W, Wang Q, Liang Y, Dong Q. CircRNA Arf3 suppresses glomerular mesangial cell proliferation and fibrosis in diabetic nephropathy via miR-107-3p/Tmbim6 axis. *J Bioenerg Biomembr*. 2024;56(5):543-552. [CrossRef]
13. Marques FZ, Vizi D, Khammy O, Mariani JA, Kaye DM. The transcardiac gradient of cardio-microRNAs in the failing heart. *Eur J Heart Fail*. 2016;18(8):1000-1008. [CrossRef]
14. Liu K, Xu Y, Gong S, et al. The disadvantage of morning blood pressure management in hypertensive patients. *Medicine*. 2020;99(8):e19278. [CrossRef]
15. Wu QS, He Q, He JQ, et al. The role of mitofilin in left ventricular hypertrophy in hemodialysis patients. *Ren Fail*. 2018;40(1):252-258. [CrossRef]
16. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57(6):450-458. [CrossRef]
17. Liu C, Yan ZN, Fan L, Huang J, Shen D, Song XT. Layer-specific speckle tracking analysis of left ventricular systolic function and synchrony in maintenance hemodialysis patients. *BMC Cardiovasc Disord*. 2020;20(1):126. [CrossRef]
18. Dussold C, Gerber C, White S, et al. DMP1 prevents osteocyte alterations, FGF23 elevation and left ventricular hypertrophy in mice with chronic kidney disease. *Bone Res*. 2019;7:12. [CrossRef]
19. Wu HB, Yang CS, Wang YC, et al. The expression of miR-365 in serum of hypertension patients with left ventricular hypertrophy was up-regulated, which was positively correlated with left ventricular mass index. *Pharmacogenomics Pers Med*. 2021;14:905-913. [CrossRef]
20. Nie X, Fan J, Li H, et al. miR-217 promotes cardiac hypertrophy and dysfunction by targeting PTEN. *Mol Ther Nucleic Acids*. 2018;12:254-266. [CrossRef]
21. Ding Y, Wang J, Lu J. miR-337-5p promotes the development of cardiac hypertrophy by targeting Ubiquilin-1 (UBQLN1). *Bioengineered*. 2021;12(1):6771-6781. [CrossRef]
22. Zeng J, Wang L, Zhao J, et al. MiR-100-5p regulates cardiac hypertrophy through activation of autophagy by targeting mTOR. *Hum Cell*. 2021;34(5):1388-1397. [CrossRef]
23. Trajkovski M, Hausser J, Soutschek J, et al. MicroRNAs 103 and 107 regulate insulin sensitivity. *Nature*. 2011;474(7353):649-653. [CrossRef]
24. Zheng M, Wang M. A narrative review of the roles of the miR-15/107 family in heart disease: lessons and prospects for heart disease. *Ann Transl Med*. 2021;9(1):66. [CrossRef]
25. Sahib A, Choudhury C, Wani IA, Wani MM. Evaluation of inflammatory status in chronic kidney disease patients and a comparison between hemodialysis and peritoneal dialysis patients. *Cureus*. 2024;16(9):e69443. [CrossRef]
26. Devine PA, Courtney AE, Maxwell AP. Cardiovascular risk in renal transplant recipients. *J Nephrol*. 2019;32(3):389-399. [CrossRef]
27. Siranart N, Deepan N, Techasatian W, et al. Diagnostic accuracy of artificial intelligence in detecting left ventricular hypertrophy by electrocardiograph: a systematic review and meta-analysis. *Sci Rep*. 2024;14(1):15882. [CrossRef]
28. Li J, Lin Y, Wang L, Wang Q, Wu Q. Analysis of the application effect of the Clark comfortable nursing approach in hemodialysis patients with end stage renal failure. *Ren Fail*. 2024;46(2):2423011. [CrossRef]
29. Ezzatt OM, Hamed MG, Gamil Y. Oropharyngeal and otorhinological changes in end stage renal patients undergoing hemodialysis. *J Clin Exp Dent*. 2021;13(7):e701-e708. [CrossRef]
30. Cao M, Tang B, Yang L, Zeng J. A machine learning-based model for predicting the risk of cognitive frailty in elderly patients on maintenance hemodialysis. *Sci Rep*. 2025;15(1):2525. [CrossRef]
31. Hendriks FK, Smeets JSJ, van der Sande FM, Kooman JP, van Loon LJC. Dietary protein and physical activity interventions to support muscle maintenance in end-stage renal disease patients on hemodialysis. *Nutrients*. 2019;11(12):2972. [CrossRef]
32. Abreo AP, Herzog CA, Kutner NG, Lea J, Johansen KL. Estimated pulmonary artery systolic pressure and self-reported physical function in patients on hemodialysis. *Am J Nephrol*. 2015;41(4-5):313-319. [CrossRef]
33. Gou WJ, Zhou FW, Providencia R, et al. Association of mineralocorticoid receptor antagonists with the mortality and cardiovascular effects in dialysis patients: a meta-analysis. *Front Pharmacol*. 2022;13:823530. [CrossRef]

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Concomitant Percutaneous Left Atrial Appendage Closure and Transcatheter Aortic Valve Implantation: Double Hit Combo in Atrial Fibrillation

ABSTRACT

Background: Patients with atrial fibrillation (AF) undergoing transcatheter aortic valve implantation (TAVI) often require long-term oral anticoagulation (OAC), which may not be appropriate for those at high bleeding risk. Performing left atrial appendage closure (LAAC) during TAVI can reduce the risk of thromboembolism while avoiding the need for prolonged anticoagulation.

Methods: This single-center study included 5 consecutive patients with severe aortic stenosis and AF who underwent same-session TAVI and LAAC between October 2024 and March 2025. All had contraindications to OAC or high bleeding risk. Procedural details and early outcomes were recorded. Technical success was defined according to Valve Academic Research Consortium-3 (VARC-3) (TAVI) and Munich/The Society for Cardiovascular Angiography & Interventions (SCAI) and the Heart Rhythm Society criteria (LAAC). Continuous variables are presented as mean ± SD or median interquartile range (IQR), and categorical variables as n (%).

Results: Mean age was 75.6 ± 8.4 years; 40% were male. The median Society of Thoracic Surgeons score was 6.0% [IQR 5.5-7.0], median CHA_2DS_2-VA was 4 [4-5], and median hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly was 3 [3-4]. All patients received a Meril valve; LAAC devices included Amulet (n=3) and LAmbre (n=2). Technical success was achieved in all cases. There were no intra-periprocedural complications, major bleeding (Bleeding Academic Research Consortium ≥3), stroke/transient ischemic attack, or vascular complications. But Kidney Disease: Improving Global Outcomes stage 1 acute kidney injury was observed only in 1 (20%) patient. The median hospital stay was 4 [IQR 3-6] days.

Conclusion: In this study, same-session TAVI and LAAC in AF patients with high bleeding risk were technically feasible and showed an acceptable short-term safety profile. Larger, prospective studies with longer follow-up are needed to confirm these results.

Keywords: Concomitant procedure, high bleeding risk, left atrial appendage closure, transcatheter aortic valve implantation

INTRODUCTION

Severe aortic stenosis (AS) presents a significant procedural challenge, especially in elderly patients with atrial fibrillation (AF), a subgroup characterized by both thromboembolic and hemorrhagic risks.[1,2] Transcatheter aortic valve implantation (TAVI) has become a preferred alternative to surgical valve replacement in high-risk and inoperable patients, with expanding indications beyond traditional high-risk cases. However, the concurrent presence of AF complicates management, as these patients need effective stroke prevention with oral anticoagulation (OAC), which can increase both periprocedural and long-term bleeding risks, particularly when antiplatelet therapy is also involved.[3]

Patients with AF who are poor candidates for OAC due to either prior major bleeding, frailty, or inability to tolerate therapy remain at high risk for stroke and vulnerable to hemorrhagic complications. LAAC offers a non-pharmacological

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alternative by eliminating the primary source of thrombus formation in non-valvular AF and is particularly useful in those with contraindications to OAC or a high bleeding risk (HAS-BLED score of ≥3).[4] In TAVI candidates, who are often elderly and have comorbidities, the combined approach of LAAC and TAVI in a single session has demonstrated technical feasibility and safety in small case series, especially in OAC-ineligible patients.[5]

The concept of performing TAVI and LAAC in a single session aims to minimize procedural burden, reduce cumulative exposure to anesthesia and vascular access, and potentially shorten hospital stay. Several small case series and observational studies have reported high technical success rates with acceptable complication profiles, suggesting that the approach may be a viable option for selected high-risk patients.[3,5,6] Nonetheless, data remain limited, and most available reports involve heterogeneous patient populations, varied procedural sequences, and different device types, underscoring the need for additional evidence from real-world practice.

Given the lack of data from real-world cohorts and the limited representation of OAC-ineligible patients in larger trials, further evidence is required to define the procedural feasibility and short-term safety of same-session TAVI and LAAC. In this study, a single-center experience with 5 high-risk AF patients who underwent combined TAVI and LAAC in a single session was reported. All patients had contraindications to long-term OAC due to major bleeding events or thromboembolic events occurring while on therapy. The primary objective of this study was to assess technical success, while secondary endpoints focused on in-hospital complications and early post-procedural outcomes.

METHODS

Study Population

This was a single-center, retrospective, observational study including 5 consecutive patients with severe, symptomatic AS and coexisting AF who underwent combined TAVI and LAAC in a single procedural session between October 2024 and March 2025. All patients were ineligible for long-term OAC due to a history of major bleeding (e.g., gastrointestinal or ocular hemorrhage) or thromboembolic events occurring while on therapeutic OAC. The decision to perform combined TAVI and LAAC was made by the institutional Heart Team, based on clinical presentation and comorbidities. The study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Hacettepe University Health Sciences Research Ethics Committee (Date: August 26, 2025; Decision number: 2025/16-61; Study registration number: SBA 25/746). Waived by the ethics committee for this retrospective analysis of anonymized medical records.

Pre-procedural Evaluation

All patients underwent a comprehensive pre-procedural assessment, including detailed clinical history, physical examination, laboratory testing, transthoracic echocardiography, and multislice computed tomography (CT) for annular sizing and vascular access evaluation. Transesophageal echocardiography (TEE) was performed to assess the morphology and dimensions of the left atrial appendage (LAA) and to exclude pre-existing thrombus. Echocardiographic parameters, including peak and mean transvalvular gradients and aortic valve area measurements, confirmed the severity of AS in accordance with current guidelines. Risk stratification was performed using the Society of Thoracic Surgeons (STS) score, CHA_2DS_2-VA, and HAS-BLED scores, calculated from baseline clinical and echocardiographic data.

Procedural Details

All procedures were performed under general anesthesia in a cardiac catheterization laboratory. Following sterile preparation and obtaining vascular access, transfemoral TAVI was performed using the balloon-expandable Myval transcatheter heart valve (Meril Life Sciences, Vapi, India), with device size selection based on pre-procedural multislice CT annular measurements. After successful valve implantation, TEE was introduced for LAAC planning. Venous access was obtained via the contralateral femoral vein, and transseptal puncture was performed at the inferoposterior aspect of the interatrial septum under fluoroscopic and TEE guidance. Device sizing and selection were based on TEE measurements of the LAA landing zone and ostium. Zero-contrast LAAC was performed using Amulet LAA Occluder (Abbott, Chicago, IL, USA) in 3 patients and LAmbre LAA Closure System (Lifetech Scientific, Shenzhen, China) in 2 patients. Devices were deployed under fluoroscopic and TEE visualization, ensuring optimal position and seal before release, as described in previous studies (Figure 1).[7,8] Final TEE and fluoroscopy confirmed stable device position, absence of peri-device leak, and no pericardial effusion.

Study Endpoints

The primary endpoint was technical success, defined as successful deployment of both the transcatheter aortic valve and the LAAC device in the intended position, with no need for additional unplanned interventions and without

HIGHLIGHTS

- The combined transcatheter aortic valve implantation–left atrial appendage closure (TAVI-LAAC) procedure was technically successful in all 5 patients (100%) with no procedural complications, demonstrating the safety and feasibility of this approach.
- Median procedure time was 72 minutes with a contrast volume of 65 mL, indicating that the combined procedure can be performed efficiently without excessive procedural burden.
- No major adverse events, including stroke, major bleeding, or pericardial complications, occurred during the index hospitalization, supporting the early safety profile of simultaneous TAVI-LAAC.
- This combined approach may be particularly beneficial for high-risk elderly patients with atrial fibrillation requiring both TAVI and stroke prevention, potentially reducing the need for multiple procedures and prolonged anticoagulation.

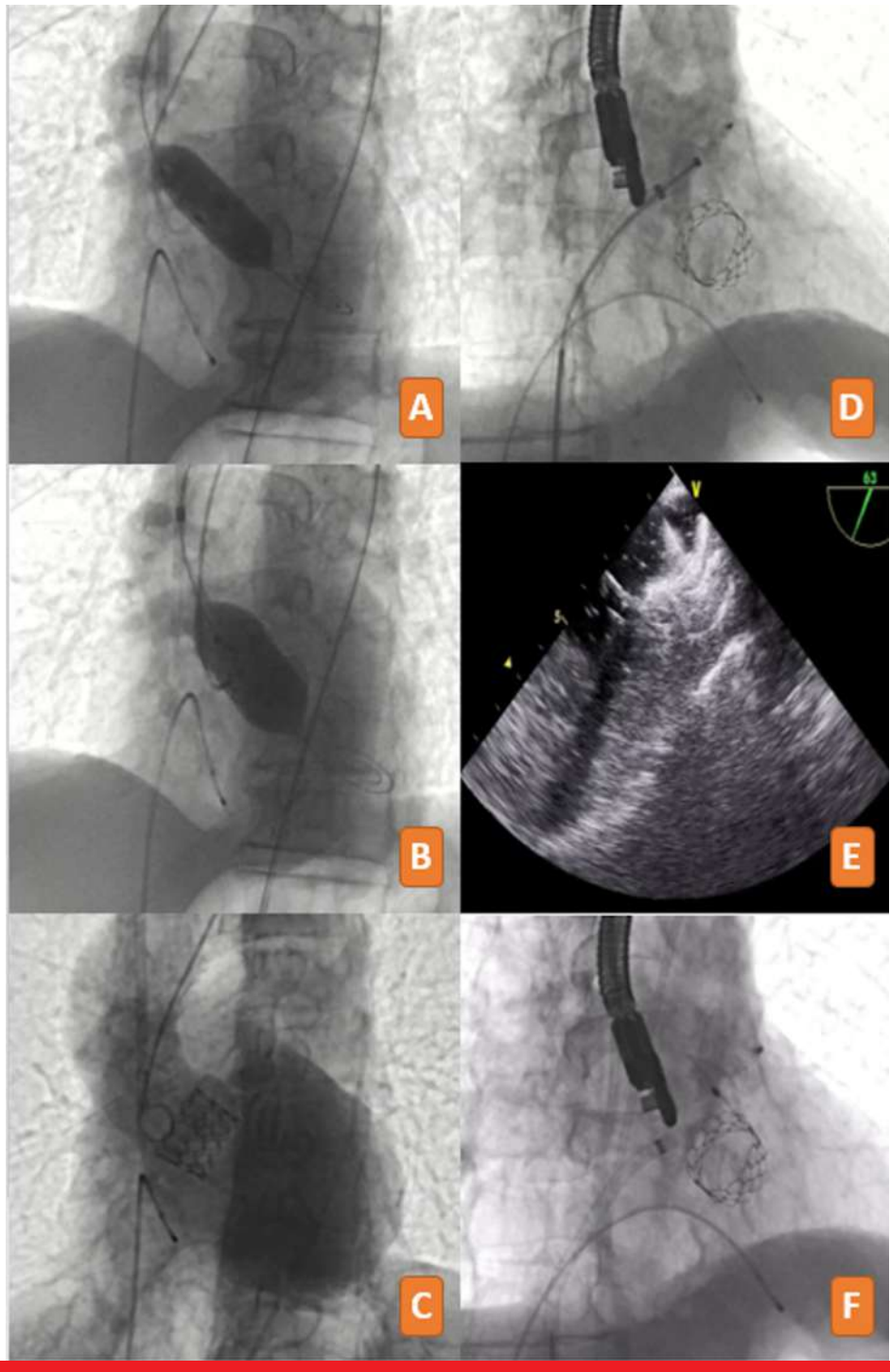

Figure 1. Stepwise fluoroscopic and echocardiographic images of the same-session TAVI and LAAC. (A, B) Balloon valvuloplasty and transcatheter aortic valve deployment. (C) Final valve position without paravalvular leak. (D) Fluoroscopic view of LAA occluder positioning. (E) TEE confirmation of correct device placement without leak. (F) Final fluoroscopic image showing a stable valve and occluder.

in-hospital mortality. For the TAVI procedure, technical success was defined according to the Valve Academic Research Consortium-3 (VARC-3) criteria, which include the absence of procedural mortality, correct positioning of a single prosthetic heart valve into the proper anatomical location, and intended valve performance with no prosthesis-patient mismatch or significant paravalvular leak at hospital discharge.[9]

For the LAAC procedure, technical success was defined based on the Munich Consensus Document, which provides standardized definitions for procedural outcomes, endpoints, and data collection in clinical studies.[10] These criteria require successful device deployment with complete LAAC or residual peri-device leak $\leq$ 5 mm, stable device position confirmed by imaging, and no device embolization or surgical intervention.

Secondary endpoints included the occurrence of vascular complications (major or minor) according to VARC-3, major bleeding events defined as Bleeding Academic Research Consortium (BARC) type ≥ 3[11] pericardial effusion or tamponade requiring intervention, stroke or transient ischemic attack (TIA), new permanent pacemaker implantation, and acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for distribution using the Shapiro–Wilk test. Given the small sample size and non-normal distribution of most variables, continuous data are presented as median [interquartile range (IQR)], and categorical data are presented as counts and percentages. No imputation was performed for missing data. Descriptive statistics were used to summarize baseline characteristics, procedural details, and outcomes.

RESULTS

The study included 5 patients with a mean age of 75.6 ± 8.4 years, of whom 2 (40.0%) were male. The mean body mass index was 24.45 ± 2.11 kg/m^2. Four patients (80.0%) had a history of coronary artery disease and hypertension, and 1 patient (20.0%) had diabetes mellitus. Non-paroxysmal AF was documented in 4 patients (80.0%). The median STS score was 6.0 (IQR 5.5-7.0). The median CHA_2DS_2-VA and HAS-BLED scores were 4 (IQR 4-5) and 3 (IQR 3-4), respectively. The primary indications for LAAC included gastrointestinal bleeding in 2 patients (40.0%), ischemic stroke despite OAC in 2 patients (40.0%), and systemic embolism (retinal artery occlusion) despite OAC in 1 patient (20.0%) (Table 1).

All procedures were completed in a single session without intraprocedural complications. The median procedural time was 72 minutes (IQR 68-78), and the median contrast volume was 65 mL (IQR 60-70), reflecting the use of a zero-contrast strategy for LAAC with TEE and fluoroscopic guidance. All TAVI procedures were performed using balloon-expandable Myval valves (Meril Life Sciences, Gujarat, India), and LAAC was achieved with either Amulet (Abbott, Chicago, IL, USA) or LAmbre (Lifetech Scientific, Shenzhen, China) devices.

Postprocedural antithrombotic therapy at discharge involved clopidogrel alone in 2 patients (40.0%) due to prior gastrointestinal bleeding, and aspirin plus apixaban in the remaining 3 patients (60.0%) who had a history of thromboembolism despite OAC, as shown in Table 2.

During the in-hospital period, no deaths, myocardial infarctions, or strokes were recorded. There were no cases of

Table 1. Baseline Characteristics of the Study Population

Characteristic	Value (n = 5)
Demographics	
Age, years	75.6 ± 8.4
Male sex, n (%)	2 (40.0)
BMI, kg/m^2	24.45 ± 2.11
Risk factors and comorbidities	
Ex-smoker, n (%)	2 (40.0)
History of CAD, n (%)	4 (80.0)
Diabetes mellitus, n (%)	1 (20.0)
Hypertension, n (%)	4 (80.0)
STS score, %	6.0 (IQR 5.5-7.0)
CHA_2DS_2-VA score	4 (IQR 4-5)
HAS-BLED score	3 (IQR 3-4)
Atrial fibrillation type	
Non-paroxysmal AF, n (%)	4 (80.0)
Paroxysmal AF, n (%)	1 (20.0)
Indication for LAAC	
Gastrointestinal bleeding, n (%)	2 (40.0)
Ischemic stroke on apixaban, n (%)	1 (20.0)
Ischemic stroke on warfarin, n (%)	1 (20.0)
Retinal artery occlusion on rivaroxaban, n (%)	1 (20.0)

Data are presented as mean ± SD for continuous variables and as number (percentage) for categorical variables.
AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHA_2DS_2-VA, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/TIA, vascular disease, age 65–74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio, elderly, drugs/alcohol concomitantly; IQR, interquartile range; LAAO, left atrial appendage closure; STS, Society of Thoracic Surgeons.

Table 2. Procedural Characteristics

Characteristic	Value (n = 5)
TAVI procedure	
Valve type	Meril (Meril Life Sciences, India): 5 (100.0)
Valve size, mm	25.7 ± 2.2
Peak gradient, mm Hg	74.0 ± 22.8
Mean gradient, mm Hg	42.6 ± 12.0
Aortic valve area, cm^2	0.79 ± 0.16
LAAC procedure	
Amulet (Abbott, USA), n (%)	3 (60.0)
Lambre (Lifetech Scientific, China), n (%)	2 (40.0)
Device size, mm	22, 22/28, 22, 24, 25
Total procudure time, min	72 (IQR 68-78)
Contrast volume, mL	65 (IQR 60-70)
Procedural outcome	
Technical success, n (%)	5 (100.0)
Any procedural complication, n (%)	0 (0.0)
Discharge antithrombotic regimen	
ASA + OAC (apixaban)	3 (60.0)
Clopidogrel only	2 (40.0)
Duration of Index Hospitalization	
Median hospital stays, days	4 (IQR 3-6)

Data are presented as mean ± SD, median [interquartile range (IQR)], or number (percentage).
ASA, acetylsalicylic acid; IQR, interquartile range; LAAC, left atrial appendage closure; OAC, oral anticoagulant; TAVI, transcatheter aortic valve implantation.

Table 3. Early Clinical Outcomes

Variables	Value (n = 5)
Clinical outcomes	
Stroke/TIA, n (%)	0 (0.0)
Major bleeding (BARC ≥ 3), n (%)	0 (0.0)
Pericardial effusion/tamponade, n (%)	0 (0.0)
Vascular complication (VARC-3), n (%)	0 (0.0)
Permanent pacemaker implantation, n (%)	0 (0.0)
Acute kidney injury (KDIGO), n (%)	1 (20.0)

Data are presented as number (percentage) unless otherwise indicated.
BARC, Bleeding Academic Research Consortium; KDIGO, Kidney Disease: Improving Global Outcomes; TIA, transient ischemic attack; VARC, Valve Academic Research Consortium.

device embolization, pericardial effusion, or major vascular complications. One patient developed AKI, which was classified as stage 1 according to the KDIGO criteria, and was managed conservatively without the need for renal replacement therapy. No major or life-threatening bleeding events were observed, and there were no cases of clinically significant paravalvular leak after TAVI or residual peri-device leak following LAAC (Table 3).

DISCUSSION

Performing TAVI and LAAC simultaneously has become a viable treatment option for patients with AF and severe AS who are at high risk for repeated procedures. This combined approach may help reduce risks associated with multiple interventions, such as repeated anesthesia, longer hospital stays, vascular access issues, and increased contrast use. Previous studies, including the randomized study reported by Kapadia et al,[6] have shown promising results in terms of procedural success and early safety.[3,12] In the present cohort, combining both structural interventions into a single session was accomplished with high technical success and low complication rates, supporting the use of this approach in carefully selected high-risk patients.

An increasing amount of evidence shows that performing both TAVI and LAAC in a single session is feasible and can help avoid repeated anesthesia and vascular access, which is especially important in high-risk patients. In the authors' experience, this combined approach was further supported by using a zero-contrast method for LAAC, relying on TEE and fluoroscopic guidance. This minimized renal risk while ensuring procedural safety. On the other hand, cardiovascular interventions using general anesthesia are generally safe, but cumulatively are associated with cognitive decline and neurodegeneration in the elderly. Perioperative brain health should be prioritized for older and vulnerable patients, particularly those who have multiple interventional procedures using anesthesia.[13] These findings align with previous reports of technical success and positive early outcomes in similar populations.[6,12]

Our findings support previous observational and randomized studies indicating that concomitant TAVI and LAAC are both feasible and safe in selected high-risk patients. The "One-Stop Shop" study showed comparable 30-day outcomes with combined versus isolated TAVI,[3] while Kleinecke et al[14] found no increase in complications when LAAC was performed with other structural interventions. More recently, the WATCH-TAVR trial confirmed that the combined approach is not inferior in terms of death, stroke, and major bleeding at 2 years.[6] Collectively, this data support LAAC integration during TAVI as a viable alternative for AF patients with high bleeding risk or contraindications to OAC.

An essential part of this study is the use of a zero-contrast strategy during LAAC, which led to a relatively low median contrast volume compared to larger cohorts. In WATCH-TAVR, the excessive contrast used for the combined procedure was about 119 mL, significantly higher than the median 65 mL reported in the present cohort. Excessive contrast exposure is a known factor contributing to AKI after TAVI, especially in elderly patients with baseline renal dysfunction. Previous consensus statements have highlighted strategies for kidney protection, including reducing contrast and relying on echocardiographic guidance whenever possible.[15] Based on the authors' experience, only 1 patient developed stage 1 AKI and was managed conservatively, highlighting the potential benefit of a contrast-sparing approach in high-risk groups.

In this cohort, there were no major periprocedural complications such as device embolization, pericardial effusion, stroke, or major bleeding, which aligns with findings from prior series. The case series by Freire et al[5] reported 7 patients undergoing concomitant TAVR and LAAC, all with successful implantation and no major adverse events during follow-up. Similarly, a meta-analysis including 482 patients indicated that combined procedures did not significantly raise the risk of stroke, bleeding, or death compared to isolated TAVR. However, a higher rate of vascular complications was observed.[16] These results suggest that although the overall safety profile of simultaneous TAVI and LAAC is acceptable, managing vascular access remains crucial, especially considering the added procedural complexity and the common frailty in this patient group.

The best antithrombotic strategy after combined TAVI and LAAC remains uncertain. Current European Society of Cardiology guidelines recommend lifelong OAC for AF after TAVI, but the high bleeding risk in elderly and frail patients challenges this approach.[17] By eliminating the need for long-term anticoagulation, LAAC provides a potential advantage in this subgroup. Kapadia et al[6] demonstrated in the WATCH-TAVR trial that dual antithrombotic therapy after combined procedures offered acceptable thromboembolic protection and a lower bleeding risk compared with OAC. The present practice of using short-term dual antithrombotic treatment followed by single antiplatelet therapy aligns with this evidence. This indicates that a personalized antithrombotic regimen after combined procedures can be both safe and effective.

These findings contribute to the growing evidence supporting the feasibility of performing concomitant TAVI and LAAC in selected patients with severe AS and AF who are

at high risk of bleeding. While previous studies have mostly included diverse patient populations or single-center experiences,[3,5,6,12] the present study offers further insight into procedural strategies such as contrast minimization and stepwise antithrombotic management.

This study is limited by its single-center, retrospective design and relatively small sample size, which may restrict the generalizability of the findings. Additionally, the short follow-up duration prevents definitive conclusions about long-term outcomes, and the lack of a control group limits direct comparisons with isolated TAVI or LAAC procedures. Despite these limitations, these results support the feasibility and short-term safety of performing TAVI and LAAC together in carefully selected high-risk patients with severe AS and AF. These findings suggest that the combined approach could be a reasonable treatment option for patients with contraindications to long-term anticoagulation, warranting validation in larger multicenter studies with longer follow-up.

Ethics Committee Approval: This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Hacettepe University Health Sciences Research Ethics Committee (Date: August 26, 2025; Decision no.: 2025/16-61; Study registration number: SBA 25/746).

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

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Declaration of Interests: U.C. is an Associate Editor of the Archives of the Turkish Society of Cardiology. N.Ö. is an Associate Editor; H.Y. and E.B.K. are members of the International Editorial Board of The Anatolian Journal of Cardiology. Given the affiliation between these journals/societies, this relationship is declared for transparency; however, it had no influence on the peer-review process or the decision to publish. The other authors have no conflicts of interest to declare.

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REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364(23):2187-2198. [CrossRef]
2. Achenbach S, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA. SCCT expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). *J Cardiovasc Comput Tomogr*. 2012;6(6):366-380. [CrossRef]
3. Attinger-Toller A, Maisano F, Senn O, et al. "One-Stop Shop": safety of combining transcatheter aortic valve replacement and left atrial appendage occlusion. *JACC Cardiovasc Interv*. 2016;9(14):1487-1495. [CrossRef]
4. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol*. 2013;61(25):2551-2556. [CrossRef]
5. Freire AFD, Filippini FB, Bignoto TC, et al. Combined transcatheter aortic valve replacement and left atrial appendage occlusion in patients ineligible for oral anticoagulation: a case series. *J Cardiol Cases*. 2022;26(3):181-185. [CrossRef]
6. Kapadia SR, Krishnaswamy A, Whisenant B, et al. Concomitant left atrial appendage occlusion and transcatheter aortic valve replacement among patients with atrial fibrillation. *Circulation*. 2024;149(10):734-743. [CrossRef]
7. Ates AH, Kivrak A, Karakulak UN, et al. Should left atrial appendage closure be considered in resistant left atrial appendage thrombus cases? 'Former Foe, New Ally'. *Pacing Clin Electrophysiol*. 2024;47(4):583-590. [CrossRef]
8. Kivrak A, Ates AH, Canpolat U, et al. Management of device embolization following left atrial appendage closure: two cases and a review of the literature. *J Arrhythm*. 2025;41(4):e70139. [CrossRef]
9. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: Updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77(21):2717-2746. [CrossRef]
10. Tzikas A, Holmes DR, Jr, Gafoor S, et al. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace*. 2017;19(1):4-15. [CrossRef]
11. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123(23):2736-2747. [CrossRef]
12. Taramasso M, Maisano F, Nietlispach F. TAVI and concomitant procedures: from PCI to LAA closure. *EuroIntervention*. 2015;11(Suppl W):W96-W100. [CrossRef]
13. Taylor J, Robledo KP, Medel V, et al. Association between surgical admissions, cognition, and neurodegeneration in older people: a population-based study from the UK Biobank. *Lancet Healthy Longev*. 2024;5(9):100623. [CrossRef]
14. Kleinecke C, Buffle E, Link J, et al. Amplatzer left atrial appendage closure: single versus combined procedures. *Catheter Cardiovasc Interv*. 2021;97(7):E973-E981. [CrossRef]
15. Barbanti M, Gargiulo G, Tamburino C. Renal dysfunction and transcatheter aortic valve implantation outcomes. *Expert Rev Cardiovasc Ther*. 2016;14(12):1315-1323. [CrossRef]
16. Ahmed H, Ismayl M, Palicherla A, et al. Outcomes of simultaneous left atrial appendage closure in atrial fibrillation patients undergoing transcatheter aortic valve replacement. *Ann Med Surg (Lond)*. 2024;86(8):4316-4318. [CrossRef]
17. Van Gelder IC, Rienstra M, Bunting KV, et al. ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) Developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. 2024;2024:ehae176.

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Could We Maintain the Initial Efficacy of Triple Sequential Combination Therapies with Selexipag Against Progressive Deterioration Risk in Patients with Pulmonary Arterial Hypertension: Insights from a Single-Center Study?

ORIGINAL INVESTIGATION

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ABSTRACT

Background: This study assessed the efficacy and tolerability of the oral prostacyclin receptor agonist selexipag as part of sequential triple combination therapy in patients with pulmonary arterial hypertension (PAH).

Methods: The study retrospectively analyzed 127 of 1160 PAH patients from a single-center registry who received sequential triple therapy including selexipag. Clinical, echocardiographic, and hemodynamic variables and multiparametric risk scores (MRS) were evaluated to assess changes in risk and outcomes.

Results: The mean age was 43.2 ± 16.4 years, and 84.3% were female. Prior to selexipag initiation, Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension 2.0 risk strata were: 15% first, 31.5% second, 44.1% third, and 9.4% fourth; European Society of Cardiology/European Respiratory Society low-, intermediate-, and high-risk rates were 20.5%, 61.4%, and 18.1%, respectively. Mean REVEAL Lite 2.0 score was 6.3 ± 2.7. Maximal selexipag dosing reached 1600 µg BID in 18.1% of patients, while 64.6% remained at ≤1000 µg BID. Patients were grouped into low-, intermediate-, and high-dose cohorts. Median follow-up was 727.5 days (interquartile range (IQR) 224-985). Selexipag was discontinued in 15% of patients. Across dosing cohorts, initial improvements in functional class, 6-minute walk distance, right ventricular and pulmonary echocardiographic parameters, and MRSs during the first year attenuated thereafter, except for N-terminal pro-brain natriuretic peptide and Tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure ratio. Lower baseline REVEAL Lite 2.0 score predicted low-risk status at final assessment ($P = .017$). Three-year survival was 72.5%, 85.7%, and 75.1% in low-, medium-, and high-dose cohorts ($P > .05$). Mortality was independently predicted by baseline Swedish PAH Registry, REVEAL 2.0, REVEAL Lite 2.0, and REVEAL Echo scores.

Conclusion: Earlier escalation to triple therapy with selexipag may improve outcomes. Baseline risk—but not achieved selexipag dose—was associated with survival. A possible decline in treatment effect after 1 year warrants further investigation.

Keywords: EUPHRATES, pulmonary arterial hypertension, Selexipag

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by progressive obliteration of small pulmonary arteries, resulting in increased pulmonary vascular resistance (PVR) and pulmonary arterial pressures (PAP), and eventually leading to right-heart failure and death.[1-4] The endothelin, nitric oxide, and prostanoid pathways have been shown to be involved in the development of PAH, and several parenteral, inhaled, or oral PAH-specific drugs targeting these pathways have been developed.[1-4] Among these, the non-prostanoid drug selexipag and its 37-fold more potent metabolite ACT-333679 are selective agonists of the prostacyclin (IP) receptor, 1 of the 5 prostanoid receptors. Stimulation of the IP receptor leads to vasodilation, decreased smooth muscle cell proliferation, and

inhibition of platelet aggregation and inflammation within the pulmonary arteries.[5]

The efficacy and safety of selexipag in patients with PAH have been evaluated in the GRIPHON randomized controlled trial, the SelexiPag: tHe usEr dRug rEgistry (SPHERE) and EXPOSURE multicenter registries, single-center studies, and meta-analyses.[6-23] Currently, selexipag is indicated for PAH to delay disease progression and to reduce the risk of PAH-related hospitalization.[1-5]

This single-center study aimed to evaluate the efficacy and tolerability of selexipag as part of triple sequential combination therapy in patients with PAH.

METHODS

The study group comprised a subgroup of 127 patients with PAH who were receiving sequential combination therapy with selexipag, extracted from 1160 patients with pulmonary hypertension recruited in the single-center EvalUation of Pulmonary Hypertension Risk Factors AssociaTEd with Survival (EUPHRATES) study.

The diagnostic algorithms, hemodynamic confirmation, clinical sub-classification of pulmonary hypertension (PH), and definitions of incident and prevalent PAH have been based on the recommendations of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) 2015 and 2022 PH guidelines, according to the time of selexipag initiation.[1,2] For the hemodynamic definition of PH by right heart catheterization, cut-off values of mean PAP (PAMP) >25 mm Hg and >20 mm Hg were adopted before and after the ESC/ERS 2022 PH guidelines, respectively.[1,2] For the diagnosis of pre-capillary pulmonary hypertension, pulmonary arterial wedge pressure ≤15 mm Hg and PVR >3 and >2 Wood units were used as criteria before and after the ESC/ERS 2022 PH guidelines, respectively.[1,2]

During the follow-up period after the initiation of selexipag, longitudinal changes in World Health Organization functional class (FC), 6-minute walk distance (6MWD), blood biochemistry and cell counts, N-terminal pro-brain natriuretic peptide (NT-proBNP), echocardiographic measures of pulmonary circulation and right heart function, and multiparametric risk scores (MRSs) were evaluated. For risk assessment, the 3-strata risk prediction model from the 2022 ESC/ERS guidelines for PAH, adapted from the Swedish PAH Registry (SPAHR),[24] the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry,[25] 4 strata-risk model of COMPERA 2.0, and the French Pulmonary Hypertension Network (FPHN) registry low-risk models,[26] as well as the REVEAL 2.0 registry, its abridged 6-component REVEAL Lite 2.0, and REVEAL ECHO scores, were used both at the time of selexipag initiation and at follow-up visits.[27,28,29] All patients under regular follow-up were informed, and written informed consent was obtained from each patient. The study protocol was reviewed and approved by the Institutional Ethics Committee (Ethics committee approved in July 12, 2013, approval number: 2013.3/4). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The normality of continuous variables was assessed using Shapiro–Wilk's test and histogram. Numerical variables were expressed as mean ± standard deviation or median and interquartile ranges (IQR: 25th-75th) according to distribution. Discrete data were shown as percentages and absolute numbers. For continuous data comparison according to survival status, the *t*-test or Mann–Whitney *U*-test were used; for discrete data comparison according to survival status, the Pearson chi-square test were used. For longitudinal changes, continuous data comparison was made using analysis of variance or Kruskal–Wallis's test according to the normality of data, and pairwise comparison was performed using Tukey HSD or Bonferroni multiple comparison test.

The cumulative risk of all-cause mortality was displayed using Kaplan–Meier plots. Differences between groups, including dose and baseline risk strata, were assessed using the log-rank test, and risk tables were presented below the plots. Selexipag dose was categorized as low (200 or 400 µg twice daily), medium (600, 800, or 1000 µg twice daily), and high (1200, 1400, or 1600 µg twice daily). To evaluate the independent association of selexipag dose with mortality, Cox proportional hazards regression models were constructed. Due to the limited number of events, only selexipag dose (low, medium, high) and baseline risk scores were included in the models to avoid overfitting. Hazard ratios (HRs) with 95% CIs were reported. Proportional hazards assumptions were checked using Schoenfeld residuals.

All statistical analyses were performed using R software v. 4.0.2 with the "survival," "survminer," "ggplot2," and "Hmisc" packages (Vienna, Austria). A 2-sided *P* value <.05 was considered statistically significant.

RESULTS

Patient characteristics and background therapies prior to the addition of selexipag are shown in Table 1. The mean age of the patients was 43.2 ± 16.4 years, and 84.3% were

HIGHLIGHTS

- Sequential triple combination therapy including selexipag demonstrated marked early improvement in clinical risk profile in patients with pulmonary arterial hypertension (PAH).
- Selexipag was well-tolerated, and treatment continuation was not limited by adverse effects in the majority of patients.
- The initial therapeutic benefits showed attenuation beyond the first year, underscoring the progressive nature of PAH despite aggressive escalation.
- Baseline clinical risk status was the key determinant of long-term outcomes, while response magnitude and maintenance did not correlate with selexipag dose.
- Early implementation of triple therapy may be crucial for optimizing long-term risk trajectory and functional stabilization in advanced PAH.

Table 1. Demographics, Clinical, Echocardiographic and Hemodynamic Characteristics and Treatment Patterns in Study Population

	n = 127 patients
Demographics, clinical and laboratory	
Age (years)	43.2 (16.4)
Female sex, n (%)	107 (84.3)
Idiopathic PAH, n (%)	58 (45.7)
PAH associated with CHD, n (%)	58 (45.7)
Eisenmenger Syndrome, n (%)	32 (25.2)
Prevalent systemic-to-pulmonary shunt, n (%)	6 (4.7)
PAH with small shunt defect, n (%)	1 (0.8)
PAH with corrected congenital shunt, n (%)	19 (15)
Drug-associated PAH, n (%)	1 (0.8)
Hereditary PAH, n (%)	2 (1.6)
PAH associated with CTD, n (%)	8 (6.3)
WHO Functional Class II, n (%)	24 (18.9)
WHO Functional Class III, n (%)	84 (66.1)
WHO Functional Class IV, n (%)	19 (15)
6-minute walk distance (m)	330 (238-403)
NT-ProBNP levels (ng/L)	486 (171-946)
Echocardiographic measures	
Pericardial effusion, n (%)	10 (7.9)
LVEF, %	63.9 (3.25)
D-shaped septum, n (%)	104 (81.9)
PA diameter, cm	3.52 (0.79)
RA area, cm^2	23.3 (7.89)
IVC diameter, cm	1.99 (0.42)
TAPSE, cm	1.98 (0.46)
RV TDI, cm/sec	12.4 (2.79)
TR grade not traceable, n (%)	1 (0.8)
TR grade 1, n (%)	46 (36.2)
TR grade 2, n (%)	47 (37)
TR grade 3, n (%)	20 (15.7)
TR grade 4, n (%)	13 (10.2)
TR Vmax, m/sec	4.3 (3.4-4.93)
TAPSE/PASP ratio	0.25 (0.17-0.38)
Right heart catheterization	
PASP, mm Hg	93.8 (27.3)
PAMP, mm Hg	59.2 (19.6)
PVR, Wood unit	10 (6-16)
ESC/ERS 2022 Risk Model (3-component)	
Low risk, n (%)	26 (20.5)
Intermediate risk, n (%)	78 (61.4)
High risk, n (%)	23 (18.1)
COMPERA 1.0 (3-component)	
Low risk, n (%)	37 (29.1)
Intermediate risk, n (%)	69 (54.3)
High risk, n (%)	21 (16.5)
COMPERA 2.0 (4-component)	
1, n (%)	19 (15)
2, n (%)	40 (31.5)
3, n (%)	56 (44.1)
4, n (%)	12 (9.4)
FPHN—non-invasive risk model	
0 (%)	89 (70.1)
1 (%)	19 (15)
2 (%)	13 (10.2)
3 (%)	6 (4.7)
REVEAL 2.0 score	8.45 (1.9)
REVEAL Lite 2.0 score	6.3 (2.7)
REVEAL—Echo score	
Low risk (%)	62 (48.8)
Intermediate risk (%)	48 (37.8)
High risk (%)	17 (13.4)
Back-ground PAH therapies	
Monotherapy	
Bosentan, n (%)	1 (0.8)
Double combination therapy	118 (92.9)
Bosentan + Riociguat, n (%)	1 (0.8)
Bosentan + Sildenafil, n (%)	20 (15.7)
Bosentan + Tadalafil, n (%)	11 (8.6)
Ambrisentan + Sildenafil, n (%)	2 (1.6)
Ambrisentan + Tadalafil, n (%)	3 (2.3)
Macitentan + Riociguat, n (%)	6 (4.7)
Macitentan + Sildenafil, n (%)	17 (13,4)
Macitentan + Tadalafil, n (%)	58 (45.6)
Triple combination therapy—switch to selexipag	8 (6.3)
Ambrisentan + Tadalafil + inhaled Iloprost, n (%)	1 (0.8)
Macitentan + Sildenafil + inhaled Iloprost, n (%)	2 (1.6)
Macitentan + Tadalafil + inhaled Iloprost, n (%)	5 (3.9)
Daily Selexipag dose, ug	
400, n (%)	14 (11)
800, n (%)	19 (15)
1200, n (%)	13 (10.2)
1600, n (%)	18 (14.2)
2000, n (%)	18 (14.2)
2400, n (%)	14 (11)
2800, n (%)	8 (6.3)
3200, n (%)	23 (18.1)
Follow-up time, days	682 (224-985)
Clinical worsening before therapy, n (%)	34 (26.7)
Clinical worsening after therapy, n (%)	29 (22.8)
Patients discontinued therapy, n (%)	19 (15)
Long-term mortality, n (%)	19 (15.1)

female. Idiopathic PAH (IPAH) was observed in 45.7% of patients, while hereditary PAH and PAH associated with congenital heart disease, connective tissue disease (CTD), and drugs were documented in 1.6%, 45.7%, 6.3%, and 0.8% of patients, respectively. Background combination therapies were as follows: macitentan and tadalafil in 58 (45.6%), macitentan and sildenafil in 17 (13.4%), macitentan and riociguat in 6 (4.7%), bosentan and tadalafil in 11 (8.6%), bosentan and sildenafil in 20 (15.7%), bosentan and riociguat in 1 (0.8%), ambrisentan and tadalafil in 3 (2.3%), and ambrisentan and sildenafil in 2 (1.6%) of the 127 patients (Table 1).PAH, pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; WHO, World Health Organization; NT-proBNP, N-terminal pro–B-type natriuretic peptide; LVEF, left ventricular ejection fraction; PA, pulmonary artery; RA, right atrium; IVC, inferior vena cava; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; TDI, tissue Doppler imaging; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; PAMP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; ESC, European Society of Cardiology; ERS, European Respiratory Society; FPHN, French Pulmonary Hypertension Network.

Baseline Parameters Before Selexipag Addition to Dual Therapy

The FC was II, III, and IV in 18.9%, 66.1%, and 15% of patients, respectively. Median 6MWD was 330 m (IQR 238-403), and median serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level was 486 ng/L (IQR 171–946) (Table 1). Tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular tissue Doppler velocity (RV TDI), right atrial area, and pulmonary arterial diameter were 1.98 ± 0.46 cm, 12.4 ± 2.79 cm/sec, 23.3 ± 7.89 cm^2, and 3.52 ± 0.79 cm, respectively. Invasively measured pulmonary arterial systolic and mean pressures (PASP and mPAP) were 93.8 ± 27.3 mm Hg and 59.2 ± 19.6 mm Hg, respectively. Median PVR was 10 Wood units (IQR 6-16).

Before the addition of selexipag to background therapies, COMPERA 2.0 first, second, third, and fourth risk strata were noted in 15%, 31.5%, 44.1%, and 9.4% of patients, and ESC/ERS low-, intermediate-, and high-risk status were noted in 20.5%, 61.4%, and 18.1% of patients, respectively. The REVEAL Lite 2.0 score was 6.3 ± 2.7. Non-invasive FPHN scores of 0, 1, 2, and 3 were documented in 70.1%, 15%, 10.2%, and 4.7% of patients, respectively. The REVEAL ECHO score showed low risk in 48.8%, intermediate risk in 37.8%, and high risk in 13.4% of patients (Table 1).

Maximally tolerated selexipag doses were 1600 µg BID in 18.1% of patients, 1400 µg BID in 6.3%, 1200 µg BID in 11%, and ≤1000 µg BID in 64.6% (Table 2). Consistent with definitions in the GRIPHON study, patients were categorized as low-dose, intermediate-dose, and high-dose cohorts in 26%, 38.6%, and 35.4% of cases, respectively. Median and mean follow-up periods were 682 days (IQR 224-985) and 683 ± 481 days, respectively.

The Evolution of Measures and Risk Scores

The progressive improvements in FC, NT-proBNP, PASP, right atrial area and pressure estimates, pulmonary artery and inferior vena cava diameters, pericardial effusion grade assessed by echocardiography, and MRSs evaluated using COMPERA, FPHN, REVEAL Lite 2.0, and REVEAL ECHO models during the first 12 months of selexipag treatment were found to be attenuated thereafter (Supplementary Figures 1 and 2).

Regardless of dose status, 6MWD showed significant improvement at 12 months compared with baseline (P = .022), followed by attenuation thereafter (Figure 1A), while NT-proBNP levels demonstrated significant reduction at the final assessment (P = .018) (Figure 1B). All dose cohorts exhibited significant improvements in TAPSE at 6 and 12 months compared with baseline (P = .040 and P = .027, respectively), with high- vs. low-dose associated with a greater increase at 6 months (Figure 1C). Increases in RV TDI were consistent across the 3 dose cohorts, although high- vs. low-dose was linked to a greater increase at 6 months (P = .037) (Figure 1D). Comparable reductions in PASP were observed at 6 and 12 months (P = .037 and P = .009, respectively), followed by subsequent increases (Figure 1E). Significant reductions in mPAP were noted at 12 months across all cohorts (P = .049), and low- vs. medium-dose associated with a more pronounced reduction (P = .031). However, mPAP increased in all cohorts after 12 months (Figure 1F). The TAPSE/PASP ratio showed a marked but non-significant trend toward increase from baseline to the final assessment, consistent across all 3 dose cohorts (P > .05) (Figure 1G). Similarly, FC status improved up to 12 months across all dose cohorts, followed by attenuation of this trend (Figure 1H).

Table 2. Kaplan–Meier Estimated 1-, 3-, and 5-Year Survival According to Selexipag Dose Cohorts, Including Number at Risk and Events

1, 3, 5 year Survival—Dose						
					95% CI	
Levels	time	Number at Risk	Number of Events	Survival, %	Lower, %	Upper, %
Low dose (200-400 mcg)	12	16	3	89.8	79.3	100.0
Low dose (200-400 mcg)	36	3	2	72.5	52.6	100.0
Medium dose (600-1000 mcg)	12	36	2	95.3	89.1	100.0
Medium dose (600-1000 mcg)	36	10	3	85.7	74.6	98.4
High dose (1200-1600 mcg)	12	35	2	95.0	88.5	100.0
High dose (1200-1600 mcg)	36	12	6	75.1	61.2	92.2

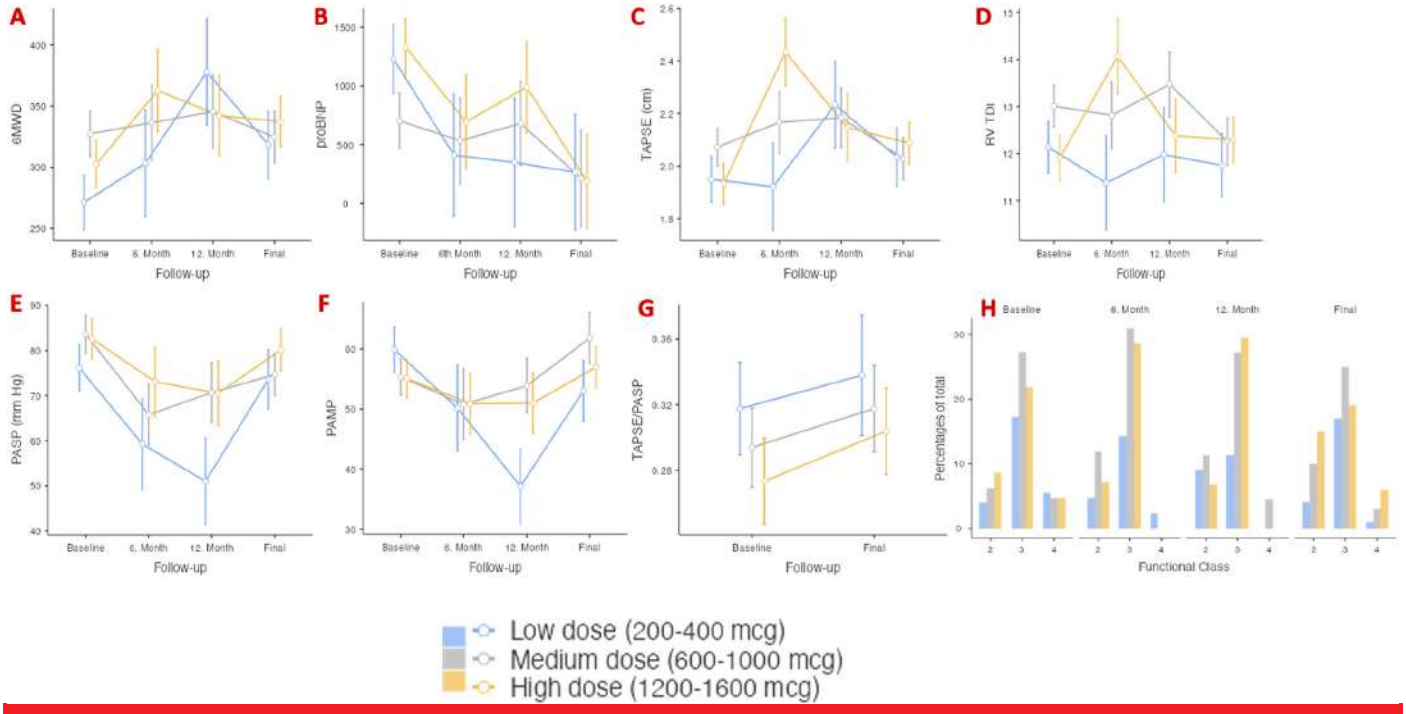

Figure 1. Longitudinal changes in functional, biochemical, and echocardiographic parameters according to selexipag dose cohorts. (A) Six-minute walk distance (6MWD), (B) N-terminal pro–brain natriuretic peptide (NT-proBNP), (C) tricuspid annular plane systolic excursion (TAPSE), (D) right ventricular tissue Doppler imaging velocity (RV TDI), (E) pulmonary arterial systolic pressure (PASP), (F) pulmonary arterial mean pressure (mPAP), (G) TAPSE/PASP ratio, and (H) World Health Organization functional class (FC). Data are presented at baseline, 6 months, 12 months, and final follow-up.

The 19 patients (15%) discontinued selexipag due to side effects. The most common adverse events (AEs) were headache; pain in the jaw, muscles, or legs; diarrhea; nausea; vomiting; and flushing. Clinical worsening and all-cause mortality were documented in 29 (22.8%) and 19 (15.1%) patients, respectively. During the follow-up period, 5 of the 19 patients who discontinued selexipag died.

Table 2 demonstrated survival estimates in 3 maximally tolerable selexipag dose cohorts. The 12-month and 36-month survival were 89.8% (79.3%-100%) and 72.5% (52.6%-100%) in low-dose cohort, 95.3% (89.1%-100%) and 85.7% (74.6%-98.4%) in medium-dose cohort, and 95% (88.5%-100%) and 75.1 % (61.2%-92.2%) in high-dose cohort, respectively.

Figure 2A shows that Kaplan–Meier survival estimates were comparable among the 3 dose cohorts. Baseline multiparametric risk status at the time of selexipag initiation, as assessed by the 4-component COMPERA 2.0 (Figure 2C), but not by the 3-component COMPERA 1.0 (Figure 2B) or FPHN (Figure 2D), was associated with significant differences in Kaplan–Meier survival estimates.

Forest plots revealed that COMPERA 1.0, COMPERA 2.0, and FPHN scores were not significantly associated with mortality after adjustment for dose groups, (Figure 3A-C). In contrast, the SPAHR score at baseline remained significantly associated with mortality after adjustment for dose groups (HR 6.41; 95% CI 2.49-16.49; $P < .001$) (Figure 3D).

REVEAL Lite 2.0 risk status was associated with significant survival differences in Kaplan–Meier estimates ($P = .0014$) (Figure 4A). Forest plots demonstrated that baseline REVEAL 2.0, REVEAL Lite 2.0, and REVEAL Echo scores were significantly associated with mortality after adjustment for dose groups in 3 separate models (Figures 4B-D). The HRs for REVEAL 2.0 and REVEAL Lite 2.0 were 1.22 (95% CI 1.03-1.46, $P = .024$) and 1.48 (95% CI 1.25-1.75, $P < .001$), respectively. For the REVEAL Echo score, the HR increased incrementally with higher risk strata, from 6.01 (95% CI 1.09-33.15, $P = .040$) at score 3, to 8.09 (95% CI 1.46-44.72, $P = .017$) at score 4, and to 26.34 (95% CI 3.39-204.86, $P = .002$) at score 5 (Figure 4D). Moreover, initial REVEAL Lite 2.0 score was an independent predictor of low-risk status at the final assessment according to REVEAL Lite 2.0 (HR: 0.74; 95% CI 0.57-0.95, $P = .017$).

Follow-up showed that none of the risk scores, as assessed by COMPERA 2.0, FPHN, or REVEAL Lite 2.0 models at 6 months of selexipag triple combination therapy, were significantly associated with survival differences, although there was a trend toward worse outcomes in the high-risk cohorts of each model (Figures 5A-C).

DISCUSSION

The results of single-center follow-up data appear to be consistent with previously reported studies regarding the efficacy and tolerability of selexipag-based triple sequential combination therapy, the maximally tolerated doses achieved, and the patterns of discontinuation in patients with PAH. Regardless of the maximally tolerated selexipag dose, progressive improvements in FC, 6MWD, echocardiographic measures of pulmonary and right ventricular

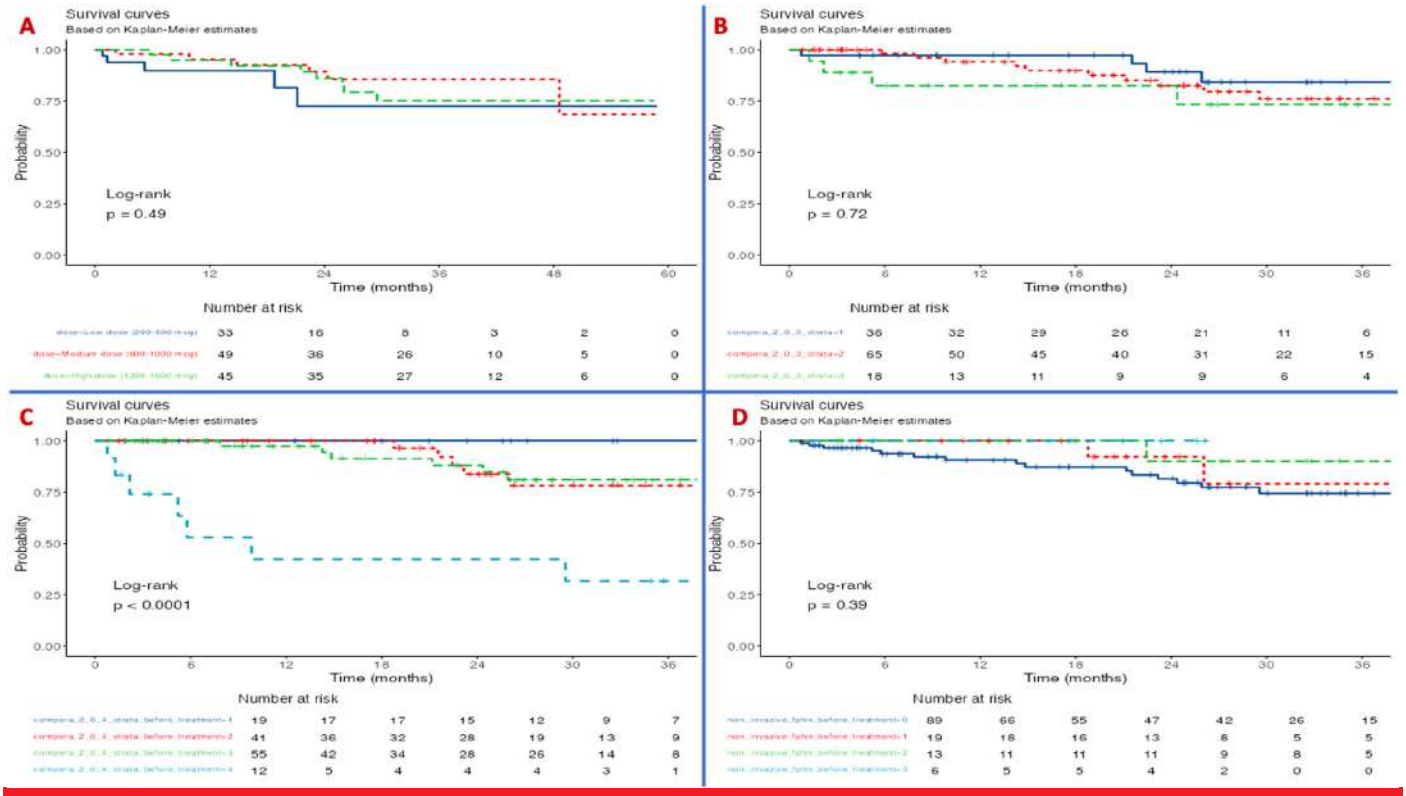

Figure 2. Kaplan–Meier survival estimates according to selexipag dose and baseline risk status. (A) Survival estimates were comparable among low-, medium-, and high-dose cohorts. (B) Baseline risk stratification using 3-component COMPERA 1.0 showed no significant difference in survival estimates. (C) Four-component COMPERA 2.0 was associated with significant differences in survival estimates. (D) FPHN risk assessment showed no significant difference in survival estimates.

hemodynamics, and MRSs during the first 12 months of treatment were uniformly attenuated thereafter, except for NT-proBNP levels and TAPSE. There were no differences in 3-year survival estimates among the 3 different maximally tolerated dose cohorts. Mortality was found to be associated with baseline SPAHR, REVEAL 2.0, REVEAL Lite 2.0, and REVEAL Echo scores at the time of initiating selexipag add-on therapy, but not with selexipag doses or other MRSs at baseline or at the first 6-month follow-up. However, a low final REVEAL Lite 2.0 score could be predicted by the REVEAL Lite 2.0 score at the initiation of selexipag therapy.

The GRIPHON randomized clinical trial showed that selexipag use was associated with a consistent 40% reduction in morbidity and mortality across subgroups and in mono-, dual-, and triple-combination therapies, regardless of the maximally tolerated dose attained.[6] The open-label extension phase of the GRIPHON study provided outcome data, as well as safety and tolerability profiles of selexipag over a 7-year follow-up period. Kaplan–Meier survival estimates at 1, 3, 5, and 7 years for patients randomized to selexipag were 92.0%, 79.3%, 71.2%, and 63.0%, respectively.[7] The most frequently reported AEs were related to well-known prostacyclin-related effects and/or underlying disease.[7,14] A greater benefit from earlier initiation of selexipag on background endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (PDE5i) combination therapy has been shown in 2 sub-analyses of the GRIPHON data.[8,9] Consistent with these results, a retrospective study by Tsang et al[19] found that initiation of selexipag within 12 months of PAH diagnosis, compared with no selexipag therapy during that period, was associated with a lower rate of all-cause hospitalizations and reduced all-cause and PAH-related total medical costs, but showed no significant difference in PAH-related hospitalization rates or risk of disease progression.[17] In the SPHERE (NCT03278002) prospective, real-world registry including patients with PAH treated with selexipag, newly initiated (≤60 days) and previously initiated (>60 days) selexipag cohorts were compared.[10] At the initiation of selexipag, 55.6% of patients were in FC III/IV, and 57.3% were classified as intermediate- or high-risk according to the REVEAL 2.0 score.[10] Over a median titration period of 8.1 weeks, the lowest, intermediate, and highest (≥1200 µg) maintenance doses were achieved in 15%, 31%, and 41% of patients, respectively.[10] This dose range was comparable to those in the GRIPHON trial, in which the reported rates of lowest, intermediate, and highest maintenance doses were 23%, 31%, and 43%, respectively.[6,10] The FC and REVEAL 2.0 risk status were reported to improve in 25% and 21% of patients, respectively, while remaining stable in 61% and 57% of patients.[10] The 18-month survival rates were 89.4%, 84.2%, and 94.5%, and discontinuation rates for AEs were 22%, 32%, and 11.9%, in the overall, newly, and previously initiated patient groups, respectively.[10] Importantly, discontinuation for AEs, hospitalization, and survival were comparable regardless of maximally tolerable selexipag doses attained,[10] and were consistent with

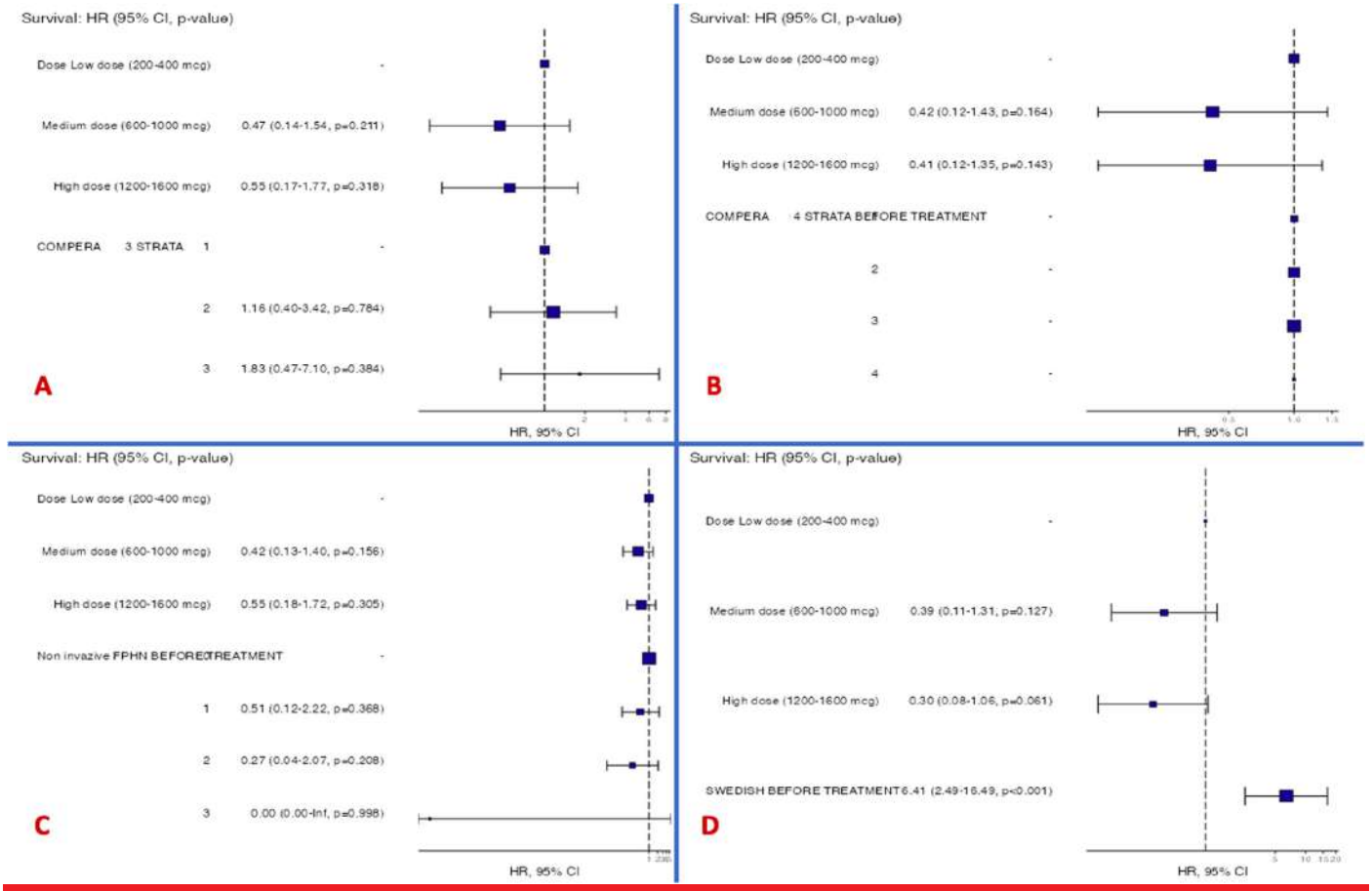

Figure 3. Forest plot of baseline risk scores for mortality after adjustment for dose groups. (A) COMPERA 1.0, (B) COMPERA 2.0, and (C) FPHN scores were not significantly associated with mortality after adjustment. (D) The Swedish (SPAHR) score remained significantly associated with mortality after adjustment for dose groups (HR 6.41; 95% CI 2.49-16.49; *P* < .001).

GRIPHON and the US prescribing information for prostacyclin therapies.[6,10,15] The main limitations of SPHERE seem to have originated from its observational nature and the potential bias that might be associated with the previously initiated selexipag cohort in which immortal time bias was possible and no data were collected between treatment initiation and study enrollment.[10] Moreover, results of SPHERE suggest that the adoption status of guideline recommendations in real-world clinical practice remains unsatisfactory.

EXPOSURE (EUPAS19085) is an ongoing, multicenter, prospective, observational study of patients with PAH who are initiating a new PAH-specific therapy in Europe or Canada.[11-14] Although half of incident patients were on combination therapy, this rate seems to be insufficient in the presence of the 70% rate of intermediate-high- or high-risk status in the study population. Utilization of selexipag across risk groups ranged from 74% to 81%. The survival rates in EXPOSURE were comparable between the incident and prevalent patients. Survival estimates were 98%, 98%, 93%, and 80% at 1 year and 98%, 92%, 81%, and 67% at 2 years, in 4 risk strata from low to high, respectively.[11-14] Similar to those in SPHERE, the low rates of selexipag initiation in the EXPOSURE trial also suggest a gap between real-life practice and guidelines recommendations for treatment escalations.[10-14]

In a subgroup analysis of EXPOSURE, rates of selexipag including triple combinations were similar, and titration duration, maximally tolerable doses, and discontinuation rates were comparable between Idiopathic Pulmonary Arterial HypertensionIPAH and CTD-PAH patients.[13] However, the proportion of triple-combination therapy including selexipag decreased from 81% to 53% in IPAH and to 56% in CTD-PAH cohorts at 12 months of selexipag treatment. Time to all-cause hospitalizations and time to all-cause death curves showed relatively better 36-month outcomes in IPAH compared with CTD-PAH.[13] Moreover, in a recently published paper from the EXPOSURE study, pre-specified comparative survival analyses based on propensity score weighting between patients who newly initiated selexipag vs. other PAH-specific therapies revealed that the mortality rate ratio was significantly lower for selexipag-treated patients (0.55; 95% CI 0.31-0.99).[14]

In this study, the majority of patients at intermediate risk status, and the mean and median time delay for the combination of selexipag with background therapies were 1705 ± 1363 days and 1424 days (IQR 541-2523), respectively. Selexipag was titrated over a median of 8 weeks, with 200 µg twice-daily increments every 2 weeks in the absence of AEs attributable to the drug. Maximally tolerable doses

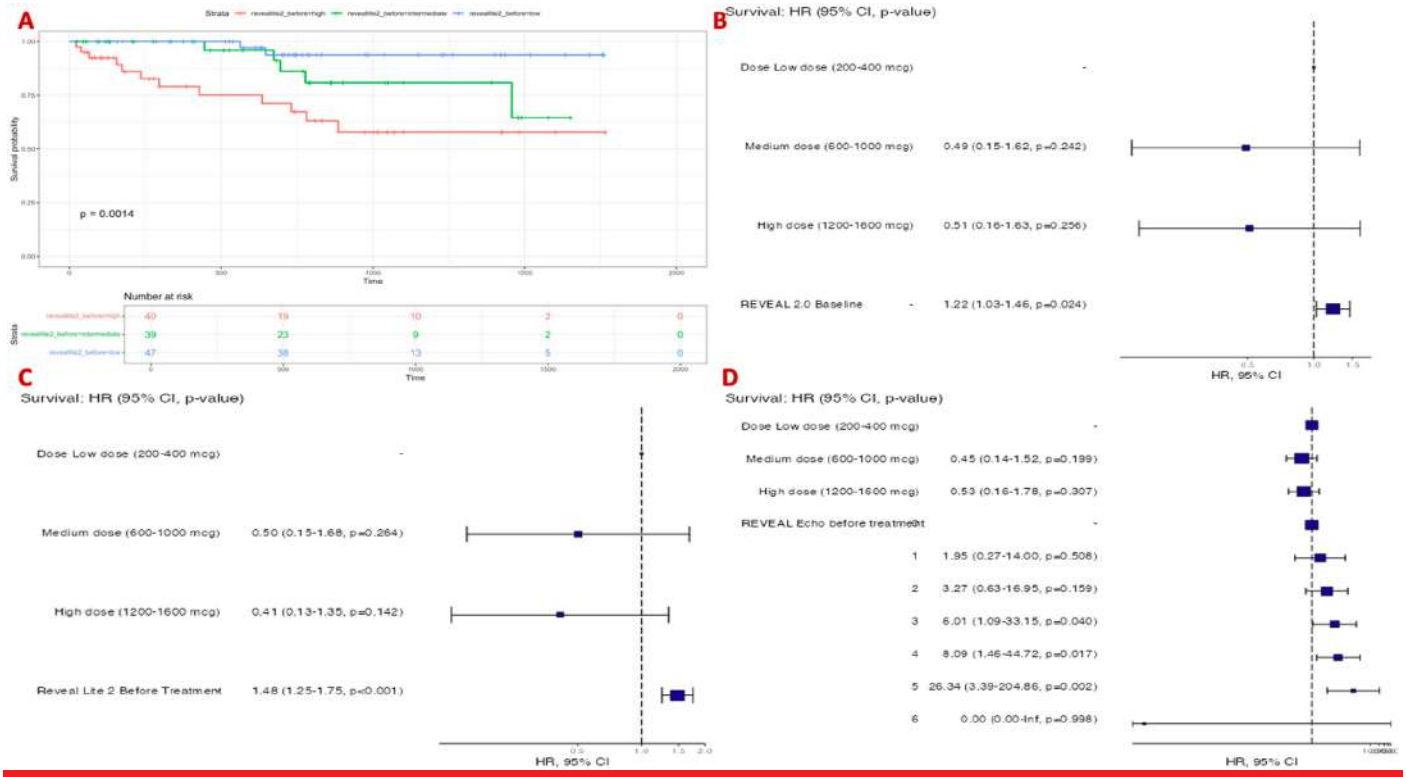

Figure 4. Kaplan–Meier and forest plot analyses for REVEAL risk models. (A) Kaplan–Meier survival curves according to baseline REVEAL Lite 2.0 risk status. (B-D) Forest plot analyses demonstrating the association of baseline REVEAL 2.0 (B), REVEAL Lite 2.0 (C), and REVEAL Echo (D) scores with mortality after adjustment for dose groups. The REVEAL Echo score showed an incremental increase in hazard ratios with higher scores, indicating a dose–response relationship between risk category and mortality.

were maintained at lowest, intermediate, and highest dose stratum in 11.7%, 70.4%, and 17.9%, respectively. In comparison to those in SPHERE and GRIPHON studies, the rate of the highest dose was lower, but the discontinuation rate was also lower. Side effects were not different from previously reported series. The study revealed that the marked improvements in FC, 6MWD, NT-proBNP, echocardiographic measures, and risk status as assessed by MRSs during the first 12 months of selexipag treatment were followed by an attenuation of these benefits in a nearly uniform pattern. However, this trend was not seen for NT-proBNP and TAPSE, and the statistically significant decrease from baseline to final analysis was maintained in these 2 measures regardless of the selexipag dose. The non-significant trend toward increase in TAPSE/PASP ratio was also consistent across all 3 dose cohorts. These results seem to implicate the progressive deteriorating nature of the disease rather than a potential risk for loss in the efficacy of selexipag at the mid-term period. In consistency with GRIPHON sub-analyses and real-life data[30], the lower risk status according to SPAHR, REVEAL 2.0, REVEAL lite 2.0, and REVEAL-Echo models at the start of selexipag was found to be independently associated with improved survival in the study. Moreover, a lower REVEAL Lite 2.0 score at the start of selexipag begets a lower final REVEAL Lite 2.0 score. Despite a signal implying a relation between the risk status attained at the sixth month of selexipag and survival, this trend did not achieve statistical significance.

Early addition of selexipag to double PAH therapy has been evaluated in Komodo Health payer-complete dataset, and all-cause hospitalizations, PAH-related hospitalizations,

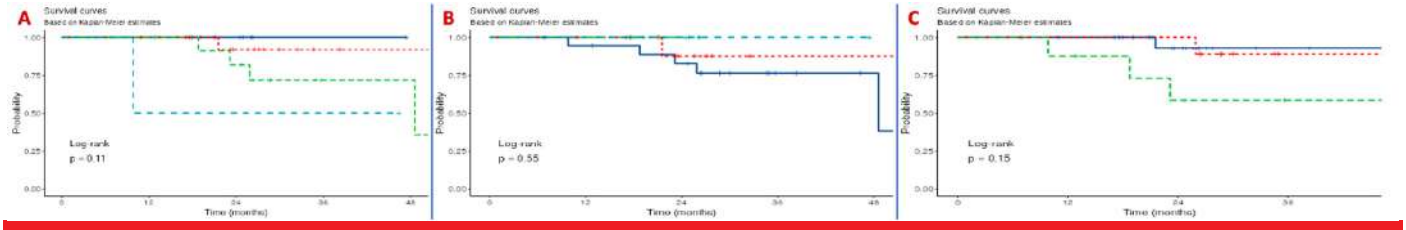

Figure 5. Kaplan–Meier survival estimates of selexipag triple combination therapy according to baseline risk status. (A) COMPERA 2.0, (B) FPHN, and (C) REVEAL Lite 2.0 risk models. No statistically significant differences in survival were observed between risk strata, although high-risk cohorts showed a trend toward worse outcomes.

and PAH-related progression were found to be significantly improved if selexipag was added within 6 months as compared to dual therapies without selexipag.[17] These benefits were more pronounced when selexipag was added within the first 3 months, and a treatment gap of no more than 45 days was allowed. However, these benefits were not documented in those whom selexipag was added to dual therapies after 12 months.[17]

In a retrospective study including 192 patients with PAH from 10 centers, different oral sequential triple combination therapies based on selexipag improved FC, number of low-risk parameters, 6MWD, PASP, RV functions, eccentricity index, and in NT-proBNP after 6 months of treatment.[18] However, selexipag combined with background macitentan vs. ambrisentan, or riociguat vs. tadalafil or sildenafil were not associated with any difference in 6-month event-free survival and all-cause survival.[18] Selexipag initiation within 12 months of PAH diagnosis demonstrated reductions in all-cause hospitalization rate and medical costs,[19] and improved prognosis in PAH.[20]

The efficacy and safety of selexipag against oral treprostinil, beraprost, or placebo have been evaluated in 3 recent meta-analyses.[21-23] In the first meta-analysis based on 7 randomized controlled studies and 6 cohort studies, selexipag was reported to be associated with improvements in the 6MWD, NT-proBNP, cardiac index, and WHO-FC.[21] Selexipag dose status was not associated with a difference in 6MWD benefit, but highest doses related to more reduction in PVR. Moreover, the increase in 6MWD and decrease in PVR became more pronounced with selexipag treatment longer than 6 months.[21] In another recent meta-analysis based on selexipag-including randomized controlled trials, selexipag was safe and was associated with significant improvements in the mPAP, NT-proBNP, cardiac index, FC, and hospitalization for worsening of PAH.[22] In the last meta-analysis based on data from 8 randomized controlled studies including 3023 patients receiving oral treprostinil, selexipag, or beraprost and placebo, the risk of clinical worsening was significantly reduced with selexipag and oral treprostinil, but not with beraprost.[23]

Current results from a nation-wide SIMURG registry and a single-center EUPHRATES study demonstrated a trend towards better clinical, echocardiographic, and hemodynamic presentations and improved survival in the overall PH population, PAH subgroups, and group IV PH across the 3 consecutive time periods, i.e., before 2016, between 2016 and 2019, and after 2019, that might be attributed to more proactive management strategies favoring earlier initiation of targeted combinations including selexipag.[31-35]

In an upcoming 2 × 2 randomized crossover trial including patients with PAH established on guideline-recommended dual therapy and implanted with CardioMEMS (a wireless pulmonary artery sensor) and ConfirmRx (an insertable cardiac rhythm monitor), triple combinations with ERA, riociguat, and selexipag or ERA, PDEi, and selexipag regimens will be compared.[36] In this very complex design, the primary endpoint will be the change in RV systolic volume measured by magnetic resonance imaging from baseline to maximal tolerable dose with each therapy. Moreover, secondary endpoints including physiological measures, hemodynamics, physical activity, quality of life, and side effects will assess whether remote technology facilitates early evaluation of clinical efficacy and compare intra-patient efficacy of the 2 treatment strategies.[36]

Study Limitations

The size of the patient population, retrospective analysis, and non-randomized nature of this study are the main limitations. The absence of routine periodical right heart catheterization during follow-up might limit reflections on the impact of the triple sequential combinations with selexipag on pulmonary and right-heart hemodynamics. However, nearly uniform changes in all measures and MRSs, regardless of the selexipag dose status, should be meaningful. Longer follow-up periods might provide more comprehensive evidence for efficacy and safety concerns of selexipag. Most importantly, the cumulative data suggest a delay in the initiation of selexipag. However, reimbursing the upfront combinations with ERA and PDE5i in the country can also be expected to shorten the time to escalations to triple combinations and may augment clinical benefit. The last limitation was related to the low rate of triple combinations including parenteral prostacyclins in high-risk status at baseline or follow-up, despite the proven benefits. This might be related to the unwillingness of some patients to use parenteral prostacyclin and transient problems in cooperation between the social security agency and the pharmaceutical industry.

CONCLUSIONS

The results highlighted the critical importance of earlier escalation to selexipag, including triple combinations in PAH, and a better risk status at baseline, but not maximally tolerable selexipag doses attained, seem to be associated with better survival. However, a trend for the attenuation in the efficacy after the first year of selexipag therapies should also be taken into consideration. This trend seems to be consistent with the progressive nature of PAH and may implicate earlier quadruple combinations including sotatercept even in stable patients or the need for switching to parenteral prostacyclins in the case of clinical deterioration.

Ethics Committee Approval: The study protocol was reviewed and approved by the Koşuyolu Training and Research Hospital Ethics Committee (Ethics committee approved in July 12, 2013, approval number: 2013.3/4).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.C.T., C.K.; Design – H.C.T., B.K.; Supervision – C.K., İ.H.T.; Resources – C.K., S.T.; Materials – Ç.B., D.S.; Data Collection and/or Processing – Ş.Z.A., M.K., A.K., Ş.N.Ç., A.V., C.E., F.B.E., F.D., Z.B., A.S.; Analysis and/or Interpretation – B.K., B.Ke., A.H., A.Ka.; Literature Search – H.C.T., S.T.; Writing – H.C.T., C.K.; Critical Review – C.K., İ.H.T., N.Ö.

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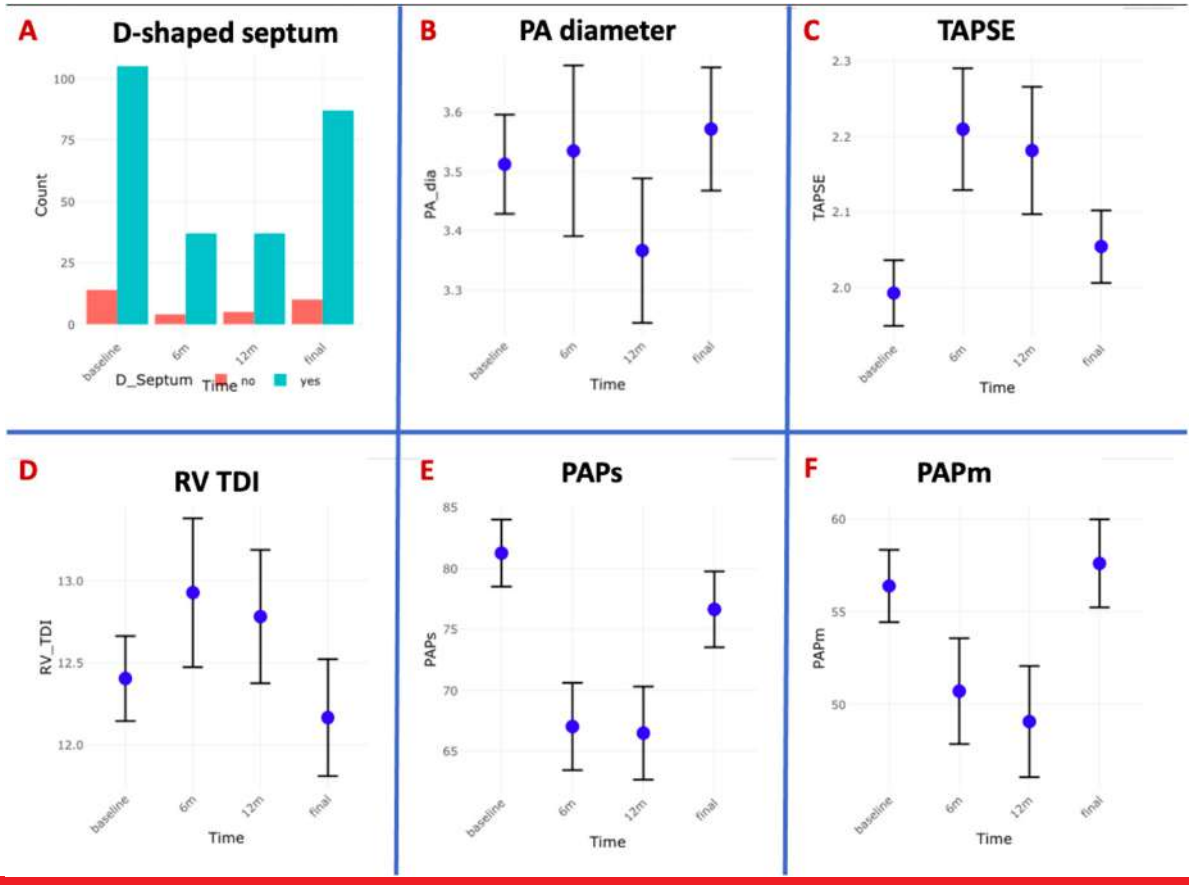
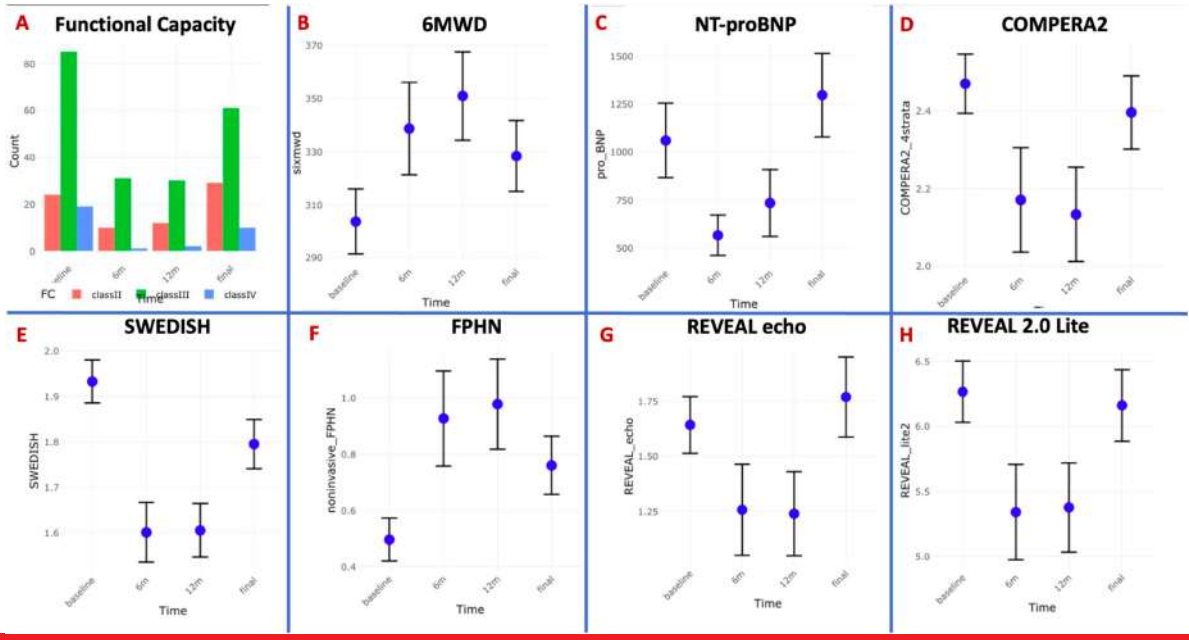
REFERENCES

1. Galié N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119. [CrossRef]
2. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731. [CrossRef]
3. Kovacs G, Bartolome S, Denton CP, et al. Definition, classification and diagnosis of pulmonary hypertension. *Eur Respir J*. 2024;64(4):2401324. [CrossRef]
4. Dardi F, Boucly A, Benza R, et al. Risk stratification and treatment goals in pulmonary arterial hypertension. *Eur Respir J*. 2024;64(4):2401323. [CrossRef]
5. Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. *Eur Respir J*. 2024;64(4):2401325. [CrossRef]
6. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522-2533. [CrossRef]
7. Galiè N, Gaine S, Channick R, et al. Long-term survival, safety and tolerability with selexipag in patients with pulmonary arterial hypertension: Results from GRIPHON and its open-label extension. *Adv Ther*. 2022;39(1):796-810. [CrossRef]
8. Coghlan JG, Gaine S, Channick R, et al. Early selexipag initiation and long-term outcomes: insights from randomised controlled trials in pulmonary arterial hypertension. *ERJ Open Res*. 2023;9(1):00456-2022. [CrossRef]
9. Gaine S, Sitbon O, Channick RN, et al. Relationship between time from diagnosis and morbidity/ mortality in pulmonary arterial hypertension. *Chest*. 2021;160(1):277-286. [CrossRef]
10. McLaughlin V, Farber HW, Highland KB, et al. Disease characteristics, treatments, and outcomes of patients with pulmonary arterial hypertension treated with selexipag in real-world settings from the SPHERE registry (SelexiPag: tHe usErs dRug rEgistry). *J Heart Lung Transplant*. 2024;43(2):272-283. [CrossRef]
11. Muller A, Escribano-Subias P, Fernandes CC, et al. Real-world management of patients with pulmonary arterial hypertension: insights from EXPOSURE. *Adv Ther*. 2024;41(3):1103-1119. [CrossRef]
12. Lange TJ,Escribano-Subias P, Muller A, et al. Four-strata risk assessment in patients with pulmonary arterial hypertension treated with selexipag in real-world settings (EXPOSURE study). *Adv Ther*. 2024;41(9):3645-3663. [CrossRef]
13. Gaine S, Escribano-Subias P, Muller A, et al. Selexipag in patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD): real-world experience from EXPOSURE. *Pulm Circ*. 2024;14(3):e12403. [CrossRef]
14. Söderberg S, Escribano-Subias P, Archey C, et al. Comparative analysis of survival in pulmonary arterial hypertension for patients treated with selexipag in clinical practice (EXPOSURE study). *Drugs Real World Outcomes*. 2025;12(2):189-199. [CrossRef]
15. McLaughlin VV, Channick R, de Marco T, et al. Results of an expert consensus survey on the treatment of pulmonary arterial hypertension with oral prostacyclin pathway agents. *Chest*. 2020;157(4):955-965. [CrossRef]
16. Sargent T, Tsang Y,Panjabi S, et al. Real-world treatment patterns among patients with connective tissue disorder-related pulmonary arterial hypertension in the United States: a retrospective claims-based analysis. *Adv Ther*. 2023;40(11):5037-5054. [CrossRef]
17. Burger CD, Tang W, Tsang Y, Panjabi S. Early addition of selexipag to double therapy for pulmonary arterial hypertension. *JAMA Netw Open*. 2024;7(9):e2434691. [CrossRef]
18. Hu X, Yuan P, Chen J, et al. Impact of different sequential triple oral combination therapies based selexipag on outcomes in pulmonary arterial hypertension. *Clin Cardiol*. 2024;47(2):e24245. [CrossRef]
19. Tsang Y, Stokes M, Kim YJ, Tilney R, Panjabi S. Impact of selexipag use within 12 months of pulmonary arterial hypertension diagnosis on hospitalizations and medical costs: a retrospective cohort study. *Clin Respir J*. 2023;17(12):1209-1222. [CrossRef]
20. Cui X, Lu W, Zhang D, et al. Selexipag-based triple combination therapy improves prognosis in Chinese pulmonary arterial hypertension patients. *Front Cardiovasc Med*. 2022;9:991586. [CrossRef]
21. Wang S, Yan Y, Zhang J, et al. Comparing the efficacy and safety of low, medium, and high dosages of selexipag for treating pulmonary hypertension: a systematic review and meta-analysis. *Anim Models Exp Med*. 2024;7(1):56-70. [CrossRef]
22. Qin J, Wang G, Han D. Selexipag in patients with pulmonary hypertension: a systematic review and meta-analysis of randomized controlled trials. *Curr Probl Cardiol*. 2023;48(2):101466. [CrossRef]
23. Manzi G, Mariani MV, Filomena D, et al. Comparative effectiveness of oral therapies targeting the prostacyclin pathway in pulmonary arterial hypertension: a systematic review and network meta-analysis. *Vasc Pharmacol*. 2024;154:107280. [CrossRef]
24. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2018;39(47):4175-4181. [CrossRef]
25. Hoeper MM, Pausch C, Olsson KM, et al. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. *Eur Respir J*. 2022;60(1):2102311. [CrossRef]
26. Boucly A, Weatherald J, Savale L, et al. External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry. *Eur Respir J*. 2022;59(6):2102419. [CrossRef]
27. Benza R, Chin K, Gaine S, et al. REVEAL Lite 2 risk assessment in patients with pulmonary arterial hypertension from the GRIPHON study: a post-hoc analysis demonstrates association of risk status with long-term outcomes. *Chest*. 2021;160(4):A2318-A2321. [CrossRef]
28. El-Kersh K, Zhao C, Elliott G, et al. Derivation of a risk score (REVEAL-ECHO) based on echocardiographic parameters of patients with pulmonary arterial hypertension. *Chest*. 2023;163(5):1232-1244. [CrossRef]
29. Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest*. 2019;156(2):323-337. [CrossRef]
30. Sitbon O, Chin KM, Channick RN, et al. Risk assessment in pulmonary arterial hypertension: insights from the GRIPHON study. *J Heart Lung Transplant*. 2020;39(4):300-309. [CrossRef]

31. Kaymaz C, Tanyeri S, Tokgöz HC, et al. The consistent effectiveness and safety of macitentan therapies across idiopathic and congenital heart disease-associated PulmonaryArterial hypertension: a single-center experience. *Anatol J Cardiol*. 2022;26(10):778-787. [CrossRef]
32. Kaymaz C, Mutlu B, Küçükoğlu MS, et al. Preliminary results from a nationwide adult cardiology perspective for pulmonary hypertension: Registry on clinical outcome and survival in pulmonary hypertension Groups (SIMURG). *Anatol J Cardiol*. 2017;18(4):242-250. [CrossRef]
33. Akbulut M, Kaymaz C, Basarici I, et al. Clinical, echocardiographic and haemodynamic predictors of morbidity and mortality in pulmonary hypertension: a nation-wide registry. *Eur Heart J*. 2024;45(Suppl 1):ehae666.2232. [CrossRef]
34. Basarici I, Kaymaz C, Akbulut M, et al. Multiparametric risk predictions for morbidity and mortality in patients with pulmonary arterial hypertension: insights from a nation-wide registry. *Eur Heart J*. 2024;45(Suppl 1):ehae666.2231. [CrossRef]
35. Kaymaz C, Tokgoz HC, Hakgor A, et al. Changing patterns in clinical, echocardiographic and haemodynamic characteristics, and management strategies that may be translated to improved survival in pulmonary hypertension. *Eur Heart J*. 2024;45(Suppl 1):ehae666.2226. [CrossRef]
36. Varian F, Dick J,Battersby C, et al. Pulmonary hypertension: intensification and Personalization of Combination Rx (Phoenix): a phase IV randomized trial for the evaluation of dose-response and clinical efficacy of Riociguat and selexipag using implanted technologies. *Pulm Circ*. 2024;14(1):e12337. [CrossRef]



Supplementary Figure 1. a. Baseline and follow up bar plot for D-shaped septum. b. Baseline and follow up plot for pulmonary artery diameter. c. Baseline and follow up plot for TAPSE. d. Baseline and follow up plot for RV-TDI. e. Baseline and follow up plot for echocardiography estimated PAPs. f. Baseline and follow up plot for estimated PAMP.



Supplementary Figure 2. Baseline and follow-up assessments of clinical and risk parameters: (A) World Health Organization functional class (FC), (B) six-minute walk distance (6MWD), (C) N-terminal pro–brain natriuretic peptide (NT-proBNP), (D) COMPERA risk score, (E) Swedish PAH Registry (SPAHR) risk score, (F) non-invasive FPHN score, (G) REVEAL ECHO score, and (H) REVEAL Lite 2.0 score.

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Editorial Comment: "Could We Maintain the Initial Efficacy of Triple Sequential Combination Therapies with Selexipag Against Progressive Deterioration Risk in Patients with Pulmonary Arterial Hypertension: Insights from a Single-Centre Study"

EDITORIAL COMMENT

Pulmonary arterial hypertension (PAH) remains a progressive, fatal disease characterized by progressive increase in pulmonary vascular resistance leading to right ventricular failure. While modern pharmacotherapy targets the endothelin, nitric oxide, and prostacyclin pathways, the timing of therapeutic escalation remains a subject of intense clinical debate. The recent original investigation published in *The Anatolian Journal of Cardiology* offers compelling real-world evidence suggesting that the efficacy of the oral IP receptor agonist selexipag is tightly linked to the patient's risk status at the time of initiation, thereby advocating for a paradigm shift toward earlier intervention.[1]

The retrospective single-center study analyzed 127 patients receiving sequential triple therapy including selexipag. The authors observed that while selexipag elicited significant initial improvements in functional class, 6-minute walk distance, and echocardiographic parameters (such as TAPSE) during the first 12 months, these benefits appeared to attenuate in the longer term.[1] Crucially, the study demonstrated that long-term survival was not dependent on the maximum achieved dose of the drug. Instead, mortality was independently predicted by baseline risk scores—specifically the SPAHR, REVEAL 2.0, and REVEAL Lite 2.0 scores—at the moment selexipag was introduced.

These findings underscore a critical clinical axiom: the window of opportunity to alter the disease trajectory is narrow. The study noted a substantial delay in treatment escalation, with a mean time delay for combining selexipag with background therapies of over 1700 days. The authors suggested that the observed attenuation of benefit after one year likely reflects the "progressive deteriorating nature of the disease" rather than a loss of drug efficacy. Consequently, delaying triple therapy until a patient creates a high-risk profile significantly diminishes the survival benefit, regardless of the dose titrated.

This "earlier is better" concept is strongly supported by the broader literature. The pivotal GRIPHON randomized clinical trial established that selexipag reduces the risk of morbidity and mortality by 40%.[2] However, subsequent sub-analyses of GRIPHON data have highlighted that patients derive greater benefit when selexipag is initiated earlier on background double therapy rather than waiting for clinical deterioration.[3] Furthermore, a retrospective analysis by Tsang et al[4] demonstrated that initiating selexipag within 12 months of a PAH diagnosis was associated with reduced hospitalization rates and medical costs compared to delayed initiation.

In conclusion, the current study serves as a stark reminder that "treating to failure" is an obsolete strategy in PAH management. The correlation between lower baseline risk scores and improved survival mandates a proactive approach. Clinicians should not wait for overt right heart failure to escalate therapy. To maintain

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efficacy and improve prognosis, selexipag must be utilized not merely as a rescue therapy for late-stage disease, but as an early, integral component of sequential triple combination therapy.

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REFERENCES

1. Tokgöz HC, Kaymaz C, Kültürsay B, et al. Could we maintain the initial efficacy of triple sequential combination therapies with selexipag against progressive deterioration risk in patients with pulmonary arterial hypertension: Insights from a single-center study? *Anatol J Cardiol*. 2026;30(4):248-258. [CrossRef]
2. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522-2533. [CrossRef]
3. Coghlan JG, Channick R, Chin K, et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension receiving double combination therapy: insights from the randomized controlled GRIPHON study. *Am J Cardiovasc Drugs*. 2018;18(1):37-47. [CrossRef]
4. Tsang Y, Stokes M, Kim YJ, Tilney R, Panjabi S. Impact of selexipag use within 12 months of pulmonary arterial hypertension diagnosis on hospitalizations and medical costs: a retrospective cohort study. *Clin Respir J*. 2023;17(12):1209-1222. [CrossRef]

THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Multimodal Cardiovascular Risk Discrimination: Clinical, Biochemical, and Doppler Ultrasound Insights from a Contemporary Atherosclerotic Cardiovascular Disease Cohort

ABSTRACT

Background: Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of global morbidity and mortality, underscoring the need for improved early detection strategies for preclinical atherosclerosis. This study evaluated comprehensive multimodal cardiovascular risk predictors—clinical, biochemical, and vascular imaging parameters—in dyslipidemic adults without established ASCVD.

Methods: A total of 847 adults underwent standardized clinical assessment, laboratory profiling, and duplex-based vascular imaging, including carotid intima–media thickness (IMT), plaque assessment, flow-mediated dilation (FMD), and ankle–brachial index. Statistical analyses included multivariate logistic regression, receiver operating characteristic (ROC) curve analysis, model calibration metrics, and correlation matrices using Pearson or Spearman tests as appropriate. High-density lipoprotein cholesterol (HDL-C) exhibited a strong inverse correlation with AIP ($r = -0.57$, $P < .001$).

Results: Triglycerides (TG) demonstrated a strong positive correlation with the atherogenic index of plasma (AIP) ($r = 0.80$, $P < .001$). Moderate correlations were observed between age and left ventricular mass index ($r = 0.31$, $P < .001$), age and fibrinogen ($r = 0.32$, $P < .001$), HbA1c and TG ($r = 0.26$, $P < .001$), and HbA1c and AIP ($r = 0.30$, $P < .001$). ASCVD and atherosclerosis total score positivity were independently associated with age, HbA1c, IMT, and FMD in multivariable analyses, while model discrimination remained robust (area under the curve values reported).

Conclusion: Multimodal integration of clinical, biochemical, and vascular imaging markers provides meaningful refinement of cardiovascular risk stratification and may enhance early detection of preclinical ASCVD.

Keywords: Atherosclerosis, Duplex ultrasound, dyslipidemia, preclinical vascular disease, risk discrimination

ORIGINAL INVESTIGATION

INTRODUCTION

Despite advances in preventive and therapeutic measures, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide. Coronary artery disease (CAD) and stroke account for nearly half of all cardiovascular deaths, and projections suggest a further rise in disease burden until 2050, driven mainly by aging populations and the growing prevalence of metabolic syndrome, obesity, and hypertension.[1-4] These trends underscore the need for improved risk estimation models to optimize prevention and reduce global health impact.

Conventional risk factors such as age, sex, smoking, DM, hypertension, dyslipidemia, and heart failure (HF) form the cornerstone of ASCVD discrimination but often lack accuracy, particularly for patients at intermediate risk. Novel contributors, including biochemical markers and vascular imaging, may provide added value for individual risk stratification.[5-8]

Emerging evidence highlights the prognostic role of markers such as glycated hemoglobin (HbA1c), C-reactive protein (CRP), fibrinogen, and the atherogenic

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index of plasma (AIP), reflecting metabolic and inflammatory pathways of atherosclerosis. In parallel, vascular imaging—especially duplex ultrasonography—has proven effective for detecting preclinical disease. Parameters such as carotid intima–media thickness (IMT) and plaque burden are recognized predictors of future myocardial infarction (MI) and stroke, offering complementary information to conventional scores.[9-15]

In Türkiye, the high prevalence of hypertension, dyslipidemia, and metabolic risk factors has drawn attention to the limitations of traditional risk scores and the potential added value of new biomarkers and imaging techniques. However, limited evidence exists on the combined prognostic value of clinical, biochemical, and imaging measures in dyslipidemic populations. Therefore, the present study aimed to assess the prognostic significance of clinical, biochemical, and duplex ultrasound (DUS) parameters in predicting ASCVD, and to determine the prevalence and predictors of preclinical atherosclerosis in dyslipidemic patients without clinically evident CAD.[16-24]

METHODS

Study Population

This cross-sectional study included 950 consecutive patients diagnosed with dyslipidemia between January 2019 and March 2025. Patients with established CAD, defined as a history of MI or obstructive CAD on angiography not previously revascularized, were excluded. Inclusion criteria were as follows: age 30 years or older and a signed informed consent form. Of 950 screened patients, a total of 847 consecutive dyslipidemic adults without overt CAD were included in this contemporary cohort study. Patients with missing clinical, biochemical, or vascular imaging data were excluded to ensure analytic consistency. Patient selection and exclusion are summarized in the flowchart (Figure 1).

All participants underwent standardized clinical evaluation, anthropometric measurements, blood sampling, and vascular imaging.

Data Collection

All individuals were submitted to a comprehensive clinical examination including an extensive medical history and anthropometric measures [body mass index (BMI), waist circumference (WC), neck circumference (NC)], as well as hemodynamic parameters such as blood pressure [systolic (SBP), diastolic (DBP), and mean arterial pressure (MBP)] and pulse pressure (PP). Smoking status; history of DM, hypertension, and HF; chronic kidney disease (CKD); and family history of cardiovascular disease (FH of CVD) were recorded.

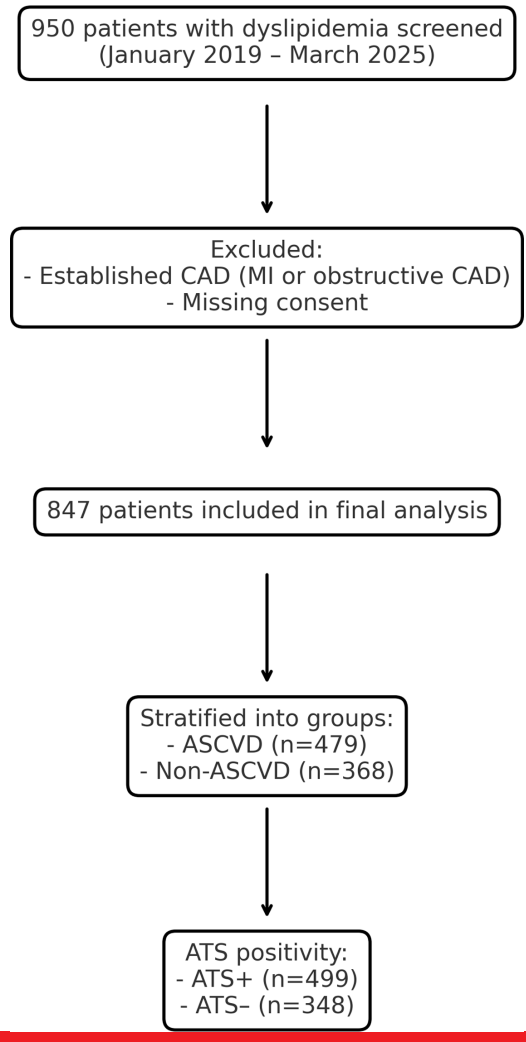

Figure 1. Flowchart of the study population. A total of 950 patients with dyslipidemia were screened. After exclusions, 847 participants were included in the final analysis.

Clinical and Anthropometric Assessment

Height, weight, BMI, WC, and NC were recorded by trained clinicians.

Blood pressure (systolic, diastolic, mean arterial pressure, and PP) was measured after ≥10 minutes resting in a seated position.

Biochemical Measurements

Venous blood samples were analyzed for lipid profile [low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides] [Total cholesterol (TC), LDL-C, HDL-C, triglycerides], HbA1c, thyroid-stimulating hormone (TSH), and high-sensitivity CRP (hs-CRP).

HIGHLIGHTS

- Cross-sectional study of 847 dyslipidemic patients evaluating clinical, biochemical, and imaging predictors of atherosclerotic cardiovascular disease (ASCVD).
- Male sex, older age, diabetes mellitus, chronic kidney disease, heart failure, and revascularization independently predicted ASCVD and major adverse cardiovascular events.
- Duplex ultrasound positivity (ATS+) was a strong indicator of systemic atherosclerosis.
- Final models achieved good discrimination (area under the curve up to 0.855) and acceptable calibration.
- Supports a multimodal, patient-centered approach to cardiovascular risk stratification.

Standardized enzymatic assays traceable to international reference methods were used.

Echocardiographic Assessment

Transthoracic echocardiography was performed in accordance with the American Society of Echocardiography's recommendations. Parameters collected were left ventricular mass index (LVMI), relative wall thickness (RWT), and ejection fraction (EF); LVMI was indexed to body surface area.

Vascular Ultrasound Assessment

Carotid IMT, presence of carotid plaque, flow-mediated dilation (FMD), and ankle–brachial index (ABI) were assessed using DUS.

Measurements were obtained following international consensus recommendations.

The carotid IMT was measured at the distal 1 cm of the common carotid artery, in plaque-free segments, as the distance between the lumen–intima and media–adventitia interfaces. A mean IMT value ≥0.9 mm or the presence of a focal luminal protrusion >1.5 mm was classified as carotid plaque.

Ankle–brachial index was assessed as the ratio of SBP at the posterior tibial/dorsalis pedis arteries to the higher of the right or left brachial systolic pressure. An ABI <0.9 was considered abnormal, reflecting peripheral arterial disease, while values >1.40 were indicative of non-compressible vessels.

Flow-mediated dilation of the brachial artery was measured using standard protocols. The diameter of the brachial artery was recorded at rest and 1 minute after cuff release following 5 minutes of suprasystolic occlusion. Flow-mediated dilation was expressed as the percentage change from baseline, with impaired endothelial function defined as FMD <7%.

Definition of Atherosclerosis

ATS positivity was defined as: Carotid IMT ≥ 0.9 mm, and/or presence of carotid plaque, and/or ABI < 0.9, and/or impaired FMD in accordance with guidelines for subclinical atherosclerosis assessment.

Clinical Endpoints

The primary clinical endpoint was a major adverse cardiovascular event (MACE). A MACE was defined as a composite of cardiovascular death, nonfatal MI, nonfatal stroke, and any events requiring percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as extracted from medical records. This combined definition was intended to capture systemic atherosclerotic disease burden and is congruent with prior cardiovascular outcome trials.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) and R software Version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Continuous variables were presented as mean ± SD or median (interquartile range, IQR) depending on distribution according to the Shapiro–Wilk test. Categorical variables were expressed as counts and percentages. Group comparisons (ASCVD vs. non-ASCVD; ATS+ vs. ATS–) were performed using: Student's *t*-test or Mann–Whitney *U*-test for continuous variables, chi-square test or Fisher's exact test for categorical variables.

Correlation Analyses

Pearson correlation was applied only to normally distributed continuous variables, while Spearman rank correlation was used for non-normally distributed variables, as required by the reviewer.

Table 1. Baseline Characteristics of Study Participants (n = 847)

Variables	Value
Anthropometric	
Age (years)	59.0 (52.0-66.0)
BMI (kg/m^2)	28.54 (25.39-31.91)
WC (m)	1.02 ± 0.10
NC (cm)	39.47 ± 3.18
Hemodynamic	
SBP (mm Hg)	140.0 (130.0-160.0)
DBP (mm Hg)	90.0 (80.0-90.0)
MBP (mm Hg)	105.9 ± 14.8
PP (mm Hg)	55.56 (45.45-70.71)
Echocardiographic	
LV mass index (g/m^2)	100.84 (82.21-121.65)
RWT	0.44 ± 0.09
EF (%)	57.0 (45.0-61.0)
Lipid Profile	
TC (mg/dL)	209.6 ± 56.69
LDL-C (mg/dL)	135.14 ± 46.21
HDL-C (mg/dL)	44.3 (37.0-54.0)
TG (mg/dL)	148.9 (106.3-203.7)
AIP	0.16 (–0.02 to 0.36)
Glycemic	
HbA1c (%)	6.05 (5.5-7.13)
Inflammatory / Endocrine	
Fibrinogen (mg/dL)	299.19 ± 85.65
CRP (mg/L)	4.7 (1.9-12.45)
TSH (mU/L)	2.05 (1.25-3.56)
Categorical, n (%)	
Obesity	316 (37.3)
Smoking (current or former)	316 (37.3)
Diabetes mellitus	335 (39.6)
FH of CVD	241 (28.5)
ASCVD	479 (56.6)

Values are expressed as mean ± SD for normally distributed variables, or median (interquartile range, IQR) for skewed variables (Shapiro–Wilk test). Categorical variables are presented as n (%).
AIP, atherogenic index of plasma; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; NC, neck circumference; PP, pulse pressure; RWT, relative wall thickness; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

Regression Analysis

Multivariate logistic regression models evaluated the independent association of clinical, biochemical, and vascular imaging variables with ASCVD, ATS positivity, and MACE.

Covariates with $P < .10$ in univariate analysis were entered into multivariable models.

Model Performance

Model discrimination was assessed using receiver operating characteristic (ROC) curves with area under the curve (AUC) values reported. Model accuracy was evaluated using precision, recall, and F1 score.

Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. For comparison, pairwise Pearson/Spearman correlation matrices were computed.

Statistical significance was set at $P < .05$ (three-decimal precision as requested).

Clarification added: Definitions were clarified. Atherosclerotic cardiovascular disease was defined as a history of MI, coronary or peripheral revascularization, or ischemic stroke. ATS positivity was defined by carotid IMT ≥0.9 mm or plaque presence on ultrasound. Major adverse cardiovascular events were ascertained retrospectively from hospital records over a median follow-up of 24 months.

RESULTS

Baseline Characteristics

Baseline characteristics of the 847 included patients are summarized in Table 1.

The median age was 59.0 years (IQR 52.0-66.0), and 48% were male. Obesity (BMI ≥30 kg/m^2) was present in 316 participants (37.3%), diabetes mellitus in 335 (39.6%), and current or former smoking in 316 (37.3%). Hypertension was highly prevalent, with a median SBP of 140 mm Hg and DBP of 90 mm Hg, yielding a median PP of 55.6 mm Hg. The mean MBP was 105.9 mm Hg. Echocardiography showed preserved systolic function with a median EF of 57% and moderately elevated LVMI of 100.8 g/m^2. The mean RWT was 0.44. Lipid profile revealed: mean TC 210 mg/dL, LDL-C 135 mg/dL, median HDL-C 44 mg/dL, triglycerides (TG) 149 mg/dL, with a median AIP of 0.16. Median HbA1c was 6.05%, fibrinogen 299 mg/dL, and CRP 4.7 mg/L. Median TSH was 2.05 mU/L.

Group Comparisons

In group comparisons (Table 2), ASCVD patients (n = 479) were older (median 61 vs. 56 years, $P < .001$) and had higher SBP (145 vs. 140 mm Hg, $P = .05$), PP (60.6 vs. 50.5 mm Hg, $P = .03$), and LVMI (112 vs. 97 g/m^2, $P < .01$) compared with non-ASCVD (n = 368). They also showed higher: TG (157 vs.

Table 2. Comparison of Clinical and Biochemical Parameters Between Patients with and Without Atherosclerotic Cardiovascular Disease

Variables	No ASCVD Median (IQR)	ASCVD Median (IQR)	*P*
Anthropometric			
Age (years)	56.0 (47.0-63.0)	61.0 (55.0-67.0)	<.001***
BMI (kg/m^2)	28.4 (24.94-31.87)	28.73 (25.8-31.9)	.30
WC (m)	1.02 (0.94-1.09)	1.03 (0.95-1.08)	.98
NC (cm)	39.0 (38.0-42.0)	40.0 (38.0-42.0)	.25
Hemodynamic			
SBP (mm Hg)	140.0 (127.5-160.0)	145.0 (130.0-160.0)	.05
DBP (mm Hg)	90.0 (80.0-90.0)	90.0 (80.0-95.0)	.50
MBP (mm Hg)	106.67 (95.17-113.33)	106.67 (96.67-116.67)	.12
PP (mm Hg)	50.51 (40.4-70.71)	60.61 (50.51-70.71)	.03*
Lipid profile			
LDL (mg/dL)	136.0 (102.55-161.4)	132.1 (102.0-164.6)	.93
HDL (mg/dL)	46.0 (38.7-54.1)	44.0 (35.5-52.0)	.06
TG (mg/dL)	136.0 (97.4-198.5)	157.0 (111.5-210.65)	.01**
Glycemic			
HbA1c (%)	5.7 (5.29-6.1)	6.4 (5.7-7.7)	<.001***
Inflammatory			
CRP (mg/L)	3.1 (1.5-5.91)	6.6 (2.2-17.9)	<.001***
Fibrinogen (mg/dL)	267.0 (218.0-328.5)	317.0 (268.0-381.0)	.002**
Endocrine			
TSH (mU/L)	2.05 (1.26-3.55)	2.04 (1.24-3.56)	.67

Values are presented as median (interquartile range, IQR). *P*-values from Mann–Whitney *U*-test.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; NC, neck circumference; PP, pulse pressure; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.
*$P < .05$.
**$P < .01$.
***$P < .001$.

Table 3. Multivariable Logistic Regression of Predictors of MACE, Atherosclerotic Cardiovascular Disease, and ATS Positivity

Variables	MACE OR (95% CI)	*P*	ASCVD OR (95% CI)	*P*	ATS Positivity OR (95% CI)	*P*
Male	1.75 (1.32-2.33)	<.001*	1.75 (1.32-2.33)	<.001*	1.62 (1.25-2.11)	<.001*
Age (years)	1.34 (1.10-1.63)	.004*	1.29 (1.08-1.55)	.005*	1.31 (1.10-1.57)	.003*
LDL-C	1.09 (0.85-1.40)	.52	1.14 (0.89-1.46)	.31	1.05 (0.83-1.33)	.68
HDL-C	0.83 (0.68-1.02)	.08*	0.83 (0.64-1.09)	.18	0.87 (0.71-1.07)	.19
HbA1c	1.32 (1.12-1.55)	.001*	1.32 (0.99-1.75)	.06	1.28 (1.05-1.56)	.014*
CRP	1.14 (0.93-1.39)	.19	1.09 (0.87-1.35)	.47	1.12 (0.91-1.38)	.28
CKD	2.05 (1.47-2.85)	<.001*	1.69 (1.02-2.82)	.04*	1.92 (1.33-2.76)	<.001*
HF	3.43 (2.10-5.61)	<.001*	3.43 (2.00-5.88)	<.001*	3.27 (2.05-5.22)	<.001*
Revascularization (PCI or CABG).	6.29 (4.45-8.89)	<.001*	6.29 (4.45-8.89)	<.001*	6.01 (4.26-8.47)	<.001*

*Statistically significant (P < 0.05). Multivariable logistic regression with harmonized and single-imputed dataset. Continuous predictors standardized to 1 SD.
ASCVD, atherosclerotic cardiovascular disease; ATS, composite atherosclerosis (ASCVD + DUS positivity); CKD, chronic kidney disease; CRP, C-reactive protein; HF, heart failure; MACEs, major adverse cardiovascular events; OR, odds ratio.

136 mg/dL, *P* = .01), HbA1c (6.4% vs. 5.7%, *P* < .001), CRP (6.6 vs. 3.1 mg/L, *P* < .001), fibrinogen (317 vs. 267 mg/dL, *P* = .002). HDL-C tended to be lower in ASCVD (44 vs. 46 mg/dL, *P* = .06). Supplementary Table 1 demonstrated that ATS-positive patients (n = 499) were older, more often male, and had significantly worse glycemic and inflammatory profiles compared with ATS negative (n = 348).

Multivariable Regression Analysis

Multivariable regression analyses (Table 3, Figure 2) identified male sex (odds ratio [OR] 1.75, 95% CI 1.32-2.33), age (OR 1.34, 95% CI 1.10-1.63), HbA1c (OR 1.32, 95% CI 1.12-1.55), CKD (OR 2.05, 95% CI 1.47-2.85), HF (OR 3.43, 95% CI 2.10-5.61), and prior revascularization (OR 6.29, 95% CI 4.45-8.89) as independent predictors of MACE.

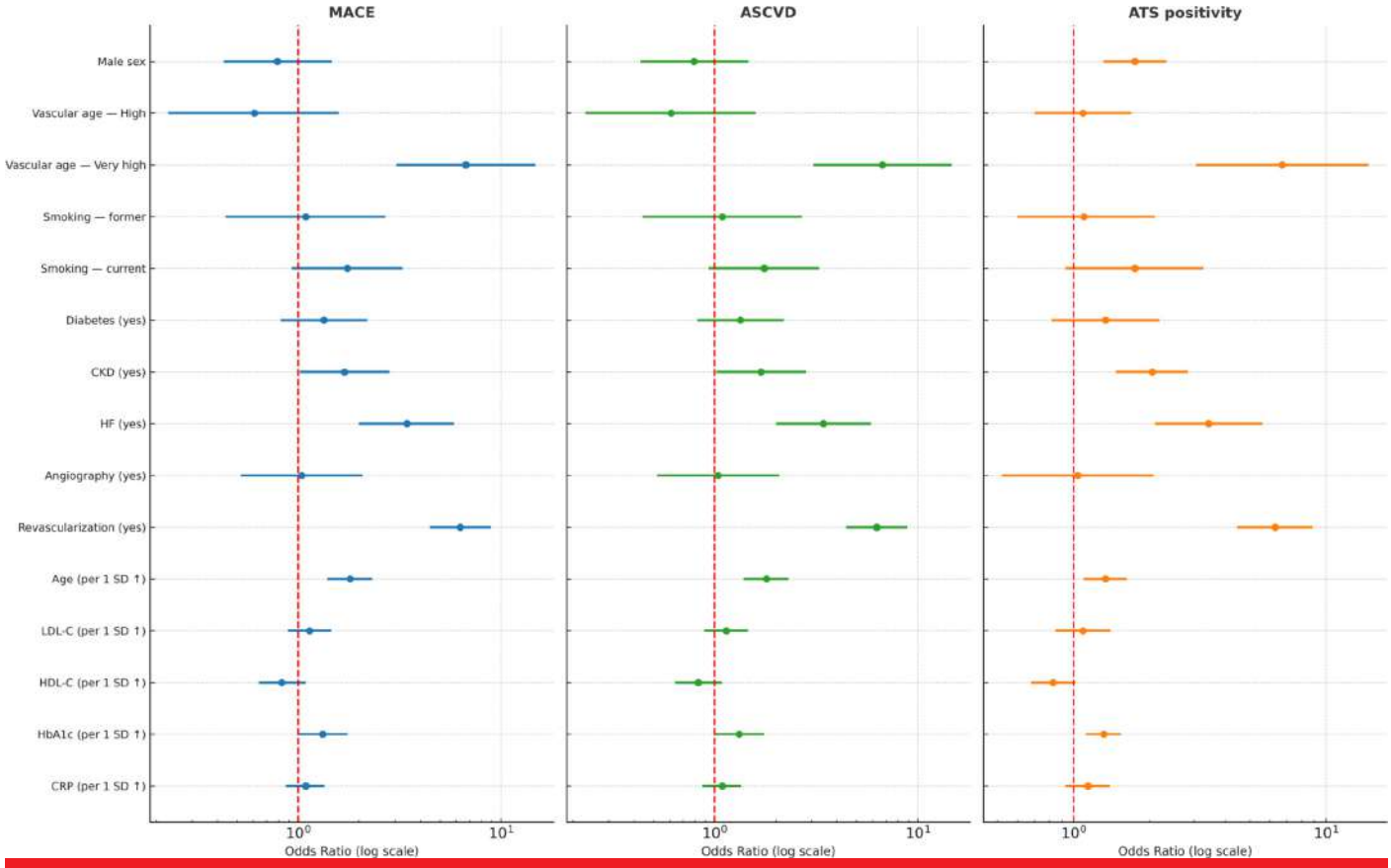

Figure 2. Forest plots of multivariable logistic regression analyses for MACE, ASCVD, and ATS positivity. ORs with 95% CIs are shown on a logarithmic scale. Male sex, age, HbA1c, CKD, HF, and prior revascularization were consistently significant predictors. ATS positivity independently predicted MACE.

Table 4. Performance Metrics of Multivariable Logistic Regression Models

Metric	MACE Model	ASCVD Model	ATS Positivity Model
Accuracy (%)	79.8	85.5	83.2
Precision (%)	87.0	88.2	84.1
Recall (sensitivity) (%)	74.4	72.5	77.8
F1 score (%)	80.2	79.9	80.8
AUC (ROC area)	0.804	0.855	0.842

Model performance metrics for multivariable logistic regression of predictors of MACE, ASCVD, and ATS positivity. Values are expressed as percentages except AUC.
ASCVD, atherosclerotic cardiovascular disease; ATS, composite atherosclerosis (ASCVD + DUS positivity); AUC, area under the curve; F1, harmonic mean of precision and recall; MACEs, major adverse cardiovascular events; ROC, receiver operating characteristic.

Revascularization history showed the strongest association across all outcomes. Similar predictors were significant for ASCVD and ATS positivity. Notably, ATS positivity itself remained an independent predictor of MACE.

Model Performance

Model performance (Table 4, Figure 3) was robust. Accuracy ranged from 79.8% (MACE) to 85.5% (ASCVD). ROC AUC values were 0.804 for MACE, 0.855 for ASCVD, and 0.842 for ATS positivity. The ROC curve confirmed good discrimination, while the confusion matrix showed a balanced trade-off between sensitivity and specificity at a cutoff of 0.44. Sensitivity for ATS positivity reached 77.8%, precision for ASCVD discrimination was 88.2%, and the F1 score exceeded 0.79 across all models, indicating overall robustness.

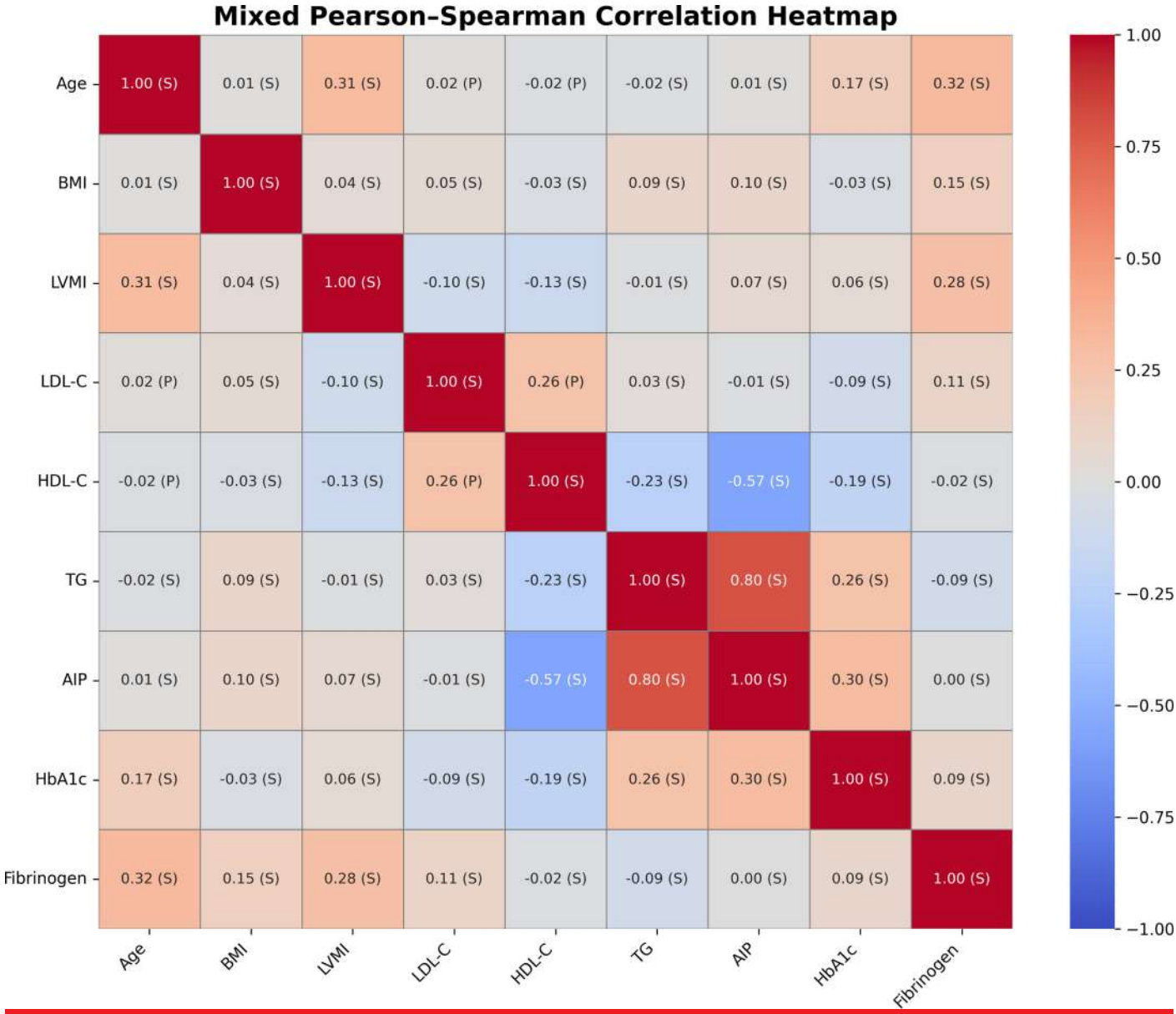

Figure 3. Heatmap of correlation coefficients between clinical, anthropometric, biochemical, and vascular parameters. Pearson or Spearman correlation was applied depending on variable distribution. Values reflect direction and strength of correlations.

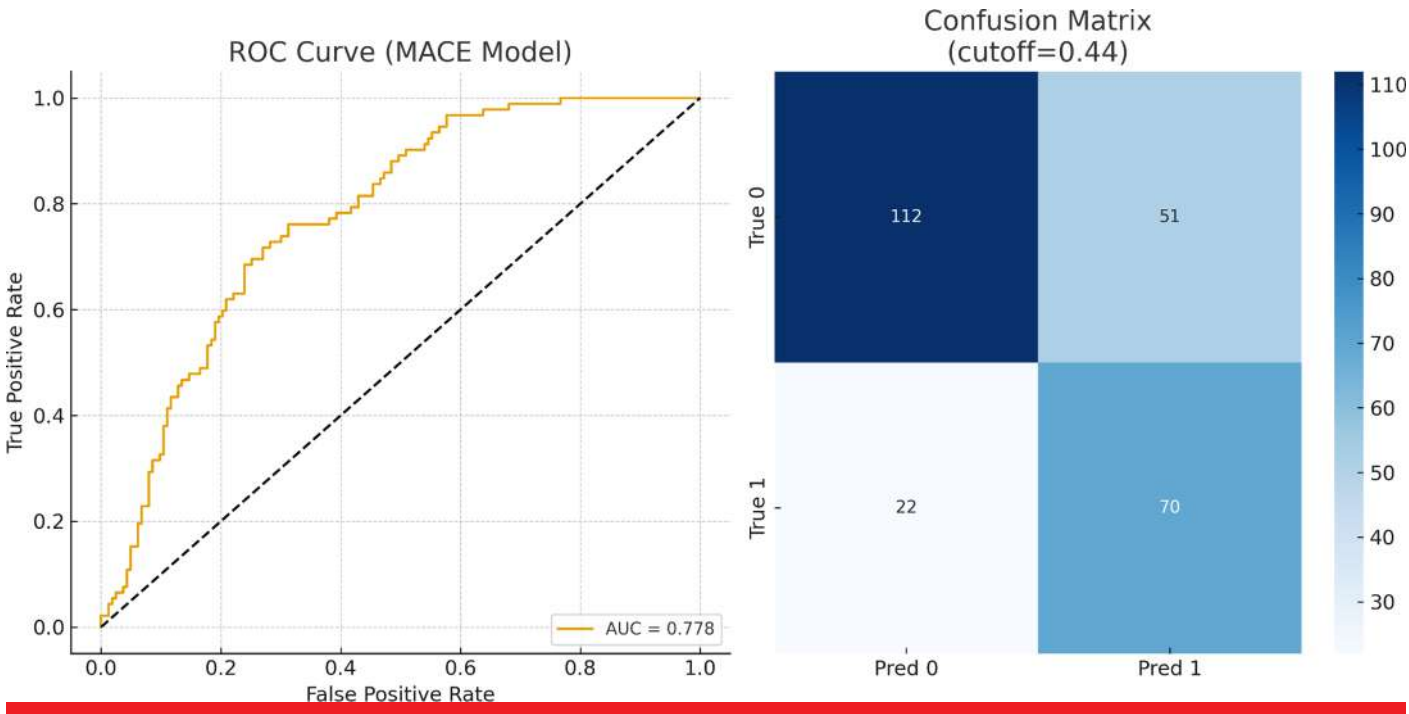

Figure 4. Receiver operating characteristic (ROC) curve (A) and confusion matrix (B) for the MACE discrimination model. The ROC curve demonstrates good discrimination (AUC = 0.778). The confusion matrix (cutoff = 0.44) illustrates the balance between sensitivity and specificity. Supplementary correlation findings are presented in Supplementary Table 2.

Correlation Analysis

Correlation analysis (Figure 4, Supplementary Table 2) revealed several clinically meaningful associations.

The strongest positive correlation was observed between TG and the AIP ($r = 0.80$, $P < .001$). Moderate positive correlations were noted between age and LVMI ($r = 0.31$, $P < .001$), age and fibrinogen ($r = 0.32$, $P < .001$), HbA1c and TG ($r = 0.26$, $P < .001$), and HbA1c and AIP ($r = 0.30$, $P < .001$).

HDL-C exhibited a strong inverse correlation with AIP ($r = -0.57$, $P < .001$).

These findings indicate clustering of metabolic and inflammatory factors with preclinical atherosclerotic burden, whereas remaining associations were weak, supporting minimal multicollinearity among predictors.

Clinical Outcomes

During follow-up, 372 patients experienced MACE (43.9%), highlighting the systemic burden of atherosclerosis. Patients with ATS positivity showed higher cumulative incidence of MACE, consistent with their adverse risk profile.

Graphical Abstract

The graphical abstract (Figure 5) summarizes how integration of clinical, biochemical, and vascular imaging parameters improves risk discrimination compared with conventional risk scores. This multimodal strategy provided superior discrimination for ASCVD, ATS positivity, and MACE, supporting its potential clinical utility for individualized prevention.

DISCUSSION

This study provides comprehensive evidence supporting the value of a multimodal cardiovascular risk assessment framework that integrates clinical, biochemical, and vascular imaging parameters.

These findings confirm the complex interplay among metabolic, inflammatory, and vascular factors in the progression of preclinical atherosclerosis and ASCVD risk.

Integration of Clinical, Biochemical, and Vascular Indicators

Age, systemic inflammation, dyslipidemia, and vascular dysfunction emerged as central contributors to atherosclerotic burden. This aligns with established pathophysiological pathways in which chronic metabolic stress promotes endothelial injury, vascular remodeling, and plaque formation. ATS positivity demonstrated strong associations with age, HbA1c, CRP, and fibrinogen, underscoring the additive effect of glycemic and inflammatory dysregulation.

Interpretation of Correlation Patterns

Correlation analysis revealed a notably strong relationship between TG and AIP ($r = 0.80$), reflecting the shared metabolic determinants of atherogenic dyslipidemia. Moderate correlations between age–LVMI, age–fibrinogen, and HbA1c–AIP/TG highlight the clustering of cardiometabolic risk factors, consistent with previous literature describing combined metabolic and inflammatory pathways in early atherosclerosis. Most other correlations were weak, demonstrating minimal multicollinearity among predictors and supporting the reliability of multivariable modeling.

Predictors of Clinical Outcomes

Multivariable analyses demonstrated that male sex, older age, CKD, HF, and prior revascularization remained strong, independent determinants of MACE. Notably, ATS positivity independently predicted MACE, suggesting that preclinical

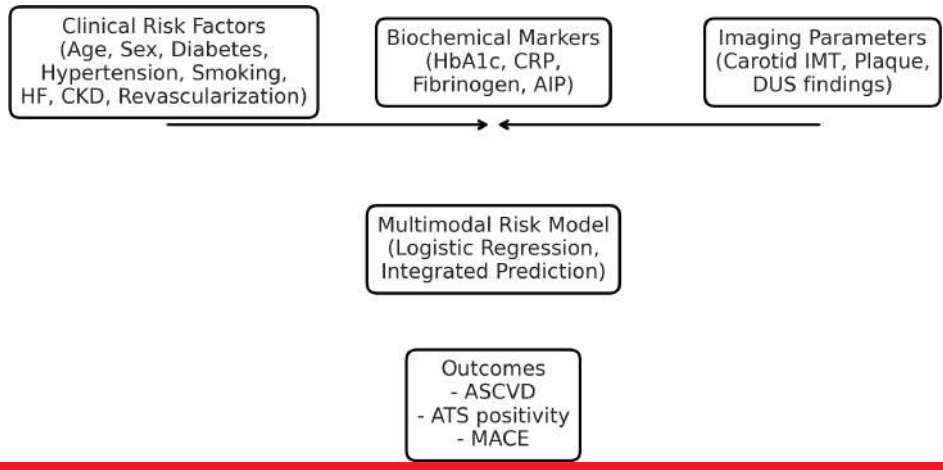

Figure 5. Graphical abstract illustrating the multimodal cardiovascular risk discrimination model. Clinical factors (age, sex, diabetes, hypertension, smoking, HF, CKD, prior revascularization), biochemical markers (HbA1c, CRP, fibrinogen, AIP), and imaging parameters (carotid IMT, plaque, duplex ultrasound findings) were integrated into logistic regression models. This multimodal approach improved predictive accuracy for ASCVD, ATS positivity, and MACE.

vascular disease confers additional prognostic value beyond traditional risk factors.

This work also validates the utility of DUS as an effective and sensitive screen for preclinical carotid disease prior to ASCVD clinical presentation. This is in accordance with the present European Society of Cardiology proposal to take vascular imaging into account among intermediate-risk subjects in order to better estimate the risk.[9] In this context, Tokgözoğlu et al[14] have emphasized the need to include vascular imaging within current risk algorithms, especially in European and Turkish practices.[15] Importantly, this data point out that a history of revascularization—very much a marker of advanced macrovascular disease—is still significantly associated with preclinical ATS in other territories. This observation highlights the systemic atherosclerotic burden, with disease development and progression in 1 vascular territory being often matched by changes in other territories, as has been seen in longitudinal studies.[10,11]

The relationship between higher HbA1c level and preclinical ATS in this study is of particular interest in relation to type 2 DM. Long-term hyperglycemia induces endothelial dysfunction, oxidative stress, and subclinical inflammation, which accelerate the atherosclerotic process.[11] This pathophysiological connection underscores the need to add glucose-lowering measures to primary prevention programs in persons with dyslipidemia, before overt CAD appears. Methodologically, the combination of biochemical markers and imaging contributed to model discrimination with strong ORs and narrow CIs for salient predictors. The combination of multimodal factors is gradually accepted as better than using clinical risk scores alone for risk stratification.[12,13] Consistent with Turkish experience among the latter group is that low HDL-C and high blood pressure predispose to both CVD risk factors, as evidenced in the work by Kılıçkap et al[17] in traditional coronary risk factors among healthy young military recruits, together with a review of meta-analytic rates on hypertension prevalence in other such Turkish cohorts. In addition, studies by Güleç and Erol[18] suggested that the prognostic value of HDL-C in CV risk discrimination needs to be re-assessed, thus validating the clinical significance of these results.

Furthermore, several recent studies from the Anatolian Journal of Cardiology support the growing role of integrated multimodal and AI-assisted approaches in cardiovascular risk evaluation. Koçak et al[20] provided regional data on multimodal cardiovascular risk assessment, while Kırboğa et al[21] and Bozyel et al[22] highlighted the value of explainable artificial intelligence and clinical decision support systems in improving risk discrimination. Complementary evidence from the the Prospective Urban Rural Epidemiology (PURE) Türkiye cohort by Oğuz et al[23] and the Anatolian Ischemic Heart Disease Registry (AIZANOI) Study by Şen et al[24] underscored the importance of adherence to preventive strategies in dyslipidemic and diabetic populations. Additionally, Alrahimi et al[25] emphasized the interplay between atherothrombotic processes and the evolving landscape of atherosclerotic cardiovascular disease in Turkish practice, aligning with the systemic nature of atherosclerosis observed in these findings.

In conclusion, this study demonstrates that a multimodal approach combining clinical, biochemical, and vascular imaging markers significantly improves the detection of subclinical atherosclerosis and ASCVD risk in dyslipidemic patients. This strategy may support more personalized and effective prevention pathways in clinical practice.

These results align with recent large-scale studies demonstrating the incremental prognostic value of carotid plaque burden, IMT progression, and endothelial dysfunction markers in identifying intermediate-risk individuals. Nevertheless, differences in population structure, imaging techniques, and biomarker panels may partly explain variability across studies.

Clinical Implications

The combined assessment of IMT, FMD, ABI, and biochemical markers strengthens early detection strategies by capturing distinct but complementary components of vascular health (structural, functional, and systemic). Such multimodal profiling may improve risk stratification in dyslipidemic adults without overt ASCVD and help tailor preventive interventions.

Strengths and Novel Aspects

Key strengths include:

- a large contemporary dyslipidemic cohort (n = 847),
- simultaneous evaluation of clinical, biochemical, and ultrasound-based vascular markers,
- robust modeling with low multicollinearity,
- integration of ATS positivity as a predictive variable.

To the authors' knowledge, few prior studies have concurrently examined these predictors in a unified model, highlighting the novelty of this integrated approach.

Study Limitations

This study has several limitations. First, its observational design limits causal inference.

Second, residual confounding cannot be excluded despite multivariable analyses.

Third, vascular imaging assessments (e.g., FMD) may exhibit operator dependence, although standardized protocols were used. Finally, follow-up was limited to MACE assessment without detailed cause-specific outcomes.

In this cohort of 847 dyslipidemic patients without overt CAD, 56.6% demonstrated ASCVD and 43.9% experienced MACE during follow-up, reflecting a substantial burden of subclinical and clinical atherosclerotic disease. Independent predictors of adverse outcomes included male sex, older age, elevated HbA1c, CKD, and HF. The multimodal model integrating clinical variables with biochemical markers (HbA1c, CRP, fibrinogen, AIP) and DUS-derived vascular parameters (carotid IMT, plaque burden, FMD, and ABI) significantly improved risk stratification. The multimodal discrimination model achieved strong predictive performance (AUC up to 0.855 for ASCVD and 0.842 for ATS positivity), thereby outperforming traditional risk scores and demonstrating enhanced prognostic utility. These findings highlight the clinical utility of combining vascular imaging with biochemical profiling for early detection and individualized prevention of atherosclerosis.

This integrated approach offers more accurate identification of high-risk individuals than traditional assessment strategies and may help refine preventive management.

The independent associations observed for carotid IMT, carotid plaque, FMD, ABI, and hs-CRP further emphasize the incremental value of incorporating vascular imaging and inflammatory markers into risk-stratification workflows.

Overall, these findings support the utility of multimodal cardiovascular risk profiling and underscore the importance of integrating metabolic, inflammatory, and vascular imaging markers to refine ASCVD risk prediction.

Further longitudinal studies are warranted to explore how combining these modalities can optimally guide preventive therapy decisions and improve long-term cardiovascular outcomes.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Scientific Research Institute of Cardiology, Baku, Azerbaijan (Approval No. #05-EK/2025).

Informed Consent: Written informed consent was obtained from all participants prior to inclusion in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.N.N., E.Z.A.; Design – R.N.N., E.Z.A.; Supervision – R.N.N.; Resources – R.N.N.; Materials – R.N.N.; Data Collection and/or Processing – R.N.N., E.Z.A.; Analysis and/or İnterpretation – R.N.N.; Literature Search – R.N.N.; Writing – R.N.N.; Critical Review – R.N.N., E.Z.A.

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REFERENCES

1. Chong B, Jayabaskaran J, Jauhari SM, et al. Global burden of cardiovascular diseases: projections from 2025 to 2050. *Eur J Prev Cardiol*. 2025;32(11):1001-1015. [CrossRef]
2. Xu S, Liu Y, Zhu M, Chen K, Xu F, Liu Y. Global burden of atherosclerotic cardiovascular disease attributed to lifestyle and metabolic risks. *Sci China Life Sci*. 2025;68(9):2739-2754. [CrossRef]
3. World Heart Federation. *World Heart Report 2025*. Available at: https://world-heart-federation.org/wp-content/uploads/World_Heart_Report_2025_Online-Version.pdf. Accessed August 2025.
4. Savic L, Simic D, Lasica R, et al. Predictors of Major Adverse Cardiovascular Events in Stable Patients After ST Elevation Myocardial Infarction. *Clin Pract*. 2025;15(6):106. [CrossRef]
5. Zhan W, Luo Y, Luo H, et al. Predicting major adverse cardiovascular events in angina patients: multivariate modeling. *Front Cardiovasc Med*. 2024;11:1462451. [CrossRef]
6. Zhang XR, Zhong WF, Liu RY, et al. *Improved prediction and risk stratification of major adverse cardiovascular events using an explainable machine learning approach combining plasma biomarkers and traditional risk factors*. Cardiovasc Diabetol. 2025;24(1):153. [CrossRef]
7. Mannina C, Chopra L, Maenza J, et al. Left ventricular remodeling in patients with low flow aortic stenosis undergoing

transcatheter aortic valve replacement. *Am J Cardiol*. 2024;225:125-133. [CrossRef]
8. Carerj ML, Restelli D, Poleggi C, et al. The Role of Imaging in Cardiovascular Prevention: A Comprehensive Review. *J Cardiovasc Echogr*. 2025;35(1):8-18. [CrossRef]
9. Afkhami S M, Arzani Shams Abadi M, Azimi Aval M R, et al. Enhancing Cardiopulmonary Resuscitation: A Hemodynamic Approach Using Doppler Ultrasound and Echocardiography. Ann Mil Health Sci Res. 2025; 23 (2): e160160. [CrossRef]
10. Cohen I, Lakritz A, Maor E. AI assisted focused cardiac ultrasound in preventive cardiology – a perspective. *npj Cardiovasc Health* 2, 27 (2025). [CrossRef]
11. Antoniou S, Naka KK, Papadakis M, et al. Effect of glycemic control on markers of subclinical atherosclerosis in patients with type 2 diabetes mellitus: A review. *World J Diabetes*. 2021;12(11):1856-1874. [CrossRef]
12. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381. [CrossRef]
13. Goh RSJ, Chong B, Jayabaskaran J, et al. The burden of cardiovascular disease in Asia from 2025 to 2050: a forecast analysis for East Asia, South Asia, South-East Asia, Central Asia, and high-income Asia Pacific regions. *Lancet Reg Health West Pac*. 2024;49:101138. [CrossRef]
14. Tokgözoğlu L, Torp-Pedersen C. Redefining cardiovascular risk prediction: is the crystal ball clearer now? *Eur Heart J*. 2021;42(25):2468-2471. [CrossRef]
15. Tokgözoğlu L. The challenge of risk discrimination: how good are we? *Eur Heart J*. 2018;39(25):2301-2303. [CrossRef]
16. Asil S, Murat E, Taşkan H, et al. Relationship between cardiovascular disease risk and neck circumference shown in the systematic coronary risk estimation (SCORE) risk model. *Int J Environ Res Public Health*. 2021;18(20):10763. [CrossRef]
17. Kılıçkap M, Barçın C, Göksülük H, et al. Data on prevalence of hypertension and blood pressure in Turkey: Systematic review, meta-analysis and meta-regression of epidemiological studies on cardiovascular risk factors. *Turk Kardiyol Dern Ars*. 2018;46(7):525-545. [CrossRef]
18. Güleç S, Erol C. The role of HDL cholesterol as a measure of 10-year cardiovascular risk should be re-evaluated. *Eur J Prev Cardiol*. 2022;29(16):2132-2134. [CrossRef]
19. Güleç S, Erol Ç. High-density lipoprotein cholesterol and risk of cardiovascular disease. *E-J Cardiol Pract*. 2020;19(3):1-6.
20. Koçak A, Senol C, Yildirim O, Cosgun A, Eyyupkoca F. The evaluation of the metabolic and autonomic predictors of cardiovascular diseases in relation to prostatic hyperplasia symptoms. *Bratisl Lek Listy*. 2022;123(10):740-744. [CrossRef]
21. Kırboğa KK, Küçüksille EU. Identifying cardiovascular disease risk factors in adults with explainable artificial intelligence. *Anatol J Cardiol*. 2023;27(11):657-663. [CrossRef]
22. Bozyel S, Şimşek E, Koçyiğit Burunkaya D, et al. Artificial intelligence-based clinical decision support systems in cardiovascular diseases. *Anatol J Cardiol*. 2024;28(2):74-86. [CrossRef]
23. Oğuz A, Kılıçkap M, Güleç S, et al. Risk factors, use of preventive drugs, and cardiovascular events in diabetes mellitus: the PURE Türkiye cohort. *Anatol J Cardiol*. 2023;27(8):453-461. [CrossRef]
24. Şen T, Dinç Asarcıklı L, Güven S, et al. Adherence to current dyslipidemia guideline in patients utilizing statins according to risk groups and gender differences: the AIZANOI Study. *Anatol J Cardiol*. 2024;28(6):273-282. [CrossRef]
25. Alrahimi J, Ahmed FA, Atar D. The interplay of atherothrombotic factors and the evolving landscape of atherosclerotic cardiovascular disease: comprehensive insights from recent studies. *Anatol J Cardiol*. 2024;28(8):375-380. [CrossRef]

Supplementary Table 1. Comparison of clinical, anthropometric, and biochemical parameters between ATS− and ATS+ participants

Variables	ATS− Median (IQR) / n (%)	ATS+ Median (IQR) / n (%)	*P*
Anthropometric			
Age (years)	55.0 (47.0–62.0)	61.0 (55.0–67.0)	<0.001***
BMI (kg/m^2)	28.37 (24.9–31.69)	28.73 (25.8–31.94)	0.200
WC (m)	1.02 (0.94–1.09)	1.03 (0.93–1.08)	0.970
NC (cm)	39.0 (38.0–42.0)	40.0 (38.0–42.0)	0.220
Hemodynamic			
SBP (mm Hg)	140.0 (125.0–160.0)	145.0 (130.0–160.0)	0.040*
DBP (mm Hg)	90.0 (80.0–90.0)	90.0 (80.0–92.5)	0.530
MBP (mm Hg)	106.67 (95.0–113.33)	106.67 (96.67–116.67)	0.100
PP (mm Hg)	50.51 (40.4–70.71)	60.61 (50.51–70.71)	0.020*
Lipid profile			
LDL-C (mg/dL)	136.4 (105.55–162.65)	132.0 (101.0–163.9)	0.620
HDL-C (mg/dL)	46.0 (38.7–54.1)	44.0 (35.0–52.0)	0.040*
TG (mg/dL)	136.0 (97.85–197.25)	156.9 (109.68–210.65)	0.010**
AIP	0.14 (−0.06–0.32)	0.18 (0.02–0.39)	0.002**
Glycemic			
HbA1c (%)	5.68 (5.26–6.1)	6.38 (5.7–7.7)	<0.001***

Values are median (IQR) or n (%). Continuous variables: Mann–Whitney U test.
Categorical variables: Chi-square or Fisher's exact test. *$P < .05$, **$P < .01$, ***$P < .001$.

Supplementary Table 2. Correlation matrix of clinical, biochemical, and vascular variables

Variable 1	Variable 2	r	*P*	Method
Age	BMI	0.01	0.746	Spearman
Age	LVMI	0.31	<0.001	Pearson
Age	LDL-C	0.02	0.563	Pearson
Age	HDL-C	−0.02	0.557	Pearson
Age	TG	−0.02	0.542	Spearman
Age	AIP	0.01	0.798	Spearman
Age	HbA1c	0.17	<0.001	Spearman
Age	Fibrinogen	0.32	<0.001	Spearman
BMI	LVMI	0.04	0.264	Spearman
BMI	LDL-C	0.05	0.184	Pearson
BMI	HDL-C	−0.03	0.420	Spearman
BMI	TG	0.09	0.009	Spearman
BMI	AIP	0.10	0.003	Spearman
BMI	HbA1c	−0.03	0.407	Spearman
BMI	Fibrinogen	0.15	<0.001	Spearman
LVMI	LDL-C	−0.10	0.003	Pearson
LVMI	HDL-C	−0.13	<0.001	Pearson
LVMI	TG	−0.01	0.762	Spearman
LVMI	AIP	0.07	0.040	Spearman
LVMI	HbA1c	0.06	0.059	Spearman
LVMI	Fibrinogen	0.28	<0.001	Spearman
LDL-C	HDL-C	0.26	<0.001	Pearson
LDL-C	TG	0.03	0.393	Spearman
LDL-C	AIP	−0.01	0.806	Spearman
LDL-C	HbA1c	−0.09	0.008	Pearson
LDL-C	Fibrinogen	0.11	0.001	Spearman
HDL-C	TG	−0.23	<0.001	Spearman
HDL-C	AIP	−0.57	<0.001	Spearman
HDL-C	HbA1c	−0.19	<0.001	Pearson
HDL-C	Fibrinogen	−0.02	0.501	Spearman
TG	AIP	0.80	<0.001	Spearman
TG	HbA1c	0.26	<0.001	Spearman
TG	Fibrinogen	−0.09	0.011	Spearman
AIP	HbA1c	0.30	<0.001	Spearman
AIP	Fibrinogen	0.00	0.987	Spearman
HbA1c	Fibrinogen	0.09	0.010	Spearman

Pearson correlation was used for normally distributed variables; Spearman correlation for non-normally distributed variables (Shapiro–Wilk test). **P* < .05, ***P* < .01, ****P* < .001.

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A New Technique in the Surgical Treatment of Secondary Tricuspid Regurgitation: Crescent-Like Annuloplasty With Asymmetric Circular Pericardial Band

CASE REPORT

INTRODUCTION

Tricuspid regurgitation (TR) may be classified as either primary or secondary (functional), with over 90% of cases falling into the latter category. Secondary TR is most commonly associated with left-sided valvular pathology or myocardial dysfunction. It typically arises due to right ventricular (RV) remodeling in response to pressure and/or volume overload, leading to annular dilatation and leaflet tethering.[1]

Severe TR is an independent risk factor associated with poor prognosis. In a large echocardiographic study involving 5223 patients, the 1-year survival rates were 91.7% in patients without TR, 90.3% with mild TR, 78.9% with moderate TR, and 63.9% in those with severe TR.[2] These observations underscore the critical importance of effectively treating TR in order to improve patient outcomes.[2,3]

Unlike other cardiac valves, the tricuspid valve has historically attracted limited attention from cardiac surgeons, earning it the designation of the "forgotten valve." This may be partly due to the fact that even severe TR can remain clinically silent for a prolonged period. However, the more fundamental issue lies in the limited success of current surgical techniques for tricuspid valve repair or replacement, which have yet to achieve the early and long-term outcomes seen with left-sided valve procedures.[4] Limited durability of current repair methods or incomplete correction, moreover, persistent pulmonary hypertension, atrial fibrillation, and RV dysfunction after left-sided valve surgery may lead to residual or recurrent TR.[5]

Although novel techniques have been proposed to break this vicious cycle of tricuspid regurgitation, their reproducibility or effectiveness remains low. The search for a surgical technique that will provide a standard of success in the treatment of TR continues.[6] The case presented here is the result of such a search. The technique also has the important advantage of being cost-effective.

Case Reports Surgical Technique

The surgeries were performed via median sternotomy. A sufficiently sized pericardial patch was then removed, treated with glutaraldehyde, rinsed thoroughly, and stored in saline solution. Following cannulation, a cross-clamp was applied. Myocardial protection was achieved using alternating antegrade and retrograde blood cardioplegia enriched with potassium. First, mitral procedures were performed. In both patients, the mitral valve was explored via a superior septal approach. Intraoperative evaluation revealed that the valves were unsuitable for repair. In case 1, a 29 mm St. Jude Epic bioprosthetic valve was used for mitral valve replacement, and in case 2, a 29 mm Corcym mechanical valve was used.

Tricuspid valve exploration revealed secondary tricuspid insufficiency due to annular dilatation, consistent with echocardiographic findings. In the second case, there were also mild rheumatic changes in the anterior leaflet. The cases were

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evaluated as suitable for the planned repair. Using Edwards MC3 tricuspid annuloplasty scales, it was determined that size 32 was appropriate for the first case and size 34 was appropriate for the second case. Next, a circular pericardial band was created by cutting out the center of the autologous pericardium according to the selected sizer. This band was then approximated to the natural annulus and shaped so that its outer border was consistent with the contour of the natural annulus. Special care was taken to ensure that the band was slightly narrower than the natural annulus. Given that the annulus expansion of the TR is most pronounced in the anteroposterior commissure, the band was cut to be widest in this segment and narrowest in the septal leaflet segment, resulting in a crescent-like configuration (Figure 1).

The native leaflets were then completely detached from the annulus. The outer edge of the pericardial band was continuously sutured to the native annulus using 5-0 polypropylene. The leaflets were subsequently reattached to the inner edge of the pericardial ring with a continuous 5-0 polypropylene suture as well (Figures 2, 3).

Case 1

An 80-year-old female patient, with a history of multiple hospital admissions for palpitations and shortness of breath, presented to the emergency department with similar complaints. Transthoracic (TTE) and transesophageal

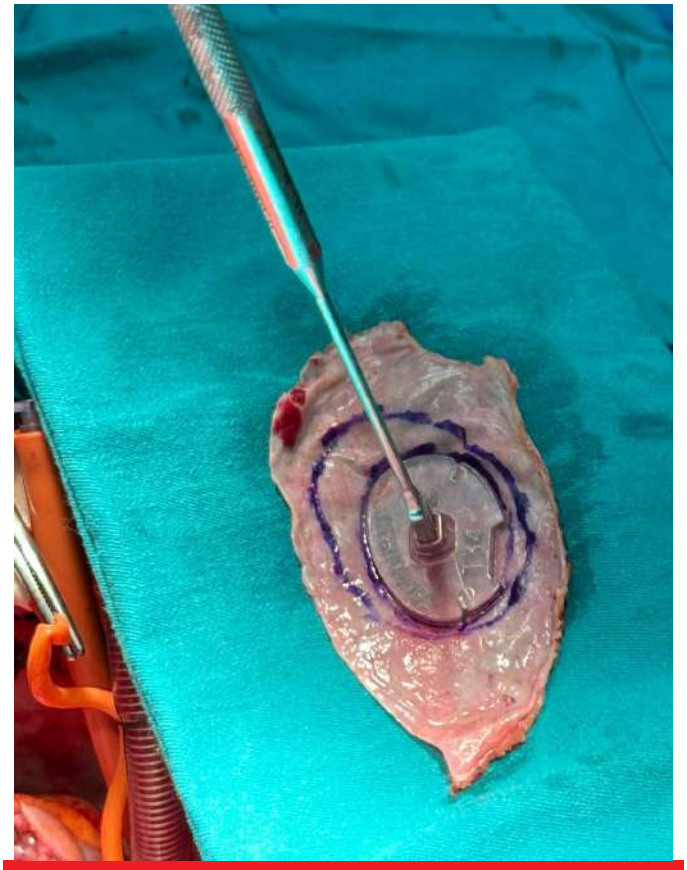

Figure 1. Determining the size of the pericardial annulus using tricuspid ring scales and cutting it in a crescent shape.

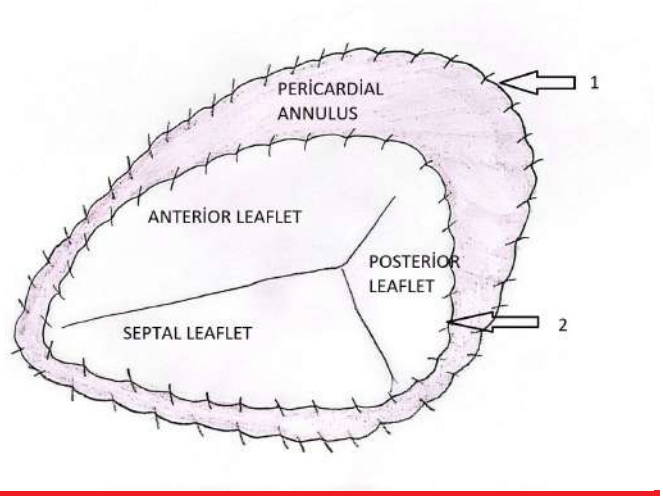

Figure 2. Illustration of the tricuspid valve after repair. 1: previous annulovalvular junction, 2: new annulovalvular junction.

echocardiography (TEE) revealed severe mitral and tricuspid regurgitation. The patient was weaned from cardiopulmonary bypass with moderate inotropic support. Intraoperative TEE showed only mild residual TR. She remained in the ICU for 3 days. On day 5, echocardiography revealed only trace TR. With no complications during ward follow-up and once she regained adequate physical condition, the patient was discharged in sinus rhythm on postoperative day 13. At 1, 3, 6, and 12 month follow-ups, the patient remained asymptomatic, showing marked improvement in her overall condition. At the last checkup (12 months), the patient had trace TR (Video 1). The annulus diameter, which was 41 mm preoperatively, was measured at 20 mm. The leaflet mobility and coaptation were excellent (Video 2).

Case 2

A 58-year-old female patient with a history of hospitalization due to pulmonary edema. The TTE and TEE revealed

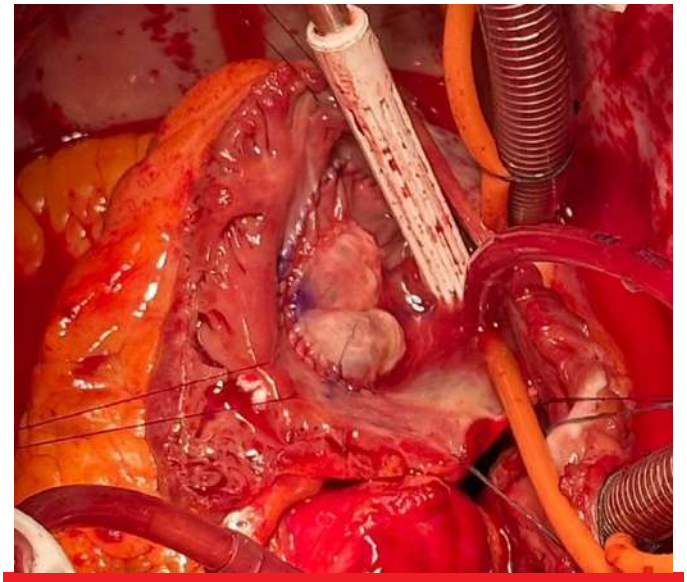

Figure 3. Surgical image of the completed repair.

severe rheumatic mitral and tricuspid insufficiency. The patient was weaned from cardiopulmonary bypass with mild inotropic support. Mild residual TR was observed on TEE. The patient remained in the intensive care unit for 2 days. Mild TR was detected on TTE on the fifth day. The annulus diameter, which was 43 mm preoperatively, was measured as 25 mm. The patient, who had an uneventful postoperative course, is scheduled for discharge once the INR level stabilizes.

DISCUSSION

With this repair, using a novel technique, favorable clinical and imaging results were achieved in a patient with secondary advanced tricuspid regurgitation. The technique focuses on the pathophysiology of secondary TR by reconstructing the annulus to the desired size, thereby achieving an effective downsizing in the valve area. Currently, the most common treatment for TR is ring annuloplasty; however, TR may not be effectively treated due to challenges such as selecting the appropriate ring size, variability in surgical experience regarding suture placement and depth, and the risk of suture dehiscence. Even in the hands of the most experienced surgeons, it may not be curative, especially in patients with significant annular dilation. Annuloplasty does not guarantee the same level of success in every patient. In fact, it has been reported that approximately 40% of patients experience recurrent TR in the long term following a seemingly successful repair.[7]

For secondary tricuspid regurgitation to develop, there must be dilation of the right ventricle and tricuspid annulus. The severity of TR and the clinical presentation are determined by the size of the annulus.[8] Tricuspid regurgitation typically occurs when the annulus diameter exceeds 33-34 mm, and as the size of the annulus increases, the regurgitant volume also proportionally increases. A critical threshold is considered at 40 mm.[9] Therefore, the effective and permanent reduction of the annular ring to which the leaflets are attached should be the primary goal of tricuspid valve repair.

In this technique, the annulus is reduced in 2 stages with 2 suture lines. The first stage involves suturing the outer circumference of the pericardial ring to the native annulus, slightly narrowing the native annulus. In the second stage, the inner circumference of the pericardial ring, where the leaflets are sutured, is adjusted to the size measured with the sizer, achieving a clear and measurable narrowing at the valve orifice. In the patient, the preoperative end-diastolic annular diameter of 41 mm was reduced to 20 mm postoperatively. The width of the pericardial ring changes according to the difference between the wide native annulus and the targeted annular size. This procedure can be easily performed by all surgeons and, most importantly, this method provides a standard success similar to that of a prosthetic valve.

In ring annuloplasty, surgical procedures are performed at the periphery of the natural annulus-valve junction, indirectly reducing the orifice. In this approach, as shown in Figure 1, all interventions are performed centrally, targeting the orifice region directly on the orifice side of the natural annulus.

The expansion of the tricuspid annulus is possible only in the anterior and posterior aspects. These correspond to the free wall of the right ventricle.[8] Due to this asymmetric nature of tricuspid annular expansion, the area between where the annulus should be and where it currently is resembles a crescent shape with its ends at the anteroseptal commissure and posteroseptal commissure and its widest point at the anteroposterior commissure. Considering the shape of this area, the pericardial patch was shaped similarly to a crescent. An asymmetrical shape with the widest part at the anteroposterior commissure was created, narrowing in both directions, with the narrowest part matching the septal leaflet annulus.

The long-term success rates of existing treatment methods decrease over time. Continued annular dilation and changes in RV geometry can lead to recurrent insufficiency after a successful repair. Therefore, to ensure durable repair, stabilization of the RV base is essential.[6] In this technique, the glutaraldehyde-treated, robust pericardial tissue, with the advantage of maintaining complete ring integrity, supports the entire annulus in a circular fashion, creating excellent stabilization at the right ventricular base. It was believed that, especially in patients with severe pulmonary hypertension and/or large annular diameters, this method will remain stable over the long term and prevent insufficiency, even in cases where recurrence is common.

The technique described is novel and has not been previously performed, although it bears some resemblance to tricuspid anterior leaflet augmentation.[10] Augmentation is used in cases where ring annuloplasty alone is insufficient and is typically combined with ring implantation. The aim is to enlarge the anterior leaflet, thereby increasing the coaptation surface. Although successful early outcomes have been reported, it has not found widespread clinical application. This may be attributed to the inability to standardize the technique, which is highly dependent on the surgeon's experience. Furthermore, it is not suitable for all cases of functional tricuspid regurgitation, and clear criteria for determining which patients would benefit from it have not yet been defined. However, it is believed that the technique can be applied to most TR cases resulting from annular dilation and tethering.

Although tricuspid valve repair was performed simultaneously with mitral valve surgery in the case, this technique is also suitable for isolated tricuspid valve procedures. Depending on the surgeon's preference, it can be performed via sternotomy or right thoracotomy, either under cross-clamp or on a beating heart.

CONCLUSION

It is believed that if the favorable clinical and imaging results seen in the initial cases are achieved in more cases, this technique will make significant contributions to the surgical treatment of secondary tricuspid regurgitation caused by annular dilation and tethering.

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

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

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Video 1: Trace tricuspid regurgitation on postoperative 6th month echocardiography.

Video 2: Visualization of valve coaptation on postoperative 6th month echocardiography.

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561-632.
2. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol*. 2004;43(3):405-409. [CrossRef]
3. Chikwe J, Anyanwu AC. Surgical strategies for functional tricuspid regurgitation. *Semin Thorac Cardiovasc Surg*. 2010;22(1):90-96. [CrossRef]
4. McCarthy PM, Bhudia SK, Rajeswaran J, et al. Tricuspid valve repair: durability and risk factors for failure. *J Thorac Cardiovasc Surg*. 2004;127(3):674-685. [CrossRef]
5. Fukuda S, Gillinov AM, McCarthy PM, et al. Determinants of recurrent or residual functional tricuspid regurgitation after tricuspid annuloplasty. *Circulation*. 2006;114(1 Suppl):I582-I587. [CrossRef]
6. Köksal C, Selçuk E, Kahveci G, Erdem H. A novel approach of tricuspid valve repair: mitralization of tricuspid valve. *Interact Cardiovasc Thorac Surg*. 2022;35(1):ivac049. [CrossRef]
7. Matsunaga A, Duran CMG. Progression of tricuspid regurgitation after repaired functional ischemic mitral regurgitation. *Circulation*. 2005;112(9 Suppl):I453-I457. [CrossRef]
8. Dreyfus GD, Corbi PJ, Chan KMJ, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg*. 2005;79(1):127-132. [CrossRef]
9. Sugimoto T, Okada M, Ozaki N, Hatakeyama T, Kawahira T. Long-term evaluation of treatment for functional Tiicuspid Regurgıtatıon Wıth regurgitant volume: characteristic Dıfferences based on Prımary Cardıac lesion. *J Thorac Cardiovasc Surg*. 1999;117(3):463-471. [CrossRef]
10. Dreyfus GD, Raja SG, John Chan KM. Tricuspid leaflet augmentation to address severe tethering in functional tricuspid regurgitation. *Eur J Cardiothorac Surg*. 2008;34(4):908-910. [CrossRef]

THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Methodological Considerations in Non-Sustained Atrial Fibrillation and Stroke Risk

LETTER TO THE EDITOR

To the Editor,

We read with great interest the study by Yurtseven et al,[1] which evaluated the association between atrial fibrillation (AF) episodes <30 seconds detected on 24-hour Holter monitoring and stroke risk, and we commend the authors for addressing this frequent clinical dilemma and for aligning their message with current European Society of Cardiology (ESC) recommendations based on CHA_2DS_2-VA scores.

That said, several aspects may limit the interpretability of the findings. First, there is an inconsistency in sample size reporting: the Abstract/Methods section states 133 non-sustained AF (NS-AF) cases, whereas the Results mention 163, and[1] again lists n = 133 for NS-AF. This discrepancy should be clarified, and the manuscript's text and tables made internally consistent. Additionally, because events occurred over a follow-up of approximately 66 ± 6 months, the use of binary logistic regression may not fully capture time-dependent risk. Sensitivity analyses using Cox proportional hazards and, if applicable, competing risk models (e.g., Fine–Gray) could provide a more robust evaluation. Furthermore, even after propensity score matching, age differences remained statistically significant, raising the possibility that the observed association between NS-AF and stroke risk may be partially explained by age. Closer matching or additional adjustment for age would strengthen the findings.

Clarifying these points and incorporating time-dependent statistical approaches would enhance the validity and clinical applicability of the study's conclusions.

Declaration of Interests: Bülent Özlek serves as an editorial board member for the following journals: Cell Cycle, Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi, Cardiovascular Diabetology – Endocrinology Reports. Other authors have no conflicts of interest to declare.

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REFERENCE

1. Yurtseven E, Ural D, Karaüzüm K, et al. Nonsustained atrial fibrillation in ambulatory ECG recording and thromboembolic events in longterm follow-up. *Anatol J Cardiol*. 2025;29(8):401-408. [CrossRef]

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Reply to Letter to the Editor: "Methodological Considerations in Non-Sustained Atrial Fibrillation and Stroke Risk"

LETTER TO THE EDITOR
REPLY

To the Editor,

We would like to thank the authors[1] for their thoughtful comments on our article[2] entitled "Nonsustained Atrial Fibrillation in Ambulatory ECG Recording and Thromboembolic Events in Long-Term Follow-Up." We would like to clarify that the number "163" stated in the first sentence of the Results section was a typographical error; the correct number of patients with nonsustained atrial fibrillation (NS-AF) included in the study was 133, and this has been corrected in the published version of the article. After propensity score matching, 20 cases were excluded, resulting in 113 patients in the NS-AF group and 113 in the control group for the subsequent analyses. Regarding the statistical approach, we did not perform Cox proportional hazards or competing risk analyses because the exact timing of stroke events could not always be determined with sufficient precision from hospital records and telephone interviews. Given this limitation, binary logistic regression was selected as the most appropriate approach to assess the association between NS-AF and stroke. Finally, although age remained statistically different between groups after matching, age was included in the multivariate model, and NS-AF persisted as an independent predictor of ischemic stroke, suggesting that the association is not solely explained by age. We appreciate these constructive remarks and believe that our clarifications address the methodological concerns and improve the interpretability of our findings.

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

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

REFERENCES

1. Akbuğa K, Tunca Ç, Özlek B, Tanık VO. Methodological considerations in non-sustained atrial fibrillation and stroke risk. *Anatol J Cardiol*. 2026;30(4):275.
2. Yurtseven E, Ural D, Karaüzüm K, et al. Nonsustained atrial fibrillation in ambulatory ECG recording and thromboembolic events in longterm follow-up. *Anatol J Cardiol*. 2025;29(8):401-408. [CrossRef]

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Translating Multimodal Intelligence into Cardiac Diagnostics: A Critical Perspective on Large Language Model–Assisted Electrogram Interpretation

LETTER TO THE EDITOR

To the Editor,

We read with great interest the study by Bozyel et al,[1] exploring scenario-based evaluation of ChatGPT-4o for intracardiac electrogram (EGM) interpretation in pacemaker patients. The staged design—from isolated signals to multiple-choice decisions—captures real diagnostic gradients, and the pairing of visual EGM inputs with device context mirrors clinical workflows in cardiac implantable electronic device (CIED) care. Repeating the experiments over 2 months and using consensus adjudication are additional strengths that facilitate a structured appraisal of repeatability. Several methodological choices, however, may constrain clinical translation.

First, the reference standard is derived from The European Heart Rhythm Association case book answers. These keys are optimized for teaching rather than for adjudicating device-specific algorithms across manufacturers.[2] Without an explicit device-vendor ground truth (e.g., programmer logs, marker channels, and algorithm state), the study risks construct drift—particularly for pacing mode, atrioventricular relationships, and pseudomalfunction, where small labeling nuances alter clinical action.

Second, the variable set includes broad constructs (e.g., "understanding") alongside technical items (e.g., "timing intervals"). Collapsing heterogeneous targets into a single accuracy figure obscures domain-specific failure modes.[3] A per-case error taxonomy with clinically anchored severities (benign vs. action-triggering mistakes such as pacing inhibition or oversensing) would reveal whether observed gains translate into safer decisions. Likewise, the "No Answer/Non-Relevant" categories may dilute misclassification rates; a pre-specified handling plan (penalization or imputation) is needed to avoid optimistic accuracy.

Third, the statistical framework mixes raw accuracy with Cohen's Kappa and Prevalence- and Bias-Adjusted Kappa across multiple features and scenarios without interval estimates or multiplicity control. Given known prevalence effects on agreement metrics, reporting CIs, decision-relevant thresholds, and a correction plan for multiple comparisons would prevent over-interpretation.[4] Calibration analyses (e.g., Brier score for probabilistic outputs or thresholded decision curves) are also needed if the goal is clinical support.

Fourth, experimental control and reproducibility require fuller disclosure. Prompt templates, system parameters (temperature, top-p), image fidelity (resolution, compression), and any pre-processing materially affect multimodal performance.[5] Without these details, replicability and fair benchmarking against electrophysiologists under time constraints remain uncertain.

To advance clinical usefulness, future work may: (i) use programmer-verified ground truth spanning major vendors and modes; (ii) define primary endpoints tied to patient management (alert triage yield in remote monitoring, detection of pacing

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inhibition/oversensing); (iii) compare against device specialists with timed reads; (iv) report per-phenotype performance with severity weighting; (v) pre-register analysis plans with CIs and correction for multiplicity; and (vi) explore manufacturer-specific fine-tuning and human-in-the-loop deployment for CIED remote monitoring. Such steps would clarify whether the observed gains in context-rich scenarios can meaningfully reduce clinician workload while maintaining safety.

In conclusion, while large language models show potential for assisting in intracardiac electrogram interpretation, their current performance remains exploratory. Robust validation with real device data, clinical benchmarks, and reproducible methods will be essential before integration into routine cardiac diagnostics.

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

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REFERENCES

1. Bozyel S, Duman AB, Dalgıç ŞN, et al. Large language models in intracardiac electrogram interpretation: A new frontier in cardiac diagnostics for pacemaker patients. *Anatol J Cardiol*. 2025;29(10):533-542. [CrossRef]
2. Arias MA. The EHRA book of interventional electrophysiology. *Rev Española Cardiol* [Internet]. Elsevier; Amsterdam. 2017;70(10):889-890. [CrossRef]
3. Orouji S, Liu MC, Korem T, Peters MAK. Domain adaptation in small-scale and heterogeneous biological datasets. *Sci Adv*. 2024;10(51):eadp6040. [CrossRef]
4. Turovsky YaA, Borzunov SV, Vahtin AA. An Algorithm for Correction of Statistical Estimations Taking into Account the Effect of Multiple Comparisons based on Test Results Grouping. *Prin*. 2022;13(3):148-152. [CrossRef]
5. Wanaskar K, Jena G, Eirinaki M. Multimodal benchmarking and recommendation of text-to-image generation models. In: 11th International Conference on Big Data Computing Service and Machine Learning Applications (BigDataService); Tucson, AZ, USA. Piscataway (NJ): IEEE; 2025. [CrossRef]

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Reply to Letter to the Editor: "Translating Multimodal Intelligence into Cardiac Diagnostics: A Critical Perspective on Large Language Model–Assisted Electrogram Interpretation"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the authors[1] for their interest in our study.[2] The scenario-based design reflects the stepwise cognitive processes involved in intracardiac electrogram (EGM) interpretation in clinical practice. Our aim was not to evaluate model performance with a single overall metric, but rather to make visible the stages of the diagnostic process in which the model performs robustly or shows vulnerability. Therefore, the assessment was structured progressively, from isolated signal analysis toward context-based decision scenarios.

The EHRA case book was chosen as an initial reference because it provides an accessible and standardized assessment framework. This offers a neutral and reproducible test environment; our study does not propose EHRA as the absolute clinical gold standard.

The heterogeneity of the evaluated variables was a deliberate methodological choice to map the distribution of errors. Each variable was reported independently, and the result tables clearly demonstrate that the model is more fragile particularly in the interpretation of pacing mode and chamber relationships.

Due to class prevalence imbalance in certain EGM categories, using Cohen's Kappa alone could underestimate agreement. Therefore, the addition of PABAK represents a standard statistical adjustment to ensure a more accurate and balanced interpretation of the results.

This study is not a model optimization attempt, but an observational evaluation of raw usage behavior. Thus:

- No prompt optimization,
- No image preprocessing,
- No parameter tuning was applied. The intention was to approximate real-world clinical interaction conditions as closely as possible.

The suggestions raised in the letter are consistent with the scope and limitations already stated in our manuscript. The model:

- Is not intended to act as an autonomous clinical decision-maker,
- May serve as an assistive tool in selected situations,
- Requires additional validation before any clinical deployment.

The main contribution of this study is the first systematic characterization of the diagnostic behavior profile of large language models in EGM interpretation.

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REFERENCES

1. Sah SS, Kumbhalwar A. Translating multimodal intelligence into cardiac diagnostics: a critical perspective on large language model-assisted electrogram interpretation. *Anatol J Cardiol*. 2026;30(4):277-278.
2. Bozyel S, Duman AB, Dalgıç ŞN, et al. Large language models in intracardiac electrogram interpretation: a new frontier in cardiac diagnostics for pacemaker patients. *Anatol J Cardiol*. 2025;29(10):533-542. [CrossRef]

THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Revisiting Triglyceride-Glucose Index in HCM and HFpEF: Clarifying Confounders and Interpretative Limitations

LETTER TO THE EDITOR

To the Editor,

We read with great interest the study by Liu et al[1] investigating the association between the triglyceride-glucose (TyG) index and prognosis in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF).[1] The finding that higher TyG levels were associated with lower all-cause and cardiovascular mortality is intriguing, as it challenges the well-established adverse role of insulin resistance in cardiovascular disease. Several methodological and clinical aspects warrant clarification before these findings can be integrated into clinical interpretation.

The study measured TyG values at "admission," but did not clarify whether patients were enrolled during acute decompensation, elective hospitalization, or outpatient evaluation. Since metabolic and hemodynamic profiles vary significantly across these contexts, the absence of this information restricts the interpretation of TyG's prognostic significance. Although all participants were symptomatic (NYHA class II-IV, NT-proBNP ≥300 pg/mL), these inclusion criteria alone do not confirm an acute heart failure state. Given that metabolic indices fluctuate under acute stress, distinguishing between acute and chronic presentations is crucial for accurate prognostic assessment.

A paradoxical observation was that the highest TyG quartile, which also had the highest prevalence of diabetes (21.3%), exhibited the most favorable survival outcomes.[1] The authors hypothesized that this reflects adaptive metabolic remodeling in HCM, where glucose oxidation becomes a compensatory energy pathway under chronic pressure overload.[1] However, subgroup analyses by diabetes status were not reported, limiting mechanistic inference.

Therapeutic management variables likely influenced outcomes. Despite an atrial fibrillation prevalence of 21.7%, only 13.3% of patients were anticoagulated.[1] Such underuse could have increased the incidence of cardiovascular events, confounding survival differences. Additionally, digoxin use, discouraged in obstructive HCM due to potential worsening of outflow obstruction, was significantly higher in the lowest TyG quartile (6.6% vs. 1.8%, $P = .049$). Furthermore, data on aldosterone antagonists, SGLT2 inhibitors, and device therapy (implantable cardioverter defibrillator or pacemaker) were not provided. Contemporary HCM and HFpEF management guidelines emphasize evidence-based therapies and comprehensive device consideration to improve survival outcomes.[2,3]

Echocardiographic data also appear incomplete. While the authors reported left atrial diameter, neither left atrial volume index nor left ventricular mass index was included, despite their established roles in HFpEF diagnosis and phenotyping.[4]

In summary, Liu et al[1] provide a thought-provoking contribution suggesting that higher TyG levels may represent adaptive metabolic remodeling rather than maladaptive insulin resistance in HCM-HFpEF. However, incomplete data on clinical recruitment, diabetes stratification, medical therapy, and structural characterization limit interpretability. Future prospective studies incorporating standardized

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heart failure management, advanced metabolic imaging, and explicit differentiation of acute versus chronic HF states are required to validate whether TyG reflects true metabolic adaptation or residual confounding.

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REFERENCES

1. Liu L, Zheng Y, Ma H, et al. Association between triglyceride-glucose index and prognosis of patients with hypertrophic cardiomyopathy and heart failure with preserved ejection fraction. *Anatol J Cardiol*. 2025;29(11):619-629. [CrossRef]
2. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-3639. [CrossRef]
3. Ommen SR, Ackerman MJ, Ashley EA, et al. AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2024;83(10):1121-1202.
4. Gehlken C, Screever EM, Suthahar N, et al. Left atrial volume and left ventricular mass indices in heart failure with preserved and reduced ejection fraction. *ESC Heart Fail*. 2021;8(4):2458-2466. [CrossRef]

THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Reply to the Letter to the Editor: "Revisiting Triglyceride-Glucose Index in HCM and HFpEF: Clarifying Confounders and Interpretative Limitations"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the readers for their thoughtful comments[1] and interest in our study investigating the association between the triglyceride-glucose (TyG) index and prognosis in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF). We appreciate the opportunity to clarify several key methodological and clinical aspects raised in the letter.

The readers emphasize the importance of the clinical context in which TyG was measured. Our study predominantly enrolled patients during stable clinical states, primarily from outpatient or elective hospital evaluations. We acknowledge that in a retrospective multicenter study, it is challenging to uniformly ascertain and document the acuteness of presentation for every patient. This is a recognized limitation of the study design. However, to mitigate the potential confounding effect of acute hemodynamic stress on our primary findings, our statistical models extensively adjusted for key markers of disease severity and potential instability, including New York Heart Association class, N-terminal pro-B-type natriuretic peptide levels, systolic blood pressure, and renal function.[2] This helps to control for the influence of clinical status on the observed associations. We agree with the readers that future prospective studies should explicitly stratify enrollment based on acute versus chronic status to validate and refine these findings.

The observation that the highest TyG quartile was associated with better survival is indeed intriguing. We agree that subgroup analyses by diabetes status would have been informative. In fact, as presented in Figure 4, a pre-specified subgroup analysis based on diabetes status was indeed performed.[2] The results demonstrated that the association between a higher TyG index and reduced risk of all-cause mortality (Figure 4A) and cardiovascular mortality (Figure 4B) was consistent in both non-diabetic and diabetic subgroups. Specifically, in non-diabetic patients, the TyG index was significantly associated with lower all-cause mortality (hazard ratio (HR): 0.63, 95% CI: 0.48-0.82, $P = .001$) and cardiovascular mortality (HR: 0.49, 95% CI: 0.35-0.68, $P < .001$). In diabetic patients, the point estimates for the TyG index also suggested a trend toward reduced risk for both all-cause mortality (HR: 0.92, 95% CI: 0.53-1.58, $P = .755$) and cardiovascular mortality (HR: 0.89, 95% CI: 0.45-1.78, $P = .750$), although these associations did not reach statistical significance, likely due to the small sample size of this subgroup (n = 137, 12.5% of the cohort). Critically, the P-values for interaction for diabetes status were non-significant ($P = .213$ for all-cause mortality and $P = .097$ for cardiovascular mortality). This indicates that the relationship between the TyG index and survival outcomes was not statistically different between diabetic and non-diabetic patients. The protective trend observed in the overall cohort was thus consistent across diabetes status, strengthening the notion that the TyG index may reflect a broader metabolic state relevant to HCM-HFpEF prognosis, rather than being merely a proxy for diabetic dysglycemia.

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We acknowledge the readers' concerns regarding the underuse of anticoagulation in atrial fibrillation and the uneven distribution of digoxin use across TyG quartiles. Our multivariable models adjusted for a wide range of clinical covariates. However, we recognize that unmeasured or residual confounding, such as differential use of sodium-dependent glucose transporters 2 inhibitors, aldosterone antagonists, or device therapy may persist. Future prospective studies should incorporate detailed treatment data to better account for these factors.

Although left atrial volume index and left ventricular mass index are valuable in HFpEF phenotyping, our diagnostic criteria for HFpEF incorporated multiple echocardiographic parameters. Echocardiographic parameters for the diagnosis of HFpEF in our study include septal early diastolic mitral annular velocity (e') <7 cm/s, lateral e' <10 cm/s, tricuspid regurgitation velocity >2.8 m/s, left atrial volume index >34 mL/m^2, left ventricular ejection fraction ≥50%, E/e' >8, and E/A ≤0.8, or defined according to reported diastolic dysfunction.[2] While left ventricular mass index was not routinely available in this multicenter retrospective cohort, we include other structural and functional indices to minimize bias.

In conclusion, we agree that the relationship between the TyG index and prognosis in patients with HCM and HFpEF is complex and may reflect both metabolic adaptation and residual confounding. This highlights the need for prospective studies incorporating standardized metabolic imaging, detailed phenotyping, and comprehensive treatment data.

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REFERENCES

1. Bektaş H, Akkaya F, Hoşoğlu Y. Revisiting triglyceride glucose index in HCM and HFpEF: clarifying confounders and interpretative limitations. *Anatol J Cardiol*. 2026;30(4):281-282.
2. Liu L, Zheng Y, Ma H, et al. Association between triglyceride-glucose index and prognosis of patients with hypertrophic cardiomyopathy and heart failure with preserved ejection fraction. *Anatol J Cardiol*. 2025;29(11):619-629. [CrossRef]

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When Myxoma Jumps Chambers: Direct Seeding from Left Atrium to Right Ventricular Outflow Tract via Patent Foramen Ovale

E-PAGE ORIGINAL IMAGE

A 57-year-old man presented with progressive exertional dyspnea and paroxysmal nocturnal dyspnea over 2 weeks. On auscultation, a low-pitched diastolic rumbling murmur was audible at the apex. Transthoracic echocardiography revealed a large, mobile mass (7.5 × 4.5 cm) attached to the mid-atrial septum, prolapsing into the mitral orifice during diastole and generating a mean transvalvular gradient of 32 mm Hg (Figure 1A). Strikingly, a second, well-circumscribed mass (2.7 × 2.0 cm) was identified in the right ventricular outflow tract, with no internal vascularity on Doppler imaging (Figure 1B). Contrast-enhanced cardiac computed tomography confirmed dual intracardiac masses and visualized a patent foramen ovale (PFO) connecting the 2 chambers (Figure 1C–E). Both tumors were surgically resected (Figure 1F–G), and histopathology confirmed identical benign myxoma morphology in both specimens—stellate cells embedded in a myxoid stroma (Figure 1H). The patient recovered uneventfully and remained recurrence-free at 2-year follow-up.

Cardiac myxoma, the most common primary cardiac tumor, typically presents as a solitary lesion with approximately 75% occurring in the left atrium.[1,2] While

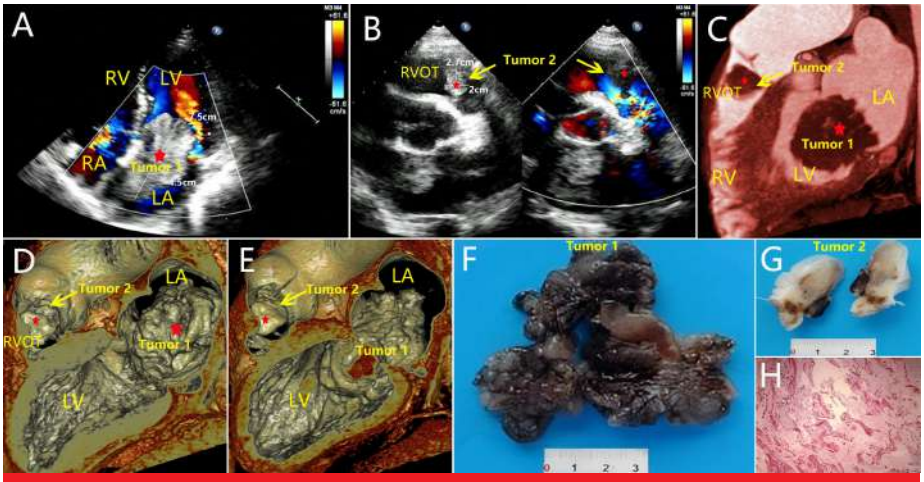

Figure 1. (A-B) Transthoracic echocardiography showing a large, mobile mass (7.5 × 4.5 cm) attached to the mid-atrial septum, prolapsing into the mitral orifice during diastole with a mean transvalvular gradient of 32 mm Hg (A), and a second well-circumscribed mass (2.7 × 2.0 cm) in the right ventricular outflow tract with no internal vascularity on Doppler imaging (B). (C-E) Contrast-enhanced cardiac computed tomography confirming dual intracardiac masses and visualizing a patent foramen ovale (PFO). (F-G) Intraoperative photographs of the surgically resected left atrial mass (F) and right ventricular outflow tract mass (G). (H) Histopathological examination (hematoxylin and eosin staining, ×200) confirming identical benign myxoma morphology in both specimens, characterized by stellate cells embedded in a myxoid stroma with similar cellular density and distribution patterns.

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multifocal myxomas occur in 7-10% of cases, they usually follow genetic syndromes and maintain chamber-specific localization.[3] Simultaneous involvement of the left atrium and right ventricle is exceedingly rare. We report a unique case where a left atrial myxoma directly seeded into the right ventricular outflow tract through a PFO, without right atrial involvement. Our multimodal imaging approach provided definitive evidence of this rare phenomenon, underscoring a critical clinical implication: comprehensive four-chamber echocardiographic evaluation is essential in all cardiac myxoma cases with interatrial communications, as standard assessment limited to anatomically adjacent chambers may miss distal seeding sites.[4] For patients with cardiac myxoma and PFO, systematic four-chamber echocardiographic evaluation holds significant clinical value in identifying atypical dissemination patterns and guiding appropriate therapeutic strategies.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author.

Informed Consent: This report has obtained the patient's informed consent for the publication of their anonymized clinical data.

Declaration of Interests: All authors have read and approved submission of the manuscript and have no conflict of interest to disclose.

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REFERENCES

1. Okongwu CC, Olaofe OO. Cardiac myxoma: a comprehensive review. *J Cardiothorac Surg*. 2025;20(1):151. [CrossRef]
2. Alhasso AA, Ahmed OF, Mohammed-Saeed DH, et al. Operative management and outcomes in patients with myxomas: a single-center experience. *Front Surg*. 2023;10:1084447. [CrossRef]
3. Yalta K, Yetkin E, Yalta T. Recurrent cardiac myxoma: a puzzle to be solved. *Anatol J Cardiol*. 2023;27(8):497-498. [CrossRef]
4. De Martino A, Pattuzzi C, Garis S, et al. A comprehensive review of cardiac tumors: imaging, pathology, treatment, and challenges in the third millennium. *Diagnostics (Basel)*. 2025;15(11):1390. [CrossRef]

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Adolescent with Unexplained Cardiac Hypertrophy, Ventricular Pre-Excitation, Conduction System Disease: *PRKAG2* Cardiac Syndrome as a Rare Mimicker of Hypertrophic Cardiomyopathy

E-PAGE ORIGINAL IMAGE

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A 19-year-old male presented to the hospital with chest pain and recurrent syncope. Electrocardiogram and Holter monitoring demonstrated right bundle branch block, left anterior fascicular block, intermittent ventricular pre-excitation, and left ventricular hypertrophy (Figure 1A and B). Echocardiography revealed uniform hypertrophy of the interventricular septum and left ventricle. No significant left ventricular outflow tract obstruction or systolic anterior motion of the mitral valve was observed at rest (Figure 1C and D; Videos 1 and 2). Cardiac magnetic resonance imaging demonstrated biventricular hypertrophy, with evidence of myocardial edema, injury, and fibrosis in hypertrophied regions (Figure 1E-H; Video 3). Based on these initial findings, a preliminary diagnosis of hypertrophic cardiomyopathy was made. Clinical whole-exome sequencing (WES) identified a heterozygous missense rare variant in the *PRKAG2* gene (chr7:151576412; c.905G>A; p.Arg302Gln) (Figure 2A and B). The patient was definitively diagnosed with *PRKAG2* cardiac syndrome.

PRKAG2 cardiac syndrome is a rare autosomal dominant genetic disorder caused by variants in the *PRKAG2* gene, which encodes the γ2 regulatory subunit of 5′-adenosine monophosphate-activated protein kinase.[1] Hallmark features include ventricular preexcitation, supraventricular arrhythmias, conduction system disease, and cardiac hypertrophy.[2] *PRKAG2* cardiac syndrome is frequently misdiagnosed as hypertrophic cardiomyopathy; thus, genetic testing is warranted in patients clinically diagnosed with hypertrophic cardiomyopathy. This case emphasizes that clinicians should consider *PRKAG2* cardiac syndrome in adolescents presenting with myocardial hypertrophy, ventricular pre-excitation, and conduction system disease.

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

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

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Video 1: Echocardiography revealed uniform hypertrophy of the interventricular septum and left ventricle.

Video 2: No significant left ventricular outflow tract obstruction or systolic anterior motion of the mitral valve was observed at rest.

Video 3: The short-axis cine images of the entire heart demonstrate uniform hypertrophy of the interventricular septum and left ventricular myocardium. The hypertrophied segments exhibit reduced wall motion amplitude and decreased systolic wall thickening rate.

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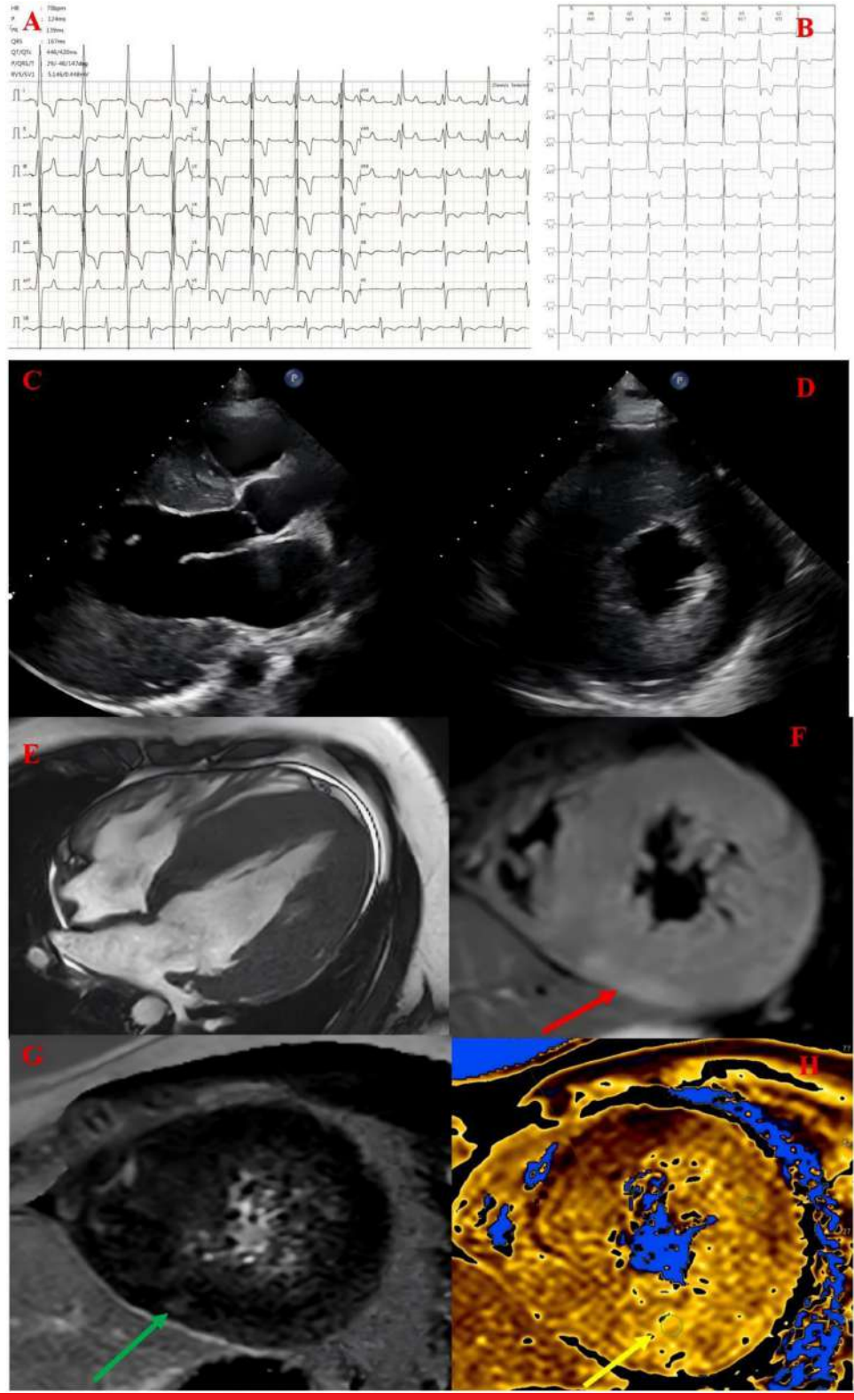

Figure 1. (A) Electrocardiography demonstrated right bundle branch block, left anterior fascicular block, left ventricular hypertrophy, abnormal Q waves in the high lateral leads, and nonspecific ST-T changes; (B) 24-hour Holter Monitoring: Revealed intermittent ventricular pre-excitation, characterized by the occasional presence of delta waves and a short PR interval, suggestive of an accessory pathway; (C-D) Echocardiography revealed uniform hypertrophy of the interventricular septum and left ventricle; (E-F) Cardiac magnetic resonance imaging demonstrates uniform left ventricular hypertrophy with myocardial edema (red arrow); (G) Quantitative T2 mapping revealed myocardial edema with prolonged relaxation times (66.3 ms, green arrow); (H) Cardiac magnetic resonance imaging demonstrates myocardial fibrosis (yellow arrow).

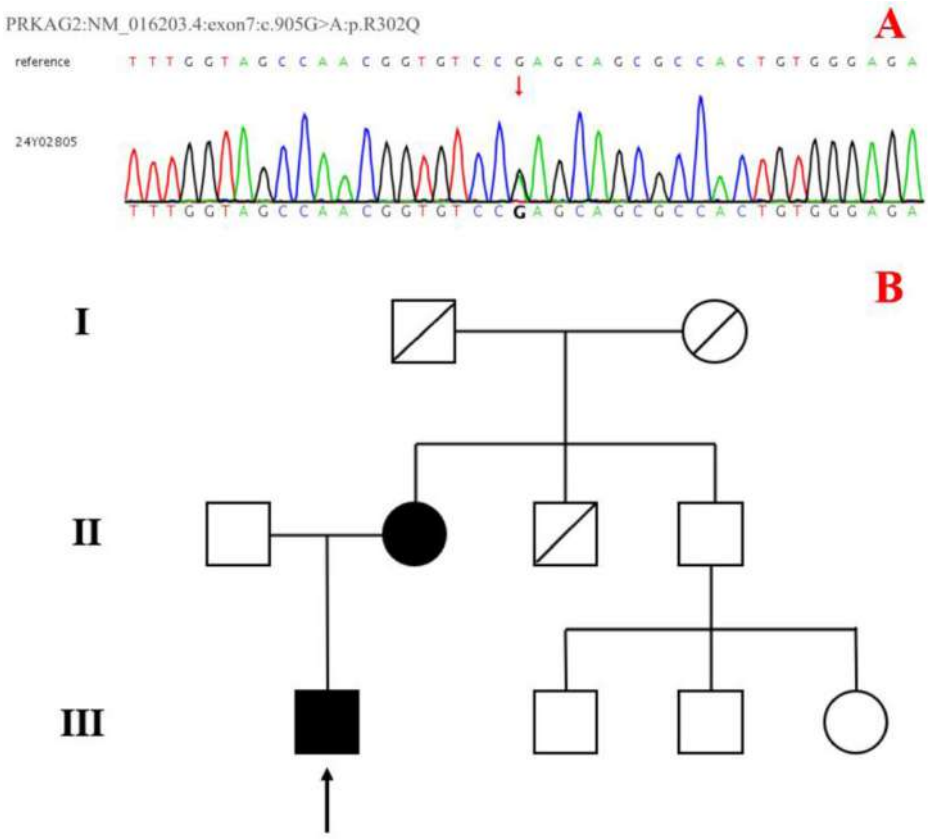

Figure 2. (A) Whole-exome sequencing (WES) identified a heterozygous missense rare variant in the *PRKAG2* gene (chr7:151576412; c.905G>A; p.Arg302Gln), resulting in substitution of arginine by glutamine at codon 302; (B) Pedigree of the family. Whole-exome sequencing revealed that the patient's mother carries the same rare variant, while the father, one of the maternal uncles, and the maternal uncle's three children do not carry the rare variant. The maternal grandparents and another maternal uncle are deceased, and their status is unknown. (The proband is indicated by a black arrow; filled symbols represent carriers of the rare variant, unfilled symbols represent non-carriers; circles represent female family members, squares represent male family members; a slash through the symbol indicates deceased family members).

REFERENCES

1. Porto AG, Brun F, Severini GM, et al. Clinical spectrum of *PRKAG2* syndrome. *Circ Arrhythm Electrophysiol*. 2016;9(1):e003121. [CrossRef]
2. Cheng WP, Song XW, Zhang BL. Research progress of *PRKAG2* cardiac syndrome. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2024;52(8):966-972. [CrossRef]