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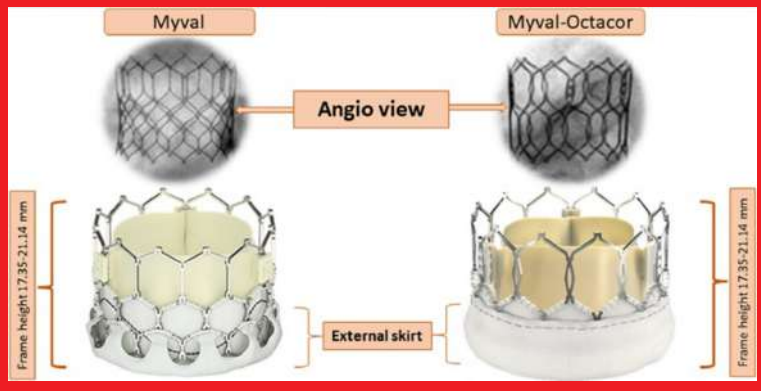
Original Investigations



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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 Alassisted technologies as an author or co-author, nor cite AI as an author. Authors should be able to assert that there is no plagiarism in their paper, including in text and images produced by the AI. Humans must ensure there is appropriate attribution of all quoted material, including full citations.

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1. Title Page

2. Main Text

3. Tables, Graphs and Figures

4. Copyright Transfer Form

5. Author Contribution Form

6. ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

1. Title Page

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

2. Main Text

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

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

B. References

C. Special Terms and Conditions

A. Manuscript types

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

- **Editorial Comment**

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

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

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Headings (MeSH) terms prepared by the National Library of Medicine (NLM) and should be provided just below the abstract.
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- Abstract: It should not include subheadings and it should be limited to 250 words.
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  Manuscripts which announce a new scientific invention, are clinically significant, and are in the form of a preliminary report are accepted for publication as scientific letters.
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- Abstract and Keywords should not be included.
- For scientific letters submitted by Turkish authors or from Türkiye, the Title should also be provided in Turkish. For letters submitted by foreign authors outside Türkiye, the translation of these sections will be carried out by Editor-in-Chief's Office.

- **Case Report**
  Since a limited number of case reports is published, only reports which are related to rare cases and conditions that constitute challenges in diagnosis and treatment, offer new methods or suggest knowledge not included in books, and are interesting and educational are accepted for publication.
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- Main Text: It should include Introduction, Case Report, Discussion and Conclusion sections and should not exceed 700 words excluding the references.
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- Tables, Figures and Images: They should be provided after the reference list according to their order of appearance in the text and should be limited to two.
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NOTE 1: Case reports that include video images have a better chance of publication.

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  Impressive and rare images that reflect significant findings based on clinical science,
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  introduce new treatment methods are accepted for publication.
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  Letters to the Editor aim to discuss the importance of a manuscript previously published in the journal. This type of manuscripts should also include a comment on the published manuscript. Moreover, articles on topics of interest to readers within the scope of the journal, especially on educational issues, can be published in the format of a Letter to the Editor.
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  These articles include current information on research and publication ethics and also cases of ethical violation.
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Images obtained directly or on operation, visuals revealed through EKG and/or imaging methods, and macroscopic-microscopic anatomical, pathological findings of attentiongrabbing and rare cases can be published. Unlike original images, the diagnosis and outcome of the case and image are hidden at the beginning in diagnostic puzzles. Four multiple-choice questions are prepared. In the following pages of the journal, the correct answer in terms of precise diagnosis and outcome is given with an explanation and didactic images and then discussed. The Editor-in-Chief will convert suitable images into the format of a diagnostic puzzle with the authors' permission.

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

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

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

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

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

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

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

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

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

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

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- Tables, Graphs, Figures and other visuals should be numbered in the order of their citation within the text and names of patients, doctors and institutions should not be disclosed.
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- Tables should not be submitted in JPEG, TIFF or other visual formats. For microscopic images, the magnification ratio and staining technique used should be specified in addition to figure legends.
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- The thickness of the lines in graphs should be sufficient to minimize loss of quality if size reduction is needed during the printing process. The width of the graphs should be 9 cm or 18 cm. Drawings should be performed by professionals. No grey colours should be used.
- Abbreviations should be explained in alphabetical order at the bottom of the tables, graphs and figures
- Roman numbers should be avoided in tables and figures within the text and their titles.
- Decimal numbers used in text, tables and figures should be separated by commas in Turkish sections and by dots in English sections.
- Tables should be easily understandable and should not repeat the data in the main text.
- In addition to the pictures included in case reports and original images, video and movie images are published on the journal's website. These images should be prepared in MPEG format with a maximum size of 2 MB. They should be submitted to the journal with the manuscript documents. The names of patients, doctors, institutions and places should be omitted from all documents.

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

EVALUATION AND PUBLICATION

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

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Şafak et al from Türkiye evaluated the effects of pulmonary rehabilitation on respiratory and echocardiographic parameters in patients with primary lung disease. Look at the improvement in both respiratory and cardiac functions and quality of life.

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Intermediate-high-risk pulmonary embolism is defined by right ventricular dysfunction and elevated cardiac troponin in the absence of hemodynamic instability. While full-dose thrombolysis may improve outcomes, it poses a high bleeding risk. So Kültürsay et al from Türkiye assessed the safety and efficacy of a reduced-dose, slow-infusion thrombolytic regimen. What happened?

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

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

Çetin Erol

Editor-in-Chief, Ankara, Türkiye

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Myval versus Contemporary Valves in Patients Undergoing Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis

ABSTRACT

Background: Myval is a balloon-expandable valve (BEV) used in transcatheter aortic valve implantation (TAVI) with distinguished features. Data comparing Myval with contemporary transcatheter heart valves (THVs) is limited. The authors performed a meta-analysis of studies comparing Myval with contemporary THVs (Sapien series and Evolut series).

Methods: The authors searched PubMed, EMBASE, and Cochrane databases. The primary composite endpoint of early safety (freedom from death and major complications) and other outcomes were extracted as defined by the Valve Academic Research Consortium 3 (VARC 3). The authors computed risk ratios (RRs) with 95% CIs using a Mantel–Haenszel method with a random-effects model with Review Manager (Cochrane Collaboration).

Results: Six studies with 2084 patients were included. Myval had better early safety at 30 days as per VARC 3 (RR 1.12; 95% CI: 1.02-1.22; *P* = .01) and lower need for permanent pacemaker implantation (PPI) (RR 0.62; 95% CI: 0.45-0.86; *P* = .004). Other outcomes were comparable in both groups. Vis-à-vis Evolut, Myval had better 30-day device success and lower rates of moderate or severe paravalvular leak (PVL) in addition to better early safety and lower need for PPI. Subgroup analyses of Myval with Sapien showed non-inferiority of Myval.

Conclusion: Myval showed better safety and lower need for PPI and may become a promising alternative for concurrent THVs.

Keywords: Aortic valve replacement, interventional cardiology, Myval, transcatheter aortic valve implantation, valve disease

META-ANALYSIS

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a minimally invasive procedure for symptomatic and asymptomatic patients with severe aortic valve stenosis.[1] Previously considered a preferred treatment in patients with high risk for surgical aortic valve replacement,[2-6] it has become a treatment of choice in intermediate- and low-risk patients as well.[7-10] There are mainly 2 types of transcatheter heart valves (THVs) used in TAVI: balloon-expandable THV (BEV) and self-expandable THV. The former include Sapien family (Edwards Lifesciences, USA) and Myval family (Meril, India). Self-expandable THVs include Evolut R/Pro (Medtronic, USA), Navitor (Abbott Cardiovascular, USA), Acurate Neo, Acurate Neo 2 (Boston Scientific, USA), Allegra (Biosensors, Singapore), and Hydra THV (Sahajanand Medical Technologies, India). Self-expandable THVs with supra-annular leaflet position provide larger effective orifice area with lower gradients but a relatively increased chance of PVL as well as a need for permanent pacemaker implantation (PPI).[11,12]

Myval (Meril, India) is a novel BEV that has 1.5 mm incremental sizing capacity providing more accurate and precise annular matching. It does have extra-large sizes as well (30.5 mm and 32 mm).[13,14] It also has a lower unit cost compared to traditionally used THVs like Sapien or Evolut series. Myval has a 40-50% cost benefit when compared to Sapien or Evolut series THVs. However, Myval is CE

(Conformity to European standards) approved whereas Sapien and Evolut series THVs are CE as well as USFDA (United States Food and Drug Administration) approved for use in TAVI. Hence, Sapien and Evolut series THVs have much more acceptance globally. Myval Octacor is the newly designed version of Myval THV. It has the same frame height as the previous Myval version (17.35-21.14 mm) but only 2 rows of identical octagonal cells which reduce the foreshortening during expansion and facilitate accurate deployment (Figure 1). Moreover, it has a better-designed crimping process in which it is directly mounted on its balloon delivery system, which reduces the need for in situ maneuvering. This minimizes the procedural steps and ensures procedural success with less effort. A low-profile 14Fr Python introducer sheath is suitable for all Myval THV diameters (from 20 mm to 32 mm) with full retrievability in case the annulus cannot be crossed. The external skirt in Myval Octacor THV is up to 50% of the frame height which minimizes the propensity for paravalvular leak (PVL). A landing zone marker toward the ventricular end of the Navigator Inception THV delivery system facilitates precise positioning of Myval Octacor THV at the annulus.[15]

The safety and efficacy of Myval have been suggested in multiple studies, including in high, intermediate, and low-risk symptomatic severe aortic stenosis, as well as in patients with bicuspid aortic valve morphology.[16-25] Myval has been studied for long-term outcomes in patients undergoing TAVI and found to be safe and effective.[26] Further research has also shown that the need for PPI after TAVI with Myval can be predicted beforehand by using aortic knob calcification, which is a useful tool for planning the procedure.[27]

Myval has not been extensively studied in comparison to the contemporary THVs. There have been a few observational studies in the past comparing Myval with other THVs.[20,22-24,28] Vast majority of the data with Myval has been generated using Myval Gen 1 and Myval Octacor has been studied in a small number of patients. Recently, 1 RCT compared Myval THV with contemporary THVs, including Sapien THV series and Evolut THV series, and found that Myval THV is non-inferior to contemporary THVs for the primary endpoint, which was a composite of VARC-3[29] defined endpoints at 30 days.[30] How this data fares collectively is unknown. Considering its cost-effectiveness and ease of use, Myval may gain global acceptance provided further regulatory approvals. Large data is required for any change in the regulatory status of Myval as well as widespread acceptance in the global healthcare sector. The authors conducted a systematic review and meta-analysis to assess the aggregate data of studies comparing Myval THV with contemporary THVs.

HIGHLIGHTS

- Myval is a novel, low-cost and broadly available BEV.
- Myval appears to be safe and effective compared to Sapien series and fares better than Evolut in 30-day outcomes.
- Further larger and longer duration randomized controlled trials are needed to compare Myval with contemporary THVs.

METHODS

Eligibility Criteria

This systematic review and meta-analysis was performed and reported in accordance with the Cochrane Collaboration Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines.[31,32]

The authors included studies that met all the following eligibility criteria: (1) observational studies or randomized controlled trials (RCTs); (2) comparing Myval THV to contemporary THVs (Sapien or Evolut or both); and (3) enrolling patients who underwent TAVI for severe aortic stenosis. In addition, studies were only included if they reported any of the outcomes of interest.

Search Strategy

The authors systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials from inception to June 2024 with the following search terms: "Myval," "Evolut," "Sapien," "Transcatheter Aortic Valve Replacement," "balloon-expandable valves," and "self-expandable valves."

The references from all included studies, previous systematic reviews, and meta-analyses were also searched manually for any additional studies. Two authors (H.A. and L.C.) independently extracted the data following predefined search criteria and quality assessment. The prospective meta-analysis protocol was registered on PROSPERO under protocol ID CRD42024562100.

End Points

Primary endpoint was a composite of clinical endpoints defined as "Early Safety" as per VARC 3 criteria, which translates to freedom from all-cause mortality; stroke; VARC type 2-4 bleeding; major vascular, access related or cardiac structural complication; stage 3 or 4 AKI; moderate or severe aortic regurgitation; new PPI; surgery or intervention related to device. Secondary endpoints included outcomes like technical success, procedural death, valve embolization or malpositioning, coronary artery occlusion, annulus rupture, major vascular complication, major bleeding, moderate or severe PVL, need for PPI, 30-day device success, all-cause mortality, cardiovascular (CV) mortality, acute kidney injury (AKI), stroke, and myocardial infarction (MI).

VARC 3

Thirty-day device success was defined by VARC 3, which translates to technical success; intended performance of the THV; freedom from mortality or surgery or intervention related to the device; and freedom from major vascular, access related or cardiac structural complications.[29] Major bleeding was defined as VARC type 2-4 bleeding events, which are defined as follows.

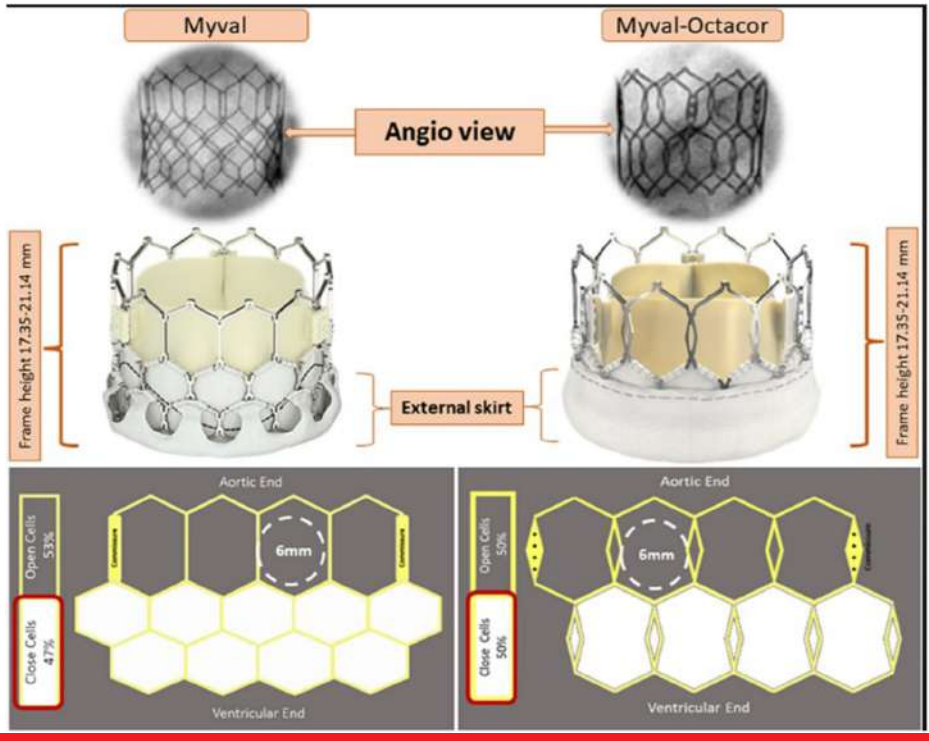

Figure 1. Features and differences between Myval and Myval Octacore devices.

Type 2

- Overt bleeding that requires a transfusion of 2-4 units of whole blood/red blood cells.
- Overt bleeding associated with a hemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/day (<3.1 mmol/L).

Type 3

- Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial associated with hemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome.
- Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mm Hg lasting >30 minutes and not responding to volume resuscitation) or requiring vasopressors or surgery.
- Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding.
- Post-thoracotomy chest tube output ≥ 2 L within a 24-hour period.
- Overt bleeding requiring a transfusion of ≥ 5 units of whole blood/red blood cells.
- Overt bleeding associated with a hemoglobin drop ≥ 5 g/dL (≥3.1 mmol/L).

Type 4

- Overt bleeding leading to death. Should be classified as:
- Probable: Clinical suspicion.
- Definite: Confirmed by autopsy or imaging.

Major vascular complications as per VARC 3 include any one of the following: aortic dissection or aortic rupture; vascular injury or compartment syndrome resulting in death, VARC type ≥ 2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment; distal embolization from a vascular source resulting in death, amputation, limb or visceral ischemia, or irreversible end-organ damage; unplanned endovascular or surgical intervention resulting in death, VARC type ≥ 2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment; and closure device failure resulting in death, VARC type ≥ 2 bleeding, limb or visceral ischemia, or irreversible neurologic impairment.[29]

The authors performed subgroup analyses comparing Myval with self-expandable THV Evolut series and Myval with BEV Sapien series.

Statistical Analysis and Software

The authors used DerSimonian and Laird random effects models, as recommended by the Cochrane Collaboration, in anticipation of high heterogeneity. Risk ratios (RRs) with 95% CIs were used to compare treatment effects for categorical endpoints. Cochran Q test and I^2 statistics were used to assess for heterogeneity; *P* values inferior to 0.10 and I^2 > 25% were considered significant for heterogeneity. Review Manager Web (manufactured in 2022 by The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis.[33]

Quality Assessment

Nonrandomized studies were appraised with the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.[34] Quality assessment of RCT was performed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (ROB-2), in which studies are scored as high, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting biases.[35]

Publication bias was investigated by funnel-plot analysis of point estimates according to study weights. The authors performed sensitivity analyses of early safety and need for PPI outcomes with leave-one-out method.

Subgroups and Sensitivity Analyses

Myval was compared with Evolut and Sapien series THVs in subgroup analyses. The authors also performed a sensitivity analysis with the leave-one-out method. The authors performed odds ratio (OR) as well as risk difference for selected outcomes in sensitivity analyses.

RESULTS

Study Selection and Baseline Characteristics

As detailed in Figure 2, the initial search yielded 218 results. After removal of duplicate records and ineligible studies, 9 remained and were fully reviewed based on inclusion criteria. Of these, a total of 6 studies were included, comprising 2084 patients from 1 RCT[30] and 5 observational studies.[20,22-24,28]

A total of 892 (42.8%) patients received Myval and 1192 (57.2%) received contemporary THVs. Study characteristics are reported in Table 1. Mean age ranged from 73 years to 83 years. Male patients constituted 59.4% of the total population. Significant between-study variability existed as to follow-up periods (Table 1). Mean society of thoracic surgeons (STS) scores ranged between 2.6% and 4.7% across studies.

Pooled Analysis of All Included Studies

Myval had higher early safety at 30 days (RR 1.12; 95% CI 1.02-1.22; P = .01; I^2 = 58%; Figure 3A demonstrates better early safety with Myval) and lower need for PPI (RR 0.62; 95% CI 0.45-0.86; P = .004; I^2 = 34%; Figure 3B depicting lower need for PPI with Myval) as compared to contemporary THVs.

Technical success (RR 1; 95% CI 0.96-1.03; P = .76; I^2 = 64%); procedural death (RR 0.77; 95% CI 0.08-7.23; P = .82; I^2 = 28%); valve embolization or malpositioning (RR 0.72; 95% CI 0.25-2.08; P = .54; I^2 = 0%); coronary artery occlusion (RR 0.57; 95% CI 0.15-2.09; P = .39; I^2 = 0%); annulus rupture (RR 0.70; 95% CI 0.11-4.28; P = .70; I^2 = 0%); major vascular complication

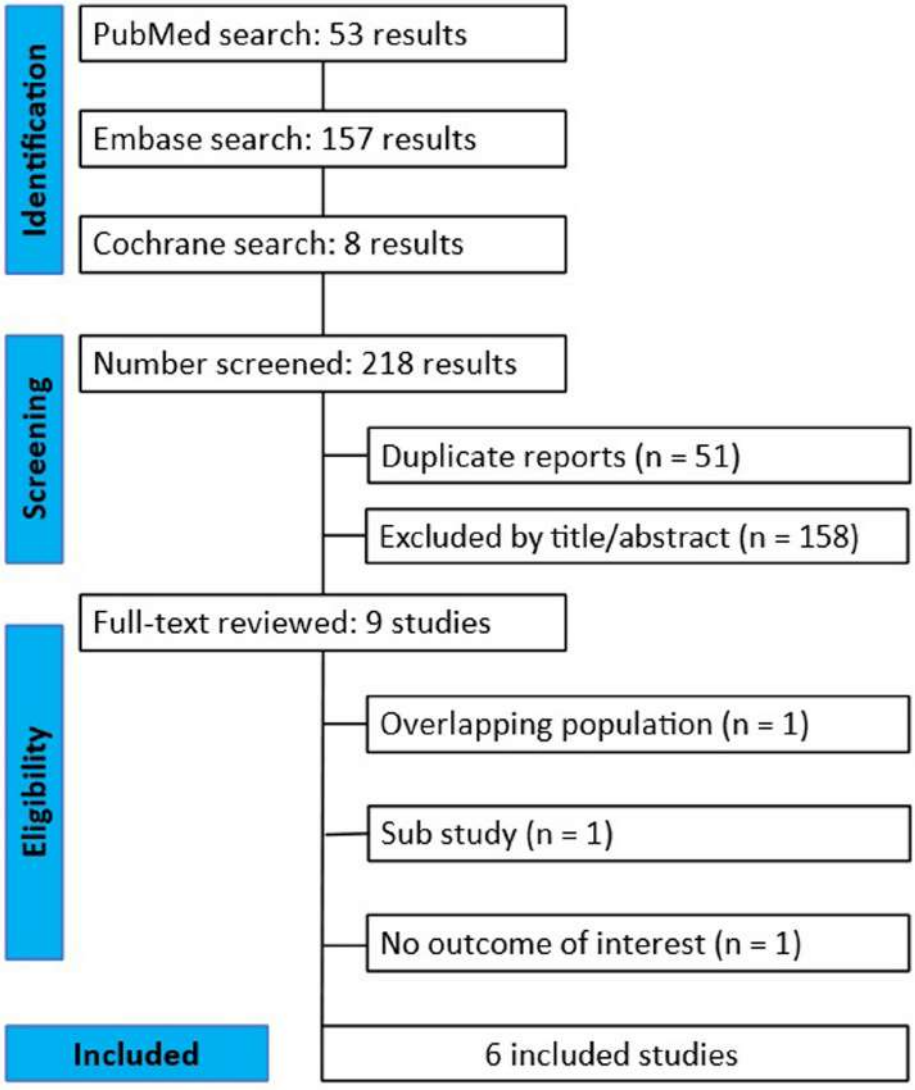

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of study screening and selection.

Table 1. Baseline Characteristics of the Included Studies

	Barki 2022	Delgado-Arana 2022	Amat-Santos 2023	Halim 2023	Baumbach 2024	Ubben 2024
Type of study	Observational	Observational	Observational	Observational	RCT	Observational
Intervention/control	Myval/Evolut R	Myval/Sapien 3	Myval/EvolutPro+ / Sapien3 Ultra	Myval/Evolut	Myval/(Evolut or Sapien)	Myval/Sapien
No. of patients	58/108	103/103	122/109/129	91/91	384/384	134/268
Age (years) (mean)	82/83	81/80.6	73/79/78	80/80.5	80/80.4	81/79.7
Male (%)	50/61	56.3/63.1	77.9/62.4/74.4	51/51	50/54	66/68
BMI (kg/m^2) (mean)	NA	26.6/28.2	25.5/25.6/27.1	28.3/28.2	28.2/28	26.9/27.3
NYHA class III-IV (%)	50/45	47.6/44.7	64/35/61	31/46	54/51	NA
STS score (mean/median)	3.3/3.9	3.3/3.5	4/4/2.7	NA	2.6/2.6	4.7/3.9
Prior stroke (%)	5/10	13.6/21.4	4.9/4.6/8.5	21/21	3/2	8.2/8.6
Prior PCI (%)	43/35	NA	NA	NA	8/7	44/43
Prior CABG (%)	5/10	6.8/3.9	7.4/3.7/1.6	14/11	3/5	14/11
Prior PPI (%)	5/16	6.8/8.7	9/14.7/14.7	7/5	3/5	13/13
Hypertension (%)	90/81	NA	NA	71/65	67/66	92/93
DM (%)	21/31	31.1/36.9	NA	37/35	29/30	25/31
CKD (%)	48/49	33/32	14.8/21.1/16.1	34/33	47/49	23/24
Atrial fibrillation (%)	31/38	18.4/19.4	8.2/9.2/10.9	29/27	24/26	NA
CAD (%)	60/48	41.7/36.9	34.4/36.7/43.4	45/41	14/15	NA
PAD (%)	31/14	9.7/19.4	9.8/12.1/6.3	13/13	NA	NA
Bicuspid aortic valve (%)	NA	NA	100/100/100	NA	6/8	9.8/11
Follow-up	180 days	30 days	30 days	365 days	30 days	1 day

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; MI, myocardial infarction; NA, not available; NYHA, New York heart association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, permanent pacemaker implantation; RCT, randomized controlled trial; STS, society of thoracic surgeons.

Figure 3A) Myval showed higher Early safety at 30 days compared to contemporary THVs (p=0.01)

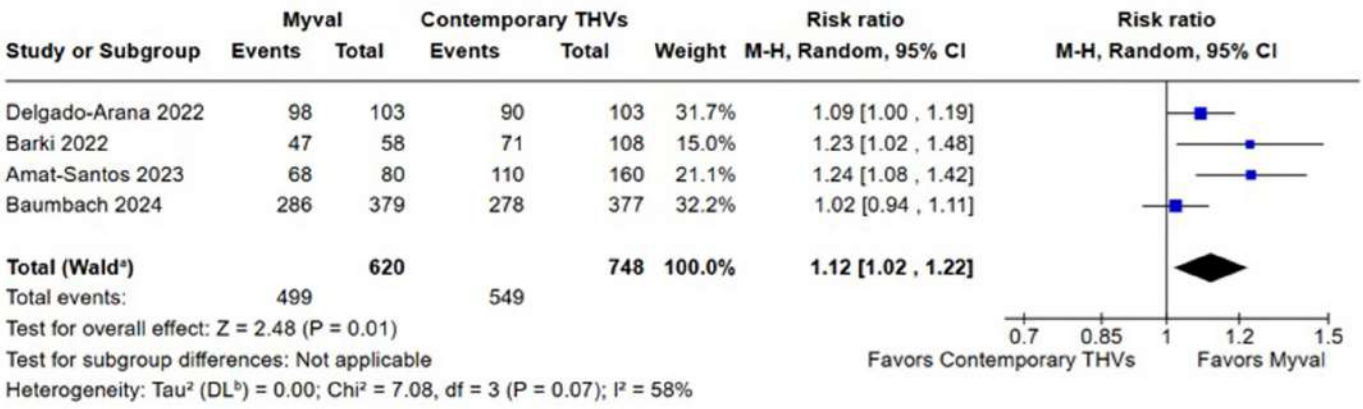

Figure 3B) Forest plot for Need for PPI outcome showing lower rates of need for PPI in Myval group as compared to Contemporary THVs (p=0.004)

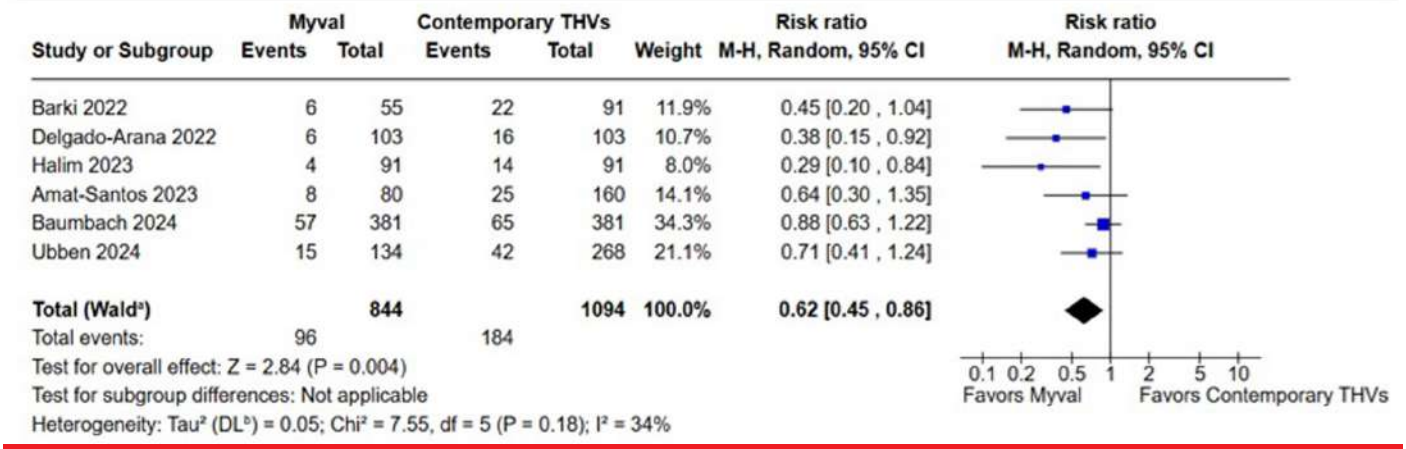

Figure 3. Forest plots for main analysis Myval vs. Contemporary thoracic heart valves. (A) Myval showed higher early safety at 30 days compared to contemporary thoracic heart valves (*P* = .01). (B) Forest plot for need for permanent pacemaker implantation outcome showing lower rates of need for permanent pacemaker implantation in Myval group as compared to contemporary thoracic heart valves (*P* = .004).

(RR 1.18; 95% CI 0.42-3.33; $P = .76$; $I^2 = 54\%$); major bleeding (RR 1.12; 95% CI 0.53-2.34; $P = .77$; $I^2 = 32\%$); and moderate or severe PVL (RR 0.58; 95% CI 0.33-1.02; $P = .06$; $I^2 = 0\%$) were comparable in both groups. There was no statistical difference between the groups regarding 30-day device success (RR 1.10; 95% CI 0.99-1.23; $P = .07$; $I^2 = 86\%$); all-cause mortality (RR 0.79; 95% CI 0.43-1.46; $P = .45$; $I^2 = 0\%$); CV mortality (RR 0.81; 95% CI 0.39-1.68; $P = .58$; $I^2 = 0\%$); AKI (RR 0.82; 95% CI 0.33-2.04; $P = .67$; $I^2 = 43\%$); stroke (RR 0.85; 95% CI 0.48-1.52; $P = .59$; $I^2 = 0\%$); and MI (RR 0.54; 95% CI 0.11-2.77; $P = .46$; $I^2 = 0\%$).

In subgroup analyses, Myval had higher early safety at 30 days (RR 1.16; 95% CI 1.04-1.29; $P = .006$; $I^2 = 33\%$; Figure 4A showing improved early safety with Myval); lower need for PPI (RR 0.57; 95% CI 0.35-0.95; $P = .03$; $I^2 = 46\%$; Figure 4B showing lesser PPI need with Myval); lower moderate or severe PVL (RR 0.36; 95% CI 0.20-0.65; $P = .0007$; $I^2 = 0\%$; Figure 5A demonstrates low PVL with Myval); and better 30-day device success (RR 1.13; 95% CI 1.03-1.24; $P = .01$; $I^2 = 69\%$; Figure 5B depicts better device success with Myval) as compared to Evolut series THVs.

When compared to Sapien series THVs, Myval had no significant difference with regards to early safety (RR 1.08; 95% CI 0.98-1.19; $P = .14$; $I^2 = 57\%$; Figure 6A showing non-inferiority of Myval) and need for PPI (RR 0.75; 95% CI 0.56-1; $P = .05$; $I^2 = 0\%$; Figure 6B depicting similar rates for Myval and Sapien). All the procedural and early clinical outcomes were also comparable in both subgroups, suggesting non-inferiority of Myval

Figure 4A) Forest plot for early safety showing better outcome with Myval than Evolut (p=0.006)

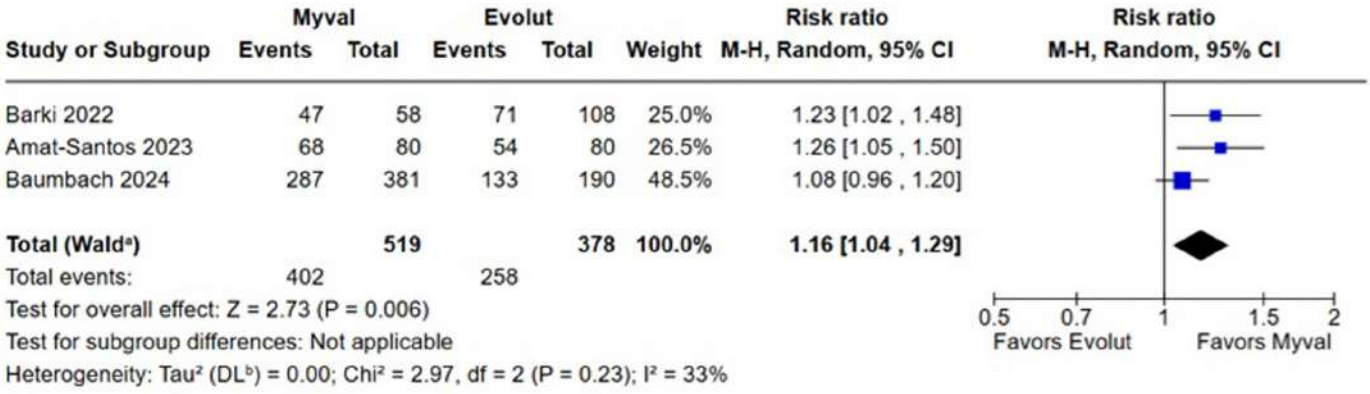

Figure 4B) Need for PPI was lower with Myval as compared to Evolut (p=0.03)

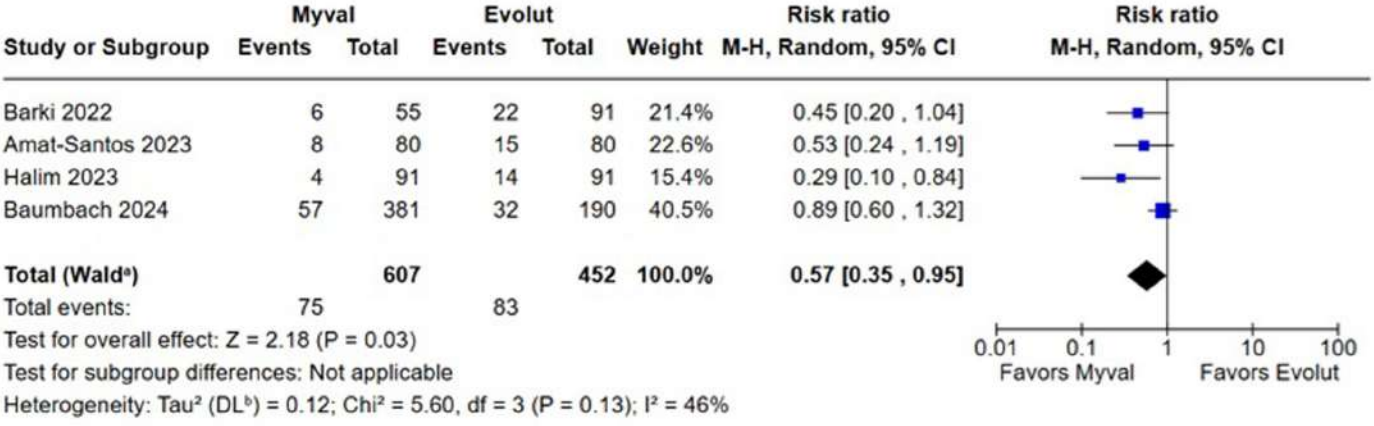

Figure 4. Forest plots for subgroup analysis Myval vs. Evolut. (A) Forest plot for early safety showing better outcome with Myval than Evolut (*P* = .006). (B) Need for permanent pacemaker implantation was lower with Myval as compared to Evolut (*P* = .03).

compared to Sapien series. (Supplementary Appendix: Supplementary Tables 1 and 2).

Sensitivity analysis with leave-one-out method showed no effect of a single study altering the results in 1 direction. The authors also performed OR, risk difference, and RR with fixed and random effects model and found similar results (Supplementary Appendix: Supplementary Figures 2 and 3).

Quality Assessment

Randomized controlled trial (RCT) appraisal is reported in the Supplementary Figure 1A (Supplementary Appendix). Three non-randomized studies matched intervention and control patients according to baseline characteristics.[22-24] In 2 studies, groups were not matched and therefore had few dissimilar baseline characteristics. Individual appraisal of non-randomized studies is reported in Supplementary Figure 1B (Supplementary Appendix). None of the included studies were considered at serious or critical risk of bias as assessed by 2 independent authors (Z.M. and T.T.). As shown in Figure 7, there was no evidence suggestive of publication bias; the funnel plot showed a symmetrical distribution of similar-weight studies with convergence toward the pooled treatment effect size as weights increased. As shown in Supplementary Table 3 (Supplementary Appendix), most of the studies reported outcomes in compliance with VARC 3 criteria, and Halim et al reported outcomes based on VARC 2, but they were included in analyses as they could be retrofitted to VARC 3 criteria as per definitions. There was significant heterogeneity in outcomes like 30-day device success and procedure success where I^2 was upward of 60%. In these cases, it would be prudent to acknowledge the heterogeneity involving patient characteristics (low risk vs. high risk; young vs. old; male vs. female), valve morphology (bicuspid

Figure 5A) Moderate or severe PVL was less with Myval compared to Evolut (p=0.0007)

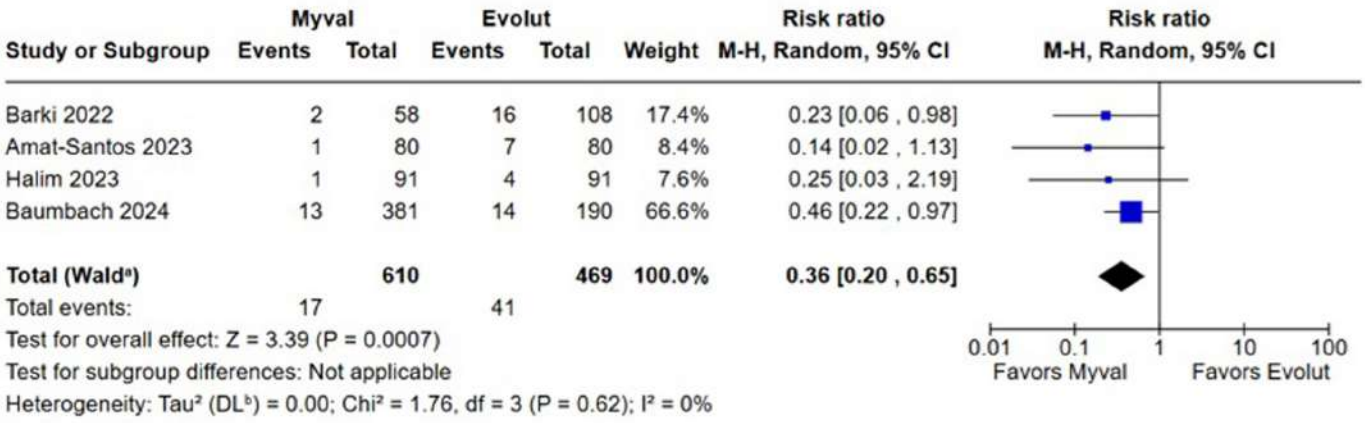

Figure 5B) 30-day device success was seen more with Myval compared to Evolut (p=0.01)

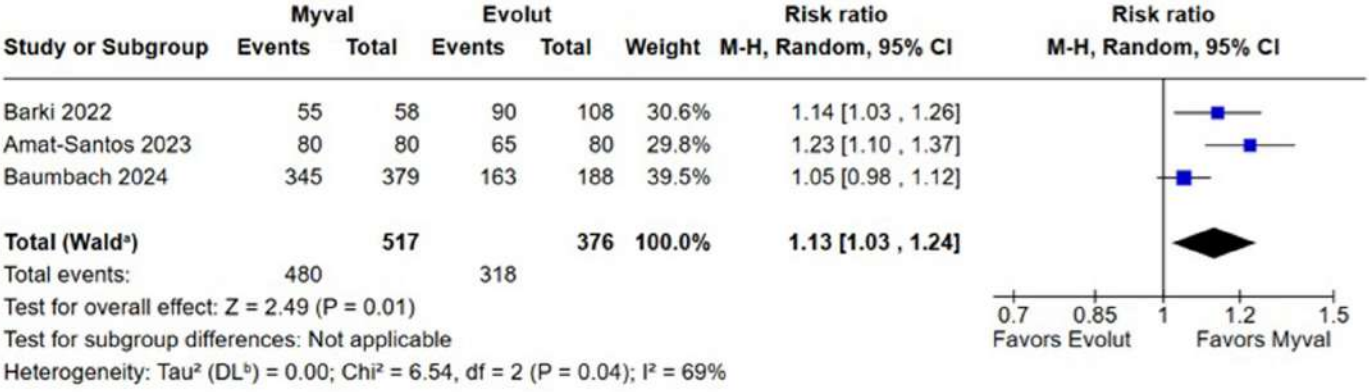

Figure 5. Forest plots for subgroup analysis Myval vs. Evolut. (A) Moderate or severe PVL was less with Myval compared to Evolut (*P* = .0007). (B) 30-day device success was seen more with Myval compared to Evolut (*P* = .01).

vs. tricuspid), and generation of THV (Sapien vs. Sapien3; Myval Gen 1 vs. Myval Octacor). The authors could not perform meta-regression due to lack of comprehensive data with respect to the covariates at hand, but it would have strengthened the association of the outcomes and made the authors' data more robust.

DISCUSSION

In this systematic review and meta-analysis of 6 studies involving 2084 patients, the authors compared the performance of Myval with contemporary THVs. Myval appeared to be associated with improved early safety, as defined by the VARC-3 criteria, and a reduced need for PPI. Although causality cannot be established due to the observational nature of most included studies, subgroup analyses based on the type of contemporary THVs showed no significant difference between Myval and Sapien, suggestive of non-inferiority of Myval. Furthermore, Myval appeared to have better 30-day device success and lower rates of moderate or severe PVL compared to the Evolut THV.

The authors' findings align with the outcomes observed in previous studies involving Myval, supporting the safety of this THV. In an open-label single-arm study involving intermediate-to-high-risk patients, Myval has been associated with very low rates of peri-procedural mortality, 1-year mortality, minimal residual PVL, and reduced need for PPI.[13] Additionally, another study on low-risk patients with a mean STS score of 2.4% reported favorable hemodynamic performance and short-term outcomes, with a similarly low risk of requiring PPI.[16]

Figure 6A) No significant difference seen in Early safety with Myval compared to Sapien (p=0.14)

Study or Subgroup	Myval Events	Myval Total	Sapien Events	Sapien Total	Weight	Risk ratio M-H, Random, 95% CI
Delgado-Arana 2022	98	103	90	103	41.2%	1.09 [1.00 , 1.19]
Amat-Santos 2023	68	80	56	80	21.4%	1.21 [1.02 , 1.44]
Baumbach 2024	287	381	145	191	37.4%	0.99 [0.90 , 1.09]
Total (Wald[a])		**564**		**374**	**100.0%**	**1.08 [0.98 , 1.19]**
Total events:	453		291			

Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 4.64, df = 2 (P = 0.10); I² = 57%

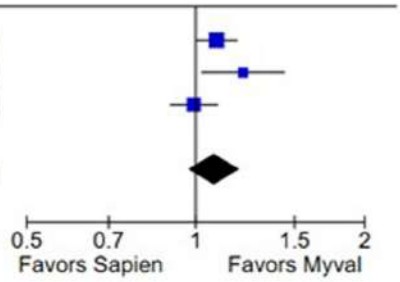

Figure 6B) No significant difference seen in Need for PPI with Myval compared to Sapien (p=0.05)

Study or Subgroup	Myval Events	Myval Total	Sapien Events	Sapien Total	Weight	Risk ratio M-H, Random, 95% CI
Delgado-Arana 2022	6	103	16	103	10.1%	0.38 [0.15 , 0.92]
Amat-Santos 2023	8	80	10	80	10.6%	0.80 [0.33 , 1.92]
Baumbach 2024	57	381	33	191	52.8%	0.87 [0.59 , 1.28]
Ubben 2024	15	134	42	268	26.6%	0.71 [0.41 , 1.24]
Total (Wald[a])		**698**		**642**	**100.0%**	**0.75 [0.56 , 1.00]**
Total events:	86		101			

Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%

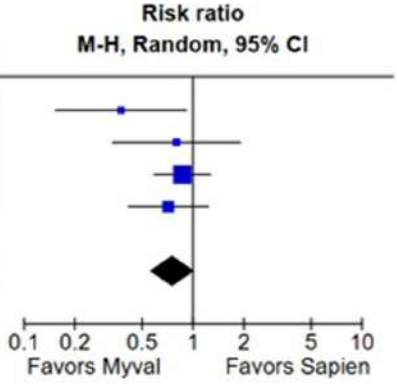

Figure 6. Forest plots for sub group analysis Myval vs. Sapien. (A) No significant difference seen in early safety with Myval compared to Sapien (*P* = .14). (B) No significant difference seen in need for permanent pacemaker implantation with Myval compared to Sapien (*P* = .05).

However, few head-to-head studies have directly compared contemporary THVs.[36-39] The SCOPE II trial, for instance, compared 2 self-expanding THVs (SEVs) and found that the Accurate neo valve failed to meet prespecified non-inferiority criteria and had higher incidences of all-cause mortality and stroke compared to the CoreValve Evolut valve.[36] Similarly, the PORTICO IDE trial showed that the intra-annular SEV Portico valve did not demonstrate advantages over other commercially available THVs, such as the intra-annular BEVs like Sapien, Sapien XT, or Sapien 3, or supra-annular SEVs like CoreValve, Evolut-R, or Evolut-PRO.[37] The SOLVE-TAVI trial compared the Evolut-R SEV with the Sapien 3 BEV and found that all-cause mortality, need for PPI, and PVL were higher in the SEV group, while the incidence of stroke was higher in the BEV group.[38] A recent meta-analysis comparing BEV and self-expandable THVs reported a lower incidence of mortality, shorter hospitalization durations, and reduced need for PPI with BEVs.[39]

In this context, Myval may emerge as a promising option as a BEV and has been compared with contemporary THVs in several studies. However, most of these studies were limited by small sample sizes, non-randomized designs, and short follow-up periods. Hence, large-scale RCTs with long-duration follow-up are warranted to validate these findings.

Transcatheter aortic valve implantation is usually associated with very high cost, and the cost-benefit ratio is skewed. This is the reason it is still not available to a larger part of the global community. Myval could fill this gap by being a safe and effective alternative to contemporary THVs. It also provides drastic cost reduction, making it available to the mass markets at a reduced burden to the healthcare community, especially in resource-limited settings.

Figure 7 A) Funnel plot analysis of early safety outcome showed a symmetrical distribution of study effects per different study weights, indicative of no evidence of publication bias

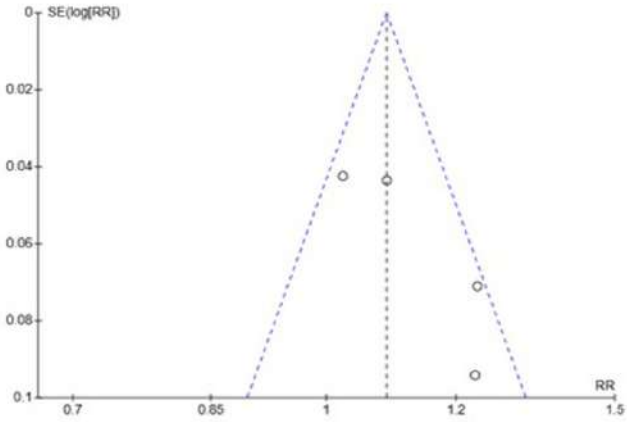

Figure 7 B) Funnel plot analysis of need for PPI outcome showed a symmetrical distribution of study effects per study weights showing no publication bias.

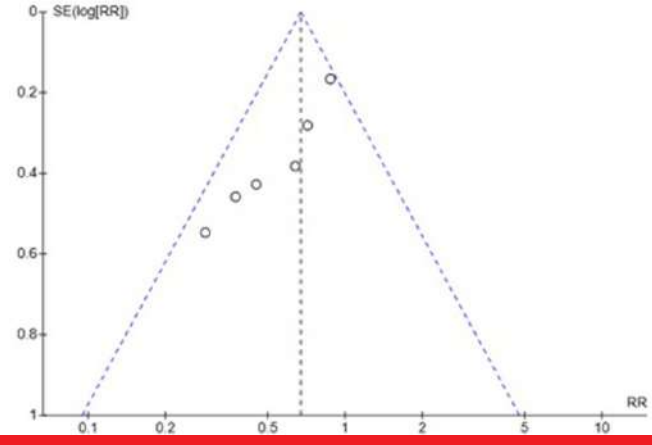

Figure 7. Funnel plots for publication bias for the main analysis of Myval vs. Contemporary thoracic heart valves. (A) Funnel plot analysis of early safety outcomes showed a symmetrical distribution of study effects per different study weights, indicative of no evidence of publication bias. (B) Funnel plot analysis of the need for permanent pacemaker implantation outcomes showed a symmetrical distribution of study effects per study weights showing no publication bias.

With an expanded patient population and consistent results across sensitivity analyses, the authors' findings provide a clearer understanding of the treatment effect of Myval compared to contemporary THVs. Myval may become a valuable therapeutic option for patients with aortic stenosis considering that its efficacy and safety hold true when compared with concurrent THVs. Nevertheless, it is important to emphasize that the current data are insufficient to draw definitive conclusions. These findings lay the groundwork for future, well-designed studies. Larger RCTs are necessary to further test this hypothesis and assess the performance of Myval compared to the latest generations and iterations of contemporary THVs. There are ongoing studies designed to compare Myval THV with contemporary THVs, and although the results are yet to be published, early data have suggested that Myval THV fares well compared to contemporary THVs.[40]

This study has several limitations. Most of the included studies are observational in nature, and only 1 study is an RCT, which limits the generalizability of the data. The heterogeneity in terms of population characteristics (low risk vs. high risk), valve morphology (bicuspid vs. tricuspid), VARC 3 criteria application, THV generations and iterations, follow-up periods, and the underrepresentation of female patients in the observational studies is particularly notable. For instance, Amat-Santos et al included only patients with bicuspid aortic valves, which further increased the heterogeneity of the population. However, even when the authors conducted a leave-one-out analysis excluding this specific study, the overall results remained consistent. Myval Gen 1 and Myval Octacor were used in different studies in different proportions, which may have an impact on the outcomes; however, due to a lack of pre-specified data, a subgroup analysis could not be performed. There was significant heterogeneity in

the application of VARC 3 criteria in all studies. Barki et al,[20] Delgado-Arana et al,[24] Amat-Santos et al,[23] and Baumbach et al[30] reported outcomes that are fully compliant with VARC 3. Halim et al[22] reported outcomes based on VARC 2, whereas Ubben et al[28] reported outcomes in compliance with VARC 3, but there was a lack of 30-day outcome data and early safety parameters.

Additionally, there is only 1 RCT in the authors' review, which was designed to assess non-inferiority, and its findings favored Myval. However, a predefined sub-study from this RCT compared Myval to both the Sapien and Evolut THVs individually and that helped in the authors' subgroup analyses.[41] The authors' assessment of bias found that none of the studies were classified as having a critical or high risk of bias. Still, the authors recognize that some biases may have gone undetected, particularly given the variability in THV iterations and generations across the studies.

There are many limitations of current data and to further improve the scientific integrity and future direction, large and long-term RCTs are needed to fill the gap in current evidence and to validate all the findings observed to date.

CONCLUSION

Systematic review and meta-analysis of 2084 patients suggests that Myval may represent a promising alternative to currently available THVs in TAVI. However, given the predominance of observational data and limited long-term follow-up, larger randomized studies are warranted to confirm these findings.

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Figure S1 A) Risk of bias assessment for randomized controlled trial as per ROB2 tool showed low risk of bias

Study ID	D1	D2	D3	D4	D5	Overall	
Baumbach 2024	+	+	+	+	+	+	
			D1	Randomisation process			
+	Low risk		D2	Deviations from the intended interventions			
!	Some concerns		D3	Missing outcome data			
-	High risk		D4	Measurement of the outcome			
			D5	Selection of the reported result			

Figure S1 B) Risk of bias assessment for observational studies as per ROBINS I tool showing that none of the studies were having serious or critical risk of bias

Study ID	D1	D2	D3	D4	D5	D6	D7	Overall		
Barki 2022	!	!	+	+	+	+	+	!		
Delgado-Arana 2022	+	+	+	+	+	+	+	+		
Amat-Santos 2023	+	+	+	+	+	+	+	+		
Halim 2023	+	+	+	+	+	+	+	+		
Ubben 2024	!	!	+	+	+	+	+	!		
					D1	Bias due to confounding				
					D2	Selection bias				
					D3	Bias in classification of interventions				
+	Low risk				D4	Deviations from the intended interventions				
!	Moderate risk				D5	Missing outcome data				
-	Severe risk				D6	Measurement of the outcome				
-	Critical risk				D7	Selection of the reported result				

Supplementary Figure 1. Summary of risk of bias. (A) Risk of bias assessment for randomized controlled trial as per ROB2 tool showed low risk of bias. (B) Risk of bias assessment for observational studies as per ROBINS I tool showed that none of the studies had serious or critical risk of bias.

Figure S2 A) Leave one out method

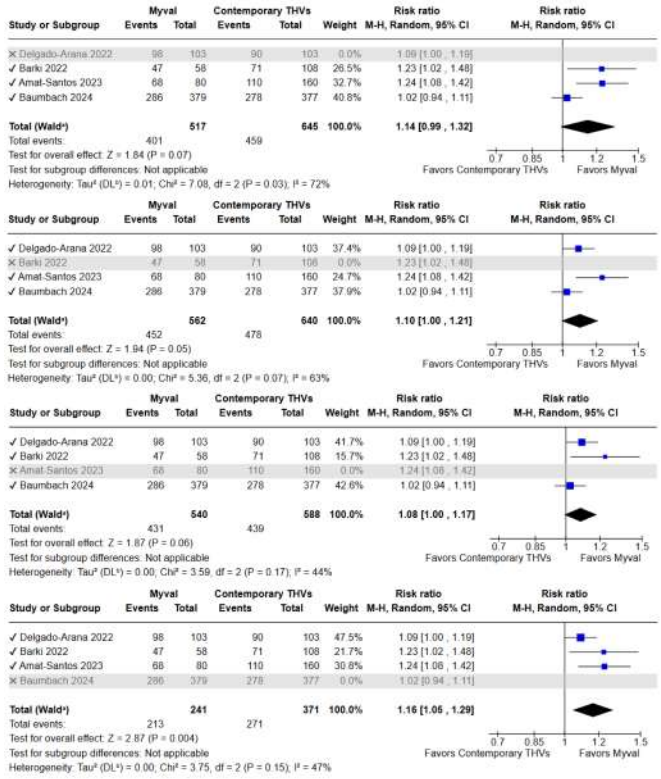


Figure S2 B) Risk ratio fixed vs random effects

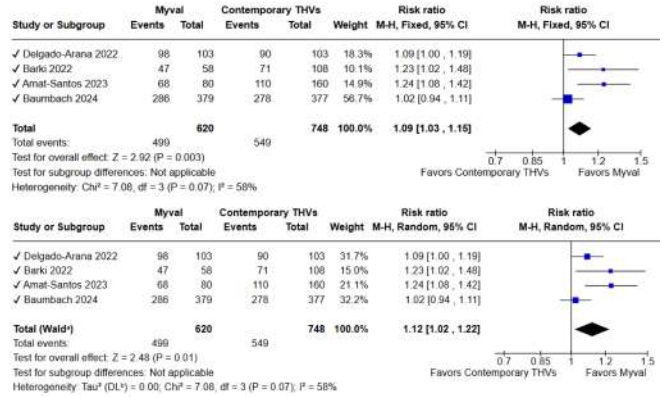
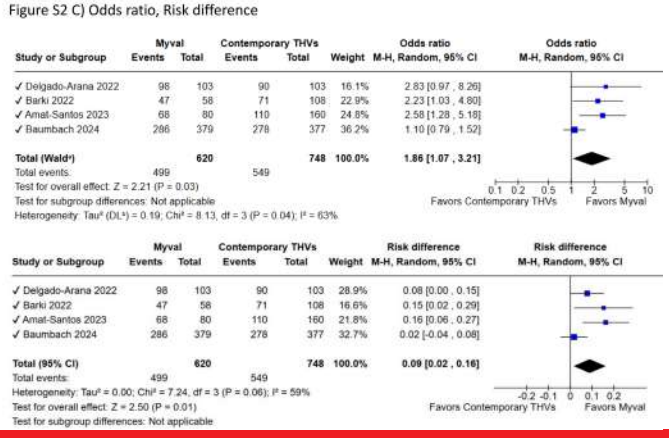
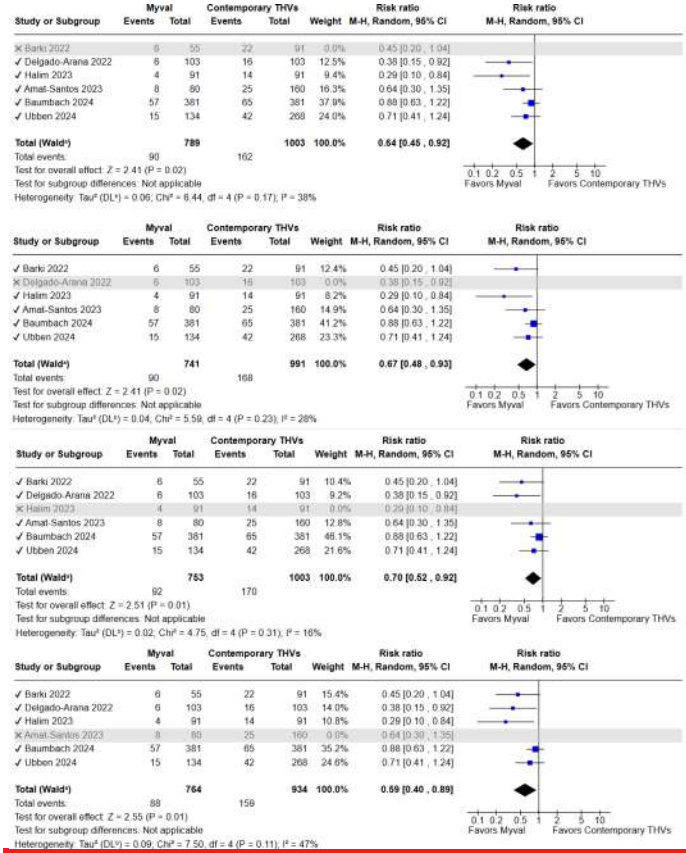
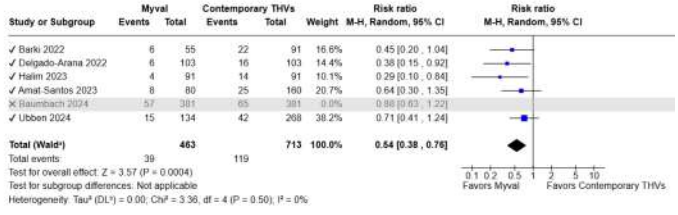


Figure S2 C) Odds ratio, Risk difference



Supplementary Figure 2. sensitivity analysis for Early safety outcome. (A) Leave-one-out method. (B) Risk ratio fixed vs random effects. (C) Odds ratio, Risk difference.





Supplementary Figure 3. Sensitivity analysis for need for PPI outcome. (A) Leave one out method. (B) Risk ratio fixed vs random effects. (C) Odds ratio, Risk difference.

Supplementary Table 1. Subgroup analysis of Myval vs Evolut showing procedural and clinical outcomes

Outcomes	RR	95% CI	*P*	I^2
Technical success	1.02	1.00 – 1.05	0.09	4%
Procedural death	2.00	0.18 – 21.67	0.57	NA
Valve embolization or malpositioning	0.52	0.09 – 2.87	0.45	0%
Coronary artery occlusion	0.56	0.11 – 2.87	0.49	0%
Annulus rupture	NA	NA	NA	NA
Major vascular complication	1.15	0.21 – 6.40	0.87	48%
Major bleeding	0.69	0.22 – 2.17	0.53	41%
Moderate or severe PVL	0.36	0.20 – 0.65	0.0007*	0%
Need for PPI	0.57	0.35 – 0.95	0.03*	46%
Early safety	1.16	1.04 – 1.29	0.006*	33%
30-day device success	1.13	1.03 – 1.24	0.01*	69%
All-cause mortality	0.75	0.34 – 1.64	0.47	0%
CV mortality	0.45	0.07 – 2.89	0.40	0%
AKI	0.55	0.15 – 2.07	0.38	56%
Stroke	0.88	0.42 – 1.85	0.73	0%
MI	0.54	0.11 – 2.77	0.46	0%

AKI, acute kidney injury; CV mortality, cardiovascular mortality; MI, myocardial infarction; NA, not available, RR, risk ratio; PPI, permanent pacemaker implantation
*: statistically significant

Supplementary Table 2. Subgroup analysis of Myval vs Sapien showing procedural and clinical outcomes

Outcomes	RR	95% CI	*P*	I^2
Technical success	0.98	0.95 – 1.01	0.15	54%
Procedural death	1.05	0.04 – 29.56	0.98	57%
Valve embolization or malpositioning	0.93	0.11 – 7.49	0.94	0%
Coronary artery occlusion	0.14	0.01 – 2.73	0.20	NA
Annulus rupture	0.35	0.04 – 3.17	0.35	0%
Major vascular complication	1.14	0.33 – 4.02	0.83	59%
Major bleeding	1.31	0.42 – 4.08	0.64	43%
Moderate or severe PVL	2	0.74 – 5.43	0.17	0%
Need for PPI	0.75	0.56 – 1.00	0.05	0%
Early safety	1.08	0.98 – 1.19	0.14	57%
30-day device success	1.06	0.91 – 1.22	0.47	88%
All-cause mortality	0.77	0.34 – 1.74	0.53	0%
CV mortality	0.67	0.14 - 3.26	0.62	NA
AKI	0.89	0.18 – 4.46	0.89	54%
Stroke	0.67	0.24 – 1.85	0.44	34%
MI	NA	NA	NA	NA

AKI, acute kidney injury; CV mortality, cardiovascular mortality; MI, myocardial infarction; NA, not available, RR, risk ratio; PPI, permanent pacemaker implantation
*: statistically significant

Supplementary Table 3. Study wise outcomes and VARC 3 compliance

Study	Endpoint	VARC 3 compliant or non-compliant
Barki 2022	Early safety	VARC 3 compliant
	30-day Device success	VARC 3 compliant
	Major bleeding	VARC 3 compliant
	Major vascular complications	VARC 3 compliant
	Procedure success	VARC 3 compliant
	Valve embolization or malpositioning	VARC 3 compliant
	Need for PPI	VARC 3 compliant
	Moderate or severe PVL	VARC 3 compliant
	Coronary artery occlusion	VARC 3 compliant
	Annulus rupture	VARC 3 compliant
	All-cause mortality	VARC 3 compliant
	CV mortality	VARC 3 compliant
	Procedure death	VARC 3 compliant
	AKI	VARC 3 compliant
	Stroke	VARC 3 compliant
	MI	VARC 3 compliant
Delgado-Arana 2022	Early safety	VARC 3 compliant
	Device success	Not reported
	Major bleeding	VARC 3 compliant
	Major vascular complications	VARC 3 compliant
	Procedure success	VARC 3 compliant
	Valve embolization or malpositioning	VARC 3 compliant
	Need for PPI	VARC 3 compliant
	Moderate or severe PVL	VARC 3 compliant
	Coronary artery occlusion	VARC 3 compliant
	Annulus rupture	VARC 3 compliant
	All-cause mortality	VARC 3 compliant
	CV mortality	Not reported
	Procedure death	VARC 3 compliant
	AKI	VARC 3 compliant
	Stroke	VARC 3 compliant
	MI	Not reported
Amat-Santos 2023	Early safety	VARC 3 compliant
	Device success	VARC 3 compliant
	Major bleeding	VARC 3 compliant
	Major vascular complications	VARC 3 compliant
	Procedure success	VARC 3 compliant
	Valve embolization or malpositioning	VARC 3 compliant
	Need for PPI	VARC 3 compliant
	Moderate or severe PVL	VARC 3 compliant
	Coronary artery occlusion	VARC 3 compliant
	Annulus rupture	VARC 3 compliant
	All-cause mortality	VARC 3 compliant
	CV mortality	Not reported
	Procedure death	VARC 3 compliant
	AKI	
	Stroke	VARC 3 compliant
	MI	VARC 3 compliant

(*Continued*)

Supplementary Table 3. Study wise outcomes and VARC 3 compliance (*Continued*)

Study	Endpoint	VARC 3 compliant or non-compliant
Halim 2023	Early safety	Not reported
	Device success	Not reported
	Major bleeding	As per VARC 2
	Major vascular complications	As per VARC 2
	Procedure success	Not reported
	Valve embolization or malpositioning	As per VARC 2
	Need for PPI	As per VARC 2
	Moderate or severe PVL	As per VARC 2
	Coronary artery occlusion	As per VARC 2
	Annulus rupture	As per VARC 2
	All-cause mortality	As per VARC 2
	CV mortality	As per VARC 2
	Procedure death	As per VARC 2
	AKI	As per VARC 2
	Stroke	As per VARC 2
	MI	As per VARC 2
Baumbach 2024	Early safety	VARC 3 compliant
	Device success	VARC 3 compliant
	Major bleeding	VARC 3 compliant
	Major vascular complications	VARC 3 compliant
	Procedure success	VARC 3 compliant
	Valve embolization or malpositioning	VARC 3 compliant
	Need for PPI	VARC 3 compliant
	Moderate or severe PVL	VARC 3 compliant
	Coronary artery occlusion	VARC 3 compliant
	Annulus rupture	VARC 3 compliant
	All-cause mortality	VARC 3 compliant
	CV mortality	VARC 3 compliant
	Procedure death	VARC 3 compliant
	AKI	VARC 3 compliant
	Stroke	VARC 3 compliant
	MI	Nor reported
Ubben 2024	Early safety	Not reported
	Device success	Not reported
	Major bleeding	VARC 3 compliant
	Major vascular complications	VARC 3 compliant
	Procedure success	VARC 3 compliant
	Valve embolization or malpositioning	VARC 3 compliant
	Need for PPI	VARC 3 compliant
	Moderate or severe PVL	VARC 3 compliant
	Coronary artery occlusion	Not reported
	Annulus rupture	VARC 3 compliant
	All-cause mortality	VARC 3 compliant
	CV mortality	VARC 3 compliant
	Procedure death	Not reported
	AKI	VARC 3 compliant
	Stroke	VARC 3 compliant
	MI	VARC 3 compliant

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The Effect of Pulmonary Rehabilitation on Echocardiographic Parameters and Quality of Life in Patients with Primary Lung Disease

ABSTRACT

Background: The authors aimed to evaluate the effects of pulmonary rehabilitation (PR) on respiratory and echocardiographic parameters in patients with primary lung disease.

Methods: This retrospective cohort study included 55 patients who were admitted to the authors' hospital between January 2018 and December 2019 with respiratory complaints, diagnosed with primary lung disease and underwent PR. Echocardiographic parameters, respiratory parameters, 6-minute walk distance (6-MWT), body mass index, Modified Medical Research Council (mMRC) dyspnea score, and quality of life measurement score values measured before and after PR were retrieved from the patient database.

Results: After PR, a significant improvement was observed in systolic pulmonary artery pressure (PABs), Tricuspid annular plane systolic excursion (TAPSE), TAPSE/PABs, and 6-minute walk test (6-MWT) compared to before PR. As the effectiveness of PR at quality of life was evaluated with the SF-36 test, improvement was found in all variables in the asthma group. However, a statistically significant improvement was found in parameters other than general health and pain in the chronic obstructive pulmonary disease (COPD) group.

Conclusion: Pulmonary rehabilitation in patients with chronic lung disease is associated with improvement in both respiratory and cardiac functions and quality of life.

Keywords: Pulmonary rehabilitation, echocardiography, right ventricular functions, chronic obstructive pulmonary disease, asthma

ORIGINAL INVESTIGATION

INTRODUCTION

Pulmonary rehabilitation (PR) is a treatment designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote long-term adherence to health-promoting behaviors. Pulmonary rehabilitation is a comprehensive intervention that includes individualized exercise training, education, and behavior modification following a thorough patient assessment.[1,2] Pulmonary rehabilitation has demonstrated physiological, symptom-reducing, psychosocial, and health economic benefits in multiple outcome areas for patients with chronic respiratory diseases (COPD,[3] interstitial lung disease,[4] bronchiectasis,[5] cystic fibrosis,[6] asthma,[7] pulmonary hypertension,[8] lung cancer,[9] lung volume reduction surgery,[10] and lung transplantation[11]).

Patients with chronic respiratory diseases experience disabling symptoms (including dyspnea and fatigue) and exercise intolerance have low physical activity levels and impaired quality of life. Pulmonary rehabilitation reduces patients' symptoms and improves limb muscle function, exercise capacity, emotional function, quality of life, knowledge, and self-efficacy. Pulmonary rehabilitation is implemented by a dedicated, interdisciplinary team, including physicians, and other health care professionals; the latter may include physiotherapists, respiratory therapists, nurses, psychologists, behavioral specialists, exercise physiologists, nutritionists, occupational therapists, and social workers.[1,2]

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Pulmonary rehabilitation programs (sessions) may be conducted in hospital, outpatient, or home settings. Most of the research has involved outpatient PR programs with 1 to 3 visits per week over a period of at least 8 weeks. The essential components of PR include an initial center-based assessment conducted by a healthcare professional, an exercise test performed at the time of assessment, a field exercise test, quality-of-life measurement, dyspnea assessment, evaluation of nutritional and occupational status, endurance and resistance training, an individually prescribed and progressively adjusted exercise program, and a multidisciplinary team that includes healthcare professionals experienced in exercise prescription and progression. Additionally, healthcare professionals must be adequately trained to deliver the components of the implemented rehabilitation model.[12]

Studies showed improvements in exercise capacity and some items of pulmonary function tests (PFT), Saint George Respiratory Questionnaire (SGRQ) scores, and BODE indexes of patients after PR programs.[13,14] Diaphragmatic thickness at the end of expiration also significantly improved after PR and was positively correlated with functional performance.[14]

Cardiac effects of PR are not well-known (except pulmonary hypertension) compared to the pulmonary effects of PR in patients with chronic respiratory disease. There is a limited number of studies on the cardiac effects of PR, and these studies were generally limited to the idiopathic pulmonary hypertension and chronic thromboembolic pulmonary hypertension groups. In these studies, the 6-minute walk distance (6-MWT), which is a mortality predictor of pulmonary hypertension and is used in the diagnosis and treatment of pulmonary hypertension, was utilized as the basic parameter.[15] In this study, the authors aimed to investigate the effects of PR on respiratory and echocardiographic parameters as well as health related quality of life in subjects with primary pulmonary disease.

METHOD

Study Design

This retrospective cohort study was conducted in accordance with the guidelines recommended in the Declaration of Helsinki. The present study was approved by an Institutional Review Board (29/4/2020/71). Artificial intelligence (AI)–assisted technologies (such as Large Language Models [LLMs], chatbots, or image generators) were not used at any stage of the presented study.

HIGHLIGHTS

- Pulmonary rehabilitation in patients with chronic lung disease is associated with improvement in both respiratory and cardiac functions and quality of life.
- After PR, significant improvement was found in PABs, TAPSE, TAPSE/PABs, and 6-MWT compared to before PR.
- When the effectiveness of PR at quality of life was evaluated with the SF-36 test, improvement was found in all variables in the asthma group.

Study Participants

We enrolled adult subjects who presented with respiratory symptoms to the chest diseases clinic secondary to primary lung disease and underwent PR between January 2018 and December 2019. Exclusion criteria were acute pulmonary embolism, acute pulmonary edema, and acute coronary syndrome. Patients who had a change in their medical treatment during the PR period were also excluded from the study (n = 10). In addition, patients who did not undergo echocardiographic evaluation before and after respiratory physiotherapy were not included in the study (n = 13). A total of 55 patients were included in the study.

Data Collection

Respiratory and echocardiographic data of the patients before and after PR were retrieved from the hospital electronic database.

Body mass index (BMI) was calculated using the formula of body weight (kg)/height^2 (m^2). Biochemical analyses were conducted on venous blood samples taken after 12 hours of fasting.

Echocardiography

Echocardiographic evaluation was performed before and after PR by the same operator with a Philips Vivid 3 device. Ejection fraction was calculated using the modified Simpson's method. Pulmonary arterial pressure was calculated using the peak velocity on the tricuspid valve in apical 4-chamber imaging. TAPSE was evaluated using M mode echocardiography in the lateral tricuspid annulus.

Pulmonary Function Testing

All patients performed a PFT (Cosmed Pony FX Desktop Spirometer—MIR Intermedical Spirolab Spirometer) according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. Pulmonary function testings were forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC.

Six-Minute Walk Test

The 6-MWT was performed in accordance with the ATS/ERS guidelines, and parameters such as dyspnea (mMRC scale), oxygen saturation (SpO_2), blood pressure, and pulse rate were measured at the beginning and end of the test. Each patient was asked to walk at his or her own pace to cover the maximum distance possible in the allotted time. The distance covered by the patient in 6 minutes was recorded and reported in meters.

Psychometric Evaluation

The Survey Short Form 36-item questionnaire (SF-36) was used to assess quality of life. Processing the answers of a participant comprises the calculation of 10 scores corresponding to 8 scales measuring several aspects of perceived health and 2 summary components (physical and mental). The Hospital Anxiety and Depression Scale (HADS) was used for detecting states of depression and anxiety in patients (HADS; scores range from 0 to 42, with higher scores indicating worse symptoms). The Asthma Control Test (ACT) was used to measure the control in asthma patients. The ACT is a patient-completed questionnaire and consists of

5 items evaluating different dimensions of asthma control over the preceding 4 weeks (limitation of activities, shortness of breath, awakenings at night, use of reliever medication, and own perception of asthma control). Each question has 5 response levels, resulting in scores of 1-5. The sum of all scores gives the total ACT score, ranging from 5 (poorest asthma control) to 25 (optimal asthma control). The COPD assesment test (CAT) was used to measure symptom control in COPD patients. There are 8 questions in total in the scale, which is scored as an increasing Likert scale between 0 and 5. The Turkish validity and reliability study of the scale was conducted by Yorgancıoglu et al[16] and reported to be appropriate.

Pulmonary Rehabilitation Program

The patients attended a structured, comprehensive PR program including 16 sessions over 8 weeks. Pulmonary rehabilitation program was institution-based and performed under the supervision of a qualified physiotherapist at a hospital. The PR program consisted of stretching of upper and lower extremity muscles, breathing exercises, supervised endurance and resistance training, self-management, and patient education. Breathing exercises lasted for 30 minutes in each session; diaphragmatic and pursed-lip breathing were performed on patients with COPD. A stationary cycle ergometer exercise was performed for 30 minutes, twice a week, to determine the training heart rate. The training heart rate was calculated using the results of the 6-MWT, according to the following formula: [(max HR − resting HR) × (60% or 70%)] + resting HR (moderate to high-intensity exercise training). The training was performed under the supervision of a physiotherapist, and the heart rate was monitored continuously.

Statistical Analysis

SPSS, version 17.0 (SPSS Inc., Chicago, Ill, USA) was used for performing all statistical analyses of the present study. A level of $P < .05$ was defined as statistically significant. One-sample Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution of the data. Normally distributed continuous variables are defined as the mean and SD, and non-normally distributed continuous variables are defined as the median and interquartile range. Categorical variables are described as numbers and percentages. To compare sample characteristics before and after PR, paired t-tests and Wilcoxon Signed-Rank tests were conducted for normally distributed parameters and non-normally distributed parameters, respectively.

RESULTS

A total of 55 patients, 27 of whom were women, were included in the study. The mean age, height, weight, and BMI of the sample were 57.35 (±12.76), 161.95 (±9.48), 80.7 (±15.67), and 30.99 (±6.50), respectively. About 32 (58.18%) of the participants had asthma, and 23 (41.82%) had COPD. About 26 (47.3%) of the participants were active smokers. This table also presents the same features for both conditions (asthma and COPD) separately. While women are more frequent in the asthma group, men are more frequent in the COPD group. Active smoking is more common in the COPD group. Mean BMI was higher in the asthma group [33.14 (±7.13)] compared to the COPD group [27.99 (±3.97)] (Table 1).

Table 1. General Characteristics of the Study Population

Variables	Total = 55	Asthma, n (%) 32 (58.18%)	COPD, n (%) 23 (41.82%)
Gender (male/female) %	28 (50.9) / 27 (49.1)	6 (18.8) / 26 (81.2)	22 (95.7) / 1 (4.3)
Age (years)	57.35 (±12.76)	54.06 (±13.13)	61.91 (10.94)
Height (cm)	161.95 (±9.48)	158.25 (±9.52)	167.09 (6.74)
Weight (kg)	80.7 (±15.67)	82.47 (±17.48)	78.23 (±12.70)
BMI (kg/m^2)	30.99 (±6.50)	33.14 (±7.13)	27.99 (±3.97)
Cigarette smokers (n, %)	26 (47.3)	7 (21.9)	19 (82.6)
Cigarette (Pocket/year)	40 (35)	0 (0)	40 (35)

A statistically significant difference was found between the PABs, TAPSE, and TAPSE/PABs values of the population before and after PR (Table 2).

Improvement was observed in the PFT parameters of the patients. However, since these values were performed with different devices, the values were not included in the study.

A statistically significant difference was found between the 6-MWT, mMRC scale, ACT, physical function, physical roll

Table 2. Functional and Echocardiographic Parameters of the Entire Population Before and After Pulmonary Rehabilitation

Variables	Pre	Post	*P*
EF (%)	60 (0)	60 (0)	.439
PABs (mm Hg)	27.91 (±6.07)	23.67 (±3.60)	.006
TAPSE (mm)	21.64 (±5.75)	23.56 (±4.11)	<.001
TAPSE (mm)/ sPAB (mm Hg)	0.81 ± 0.28	1.01 ± 0.24	<.001
6-MWT	407.29 (±106.79)	501.81 (±144.95)	<.001
mMRC scale	2 (1)	1 (2)	<.001
ACT (only Asthma)	16.53 (±3.93)	20.34 (±4.31)	<.001
SF-36 Physical function	59 (±24.24)	73.91 (±24.30)	<.001
SF-36 Physical roll function	6 (100)	75 (50)	<.001
SF-36 General health	41.84 (±24.94)	52.87 (±21.82)	.003
SF-36 Mental health	59.13 (±20.44)	75.42 (±15.27)	<.001
SF-36 Pain	74 (58)	100 (28)	.006
SF-36 Vitality	51.55 (±20.48)	67.91 (±16.77)	<.001
Anxiety	6.45 (±3.67)	4.85 (±3.60)	<.001
Depression	5.31 (±3.88)	3.42 (±3.36)	<.001

EF, Ejection Fraction, PABs, Systolic Pulmonary Artery Pressure, TAPSE, Tricuspid Annular Plane Systolic Excursion, mMRC, Modified Medical Research Council, 6-MWT, six-minute walk distance; SF-36, Short Form 36-item questionnaire.

Table 3. Functional and Echocardiographic Parameters of the Astma and COPD Groups Before and After Pulmonary Rehabilitation

	Asthma, n (%); 32 (58.18%)			COPD, n (%); 23 (41.82%)		
Variables	**Pre**	**Post**	***P***	**Pre**	**Post**	***P***
EF (%)	60 (5)	60 (5)	.405	60 (0)	60 (0)	.99
PABs (mm Hg)	28.06 ± 6.73	23.34 ± 4.29	<.001	27.70 ± 5.17	24.13 ± 2.34	.006
TAPSE (mm)	21.38 ± 5.59	23.63 ± 4.04	.023	22.00 ± 6.07	23.48 ± 4.31	.127
TAPSE (mm)/sPAB (mm Hg)	0.81 ± 0.29	1.04 ± 0.26	<.001	0.82 ± 0.26	0.98 ± 0.22	.006
6-MWT	396.06 ± 83.84	489.91 ± 134.15	<.001	431.64 ± 129.05	519.14 ± 161.02	<.001
mMRC scale	1.5 (1)	1 (1)	<.001	2 (2)	1 (2)	.004
ACT (only asthma)	16.53 ± 3.93	20.34 ± 4.31	<.001	–	–	–
SF-36 Physical function	45.41 ± 23.49	70.00 ± 25.37	.003	62.61 ± 25.31	79.35 ± 22.12	<.001
SF-36 Physical roll function	0 (100)	75 (50)	.006	50 (100)	100 (25)	.005
SF-36 General health	42.69 ± 24.87	57.13 ± 18.49	.002	40.65 ± 25.53	46.96 ± 24.98	.316
SF-36 Mental health	56.13 ± 21.71	74.75 ± 16.89	<.001	63.30 ± 18.16	76.35 ± 12.99	.003
SF-36 Pain	62 (47)	74 (38)	.007	100 (26)	100 (16)	.503
SF-36 Vitality	48.28 ± 21.08	67.81 ± 17.96	<.001	56.09 ± 19.13	68.04 ± 15.36	.009
Anxiety	7.09 ± 4.04	5.56 ± 3.93	.011	5.57 ± 2.92	3.87 ± 2.90	.004
Depression	5.69 ± 4.48	3.69 ± 3.69	.009	4.78 ± 2.86	3.04 ± 2.87	.018

EF, Ejection Fraction, PABs, Systolic Pulmonary Artery Pressure, TAPSE, Tricuspid Annular Plane Systolic Excursion, mMRC, Modified Medical Research Council, 6-MWT, six-minute walk distance; SF-36, Short Form 36-item questionnaire.

function, general health, mental health, pain, vitality, anxiety, and depression values of the population before and after PR (Table 2).

Meanwhile, the same statistics were made separately for each disease (asthma and COPD) (Table 3); in asthma patients, the results were similar to the entire population's results. However, in COPD patients, there was a statistically significant difference between pre- and post-PR values of PABs, TAPSE/PABs, 6-MWT, mMRC scale, physical function, physical roll function, mental health, vitality, anxiety, and depression. In contrast, in COPD patients, EF, TAPSE, general health, and pain were not statistically significantly different before and after the PR.

DISCUSSION

This multidisciplinary study has shown that PR improves echocardiographic parameters as well as health-related quality of life in subjects with primary pulmonary disease and may be a potential approach to prevent the development of pulmonary hypertension in such patients. In this study, 16 sessions of PR over 8 weeks were applied to patients who were symptomatic despite optimal asthma or COPD treatment. Physical and psychosocial parameters and cardiac functions were evaluated before and after PR. The echocardiographic evaluation of the cardiac effects of PR distinguishes this study from other studies.

In this study, the 6-MWT, which is one of the important parameters used in the follow-up and treatment of pulmonary hypertension, improved significantly after PR. This improvement is statistically significant in both asthma and COPD groups. When PR efficacy was evaluated with the SF-36 test, improvement was observed in all variables in the asthma group. However, this level of efficacy was not achieved in the COPD group. These results may be related to the higher disease awareness and treatment adherence in the asthma patient group. The BMI of the asthma group is higher than that of the COPD group. This may explain the greater improvement in poor quality of life in the asthma group. The study concluded after 8 weeks of PR. However, increased physical activity and improved mental well-being following PR are expected to lead to weight loss, suggesting that long-term improvements may be even more pronounced—especially in the asthma group with a higher BMI. In overweight patients with asthma, neutrophilic inflammation has been shown to be more pronounced, which may be mitigated by weight loss and exercise.[17] Although asthmatic patients might display a slightly lower baseline exercise capacity, this difference is generally not significant, and those with lower exercise capacity may experience a relatively greater benefit from PR.[1] Moreover, the typically younger age and better treatment and exercise compliance in asthmatic patients may further enhance PR outcomes.

In contrast, many COPD patients experience exercise-induced desaturation, which can negatively affect exercise capacity and increase pulmonary vascular resistance during exertion.[18] Exercise training itself appears to improve right heart function through mechanisms such as myocardial remodeling, increased capillarization, and reduced systemic inflammation.[19] However, because COPD is a chronic and progressive disease, the development of right heart dysfunction in these patients is often long-standing and irreversible. This may explain the less pronounced improvement in right ventricular function in response to short-term PR.[20] Additionally, respiratory exercises in PR can improve oxygenation and indirectly benefit right heart performance, while enhanced peripheral muscle strength may facilitate better

capillarization and venous return.[19,20] Moderate-to-high-intensity exercise training has also been associated with increased endurance by delaying the onset of lactic acidosis, thereby reducing acidosis and hypercapnia—all of which favorably impact right heart pressures.[21]

There is limited research on the cardiac effects of PR. There is controversy regarding the effects of exercise in patients with severe pulmonary hypertension. In the past, some physicians have even recommended avoiding physical exercise in this patient group.[19,22] However, studies on patient coronary artery disease and severe left heart failure have shown that exercise has positive effects on endothelial function, exercise capacity, and quality of life.[8,23,24] Improvements in functional capacity and respiratory functions were demonstrated with a medically supervised treadmill program in group 1 pulmonary hypertension patients.[25] In a multicenter study evaluating the effects of exercise training in PAH/CTEPH patients, improvements were observed in 6-MWT, quality of life, WHO functional class, and peak oxygen consumption during exercise after exercise programs conducted both in and out of the hospital.[26]

In this study, no change was observed in left heart functions after PR, which is consistent with other studies. However, after PR, sPAB decreased, and TAPSE and TAPSE/sPAB ratios increased. This is an indicator of improvement in right ventricular functions after PR. Since right ventricular longitudinal contraction provides 80% of right ventricular function, TAPSE is an important marker in the assessment of right ventricular function.[27] However, the geometry of the right ventricle is relatively difficult to understand compared to the symmetrical left ventricle. Therefore, the incorporation of echocardiographic parameters other than TAPSE and systolic pulmonary artery pressure, and the use of cardiac MR into the clinical practice should be accelerated.[28] There are studies evaluating the effects of PR on right ventricular function with different imaging modalities. In a study examining the effects of PR on right heart function using cardiac MRI, a significant reduction in patients' dyspnea complaints was observed after PR, while a slight reduction in RV GLS and RV mass was observed.[29] In another study investigating the effects of intensive endurance exercise in athletes, a decrease in RV fractional area change and tricuspid annular plane systolic excursion was observed following intensive exercise.[30] It is widely accepted that the cardiac effects of PRare related to exercise intensity. However, there is no consensus on the exercise program to be applied according to the severity of the disease and the type of disease.

The mechanism of the beneficial effects of PR on pulmonary hypertension PABs and TAPSE is not fully understood. There are some theories regarding the mechanism of action of PR on pulmonary hypertension. Improvement in exercise capacity after PR was associated with regression in muscle atrophy, improvement in muscular metabolism, and gas exchange. However, the improvement in ventilation capacity also has an effect on this process.[31] It has been stated that it is associated with changes in inflammatory mediators, endothelial nitric oxide synthase activity, and decreased vascular oxidative stress in this patient group.[31]

Study Limitations

The limited number of patients included in this study and the absence of a control group limit the impact of the study on clinical practice. However, considering the positive results of PR, the presence of a control group that did not receive PR would cause ethical problems. Pulmonary function tests were performed before and after PR in the patients who participated in this study, and improvement was observed in the PFT parameters of the patients. However, since these values were performed with different devices, the values were not included in the study. The possible positive effects of weight loss in patients during the PR process could not be evaluated.

Another limitation is that the PR intensity applied in the study could not be classified and the cardiac effects of PR intensity were not evaluated. In addition, the fact that fractional area change was not calculated in the evaluation of right ventricular function in patients represents another limitation of the study. Moreover, there were no Brain Natriuretic Peptide measurements in this study.

CONCLUSION

In patients with primary lung disease, a significant improvement was achieved in the pulmonary, cardiac, physical, and psychological functions of the patients with PR.

Ethics Committee Approval: This study was conducted in accordance with the rules recommended in the Declaration of Helsinki and approved by the Ethics Committee of Balıkesir University Faculty of Medicine (Approval No: 71, Date: 29.4.2020).

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

Peer-review: Externally peer reviewed.

Author Contributions: Concept – D.E.A., O.S., F.E., S.S.O.; Design – E.A., O.S., F.E.; Supervision – E.A., A.N.; Resources – D.E.A., O.S., A.N.; Materials – D.E.A., O.S., F.E., S.S.O.; Data Collection and/or Processing – D.E.A., O.S., F.E., S.S.O.; Analysis and/or Interpretation – D.E.A., O.S., S.S.O.; Literature Search – D.E.A., O.S., S.S.O., A.N.; Writing – D.E.A., O.S., S.S.O., A.N.; Critical Review – D.E.A., O.S., S.S.O., A.N., E.A., F.E.

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Dysregulation of Serum miR-212-3p Serves as a Biomarker to Predict Disease Onset and Short-Term Prognosis in Acute Coronary Syndrome Patients

ABSTRACT

Background: This study was conducted to investigate the clinical value of microRNA (miR)-212-3p in acute coronary syndrome (ACS) patients.

Methods: This study involved 128 ACS patients and 110 patients with coronary arterial atherosclerosis. Real-time fluorescence quantitative polymerase chain reaction was employed to measure serum miR-212-3p levels and assessed its correlation with disease severity. The diagnostic efficacy of miR-212-3p was evaluated through receiver operating characteristic (ROC) curve and logistic regression modeling. Furthermore, Kaplan–Meier and Cox regression analyses were utilized to determine the predictive value of miR-212-3p for the occurrence of major adverse cardiovascular events (MACE).

Results: The serum miR-212-3p was elevated in ACS patients, with levels in acute myocardial infarction (AMI) patients being greater than unstable angina pectoris (UAP) patients. Serum miR-212-3p demonstrated considerable diagnostic utility in the identification of ACS patients and in differentiating between AMI and UAP cases. Furthermore, miR-212-3p levels correlated with myocardial injury markers [cardiac troponin I (cTnI), high-sensitivity C-reactive protein (hs-CRP), and creatine kinase-MB (CK-MB)], as well as with coronary artery scores (Gensini and SYNTAX). Elevated levels of miR-212-3p were associated with MACE incidence. Serum miR-212-3p, cTnI, Gensini, and SYNTAX score served as independent risk factors for MACE occurrence, with higher expression of miR-212-3p being linked to a poorer clinical prognosis.

Conclusion: Serum miR-212-3p might serve as a non-invasive biomarker for ACS diagnosis and MACE prediction and as a supplementary molecular tool in clinical practice.

Keywords: Acute coronary syndrome, biomarker, diagnosis, miRNA, prognosis

ORIGINAL INVESTIGATION

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INTRODUCTION

Cardiovascular diseases have emerged as the leading cause of mortality, with coronary heart disease (CHD) identified as the most prevalent etiology.[1] Acute coronary syndrome (ACS) represents the most severe type of CHD, primarily characterized by acute myocardial infarction (AMI) and unstable angina pectoris (UAP).[2] It is characterized by acute onset, rapid progression, elevated mortality rates, and significant inflammatory response.[3] Currently, ACS diagnosis relies on clinical symptoms, electrocardiogram (ECG) findings, and serum biomarkers.[4] Cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB) are the preferred biomarkers for ACS diagnosis; however, their late rise and low specificity hinder early detection.[5] Furthermore, percutaneous coronary intervention (PCI) is the primary therapeutic approach for ACS, effectively enhancing myocardial blood flow.[6] Nonetheless, some individuals may experience major adverse cardiovascular events (MACE) post-procedure, raising the risks of readmission and death.[7] Hence, finding fast and accurate diagnostic and prognostic markers is vital for better ACS care.

MicroRNAs (miRNAs) are endogenous, single-stranded non-coding RNAs in biological fluids. Their dysregulation is associated with cardiovascular development,

myocardial cell injury, and heart failure,[8] suggesting potential as ACS biomarkers.[9] In cardiovascular research, miRNAs impact cell processes[10] and disease progression.[11] In controlled experimental settings, individual miRNAs have demonstrated promising capabilities in disease diagnosis and prognostication. However, their instability in clinical settings limits utility. Inconsistent expression and undetected levels reduce diagnostic accuracy.[12] Consequently, there is a pressing need for the identification and development of additional miRNAs. The utilization of multiple miRNA combinations has the potential to enhance diagnostic and predictive accuracy for diseases, as well as to refine detection methodologies.[13] Given the clinical significance of miR-212-3p in relation to cardiovascular disease, for instance, the rupture of coronary arterial atherosclerosis (CAA) plaques is identified as the primary etiological factor for ACS. Notably, miR-212-3p is linked to several cardiovascular conditions. It is upregulated during coronary plaque rupture,[14] correlates with coronary artery disease (CAD) risk factors,[15] and predicts pulmonary hypertension in acute right heart failure.[16] It has also been demonstrated that miR-212-3p plays a role in regulating myocardial cell injury following myocardial infarction by targeting NR4A2 and p53/Bax.[17] Consequently, it was speculated that miR-212-3p might have analogous functions in the onset and progression of ACS, potentially serving as a non-invasive diagnostic and prognostic marker for this condition. Furthermore, this molecular marker could facilitate multi-miRNA diagnostic strategies for ACS. Nevertheless, there is a paucity of clinical studies addressing this topic at present.

Consequently, this investigation measured miR-212-3p levels in ACS patients' serum, evaluated its predictive value for ACS occurrence and MACE after PCI, and explored its potential as an auxiliary diagnostic and prognostic marker. The findings of this study offer valuable insights for early identification and timely postoperative intervention in ACS patients.

METHODS

AI Statement

AI was not used in the writing process of the article.

Ethical Statement

This study was performed in line with the principles of the Declaration of Helsinki. This study received approval from the Research Ethics Committee of The First Hospital of Lanzhou University, and all participants provided informed consent.

Study Object

A total of 128 ACS patients who underwent PCI at The First Hospital of Lanzhou University between 2021 and 2024 were designated as the experimental group. All patients were diagnosed with ACS for the first time upon admission. In accordance with the established definition of ACS, the patients were further categorized into 2 subgroups: the AMI group, which comprised 67 individuals [including 32 with ST-elevation myocardial infarction (STEMI) and 35 with non-ST-elevation myocardial infarction (NSTEMI)], and the UAP group, consisting of 61 individuals.

Additionally, a control group was formed from 110 CAA patients who received treatment during the same period. Patients classified as having CAA are individuals who exhibit no overt symptoms or clinical manifestations of CHD during the course of attendance. These patients might describe discomfort in the precordial region following intense physical activity. Subsequent imaging examinations confirmed the presence of coronary atherosclerotic plaques, with the degree of vascular stenosis not significant, measuring less than 50% or even 25%. These patients exhibit signs of coronary atherosclerosis. Not all individuals diagnosed with coronary artery disease received magnetic resonance imaging (MRI) of the chest (main) or heart (fewer than 20%); consequently, some patients were subjected to MRI, while others underwent coronary angiography. The CAA patients fulfilled the diagnostic criteria outlined in the Chinese Guidelines for the Prevention of Cardiovascular Disease (2017).[18] The exclusion criteria for this group were aligned with those for ACS.

Inclusion and Exclusion Criteria for Acute Coronary Syndrome

The inclusion criteria for ACS were as follows: (1) adherence to the diagnostic standards outlined in the Emergency Rapid Diagnosis and Treatment Guidelines for Acute Coronary Syndrome (2019);[19] (2) the presence of clinical symptoms indicative of angina pectoris or myocardial infarction, which may present as UAP, NSTEMI, or STEMI; (3) verification of stenosis or occlusion via coronary angiography; and (4) fulfillment of the criteria for PCI and subsequent receipt of PCI treatment.

The exclusion criteria for ACS encompassed: (1) individuals with concurrent other cardiac conditions; (2) individuals experiencing chest pain attributable to alternative causes; (3) individuals exhibiting severe organ dysfunction, acute trauma, infections, or other inflammatory conditions; (4) individuals with coexisting immunodeficiency disorders or chronic systemic illnesses; (5) pregnant or breastfeeding women; and (6) individuals with incomplete clinical records.

Baseline Data Collection

The clinical data from the initial admission of 2 patient groups were gathered, encompassing variables such as age, gender, body mass index (BMI), as well as the history of smoking, drinking, hypertension, and diabetes. Additionally, the patients' heart rate, white blood cell count (WBC), blood lipid

HIGHLIGHTS

- miR-212-3p shows a significantly increased level in the serum of acute coronary syndrome (ACS) patients.
- miR-212-3p serves as a non-invasive biomarker for ACS diagnosis.
- miR-212-3p is a significant parameter for the severity of ACS.
- miR-212-3p has a high predictive value for the major adverse cardiovascular event occurrence.
- Low expression of miR-212-3p exhibits a more favorable prognosis.

levels [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], and levels of serum markers of myocardial injury [cTnI, high-sensitivity C-reactive protein (hs-CRP), and CK-MB] were extracted from various diagnostic reports at the time of admission. Furthermore, scoring data for the Gensini[20] and SYNTAX scores[21] were obtained in accordance with the coronary artery scoring system.

Follow-Up Method

The follow-up of ACS patients who have undergone PCI was carried out through various methods, including outpatient visits, readmissions, telephone consultations, and WeChat communications, over a period of 6 months. This follow-up process commenced 1 week post discharge and continued until the occurrence of MACE or 6 months had elapsed since discharge. The timing of MACE experienced by the patient was documented. The MACE indicators to be monitored include new onset myocardial infarction, new onset stroke, malignant arrhythmia, unstable angina, new-onset heart failure, cardiogenic shock, sudden death, unexpected coronary revascularization, stent thrombosis, and all-cause death. ACS patients who underwent PCI were categorized into 2 subgroups based on the occurrence of MACE: the MACE group, consisting of 37 cases, and the non-MACE group, comprising 91 cases.

Serum Collection

Upon admission, a volume of 6 mL of venous blood was promptly obtained from patients diagnosed with ACS and CAA utilizing a procoagulant tube. The collected blood sample was allowed to incubate at room temperature for 30 minutes, followed by centrifugation in a low-temperature centrifuge for 15 minutes at 4°C and 3000 xg. The resulting supernatant was then carefully transferred to an RNase-free EP tube and subsequently stored in a freezer at −80°C.

Real-time Quantitative Polymerase Chain Reaction

Total RNA was extracted from the serum of ACS and CAA patients utilizing an RNA extraction kit (whole blood, plasma, and serum total RNA extraction kit, HaiGene, China). The quality of the extracted RNA was assessed using a Qubit™ 4 Fluorometer (Thermo Fisher, USA). Following this, cDNA synthesis was performed using a reverse transcription kit (Hifair® Ⅱ 1st Strand cDNA Synthesis Kit, Yeasen, China), with the resulting cDNA serving as a template for RT-qPCR.

A 20 μL reaction system was prepared in accordance with the guidelines provided in the MicroRNAs qPCR Kit-SYBR Green Method (Sangon Biotech, China). Subsequently, the relative expression levels of miR-212-3p in the serum samples from all participants were conducted using a Roche LightCycler480 (Switzerland). The thermal cycling conditions were set to 30 s at 95°C, followed by 5 seconds at 95°C and 30 seconds at 60°C, with a total of 40 cycles for the latter 2 steps. The dissolution curve program referenced instrument settings. The primers for miR-212-3p were synthesized by GeneWiz Biotechnology Co., Ltd. in Suzhou, China, with the forward sequence (5′-3′) being GGTAACAGTCTCCAGTCA and the reverse sequence (5′-3′) GCAATTGCACTGGATACG. U6 was employed as an internal reference, with the forward primer (5′-3′) sequence GCTTCGGCACATATACTAAAAT and the reverse sequence (5′-3′) CGCTTCACGAATTTGCGTGTCAT. The relative expression level of miR-212-3p was calculated using the $2^{-\Delta\Delta Ct}$ method.

Data Analysis

The experimental data were analyzed using SPSS IBM Version 23.0 (SPSS Inc., Chicago, Illinois, USA) and GraphPad Prism 9.0 (Dotmatics, Boston, Massachusetts, USA) software. The normality of continuous ratio scale data was assessed utilizing the Shapiro–Wilk test, which indicated that all continuous ratio scale data in this study adhered to a normal distribution ($P > .05$). For continuous ratio scale data, the mean ± standard deviation (SD) was employed for representation. The independent samples *t*-test was utilized for comparisons between 2 groups, while 1-way analysis of variance was applied for comparisons among multiple groups.

The diagnostic performance of miR-212-3p was assessed using receiver operating characteristic (ROC) curves. The relationship between miR-212-3p expression levels and various indicators, including blood lipids, serum myocardial injury biomarkers, and coronary artery scores, was examined using the Pearson correlation method. To identify risk factors for ACS in CAA patients, a multiple logistic regression model was employed, while the Cox proportional hazards model was utilized to determine potential risk factors for MACE following PCI. Additionally, Kaplan–Meier survival curves were generated to illustrate the MACE incidence of ACS patients stratified by different levels of miR-212-3p expression.

RESULTS

Comparison of General Clinical Data Between Acute Coronary Syndrome Patients and Controls

This study used the G*Power 3.1.9.7 software to estimate the sample size and ensure adequate statistical test power. At least 102 research subjects needed to be included in each group when the effect size was set at a moderate level [Cohen's *d* value = 0.5, significance level (α) = 0.05, test power (1 − β) = 0.8]. This study included 128 cases in the ACS group and 110 cases in the CAA group, with the sample sizes of both groups exceeding the threshold. Additionally, the post-hoc power analysis showed that, with an estimated effect size (d) of 0.5 and a significance level (α) of 0.05, the power (1-β) of a sample size of 238 was 0.9693, significantly higher than the standard threshold of 0.8. This suggested that this study had sufficient power to detect the expected effect.

Within the ACS group, 32 patients were diagnosed with STEMI, 35 with NSTEMI, and 61 with UAP. Statistical analysis revealed no significant differences between the 2 groups regarding age distribution, gender ratio, history (including smoking, alcohol consumption, hypertension, and diabetes), and heart rate ($P > .05$). Notably, the BMI, WBC, and lipid profile indicators, specifically TC and LDL-C levels, were significantly elevated in the ACS group compared to the CAA group ($P < 0.01$, Table 1).

Furthermore, the study performed a statistical analysis of serum myocardial injury biomarkers and coronary artery scoring indicators in ACS patients, revealing elevated

Table 1. The Basic Information of All Subjects

Factors	Control (n = 110)	ACS (n = 128)	*P*
Age (years)	57.08 ± 8.04	56.73 ± 8.00	.734
Gender n (%)			.807
Male	61 (55.45)	73 (57.03)	
Female	49 (44.55)	55 (42.97)	
BMI (kg/m^2)	24.69 ± 2.05	25.88 ± 1.81	<.001
Smoking history n (%)			.453
Yes	60 (54.55)	76 (59.38)	
No	50 (45.45)	52 (40.62)	
Drinking history n (%)			.631
Yes	49 (45.55)	61 (47.66)	
No	61 (55.45)	67 (52.34)	
Hypertension history n (%)			.396
Yes	69 (62.73)	87 (67.97)	
No	41 (37.27)	41 (32.03)	
Diabetes history n (%)			.214
Yes	53 (48.18)	72 (56.25)	
No	57 (51.82)	56 (43.75)	
Heart rate (bpm)	75.25 ± 9.19	74.19 ± 6.02	.284
WBC (10^9/L)	8.08 ± 1.52	9.62 ± 1.71	<.001
Blood lipids			
TC (mmol/L)	4.62 ± 0.88	4.93 ± 0.52	.001
TG (mmol/L)	1.48 ± 0.28	1.51 ± 0.30	.546
LDL-C (mmol/L)	2.48 ± 0.27	2.60 ± 0.27	.001
HDL-C (mmol/L)	1.34 ± 0.32	1.25 ± 0.44	.087
Myocardial injury markers			–
cTnI (ng/mL)	–	1.01 ± 0.56	
hs-CRP (mg/L)	–	5.98 ± 1.54	
CK-MB (IU/L)	–	123.26 ± 34.83	
Gensini Score	–	49.55 ± 16.58	–
SYNTAX Score	–	28.46 ± 6.00	–
Types			–
STEMI	–	32 (25.00)	
NSTEMI	–	35 (27.34)	
UAP	–	61 (47.66)	

P < .05 means a significant difference.

average levels. Specifically, cTnI averaged 1.01 ± 0.56 ng/mL, hs-CRP averaged 5.98 ± 1.54 mg/L, and CK-MB averaged 123.26 ± 34.83 IU/L. Additionally, the coronary artery scoring indicators, including the Gensini score and SYNTAX score, averaged 49.55 ± 16.58 and 28.46 ± 6.00, respectively (Table 1).

Up-regulation and High Diagnostic Value of Serum miR-212-3p Expression in Acute Coronary Syndrome Patients

The expression levels of miR-212-3p in the serum of ACS patients were found to be significantly elevated, approximately double that of the CAA group (*P* < .001, Figure 1A). Serum miR-212-3p demonstrated a robust capacity for differentiating ACS patients from those with CAA, achieving

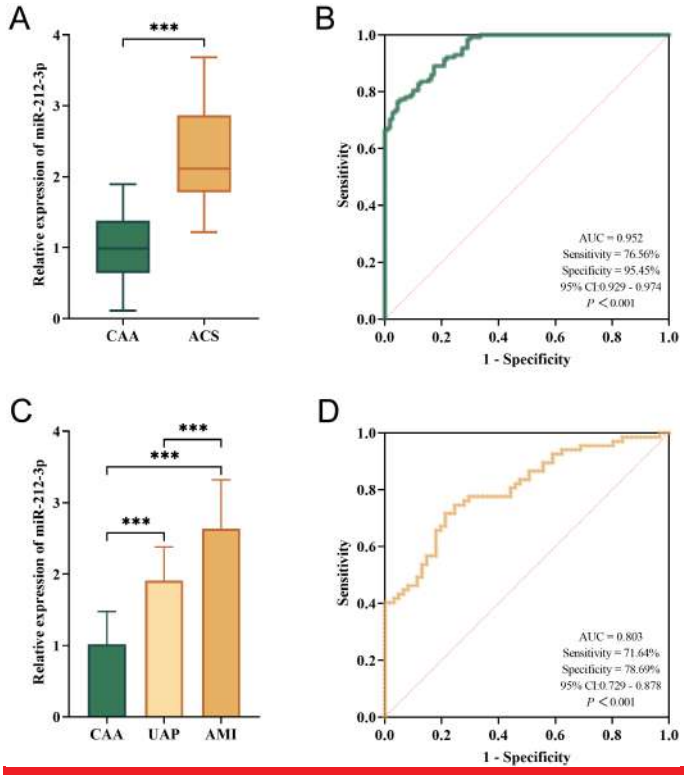

Figure 1. The expression levels of serum miR-212-3p in CAA and ACS groups (A), and its diagnostic value for ACS (B). The expression levels of serum miR-212-3p in AMI and UAP group (C), and its discriminatory efficacy for AMI and UAP (D). *, *P* < .001.**

an area under the curve (AUC) of 0.952 [95% CI: 0.929-0.974]. The sensitivity and specificity for this differentiation were recorded at 76.56% and 95.45%, respectively (*P* < .001, Figure 1B).

Furthermore, the levels of miR-212-3p in the serum of patients AMI and UAP were significantly higher than those observed in the CAA group (*P* < .001). Notably, the relative level of miR-212-3p in AMI patients was significantly greater than that in UAP patients (*P* < .001, Figure 1C). The AUC for serum miR-212-3p in distinguishing between AMI and UAP patients was 0.803 (95% CI: 0.729-0.878), with sensitivity and specificity values of 71.64% and 78.69%, respectively (*P* < .001, Figure 1D).

Up-regulated Serum miR-212-3p was Significantly Associated with Diagnostic and Prognostic Indices of Acute Coronary Syndrome Patients

In ACS patients, serum levels of miR-212-3p exhibited a significant positive correlation with various lipid parameters, including TC, TG, and LDL-C. Additionally, there were notable positive correlations with serum myocardial injury biomarkers such as cTnI, hs-CRP, and CK-MB. Furthermore, significant positive correlations were observed with coronary artery scoring metrics, specifically the Gensini score and the SYNTAX score (*P* < .001). Conversely, a significant negative correlation was identified between serum miR-212-3p levels and HDL-C (*P* < .001, Table 2). Notably, the strongest

Table 2. Correlation Between Expression Level of miR-212-3p and Various Clinical Indexes of ACS Patients

Factors	Correlation (r)	95% CI	*P*
TC (mmol/L)	0.685	0.581-0.768	<.001
TG (mmol/L)	0.746	0.658-0.814	<.001
LDL-C (mmol/L)	0.875	0.827-0.911	<.001
HDL-C (mmol/L)	−0.886	−0.918 to −0.841	<.001
cTnI (ng/mL)	0.936	0.911-0.955	<.001
hs-CRP (mg/L)	0.756	0.671-0.822	<.001
CK-MB (IU/L)	0.762	0.678-0.826	<.001
Gensini Score	0.905	0.868-0.933	<.001
SYNTAX Score	0.900	0.861-0.928	<.001

P < .05 means a significant difference.
ACS, acute coronary syndrome; CK-MB, creatine kinase isoenzymes; cTnI, cardiac troponin I; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

correlations were found between serum miR-212-3p and cTnI, as well as the Gensini and SYNTAX scores.

Serum miR-212-3p Was a Risk Factor for Acute Coronary Syndrome in Coronary Arterial Atherosclerosis Patients

The demographic and clinical characteristics of patients with CAA, including age, sex, smoking history, alcohol consumption, diabetes history, heart rate, TG, LDL-C, and HDL-C, did not demonstrate a statistically significant correlation with the occurrence of ACS (*P* > .05). In contrast, BMI [odds ratio (OR) = 2.152, 95% CI: 1.060-4.479, *P* = .036], a history of hypertension (OR = 2.931, 95% CI: 1.038-8.929, *P* = .048), WBC (OR = 3.318, 95% CI: 1.682-6.758, *P* < .001), TC (OR = 2.010, 95% CI: 1.016-4.054, *P* = .047), and miR-212-3p (OR = 13.040, 95% CI: 6.595-27.320, *P* < .001) were identified as significant risk factors for ACS occurrence in CAA patients (Figure 2A). Notably, serum levels of miR-212-3p exhibited the most pronounced influence on the ACS occurrence.

Comparison of General Clinical Data Between Non-Major Adverse Cardiovascular Events and Major Adverse Cardiovascular Events Groups in Acute Coronary Syndrome Patients

In ACS patients, 37 individuals experienced MACE, while 91 did not, resulting in an incidence rate of 28.91% for MACE. Statistical analysis revealed no significant differences in demographic and clinical characteristics, including age distribution, gender ratio, BMI, blood lipid indicators (TC, TG, LDL-C, and HDL-C), hs-CRP, and CK-MB between the 2 patient groups (*P* > .05). However, the levels of cTnI (*P* < .01), Gensini score (*P* < .05), and SYNTAX score (*P* < .05) were significantly elevated in the MACE group compared to the non-MACE group (Table 3).

Up-regulation of Serum miR-212-3p Expression in Major Adverse Cardiovascular Events Group

The serum expression level of miR-212-3p in ACS patients experiencing MACE was found to be significantly elevated, approximately 1.67 times greater than that observed in non-MACE patients (*P* < .001, Figure 2B).

Serum miR-212-3p Had High Prognostic Significance for Acute Coronary Syndrome Patients

In ACS patients, it was found that there was no statistically significant correlation between age, gender, BMI, blood lipid parameters (TC, TG, LDL-C, and HDL-C), and serum myocardial injury biomarkers (hs-CRP and CK-MB) with patient prognosis (*P* > .05). Notably, the cTnI [hazard ratio (HR) = 2.217, 95% CI: 1.060-4.638, *P* = .035], coronary artery scoring metrics, specifically the Gensini score (HR = 2.662, 95% CI: 1.028-6.895, *P* = .044) and the SYNTAX score (HR = 2.024, 95% CI: 1.015-4.034, *P* = .045), as well as serum miR-212-3p (HR = 5.077, 95% CI: 1.882-13.700, *P* = .001) emerged as predictors of MACE occurrence, demonstrating a significant correlation with poor prognosis in ACS patients (Figure 3A). Among them, miR-212-3p exerted the most significant influence on the occurrence of MACE.

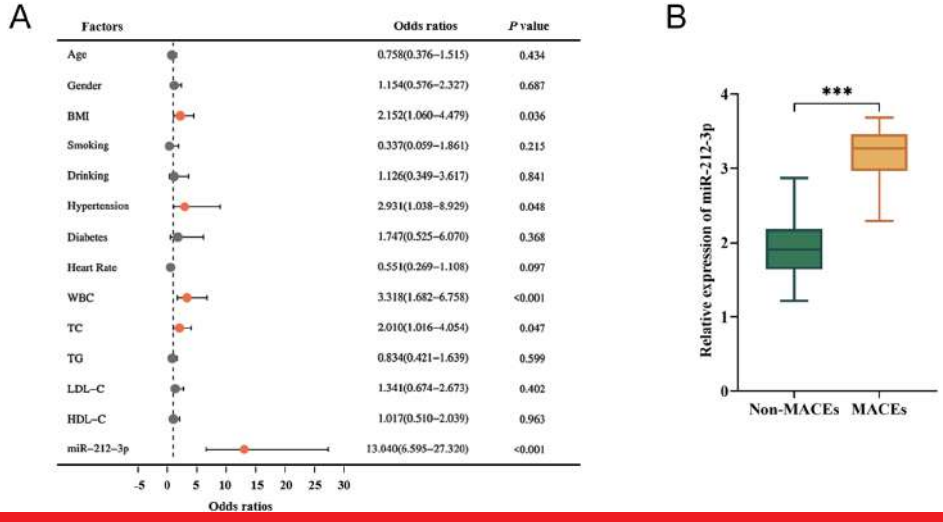

Figure 2. The prediction of risk factors for ACS in CAA patients (A), as well as the expression levels of serum miR-212-3p in non-MACE and MACE groups (B). *, *P* < .001.**

Table 3. The Clinical Variables of ACS Patients in Non-MACEs and MACEs Groups

Factors	Non-MACEs (n = 91)	MACEs (n = 37)	*P*
Age (years)	56.22 ± 7.73	57.97 ± 8.62	.263
Gender n (%)			.408
Male	54 (59.34)	19 (51.35)	
Female	37 (40.66)	18 (48.65)	
BMI (kg/m^2)	25.82 ± 1.77	26.02 ± 1.91	.568
Blood lipids			
TC (mmol/L)	4.87 ± 0.47	5.06 ± 0.63	.071
TG (mmol/L)	1.48 ± 0.26	1.57 ± 0.36	.114
LDL-C (mmol/L)	2.58 ± 0.24	2.66 ± 0.33	.136
HDL-C (mmol/L)	1.29 ± 0.41	1.16 ± 0.47	.112
Myocardial injury markers			
cTnI (ng/mL)	0.93 ± 0.53	1.23 ± 0.57	.005
hs-CRP (mg/L)	5.85 ± 1.47	6.28 ± 1.66	.155
CK-MB (IU/L)	120.80 ± 32.41	129.20 ± 40.02	.219
Gensini score	47.27 ± 16.05	54.08 ± 17.16	.035
SYNTAX score	27.76 ± 5.78	30.19 ± 6.27	.037

P < .05 means a significant difference.
ACS, acute coronary syndrome; BMI, body mass index; cTnI, cardiac troponin I; CK-MB, creatine kinase isoenzymes; HDL-C, high-density lipoprotein cholesterol hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACEs, major adverse cardiovascular events; TC, total cholesterol; TG, triglyceride.

Based on the average expression levels of miR-212-3p in the serum of ACS patients, individuals were categorized into high and low expression groups. The group exhibiting higher levels of serum miR-212-3p experienced a higher incidence of MACE, correlating with a poorer prognosis for ACS patients (*P* < .001, Figure 3B).

DISCUSSION

Acute coronary syndrome is a common cardiac emergency[22] and a major cause of mortality in CHD.[23] Although coronary angiography is the "gold standard" for diagnosing ACS[24] due to its high accuracy, it is an invasive procedure that may lead to complications.[25] The ECGs are useful for dynamic monitoring but may show no significant changes in patients with severe coronary lesions or during suspected ischemic episodes.[26] Certain serum biomarkers released after myocardial necrosis have limited early diagnostic value, with a sensitivity of only 19%-43% within the first 3 hours post-event.[27] Consequently, finding new biomarkers for ACS auxiliary diagnosis remains a key clinical research priority.

The miRNAs are valuable auxiliary diagnostic markers due to their stable expression, easy detectability, and strong clinical relevance.[28] In ACS research, specific miRNAs such as miR-335-5p,[29] miR-483-5p,[3] and miR-140-3p[30] have shown potential. Recently identified, miR-212-3p is associated with atherosclerosis and early vascular inflammation.[31] As previously noted, miR-212-3p has been linked to CAA plaque rupture, CAD, and acute right heart failure.[14-16] This study revealed significantly elevated serum miR-212-3p levels in ACS patients, and even more elevated levels in AMI patients compared to UAP patients. The ROC curve is a widely utilized tool for assessing the accuracy of diagnostic biomarkers.[32] Using the ROC curve, it was demonstrated that miR-212-3p effectively discriminates ACS patients and differentiates between AMI and UAP. Logistic analysis further indicated that miR-212-3p could be a risk factor for ACS in CAA patients.

Abnormalities in blood lipid levels contribute to ACS and MACE,[33] while cTnI, hs-CRP, and CK-MB indicate myocardial injury and vascular inflammation.[34] The Gensini and SYNTAX scores assess arterial stenosis and the severity of atherosclerosis.[35] This study identified a significant correlation between serum miR-212-3p and the aforementioned factors, indicating that miR-212-3p correlates with these factors, suggesting it could reflect the severity of coronary artery disease in ACS patients and could be linked to the MACE incidence.

The PCI is a critical surgical approach for the revascularization of ACS, demonstrating a significant reduction in infarct size.[6] Nevertheless, post-PCI MACE remains common, worsening patient outcomes and healthcare burdens.[7] Identifying MACE risk factors helps target preventive strategies.[36] The Gensini and SYNTAX scores are vital for recognizing high-risk patients and forecasting MACE risk.[37] Typically,

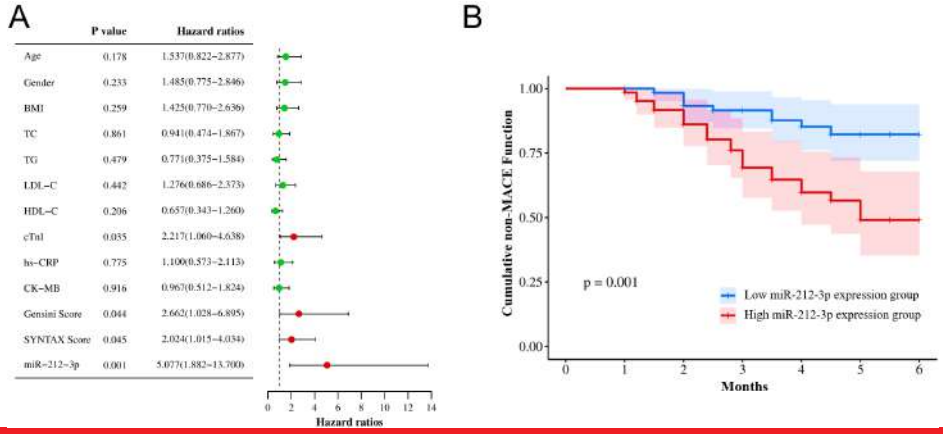

Figure 3. The prediction of risk factors for poor prognosis in ACS patients (A), as well as the MACE incidence in groups with different levels of miR-212-3p expression (B).

in patients whose cTnI levels continue to rise postoperatively, there is a concomitant increase in MACE incidence.[34] This study observed elevated miR-212-3p in most MACE cases. Subsequent analyses established that serum miR-212-3p, cTnI, Gensini score, and SYNTAX score serve as independent predictors of MACE occurrence in patients following PCI, with high miR-212-3p indicating poor prognosis. It was speculated that synergistically applied miR-212-3p alongside existing diagnostic and therapeutic methods could improve aspects such as early diagnosis, complex case differentiation, and precise prognosis evaluation. Specifically, during the hyperacute phase of ACS, when cTnI levels have not yet increased, abnormal fluctuations in serum miR-212-3p levels may occur earlier and can serve as an additional indicator to help identify high-risk patients at an early stage. In borderline/complex cases involving mild cTnI elevation or the presence of interfering factors, the combined detection of serum miR-212-3p can effectively overcome the limitations of relying on a single biomarker, thereby improving diagnostic specificity and reducing the risk of missed or misdiagnosis. Furthermore, combining the dynamic changes of cTnI and existing prognostic tools with changes in serum miR-212-3p can help construct a multidimensional risk assessment model to inform the development of personalized treatment strategies in clinical practice.

Study Limitations

This study acknowledges several limitations. This study only used CAA patients as controls, omitting healthy individuals devoid of clinical or subclinical coronary artery disease. This might lead to bias in the specific evaluation of serum miR-212-3p as a biomarker and make it difficult to distinguish its diagnostic efficacy for asymptomatic early coronary artery disease. Additionally, the diagnostic thresholds established in current research might not be directly applicable for screening individuals without coronary artery disease due to the lack of healthy population data references. Therefore, subsequent studies will include a large sample size of a healthy control population and explore the specificity and clinical applicability of serum miR-212-3p through multicentric validation.

The serum samples were collected at a single time point, which may not adequately capture their temporal and dynamic patterns throughout the progression of ACS. This limitation could potentially undermine the biomarker's effectiveness in evaluating disease prognosis and restrict a comprehensive understanding of its temporal stability and expression dynamics. Future research will systematically monitor changes in serum miR-212-3p levels at key time points, such as 6 hours, 24 hours, and 72 hours after ACS onset, as well as 1 week and 1 month after PCI surgery. A dynamic prediction model will also be constructed based on patient clinical outcomes in order to accurately determine the optimal detection window for this biomarker, providing dynamic data to support its clinical application. The investigation concentrated on the association between miR-212-3p and serum markers, while omitting data pertaining to the LVEF, a cardiac function indicator. The relationship between the dynamic monitoring of miR-212-3p and LVEF and the occurrence of MACE is a noteworthy issue in future research. The potential impact of the drugs used in the development of MACE on the outcomes warrants further investigation as a significant direction for future research.

Additionally, the absence of certain clinical data pertaining to CAA patients hindered the evaluation of the combined diagnostic efficacy of serum miR-212-3p and myocardial injury markers. The small number of patients is another important limitation in this study. Future investigations will aim to broaden the sources of samples and enhance data collection. This will facilitate a more comprehensive analysis of the clinical relevance of serum miR-212-3p utilizing larger sample sizes, thereby allowing for a more comprehensive exploration of the research evidence.

CONCLUSION

In summary, this study indicated that serum miR-212-3p might serve as a valuable diagnostic biomarker for the identification of ACS patients and differentiating between those with AMI and UAP, and was a significant parameter for the severity of coronary artery lesions. Additionally, it was a risk factor for ACS in CAA patients and demonstrated a high predictive value for the MACE occurrence in ACS patients. The prospects for clinical application of miR-212-3p are promising.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. This study protocol has been approved by the Ethics Committee of the First Hospital of Lanzhou University (No. 2021A-067, Date: March 16, 2021).

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

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Selection of Common Genes Associated with Rheumatoid Arthritis and Cardiovascular Disease via a Network- and Pathway-Based Approach

ABSTRACT

Background: Patients with rheumatoid arthritis (RA) have an increased risk of developing cardiovascular disease (CVD). However, the mechanisms underlying the comorbidity between RA and CVD remain poorly understood. This study aimed to identify the shared genes between RA and CVD and to explore their functional relationships.

Methods: Rheumatoid arthritis– and CVD-associated genes were obtained from the DisGeNET and Malacards databases, respectively. Shared genes between the 2 diseases were identified, and gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed using WebGestalt and Cytoscape (v3.9.0). To further investigate potential molecular interactions, protein–protein interaction networks were constructed based on data from the STRING database. Finally, the in silico Tabula Muris single-cell transcriptomic dataset was used to assess the tissue-specific expression of candidate genes and evaluate their potential roles in specific tissues and cell types.

Results: A total of 108 genes were shared between RA and CVD, out of the 898 and 552 genes identified for each condition. Functional enrichment analysis showed that these shared genes were predominantly associated with inflammation and immune response–related pathways. Among them, 42 candidate genes were identified, of which 7 (i.e., *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1,* and *CD44*) were highlighted based on their strong connectivity and biological relevance. For validation, the validation, Tabula Muris single-cell transcriptomic dataset revealed that these genes were highly expressed in mouse cardiac tissues.

Conclusion: Seven shared genes associated with both RA and CVD were identified, which may contribute to the comorbidity between the 2 diseases.

Keywords: Cardiovascular disease, enrichment analysis, immune response, rheumatoid arthritis, shared genes

INTRODUCTION

Rheumatoid arthritis (RA) and cardiovascular disease (CVD) have overlapping pathophysiologic mechanisms involving inflammation, immunity, and oxidative stress.[1,2] Rheumatic diseases have been considered vital in the interplay between heart disease and inflammation.[3] In the preclinical stage of RA, the self-tolerance of the immune system is decreased, and various autoantibodies are produced.[4] This subsequently activates the immune system and ultimately leads to immune infiltration into the joint synovium. It is a complex process involving a large number of cytokines and pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-1 (IL-1), which can stimulate the generation of reactive oxygen species and consequently lead to oxidative stress and cellular injury.[5,6]

Although there is definite evidence for the shared mechanisms of RA and CVD, there is still a lack of studies at the molecular level. To date, the understanding of the genes associated with RA and CVD is still limited due to lacking of appropriate techniques and approaches. The increasing availability of large-scale genomic data, such as UK Biobank data, facilitates the investigation of CVD risk-related pathways among RA patients at the molecular level.[7] Notably, recent Mendelian

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randomization (MR) studies have provided new insights into the causal relationships between RA and CVD.[8,9] For example, Qiu et al[8] performed an MR analysis and reported that RA was potentially causally associated with 6 types of cardiovascular conditions, including age-related angina pectoris, hypertension, age-related heart attack, abnormal heart rate, stroke, and general heart disease. Similarly, Wang et al[9] identified a causal relationship between RA and ischemic heart disease, as well as myocardial infarction (MI). Their study further suggested that reducing RA disease activity could potentially lower CVD risk. Based on the genome-wide data, Guo et al[10] performed a conventional meta-analysis to assess the shared genetic architecture between RA and CVD using the UK Biobank. Their results supported the idea that there is shared genetic pathogenesis in explaining the observed association between RA and CVD.

To further investigate the molecular association between CVD and RA, disease-associated genes were systematically collected from the MalaCards and DisGeNET databases. Subsequently, functional enrichment analysis was conducted to identify the key biological processes and signaling pathways enriched in the shared genes, as well as their potential interactions. Finally, the potential hub genes were identified based on their central roles in the protein–protein interaction (PPI) network, which may be involved in the comorbidity of CVD and RA.

METHODS

Selection of Rheumatoid Arthritis– and Cardiovascular Disease–Associated Genes from Databases

A flowchart of the study design is shown in Supplementary Figure 1. Rheumatoid arthritis– and CVD-associated genes were extracted from DisGeNET (https://www.disgenet.org/) and Malacards (https://www.malacards.org/).[11,12] Genes with a gene-disease association score > 0.05 were selected from the DisGeNET database, as this threshold indicates a strong disease association. Additionally, the selection of associated genes from Malacards was performed based on default parameters as described in the previous study.[12] After retrieving RA- and CVD-associated genes from each database, the shared genes between the 2 diseases were identified. These shared genes were considered as potential susceptibility genes contributing to the comorbidity of RA and CVD and were used for enrichment and network analyses.

Functional and Pathway Enrichment Analyses

To explore the biological significance of the shared genes between RA and CVD, a series of functional annotation and pathway enrichment analyses were performed. Firstly, GO analysis was conducted using WebGestalt (http://www.webgestalt.org), with a focus on biological processes significantly enriched among the shared genes [False discovery rate (FDR) < 0.05].[13] To assess interactions at the protein level, a PPI network was constructed using Metascape (http://metascape.org/), and subnetworks were identified using the molecular complex detection algorithm.[14,15]

Hub gene selection was performed using ClueGO, CluePledia and CytoHubba.[16,17] Pathway enrichment analysis was conducted with ClueGO and CluePledia, followed by the identification of key hub genes in the PPI network using the Maximal Clique Centrality algorithm in CytoHubba.

To further investigate functional relationships among biological pathways, a pathway cross-talk analysis was conducted. Enriched KEGG pathways ($P < 0.05$) were identified using ToppGene (https://toppgene.cchmc.org/enrichment.jsp, FDR < 0.05) based on RA- and CVD-associated genes. Cross-talk between pathways was quantified using the Jaccard Coefficient ($A \cap B / A \cup B$) and Overlap Coefficient ($|A \cap B| / \min(|A|, |B|)$) to assess gene overlap between pathway pairs, where A and B represent the sets of genes in 2 pathways.[18-20] The pathway interaction network was visualized using Cytoscape (version 3.9.0), providing insight into functionally connected pathways potentially contributing to RA–CVD comorbidity.

Identification of Candidate Genes Through Protein–Protein Interaction Network Analysis

We first mapped the RA-associated genes and CVD-associated genes into the PPI network, which yielded an RA-specific network and a CVD-specific network, respectively. To exclude the irrelevant interactions, the RA-specific network and CVD-specific network were merged into a combined network. Subsequently, the RA-specific network was compared with the CVD-specific network, followed by the extraction of the overlapping network. The Cytoscape software was utilized to calculate the node degree of the genes using the Network Analyzer.[21,22] Then nodes with a degree of 5 or more were selected as candidate genes after removing the RA-associated and CVD-associated genes. For validation, the specific PPI network was also obtained from the STRING database and merged a combined network.

Expression Analysis of Candidate Genes from databases

To explore the tissue and cell-type-specific expression patterns of the candidate genes, an in silico expression analysis was performed using the Tabula Muris database (https://tabula-muris.ds.czbiohub.org/). The Tabula Muris Senis (TMS) dataset is a large-scale, publicly available single-cell RNA-seq dataset of mice. All cells in the dataset have been annotated with cell types by the TMS project. Log-transformed, pre-processed data was obtained from the TMS dataset, which comprises 2 subsets generated using distinct experimental methodologies: fluorescence-activated cell sorting (FACS) and droplet-based sequencing. Using FACS methods, the expression of predicted genes was analyzed in various tissues, including heart tissue, and in different cells.

HIGHLIGHTS

- To screen the rheumatoid arthritis (RA)– and cardiovascular disease (CVD)–associated genes, with the aim to investigate their comorbidity.
- Seven shared RA- and CVD-associated genes were responsible for the comorbidity of CVD and RA.
- Inflammation and immune responses were enriched in the shared genes.

Table 1. Susceptibility Gene Shared by Cardiovascular Disease and Rheumatoid Arthritis

Gene Symbol	Gene Identifier (ID)	Gene Full Name	Uniport
LPA	4018	lipoprotein(a)	P08519
NOS3	4846	nitric oxide synthase 3	P29474
PON1	5444	paraoxonase 1	P27169
VCAM1	7412	vascular cell adhesion molecule 1	P19320
ICAM1	3383	intercellular adhesion molecule 1	P05362
CRP	1401	C-reactive protein	P02741
HP	3240	haptoglobin	P00738
MPO	4353	myeloperoxidase	P05164
CCL2	6347	C-C motif chemokine ligand 2	P13500
ALB	213	albumin	P02768
ACE	1636	angiotensin I converting enzyme	P12821
PTGS2	5743	prostaglandin-endoperoxide synthase 2	P35354
MTHFR	4524	methylenetetrahydrofolate reductase	P42898
SELE	6401	selectin E	P16581
GRK2	156	G protein-coupled receptor kinase 2	P25098
AGER	177	advanced glycosylation end-product specific receptor	Q15109
FTO	79068	FTO alpha-ketoglutarate dependent dioxygenase	Q9C0B1
VDR	7421	vitamin D receptor	P11473
COL4A1	1282	collagen type 4 alpha 1 chain	P02462
BANK1	55024	B cell scaffold protein with ankyrin repeats 1	Q8NDB2
MBL2	4153	mannose binding lectin 2	P11226
MIR21	406991	microRNA 21	nan
RETN	56729	resistin	Q9HD89
PLG	5340	plasminogen	P00747
MMP2	4313	matrix metallopeptidase 2	P08253
PIK3CG	5294	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	P48736
SERPINE1	5054	serpin family E member 1	P05121
PLA2G2A	5320	phospholipase A2 group IIA	P14555
MMP9	4318	matrix metallopeptidase 9	P14780
PPARG	5468	peroxisome proliferator activated receptor gamma	P37231
CCHCR1	54535	coiled-coil alpha-helical rod protein 1	Q8TD31
NFE2L2	4780	nuclear factor, erythroid 2 like 2	Q16236
NFKBIA	4792	NFKB inhibitor alpha	P25963
TNFRSF11B	4982	TNF receptor superfamily member 11b	O00300
ADIPOQ	9370	adiponectin, C1Q and collagen domain containing	Q15848
CD36	948	CD36 molecule	P16671
CD14	929	CD14 molecule	P08571
TGFB1	7040	transforming growth factor beta 1	P01137
SAA1	6288	serum amyloid A1	P0DJI8
PRDM16	63976	PR/SET domain 16	Q9HAZ2
LINC00452	643365	long intergenic non-protein coding RNA 452	
BDNF	627	brain derived neurotrophic factor	P23560
PTX3	5806	pentraxin 3	P26022
VEGFA	7422	vascular endothelial growth factor A	P15692
SPP1	6696	secreted phosphoprotein 1	P10451
TLR4	7099	toll-like receptor 4	O00206
TNF	7124	tumor necrosis factor	P01375
DPP4	1803	dipeptidyl peptidase 4	P27487
ESR1	2099	estrogen receptor 1	P03372

(*Continued*)

Table 1. Susceptibility Gene Shared by Cardiovascular Disease and Rheumatoid Arthritis (*Continued*)

Gene Symbol	Gene Identifier (ID)	Gene Full Name	Uniport
ESR2	2100	estrogen receptor 2	Q92731
F2	2147	coagulation factor II, thrombin	P00734
CHI3L1	1116	chitinase 3 like 1	P36222
NLRP3	114548	NLR family pyrin domain containing 3	Q96P20
ADM	133	adrenomedullin	P35318
NR3C1	2908	nuclear receptor subfamily 3 group C member 1	P04150
ANGPT2	285	angiopoietin 2	O15123
LGALS3	3958	galectin 3	P17931
LEP	3952	leptin	P41159
LCN2	3934	lipocalin 2	P80188
IL18	3606	interleukin 18	Q14116
IL10	3586	interleukin 10	P22301
IL6	3569	interleukin 6	P05231
IL1B	3553	interleukin 1 beta	P01584
IGF1	3479	insulin like growth factor 1	P05019
SIRT1	23411	sirtuin 1	Q96EB6
DLG2	1740	discs large MAGUK scaffold protein 2	Q15700
ALOX5	240	arachidonate 5-lipoxygenase	P09917
GABPA	2551	GA binding protein transcription factor subunit alpha	Q06546
GCG	2641	glucagon	P01275
GLP1R	2740	glucagon like peptide 1 receptor	P43220
IL1A	3552	interleukin 1 alpha	P01583
COX2	4513	cytochrome c oxidase subunit II	P00403
ACTB	60	actin beta	P60709
IL6R	3570	interleukin 6 receptor	P08887
MTCO2P12	107075310	MT-CO2 pseudogene 12	
CDKN2A	1029	cyclin dependent kinase inhibitor 2A	P42771
IL33	90865	interleukin 33	O95760
BGLAP	632	bone gamma-carboxyglutamate protein	P02818
PIK3CA	5290	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	P42336
CXCL12	6387	C-X-C motif chemokine ligand 12	P48061
PIK3CB	5291	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta	P42338
PIK3CD	5293	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta	O00329
SOST	50964	sclerostin	Q9BQB4
S100A9	6280	S100 calcium binding protein A9	P06702
CX3CR1	1524	C-X3-C motif chemokine receptor 1	P49238
MIR155	406947	microRNA 155	
HSD11B1	3290	hydroxysteroid 11-beta dehydrogenase 1	P28845
S100A12	6283	S100 calcium binding protein A12	P80511
MIR146A	406938	microRNA 146a	nan
CD40LG	959	CD40 ligand	P29965
HIF1A	3091	hypoxia inducible factor 1 subunit alpha	Q16665
CP	1356	ceruloplasmin	P00450
CXCL8	3576	C-X-C motif chemokine ligand 8	P10145
NAMPT	10135	nicotinamide phosphoribosyltransferase	P43490
MIR499A	574501	microRNA 499a	
NOS2	4843	nitric oxide synthase 2	P35228
SERPINA3	12	serpin family A member 3	P01011
CCR6	1235	C-C motif chemokine receptor 6	P51684

(*Continued*)

Table 1. Susceptibility Gene Shared by Cardiovascular Disease and Rheumatoid Arthritis (*Continued*)

Gene Symbol	Gene Identifier (ID)	Gene Full Name	Uniport
MIR223	407008	microRNA 223	
PTGS1	5742	prostaglandin-endoperoxide synthase 1	P23219
AKT1	207	AKT serine/threonine kinase 1	P31749
MIR150	406942	microRNA 150	
ICOSLG	23308	inducible T cell costimulator ligand	O75144
MIR132	406921	microRNA 132	
STAT3	6774	signal transducer and activator of transcription 3	P40763
IL17A	3605	interleukin 17A	Q16552
HSPD1	3329	heat shock protein family D (Hsp60) member 1	P10809
TLR2	7097	toll-like receptor 2	O60603

RESULTS

Identification and Selection of Shared Genes

Rheumatoid arthritis– and CVD-associated genes were retrieved from the DisGeNET and Malacards databases using defined thresholds. Specifically, 290 RA-related genes and 210 CVD-related genes were retrieved from the MalaCards database, and 787 RA-related genes and 433 CVD-related genes from the DisGeNET databases (Supplementary Table 1). Among these genes, 108 shared genes were identified between RA and CVD (Table 1). These shared genes comprise immune-related genes (e.g., *CDKN2A*, *ICAM1*, *IFNG*, *TNF*), oxidative stress-related genes (e.g., *LPA*, *HIF1A*, *NOS2*, *NOS3*), and interleukin-related genes (e.g., *IL6*, *IL10*, *IL1B*, *IL17A*, *IL18)*.

Functional Annotation of the Shared Genes

Gene ontology (GO) enrichment analysis was then performed on the 108 genes, which showed that 10 GO biological processes were significantly enriched (Supplementary Table 2). Among these processes, immune responses were the most significant, followed by secretion by cells, leukocyte activation, and immune effector process. Figure 1 showed the enrichment results for the biological process, cellular component (CC), and molecular function (MF) terms are shown. Notably, the significantly enriched categories included biological regulation, response to stimulus, and multicellular organismal processes. In the CC terms and MF terms, the enrichment items included extracellular space, membrane and nucleus, protein binding, ion binding, and nucleic acid binding.

Protein–Protein Interaction Network Construction for Shared Genes

A total of 6 gene modules (i.e., module 1-6) were generated after mapping all the shared genes onto the PPI network (Figure 2). These modules were mainly associated with key biological functions, including inflammatory response,

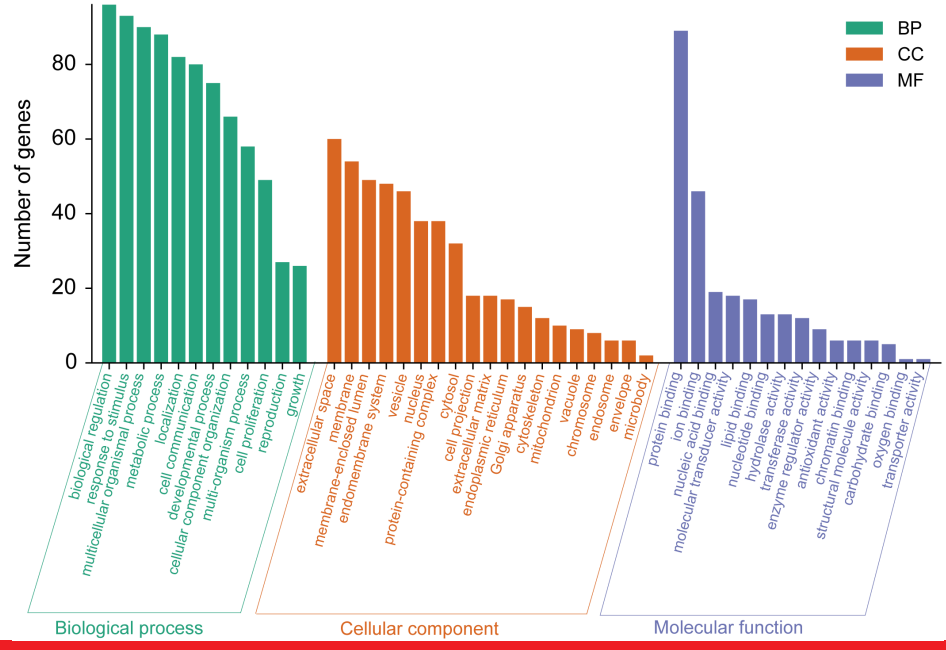

Figure 1. Functional enrichment analysis on the 108 shared genes between cardiovascular disease and rheumatoid arthritis. BP, biological process; CC, cellular component; MF, molecular function.

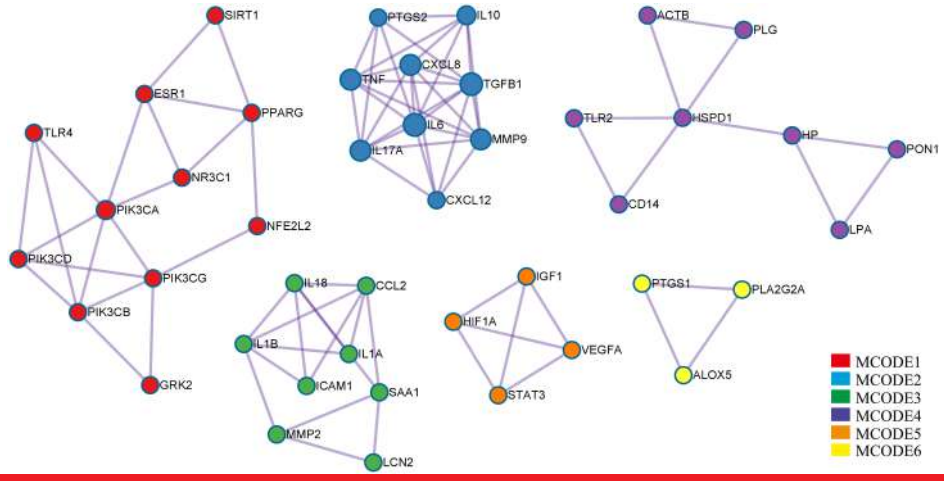

Figure 2. Six gene modules were generated after mapping all the shared genes onto the protein–protein interaction network.

interleukin signaling transmission, cytokine signaling transmission in the immune system, and lipid metabolism (Table 2).

Hub Genes Selection from the Interaction Network

As shown in Figure 3, 2554 pathway interactions involving 175 nodes were identified. Enriched pathways included lipids and atherosclerosis (AS) signaling, fluid shear stress and AS, as well as the RA and AS. Moreover, the results showed that the AGE-RAGE signaling pathway was enriched in diabetic complications, together with the HIF-1, TNF, and Toll-like receptor signaling pathways. Furthermore, 10 hub genes were identified from the network, including *IL-10*, *IL-1B*, *TNF*, *IL-6*, *AKT1*, *MMP9*, *CXCL8*, *ICAM1*, *VCAM1,* and *IL-1A*.

Pathway Enrichment of Rheumatoid Arthritis– and Cardiovascular Disease–Associated Genes

Pathway enrichment analysis revealed 69 significant pathways for RA and 48 for CVD (Supplementary Table 3). After overlapping these enriched pathways, 40 shared pathways were obtained (Supplementary Table 4). Some of the shared pathways were associated with the T cell receptor signaling pathway, B cell receptor signaling pathway, chemokine signaling pathway, and leukocyte trans-endothelial migration. In addition, others were associated with signaling transmission, such as the Janus kinase/signal transducer and activator of transcriptio (JAK-STAT) signaling pathway, mitogen-activated protein kinases (MAPK) signaling pathway, the cytokine-cytokine receptor interaction, as well as the endocrine system and cancer-related pathways.

Table 2. Gene Modules in the Protein–Protein Interaction Network of the Shared Genes

MCODE	GO Term or Pathway	Description	Log10(*P*)
MCODE_1	WP4483	Relationship between inflammation COX 2 and EGFR	–12.9
	WP5191	Resolvin E1 and resolvin D1 signaling pathways promoting inflammation resolution	–11.3
	R-HSA-9027276	Erythropoietin activates Phosphoinositide-3-kinase (PI3K)	–11.3
MCODE_2	WP5285	Immune infiltration in pancreatic cancer	–22.5
	R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	–18.7
	WP5095	Overview of pro-inflammatory and profibrotic mediators	–18.1
MCODE_3	R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	–19.7
	R-HSA-449147	Signaling by Interleukins	–14.5
	R-HSA-1280215	Cytokine Signaling in Immune system	–12.7
MCODE_4	M264	PID TOLL ENDOGENOUS PATHWAY	–7.6
	hsa05134	Legionellosis	–6.5
	GO:0032481	positive regulation of type 1 interferon production	–6.1
MCODE_5	hsa04066	HIF-1 signaling pathway	–9.8
	hsa05205	Proteoglycans in cancer	–8.7
	GO:0050679	positive regulation of epithelial cell proliferation	–8.6
MCODE_6	hsa00590	Arachidonic acid metabolism	–8.1
	R-HSA-556833	Metabolism of lipids	–4.8

GO, gene ontology.

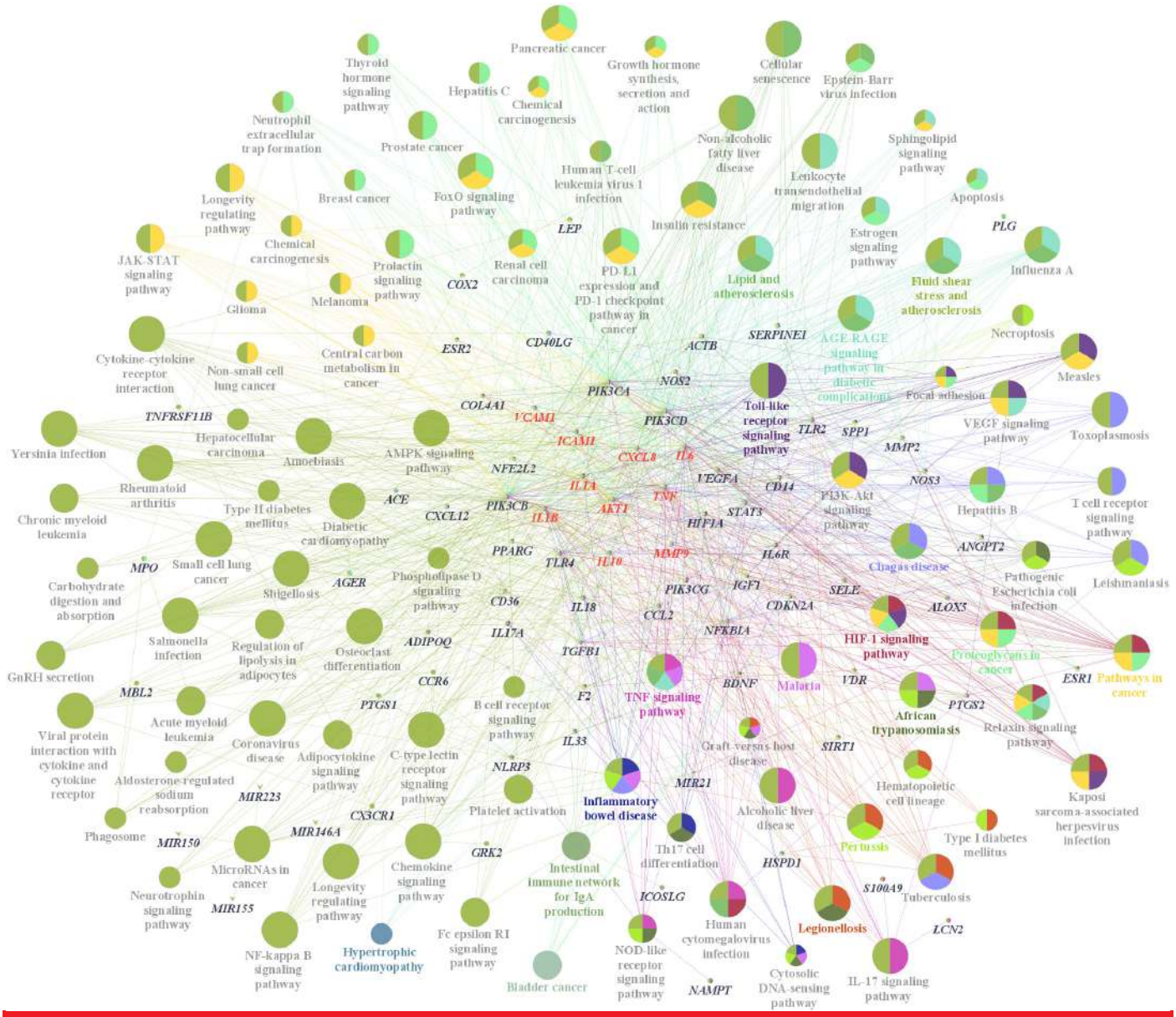

Figure 3. Pathway enrichment analysis and visualization of the hub genes between cardiovascular disease and rheumatoid arthritis. The network of interactions was generated with ClueGo and CluePedia. CytoHubba was utilized to predict the hub genes. Red genes represented the hub genes.

Pathway Cross-Talk Between Rheumatoid Arthritis and Cardiovascular Disease

Among the 40 shared pathways, 38 shared at least 3 genes with at least 1 other pathway and were included in the cross-talk analysis. Subsequently, a pathway interaction network was constructed based on shared genes to explore the underlying biological processes. In total, 52 out of the 108 shared genes were mapped to this network, resulting in 90 nodes and 734 edges (Figure 4). The network was classified into 4 functional modules, including the immune system, endocrine or metabolic system, cancer-related, and signaling transmission. Interestingly, these modules were interconnected through 1 or more key signaling pathways, suggesting coordinated biological relevance across disease mechanisms.

Selection of Candidate Genes Associated with Rheumatoid Arthritis and Cardiovascular Disease

All RA- and CVD-associated genes were mapped onto a PPI network, generating 957 nodes (540 RA-associated and 417 CVD-associated) and 9272 edges (2425 RA-associated and 6747 CVD-associated). Subsequently, a combined network including 867 nodes and 8973 edges was established to identify genes potentially linked to both diseases. According to the node degree, 42 candidate genes that were directly linked to the shared genes were selected with a score of 20 or more (Table 3). Among these genes, 21 genes showed direct association with 5 or more shared genes. In addition, 7 genes (i.e., *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1*, and *CD44)* showed direct association with 9 or more shared genes. The

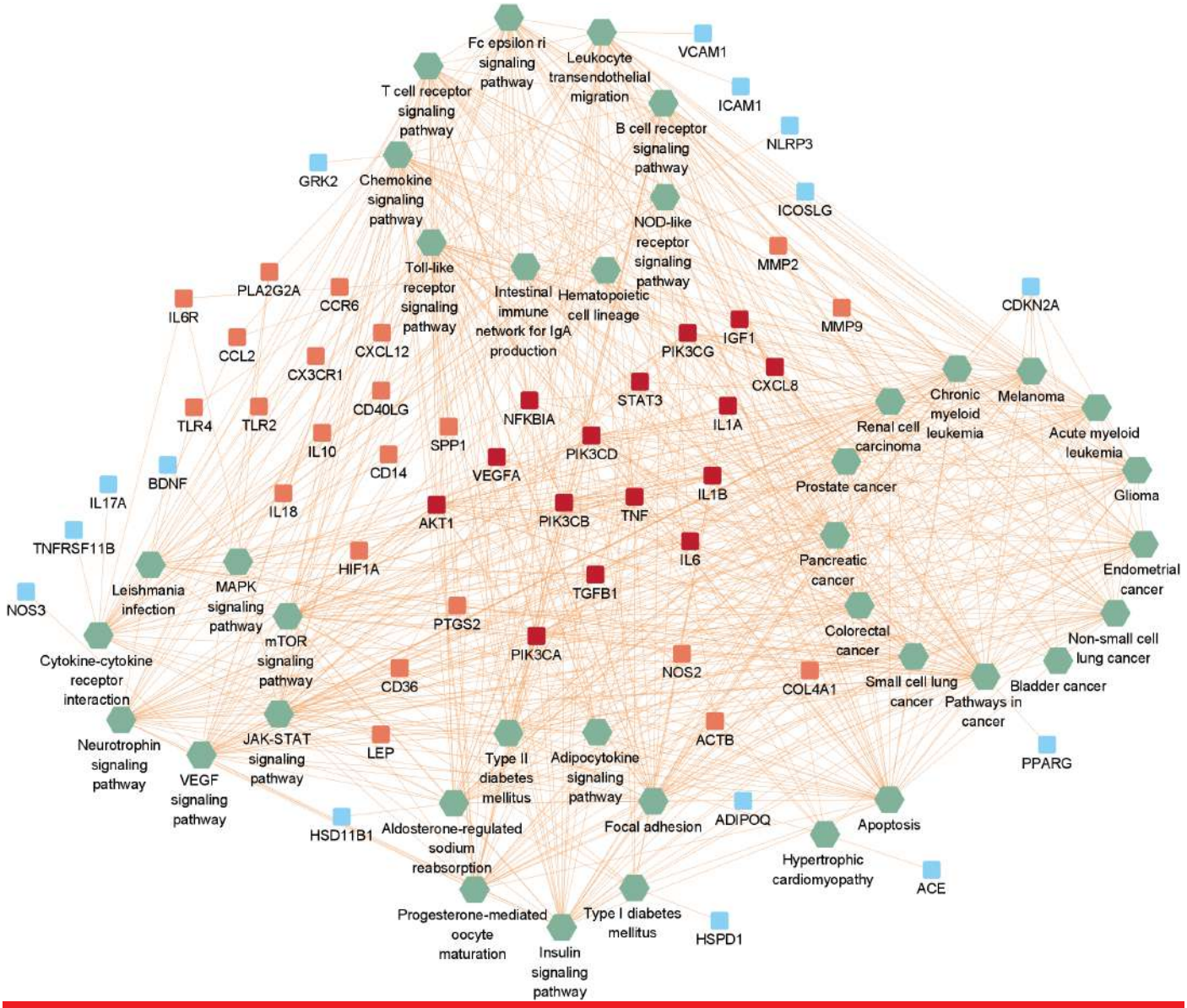

Figure 4. Pathway-pathway network of 108 shared genes between cardiovascular disease and rheumatoid arthritis. Green nodes represented pathways. Red nodes, pink nodes, and blue nodes represented genes linked to at least 3 modules, at least 2 modules, and 1 modules, respectively.

PPI network of the 7 selected candidate genes (Figure 5), which led to the generation of 102 nodes and 673 edges.

Expression Analysis of Candidate Genes from Databases

In this section, tissue- and cell-specific expression analyses of the 21 novel candidate genes were performed. All 21 novel candidate genes were RA-associated, suggesting that these genes may be involved in the molecular mechanisms of CVD. As shown in Figures 6 and 7, the *FN1*, *EGFR*, *JUN*, *CXCL1*, and *RELA* were extensively expressed in cardiac tissue. At the same time, *FN1*, *EGFR*, *JUN*, *CXCL1*, and *RELA* were extensively expressed in fibroblasts of cardiac tissue. Moreover, *CD44*, *ITGAM*, *CCL2*, *CCL4,* and *CCL3* were specifically expressed in leukocytes in cardiac tissue.

DISCUSSION

In this study, the 108 shared genes between CVD and RA were systematically analyzed. Functional enrichment analyses revealed that these shared genes are involved in immune responses, inflammatory signaling, cytokine activity, and lipid metabolism. Among them, inflammation-related and immune signaling pathways were particularly prominent. Based on degree centrality in the PPI network, 42 candidate genes were identified, of which 7 (i.e., *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1*, and *CD44*) showed direct connections to 9 or more shared genes and were highlighted for further analysis.

Rheumatoid arthritis has been consistently associated with an elevated risk of CVD, which is a leading cause of mortality

Table 3. Forty-Two New Candidate Genes Related to Cardiovascular Disease and Rheumatoid Arthritis

Gene Symbol	Node Degree	Interact with Shared Genes
CD4	61	*CD40LG, IL10, IL17A, ICAM1, TNF, IL6, IL1B, TLR4*
IFNG	61	*IL1B, IL10, TNF, IL6, IL17A, IL1A, IL18, TLR4, TLR2, STAT3*
NFKB1	42	*TNF, TLR4, TLR2, NLRP3, PPARG, STAT3, NFKBIA, SIRT1*
CCL5	39	*IL10, TNF, IL6, CXCL12, CX3CR1, CCR6, CXCL8, IL1B, IL1A*
JAK1	38	*PIK3CB, PIK3CD, STAT3, PIK3CA*
CXCL10	37	*CXCL12, CXCL8, TLR4, TNF, IL10, IL6, IL1B, IL1A, TLR2*
CXCR4	36	*HIF1A, IL6, DPP4, F2, VCAM1*
FN1	36	*SPP1, TLR4, TNF, LCN2, IGF1, IL6, PLG, VCAM1, ICAM1, STAT3, TLR2, LGALS3, TGFB1*
IL4	35	*IL6, TNF, STAT3, IL6R*
EGFR	33	*PIK3CB, IGF1, ESR1, IL6, PIK3CD, HIF1A, STAT3, PIK3CA, TLR2, LGALS3, TGFB1*
JAK2	33	*PIK3CB, PIK3CD, LEP, STAT3, PIK3CA*
IL2	32	*IL6, TNF, IL6R*
CXCL1	32	*IL6, TNF, CXCL12, IL10, IL17A, CXCL8, IL18, IL1B, IL1A*
PTPN11	32	*STAT3*
JUN	32	*TNF, NFE2L2, STAT3, NR3C1, NFKBIA, SIRT1*
RELA	31	*TNF, TLR4, STAT3, TLR2, SIRT1*
STAT1	31	*STAT3*
CD40	30	*TNF, TLR4, IL10, CD40LG, ICOSLG, ICAM1, IL1B, TLR2*
JAK3	28	*PIK3CB, PIK3CD, STAT3, PIK3CA*
CCL4	28	*IL10, TNF, IL6, CXCL12, CCR6, CXCL8, IL1B, IL1A*
CCR2	28	*CXCL8, CXCL12, CCR6*
MYD88	28	*TNF, TLR4, TLR2, NFKBIA*
LOC102723407	28	*PLG*
CCL20	26	*CXCL12, IL6, TNF, CX3CR1, CCR6, CXCL8, IL1B*
CD44	26	*CXCL12, SPP1, COL4A1, TLR4, MMP9, SELE, VCAM1, ICAM1, LGALS3, MMP2*
CD28	25	*CD40LG, ICOSLG, PIK3CD, IL10, PIK3CB, ICAM1, PIK3CA*
CCL3	25	*IL10, TNF, IL6, CX3CR1, CCR6, CXCL8, IL1B, IL1A*
CCR5	25	*CXCL12, CXCL8*
CXCL2	25	*TNF, IL6, CXCL8, IL1B, IL1A*
CCR1	24	*CXCL8, CXCL12, CCR6*
CCR7	24	*CXCL12, CXCL8*
CSF2	24	*IL6, CXCL8, TNF, IL10, IL1B, IL1A*
SYK	23	*TLR4*
CD80	23	*ICAM1, IL10, TNF*
MAPK3	23	*TNF*
MAPK1	23	*STAT3*
CCR3	21	*CXCL12, CCR6, CXCL8*
MAPK8	21	*STAT3*
CHUK	21	*TNF, NFKBIA*
CTLA4	20	*IL10, LCN2, ICOSLG*
CD86	20	*IL10, TNF, ICAM1*
ITGAM	20	*PIK3CB, TNF, PIK3CD, TLR4, VCAM1, PIK3CA*

in this population.[23] This may be attributed to the chronic inflammatory state characteristic of RA, which is marked by elevated levels of circulating inflammatory mediators and endothelial dysfunction.[24,25] This in turn, may promote the AS and cardiomyocyte dysfunction, thereby increasing the risk of CVD, MI, and congestive heart failure.[26] The understanding of how susceptibility genes contribute to the interplay between CVD and RA is still limited. To address this, a systematic analysis of the shared genes was conducted between CVD and RA. Enriched analysis identified key pathways, including lipids and AS signaling, fluid shear stress and AS, as well as the RA and AS. These findings highlight

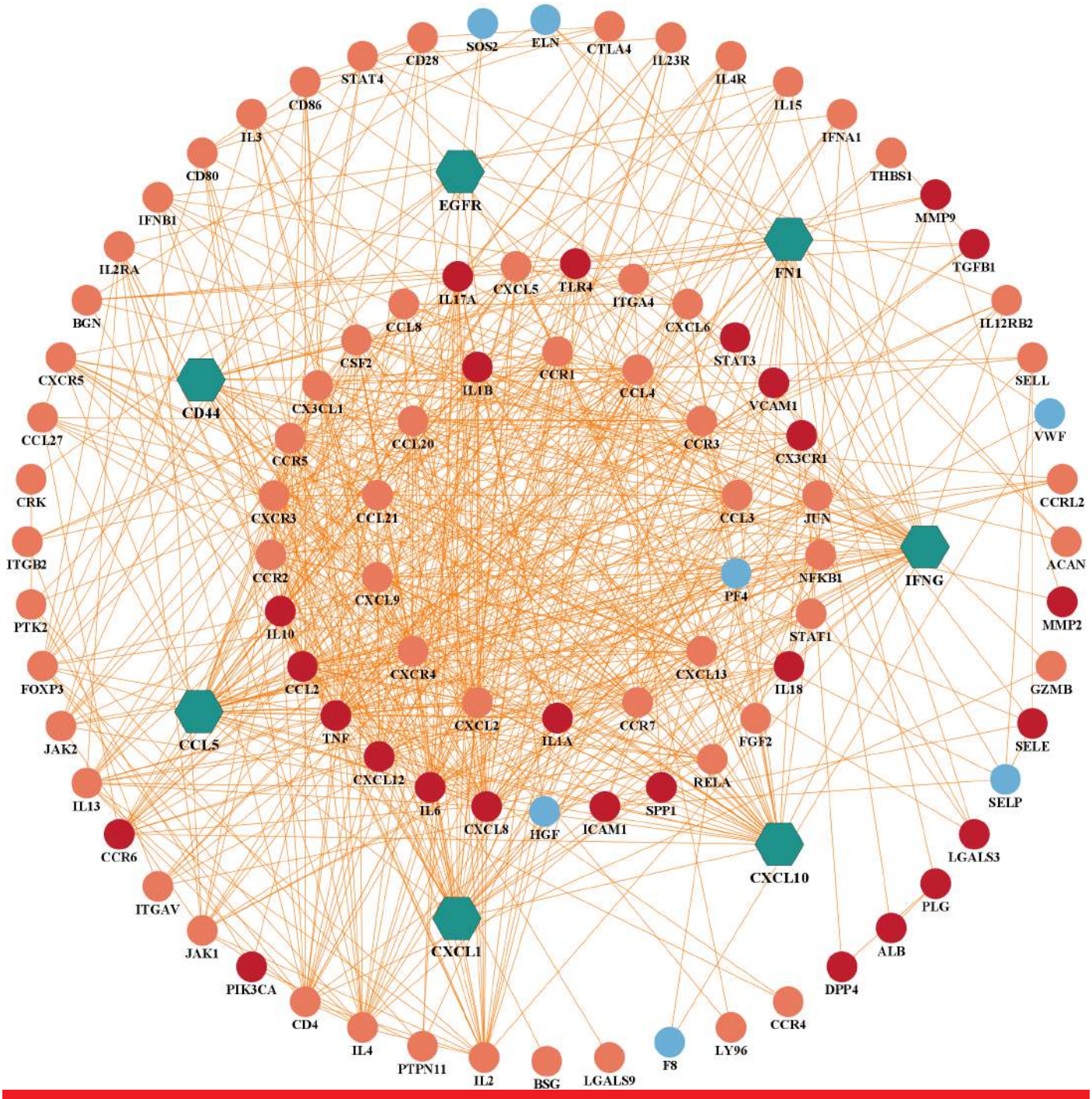

Figure 5. Protein–protein interaction network of the 7 candidate genes. Green nodes represented the candidate genes. Red nodes represented the shared genes. The blue and pink nodes represented the cardiovascular disease–associated and rheumatoid arthritis–associated genes.

potential molecular mechanisms underlying the increased CVD risk in RA patients and may guide future therapeutic strategies targeting shared pathogenic pathways.

Chronic inflammation is a central feature in the pathogenesis of both RA and CVD.[27] Lipid abnormalities, particularly the impaired atheroprotective function of high-density lipoprotein, are recognized as key contributors to the increased risk of atherosclerotic cardiovascular disease in RA patients.[28] Consistently, the shared gene modules in the PPI network encompassed interleukin signaling, cytokine-cytokine receptor interaction, and pathways regulating inflammation resolution. Additionally, pathways related to lipid metabolism and arachidonic acid were significantly enriched, supporting evidence that altered lipid profiles and inflammatory lipoproteins contribute to the pathogenesis of CVD in RA

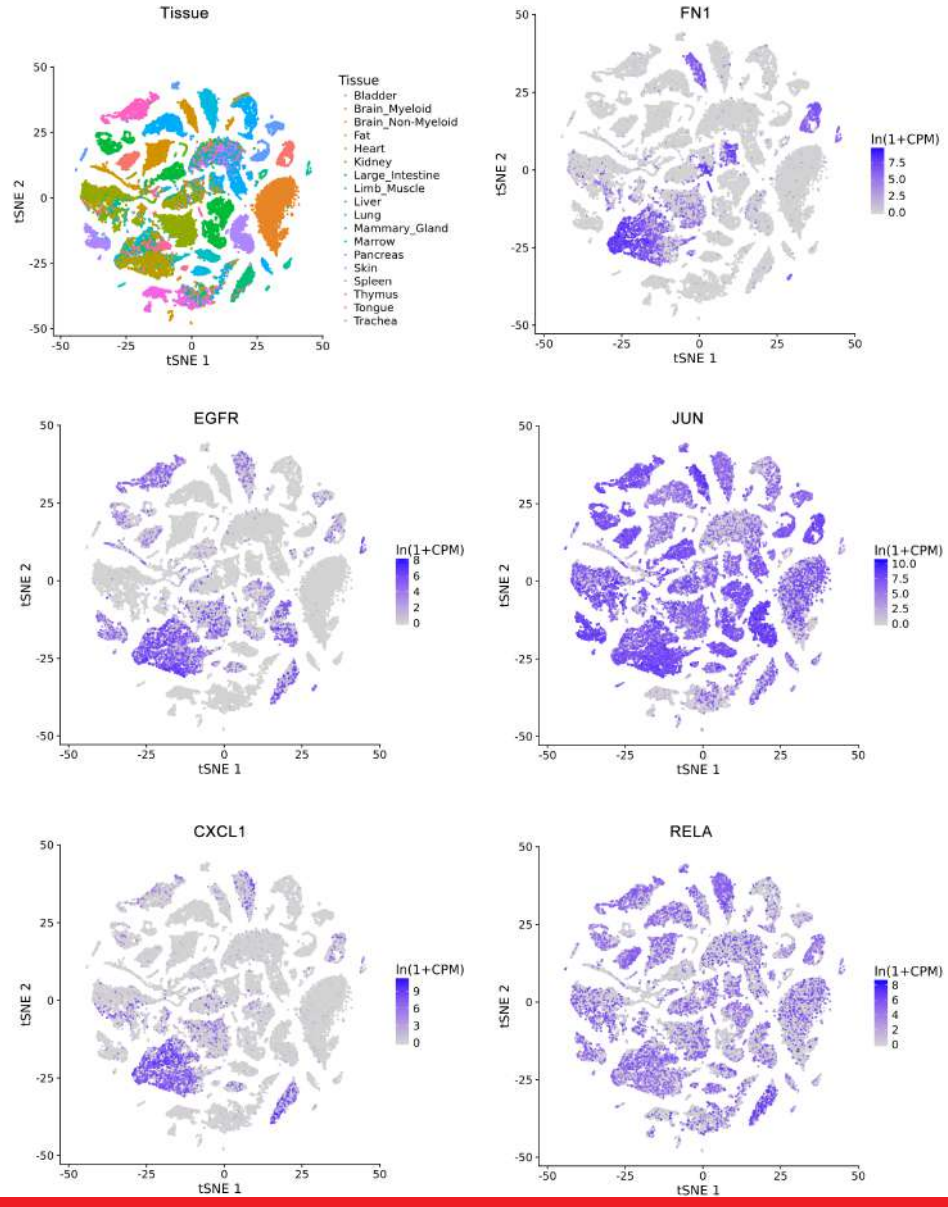

Figure 6. Expression analysis of candidate genes in different tissues.

patients.[29,30] These findings reinforce that inflammation and lipid dysregulation may constitute shared pathological mechanisms driving CVD in the context of RA.

To elucidate key molecular players bridging RA and CVD, we constructed a combined PPI network was constructed and candidate genes were identified based on their connectivity to shared disease-associated genes. Notably, 7 candidate genes that were found showed a direct link to at least 9 genes, including *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1*, and *CD44*. These genes have well-established roles in immune regulation and inflammation. *IFNG* encodes interferon-gamma (IFN-γ), a key cytokine secreted by both innate and adaptive immune systems. Variants in *IFNG* have been associated with increased susceptibility to infections and autoimmune diseases,[31] both of which are implicated in the pathogenesis of RA and CVD.[32,33] These findings suggest that *IFNG* may be involved in CVD and RA by regulating immune responses and inflammatory pathways. *CCL5* encodes a member of the chemokine superfamily involved in immunoregulatory and inflammatory processes.[31] *CCL5*-related ankylosing spondylitis was associated with hypertension and the development of obesity, both of which were common risk factors for CVD.[34] *CXCL1* is also associated with inflammation and the accumulation of neutrophils. In CVD, *CXCL1* was crucial in cardiac fibrosis, especially induced by atrial fibrillation, post-irradiation, as well as hypertension.[35] Likewise, the role of *CXCL10* in CVD has been extensively described,[36] particularly in promoting immune cell infiltration via CXCR3. Additionally, Lee et al[37] demonstrated that *CXCL10* signaling through CXCR3 and TLR4 enhances inflammatory cell migration, potentially contributing to the progression of RA.

Notably, *FN-1* has been identified as a key gene associated with RA onset.[38] Using bioinformatics methods, Xiong et al[39] identified *FN-1* as a novel biomarker for aortic valve

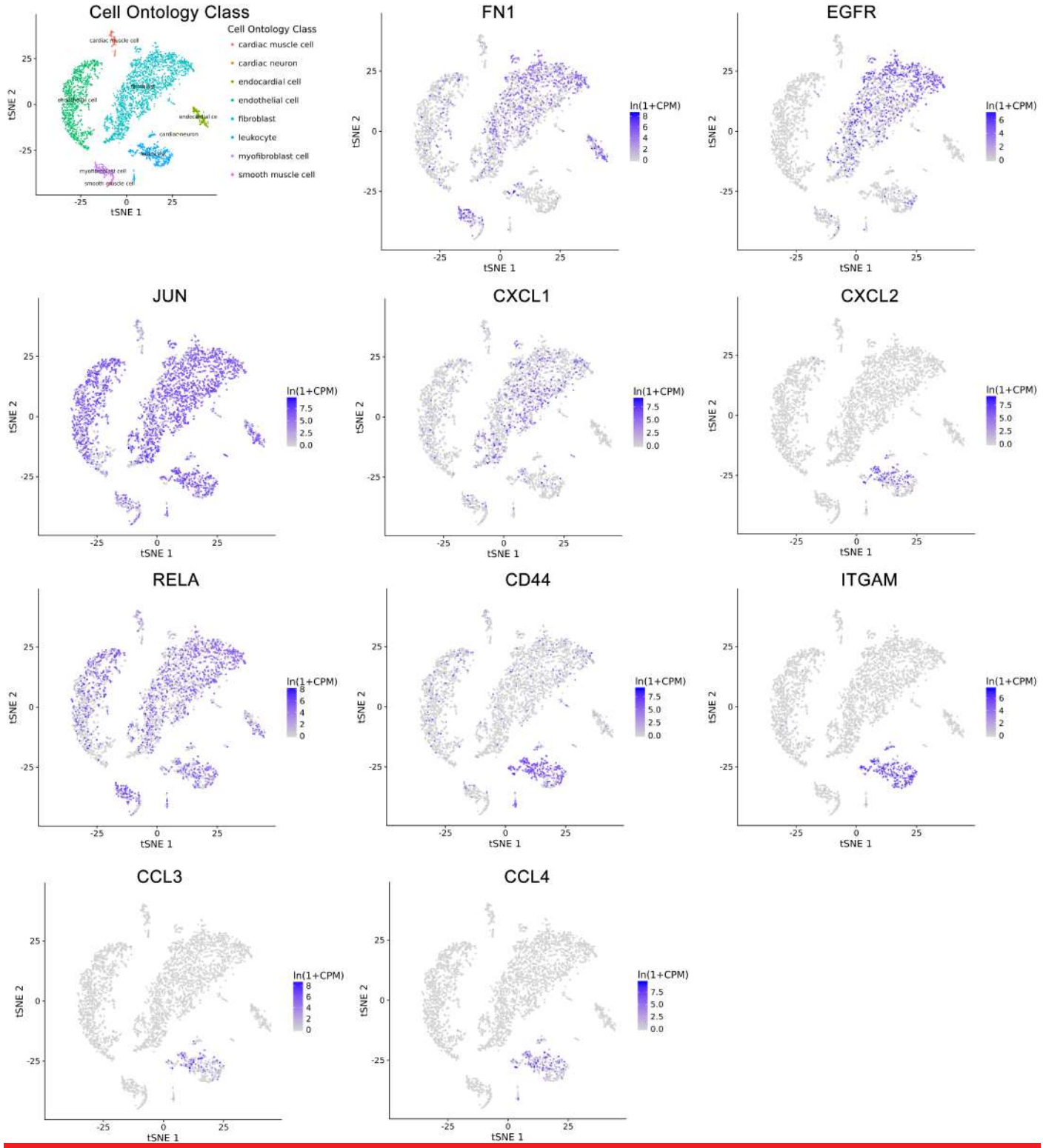

Figure 7. Expression analysis of candidate genes in different cell types.

calcification, an important event in the development of CVD. In a mouse model of collagen-induced arthritis, *FN-1* expression was linked to over a 3-fold increased risk of RA, further supporting its role in disease pathogenesis.[40] The EGFR family and its ligands function as central regulators of multiple cellular processes. Epidermal growth factor receptor (EGFR) signaling is essential for cardiac development and remodeling and has been proposed as a therapeutic target in CVD.[41] Additionally, *EGFR* contributes to synovial hyperplasia in RA through its roles in angiogenesis and tissue regulation.[42,43] *CD44* expression is significantly elevated in diseased arterial tissues and inflammatory cytokine-stimulated endothelial

cells.[44] The CD44-hyaluronic acid axis plays a critical role in inflammatory responses and AS pathogenesis, suggesting its potential as a therapeutic target for CVD.[45] In RA, *CD44* is highly expressed in inflamed synovial tissues compared to normal synovium, indicating its relevance in disease progression and its potential for targeted drug delivery.[46]

These 7 candidate genes represent potential molecular links between CVD and RA and may serve as future therapeutic targets. However, it is important to note that these findings are based on bioinformatics and in silico predictions. Functional validation is needed through experimental models and clinical cohorts to confirm causality and therapeutic relevance. In particular, interventions targeting *IFNG* or *EGFR* signaling could be explored for dual impact on inflammation and cardiovascular outcomes in RA patients. Similarly, modulation of chemokines such as CCL5 and CXCL10 may help reduce both synovial and vascular inflammation.

There are some limitations in this study. First, the analysis relied on publicly available databases, which may introduce biases or incomplete gene annotations. Second, the current human interactome is still not complete, and there might be some errors despite significant improvement in the quality of PPI databases. Third, the functional roles of candidate genes require further experimental validation, such as gene knockout or overexpression studies.

CONCLUSION

This study identified 108 shared genes between CVD and RA, with enrichment analyses highlighting their roles in immune and inflammatory processes. Among these, 7 candidate genes were considered as potential key mediators in the shared pathogenic mechanisms. These findings provide new insights into common molecular mechanisms and may offer promising targets for future diagnostic or therapeutic strategies.

Data availability statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: All data used in this study are publicly available, and studies are approved by relevant review boards and conducted according to the Declaration of Helsinki, with written informed consent from all participants. No additional ethical approval was required.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception and design: Yaobang Bai, Yunpeng Bai, Nan Jiang; database search and data extraction: Yaobang Bai, Yunpeng Bai; study evaluation: Zhenhua Wu, Qingliang Chen; planned and conducted the statistical analysis: Yaobang Bai, Zhenhua Wu; drew all the figures and tables: Yunpeng Bai, Qingliang Chen; drafted the manuscript: Yaobang Bai, Yunpeng Bai; corrected and validated the manuscript: Nan Jiang. All authors read and approved the final manuscript.

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

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Supplementary Table 1. Rheumatoid arthritis related genes from DisGeNET

Supplementary table can be accessed by clicking **here.**

Supplementary Table 2. The GO biological processes significantly enriched in the 108 shared genes between RA and CVD

Gene Set	Description	Size	Expect	Ratio	P Value	FDR
GO:0006955	immune response	1919	10.202	5.2932	<2.2e-16	<2.2e-16
GO:0046903	secretion	1605	8.5326	5.9771	<2.2e-16	<2.2e-16
GO:0032940	secretion by cell	1472	7.8255	6.006	<2.2e-16	<2.2e-16
GO:0001775	cell activation	1335	7.0972	6.9042	<2.2e-16	<2.2e-16
GO:0045321	leukocyte activation	1184	6.2944	6.8314	<2.2e-16	<2.2e-16
GO:0002252	immune effector process	1141	6.0658	6.5943	<2.2e-16	<2.2e-16
GO:0002443	leukocyte mediated immunity	760	4.0403	8.6626	<2.2e-16	<2.2e-16
GO:0002263	cell activation involved in immune response	697	3.7054	7.8264	<2.2e-16	<2.2e-16
GO:0002366	leukocyte activation involved in immune response	693	3.6841	7.8716	<2.2e-16	<2.2e-16
GO:0002274	myeloid leukocyte activation	634	3.3705	8.3074	<2.2e-16	<2.2e-16

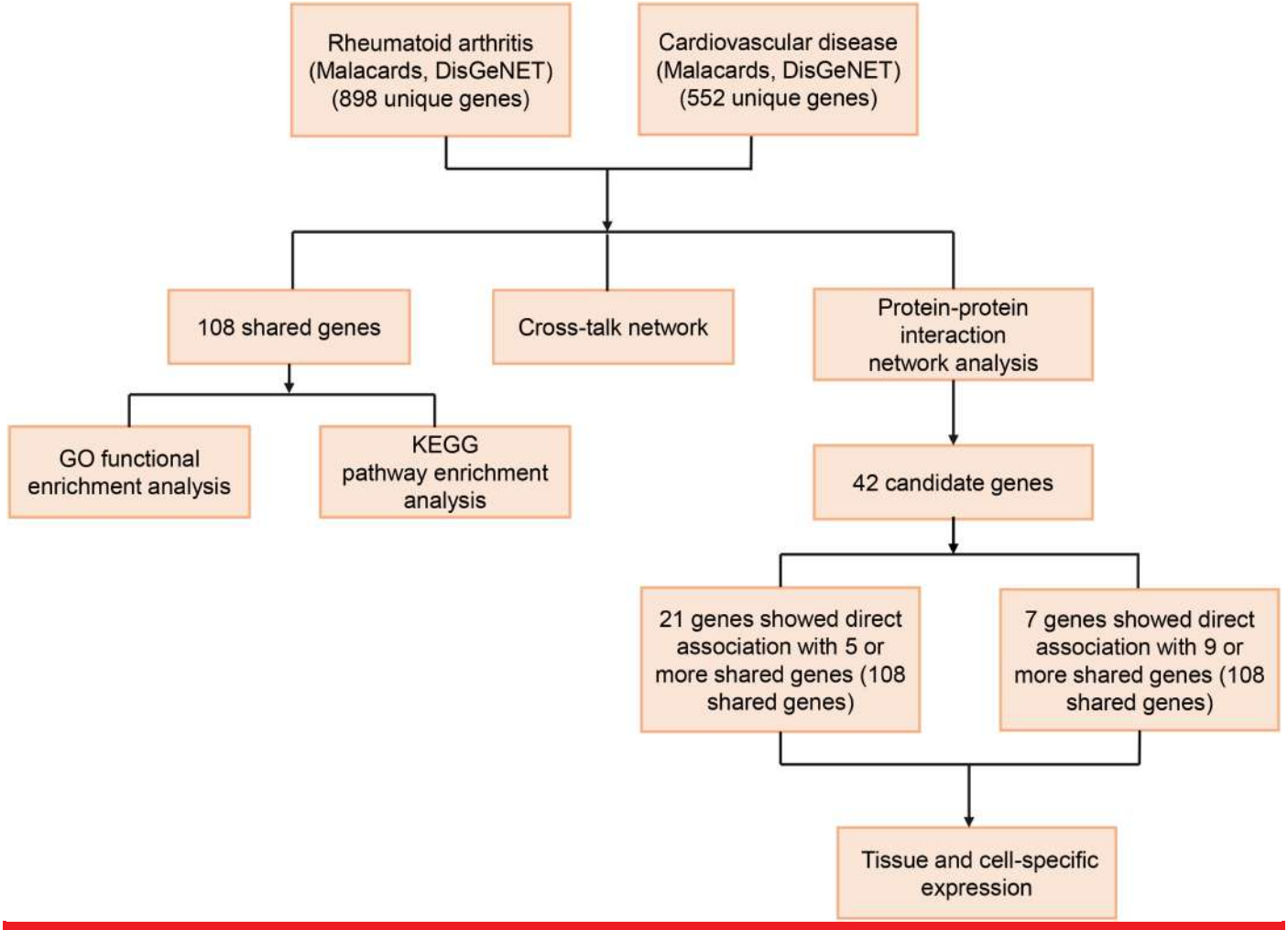
Supplementary Table 3. 69 significantly enriched pathways of RA.

XXX

Supplementary Table 4. 40 shared pathways related to RA and CVD

Category	Name	ID
Pathway	KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	M16894
Pathway	KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	M10462
Pathway	KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION	M16473
Pathway	KEGG_PATHWAYS_IN_CANCER	M12868
Pathway	KEGG_TYPE_II_DIABETES_MELLITUS	M19708
Pathway	KEGG_CHEMOKINE_SIGNALING_PATHWAY	M4844
Pathway	KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	M3261
Pathway	KEGG_MTOR_SIGNALING_PATHWAY	M7561
Pathway	KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	M8728
Pathway	KEGG_LEISHMANIA_INFECTION	M3126
Pathway	KEGG_VEGF_SIGNALING_PATHWAY	M1749
Pathway	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	M9809
Pathway	KEGG_RENAL_CELL_CARCINOMA	M13266
Pathway	KEGG_ACUTE_MYELOID_LEUKEMIA	M19888
Pathway	KEGG_MELANOMA	M15798
Pathway	KEGG_CHRONIC_MYELOID_LEUKEMIA	M321
Pathway	KEGG_FC_EPSILON_RI_SIGNALING_PATHWAY	M11816
Pathway	KEGG_ENDOMETRIAL_CANCER	M19877
Pathway	KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	M2164
Pathway	KEGG_PANCREATIC_CANCER	M9726
Pathway	KEGG_APOPTOSIS	M8492
Pathway	KEGG_JAK_STAT_SIGNALING_PATHWAY	M17411
Pathway	KEGG_PROSTATE_CANCER	M13191

Category	Name	ID
Pathway	KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY	M9904
Pathway	KEGG_FOCAL_ADHESION	M7253
Pathway	KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	M15569
Pathway	KEGG_COLORECTAL_CANCER	M14631
Pathway	KEGG_GLIOMA	M1835
Pathway	KEGG_SMALL_CELL_LUNG_CANCER	M3228
Pathway	KEGG_NON_SMALL_CELL_LUNG_CANCER	M19818
Pathway	KEGG_INSULIN_SIGNALING_PATHWAY	M18155
Pathway	KEGG_HEMATOPOIETIC_CELL_LINEAGE	M6856
Pathway	KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY	M5436
Pathway	KEGG_MAPK_SIGNALING_PATHWAY	M10792
Pathway	KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION	M9387
Pathway	KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	M615
Pathway	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	M3578
Pathway	KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	M16763
Pathway	KEGG_BLADDER_CANCER	M19096
Pathway	KEGG_TYPE_I_DIABETES_MELLITUS	M12617



Supplementary Figure 1. The flow diagram of study design.

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Effectiveness and Safety of Reduced-Dose and Slow-Infusion Intravenous Tissue-Type Plasminogen Activator Regimen in Patients with Acute Pulmonary Embolism at Intermediate-High Risk

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ABSTRACT

Background: Intermediate-high-risk (IHR) pulmonary embolism (PE) is defined by right ventricular (RV) dysfunction and elevated cardiac troponin in the absence of hemodynamic instability. While full-dose thrombolysis may improve outcomes, it poses a high bleeding risk. This study assessed the safety and efficacy of a reduced-dose, slow-infusion thrombolytic regimen.

Methods: This single-center retrospective study included 124 patients with acute IHR PE who met at least one of the following criteria: systolic blood pressure ≤110 mm Hg, heart rate >100 bpm, SpO_2 <90% on room air, respiratory rate >20/min, or lactate >2 mmol/L. Patients with contraindications to thrombolysis or symptom onset >14 days were excluded. Patients received 25 mg intravenous alteplase (t-PA) infused over 4-6 hours, along with standard anticoagulation according to the institutional protocol. Following the initial dose, a repeat infusion of 25 mg over 4-6 hours was administered if tachycardia, hypoxia, or signs of organ hypoperfusion persisted on re-evaluation.

Results: Syncope was the presenting symptom in 27.4%, and 49.2% had deep vein thrombosis. Median t-PA dose was 50 mg and median infusion duration was 6 hours. Significant improvements were observed in RV and RA size/function, thrombus burden, and clinical parameters (all $P < .001$). Qanadli score and RV/LV ratio decreased by 55% and 29%, respectively. Major and minor bleeding occurred in 4.8% and 3.2%. In-hospital mortality was 4.8%; 12-month survival was 89.5%. Chronic thromboembolic pulmonary hypertension developed in 3.2%.

Conclusion: Low-dose, slow-infusion t-PA therapy appears effective and well-tolerated, offering hemodynamic and clinical benefit with fewer bleeding complications in patients with IHR PE.

Keywords: Alteplase, pulmonary embolism, thrombolysis

INTRODUCTION

High-risk (HR) pulmonary embolism (PE), a lethal condition, presents with hemodynamic instability and requires urgent reperfusion treatment. Intermediate-high-risk (IHR) PE, on the other hand, presents with right ventricular (RV) dysfunction and elevated circulating cardiac troponin levels, even when the patient appears hemodynamically stable at the time of presentation. However, there is a residual risk of deterioration toward hemodynamic instability in patients at IHR status. Although full-dose systemic thrombolytic treatment (STT) is effective in reducing all-cause mortality and preventing hemodynamic collapse in these patients, this treatment is also associated with increased risks of intracranial or other life-threatening bleeding, which has previously been confirmed in 2 meta-analyses.[1-3] Therefore, current guidelines do not recommend STT as the first-line treatment strategy for IHR PE.[4]

Considering the balance between benefits and risks, reduced-dose STT regimens are gaining popularity in clinical practice globally. This study aimed to evaluate

the safety of a reduced-dose STT regimen while maintaining effective reperfusion in patients with acute IHR PE.

METHODS

Design

Between 2012 and April 2025, a total of 976 patients with acute PE were admitted to the center. The systematic work-up for the diagnosis of acute PE, and initial risk stratification comprising the multidetector contrast-enhanced computed tomography (CT) angiography and transthoracic echocardiography (TTE) assessments, PE severity indexes, and biomarker evaluation has been based on the criteria recommended by the European Society of Cardiology/European Respiratory Society 2019 PE guidelines.[3] Among these, patients identified as IHR were screened, and 124 patients who met the inclusion criteria were ultimately included in the study (Figure 1).

The inclusion criteria were at least one of the following: systolic blood pressure ≤ 110 mm Hg, heart rate > 100 bpm, pulse oximetric saturation (SpO_2) < 90% on room air, respiratory rate >20 breaths per minute, or serum lactate >2 mmol/L. Exclusion criteria were the presence of any contraindication for STT, age < 18 years, and duration from symptom onset to PE diagnosis >14 days. The thrombolytic treatment strategy was implemented as part of an institutional protocol. According to the institutional protocol, patients who met the inclusion criteria and none of the exclusion criteria received initial weight-adjusted UFH, followed by a 25 mg intravenous infusion of tissue-type plasminogen activator (t-PA, alteplase) over 4-6 hours. After this first infusion, a bedside clinical reassessment was performed. If any of the following criteria were still present—heart rate > 100 bpm, SpO_2 < 90%, or signs of organ hypoperfusion—a second 25 mg t-PA infusion was administered in the same manner. In the case of persistent clinical deterioration, repeated infusions were given according to the same dosing strategy.

HIGHLIGHTS

- This study evaluates a low-dose, slow-infusion alteplase protocol in intermediate-high risk pulmonary embolism (PE) patients. The median t-PA dose was 50 mg and median infusion duration was 6 hours.
- Most patients required more than 1 infusion of 25 mg alteplase for adequate response.
- Treatment led to significant improvements in hemodynamic parameters, including heart rate, oxygen saturation, pulmonary artery systolic pressure, right ventricular/left ventricular ratio, and Qanadli score.
- Major bleeding occurred in only 4.8% of patients; intracranial hemorrhage occurred in 0.8%.
- In-hospital mortality was 4.8%; 12-month survival was 89.5%. Chronic thromboembolic pulmonary hypertension developed in 3.2%.
- These findings support that low-dose slow-infusion thrombolysis is a safe and effective alternative in managing IHR PE.

Computed tomography images were acquired using 64-slice helical CT angiography (Toshiba Aquilion 64™, Toshiba Medical Systems Corp., Tokyo, Japan). A validated CT score for pulmonary arterial (PA) occlusion proposed by Qanadli et al[5] [Qanadli score (QS)], RV to left ventricle (LV) ratio, RV diameter, right atrial to left atrial diameter ratio (RA/LA ratio), and main, left, and right PA diameters were measured from CT images. Pulmonary infarction is defined as a peripheral wedge-shaped pulmonary consolidation in a hypoperfused segment of the lung. The CT images were evaluated at admission and 72-96 hours after the initiation of treatment. The TTE was performed on all patients on the first day of admission and repeated at discharge. Tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler (S') measurements were obtained to assess RV function in TTE, and estimated pulmonary artery systolic pressures (PASP) were calculated from the tricuspid regurgitation jet. All measurements and assessments were made in accordance with the American Society of Echocardiography guidelines.[6]

The data were collected retrospectively from hospital records. Given the retrospective design and inclusion of the entire eligible patient cohort, power analysis was not performed. Follow-up data were obtained through review of electronic medical records and hospital databases. The study protocol was approved by the Institutional Ethics Committee (Approval No: 2025/06/1093, Approval Date: April 22, 2025), and all procedures were conducted in accordance with the Declaration of Helsinki.

Clinical effectiveness outcomes were all-cause mortality in 30 days, resolution of thrombus on CT as assessed by QS, and reduction in right ventricle to left ventricle diameter ratio (RV/LVr) on CT. For safety outcomes, major bleeding was defined as overt bleeding associated with a fall in the hemoglobin level of at least 2 g/dL, or with transfusion of 2 units of packed red blood cells, or involvement of a critical site.[7] Clinically overt bleeding not fulfilling the criteria for major bleeding was classified as a minor bleeding complication.

Statistical Analysis

All statistical analyses were performed using R version 4.3.1 (R Project, Vienna, Austria) and Jamovi Version 2.6.19.0. Normally distributed continuous data were expressed as mean and standard deviation values, whereas non-normally distributed data were expressed as medians and interquartile ranges, and categorical data were described as absolute and percentage values. Normality of the data was determined using histograms and the Shapiro–Wilk test. The paired sample *t*-test and Wilcoxon signed-rank test were used for pre- and post-treatment comparisons, as appropriate. Single-arm Kaplan–Meier survival analysis was performed, and censoring was applied for individuals without events at the end of the follow-up period. A *P* value of <.05 was considered the limit for statistical significance. During the preparation of this article, the authors did not use artificial intelligence-assisted technologies.

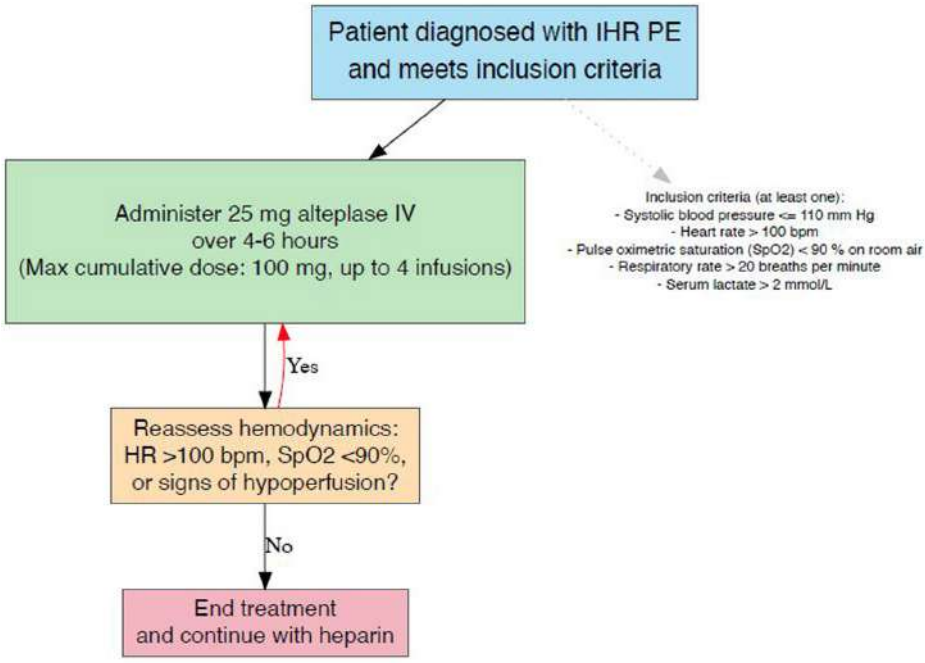

Figure 1. Treatment algorithm for reduced-dose, slow-infusion systemic thrombolysis in patients with intermediate-to-high-risk pulmonary embolism (IHR PE). Patients diagnosed with IHR PE and meeting at least one of the predefined inclusion criteria (systolic blood pressure ≤110 mm Hg, heart rate >100 bpm, pulse oximetric saturation <90% on room air, respiratory rate >20 breaths/min, or serum lactate >2 mmol/L) received an initial 25 mg intravenous infusion of alteplase over 4–6 hours. Following each infusion, bedside hemodynamic reassessment was performed, including evaluation of heart rate, oxygen saturation, and signs of hypoperfusion. In cases of persistent hemodynamic compromise, additional 25 mg alteplase infusions were administered according to the same protocol, with a maximum cumulative dose of 100 mg (up to 4 infusions). If clinical stability was achieved, thrombolysis was discontinued, and anticoagulation with unfractionated heparin was continued as per standard care.

RESULTS

Baseline Characteristics

Patient characteristics are summarized in Table 1. The mean age of patients with acute PE at IHR status was 55 ± 15.8 years, and 58.9% were female. The median duration from the onset of symptoms consistent with acute PE to confirmed diagnosis was 3 (2-7) days, and 27.4% presented with syncope. Regarding comorbidities, hypertension, diabetes mellitus, atrial fibrillation, and chronic obstructive pulmonary disease were documented in 19.3%, 10.5%, 1.6%, and 3.2% of patients, respectively. A history of PE and deep vein thrombosis was noted in 12.1% and 49.2% of patients. Potential predisposing or prothrombotic factors for acute PE included malignancy in 4.8% of patients, recent orthopedic surgery or fractures in 4.8%, postoperative status in 15.3%, long-haul travel by air or car in 3.2%, and immobility in 8.1%. The mean pulmonary embolism severity index (PESI) score was 95.5 ± 29.2, with a median PESI class of 3 (2-4), Simplified PESI score of 1 (1-2), and a mean modified shock index of 1.02 ± 0.26.[8]

Prior to treatment, the mean heart rate was 112 ± 16.6 beats per minute, systolic blood pressure was 123 ± 14.9 mm Hg, and SpO_2 was 89% (85%-93%). Laboratory analysis revealed median serum lactate levels of 2.35 mmol/L (1.6-2.9), troponin levels of 0.096 ng/mL (0.04-0.27), D-dimer levels of 9.82 U/mL (5.13-18.5), and C-reactive protein levels of 23.1 mg/L (11.6-45.3).

Clinical and Hemodynamic Outcomes

Mean and median doses of t-PA were 47.5 ± 24.1 and 50 (range: 25-50) mg, respectively. Mean and median duration of low-dose t-PA infusions were 7.44 ± 5.31 and 6 (range: 4-10) hours, respectively. Second, third, and fourth t-PA infusions were required in 73 patients (58.9%), 24 patients (19.3%), and 14 patients (11.3%), respectively. The administered overall t-PA doses were 25 mg in 51 patients (41.1%), 50 mg in 49 patients (39.5%), 75 mg in 10 patients (8.0%), and 100 mg in 14 patients (11.3%) (Table 2) (Figure 2).

Following the low-dose tPA infusion(s), significant improvements were observed in clinical and hemodynamic status, PA thrombotic obstruction, and RV function (Table 3) (Figure 3). Decrease in the heart rate from 112 ± 18.6 bpm to 82.2 ± 11.3 bpm ($\Delta = -29.7$ bpm, $P < .001$) and increase in the pulse SpO_2% from 89 (85-93) to 96 (94-97.3) ($\Delta = 6.5$, $P < .001$) were consistent with overall circulatory stabilization. Pulmonary artery systolic pressure decreased from 50.9 ± 13.3 mm Hg to 34.4 ± 12.6 mm Hg ($\Delta = -17.7$ mm Hg, $P < .001$), accompanied by a significant reduction in the QS from 20 (18-23) to 9 (6.75-13) ($\Delta = -10$, $P < .001$). Similarly, the RV/LVr improved from 1.26 ± 0.21 to 0.89 ± 0.13 ($\Delta = -0.37$, $P < .001$), reflecting a reversal of RV dilation due to pressure strain. These changes were accompanied by decreases in the main pulmonary artery diameter from 30.4 mm (28-32) to 28 mm (25.3-30) ($\Delta = -2.31$ mm, $P < .001$) and right atrial to left atrial diameter ratio (RA/LAr) from 1.31 ± 0.26 to 1.02 ± 0.18 ($\Delta = -0.30$, $P < .001$), and

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	All, n = 124
Age (years)	55 ± 15.8
Male sex, n (%)	51 (41.1)
Diabetes mellitus, n (%)	13 (10.5)
Hypertension, n (%)	24 (19.3)
Atrial fibrillation, n (%)	2 (1.6)
Syncope	34 (27.4)
Chronic obstructive lung disease, n (%)	4 (3.2)
Previous coronary artery disease, n (%)	7 (5.6)
Previous pulmonary embolism, n (%)	15 (12.1)
Presence of deep vein thrombosis, n (%)	61 (49.2)
Possible secondary causes, n (%)	
Malignancy	6 (4.8)
Orthopedic surgery/fractures	6 (4.8)
Prolonged traveling	4 (3.2)
Postoperative status	19 (15.3)
Immobility	10 (8.1)
Baseline vital signs	
Heart rate/min	112 ± 16.6
Systolic blood pressure, mm Hg	127 ± 21.9
Diastolic blood pressure, mm Hg	79 ± 18.6
Oxygen saturation, %	89 (85-93)
Baseline laboratory variables	
Troponin, ng/mL	0.096 (0.04-0.27)
Lactate, mmol/L	2.35 (1.6-2.9)
D-dimer, U/mL	9.82 (5.13-18.5)
C-reactive protein	23.1 (11.6-45.3)
Symptom duration (days)	3 (2-7)
PESI	95.5 ± 29.2
PESI class	3 (2-4)
Simplified PESI	1 (1-2)
Modified shock index	1.02 ± 0.26
Pulmonary infarction, n (%)	16 (12.9)
Pleural effusion, n (%)	12 (9.7)

PESI, pulmonary embolism severity index.

improved RV free-wall longitudinal systolic function, as evidenced by an increase in TAPSE from 1.81 ± 0.39 cm to 2.3 ± 0.3 cm (Δ = +0.46 cm, $P < .001$).

Primary Clinical Outcomes and Bleeding Complications

The observed in-hospital mortality rate was 4.8%, with 2 fatalities (1.6%) attributed to major bleeding and 4 (3.2%) due to hemodynamic decompensation. Importantly, no cases of recurrent PE or hemodynamic deterioration were recorded during the 30-day follow-up period. Notably, only 1 patient (0.8%) experienced intracranial (cerebellar) hemorrhage, which did not require surgical intervention, and the patient was discharged without neurological sequelae. Among the 6 major bleedings, 1 occurred after 100 mg t-PA infusion, 4 after 50 mg, and 1 after 25 mg.

Table 2. Thrombolytic Dosing Regimens and Safety Outcomes

	All, n = 124
tPA dose, mg	50 (25-50)
tPA infusion duration, hours	6 (4-10)
tPA infusion rate, mg/hours	6 (4-10)
Requirement following the first infusion	
Second infusion (50 mg)	73 (58.9%)
Third infusion (75 mg)	24 (19.3%)
Fourth infusion (100 mg)	14 (11.3%)
tPA dose groups	
25 mg	51 (41.1%)
50 mg	49 (39.5%)
75 mg	10 (8%)
100 mg	14 (11.3%)
Major bleeding, n (%)	6 (4.8)
Minor bleeding, n (%)	4 (3.2)
In hospital mortality	6 (4.8%)

Median follow-up duration was 3045 (2563-3096) days, and the estimated 12-month overall survival rate was 89.52% (95% CI: 84.28%-95.07%) (Figure 4). No patients were lost to follow-up within the first 12 months. During the follow-up period, chronic thromboembolic pulmonary hypertension (CTEPH) developed in 4 patients (3.2%).

DISCUSSION

This study provides compelling evidence that a low-dose, slow-infusion tPA regimen offers a favorable alternative in the management of IHR PE, while maintaining the clinical and hemodynamic benefits of full-dose STT and mitigating bleeding risks.

The fundamental goal of thrombolysis in PE is rapid pulmonary reperfusion and RV unloading, preventing hemodynamic deterioration and RV failure. However, the management of IHR PE presents a significant therapeutic challenge, balancing the need for effective reperfusion therapy against the risk of major bleeding complications. While STT remains a recommended option in select cases, concerns over hemorrhagic events have driven the exploration of alternative dosing strategies.

In this study, the inclusion criteria were designed to better define the upper zone of IHR PE patients, adopting parameters from the PEITHO trial's subgroup analysis. This approach aimed to capture patients with subtle yet clinically meaningful hemodynamic compromise, who may benefit from early reperfusion therapy but are at elevated bleeding risk with full-dose STT.[1]

The median administered t-PA dose was 50 mg (range: 25-50 mg), with a mean of 47.5 ± 24.1 mg. The median infusion duration was 6 hours (range: 4-10 hours), and the mean was 7.4 ± 5.3 hours. Multiple infusions were needed: 58.9% had a second dose, 19.3% a third, and 11.3% a fourth. Doses of 25 mg and 50 mg were used in 41.1% and 39.5% of patients, respectively. The rest required cumulative doses of 75 mg or more. The study's mortality rate was lower than that reported

Figure 2. A. Two pie charts depicting infusion data. The first pie chart shows the percentage of patients requiring second, third, and fourth t-PA infusions following the initial dose. The second pie chart illustrates the distribution of patients across different t-PA dose groups. B. Bar plot illustrating the percentages of in-hospital mortality, major bleeding, and minor bleeding events among patients. C. Bar plot comparing the incidence of major bleeding events across different t-PA dose groups. D. Changes in clinical, echocardiographic, and tomographic parameters before and after t-PA infusion.

in the fibrinolytic arm of the PEITHO trial, suggesting that low-dose tPA may reduce risk effectively with better safety. Major and minor bleeding rates were 4.8% and 3.2%, respectively, much lower than the 9%-20% major bleeding rates reported in full-dose, short-infusion STT studies.[1-3] In the PEITHO trial, the major bleeding rate in the STT arm was 11.5%, including a 2% incidence of intracranial hemorrhage.

Compared to both STT and ultrasound-assisted catheter-directed thrombolysis (USAT), the cohort's mortality was similar to previous reports, but major and minor bleeding rates were lower than 5.5% and 6.9%, respectively.[9] Compared to those who underwent AngioJet rheolytic thrombectomy, the low-dose, slow-infusion t-PA regimen was associated with lower mortality and reduced rates of both major and minor bleeding while maintaining effective reperfusion.[10,11] These findings support the hypothesis that a reduced-dose STT strategy can substantially lower bleeding risk without compromising therapeutic efficacy.

Significant reductions in PASP, RV/LV, and RA/LA ratios and improvements in TAPSE were observed, suggesting that even low-dose t-PA can improve RV function impaired by thrombotic pressure overload. These findings are consistent with prior evidence suggesting that effective pulmonary thrombus resolution can be achieved with lower doses of thrombolytics, thereby challenging the conventional reliance on full-dose STT regimens.[12-17]

Patients with worse baseline hemodynamics showed marked decreases in heart rate and modified shock index soon after low-dose tPA, indicating effective restoration of cardiac function without losing fibrinolytic effect.

Beyond the immediate hemodynamic improvements, one of the most critical long-term concerns in PE survivors is the development of CTEPH. While early and effective thrombus resolution is hypothesized to reduce this risk, long-term data remain inconclusive, and STT offers no benefit over standard anticoagulation in preventing progression to CTEPH, as demonstrated in the PEITHO trial.[1,18] Moreover, a retrospective study evaluating reperfusion therapies—including STT, catheter-directed thrombolysis (CDT), and mechanical thrombectomy—found no statistically significant difference in terms of CTEPH development between patients who underwent reperfusion therapies (8%) and those treated with anticoagulation alone (5%).[19] In contrast, studies have shown that patients with persistent residual PA obstruction after acute PE are at increased risk of developing CTEPH.[19] The role of fibrinolysis in modifying this risk remains uncertain, as interventions such as CDT and surgical pulmonary embolectomy have been associated with significant reductions in PA obstruction, which may influence long-term hemodynamics.[20] Furthermore, elevated fibrinogen and reduced plasminogen levels after pulmonary endarterectomy for CTEPH were associated with persistent pulmonary hypertension and worse long-term survival.[21] In this cohort, CTEPH developed

Table 3. Clinical and Imaging Changes Pre- and Post-Thrombolytic Treatment

Variables	Before IV tPA	After IV tPA	Mean Change (SE)	*P*
PASP (mm Hg)	50.9 ± 13.3	34.4 ± 12.6	17.7 (1.44)	<.001
RV/LV ratio	1.26 ± 0.21	0.89 ± 0.13	0.369 (0.105)	<.001
RA/LA ratio	1.31 ± 0.26	1.02 ± 0.18	0.301 (0.03)	<.001
TAPSE (cm)	1.81 ± 0.39	2.3 ± 0.3	0.46 (0.04)	<.001
S′ (cm/sec)	11.2 ± 2.74	14.1 ± 2.5	3.05 (0.43)	<.001
Qanadli score	20 (18-23)	9 (6.75-13)	10 (0.71)	<.001
Main PA diameter (mm)	30.4 (28-32)	28 (25.3-30)	2.31 (0.31)	<.001
Heart rate (bpm)	112 ± 18.6	82.2 ± 11.3	29.7 (1.76)	<.001
Systolic BP (mm Hg)	123 ± 14.9	127 ± 21.9	5 (1.86)	.015
Oxygen saturation (%)	89 (85-93)	96 (94-97.3)	6.5 (0.9)	<.001
Shock index	0.902 ± 0.22	0.682 ± 0.15	0.183 (0.02)	<.001
Modified shock index	1.02 ± 0.26	0.702 ± 0.13	0.26 (0.03)	<.001

in 3.2% of patients during follow-up, which is consistent with previously reported incidence rates. Therefore, according to the currently available data, the efficacy of reperfusion strategies in improving clot resolution and RV function during the acute phase cannot yet be mechanistically linked to a reduction in long-term CTEPH risk. The hypothesis that more effective thrombus resolution during the acute phase may causally reduce the risk of CTEPH remains biologically plausible but unproven. Future prospective studies specifically designed to assess this causal relationship are essential to determine whether optimizing reperfusion strategies can modify the long-term trajectory of pulmonary vascular disease in PE survivors.

The historical reliance on full-dose STT regimens has been predicated on the assumption that higher doses yield superior clot resolution. However, accumulating evidence, including the study, suggests that this approach may not be universally necessary. Low-dose regimens have been shown in multiple trials to reduce mortality and morbidity, indicating that a one-size-fits-all approach may not suit IHR PE.[15,22,23] The study adds to this view by showing real-world data that lower STT doses achieve similar short-term results with better safety. The ongoing PEITHO-3 trial has been designed to assess the efficacy of a reduced-dose t-PA regimen compared with standard anticoagulant therapy within 30 days of randomization as the primary end-point in patients with IHR

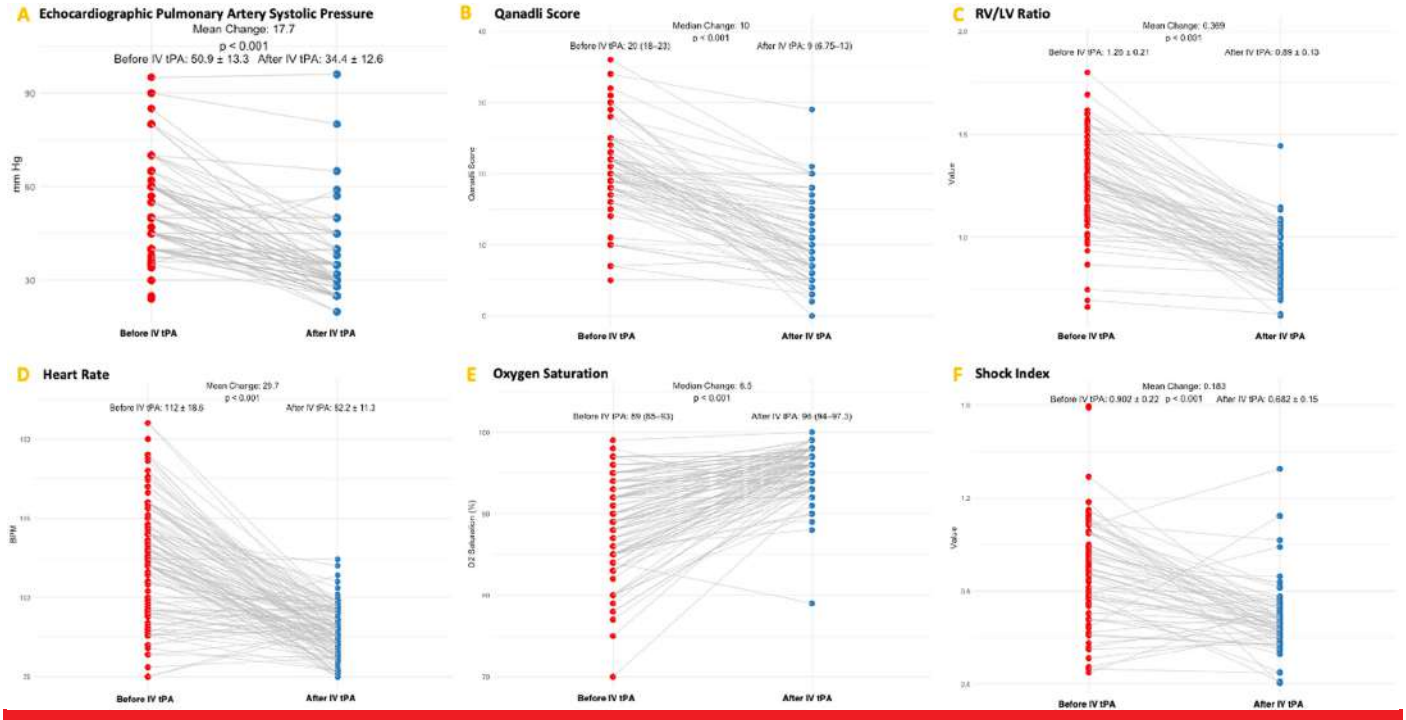

Figure 3. Paired comparison of clinical, echocardiographic, and tomographic parameters before (red dots) and after (blue dots) t-PA infusion. Panels A: Echocardiographic parameters; B and C: Tomographic parameters; D, E, and F: Clinical parameters.

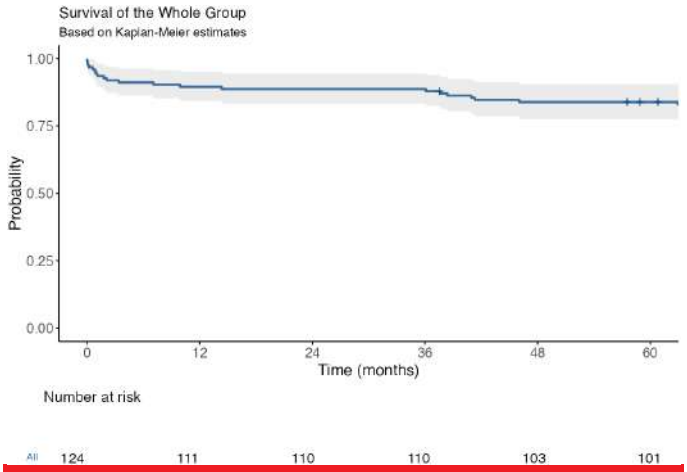

Figure 4. Kaplan-Meier survival plot depicting single-arm survival of the patient cohort.

status. The secondary endpoints include safety, net clinical benefit, impact on overall short-term and long-term mortality, as well as functional impairment, residual RV dysfunction, and incidence of CTEPH.[24] Another important ongoing randomized clinical trial in patients with IHR PE is the HI-PEITHO trial, which compares ultrasound-assisted, low-dose, rapid-infusion thrombolysis with standard anticoagulation. In addition, the STRATIFY trial is currently underway to compare the efficacy and safety of anticoagulation alone, STT, and USAT in this patient population.[25,26] This trial is part of a growing effort to improve the safety profile of reperfusion therapies by using reduced-dose thrombolytics delivered directly to the pulmonary arteries. Prior studies have shown that USAT can effectively reverse RV dysfunction and reduce thrombus burden while significantly lowering the risk of major bleeding events, including intracranial hemorrhage, compared to systemic full-dose thrombolysis.[26-32] Given these favorable safety and efficacy signals, low-dose CDT may represent a promising alternative to STT in selected patients. The results of the HI-PEITHO and STRATIFY trials are expected to clarify whether this approach can be adopted more broadly as a safer reperfusion strategy in IHR PE.[23,24]

Limitations, Clinical Implications, and Future Directions

The findings of this study suggest a rationale for integrating low-dose, slow-infusion STT with t-PA into routine management strategies for IHR PE patients. The balance between hemodynamic efficacy and safety makes it an attractive alternative to both full-dose STT and anticoagulation alone. However, this study has several limitations. First, its retrospective and single-center design may introduce selection bias and limit the generalizability of the findings to broader patient populations and different healthcare settings. Second, the absence of a direct comparator group reduces the ability to draw definitive conclusions regarding the relative effectiveness or superiority of the reduced-dose, slow-infusion regimen.

Future prospective, randomized trials with extended follow-up are essential to determine whether the acute benefits of low-dose thrombolysis translate into durable, long-term advantages, including a potential reduction in CTEPH incidence.[24-26] The causal relationship between more effective thrombus resolution during the acute phase and CTEPH prevention remains speculative and warrants focused investigation. Clarifying this link would have substantial implications for optimizing PE management strategies beyond the immediate treatment period.

Additionally, stratified treatment algorithms—taking into account baseline hemodynamic status, bleeding risk, and RV function—may optimize patient selection, further individualizing management in this setting. The results of the ongoing aforementioned trials are expected to provide answers to these questions.

CONCLUSION

This study provides robust evidence that low-dose, slow-infusion STT with t-PA offers a safe and effective alternative to full-dose STT regimens in IHR PE patients. These findings align with an emerging body of literature suggesting that less-intensive fibrinolytic strategies can maintain efficacy while dramatically improving safety outcomes. With further validation, this approach could transform care for IHR PE.

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Effects of Cardiac Rehabilitation Exercise Plus Sacubitril Valsartan Sodium on Cardiac Function, Lung Function, and Quality of Life in Patients with Chronic Heart Failure

ABSTRACT

Background: To explore the impacts of cardiac rehabilitation exercise plus sacubitril valsartan sodium on cardiac function, lung function, and quality of life in chronic heart failure (CHF) patients.

Methods: One hundred and forty-six CHF patients admitted to the hospital from January 2023 to December 2024 were chosen and divided into a control group (conventional treatment + sacubitril valsartan sodium) and a study group (conventional treatment + sacubitril valsartan sodium + cardiac rehabilitation exercise).

Results: The total effective rate of the study group was higher when comparing with the control group ($P < .05$). The study group had higher left ventricular ejection fraction level as well as lower left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and N-terminal pro B-type natriuretic peptide levels when comparing with the control group after 3 months of intervention ($P < .01$). The study group had higher forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC levels when comparing with the control group following 3 months of intervention ($P < .01$). The study group had higher SpO_2, PaO_2, and PaO_2/FiO_2 levels after 3 months of intervention ($P < .01$). The study group had longer 6-minute walking test after 3 months of intervention ($P < .01$). The study group had lower MLHFQ score when comparing with the control group after 3 months of intervention ($P < .01$). The rate of rehospitalization and incidence of major adverse cardiovascular event (MACE) in the study group were lower than in the control group ($P < .05$).

Conclusion: Cardiac rehabilitation exercise combined with sacubitril valsartan sodium is effective in treating CHF patients, which improves cardiac function, lung function and blood gas levels, promotes exercise endurance and quality of life, and reduces the rehospitalization rate and MACE incidence in CHF patients.

Keywords: Cardiac function, cardiac rehabilitation exercise, chronic heart failure, exercise endurance, lung function, sacubitril valsartan sodium

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INTRODUCTION

Chronic heart failure (CHF) is a kind of disease resulting from the development of various cardiovascular diseases to the terminal stage, characterized by symptoms such as fatigue, cardiac function, and exercise endurance.[1] High incidence, high mortality, and poor prognosis have become prominent characteristics of patients with CHF, making CHF a challenging problem to be solved urgently in clinical practice.[2] Epidemiological data show that there are more than 2 million new cases of CHF worldwide each year, the incidence rate of CHF in developed countries ranging from 1.5% to 2.0%, while in the country it is 0.9%.[3] With the increasing incidence of various cardiovascular diseases and the aging of the population, the prevalence rate of CHF continues to rise, and there are currently about 4 million CHF patients in China, which imposes a huge economic burden on families and society.[4]

The CHF is a chronic disease with a long course and poor prognosis.[5] Patients with this disease may have symptoms such as fatigue, dyspnea, exercise endurance,

and reduced ability in daily living, resulting in an obvious decline in patients' quality of life.[6] Additionally, repeated hospitalization with prolonged and persistent illness not only causes a serious psychological burden but also occupies a large part of medical resources.[7] Drug therapy is the main treatment method for CHF.[8] Sacubitril valsartan sodium can effectively increase cardiac function and reduced exercise ability in patients and reduce hospitalization and all-cause mortality to a certain extent, so it has become the first choice for the treatment of CHF.[9]

Cardiac rehabilitation exercise therapy is a comprehensive medical intervention designed to improve patients' cardiac function, exercise capacity, quality of life, and prognosis through systematic evaluation, education, guidance, and training.[10] Studies have shown that cardiac rehabilitation exercise therapy can improve patients' myocardial metabolism, increase coronary perfusion, reduce cardiac load, reduce myocardial hypoxia, and have many beneficial effects on patients with CHF.[11]

Although the efficacy of cardiac rehabilitation exercise therapy and sacubitril valsartan sodium in treating CHF has been confirmed, there are few studies on the combined application of both. Based on this, this study intends to explore the therapeutic impact of combined cardiac rehabilitation exercise therapy on CHF patients based on sacubitril valsartan sodium. It was hypothesized that sacubitril/valsartan's hemodynamic stabilization would enable safer exercise tolerance, while rehabilitation could potentiate its endothelial-protective effects through shear stress-mediated NO release.

METHODS

General Data

One hundred and forty-six CHF patients admitted to the hospital from January 2023 to December 2024 were chosen to be the study subjects. This study was approved by the Ethics Committee of the hospital (Approval Number: 2024bkky-007; Approval Date: January 16, 2024), and patients agreed to participate and signed informed consent. Inclusion criteria: (1) Met the diagnostic criteria of CHF; (2) the patient was not allergic to the drugs used in this study and could tolerate the treatment; and (3) in line with New York Heart Association (NYHA) Heart function grade II-IV. Exclusion criteria: (1) Patients with malignant tumors or liver and kidney dysfunction; (2) mental illness or cognitive impairment; (3) acute myocardial infarction, congenital heart disease, unstable angina pectoris, and other heart diseases; (4) patients with coagulation disorders, immune system disorders, or blood disorders; and (5) received other therapeutic drugs affecting cardiopulmonary function within 1 month. Following the different treatment methods, the patients were divided into a control group and a study group, with each group having 73 cases.

HIGHLIGHTS

- Cardiac rehabilitation exercise combined with sacubitril valsartan sodium can improve cardiac function, lung function and blood gas levels in chronic heart failure (CHF) patients.
- Cardiac rehabilitation exercise combined with sacubitril valsartan sodium can promote exercise endurance and quality of life in CHF patients.
- Cardiac rehabilitation exercise combined with sacubitril valsartan sodium can reduce the rate of rehospitalization and incidence of major adverse cardiovascular event in CHF patients.

Treatment Methods

After admission, all patients were given conventional treatment, including nitrates, diuretics, antihypertensive drugs, and angiotensin-converting enzyme inhibitors, according to whether patients had drug contraindications. At the same time, the vital signs of patients were closely monitored, patients' blood pressure and blood potassium were regularly measured, and patients' daily lifestyle was guided, such as controlling salt and fat intake and quitting smoking and drinking. Concomitant antianginal (nitrates, calcium channel blocker) and antithrombotic therapies were recorded (Supplementary Table 1).

Based on the conventional treatment, the control group adopted sacubitril valsartan sodium (Beijing Novartis Pharma Co. Ltd., Beijing, China). The initial dose was 100 mg orally twice a day, and the dosage was increased according to the different conditions of the patient. After 2-4 weeks, the dosage was increased to 200 mg twice a day for 3 months.

Based on the conventional treatment and sacubitril valsartan sodium, the study group was given cardiac rehabilitation exercise. The cardiac rehabilitation program was center-based and nurse-supervised, following the *2021 ESC Guidelines on Cardiac Rehabilitation*.[12] The protocol included: aerobic training: treadmill/cycle ergometry (40%-60% peak VO_2, Borg scale 11-13); resistance training: elastic bands (30%-40% 1-RM, 2 sets × 10 reps); flexibility exercises: static stretching (10 minutes pre/post session). Sessions were conducted 3 × per week in rehabilitation center of the hospital with continuous ECG monitoring. (1) Evaluation and screening: Nurses conducted a comprehensive evaluation of patients, including physical condition, cardiovascular function, exercise tolerance, and other aspects of assessment. Screening was performed to determine the patient's suitability for cardiac rehabilitation exercise. (2) Development of personalized training plans: Nurses developed training goals and plans suitable for patients according to their physical condition, heart function, exercise ability, and other relevant factors. (3) Cardiopulmonary monitoring: During cardiac rehabilitation exercise, nurses monitored the patient's heart rate, blood pressure, oxygen saturation, along with other vital signs, which helped to assess the patient's exercise tolerance and safety, and to adjust the intensity and style of training in a timely manner. (4) Exercise and strength training: According to the training program, nurses instructed the patient to do moderate aerobic exercise, including walking, cycling, as well as swimming, 3-5 times a week, 25-40 minutes each time, with light to moderate fatigue being

appropriate. At the same time, the patient was instructed to carry out moderate strength training, including the use of weight machines, elastic bands, and other muscle exercises, 2-3 times a week, 1-3 sets per muscle group, and 6-10 repetitions per group. Patients should rest for 1-2 minutes between each group and rest for at least 1 day between each exercise. Resistance training (2-3× per week) specifically targeted major muscle groups to counteract cardiac cachexia risk, consistent with recent guidelines. (5) Rest and Recovery: During training, nurses ensured that the patient had adequate rest and recovery time. Based on patient feedback and vital signs monitoring results, training intensity and rest time were adjusted to ensure patient safety and comfort. The exercise treatment period was 3 months.

Observation Indicators

All assessments were performed within 2 weeks after completing the 3-month intervention.

(1) Clinical efficacy: After treatment, the efficacy of patients was evaluated based on the recovery level of cardiac function grade. Obvious effect: the cardiac function was improved by 2 or more levels, and the cardiac function of level II was improved to level I; Effective: the cardiac function was improved by 1 grade; Ineffective: No improvement or decrease in heart function. Total effective rate = (number of effective cases + number of ineffective cases)/total number of cases × 100%.

(2) Cardiac function: Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), as well as left ventricular ejection fraction (LVEF) were measured by Mindrail DC-N3S color Doppler ultrasound system. About 4 mL of elbow venous blood was gathered from patients, and the level of plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) was detected by enzyme-linked immunosorbent double antibody sandwich method.

(3) Lung function: Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), as well as FEV1/FVC were measured with the Japanese MINATOAS-507 pulmonary function instrument.

(4) Blood gas level: Oxygen saturation (SpO_2), partial arterial oxygen concentration (PaO_2), and PaO_2/inspired oxygen fraction (PaO_2/FiO_2), which are detected by the Danish automatic blood gas analyzer.

(5) Exercise endurance: The 6-minute walking test (6MWT) was adopted for evaluating patients' exercise endurance.[13] The longer the walking distance, the better the exercise endurance.

(6) Quality of life: The Minnesota living with heart failure questionnaire (MLHFQ) was adopted to evaluate the quality of life of patients, with a total of 21 items.[14] Each item was scored on a 0-5 scale, with a total score of 105 points, and the higher the score, the worse the quality of life.

(7) The rate of rehospitalization and the incidence of major adverse cardiovascular events (MACE), including stroke, angina pectoris, and myocardial infarction, were recorded.

Statistical Analysis

GraphPad Prism 10.0 statistical software (GraphPad Software Inc., San Diego, CA, USA) was employed for analyzing the data. Normality was confirmed by the Shapiro–Wilk test ($P > .05$). The measurement data conforming to normal distribution were exhibited as mean ± standard deviation ($x \pm s$). For within-group comparisons (before vs. after intervention), a paired *t*-test was used; for between-group comparisons, an independent *t*-test was applied. The counting data were exhibited as numbers and rate (%), and the χ^2 test was applied for comparison. A priori power analysis indicated that 64 patients/group would provide 80% power ($\alpha = 0.05$) to detect a 7% LVEF difference. $P < .05$ was considered statistically significant.

RESULTS

General Data of Patients in Both Groups

As Table 1 displayed, Pearson's chi-square test was used for etiology comparison, and no difference was seen in the general data of patients between the 2 groups ($P > .05$).

Clinical Efficacy in Both Groups

As Table 2 revealed, the total effective rate of the study group was higher compared to the control group ($\chi^2 = 5.053$, $P = .080$).

Cardiac Function in Both Groups

Prior to intervention, no differences were seen in LVEF, LVESD, LVEDD, and NT-proBNP levels between 2 groups ($P > .05$). Following 3 months of intervention, LVEF levels were elevated while LVESD, LVEDD, and NT-proBNP levels were diminished in both groups ($P < .01$). Notably, the study group had higher LVEF level as well as lower LVESD, LVEDD, and NT-proBNP levels when comparing with the control group after 3 months of intervention ($P < .01$, Figure 1).

Lung Function in Both Groups

Prior to intervention, no differences were seen in FEV1, FVC, or FEV1/FVC levels between 2 groups ($P > .05$). Following 3 months of intervention, FEV1, FVC, and FEV1/FVC levels were elevated in both groups ($P < .01$). Notably, in contrast to the control group, the study group had higher FEV1, FVC, and FEV1/FVC levels when comparing with the control group following 3 months of intervention ($P < .01$, Figure 2).

Blood Gas Level in Both Groups

Prior to intervention, no differences were seen in SpO_2, PaO_2, and PaO_2/FiO_2 levels between 2 groups ($P > .05$). Following 3 months of intervention, SpO_2, PaO_2, and PaO_2/FiO_2 levels were elevated in both groups ($P < .01$). Notably, the study group had higher SpO_2, PaO_2, and PaO_2/FiO_2 levels when comparing with the control group after 3 months of intervention ($P < .01$, Figure 3).

Exercise Endurance in Both Groups

Prior to intervention, no differences were seen in the 6MWT between the 2 groups ($P > .05$). Following 3 months of intervention, 6MWT was elevated in both groups ($P < .01$). Notably, the study group had longer 6MWT compared to the control group after 3 months of intervention ($P < .01$, Figure 4).

Table 1. General Data of Patients in Both Groups

Items	Control Group (n = 73)	Study Group (n = 73)	χ^2/t	*P*
Gender			0.11	.73
Male	40 (54.79)	42 (57.53)		
Female	33 (45.21)	31 (42.47)		
Age (years)	64.17 ± 7.91	64.21 ± 8.05	0.03	.97
Grade of cardiac function			0.15	.92
Grade II	18 (24.66)	20 (27.40)		
Grade III	43 (58.90)	41 (56.16)		
Grade IV	12 (16.44)	12 (16.44)		
Course of disease (years)	3.97 ± 0.61	4.02 ± 0.65	0.47	.63
Baseline medications				
ACEI/ARB (%)	65 (89.04)	67 (91.78)	0.34	.56
Beta-blockers (%)	58 (79.45)	60 (82.19)	0.17	.68
MRA (%)	42 (57.53)	40 (54.79)	0.1	.75
Diuretics (%)	70 (95.89)	69 (94.52)	0	1
Etiology			0.110	.740
Ischemic heart disease	38 (52.05)	40 (54.79)		
Non-ischemic	35 (47.95)	33 (45.21)		
Prior revascularization			0.21	.64
PCI (%)	15 (20.55)	17 (23.29)		
CABG (%)	8 (10.96)	6 (8.22)		
None (%)	50 (68.49)	50 (68.49)		

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention.

Quality of Life in Both Groups

Prior to intervention, no differences were seen in MLHFQ scores between the 2 groups ($P > .05$). Following 3 months of intervention, MLHFQ score was decreased in both groups ($P < .01$). Notably, in contrast to the control group, the study group had lower MLHFQ score after 3 months of intervention ($P < .01$, Figure 5).

Rate of Rehospitalization and Incidence of Major Adverse Cardiovascular Events in Both Groups

As Table 3 revealed, the rate of rehospitalization (Fisher's exact test, $P = .033$) and incidence of MACE (continuity correction $\chi^2 = 3.539$, $P = .060$) in the study group were lower when comparing with the control group.

Adverse Events and Treatment Compliance Related to Rehabilitation Intervention in Both Groups

Adverse events occurred in 6 patients (8.2%) in the study group (musculoskeletal pain = 3, hypotension = 2, arrhythmia = 1) and 4 controls (5.5%, all hypotension). In the study group, 65 patients (89.0%) completed >80% of prescribed sessions. Three dropouts occurred due to noncompliance with exercise and 5 due to transportation barriers in the study group.

Table 2. Clinical Efficacy in Both Groups

Groups	Cases	Obvious Effect	Effective	Ineffective	Total Effective Rate
Control group	73	24 (32.88)	35 (47.94)	14 (19.18)	59 (80.82)
Study group	73	30 (41.10)	38 (52.05)	5 (6.85)	68 (93.15)
χ^2					5.053
P					.080

DISCUSSION

With the continuous increase of China's aging population, the incidence of cardiovascular diseases has increased significantly.[15] The CHF is the end-stage presentation of a variety of cardiovascular diseases, with high mortality and poor prognosis, which seriously threatens patients' life safety.[16] Currently, the treatment of CHF includes diuretics, ACE inhibitors or ARB, beta blockers, and aldosterone receptor antagonists. These drugs can improve cardiac function along with the prognosis of CHF patients by reducing cardiac load, dilating blood vessels, reducing neuroendocrine activity, and inhibiting myocardial remodeling.[17] Sacubitril valsartan sodium is composed of valsartan and sacubitril. The former is an angiotensin receptor antagonist, and the latter is a neutral endopeptidase inhibitor.[18] The drug can block the angiotensin II receptor, inhibit the activity of neutral endopeptidase through a dual mechanism, and then reduce harmful neuroendocrine substances, play a role in blood vessel dilation, reduce blood pressure, reduce water and sodium retention, and inhibit myocardial remodeling, among other effects.[19] However, drug therapy alone has limitations, such as side effects, resistance, and compliance.[20] Therefore, there is a need to find safer, more effective, and economical treatments to complement drug therapy.

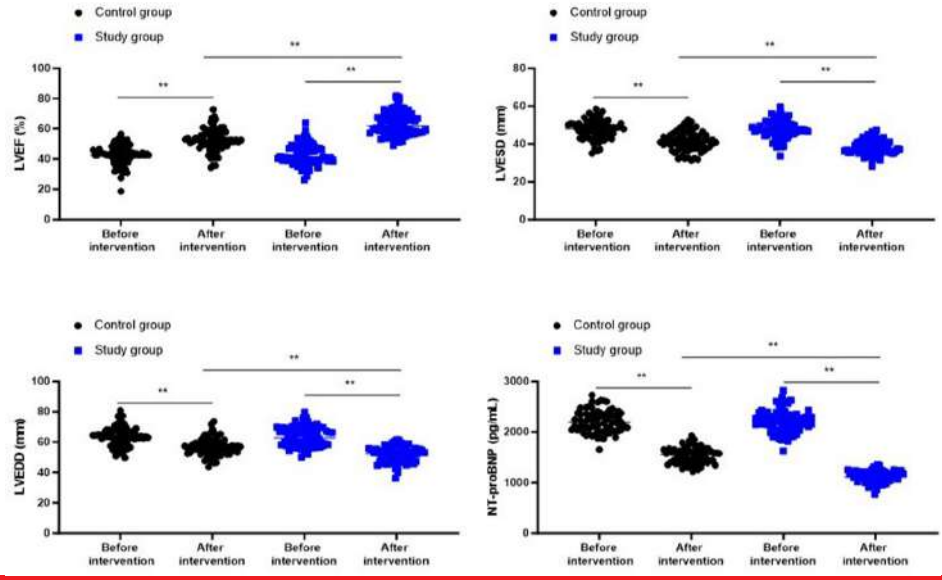

Figure 1. Cardiac function in both groups. $^{**}P < .01$.

In the early stages of medicine, it was recommended that CHF patients should mainly rest and do not recommend too much exercise.[21] However, with in-depth studies, researchers found that moderate exercise is more conducive to the rehabilitation of CHF patients.[22] Cardiac rehabilitation exercise was initially used for the rehabilitation of patients with coronary heart disease and was gradually applied to other cardiovascular diseases such as CHF.[23] At present, cardiac rehabilitation exercise therapy has become an important part of the comprehensive treatment of CHF, and NYHA has recommended cardiac rehabilitation exercise therapy as Class I A for patients with CHF.[24] The implementation of cardiac rehabilitation exercises can effectively promote the exercise tolerance of patients, avoid the activity of the sympathetic nervous system caused by overactivation, and increase the activity of the parasympathetic nervous system.[25] In addition, reasonable exercise has an accelerated effect on skeletal muscle blood circulation, can improve oxygen metabolism, and has a positive effect on controlling disease symptoms.[26] Previously, the 6MWT improvement (Δ54 m) exceeded the CHF MCID of 30 m, while NT-proBNP reduction (Δ142 pg/mL) surpassed the 25% threshold for clinical significance.[27,28] In this study, the results suggested that the total effective rate of the study group was higher when comparing with the control group, implying that cardiac rehabilitation exercise plus sacubitril valsartan sodium was more effective than single sacubitril valsartan sodium, which was similar to previous reports.[29]

Besides, the results of the study indicated that following 3 months of intervention, LVEF, FEV1, FVC, and FEV1/FVC levels were elevated while LVESD, LVEDD, and NT-proBNP

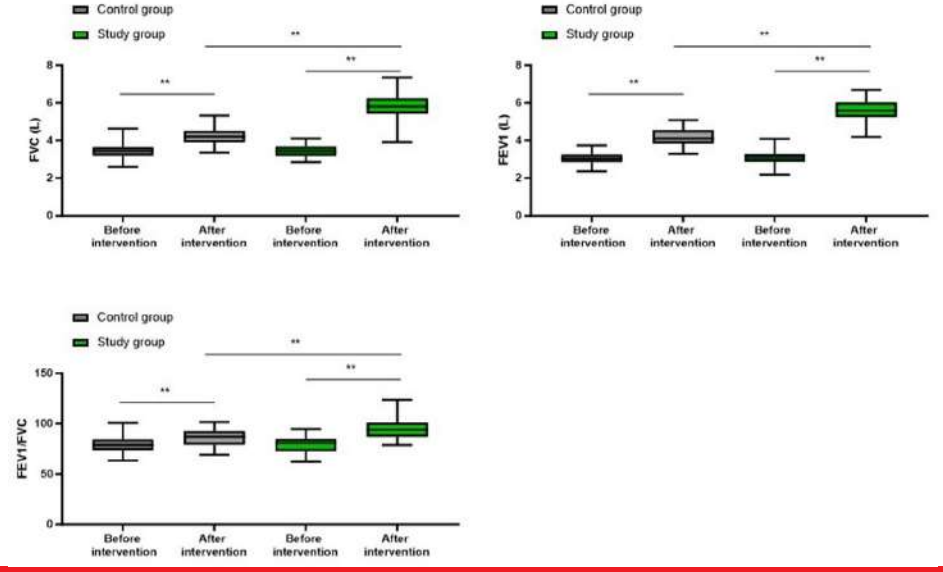

Figure 2. Lung function in both groups. $^{**}P < .01$.

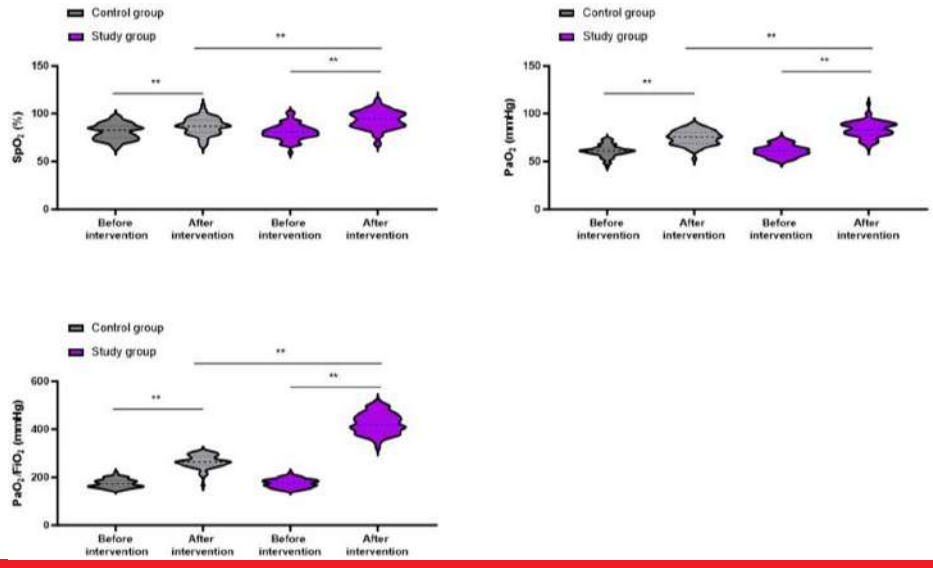

Figure 3. Blood gas levels in both groups. $^{**}P < .01$.

levels were diminished in both groups. Notably, the study group had higher LVEF level as well as lower LVESD, LVEDD, and NT-proBNP levels when comparing with the control group after 3 months of intervention. All these results suggested that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better improve cardiac function and lung function in CHF patients. The reason for the analysis is that cardiac rehabilitation exercise therapy can regulate the sympathetic nerve, inhibit the over-activation of the renin-angiotensin-aldosterone system, improve aerobic metabolism capacity in the body, and enhance blood circulation capacity.[30] Consistently, Li et al[31] suggested that comprehensive exercise programs could improve cardiac output as well as decrease restenosis rates in post-percutaneous coronary intervention patients. Wang et al[32] indicated that cardiopulmonary exercise testing-guided cardiac rehabilitation could improve cardiopulmonary function and NT-proBNP levels in CHF patients. While Torun et al[37] demonstrated sacubitril/valsartan's exercise-enhancing effects in healthy rats, the findings extend this observation to CHF patients, suggesting disease-specific modulation of cardiopulmonary adaptation.

In addition, the study indicated that after 3 months of intervention, SpO_2, PaO_2, and PaO_2/FiO_2 levels were elevated

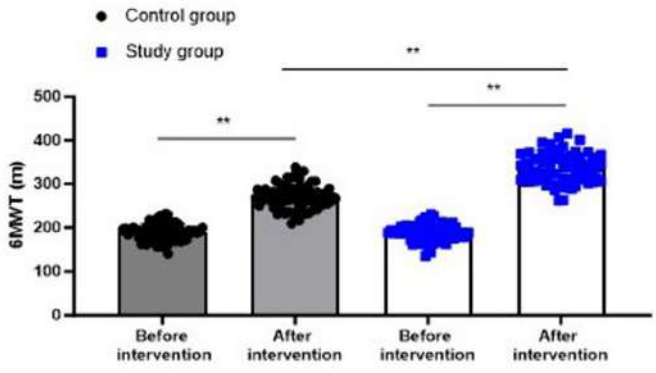

Figure 4. Exercise endurance in both groups. $^{**}P < .01$.

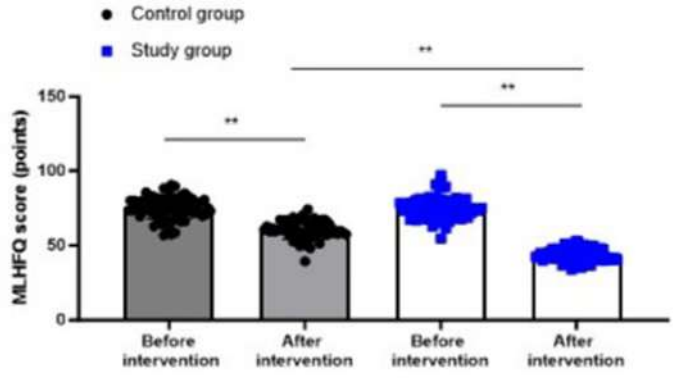

Figure 5. Quality of life in both groups. $^{**}P < .01$.

Table 3. Rate of Rehospitalization and Incidence of MACE in Both Groups

			MACE			
Groups	Cases	Rate of Rehospitalization	Stroke	Angina Pectoris	Myocardial Infarction	Total Incidence
Control group	73	8 (10.96)	2 (2.74)	3 (4.11)	4 (5.48)	9 (12.33)
Study group	73	1 (1.37)	0 (0.00)	1 (1.37)	1 (1.37)	2 (2.74)
χ^2		Fisher's exact test		3.539		
P		.033		.060		

in both groups. Notably, the study group had higher SpO_2, PaO_2, and PaO_2/FiO_2 levels when comparing with the control group after 3 months of intervention. All these results suggested that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better improve the blood gas levels of CHF patients. Cardiac rehabilitation exercise training can promote aerobic metabolism, enhance myocardial oxygen supply, prolong the ventricular ejection period, and enhance myocardial contractility.[33] Cardiac rehabilitation may improve myocardial oxygen supply, as evidenced by increased SpO_2 in the study and prior findings showing enhanced coronary flow reserve after training.[34]

Moreover, the study indicated that after 3 months of intervention, 6MWT was increased in both groups. Notably, relative to the control group, the study group had longer 6MWT after 3 months of intervention. All these results implied that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better promote the exercise endurance of CHF patients. The reason is that, through appropriate exercise intensity and frequency, cardiac rehabilitation exercise effectively enhances the strength and endurance of respiratory muscles, optimizes skeletal muscle aerobic metabolism, not only enhances the patients' lung capacity, but also improves their lung ventilation, so that the exercise endurance is stronger.[35] Consistently, Hua et al[36] suggested that exercise-based cardiac rehabilitation delivery modes could increase the 6MWT of CHF patients. Notably, the resistance training protocol aligns with Torun's recommendation for CHF patients,[37] where elastic band exercises preserve lean mass while improving functional capacity. This dual approach (aerobic + resistance) may explain the superior 6MWT outcomes compared to aerobic-only regimens.

Finally, the study indicated that following 3 months of intervention, MLHFQ score was decreased in both groups. Notably, the study group had lower MLHFQ score when comparing with the control group following 3 months of intervention. At the same time, the rate of rehospitalization and incidence of MACE in the study group were lower when comparing with the control group. All these results suggested that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better promote the quality of life, reduce the rate of rehospitalization and incidence of MACE in CHF patients. Similarly, He et al[38] suggested that a long-term exercise-based cardiac rehabilitation program could promote physical health along with reducing all-cause mortality and MACE in myocardial infarction patients. Furthermore, although exercise-related adverse events were reported, the small sample may underestimate safety risks in real-world settings. Additionally, the 3-month follow-up was sufficient to assess functional improvements but may be inadequate for long-term outcomes like mortality. Limitations also include the use of multiple statistical tests without adjustment for multiplicity, which may increase type I error. Future studies with larger samples and longer follow-up are needed to confirm these findings. Despite proven benefits, global cardiac rehabilitation participation rates remain low (30%-50%), as highlighted by Torun et al[39] in Türkiye. Herein, 89% adherence was achieved through hospital-based supervised sessions, suggesting that structured programs may overcome common barriers like lack of awareness (reported in 62% non-participants in Torun's survey) and logistical challenges. While high adherence was observed, the hospital-based setting may limit generalizability to communities with restricted healthcare access. Future studies should explore culturally adapted education strategies to further improve engagement.

CONCLUSION

The study indicates that cardiac rehabilitation exercise combined with sacubitril valsartan sodium is effective in treating CHF patients, which can improve cardiac function, lung function and blood gas levels, promote exercise endurance and quality of life, as well as reduce the rate of rehospitalization and incidence of MACE in CHF patients.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: This study was approved by the Ethics Committee of Beijing Rehabilitation Hospital Affiliated to Capital Medical University (Decision Number: 2024bkky-007; Decision Date: January 16, 2024). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed Consent: All participants had signed the informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – X.L., Z.X.; Design – X.L., Z.X.; Supervision – Z.X.; Resource – Z.X.; Materials – P.Z., J.C., L.S., Q.M.; Data Collection and/or Processing – X.L., P.Z., J.C.; Analysis and/or Interpretation – X.L., L.S., Q.M.; Literature Review – X.L., P.Z., J.C.; Writing – X.L.; Critical Review – Z.X. All authors read and approved the final manuscript.

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

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Supplementary Table 1. Concomitant antianginal and antithrombotic therapies

Medication Class	Specific Drug	Control group (n=73)	Study group (n=73)	χ^2	*P*
Antianginal Therapy					
Nitrates	Isosorbide dinitrate	18 (24.7%)	15 (20.5%)	0.38	0.54
	Isosorbide mononitrate	7 (9.6%)	8 (11.0%)	0.09	0.77
Calcium Channel Blockers	Amlodipine	12 (16.4%)	10 (13.7%)	0.22	0.64
	Diltiazem	5 (6.8%)	6 (8.2%)	0.1	0.75
Antithrombotic Therapy					
Antiplatelets	Aspirin	40 (54.8%)	42 (57.5%)	0.11	0.74
	Clopidogrel	25 (34.2%)	23 (31.5%)	0.12	0.73
Anticoagulants	Warfarin	8 (11.0%)	7 (9.6%)	0.07	0.79
	DOACs	4 (5.5%)	3 (4.1%)	Fisher's exact test	1

DOACs, Direct oral anticoagulants (rivaroxaban/dabigatran)

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

CASE REPORT

INTRODUCTION

Kounis syndrome (KS) is an acute coronary syndrome (ACS) triggered by an allergic reaction that can be precipitated by food, drugs, or environmental factors.[1] Severe stress reactions triggered by allergies can be a cause of ACS.[2] Ventricular fibrillation is a life-threatening arrhythmia for ACS patients.[3] This article reports a case of intake of levofloxacin leading to type 1 Kounis syndrome and triggering ventricular fibrillation, which was successfully treated in our hospital.

CASE REPORT

The patient is a 59-year-old female, admitted to the hospital for "paroxysmal chest pain for 1 day." She was previously healthy, denying hypertension, diabetes, hyperlipidemia, chronic kidney disease, and coronary heart disease. The patient was treated with levofloxacin tablets for a urinary tract infection 2 days ago and then developed itching on the chest and limbs, accompanied by scattered urticaria, and began to have recurrent chest burning pain 1 day ago, radiating to the pharynx, accompanied by slight sweating, each time lasting about 2-3 minutes, which can be relieved spontaneously. The outpatient clinic admitted her to the department of cardiology with "unstable angina."

Physical examination: blood pressure 114/80 mm Hg, Pulse 63 beats/min, Respiratory rate 18 breaths/min, body temperature 36.2°C; scattered urticaria on the limbs and trunk. Breath sounds are clear in both lungs. The heart rate is 63 beats/min, the rhythm is uniform, and no pathological murmur is heard. The abdominal examination is normal. There is no edema in limbs.

Blood tests: Blood analysis, liver and kidney function, electrolytes, coagulation function, Creatine kinase isoenzyme MB (CK-MB), Troponin I (TNI), and N-terminal pro-brain natriuretic peptide (NT-proBNP) were normal. Echocardiography showed a left ventricular ejection fraction (LVEF) of 56%; mild tricuspid regurgitation and decreased left ventricular diastolic dysfunction. Admission ECG: sinus rhythm, normal ECG.

Diagnosis: 1. Coronary heart disease, unstable angina; 2. Urticaria.

Treatment: After admission, aspirin 300 mg, clopidogrel bisulfate 300 mg, atorvastatin 20 mg, loratadine 10 mg orally; half an hour after admission, the patient suddenly felt chest pain and then lost consciousness with twitching. ECG monitoring showed ventricular fibrillation (Figure 1), immediately shocked with 200 Joules; the patient regained consciousness. ECG showed sinus rhythm, ST segment arch dorsal upward elevation in V1-V6, ST-segment depression in leads II, III and aVF (Figure 2), nitroglycerin 0.5 mg sublingually relieved chest pain after about 5 minutes; repeat ECG showed ST segment in leads V1-V6 resolution (Figure 3). Emergency coronary angiography showed that the left main trunk, the left anterior descending artery, left circumflex branch, and right coronary artery had no obvious stenosis and obstruction, and thrombolysis in myocardial infarction risk score (TIMI) blood flow grade 3 (Figure 4).

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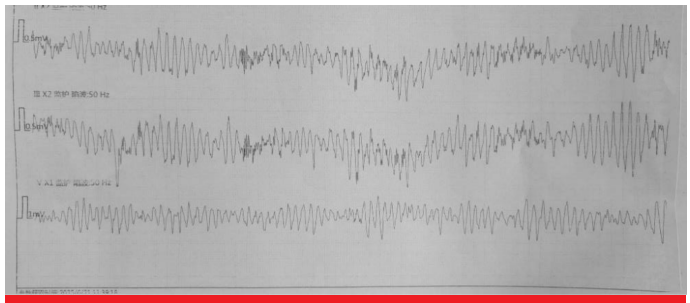

Figure 1. ECG monitoring shows ventricular fibrillation.

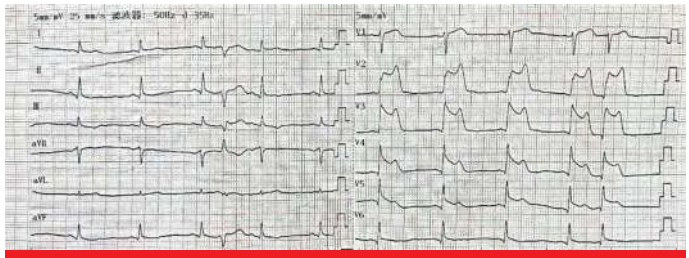

Figure 2. ST-segment arch dorsally ascending elevation in V1-V6.

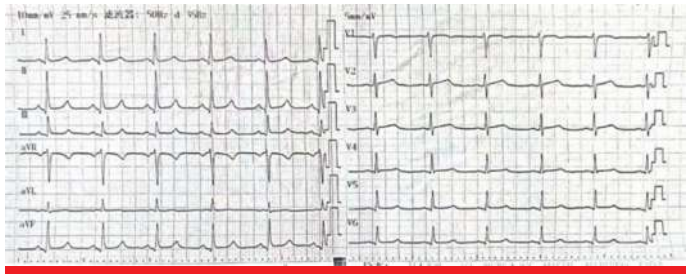

Figure 3. ECG showed ST segment in leads V1-V6 regressed.

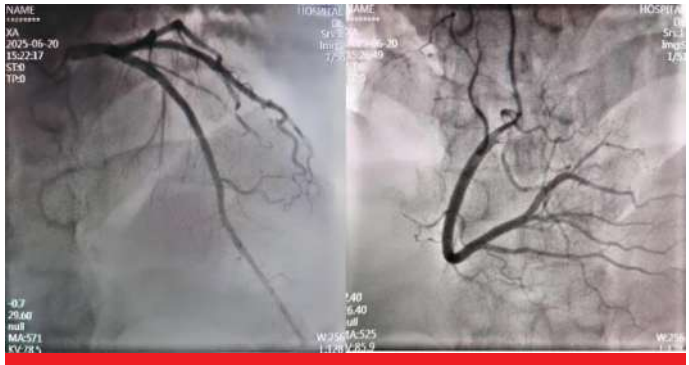

Figure 4. Coronary angiography shows no significant stenosis of the coronary vessels. (Left, left anterior descending artery and left circumflex branch, Right, right coronary artery).

Based on the patient's drug allergy history (urticaria), chest pain characteristics, dynamic ECG changes, and normal coronary angiography, delayed type 1 Kounis syndrome was diagnosed, likely triggered by drug allergy, leading to left anterior descending artery spasm (causing and angina). Cardiac enzymes remained normal. Loratadine 10 mg once daily was given for anti-allergy, diltiazem 30 mg every 8 hours for anti-coronary artery spasm. No recurrent chest pain or rash after 1 week. Discharged in stable condition.

DISCUSSION

Kounis syndrome is an anaphylactic-mediated acute coronary event that is relatively rare and can manifest as severe events such as angina, acute myocardial infarction, and even ventricular tachycardia and ventricular fibrillation.[4] Coronary artery spasm is a rare cause of acute myocardial infarction.[5] Various allergic reactions caused by different factors, such as medications and vaccines, can potentially trigger Kounis syndrome.[6] The mechanism is that the allergic reaction activates mast cells, macrophages, and T lymphocytes and releases a large number of inflammatory mediators that act directly on the coronary arteries, causing spasms, rupture, and thrombosis on the basis of vulnerable plaques.[7] According to the basic condition of the coronary artery and the characteristics of the lesion, KS can be divided into four types: [8] type 1 is the coronary artery spasm without underlying coronary artery lesion induced by allergic reaction; type 2 is an allergic reaction that induces coronary artery spasm or plaque rupture in the presence of atherosclerotic lesions; type 3 is coronary stent thrombosis due to anaphylaxis; coronary artery bypass graft thrombosis is defined as type 4.[9]

Levofloxacin is a commonly used fluoroquinolone antibiotic in clinical practice. Its allergic reactions are often characterized by rashes, papules, skin erythema, vascular prominence, toxic epidermal necrolysis, and other clinical symptoms; it can also lead to patients experiencing laryngeal edema, asthma, allergic pneumonia, and anaphylactic shock.[10] However, there are rare reports of it causing Kounis syndrome. García Núñez et al[11] report a 35-year-old man with sinusitis who had experienced an episode of the type 1 variant of Kounis syndrome after levofloxacin intake. However, the patient did not trigger ventricular fibrillation.[11] No similar reports have been seen since then.

The characteristics of this case are summarized as follows: triggers are levofloxacin allergy (urticaria); cardiac manifestations were recurrent chest pain and ventricular fibrillation; ECG features were extensive anterior ST segment elevation and then regression; coronary angiography showed that no significant stenosis was found, which supported the diagnosis of type 1 KS. Anti-allergic treatment combined with strong antispasmodics effectively controlled symptoms and arrhythmia; the interval between allergic symptoms (urticaria) and severe cardiac events (ventricular fibrillation) is about 1 day, which is in line with the characteristics of "late-onset type."

CONCLUSION

This case report describes a rare case of recurrent coronary artery spasm and ventricular fibrillation triggered by levofloxacin intake. The enlightenment of this case is that patients with chest pain after allergic reactions, especially those with ECG abnormalities, should be highly alert to the possibility of Kounis syndrome; allergies in the elderly,

underlying atherosclerosis, or chronic disease should be particularly vigilant about the risk of KS.[12]

Informed Consent: The written informed consent was acquired from the patient.

Acknowledgments: The authors sincerely thank the patient for consenting to the publication of this case report and related images.

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

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Reevaluating Prognostic Nutritional Index in Post-Coronary Artery Bypass Graft Surgery Mortality: A Call for Caution

LETTER TO THE EDITOR

To the Editor,

We read with interest the article by Toprak and Bilgiç[1] evaluating the prognostic role of pre- and postoperative prognostic nutritional index (PNI) in patients undergoing coronary artery bypass grafting (CABG). The authors are to be commended for emphasizing the clinical relevance of nutritional status and for incorporating both perioperative time points of PNI, an easily accessible and cost-effective biomarker.

However, several methodological and interpretative concerns deserve attention. First, the reported in-hospital mortality rate of 21.8% appears substantially higher than expected in contemporary CABG populations.[2,3] This raises questions about the cohort composition—particularly the proportion of urgent, frail, or high-risk patients—which is not explicitly described. The lack of subgroup analysis in these populations limits the generalizability of the findings and complicates risk interpretation.

Second, while the authors assert the predictive power of PNI, the analysis includes both PNI and its components (e.g., albumin) in multivariable models. This introduces potential collinearity and clouds interpretation. Moreover, an unexpected result emerges: postoperative lymphocyte counts were paradoxically higher in non-survivors, yet their PNI values were lower. This contradiction may reflect timing inconsistencies, inflammatory confounders, or analytical noise, and warrants clarification. It also underscores the importance of examining the individual components of composite indices rather than relying solely on the combined score.

The authors further propose that early nutritional interventions may improve outcomes in patients with low PNI. While plausible, this assumption is speculative; no interventional data are presented to support it. Whether low PNI reflects modifiable malnutrition or simply marks underlying disease severity, frailty, or systemic inflammation remains unclear. Prospective, controlled studies are needed to determine if PNI-guided nutritional optimization can alter clinical trajectories in CABG patients.

Finally, although the study suggests integrating PNI into existing risk models, it does not evaluate whether PNI adds predictive value beyond well-established tools such as EuroSCORE II or STS risk scores. Without such comparisons, the standalone utility of PNI remains questionable in preoperative planning.

In conclusion, while this study contributes to the growing body of literature linking nutritional status to surgical outcomes, its findings should be interpreted with caution. Further multicenter, prospective investigations are required to validate the prognostic utility of PNI and to determine its place in clinical decision-making.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Reply to Letter to the Editor: "Reevaluating Prognostic Nutritional Index in Post-Coronary Artery Bypass Grafting Mortality: A Call for Caution"

LETTER TO THE EDITOR
REPLY

To the Editor,

We would like to express our sincere thanks to the readers for their constructive and thoughtful comments[1] regarding our recently published article.[2] Their engagement reflects a shared commitment to improving the understanding and clinical use of nutritional indices in cardiac surgery. We welcome the opportunity to address the points raised.

Regarding the in-hospital mortality rate of 21.8%, it is important to emphasize that this figure does not reflect routine clinical outcomes at our institution. This rate is a direct consequence of the study's nested case-control design, which employed a 1 : 4 matching ratio to enhance statistical power in mortality-related analyses. Patients with emergency status, active malignancy, dialysis-dependent renal failure, or hepatic dysfunction were excluded to ensure a controlled cohort. Thus, the elevated mortality percentage is a result of methodological enrichment and does not represent our standard practice outcomes.

On the question of multicollinearity due to simultaneous inclusion of prognostic nutritional index (PNI) and albumin in the regression models, multicollinearity diagnostics (variance inflation factor <2) confirmed no statistical concern. Nonetheless, to ensure clarity, we evaluated PNI and albumin in separate multivariable models. The results consistently demonstrated the superior predictive value of PNI over albumin, supporting its use as a composite biomarker of nutritional and inflammatory status in surgical patients.[2]

The observation of elevated postoperative lymphocyte counts in non-survivors, despite lower PNI values, is notable. This finding likely results from a temporal mismatch: while PNI was calculated using laboratory data within the first 24 hours postoperatively, the lymphocyte values reflect peak measurements during ICU stay. This temporal discrepancy may capture a reactive inflammatory response, potentially secondary to complications such as infection or sepsis, and does not contradict the systemic burden suggested by low PNI.

We acknowledge the readers' concern regarding the interpretative nature of recommending early nutritional intervention based on observational data. However, our statement was not intended as a clinical directive but rather as a hypothesis-generating interpretation based on robust and consistent statistical associations. In line with previous literature, identifying patients with low PNI may provide an opportunity for closer monitoring and more individualized management strategies, especially in high-risk surgical populations.[3]

With respect to the comparison of PNI to established risk models such as EuroSCORE II or STS, we recognize their proven clinical value. However, these scores do not incorporate objective nutritional parameters such as albumin and lymphocyte count. Our study focused specifically on the prognostic relevance of

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PNI, and the findings contribute novel insight into its potential role alongside existing tools.

In summary, we appreciate the scholarly discussion generated by our work. We believe the points raised have offered an opportunity to reinforce and clarify the methodological integrity and interpretative framework of our study. The PNI remains a promising marker for mortality risk stratification in the setting of coronary artery bypass grafting.

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

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Comment on: Self-Expanding Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis Undergoing Prosthetic Mitral Valve Replacement: A Single-Center Experience

LETTER TO THE EDITOR

To the Editor,

We read with great interest and appreciation the important study by Kıvrak et al[1] published in *The Anatolian Journal of Cardiology*, titled "Self-Expanding Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis Undergoing Prosthetic Mitral Valve Replacement: A Single-Center Experience." We congratulate the authors for sharing their experience in this challenging and specific patient group, for presenting the largest single-center series reported in the literature to date, and for achieving commendable results such as a 100% procedural success rate and zero intraprocedural mortality. The fact that the center's experience is built upon their earlier pioneering work from 2016, which included the first patients of this series, is also valuable as it presents a decade of their accumulated experience.[2] We aim to contribute to the scientific discussion by contextualizing the findings of this valuable study within the framework of larger-scale registries and the center's own evolution.

One of the study's key conclusions is that self-expanding (SE) valves are the "optimal choice" in this patient group due to their repositioning capabilities. This strong assertion, however, becomes debatable when compared with broader data from the literature. The multicenter OPTIMAL registry, one of the largest in this field involving 154 patients, reported the use of balloon-expandable (BE) valves in nearly half of its cases and concluded that there was "no significant difference in TAVI procedural success rates according to the type of THV (ie, balloon-expandable vs self-expanding)."[3] The OPTIMAL registry suggests that the choice of valve should be guided by patient anatomy and operator experience, rather than being limited to a single approach.

The most striking data point in this regard is the permanent pacemaker implantation (PPI) rate. The 22.5% PPI rate in the series by Kıvrak et al, which used 100% SE valves, is nearly double the 12% rate reported in the OPTIMAL registry, which used a mix of BE and SE valves. Furthermore, the PPI rate in the same center's initial 6-case series from 2016 was 16.7% (1/6 patients). When viewed together, these data strongly suggest that the high PPI rate in the study by Kıvrak et al is associated with their SE-focused strategy. The OPTIMAL data indicates that a mixed strategy that includes BE valves could significantly reduce the need for PPI, a major complication in this patient group.

The authors note that in their own study, they found no significant difference in mortality between patients who did and did not receive a PPI ($P = .718$), which they justifiably attribute to the small sample size. However, as they also reference, a large meta-analysis of over 50 000 patients has shown that post-TAVI pacemaker implantation is associated with increased long-term mortality and rehospitalization. Therefore, even if this study's own mortality data did not show a significant difference, the known long-term adverse outcomes associated with a high PPI

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rate of 22.5% once again underscore the importance of strategies designed to minimize this rate.[4]

In addition to these clinical outcomes, the study's methodological design also presents points for discussion. The 11-year study period, from 2013 to 2023, encapsulates an impressive learning curve for the center. As seen by comparing their 2016 publication with the current one, the vascular access technique evolved from primarily surgical cut-down to standardized percutaneous closure systems, with a corresponding drop in vascular complication rates.[2] While this demonstrates a laudable improvement, analyzing the results from a decade of evolving technology (e.g., from first-generation CoreValve to Evolut R) and operator experience as a single cohort may mask important details of this evolution. We believe a subgroup analysis stratifying the data into an "early" and "late" period would more clearly reveal the evolution of the center's practice and enhance the homogeneity of the results.

Finally, the authors' emphasis on the importance of the aorto-mitral distance in pre-procedural planning is highly pertinent. They report a mean distance of 6.4 mm. In this context, we are curious as to whether the authors observed a correlation between this distance and specific complications. For instance, were shorter aorto-mitral distances associated with a higher incidence of minor vascular complications or greater difficulty in valve positioning?

In conclusion, the study by Kıvrak et al is a valuable work that proves excellent results can be achieved with an SE-focused strategy in an expert center. However, when its conclusions are interpreted in light of larger, more heterogeneous studies like OPTIMAL, the assertion that SE valves are the "single optimal choice" is weakened. The literature suggests that a more flexible, patient-tailored approach to valve selection appears to be more prudent, especially to mitigate the significant risk of PPI and its known long-term adverse outcomes. We once again congratulate the authors for this important contribution and for transparently sharing their decade of experience with the scientific community.

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

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Reply to Letter to the Editor: "Comment on: Self-Expanding Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis Undergoing Prosthetic Mitral Valve Replacement: A Single-Center Experience"

LETTER TO THE EDITOR
REPLY

To the Editor,

We are grateful to the authors[1] for their thoughtful and constructive comments regarding our recently published study titled "Self-Expanding Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis Undergoing Prosthetic Mitral Valve Replacement: A Single-Center Experience."[2] We appreciate their interest in our work and their valuable contribution to the ongoing discussion of this complex and evolving topic.

As mentioned, our study reflects the experience of our center during a specific period of time when self-expanding (SE) valves were used in all cases. However, in recent years, we have also started to use balloon-expandable (BE) valves in similar patients. Once we reach a sufficient number of BE TAVI cases, we plan to publish a separate study to compare the 2 valves. Until then, our current results should be viewed in light of the limited number of patients and the single-valve strategy used.

We would also like to clarify a point raised regarding the conclusion that SE valves were the "optimal choice." In our manuscript, this statement was intended to reflect the specific context of our cohort, which consisted entirely of patients with prior mechanical mitral valve replacement and challenging aorto-mitral anatomy. As stated in the discussion, "Despite having less experience with BE valves in the clinic, particularly in cases of prior MVR, the unique anatomical challenges in patients with mechanical mitral prostheses made the SE Evolut R valve the optimal choice in this cohort." Thus, our conclusion was not meant to imply that SE valves are universally superior, but rather that they were the most suitable option within the limitations and anatomical characteristics of the studied population.

Regarding the relatively high rate of permanent pacemaker implantation (PPI) in our study, we agree that this is a significant consideration. However, we think this may not be only due to the type of valve used. All our patients had a prior mitral valve replacement (MVR), which is known to affect the heart's conduction system and increase the risk of PPI after TAVI. Earlier studies have shown that MVR is an independent risk factor for PPI.[3,4] So, both the valve type and the patients' existing condition might have contributed to the observed rate. While there are no dedicated prospective studies directly comparing BE and SE valves specifically in MVR patients, extensive data from the general TAVI population consistently show that BE valves are associated with significantly lower PPI rates compared to SE valves. This has been demonstrated across multiple large registries and meta-analyses, underscoring the influence of valve design on conduction outcomes. Therefore, although our current series was SE-focused, we believe that growing experience with BE valves may provide an opportunity to mitigate this important complication in future practice.

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Although we did not find a statistically significant link between PPI and mortality in our study, we are aware that large studies have reported worse long-term outcomes in patients who needed a pacemaker after TAVI. This is something we take seriously, and we are working on techniques to lower the risk of PPI in our ongoing practice. As noted, our study covers an 11-year period, during which many changes occurred in both technology and procedural techniques. We agree that dividing the data into earlier and later years could give more detailed insights. We plan to do this in future studies as our patient numbers increase.

Finally, we thank the authors for their question about the aorto-mitral distance. In our study, the average distance was 6.4 mm. While it is often thought that shorter distances may make the procedure harder or increase complications, we did not clearly see such an effect. However, due to the small sample size, we aren't able to make a firm conclusion. Other studies have shown that with proper imaging and planning, even short distances may not cause major issues.[5,6] We agree that this measurement is important and will keep monitoring it in future work.

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

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

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Comment On: Protective Effect of Amifostine on Radiotherapy Applied Cardiovascular Tissue

LETTER TO THE EDITOR

To the Editor,

I read the study with great interest and appreciate the thorough approach by the authors in investigating the manuscript titled "Protective Effect of Amifostine on Radiotherapy Applied Cardiovascular Tissue."[1] Amifostine is a cytoprotective adjuvant used in cancer chemotherapy and radiotherapy to reduce the incidence of neutropenia-related fever, infection, and decrease nephrotoxicity.[2,3] The cardiovascular effect of amifostine is not well known yet; while this study lays a foundation for future exploration, it is believed that certain critical aspects warrant further investigation. The authors aim to fill an important gap in the current literature and offer valuable experimental insights.

Due to the fact that the effects of radiation therapy typically take time to manifest, evaluations conducted solely during the acute phase (day 5) are insufficient. Amifostine may be toxic.[4] Have animals been shown to experience any negative effects? No answer has been given to this query. Lesions are not named, and the visual data presentation is subpar in terms of image quality and microscopic images. They were constraints in general science and experiment.

When I evaluated the statistical procedures, I discovered that the tests utilized for ordinal data were not adequate. The studies employed the Pearson chi-square test, even though histopathological scores are ordinal data. More suitable tests would have been non-parametric or Fisher's exact test. The table in certain comparisons reports the post-hoc test results, but the text does not go into enough detail about them.

This study demonstrates that amifostine reduces this damage at both the histopathological and biochemical levels, indicating that it could be used as a preventive agent for cardiovascular complications in cancer patients receiving radiotherapy in the future.

In summary, while this study addresses an important topic and offers promising results, addressing the above limitations would greatly enhance the reliability and scientific contribution of the manuscript.

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Reply to Letter to the Editor: "Comment On: Protective Effect of Amifostine on Radiotherapy Applied Cardiovascular Tissue"

LETTER TO THE EDITOR
REPLY

To the Editor,

We would like to express our gratitude to the esteemed authors[1] who reviewed our article,[2] titled "The Protective Effect of Amifostine on Cardiovascular Tissue Receiving Radiotherapy," and who offered their suggestions for improvement. As the authors noted, the cardiovascular effects of amifostine are not yet fully known. However, its protective effect against the effects of chemotherapy and radiotherapy on other tissues has been demonstrated.[3,4] The objective of this study was to establish the foundations for subsequent research.

While the effects of radiation therapy generally manifest over time, it is acknowledged that these outcomes are long-term consequences of the acute phase response. The investigation of long-term efficacy in animal models is technically challenging due to the limited lifespan of these creatures.[5] Consequently, it is reasonable to infer indirect conclusions from the results of our study. In the present study, no toxic effects were observed during the acute phase in experimental animals following administration of amifostine. Nevertheless, this does not negate the potential for long-term toxicity associated with the administration of the drug. Consequently, initiation of different animal models and dose titration studies may be considered.[5] The authors' comments are greatly valued and acknowledged.

While we will take the recommendations regarding statistical procedures into account, we believe that the current methods are sufficient for this basic introductory study. In this study, the Pearson chi-square test was used because the three-group comparison was based primarily on categorical distributions. Due to our limited sample size, exact *P*-values are reported. Only statistically significant findings from the post-hoc analyses are presented in the text, as this increases the readability of the article. Different statistical methods and analyses may be considered when planning further studies.

We would like to thank the authors for their valuable comments,[1] scientific contributions and scientifically advancing approaches.

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A Rare Mimicker of Hypertrophic Cardiomyopathy: Infiltrative Cardiac Lipoma

E-PAGE ORIGINAL IMAGE

A 47-year-old woman with hypothyroidism was referred for cardiology evaluation before surgery for a uterine mass. She reported exertional dyspnea over the past year. Electrocardiography showed T-wave inversions in leads V1-V4 and deep S waves in leads DI and aVL (Figure 1). Transthoracic echocardiography demonstrated marked asymmetric septal hypertrophy with right ventricular (RV) cavity curvature and RV diastolic dysfunction (Figure 2A-B). The lesion lacked clear borders and showed no signs of calcification or cystic components, raising suspicion for a cardiac mass. Cardiac magnetic resonance imaging (MRI) showed a broad-based mass along the RV side of the interventricular septum, extending from base to apex and narrowing the RV cavity (65 × 60 × 25 mm). The lesion appeared hyperintense on T1- and T2-weighted images, became

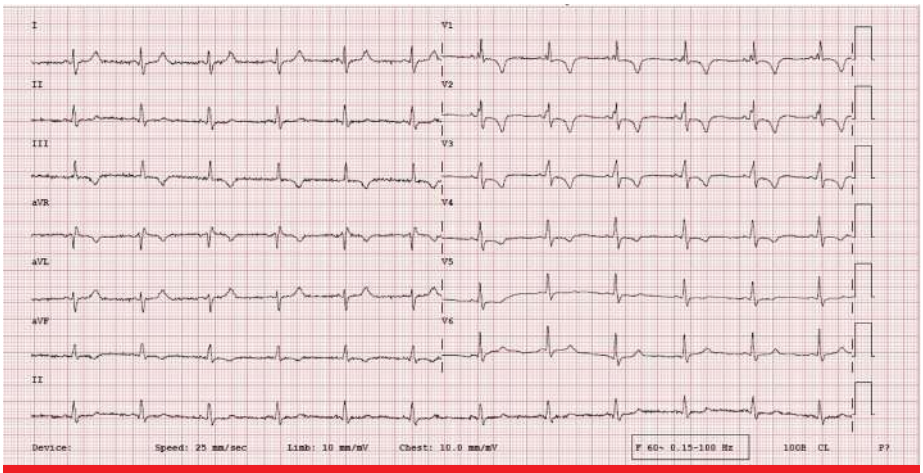

Figure 1. Electrocardiogram. T wave inversions in lead V1-V4 and deep S waves in lead D1-aVL.

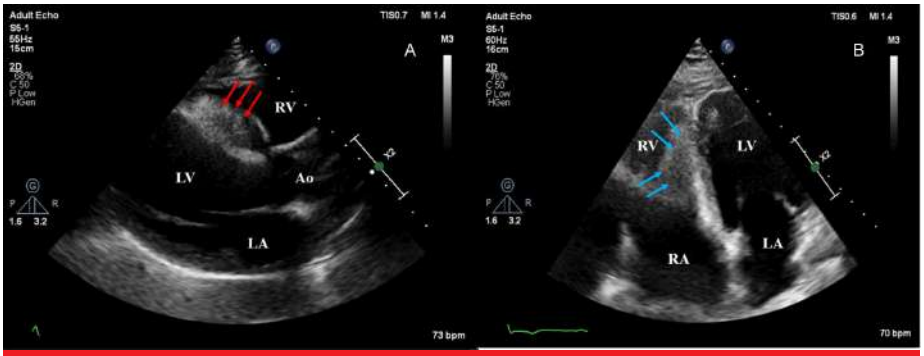

Figure 2. Transthoracic echocardiography. A) Parasternal long axis view. B) Apical 4-chamber view. There is asymmetric hypertrophy markedly seen in interventricular septum, with a right ventricular curvature. (Ao, aorta; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle).

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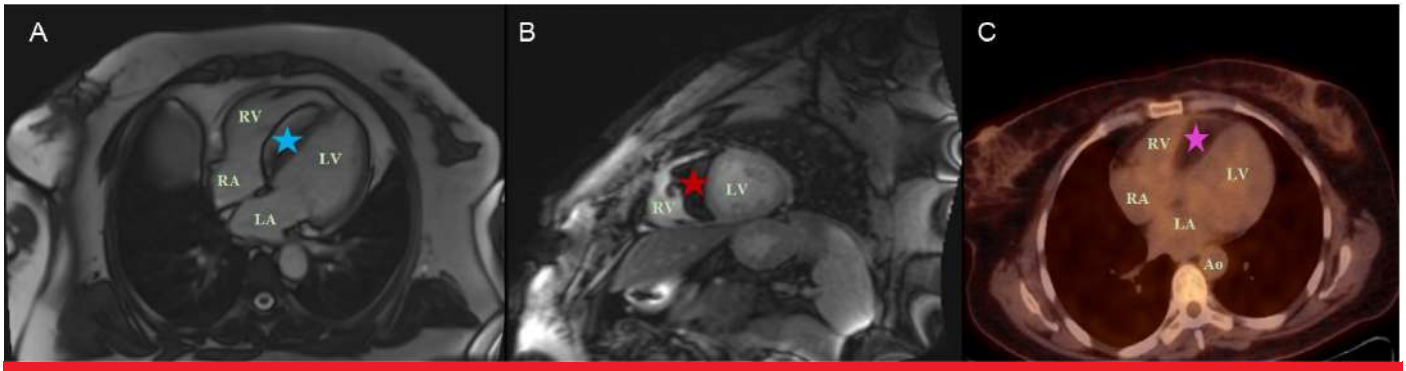

Figure 3. Cardiac MRI images showing a mass lesion along the right border of the interventricular septum, measuring 65 × 60 × 25 mm and extending from the base toward the apex. A) bSSFP sequence reveals peripheral chemical shift artifact indicating fat content. B) Fat-suppressed T2-weighted image shows the lesion as hypointense due to effective fat suppression. The mass protrudes into and narrows the right ventricular cavity. C) Whole-body PET scan (thoracic transverse section) showing a 2 cm hypodense thickening at the interventricular septum without pathological FDG uptake.

hypointense on fat-suppressed T2 sequences, and showed chemical shift artifact on bSSFP images, indicating fat content (Figure 3A-B). No contrast enhancement was observed, and T1 mapping confirmed low T1 values consistent with lipoma. Whole-body positron emission tomography (PET) demonstrated no pathological fluorodeoxyglucose uptake in the lesion, while uterine hypermetabolism was noted (Figure 3C). Despite medical therapy, symptoms persisted, and the mass was surgically excised. Histopathology confirmed infiltrative lipoma (7 × 5.6 × 2.7 cm). The uterine lesion was diagnosed as leiomyoma.

Cardiac lipomas are rare, often asymptomatic, but may cause functional compromise depending on size and location. Multimodality imaging, particularly MRI, plays a key role in distinguishing lipomas from hypertrophic cardiomyopathy and guiding management. Surgical resection should be considered in symptomatic or uncertain cases.

Informed Consent: Detailed information was given to the patient regarding possible contribution of the case report to literature. The patient gave written and verbal consent for the publication of the case report.

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