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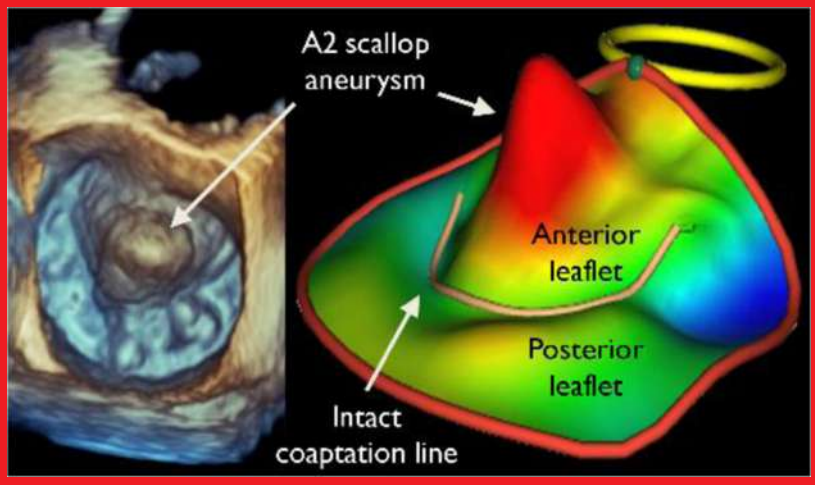
Original Investigations



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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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- 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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  Knowledge confirmed by the results of recent research studies, involved in education at academic level and used in clinical practices should be presented in detail in this type of manuscript.
- Title
- Abstract: It should not include subheadings and it should be limited to 250 words.
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  Manuscripts which announce a new scientific invention, are clinically significant, and are in the form of a preliminary report are accepted for publication as scientific letters.
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- Abstract and Keywords should not be included.
- For scientific letters submitted by Turkish authors or from Türkiye, the Title should also be provided in Turkish. For letters submitted by foreign authors outside Türkiye, the translation of these sections will be carried out by Editor-in-Chief's Office.

- **Case Report**
  Since a limited number of case reports is published, only reports which are related to rare cases and conditions that constitute challenges in diagnosis and treatment, offer new methods or suggest knowledge not included in books, and are interesting and educational are accepted for publication.
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- Main Text: It should include Introduction, Case Report, Discussion and Conclusion sections and should not exceed 700 words excluding the references.
- References: The reference list should follow the main text and the number of references should be limited to 10.
- Tables, Figures and Images: They should be provided after the reference list according to their order of appearance in the text and should be limited to two.
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NOTE 1: Case reports that include video images have a better chance of publication.

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  Impressive and rare images that reflect significant findings based on clinical science,
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  introduce new treatment methods are accepted for publication.
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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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- For double-blinded peer-review process, the names of the corresponding author and other authors, their affiliations and any information on the study centres should not be included in any part of the submitted manuscripts and images, except the Title Page.
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- Abbreviations should be explained in alphabetical order at the bottom of the tables, graphs and figures
- Roman numbers should be avoided in tables and figures within the text and their titles.
- Decimal numbers used in text, tables and figures should be separated by commas in Turkish sections and by dots in English sections.
- Tables should be easily understandable and should not repeat the data in the main text.
- In addition to the pictures included in case reports and original images, video and movie images are published on the journal's website. These images should be prepared in MPEG format with a maximum size of 2 MB. They should be submitted to the journal with the manuscript documents. The names of patients, doctors, institutions and places should be omitted from all documents.

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

EVALUATION AND PUBLICATION

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

While both sarcopenia and obesity independently elevate cardiovascular disease (CVD) risk, their combined effects, known as sarcopenic obesity (SO), remain incompletely understood. Zhang and Zeng from China reviewed and did a meta-analysis to evaluate the association between SO and the risk of CVD and CVD-related mortality.

The hemoglobin-to-red blood cell distribution width ratio (HRR) is a new inflammatory marker in evaluating tumor prognosis. However, its application in CVDs is relatively limited. Wu and Zou from China designed this study to illuminate the relation between HRR and mortality in patients with aortic dissection. Is HRR a prognostic biomarker?

Atrial tachycardia (AT) is a commonly encountered rhythm disorder and most patients require catheter ablation. Kılıç et al from Türkiye aimed to evaulate the outcomes of catheter ablation in patients with symptomatic AT, define acute and long-term outcomes and determine the clinical and electrophysiological features that affect these outcomes.

Calcific aortic valve stenosis (CAVS), the predominant valvular heart disease in developed countries, arises primarily from metabolic and inflammatory dysregulation. The triglyceride-glucose (TyG) index, a composite biomarker of insulin resistance and systemic inflammation, has been associated with cardiovascular diseases. However, its causal association with CAVS remains unclear. Song et al from China with bidirectional Mendelian randomization elucidated the potential causal relationship between the TyG index and CAVS.

Managing comorbidities alongside guideline-directed medical therapy is essential in heart failure (HF) treatment. Intravenous (IV) iron therapy is recommended for HF patients with left ventricular ejection fraction <50% to correct iron deficiency. Traditional markers such as ferritin and transferrin saturation are affected by inflammation and have delayed responses, limiting their clinical utility. Kumral et al from Türkiye evaluated early response to IV iron therapy by monitoring reticulocyte counts, a parameter unaffected by inflammation. Is it so?

The Turkish Real Life Atrial Fibrillation in Clinical Practice (TRAFFIC) study aimed to characterize the demographic features, risk profiles, treatment patterns, and two-year clinical outcomes of patients with non-valvular AF (NVAF) in Türkiye. Karabay et al from Türkiye provided all data. A great contribution to this topic.

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

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

Çetin Erol

Editor-in-Chief, Ankara, Türkiye

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Sarcopenic Obesity and Cardiovascular Disease Risk and Mortality: A Systematic Review and Meta-Analysis

ABSTRACT

Background: While both sarcopenia and obesity independently elevate cardiovascular disease (CVD) risk, their combined effects, known as sarcopenic obesity (SO), remain incompletely understood. This systematic review and meta-analysis aimed to evaluate the association between SO and the risk of CVD and CVD-related mortality.

Methods: A comprehensive search of scientific databases was conducted from inception to May 2025, including observational studies assessing SO in relation to incident CVD or CVD mortality. Pooled odds ratios (ORs) with 95% CIs were calculated using random-effects models. Subgroup analyses examined variations by age, sex, geography, study design, and CVD subtypes, with *P*-values for interaction being assessed.

Results: Sixteen studies involving 578 408 participants were included. Sarcopenic obesity was significantly associated with a 95% higher CVD risk (OR = 1.95, $P < .001$, 95% CI: 1.62-2.36) and a 64% increased CVD mortality risk (OR = 1.64, $P = .007$, 95% CI: 1.15-2.34). Subgroup analyses revealed stronger associations in males and diabetic subgroups. The highest risks were observed for myocardial infarction (OR = 4.07, $P = .015$, 95% CI: 1.31-12.63) and atrial fibrillation (OR = 2.93, $P < .001$, 95% CI: 2.23-3.86). Significant interactions were detected by sex ($P = .032$) and cardiovascular outcome type ($P = .001$), but not by age, region, or study design.

Conclusion: Sarcopenic obesity is a high-risk phenotype associated with significantly elevated CVD incidence and mortality, with effect modification by sex and outcome type. These findings highlight the need for standardized diagnostic criteria and targeted interventions to mitigate cardiovascular risk in this growing population.

Keywords: Aging, cardiovascular disease, meta-analysis, mortality, sarcopenic obesity

META-ANALYSIS

INTRODUCTION

The global rise in both obesity and population aging has led to the emergence of a complex and clinically significant phenotype known as sarcopenic obesity (SO). Defined by the concurrent presence of excessive adiposity and reduced skeletal muscle mass and strength, SO represents a convergence of 2 detrimental conditions—sarcopenia and obesity—each independently associated with increased cardiometabolic and functional risk. The combination, however, appears to exert a synergistic effect, accelerating physiological decline and disease progression, particularly in older adults.[1,2]

Aging is accompanied by significant changes in body composition, including an increase in fat mass—particularly visceral and ectopic fat—and a progressive decline in lean muscle mass and muscle function. These changes not only impair physical performance but also shift metabolic homeostasis towards insulin resistance, inflammation, and oxidative stress, key mechanisms implicated in cardiovascular disease (CVD).[3] Meanwhile, obesity, especially when characterized by central fat distribution, contributes to an inflammatory milieu through adipokine dysregulation and endothelial dysfunction.[4,5] When sarcopenia and obesity coexist, these effects are amplified, creating a proatherogenic environment and raising the risk of atherosclerosis, coronary artery disease, and heart failure.[6,7]

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While sarcopenia and obesity have long been studied as separate entities in the context of cardiovascular risk, SO has only recently gained attention as a distinct syndrome. Epidemiologic studies have shown that older adults with SO have higher rates of CVD and cardiovascular mortality than those with either condition alone.[8]

A growing body of evidence from large-scale observational studies and cohort analyses suggests that SO confers a markedly elevated risk for multiple cardiometabolic disorders. Individuals with this dual burden of excess adiposity and low muscle mass exhibit significantly higher odds of developing hypertension,[9] dyslipidemia,[10] type 2 diabetes,[11] and major cardiovascular events such as myocardial infarction and heart failure,[12] compared to those with normal body composition. The link between SO and CVD is believed to arise from a convergence of adiposity-driven inflammation and muscle-related metabolic impairment. This unfavorable interaction fosters a pro-inflammatory, insulin-resistant state that accelerates vascular dysfunction and elevates cardiometabolic risk.[9,13]

As the aging population grows, SO is expected to become increasingly prevalent. Given its strong association with CVD morbidity and mortality, there is an urgent need for heightened clinical awareness and development of targeted interventions. Due to inconsistencies and heterogeneity in findings from prior research, this meta-analysis was conducted to determine whether SO is associated with an increased risk of CVD and all-cause mortality, compared to individuals without this condition.

METHODS

Study Design and Selection Criteria

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and structured according to the PECO framework. The population included adults aged 18 years and older from any demographic background. The exposure of interest was SO, defined as the co-occurrence of sarcopenia (characterized by reduced muscle mass and/or strength) and obesity, based on diagnostic criteria specified in each individual study (Supplementary Table 1). The Comparator group comprised individuals without SO with normal body composition. The outcomes were incident CVD (such as myocardial infarction, stroke, heart failure, arrhythmias, etc.) and/or CVD mortality (if reported separately from all-cause mortality). We included observational studies (cohort, cross-sectional, and case-control designs) that investigated the association between SO and CVD or related mortality were included, and effect estimates (e.g., odds ratios [ORs], hazard ratios [HRs], or risk ratios [RRs]) with corresponding 95% CIs were reported, or sufficient data were provided to calculate them. Studies were excluded if they assessed the effects of sarcopenia or obesity alone without evaluating SO, if they focused on non-CVD outcomes (e.g., hypertension), lacked a proper definition of SO or CVD, or were case reports, case series, reviews, editorials without original data, or animal studies.

HIGHLIGHTS

- The study found that individuals with sarcopenic obesity had a 95% higher cardiovascular disease (CVD) risk than those without.
- Sarcopenic obesity was linked to a 64% higher risk of CVD-related mortality.
- The association was stronger in East Asian populations compared to Western populations.
- The association was stronger in diabetic patients compared to general patients.
- The highest CVD risk was related to myocardial infarction and atrial fibrillation.

Search Strategy

A comprehensive literature search was conducted to identify relevant studies examining the association between SO and CVD. Four electronic databases—PubMed/MEDLINE, Embase, Scopus, and Web of Science—were searched from inception to May 10, 2025. The search strategy combined Medical Subject Headings (MeSH) and relevant keywords, including but not limited to: sarcopenic obesity, sarcopenia, obesity, CVD, myocardial infarction, stroke, and cardiovascular mortality (Supplementary Table 2). In addition, grey literature and reference lists of included articles and relevant reviews were manually screened to identify additional eligible studies. No geographical, time, and language restriction was applied.

Data Extraction and Quality Assessment

Two trained reviewers (Z.Z. and X.Z.) independently screened titles, abstracts, and full texts using a standardized eligibility form in an Excel spreadsheet. Disagreements were resolved by consensus. For each included study, the following data were extracted: author, year of publication, study duration, study location, design, sample size, numbero of participants in each group (normal, sarcopenia, obesity, SO), mean follow-up duration (in cohort studies), participant characteristics (sex and age), definition of SO, outcome definitions, effect measures (OR, RR, or HR), and adjustment variables.

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort and cross-sectional studies. This tool evaluates selection, comparability, and outcome (or exposure) domains, with scores ranging from 0 to 9. Studies scoring $\geq$7 were considered high quality. The risk of bias was independently assessed by 2 reviewers, and discrepancies were resolved through discussion.

Statistical Analysis

The statistical analysis was performed following rigorous methodological standards to ensure robust and reproducible findings. All analyses were conducted using Stata version 18 (StataCorp, College Station, TX, USA), with statistical significance set at $P < .05$ using 2-tailed tests. Given the inclusion of studies reporting different effect measures, all estimates were harmonized by converting HRs and RRs to ORs for consistency. For studies reporting HRs, established conversion methods that account for baseline risk were applied,

particularly when CVD incidence was non-rare. When necessary, standard errors for log-transformed ORs were derived from reported CIs using standard methods. Random-effects meta-analysis (REM) models were employed using the restricted maximum likelihood estimator as the primary analytical approach, which accounts for between-study heterogeneity. This method was preferred over fixed-effects models due to the anticipated clinical and methodological diversity across studies. The degree of heterogeneity was quantified using 3 complementary measures: Cochran's Q-test and Higgins' I^2 statistic. I^2 values of 0%-40% were interpreted as indicating low heterogeneity, 40%-75% as moderate, and >75% as substantial heterogeneity. To explore potential sources of heterogeneity, pre-specified subgroup analyses stratified by participant sex, age categories, and specific cardiovascular outcomes were conducted. These analyses helped identify whether the association between SO and CVD risk varied across clinically relevant subgroups. The robustness of these findings was assessed through comprehensive sensitivity analyses. A leave-one-out approach was employed to evaluate whether any single study disproportionately influenced the pooled estimates. Furthermore, cumulative meta-analysis was conducted to examine how the evidence base evolved chronologically with the addition of new studies. Publication bias was systematically evaluated using multiple complementary methods. Visual inspection of funnel plots provided an initial assessment of potential asymmetry. When asymmetry was detected, trim-and-fill analysis was employed to estimate the potential impact of missing studies on the effect estimates.

RESULTS

Study Selection and Characteristics

The PRISMA flow diagram illustrates the screening and selection process (Central Figure and Figure 1). A total of 1610 records were identified through comprehensive searches of 4 electronic databases: PubMed/MEDLINE (n=111), Scopus (n=382), Embase (n=667), and Web of Science (n=428). An additional 22 records were retrieved from other sources, including reference lists of relevant articles and grey literature. Following initial screening, 1536 records were excluded, including 526 duplicates and 1010 papers deemed clearly irrelevant based on title and abstract assessment. The full texts of the remaining 74 articles were assessed for eligibility. Of these, 58 studies were excluded for the following reasons: (I) The study focused solely on sarcopenia or obesity without examining effect of SO on CVD (n=41); (II) The publication type was case reports/series (n=5); (III) The study assessed outcomes unrelated to CVD (n=11); (IV) The article was a review, systematic reviews, letter, editorial, or other non-original research format (n=17). Ultimately, 16 studies met all the eligibility criteria and were included in the final meta-analysis (Table 1).[8,11,12,14-26] Additionally, 1 study[27] assessed just CVD-related mortality and was included in the meta-analysis related to CVD-related mortality risk.

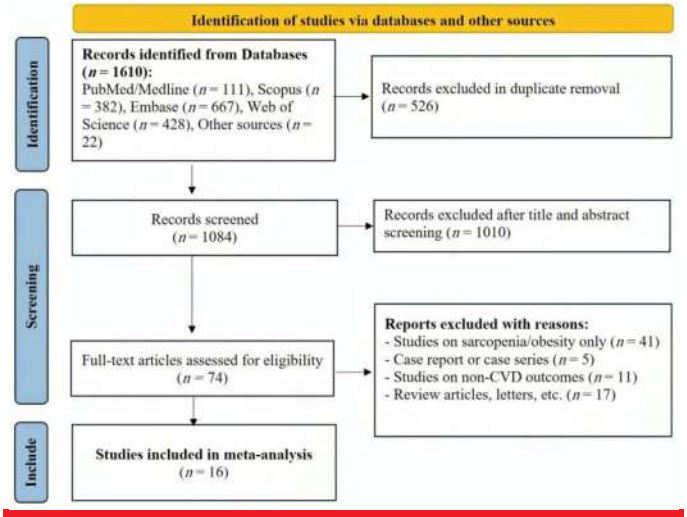

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram illustrating the study selection process for the systematic review and meta-analysis on sarcopenic obesity and cardiovascular diseases risk.

The 16 included studies (comprising 19 datasets) spanned 7 countries across East Asia (11 studies: China [6], South Korea [4], Japan [1]) and Europe/North America (5 studies: England [2], USA [1], Cyprus [1], and 1 multinational cohort from the UK Biobank). Geographically, 62.5% and 31.2% of studies were conducted in East Asia and Europe. Study designs varied: 8 prospective cohorts (50%) with follow-up periods ranging from 2.6 to 12 years, 6 cross-sectional studies (37.5%), and 2 retrospective cohorts (12.5%). The largest cohort (Farmer et al,[8] 2019; n=452 931) utilized UK Biobank data. Study populations predominantly involved general middle-aged and older adults (11 studies), though 3 studies targeted high-risk subgroups (e.g., type 2 diabetes patients), and 1 included cancer survivors. Cardiovascular outcomes were heterogeneous. Six studies assessed composite CVD endpoints, while others examined specific subtypes: heart failure/diseases, coronary artery calcification, atrial fibrillation, left ventricular dysfunction, and stroke. Five and 6 studies provided adjusted effect sizes based on sex and age, respectively. Three studies reported CVD-related mortality, with effect sizes ranging from HR=1.14 (Atkins et al,[15] 2014) to HR=2.48 (Saito et al,[27] 2022). All studies adjusted for key confounders, including age, sex, lifestyle factors (smoking, physical activity), cardiometabolic comorbidities (hypertension, diabetes) and other confounders (Supplementary Table 3). All studies were rated as high quality on the NOS, with prospective cohorts demonstrating robust methodology.

Results of Overall Meta-Analysis

As shown in Figure 2, the REM revealed that SO is significantly associated with an increased risk of CVD, with a pooled OR=1.95, $P < .001$, 95% CI: 1.62-2.36. However, substantial heterogeneity was observed across studies ($I^2=84.59\%$, $\tau^2=0.12$, Q-test $P < .001$). Moreover, the analysis of 3 studies examining the association between SO and CVD-related mortality revealed a statistically significant increased risk (OR=1.64, $P=.007$, 95% CI: 1.15-2.34; Figure 3), with moderate heterogeneity among studies ($I^2=53.65\%$,

Table 1. Mean Characteristics of Included Studies Evaluating the Association Between Sarcopenic Obesity and Cardiovascular Diseases

Studies[1]	Country	Study Design	Mean Follow-Up Period	Type CVD	Total Population	Subject Characteristics	Effect Size
Stephen & Janssen (2009)[14]	USA	PC	10 years	CVD	3366	Normal people (n = 1481); sarcopenic (n = 750); obese (n = 762); SO (n = 373)	HR, 1.06 (0.85-1.33)
Atkins et al (2014)[15]	England	PC	11.3 years	CVD	4111	Normal people (n = 1490); sarcopenic (n = 1443); obese (n = 983); SO (n = 195)	HR, 1.08 (0.77-1.52)
Kim et al (2015)[16]	South Korea	CS	NA	CVD	1458	Normal people (n = 778); sarcopenic (n = 146); obese (n = 350); SO (n = 184)	OR, 2.49 (1.53-4.06)
Kim et al (2015)[16]	South Korea	CS	NA	CVD	1862	Normal people (n = 983); sarcopenic (n = 253); obese (n = 294); SO (n = 332)	OR, 1.87 (1.02-3.41)
Fukuda et al (2018)[17]*	Japan	RC	2.6 years	CVD	716	Normal people (n = 187); sarcopenic (n = 171); obese (n = 275); SO (n = 83)	HR, 2.63 (1.1-6.28)
Farmer et al (2019)[8]	England	PC	5.1 years	CVD	452 931	Normal people (n = 296567); sarcopenic (n = 48250); obese (n = 89906); SO (n = 18208)	HR, 1.42 (1.31-1.55)
Xia et al (2020)[18]	China	CS	NA	MI	2432	Normal people (n = 662); sarcopenic (n = 576); obese (n = 1114); SO (n = 80)	OR, 4.07 (1.31-12.62)
Xia et al (2020)[18]	China	CS	NA	AF	2432	Normal people (n = 662); sarcopenic (n = 576); obese (n = 1114); SO (n = 80)	OR, 5.68 (1.34-24.12)
Yoo et al (2020)[19]	South Korea	CS	NA	LVDD	31 258	Normal people (n = 17476); sarcopenic (n = 2693); obese (n = 6875); SO (n = 4214)	OR, 1.7 (1.44-1.99)
Chung et al (2021)[20]	Cyprus	ROS	3.46 years	CAC	1282	Normal people (n = 746); sarcopenic (n = 14); obese (n = 414); SO (n = 108)	OR, 1.92 (1.16-3.18)
Lee at al (2021)[21,†]	South Korea	CS	NA	CVD	1023	Normal people (n = 611); sarcopenic (n = 106); obese (n = 277); SO (n = 29)	OR, 1.79 (0.68-4.74)
Lee at al (2021)[21]	South Korea	CS	NA	CVD	17 996	Normal people (n = 10548); sarcopenic (n = 1118); obese (n = 5800); SO (n = 530)	OR, 3.01 (2.42-3.73)
Jia et al (2024)[22,*]	England	PC	12.0 years	HF	22 496	Normal people (n = 9158); sarcopenic (n = 1254); obese (n = 11024); SO (n = 1033)	HR, 2.29 (1.92-2.73)
Jiang et al (2024)[23]	China	PC	7 years	CVD	7703	Normal people (n = 1132); sarcopenic (n = 3580); obese (n = 635); SO (n = 2356)	HR, 1.47 (1.2-1.8)
Yang et al (2024)[24]	China	CS	NA	CVD	2821	Normal people (n = 1911); sarcopenic (n = 330); obese (n = 489); SO (n = 91)	OR, 2.2 (1.16-4.19)
Yu et al (2024)[11]	China	PC	3 years	CVD	15 252	Normal people (n = 7616); sarcopenic (n = 2219); obese (n = 4568); SO (n = 849)	HR, 2.302 (1.24-4.23)
Shi et al (2025)[12]	China	PC	7 years	HF	4665	Low sarcopenic abdominal obesity (n = 2332); low sarcopenic abdominal obesity (n = 2333)	HR, 1.2 (1.01-1.4)
Yu et al (2025)[25]	China	PC	10.9 years	AF	4321	Normal people (n = 2887); sarcopenic (n = 269); obese (n = 753); SO (n = 412)	HR, 2.669 (2.11-3.38)
Shi et al (2025)[26,*]	China	PC	3 years	CVD	283	Normal people (n = 72); sarcopenic (n = 85); obese (n = 73); SO (n = 53)	HR, 3.03 (1.39-6.63)

Most studies recruited participants from the general population, except for 3 that recruited patients with type 2 diabetes (marked as *) and 1 that included cancer patients (marked as †).
AF, atrial fibrillation; CAC, coronary artery calcification; CS, cross-sectional; CVD, cardiovascular diseases; HF, heart failure; LVDD, left ventricular diastolic dysfunction; MI, myocardial infarction; PC, prospective cohort; RC, retrospective cohort; ROS, retrospective observational; SO, sarcopenic obesity.

$\tau^2 = 0.05$). However, the test for heterogeneity was not statistically significant (Q = 4.33, $P = .11$). Visual inspection of the funnel plot indicated an asymmetric distribution of studies. This was supported by Egger's test, which provided statistical evidence of potential publication bias (intercept $P = .044$; Supplementary Figure 1).

Results of Subgroup Meta-Analyses

Five studies provided stratified data on sex (Supplementary Table 4). The subgroup analysis based on sex indicated a significant association between SO and the risk of CVD in both males (OR = 2.56, $P < .001$, 95% CI: 2.15-3.06) and females (OR = 2.35, $P < .001$, 95% CI: 1.90-2.92). In the age-based subgroup analysis (6 studies), studies were stratified into younger (<60, <65, and <70) and older (≥60, ≥65, and ≥70). Among younger participants, the pooled OR was 1.97 ($P < .001$, 95% CI: 1.49-2.60), while in older participants, the pooled OR was 1.81 ($P < .001$, 95% CI: 1.32-2.47), both indicating a significant and comparable association with increased risk (Supplementary Table 4).

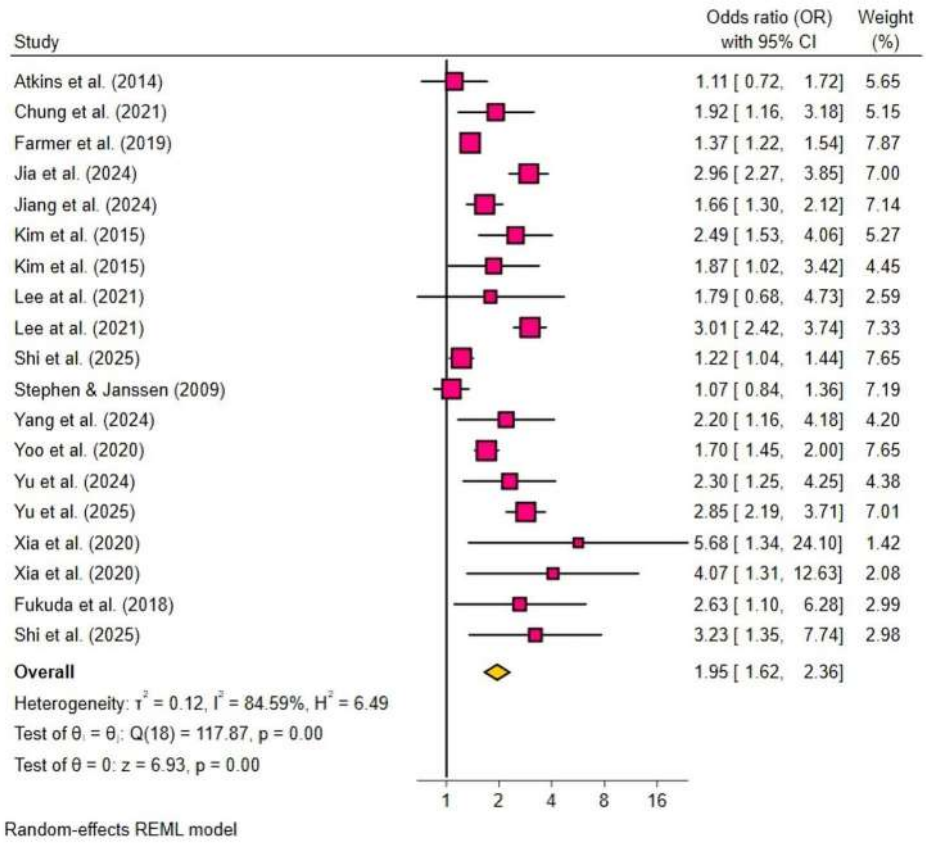

Figure 2. Forest plot of the pooled odds ratios for the association between sarcopenic obesity and overall cardiovascular diseases risk.

The subgroup analysis stratified by geographical region (Supplementary Table 4) revealed that studies performed in both categorized regions showed significant positive associations, although the effect sizes and heterogeneity patterns varied substantially. The pooled analysis of 5 studies from Europe and North America demonstrated a moderate but significant association between SO and CVD risk (OR = 1.56, $P = .023$, 95% CI: 1.06-2.28; $I^2 = 90.81\%$, $\tau^2 = 0.16$). In contrast, the East Asian subgroup showed a stronger and more consistent association (OR = 2.16, $P < .001$, 95% CI: 1.75-2.65), while still exhibiting substantial heterogeneity ($I^2 = 74.75\%$, $\tau^2 = 0.08$). The subgroup analysis by study design (Supplementary Table 4) also revealed significant positive associations in both cohort and cross-sectional studies. The analysis of prospective and retrospective cohort studies showed a significant association between SO and CVD risk (OR = 1.77, $P < .001$, 95% CI: 1.35-2.32; $I^2 = 90.13\%$, $\tau^2 = 0.15$). Cross-sectional analyses demonstrated a somewhat stronger pooled association (OR = 2.25, $P < .001$, 95% CI: 1.80-2.82) with moderate heterogeneity ($I^2 = 52.04\%$, $\tau^2 = 0.05$). With respect to population characteristics (Figure 4), analyses of the general population (OR = 1.84, $P < .001$, 95% CI: 1.50-2.26; $I^2 = 86.19\%$, $\tau^2 = 0.11$) and diabetic subgroups (OR = 2.95, $P < .001$, 95% CI: 2.32-3.76; $I^2 = 0\%$) showed significant associations

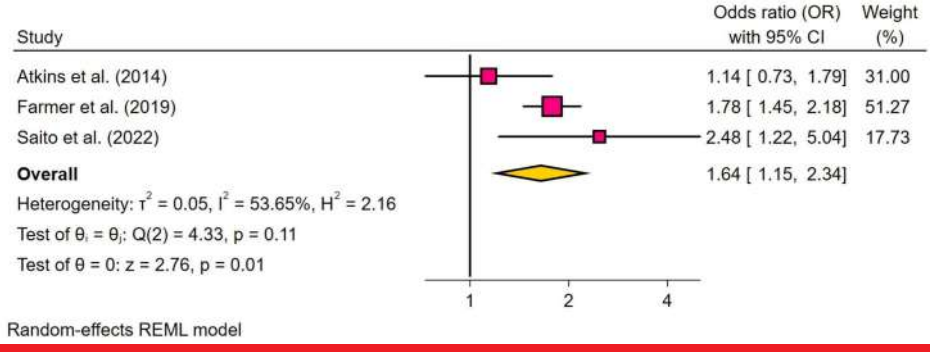

Figure 3. Forest plot of the pooled odds ratios for the association between sarcopenic obesity and cardiovascular disease–related mortality.

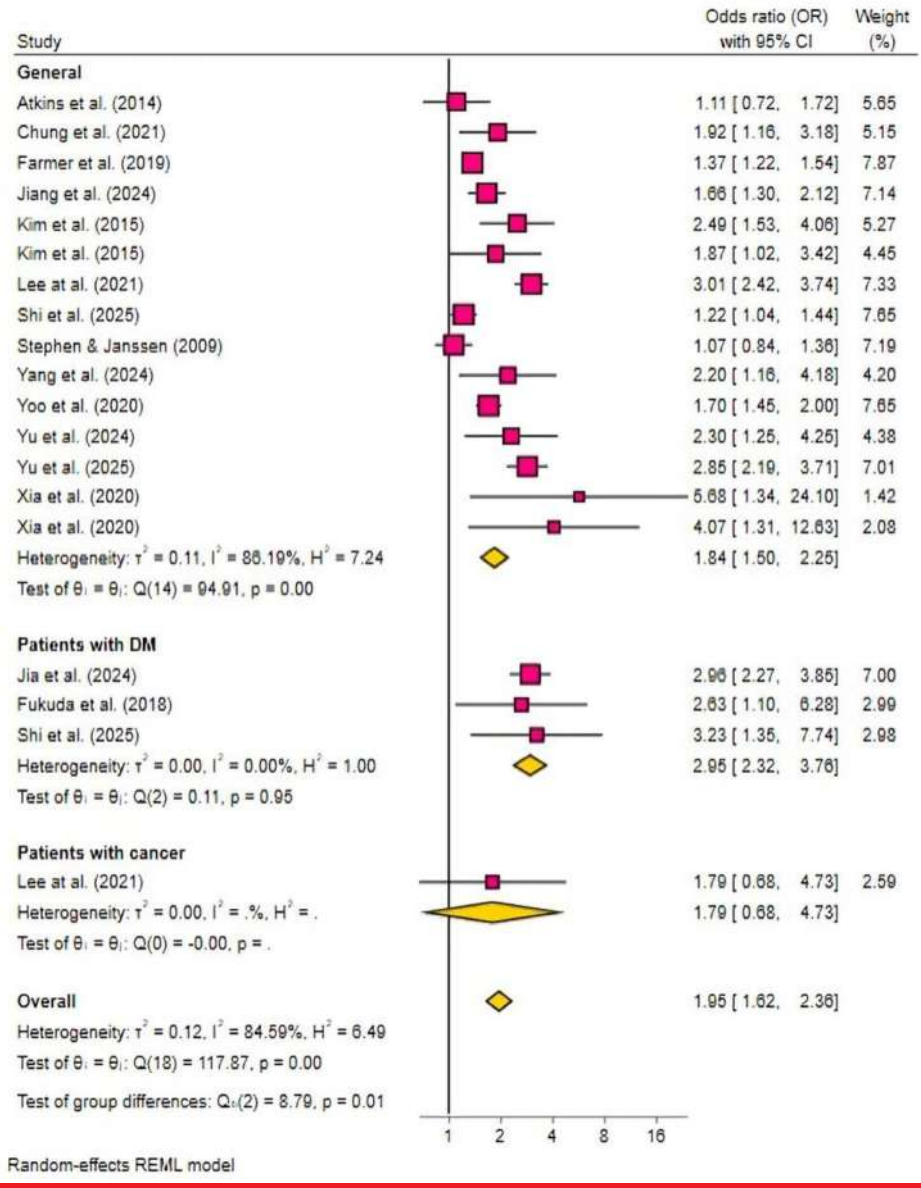

Figure 4. Subgroup analysis of the association between sarcopenic obesity and cardiovascular diseases risk stratified by population characteristics.

between SO and CVD, while the single cancer survivor study showed a non-significant association (OR = 1.79, *P* = .24, 95% CI: 0.68-4.73).

The subgroup analysis on different specific cardiovascular outcomes showed that the association between SO and CVD risk varies by outcome type (Supplementary Table 4). Four datasets examining general heart disease showed a modest but significant pooled association (OR = 1.21, *P* = .003, 95% CI: 1.11-1.70). Three studies examining heart failure demonstrated a pooled OR of 1.69 (*P* = .065, 95% CI: 0.97-2.94), which did not reach statistical significance. The strongest associations were observed for myocardial infarction (OR = 4.07, *P* = .015, 95% CI: 1.31-12.63; 1 study) and atrial fibrillation (OR = 2.93, *P* < .001, 95% CI: 2.23-3.65; 2 studies). More details are available in Supplementary Table 4.

To further investigate potential sources of heterogeneity and examine the robustness of the primary findings, *P*-values were calculated for interaction. Subgroup analyses revealed that the association between SO and CVD risk differed significantly by sex (*P*-interaction = .032) and by specific cardiovascular outcome type (*P*-interaction = .001). In contrast, the effect sizes did not differ significantly across age groups (*P*-interaction = .683), geographic regions (*P*-interaction = .143), or study designs (*P*-interaction = .181) (Supplementary Table 4). These results confirm that the strength of the association is modified by sex and the specific cardiovascular endpoint being assessed.

Sensitivity and Cumulative Analysis

In sensitivity analysis (Figure 5A), the pooled OR remained statistically significant (all *P* < .001) regardless of which

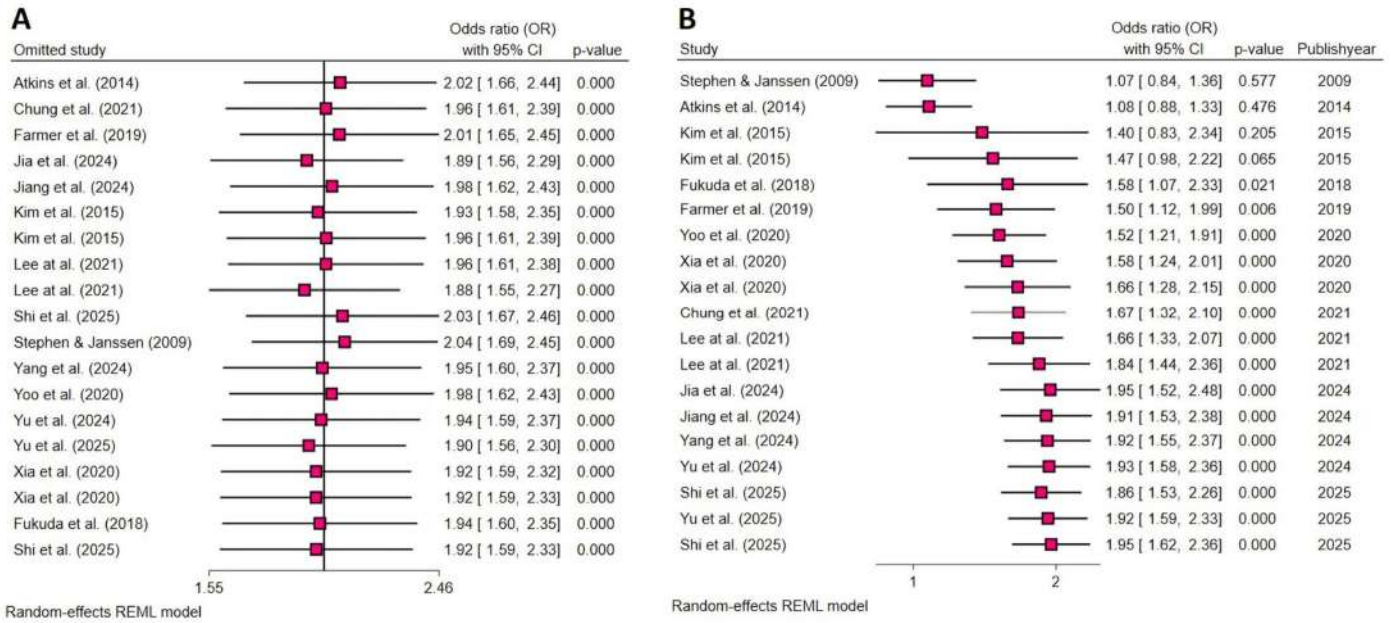

Figure 5. Sensitivity and cumulative meta-analysis. (A) Leave-one-out sensitivity analysis showing robustness of the pooled cardiovascular disease risk estimate. (B) Cumulative meta-analysis demonstrating the temporal strengthening of evidence linking sarcopenic obesity to cardiovascular disease risk as studies were added chronologically.

single study was omitted, ranging from 1.88 [1.55-2.27] to 2.04 [1.69-2.45]. Moreover, the cumulative meta-analysis revealed a progressive strengthening of evidence linking SO to CVD risk over time (Figure 5B).

DISCUSSION

Our meta-analysis demonstrates a significant association between SO and increased risk of CVDs. Individuals with SO had nearly twice the odds of developing CVD compared to non-sarcopenic, non-obese counterparts. Moreover, the analysis of CVD-related mortality indicated a 64% increase in risk among individuals with SO, further emphasizing the adverse prognostic implications of this phenotype. Subgroup analyses provided additional insight into population-specific patterns. The association between SO and CVD remained statistically significant across sex, with pooled effect sizes slightly higher in males than females (Supplementary Table 4); importantly, the *P*-value for interaction indicated a significant difference between sexes ($P = .032$). Age-stratified analyses showed a comparable risk elevation in both younger and older adults, with no significant interaction by age ($P = .683$; Supplementary Table 4). Studies conducted in East Asian populations yielded stronger and more consistent associations compared to those from Western populations, though this difference was not statistically significant (*P*-interaction = .143). Similarly, both cohort and cross-sectional studies demonstrated significant positive associations, but without evidence of a significant difference by study design ($P = .181$). Similarly, SO was more strongly associated with CVD in diabetic individuals than in the general population, suggesting heightened vulnerability in this subgroup. Notably, the association between SO and CVD risk varied significantly across cardiovascular outcomes (*P*-interaction = .001): the strongest effects were observed for myocardial infarction and atrial fibrillation, while associations with stroke and heart failure were weaker or non-significant (Supplementary Table 4). These findings confirm that the strength of the association is modified by sex and by the specific cardiovascular endpoint being assessed. The robustness of these findings was supported by sensitivity analyses, which showed that the overall effect estimates remained stable across all leave-one-out iterations. Cumulative meta-analysis further revealed a temporal strengthening of the association between SO and CVD risk, indicating consistency and growing evidence across studies over time.

The present meta-analysis is the first to comprehensively evaluate the association between SO and both CVD and CVD-related mortality. It revealed significantly increased odds of CVD and CVD-specific mortality. These results are in line with previous literature, though broader in scope, integrating various populations and cardiovascular endpoints. Among studies directly evaluating SO, Tian et al[28] (2015) reported a 24% increased risk of all-cause mortality in SO individuals (HR = 1.24, $P < .001$, 95% CI: 1.12-1.37), with a stronger effect in men (HR = 1.23, $P = .0017$, 95% CI: 1.08-1.41) than women (HR = 1.16, $P = .13$, 95% CI: 0.96-1.41). Similarly, Atkins et al[15] (2014) found SO was associated with increased CVD mortality (HR = 1.72, $P < .001$, 95% CI: 1.35-2.18) in older men. Zhang et al[29] (2019) also confirmed elevated mortality risk in SO populations (HR = 1.21, $P < .001$, 95% CI: 1.10-1.32), particularly in hospitalized patients (HR = 1.65, $P < .001$, 95% CI: 1.17-2.33). Regarding sarcopenia alone, Xu et al[30] (2022) synthesized 56 cohort studies and found sarcopenia doubled mortality risk (HR = 2.00, $P < .001$, 95% CI: 1.71-2.34), independent of population or definition. Zuo et al[31] demonstrated a

pooled sarcopenia prevalence of 35% in CVD patients versus 13% in the general population, with the highest prevalence in CAD (43%) and heart failure (32%). Zhang et al[32] estimated a similar 34% prevalence in HF patients, rising to 55% in hospitalized settings. These findings support the high CVD burden in sarcopenic patients, consistent with the present meta-analysis. In studies evaluating obesity alone, Flegal et al[33] showed that class II/III obesity increased all-cause mortality (HR = 1.18, $P < .001$, 95% CI: 1.12-1.25). Du et al[34] performed a meta-analysis of 16 studies and found significant associations between sarcopenia and metabolic syndrome components—body mass index (BMI), glucose, blood pressure, lipids, and insulin resistance—with stronger effects in males. These metabolic dysfunctions support a shared pathophysiological link between sarcopenia and CVD. Together, these studies support the current findings and indicate that SO is more detrimental than sarcopenia or obesity alone. The present meta-analysis further expands the evidence by including subgroup analyses (e.g., sex, region, age, outcome type), providing a nuanced understanding of SO's impact on cardiovascular health.

Sarcopenic obesity contributes significantly to cardiovascular risk through a convergence of metabolic, inflammatory, and hormonal dysfunctions. Visceral adiposity promotes a chronic low-grade inflammatory state characterized by elevated levels of tumor necrosis factor-alpha, interleukin-6 (IL-6), and C-reactive protein, which accelerate endothelial dysfunction and atherogenesis.[7,35] Simultaneously, sarcopenia reduces skeletal muscle insulin sensitivity and impairs glucose disposal, compounding systemic insulin resistance. These interdependent processes result in increased arterial stiffness, vascular remodeling, and higher susceptibility to hypertension, atherosclerosis, and myocardial infarction.[36] Notably, SO is more than the additive effects of obesity and sarcopenia; it represents a synergistic phenotype with a distinct inflammatory and metabolic signature.[1,2] Additionally, SO is associated with mitochondrial dysfunction, oxidative stress, and lipid accumulation within muscle fibers (myosteatosis), leading to reduced energy capacity, impaired muscle regeneration, and enhanced proteolysis.[37] This muscle deterioration further limits physical activity and metabolic rate, exacerbating fat gain and cardiometabolic burden. Hormonal alterations common in aging, such as reduced levels of testosterone, estrogen, growth hormone, and insulin-like growth factor 1 (IGF-1), impair muscle protein synthesis and promote visceral fat deposition, reinforcing the SO phenotype.[38] Reduced secretion of protective myokines (e.g., irisin, IL-15) diminishes skeletal muscle's anti-inflammatory and cardioprotective roles.[39] Collectively, these pathophysiological changes establish a high-risk cardiovascular environment, highlighting the need for SO to be incorporated into clinical cardiovascular risk stratification and targeted prevention strategies.[8,40]

This meta-analysis is one of the most comprehensive to date evaluating the association between SO and CVD, and it offers several important strengths. First, it includes a large pooled sample derived from 16 studies (19 datasets), spanning more than 7 countries across East Asia, Europe, and North America, which enhances both the statistical power and the generalizability of the findings. The geographic diversity of included studies allowed for meaningful cross-regional comparisons, highlighting potential population-specific risk patterns. Second, the analysis incorporated multiple high-quality prospective cohort studies, some with long-term follow-up, along with well-conducted cross-sectional and retrospective cohorts. The majority of included studies utilized objective and validated tools to define SO—such as dual-energy X-ray absorptiometry or bioelectrical impedance analysis—and reported standardized cardiovascular outcomes including myocardial infarction, heart failure, atrial fibrillation, and multimorbidity. Third, the extensive subgroup analyses conducted in this review—by sex, age, geographic region, study design, population characteristics, and specific cardiovascular outcomes—allowed for exploration of effect modifiers and revealed important variations in risk profiles. Fourth, sensitivity analyses and cumulative meta-analysis confirmed the robustness and temporal consistency of these findings, demonstrating that the overall results were not driven by any single study.

Despite its strengths, this meta-analysis has several limitations that warrant careful consideration. First, substantial heterogeneity was observed across the included studies ($I^2 = 84.6\%$), which may reflect differences in study design, sample characteristics, measurement tools, and outcome definitions. Although subgroup and sensitivity analyses were conducted to explore potential sources of heterogeneity, residual variation remains and may limit the precision of pooled effect estimates. Second, the diagnostic criteria for SO varied considerably among studies. Definitions of sarcopenia differed based on muscle mass index, grip strength, or gait speed, and obesity was assessed using different indices such as BMI, fat mass percentage, or visceral fat area. This inconsistency may have led to misclassification and variability in identifying affected individuals across studies. As a result, sensitivity or subgroup analyses could not be conducted based on specific definitions (e.g., BMI-based vs. other measures). Future studies should adopt standardized diagnostic criteria for SO to enable such subgroup analyses and improve comparability across research. Third, while the inclusion of both cohort and cross-sectional studies allowed for a broader synthesis, the reliance on non-longitudinal designs in a substantial portion of the dataset (6 cross-sectional, 2 retrospective) limits causal inference. Even among prospective cohorts, residual confounding remains a concern, as unmeasured or inconsistently reported variables (e.g., nutritional status, hormonal factors, inflammatory biomarkers, or physical performance metrics) were not uniformly accounted for. Fourth, although most studies adjusted for common cardiovascular risk factors such as age, sex, hypertension, and diabetes, there was variation in the covariates included in multivariable models, potentially affecting comparability and effect size estimation. Fifth, only a small number of studies (n = 3) reported CVD-related mortality as a distinct outcome, limiting the precision and generalizability of the pooled estimate for mortality risk. Sixth, few studies clearly differentiated between visceral

and subcutaneous fat or used advanced imaging to characterize body composition in more physiologically meaningful ways. Additionally, none of the included studies incorporated biomolecular markers or omics-based profiling (e.g., metabolomics, proteomics) to explore mechanistic pathways linking SO and CVD. Finally, this assessment suggests the presence of publication bias, as indicated by the funnel plot asymmetry and a significant Egger's test. Therefore, the overall estimate may be influenced by the absence of unpublished studies with null results, which may have been missed despite the comprehensive search of databases and grey literature. Collectively, these limitations highlight the methodological challenges inherent in synthesizing SO-related outcomes and emphasize the need for standardized definitions, improved reporting, and more mechanistic investigation in future research.

In conclusion, this meta-analysis provides robust evidence that SO is significantly associated with increased risk of CVDs and CVD-related mortality. The strength and consistency of this association across diverse populations, study designs, and cardiovascular outcomes underscore the clinical importance of recognizing SO as a distinct and high-risk phenotype. Compared to sarcopenia or obesity alone, SO confers a substantially higher cardiovascular burden, likely due to the synergistic interplay between metabolic dysfunction, inflammation, and physical decline. Given the growing prevalence of SO in aging populations worldwide, early identification, risk stratification, and tailored interventions are urgently needed. Future studies should prioritize the use of standardized definitions, longitudinal designs, and mechanistic investigations to further elucidate the pathophysiological links between SO and cardiovascular health.

Data availability statement: All data supporting the findings of this study are included within the manuscript and its supplementary materials. Additional datasets, if required, are available from the corresponding author upon reasonable request.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.Z., X.Z.; Design – Z.Z., X.Z.; Supervision – Z.Z., X.Z.; Resource – Z.Z., X.Z.; Materials – Z.Z., X.Z.; Data Collection and/or Processing – Z.Z., X.Z.; Analysis and/or Interpretation – Z.Z., X.Z.; Literature Search – Z.Z., X.Z.; Writing – Z.Z., X.Z.; Critical Reviews – Z.Z., X.Z.

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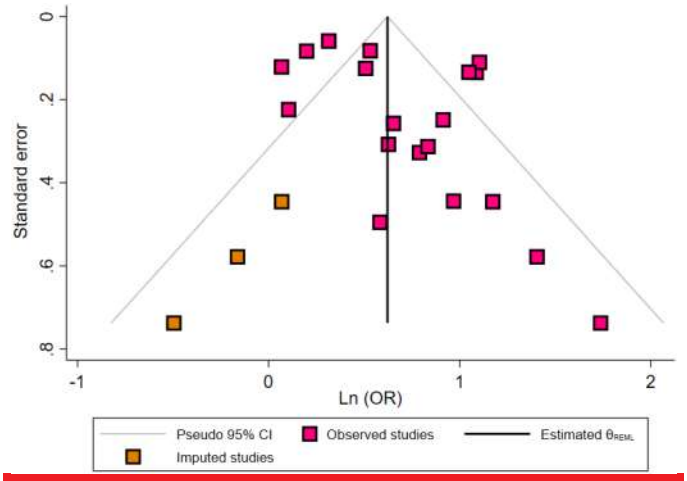

Supplementary Figure 1. Funnel plot assessing publication bias for studies included in the meta-analysis. Visual inspection revealed no significant asymmetry, suggesting evidence of publication bias.

Supplementary Table 1. Sarcopenic obesity definition in individual studies

Study	Sarcopenic obesity definition
Stephen & Janssen (2009)[12]	**Obesity:** Classified using sex-specific tertiles of waist circumference (WC). Subjects in the highest WC tertile were considered "obese." **Sarcopenia:** Classified using sex-specific tertiles of skeletal muscle mass (estimated via bioelectrical impedance analysis, BIA). Subjects in the lowest muscle mass tertile were considered "sarcopenic." **Sarcopenic-Obesity:** Subjects in the highest WC tertile (obese) and lowest muscle mass tertile (sarcopenic) were classified as "sarcopenic-obese."
Atkins et al. (2014)[13]	**Obesity:** Waist circumference (WC) > 102 cm. **Sarcopenia:** Lowest two-fifths of the midarm muscle circumference (MAMC) distribution (≤ 25.9 cm). ***Sarcopenic-Obesity:*** Participants with WC > 102 cm (obese) and MAMC ≤ 25.9 cm (sarcopenic).
Kim et al. (2015)[14]	**Obesity** • **Measurement**: Body mass index (BMI). • **Obesity Cutoff**: BMI ≥ 25 kg/m² (Asian-specific cutoff for obesity). **Sarcopenia:** • **Measurement**: Appendicular skeletal muscle mass (ASM; kg) was measured using **dual-energy X-ray absorptiometry (DXA)**. • **Sarcopenia Cutoff**: o Participants with **ASM/body weight (ASM/Wt) < 1 standard deviation (SD) below the mean** of a sex-specific healthy reference group (aged 20–39 years). o **Cutoff Values**: • **Men**: ASM/Wt < 31.30%. • **Women**: ASM/Wt < 24.76%. **Sarcopenic-Obesity:** BMI ≥ 25 kg/m² and ASM/Wt < 31.30% (men) or < 24.76% (women).
Kim et al. (2015)[14]	**Obesity** • **Measurement**: Body mass index (BMI). • **Obesity Cutoff**: BMI ≥ 25 kg/m² (Asian-specific cutoff for obesity). **Sarcopenia:** • **Measurement**: Appendicular skeletal muscle mass (ASM; kg) was measured using **dual-energy X-ray absorptiometry (DXA)**. • **Sarcopenia Cutoff**: o Participants with **ASM/body weight (ASM/Wt) < 1 standard deviation (SD) below the mean** of a sex-specific healthy reference group (aged 20–39 years). o **Cutoff Values**: • **Men**: ASM/Wt < 31.30%. • **Women**: ASM/Wt < 24.76%. **Sarcopenic-Obesity:** BMI ≥ 25 kg/m² and ASM/Wt < 31.30% (men) or < 24.76% (women).

Supplementary Table 1. Sarcopenic obesity definition in individual studies (Continued)

Study	Sarcopenic obesity definition
Fukuda et al. (2018)[15]	**Obesity** **Android-to-Gynoid Fat Ratio (A/G ratio):** Higher than the sex-specific median: Men: >0.80; Women: >0.62 **Android Fat Mass:** Higher than the sex-specific median: Men: >2.16 kg; Women: >1.95 kg **Percentage of Body Fat (%BF):** Higher than the sex-specific median: Men: >31.8%; Women: >38.8% **Body Mass Index (BMI):** BMI ≥25 kg/m^2 (standard threshold for obesity in Japan). **Sarcopenia:** Sarcopenia was defined as SMI less than 7.0kg/m2 (in men) or 5.4kg/m2 (in women) according to the criteria for Asians. **Sarcopenic-Obesity:** Coexistence of low SMI and obesity.
Farmer et al. (2019)[6]	The study used multiple definitions of sarcopenic obesity by combining different measures of adiposity and muscle quality. Here are the specific definitions employed: **Primary Definition:** • **Adiposity**: Measured by **Body Mass Index (BMI)** with obesity defined as **BMI > 30 kg/m^2**. • **Muscle Quality**: Measured by **Handgrip Strength (HGS)** with sarcopenia defined as: o **<30 kg for men** o **<20 kg for women**. **Secondary Definitions:** 1. **Alternative Adiposity Measures:** o **Waist-Hip Ratio (WHR)**: • Obesity cutoffs: **≥0.95 for men** and **≥0.80 for women**. o **Fat Mass Percentage**: • No standard cutoff for obesity was used; instead, quintiles were compared. 2. **Alternative Muscle Quality Measures:** • **Skeletal Muscle Mass Index (SMMI)**: o Calculated from bioelectrical impedance using the Janssen equation. o Sarcopenia defined as the **bottom 40% of the distribution**. **Sarcopenic obesity**: Both obese and sarcopenic.
Xia et al. (2020)[16]	The study defines sarcopenic overweight/obesity based on two criteria: 1. **Sarcopenia**: Defined using the Asian Working Group for Sarcopenia (AWGS) criteria, where sarcopenia is identified by a low appendicular skeletal muscle mass (ASM) adjusted for height (ASM/height^2). The cutoff points are: o **Men**: ASM/height^2 < 7.0 kg/m^2 o **Women**: ASM/height^2 < 5.4 kg/m^2 2. **Overweight/Obesity**: Defined according to BMI thresholds for Chinese adults: o **Overweight**: BMI ≥ 24 kg/m^2 o **Obesity**: BMI ≥ 28 kg/m^2 **Sarcopenic overweight/obese**: BMI ≥ 24 kg/m^2 with sarcopenia.
Xia et al. (2020)[16]	The study defines sarcopenic overweight/obesity based on two criteria: 3. **Sarcopenia**: Defined using the Asian Working Group for Sarcopenia (AWGS) criteria, where sarcopenia is identified by a low appendicular skeletal muscle mass (ASM) adjusted for height (ASM/height^2). The cutoff points are: o **Men**: ASM/height^2 < 7.0 kg/m^2 o **Women**: ASM/height^2 < 5.4 kg/m^2 4. **Overweight/Obesity**: Defined according to BMI thresholds for Chinese adults: o **Overweight**: BMI ≥ 24 kg/m^2 o **Obesity**: BMI ≥ 28 kg/m^2 **Sarcopenic overweight/obese**: BMI ≥ 24 kg/m^2 with sarcopenia.
Yoo et al. (2020)[17]	The study defines **sarcopenic obesity** based on two criteria: 1. **Sarcopenia**: Defined as having a **skeletal muscle mass index (SMI)** below 1 standard deviation (SD) of the sex-specific mean for a young reference group (aged 18–40 years). The cutoff points are: o **Men**: SMI < 30.0% o **Women**: SMI < 26.8% 2. **Obesity**: Defined using **three methods** (applied separately in analyses): • **BMI**: BMI ≥ 25 kg/m^2 (Asian-specific cutoff for obesity). o Men: FM% ≥ 25% o Women: FM% ≥ 35%. • **Body Fat Percentage (FM%)**: Above the 60th percentile of the study population: o Men: WC ≥ 90 cm o Women: WC ≥ 85 cm (reflecting visceral obesity). • **Waist Circumference (WC)**: **Sarcopenic Obesity**: Both sarcopenic and obese.

(*Continued*)

Supplementary Table 1. Sarcopenic obesity definition in individual studies (Continued)

Study	Sarcopenic obesity definition
Chung et al. (2021)[18]	In this study, **sarcopenic obesity (SO)** was defined based on the following criteria: 1. **Sarcopenia**: o **Men**: ASM% < 29.0 o **Women**: ASM% < 22.9 • Measured using **appendicular skeletal muscle mass (ASM)** via bioelectrical impedance analysis (BIA). • Sarcopenia was defined as an ASM% **more than two standard deviations below the sex-specific mean** for healthy young adults: 2. **Obesity**: o Defined as a **body mass index (BMI) ≥ 25 kg/m²**, based on World Health Organization recommendations for the Asian-Pacific population. 3. **Sarcopenic Obesity (SO)**: o The coexistence of **both sarcopenia (ASM% < 29.0 in men or < 22.9 in women) and obesity (BMI ≥ 25)** in the same individual.
Lee at al. (2021)[19]	In this study, sarcopenic obesity (SO) was defined based on the following criteria: 1. Sarcopenia: • These cutoffs align with the Asian Working Group for Sarcopenia (AWGS) consensus. o Men: HGS < 26 kg o Women: HGS < 18 kg • Measured using handgrip strength (HGS) via a digital dynamometer. • Defined as: 2. Obesity: • Defined as body mass index (BMI) ≥ 25 kg/m², following WHO guidelines for the Asian-Pacific population. Sarcopenic Obesity (SO): -The coexistence of sarcopenia (low HGS) and obesity (high BMI).
Lee at al. (2021)[19]	In this study, sarcopenic obesity (SO) was defined based on the following criteria: 1. Sarcopenia: • These cutoffs align with the Asian Working Group for Sarcopenia (AWGS) consensus. o Men: HGS < 26 kg o Women: HGS < 18 kg • Measured using handgrip strength (HGS) via a digital dynamometer. • Defined as: 2. Obesity: • Defined as body mass index (BMI) ≥ 25 kg/m², following WHO guidelines for the Asian-Pacific population. Sarcopenic Obesity (SO): -The coexistence of sarcopenia (low HGS) and obesity (high BMI).
Jia et al. (2024)[20]	In this study, sarcopenic obesity (SO) was defined using the following criteria: 1. Sarcopenia: • Based on the European Working Group on Sarcopenia in Older People 2019 (EWGSOP2) criteria for "probable sarcopenia." o Men: HGS < 27 kg o Women: HGS < 16 kg • Measured by handgrip strength (HGS) using a Jamar dynamometer. • Defined as: 2. Obesity: • Defined as body mass index (BMI) ≥ 30 kg/m², following standard WHO thresholds. Sarcopenic Obesity (SO): • The coexistence of sarcopenia (low HGS) and obesity (high BMI).
Jiang et al. (2024)[21]	In this study, sarcopenic obesity is defined as the co-occurrence of sarcopenia and obesity, where: 1. Sarcopenia is diagnosed based on the AWGS 2019 criteria, requiring: o Low muscle mass (measured via DXA or BIA, adjusted for height), combined with o Low muscle strength (assessed by handgrip strength) or o Low physical performance (evaluated via SPPB, 6-m walk, or five-time chair stand test). 2. Obesity is defined using two criteria: o General obesity: BMI ≥ 28.0 kg/m² (Chinese criteria). o Abdominal obesity: Waist circumference ≥ 85 cm (men) or ≥ 80 cm (women). **Sarcopenic obesity**: Both obese and sarcopenic.

(*Continued*)

Supplementary Table 1. Sarcopenic obesity definition in individual studies (Continued)

Study	Sarcopenic obesity definition
Yang et al. (2024)[22]	In this study, **sarcopenic obesity (SO)** is defined as the co-occurrence of **sarcopenia** and **obesity**, where: 1. **Sarcopenia** is diagnosed based on the **Asian Working Group for Sarcopenia (AWGS) criteria**, requiring: o **Men**: <1.05 m/s o **Women**: <1.01 m/s • **OR low gait speed**: o **Men**: <28.5 kg o **Women**: <18.6 kg • **Low handgrip strength (HGS)**: • **Low muscle function**: Either: o **Men**: ASMI <7.05 kg/m^2 o **Women**: ASMI <5.85 kg/m^2 • **Low muscle mass**: Measured via bioelectrical impedance analysis (BIA), with cutoff values for the appendicular skeletal muscle mass index (ASMI) set at: 2. **Obesity** is defined as: o **Men**: ≥32.6% body fat o **Women**: ≥41.0% body fat • **High body fat percentage**: ≥80th percentile of the study population: **Sarcopenic obesity**: Sarcopenia (low muscle mass + low muscle function) + Obesity (high body fat).
Yu et al. (2024)[9]	In this study, **sarcopenic obesity (SO)** is defined as the co-occurrence of **possible sarcopenia** and **obesity**, based on the following criteria: 1. **Possible Sarcopenia** (simplified screening definition from AWGS 2019): o **Men**: <28 kg o **Women**: <18 kg • **Low muscle strength**: Measured by handgrip strength: 2. **Obesity**: o **General obesity**: Body mass index (BMI) ≥25 kg/m^2 (Asian cutoff). o **Abdominal obesity** (used in sensitivity analysis): Waist circumference (WC) ≥85 cm (men) or ≥80 cm (women). **Sarcopenic obesity**: Low grip strength (possible sarcopenia) + High BMI (obesity).
Shi et al. (2025)[10]	In this study, **sarcopenic obesity (SO)** is defined using a novel index called the **Sarcopenic Abdominal Obesity (SAO) Index**, which combines measures of sarcopenia and abdominal obesity. Participants were stratified into high SAO Index (>91.19, the median value) and low SAO Index (≤91.19) groups for analysis.
Yu et al. (2025)[23]	In this study, **sarcopenic obesity (SO)** is defined using the **ESPEN/EASO (European Society for Clinical Nutrition and Metabolism/European Association for the Study of Obesity) consensus criteria** for Asian populations. The diagnosis involves a three-step process combining **sarcopenia** and **obesity**: 1. **Sarcopenia Definition** Sarcopenia is identified by **low muscle mass** and **low muscle strength**, based on the following criteria: • **Low skeletal muscle mass (SMM) to body weight (BW) ratio**: o Men: <38.2% o Women: <32.2% • **Low appendicular lean mass (ALM) to BW ratio**: o Men: <32.5% o Women: <25.7% • **Low handgrip strength (HGS)**:Men: <28 kg Women: <18 kg2. **Obesity Definition** Obesity is defined by **high fat mass (FM) to BW ratio**: o Men: >29% o Women: >41% • **Sarcopenic Obesity (SO) Diagnosis** Participants are classified as having SO if they meet **both sarcopenia and obesity criteria** (i.e., low muscle mass/strength + high fat mass).

(*Continued*)

Supplementary Table 1. Sarcopenic obesity definition in individual studies (Continued)	
Study	**Sarcopenic obesity definition**
Shi et al. (2025)[24]	In this study, **sarcopenic obesity (SO)** is defined using the following criteria based on **body composition and skeletal muscle mass** assessed via **cardiac MRI**: 1. **Obesity Definition** • **Body Mass Index (BMI)**: o Obesity is defined as **BMI ≥ 25 kg/m²** (adjusted for Asian populations, where lower BMI thresholds are used compared to Western standards). 2. **Sarcopenia Definition** • **Thoracic Skeletal Muscle Index (SMI)**: o Sarcopenia is defined as **SMI < 42.75 cm²/m²**, where SMI is calculated as: SMI=Total bilateral axial thoracic skeletal muscle area (cm^2)Body surface area (BSA, m^2)SMI=Body surface area (BSA, m^2)Total bilateral axial thoracic skeletal muscle area (cm^2) o The thoracic skeletal muscle area includes pectoralis major/minor, serratus anterior, periscapular, paraspinal, and trapezius muscles measured at the carina level via MRI. **Sarcopenic Obesity (SO) Diagnosis** • Patients are classified as having **SO** if they meet **both criteria**: o **BMI ≥ 25 kg/m²** (obesity) o **SMI < 42.75 cm²/m²** (sarcopenia).

Supplementary Table 2. Search strategy for systematic review on sarcopenic obesity and risk of cardiovascular disease

Database	Descriptors	Number of studies reached
PubMed/Medline	("Sarcopenic Obesity"[MeSH] OR "sarcopenic obesity"[tiab] OR ("sarcopenia"[MeSH Terms] AND "obesity"[MeSH Terms]) OR ("sarcopenia"[tiab] AND "obesity"[tiab])) AND ("cardiovascular diseases"[MeSH] OR "cardiovascular disease"[tiab] OR "CVD"[tiab] OR "heart disease"[tiab] OR "coronary artery disease"[tiab] OR "myocardial infarction"[tiab] OR "stroke"[tiab]) AND ("Mortality"[MeSH] OR "mortality"[tiab] OR "death"[tiab] OR "fatal outcome"[tiab])	**111**
Scopus	(TITLE-ABS-KEY("sarcopenic obesity") OR (TITLE-ABS-KEY("sarcopenia") AND TITLE-ABS-KEY("obesity"))) AND (TITLE-ABS-KEY("cardiovascular disease") OR TITLE-ABS-KEY("CVD") OR TITLE-ABS-KEY("heart disease") OR TITLE-ABS-KEY("coronary artery disease") OR TITLE-ABS-KEY("myocardial infarction") OR TITLE-ABS-KEY("stroke")) AND (TITLE-ABS-KEY("mortality") OR TITLE-ABS-KEY("death") OR TITLE-ABS-KEY("fatal outcome"))	**382**
Embase	('sarcopenic obesity'/exp OR 'sarcopenic obesity':ti,ab OR ('sarcopenia'/exp AND 'obesity'/exp) OR ('sarcopenia':ti,ab AND 'obesity':ti,ab)) AND ('cardiovascular disease'/exp OR 'cardiovascular disease':ti,ab OR 'CVD':ti,ab OR 'heart disease':ti,ab OR 'coronary artery disease':ti,ab OR 'myocardial infarction':ti,ab OR 'stroke':ti,ab) AND ('mortality'/exp OR 'mortality':ti,ab OR 'death':ti,ab OR 'fatal outcome':ti,ab)	**667**
Web of Sciences	TS=("sarcopenic obesity" OR ("sarcopenia" AND "obesity")) AND TS=("cardiovascular disease" OR "cardiovascular diseases" OR "CVD" OR "heart disease" OR "coronary artery disease" OR "myocardial infarction" OR "stroke") AND TS=("mortality" OR "death" OR "fatal outcome")	**428**

Supplementary Table 3. Adjusted confounders in studies examining sarcopenic obesity and risk of cardiovascular disease

Studies	Effect size	Adjusted confounders
Stephen & Janssen (2009)	HR, 1.06 (0.85-1.33)	The final model (Model 3) was adjusted for age, sex, race, income, smoking, alcohol use, cognitive function, physical activity, diabetes, hypertension, HDL-cholesterol, total cholesterol, and triglycerides.
Atkins et al. (2014)	HR, 1.08 (0.77-1.52)	The final model was adjusted for age, smoking, alcohol, occupational social class, physical activity
Kim et al. (2015)	OR, 2.49 (1.53-4.06)	The final model was adjusted for total calorie intake, protein intake, resistance exercise, flexibility exercise, regular walking, equivalent income, and alcohol use disorder identification test score category.
Kim et al. (2015)	OR, 1.87 (1.02-3.41)	The final model was adjusted for total calorie intake, protein intake, resistance exercise, flexibility exercise, regular walking, equivalent income, and alcohol use disorder identification test score category.
Fukuda et al. (2018)	HR, 2.63 (1.1-6.28)	The multivariate models included high-density lipoprotein cholesterol, HbA1c, estimated glomerular filtration ratio, the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, the use of dipeptidyl peptidase 4 inhibitors, and history of CVD as covariates
Farmer et al. (2019)	HR, 1.42 (1.31-1.55)	The model was adjusted for age (linear term), sex, smoking status, ethnic group,deprivation, diabetes mellitus status, alcohol consumption,and moderate physical activity at baseline
Xia et al. (2020)	OR, 5.68 (1.34-24.12)	The final model (Model 3) was adjusted for: Demographic & lifestyle factors (Age, gender, alcohol drinking, cigarette smoking, and menopause (in women); Cardiometabolic factors: BMI, waist circumference (WC), fasting blood glucose (FBG), systolic blood pressure (SBP), triglycerides (TG), total cholesterol (TC), and HDL cholesterol (HDL-c); Inflammatory & liver markers: White blood cell count (WBC), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).
Xia et al. (2020)	OR, 4.07 (1.31-12.62)	The final model (Model 3) was adjusted for: Demographic & lifestyle factors (Age, gender, alcohol drinking, cigarette smoking, and menopause (in women); Cardiometabolic factors: BMI, waist circumference (WC), fasting blood glucose (FBG), systolic blood pressure (SBP), triglycerides (TG), total cholesterol (TC), and HDL cholesterol (HDL-c); Inflammatory & liver markers: White blood cell count (WBC), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).
Yoo et al. (2020)	OR, 1.7 (1.44-1.99)	The final model was adjusted for age, sex, smoking status, alcohol consumption, regular exercise, and LAVI
Chung et al. (2021)	OR, 1.92 (1.16-3.18)	The model was adjusted for age, sex, hypertension, diabetes, dyslipidemia, and creatinine
Lee at al. (2021)	OR, 1.79 (0.68-4.74)	The model was adjusted for sex, educational level, income level, physical activity, alcohol use, dietary intakes of protein, vitamin A, vitamin C, and calcium, time since cancer diagnosis (for cancer survivors) and current cancer therapy (for cancer survivors)
Lee at al. (2021)	OR, 3.01 (2.42-3.73)	The model was adjusted for sex, educational level, income level, physical activity, alcohol use, dietary intakes of protein, vitamin A, vitamin C, and calcium, time since cancer diagnosis (for cancer survivors) and current cancer therapy (for cancer survivors)
Jia et al. (2024)	HR, 2.29 (1.92-2.73)	The final model (Model 2) was adjusted for age, sex, ethnicity, educational level, Townsend deprivation index, smoking status, alcohol intake frequency, regular exercise, healthy diet, sedentary time, sleep duration, diabetes duration, antihyperglycemic agents use, and family histories of cardiovascular disease and diabetes.
Jiang et al. (2024)	HR, 1.47 (1.2-1.8)	adjusted for age, sex, place of residence, education level, smoking and alcoholconsumption status, hypertension, dyslipidemia, diabetes, kidney disease, anti-hypertension drug, anti-dyslipidemia and anti-diabetes medicines.
Yang et al. (2024)	OR, 2.2 (1.16-4.19)	The model was adjusting for age and sex
Yu et al. (2024)	HR, 2.302 (1.24-4.23)	The final model (Model 4) was adjusted for age, male sex, urban residence, education level, marital status, smoking, alcohol drinking, regular exercise, hypertension, hypercholesterolemia, kidney disease, antihypertensive medications, diabetes medications, lipid-lowering therapy, systolic blood pressure (SBP), and diastolic blood pressure (DBP).
Shi et al. (2025)	HR, 1.2 (1.01-1.4)	The final model (Model 3) was adjusted for age group, sex, smoking status, drinking status, hypertension, dyslipidemia, and diabetes.
Yu et al. (2025)	HR, 2.669 (2.11-3.38)	Adjusted for age, sex, smoking, alcohol consumption, regular exercise, medical and medication histories, body mass index, blood pressure, heartbeat, plasma lipid profile data,eGFR.
Shi et al. (2025)	HR, 3.03 (1.39-6.63)	The final model (Model 3) was adjusted for age, sex, NT-proBNP, hypoproteinemia, anemia, diabetes mellitus duration, use of β-blockers, insulin, ARNI, SGLT-2 inhibitors, left ventricular ejection fraction (LVEF), and global longitudinal strain (GLS).

Supplementary Table 4. Results of subgroup analyses of the association between sarcopenic obesity (SO) and cardiovascular disease (CVD) risk

Variables	Odds ratio	Heterogeneity I^2 (%)	*P*-value	*P*-interaction
Sex				0.032
Men	2.56 (2.15–3.06)	0.0	< 0.001	
Women	2.35 (1.90–2.92)	0.0	< 0.001	
Both	1.75 (1.39–2.20)	87.3	< 0.001	
Age				0.683
Younger age	1.97 (1.49–2.60)	73.5	< 0.001	
Older age	1.81 (1.32–2.47)	65.8	< 0.001	
Geographical region				0.143
Europe and North America	1.56 (1.06–2.28)	90.8	0.023	
East Asia	2.16 (1.75–2.65)	74.7	< 0.001	
Study design				0.181
Cohort	1.77 (1.35–2.32)	90.1	< 0.001	
Cross-sectional	2.25 (1.80–2.82)	52	< 0.001	
Cardiovascular outcome				0.001
Atrial fibrillation	2.93 (2.23–3.86)	0	< 0.001	
Heart diseases	1.37 (1.11–1.70)	50.8	0.003	
Heart failure	1.69 (0.97–2.94)	92.8	0.065	
Left ventricular diastolic dysfunction	1.70 (1.45-2.0)	0.0	< 0.001	
Myocardial infarction	4.07 (1.31–12.63)	0.0	0.015	
Stroke	1.39 (0.86–2.24)	76.6	0.180	
Coronary artery calcification	1.92 (1.16–3.18)	0.0	0.011	

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The Predictive Value of Hemoglobin-to-Red Blood Cell Distribution Width Ratio for the Prognosis of Patients with Aortic Dissection: Based on the Medical Information Mart for Intensive Care-IV Database

ABSTRACT

Background: The hemoglobin-to-red blood cell distribution width ratio (HRR) is a new inflammatory marker in evaluating tumor prognosis. However, its application in cardiovascular diseases (CVDs) is relatively limited. This research was designed to illuminate the relationship between HRR and mortality in patients with aortic dissection (AD).

Methods: The Medical Information Mart for Intensive Care-IV (MIMIC-IV) database was applied in this retrospective cohort study. The primary outcome was the 30-day mortality rate. The Cox proportional hazards model was utilized to explore the relationship between HRR and mortality in AD patients. Through restricted cubic splines (RCS), the relationship between mortality and HRR levels was analyzed. The ROC curves were graphed to evaluate the prognostic value of HRR.

Results: This retrospective cohort study included 292 patients. A significant negative linkage between HRR quartiles and 30-day mortality was identified ($P < .05$). Kaplan-Meier analysis demonstrated that participants in the low-HRR group exhibited worse survival rates than those in the high-HRR group (Q1 vs. Q2, log-rank $P = .005$; Q1 vs. Q3, log-rank $P < .001$; Q1 vs. Q4, log-rank $P = .014$). No great difference was observed between other groups. In RCS analysis, a non-linear linkage between HRR and 30-day mortality rate was observed ($P < .05$). Through analyzing ROC curves, HRR was found to perform well in predicting AD mortality, with AUC values of 0.628, 0.662, and 0.669 at 7, 14, and 30 days, respectively.

Conclusion: Low levels of HRR may elevate the risk of death in AD patients. The research pinpointed the potential of HRR as a prognostic biomarker for AD patients, which can provide reliable auxiliary indicators for clinical routine and interventional treatment.

Keywords: Aortic dissection, hemoglobin-to-red blood cell distribution width ratio, Medical Information Mart for Intensive Care-IV, survival analysis

INTRODUCTION

Aortic dissection (AD) is a life-threatening, serious cardiovascular disease (CVD) characterized by the tearing of the intimal layer of the aorta or hemorrhage within the aortic wall, leading to the separation of the aortic layers and the formation of a false lumen, which in severe cases can result in aortic rupture or other fatal complications.[1,2] This disease usually has a rapid onset, manifested as sudden and severe chest pain, which often catches patients off guard and makes it difficult to identify the cause in time. In addition, the mortality rate of acute AD is high. It causes half of the AD patients to die before arriving at specialized centers, seriously threatening their life and health.[3-5] Although achievements in surgery and the application of intravascular stents have greatly elevated the survival rate of AD patients in recent years,[6,7] the treatment effectiveness of some patients is still disappointing due to the insidious onset and invasive prognosis of AD, as well as its complex and variable condition.[8] Therefore, innovating a fast, non-invasive, accurate, and timely diagnosis is instrumental for the prognosis of AD patients.

ORIGINAL INVESTIGATION

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Hematological parameters are now widely applied in diagnosing and predicting the prognosis of diseases, garnering growing attention in clinical practice.[9-11] Red blood cell distribution width (RDW) is a readily available parameter representing the volume of red blood cells, primarily used for the differentiation and diagnosis of anemia.[12] For AD patients, higher RDW is considered a strong risk factor affecting mortality and prognosis.[13,14] Similar to RDW, hemoglobin (Hb) is also an essential component of hematological parameters. It reflects, to some extent, the decline of the host immune response and malnutrition, which is linked to the patient's resistance to external invasion.[15] Preoperative Hb levels are prognostic markers for long-term adverse outcomes in patients with acute type B AD after thoracic aortic endovascular repair.[16]

The Hb-to-RDW ratio (HRR) is a simple yet powerful composite indicator, initially used to predict the prognosis of cancer.[17] With the deepening of research, it has become a new independent prognostic marker for many CVDs, such as stroke, cerebral hemorrhage, coronary atherosclerotic heart disease, and other patients.[18-21] It performed well in prediction. However, there seems to be no current data linking HRR to the prognosis of AD patients. Therefore, this research was intended to analyze the linkage between HRR and the prognosis of AD patients.

METHODS

AI statement: This article was not written using AI.

Database

The Medical Information Mart for Intensive Care-IV (MIMIC-IV) database provides an extensive collection of intensive care data.[22] It is essential for supporting in-depth studies in epidemiology, machine learning, and clinical informatics. This database is an updated version of MIMIC-III that incorporates new data and improves upon many features of the original dataset. As stated in the ethical declaration, since all protected health information was de-identified and the study had no effect on clinical care, the need for individual patient agreement was waived.[23]

Inclusion and Exclusion Criteria

This research screened 455 patients with a diagnosis code of 4410 (ICD9) or I710 (ICD10)[24,25] where AD was the primary diagnosis. Patients who met the following exclusion criteria were excluded: (1) multiple hospitalizations; (2) individuals under 18 years of age; and (3) individuals with Marfan syndrome (75982, Q874), Ehlers-Danlos syndrome (75683, Q796), and congenital aortic valve abnormalities (7464, Q231). A total of 292 patients were ultimately enrolled in this research. The selection process of participants is shown in Figure 1.

Data Collection

Based on existing literature and clinical judgment, the authors gathered the intensive care unit (ICU) variables, including demographic data, laboratory measurements, severity scores, and medical history, which were considered confounding factors for AD outcomes. Vital signs, severity scores, and laboratory measurements conducted multiple times during the ICU stay were all determined by the values corresponding to the most severe level collected within the first 24 hours following ICU admission.

Statistical Analysis

Continuous variables are represented by mean ± SD or median (interquartile range). The normal distribution was determined through the Kolmogorov–Smirnov test and combined with a histogram and Q-Q chart for comprehensive judgment. According to the distribution characteristics of the data, the *t*-test was used for inter-group comparisons that satisfy normal distribution and homogeneity of variance; otherwise, the Mann–Whitney *U*-test was used. To compare categorical variables, the chi-squared test was undertaken, and differences were expressed in percentages (%). Multiple and univariate Cox regression analyses were undertaken to assess the hazard ratio of HRR on the 30-day mortality of patients with AD. Multiple Cox prognostic models were created by comprising statistically significant variables determined by multiple regression analysis. Kaplan–Meier (K-M) survival curves were applied to assess the mortality outcomes between groups, and the log-rank test was employed for evaluation. By utilizing restricted cubic splines (RCS), the linkage between HRR and the 30-day mortality of AD patients was dissected, with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of HRR.[26] To further demonstrate the predictive efficacy of HRR for AD mortality at various follow-up time points, the receiver operating characteristic (ROC) curves of HRR were plotted.

The database lacked certain biological parameters. Variables with missing values that made up less than 5% of the entire sample were filled using the Random Forest (RF) approach throughout the parameter extraction procedure. The proportion of missing variables is displayed in Supplementary Table 1.

Data in this research were collected from the MIMIC-IV (Version 2.2) database with SQL (Structured Query Language) and analyzed by utilizing the R (Version 4.2.3) software, including R packages *rms*, *timeROC*, *mice*, *jskm*, and *tableone* (2-sided *P*-value < .05: statistically significant).

HIGHLIGHTS

- There is a negative correlation between HRR width ratio and 30-day mortality risk in AD patients.
- The relationship between HRR width ratio and the 30-day mortality rate in AD patients is non-linear.
- The HRR width ratio has a good predictive value for mortality in AD patients.

RESULTS

Baseline Characteristics

The median age of the enrolled 292 patients was 67.35 ± 13.47 years. A total of 168 were men (57.5%). Based on the 30-day survival status of the patients, 2 groups of participants were formed: the survival group (n = 261) and the death

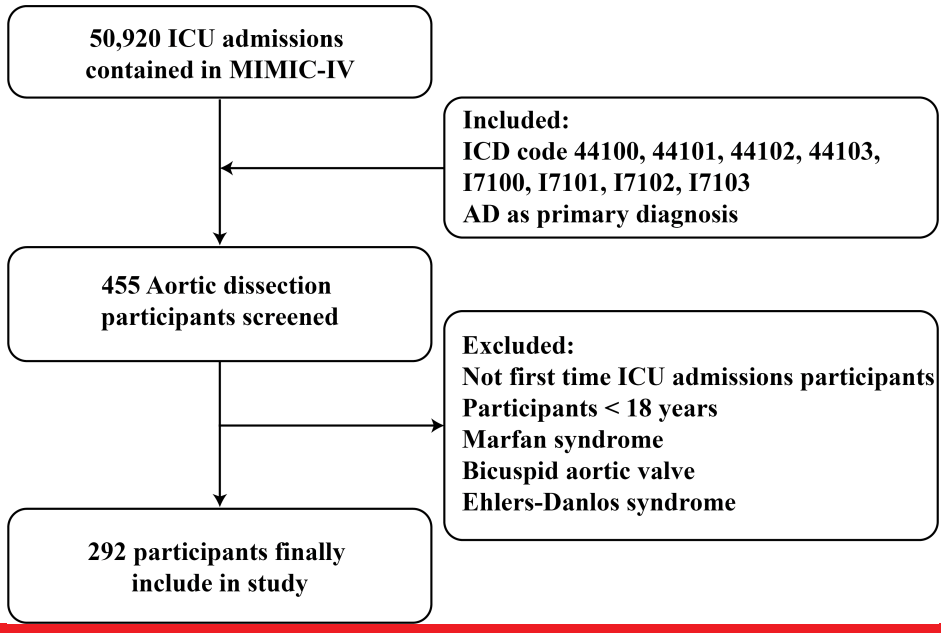

Figure 1. Flowchart of the selection process of patients.

group (n = 31). The death group had higher respiratory rates and blood glucose levels, higher SAPS II, SOFA, LODS, and SIRS scores, as well as elevated levels of anion gap, lactate, BUN, potassium ions, creatinine, ALT, AST, and pCO_2 ($P < .05$). Hemoglobin-to-RDW ratio was lower than that in the survival group (0.57 ± 0.22 vs. 0.68 ± 0.19, $P = .004$) (Table 1).

Table 1. Baseline Characteristics of Patients

Characters	Total (n = 292)	Survivor (n = 261)	Non-survivors (n = 31)	*P*
Age (years)	67.35 (13.47)	67.33 (13.12)	67.48 (16.40)	.953
Gender				.369
Female	124 (42.5)	108 (41.4)	16 (51.6)	
Male	168 (57.5)	153 (58.6)	15 (48.4)	
Race				.079
White	155 (53.1)	143 (54.8)	12 (38.7)	
Black	39 (13.4)	36 (13.8)	3 (9.7)	
Other race	98 (33.6)	82 (31.4)	16 (51.6)	
Marital status				.737
Married	126 (43.2)	114 (43.7)	12 (38.7)	
Unmarried	166 (56.8)	147 (56.3)	19 (61.3)	
LOS (days)	3.67 [2.16, 7.49]	3.62 [2.09, 7.13]	4.26 [2.44, 15.56]	.298
Height (cm)	170.59 (11.25)	170.91 (11.16)	168.04 (11.88)	.239
Weight (kg)	84.21 (22.41)	83.56 (21.78)	89.59 (26.92)	.164
Smoking status	60 (20.5)	55 (21.1)	5 (16.1)	.683
Heart rate (times/min)	77.74 (12.03)	77.75 (11.98)	77.71 (12.71)	.988
SBP (mm Hg)	114.63 (11.20)	114.68 (10.94)	114.22 (13.44)	.83
DBP (mm Hg)	59.74 (8.72)	59.59 (8.24)	61.01 (12.16)	.391
MBP (mm Hg)	76.10 (8.72)	75.97 (8.29)	77.21 (11.84)	.453
Breath rate (times/min)	18.19 (2.90)	17.98 (2.73)	19.94 (3.63)	<.001
Temperature	36.65 (0.55)	36.66 (0.54)	36.55 (0.58)	.361
SpO2	96.67 (1.92)	96.64 (1.91)	97.01 (1.99)	.319
Glucose (mg/dL)	131.15 [117.56, 143.45]	130.67 [116.85, 142.80]	137.13 [126.62, 146.07]	.049
SAPSII	38.24 (12.66)	37.39 (12.19)	45.39 (14.40)	.001

(*Continued*)

Table 1. Baseline Characteristics of Patients (*Continued*)

Characters	Total (n = 292)	Survivor (n = 261)	Non-survivors (n = 31)	*P*
SOFA	4.00 [2.00, 8.25]	4.00 [2.00, 8.00]	9.00 [4.00, 12.00]	<.001
GCS	13.94 (2.88)	13.95 (2.91)	13.81 (2.64)	.788
LODS	5.00 [2.00, 8.00]	4.00 [2.00, 7.00]	7.00 [4.00, 9.50]	.002
SIRS	2.17 (0.92)	2.14 (0.92)	2.48 (0.89)	.048
HRR	0.66 (0.20)	0.68 (0.19)	0.57 (0.22)	.004
Chloride (mmol/L)	107.24 (4.98)	107.16 (4.94)	107.94 (5.35)	.412
Hematocrit (μmol/L)	28.69 (6.74)	28.98 (6.56)	26.25 (7.75)	.033
Hemoglobin (g/dL)	9.60 (2.31)	9.72 (2.23)	8.52 (2.71)	.006
Potassium (K/μL)	4.61 (0.82)	4.57 (0.78)	4.88 (1.03)	.048
Anion gap (mEq/L)	15.69 (3.97)	15.29 (3.29)	19.03 (6.80)	<.001
Bicarbonate (mEq/L)	22.11 (3.13)	22.37 (2.86)	19.97 (4.33)	<.001
Sodium (mEq/L)	138.05 (3.50)	13800 (3.39)	138.48 (4.40)	.468
PTT (s)	36.50 [30.00, 52.30]	36.00 [30.02, 51.82]	45.30 [29.95, 63.65]	.199
INR	1.59 (0.73)	1.58 (0.74)	1.70 (0.70)	.386
PT (s)	15.30 [12.70, 19.20]	15.20 [12.70, 18.70]	16.70 [12.90, 20.70]	.136
Lactate (mmol/L)	4.75 [2.30, 7.23]	4.60 [2.30, 6.77]	7.10 [3.05, 9.98]	.011
Platelets (K/μL)	142.50 [92.75, 186.75]	147.00 [100.00, 190.00]	96.00 [73.50, 144.50]	.006
WBC (K/μL)	12.91 (5.01)	12.79 (4.96)	13.89 (5.40)	.249
RBC (M/μL)	3.20 (0.82)	3.24 (0.80)	2.86 (0.89)	.013
pO_2 (mm Hg)	77.66 (33.96)	79.90 (34.25)	62.35 (27.92)	.013
pCO_2 (mm Hg)	53.37 (13.62)	52.48 (12.74)	59.46 (17.67)	.014
pH	7.26 (0.12)	7.27 (0.11)	7.17 (0.13)	<.001
Base excess (mEq/L)	−5.00 [−8.00, −1.00]	−4.67 (4.67)	−9.58 (5.87)	<.001
MCH (pg)	29.74 (2.27)	29.81 (2.26)	29.15 (2.27)	.124
MCHC (g/dL)	32.75 (1.57)	32.88 (1.49)	31.62 (1.72)	<.001
MCV (fL)	89.06 (5.81)	89.05 (5.89)	89.13 (5.19)	.946
RDW	14.75 (1.77)	14.68 (1.77)	15.28 (1.73)	.076
Open chest surgery	136 (46.6)	120 (46.0)	16 (51.6)	.686
BUN (mg/dL)	20.00 [15.75, 27.00]	20.00 [15.00, 26.00]	25.00 [20.00, 32.00]	.006
Creatinine (mg/dL)	1.20 [0.90, 1.63]	1.10 [0.90, 1.60]	1.50 [1.15, 2.40]	.005
ALT (U/L)	22.00 [16.00, 42.75]	21.00 [15.00, 38.75]	42.50 [24.50, 174.75]	.007
ALP (U/L)	61.00 [45.00, 83.00]	61.00 [44.50, 81.50]	65.50 [47.25, 88.75]	.452
AST (U/L)	33.00 [21.00, 71.00]	29.50 [21.00, 59.00]	68.00 [30.00, 276.75]	.015
Bilirubin (mg/dL)	0.60 [0.40, 1.20]	0.60 [0.40, 1.20]	1.00 [0.43, 1.62]	.261
Site				.802
Abdominal	34 (11.6)	31 (11.9)	3 (9.7)	
Thoracic	192 (65.8)	170 (65.1)	22 (71.0)	
Thoracoabdominal	60 (20.5)	54 (20.7)	6 (19.4)	
Unspecified	6 (2.1)	6 (2.3)	0 (0.0)	
Myocardial infarct	18 (6.2)	17 (6.5)	1 (3.2)	.745
Diabetes	40 (13.7)	35 (13.4)	5 (16.1)	.889
Coronary artery disease	53 (18.2)	46 (17.6)	7 (22.6)	.667
Congestive heart failure	44 (15.1)	37 (14.2)	7 (22.6)	.331
Liver disease	15 (5.1)	11 (4.2)	4 (12.9)	.101

Continuous variables are presented as mean (SD) or median [interquartile range]; categorical variables are presented as n (%).
BUN, blood urea nitrogen; DBP, diastolic blood pressure; GCS, Glasgow Coma Score; HRR, hemoglobin-to-red blood cell distribution width ratio; INR, International Normalized Ratio; LODS, Logistic Organ Dysfunction System scoring; LOS, length of stay; MBP, mean blood pressure; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; RDW, red cell volume distribution width; SAPSII, Simplified Acute Physiology Score II; SBP, systolic blood pressure; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; SpO2, percutaneous oxygen saturation; WBC, white blood cell; Po2, Partial pressure of oxygen; Pco2, Partial pressure of carbon dioxide; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase.

The Linkage between Hemoglobin-to-Red Blood Cell Distribution and 30-Day Mortality in Aortic Dissection Patients

By constructing Cox regression models adjusted and unadjusted for confounding factors, the authors dissected the impact of HRR on the mortality of AD patients (Table 2). The constructed Crude (OR: 0.55, *P* = .005, 95% CI: 0.36-0.83) and Adjusted (OR: 0.55, *P* = .028, 95% CI: 0.32-0.94) models indicated a great negative linkage between HRR and the mortality risk of AD patients.

Subsequently, the authors grouped HRR into quartiles and treated it as a categorical variable in the multiple Cox analysis, using the lowest quartile as the reference. When HRR was considered as a categorical variable, Q2 (OR: 0.25, *P* = .014, 95% CI: 0.08-0.75) and Q3 (OR: 0.15, *P* = .005, 95% CI: 0.04-0.56) after adjustments for confounding factors demonstrated a lower mortality compared to the lowest quartile Q1.

The K-M survival curve manifested that with prolonged follow-up time, the survival rate of the Q1 group was considerably lower than that of the other groups (Q1 vs. Q2, log-rank *P* = .005; Q1 vs. Q3, log-rank *P* < .001; Q1 vs. Q4, log-rank *P* = .014) (Figure 2). Survival differences among the Q2, Q3, and Q4 groups were not significant (all *P* > .05).

The Nonlinear Linkage between Hemoglobin-to-Red Blood Cell Distribution and 30-Day Mortality Risk in Aortic Dissection Patients

The above data suggested that there may be a non-linear linkage between HRR and AD mortality risk. The authors therefore conducted an RCS analysis to evaluate the relation between the two. The RCS curves indicated a significant overall trend between HRR and AD mortality risk (*P* = .0092), with a non-linear association (*P*-non-linear = 0.0214) in the model adjusted for all confounding factors, and two inflection points at 0.63 and 0.93, respectively (Figure 3).

Table 2. Multivariate Cox Regression Models Evaluating the Association between Hemoglobin-to-Red Blood Cell Distribution Width Ratio and Hazard Ratios (95% Confidence Intervals) for 30-Day Mortality

Outcomes	HR (95% CI)	*P*
HRR (Per 1 SD increment)		
Crude	0.55 (0.36-0.83)	.005
Adjust[a]	0.55 (0.32-0.94)	.028
Quartiles[a]		
Q1 <0.509 (n = 73)	Ref.	
Q2 0.509-0.631 (n = 73)	0.25 (0.08-0.75)	.014
Q3 0.631-0.818 (n = 73)	0.15 (0.04-0.56)	.005
Q4 ≥ 0.818 (n = 73)	0.36 (0.11-1.24)	.105
P_{trend}		.018

[a]Adjusted model: adjust for age, gender, race, smoking status, heart rate, weight, mean blood pressure, percutaneous oxygen saturation, platelets, partial thromboplastin time, prothrombin time, mean corpuscular volume, white blood cell, sodium, systemic inflammatory response syndrome, coronary artery disease, diabetes, and site. HRR, hemoglobin-to-red blood cell distribution width ratio.

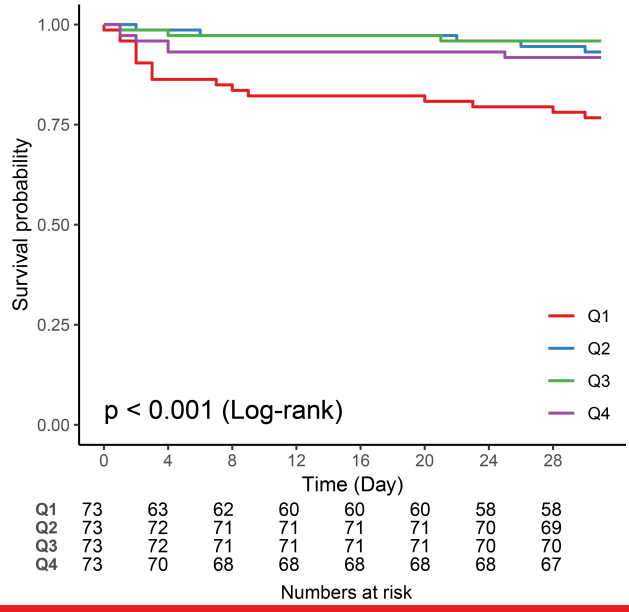

Figure 2. Kaplan-Meier survival curve of hemoglobin-to-red blood cell distribution.

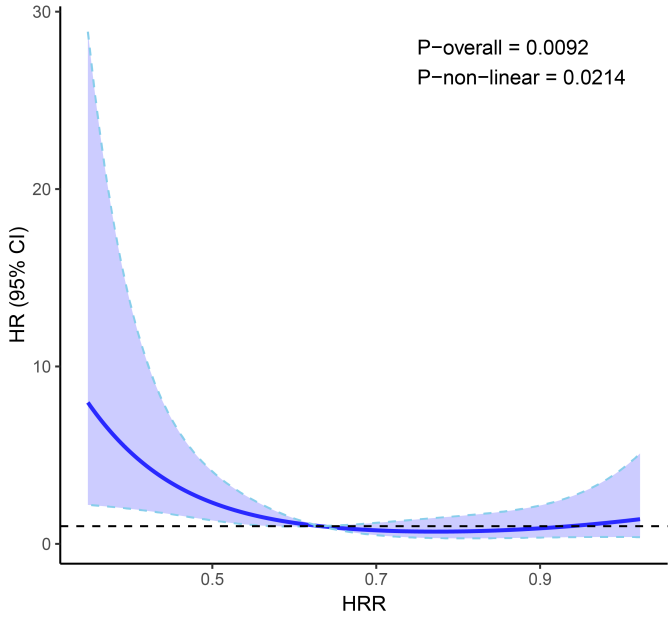

Figure 3. Association between hemoglobin-to-red blood cell distribution and 30-day mortality of participants. The Cox regression model[a] had an restricted cubic splines showing a linear relationship between HRR and the risk of 30-day mortality in the patients. The solid and shadow represented the estimated values and their corresponding 95% CIs, respectively. Model[a]: the adjusted model with adjustments for age, gender, race, smoking status, heart rate, weight, mean blood pressure, percutaneous oxygen saturation, platelets, partial thromboplastin time, prothrombin time, MCV, white blood cell, sodium, systemic inflammatory response syndrome, coronary artery disease, diabetes, and site.

Receiver Operating Characteristic Curve Analysis of Hemoglobin-to-Red Blood Cell Distribution's Predictive Value in 30-Day Mortality of Aortic Dissection Patients

The time-dependent ROC analysis was undertaken to probe into the predictive effect of HRR on the 30-day survival status of AD patients. The AUC values of HRR for 7 days, 14 days, and 30 days were 0.628, 0.662, and 0.669, respectively. In sum, HRR has good predictive value for AD mortality and can function as a promising predictor of AD patient mortality (Figure 4).

DISCUSSION

The objectives of this research were to figure out the linkage between HRR, a novel indicator, and the prognosis of AD patients and to make several important discoveries. First, the authors demonstrated that after adjustments for possible confounding factors, HRR was adversely linked with 30-day mortality. Secondly, the RCS results indicated a nonlinear linkage between HRR and AD. Thirdly, the authors applied ROC to evaluate the predictive results of HRR for AD and discovered that HRR had good predictive value for AD mortality, indicating HRR's potential as an inexpensive and easily accessible prognostic factor for AD patients.

To our knowledge, the linkage between inflammation levels and mortality has long been a concern for AD patients.[27,28] Previous studies have also shown the essential function of inflammatory cell infiltration in AD occurrence and development.[29-31] The destruction of aortic tissue triggered by dissection and thrombus in the false lumen may induce inflammatory reactions. Activated circulating white blood cells will adhere to the endothelium and be destroyed by toxic oxygen compounds and proteolytic enzymes. This change can lead to further necrosis and apoptosis of smooth muscle cells and degeneration of elastic tissue, resulting in aortic rupture.[32,33] As an indicator that combines Hb and RDW, HRR is closely related to inflammatory response levels and is readily obtainable from standard laboratory databases without the need for any additional equipment or expense. Compared with Hb and RDW alone, HRR has higher specificity and sensitivity and can better predict early inflammation levels in patients. It has become a new biomarker associated with mortality in many CVDs.[34,35] An investigation based on the MIMIC-IV database revealed that lower HRR in patients with non-traumatic subarachnoid hemorrhage is linked with an elevated risk of death.[19] In ischemic stroke patients, a study focusing on the relationship between HRR and all-cause mortality also discovered that lower HRR is linked to higher mortality in these patients.[36] These results are similar to the authors' findings, where the authors also discovered the linkage between lower levels of HRR and elevated 30-day mortality in AD patients.

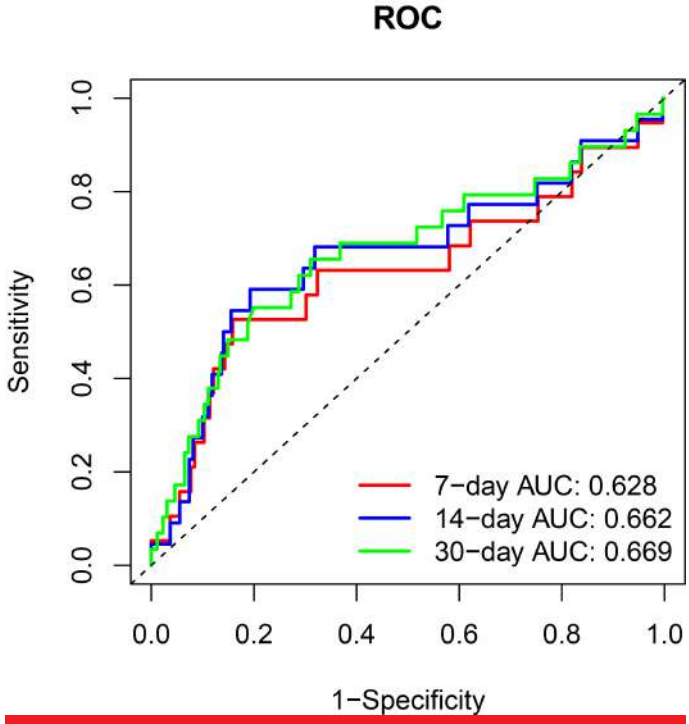

Figure 4. Time-dependent receiver operating characteristic curves of hemoglobin-to-red blood cell distribution width ratio.

The great link between lower HRR and the severity of AD suggested complex underlying mechanisms, which can be elucidated by analyzing the effects of increased RDW and decreased Hb associated with AD. The value of RDW in CVDs is implicated in multiple mechanisms in the pathophysiological process. Firstly, an increase in RDW implies impaired red blood cell maturation and a potential inflammatory state in the patient's body, which has a bearing on adverse outcomes.[37-39] By altering erythrocyte homeostasis, compromising iron metabolism, and suppressing erythropoietin synthesis, these inflammatory substances can interfere with erythrocyte maturation and cause hemolytic anemia.[12,40] Secondly, oxidative stress and microcirculation damage play essential roles.[41] Red blood cell survival and homeostasis are strongly influenced by oxidative stress, and when exposed to high inflammatory and oxidative stress environments, changes in red blood cell size may transform into pro-oxidants, further exacerbating oxidative load and reinforcing damage to AD.[42,43] The rise of RDW may lead to the loss of red blood cell deformability and changes in the half-life of red blood cells in circulation, causing high heterogeneity of red blood cell size,[41] which may hinder blood flow through the microcirculation, exacerbate ischemia, affect tissue oxygen transport, and affect the "antioxidant" function of blood vessels.[44] At present, higher RDW levels are proven to influence death and prognosis in AD patients,[13,14] which are considered strong risk factors for predicting survival. Finally, another element that could contribute to increased RDW and unfavorable prognosis is shear stress. A previous study showed that high shear stress can trigger intimal tearing, which can develop into AD.[45] Shear stress can also damage red blood cell deformation and facilitate hemolysis, leading to an elevation in RDW.[46]

The primary determinant of oxygen-carrying capacity is Hb levels, and the majority of CVDs are thought to be caused by alterations in blood flow patterns or viscosity linked to Hb,

as well as decreased oxygen-carrying ability.[47,48] A decline in Hb indicates a great reduction in oxygen delivery to the aorta, and limited tissue oxygenation may contribute to multiple organ dysfunction, influencing increased short-term mortality.[49] A relatively small retrospective study suggested that a drop in Hb in hospitalized patients with acute stroke may be linked with dismal outcomes,[50] while another study on atrial fibrillation confirmed the presence of anemia; even mild anemia (males: 10 ≤ Hb<13g/dL and females: 10 ≤ Hb < 12 g/dL) can be an independent risk factor for hospitalization.[51] An existing study in AD indicated that preoperative Hb levels are tightly linked with all-cause mortality and adverse cardiovascular events, and patients with low Hb levels seem to have a lower likelihood of survival compared to those with higher Hb levels.[16] Furthermore, changes in Hb levels can be influenced by inflammatory reactions in various ways,[52] which can affect the body's red blood cell production, shorten red blood cell survival, and reduce the production of erythropoietin.

The authors' findings are consistent with the increasing evidence of blood biochemical markers in CVD, indicating that HRR is a significant and independent predictor of mortality in AD patients. Its routine availability and low cost can become a practical tool for early risk stratification and prognosis judgment in clinical practice. However, there are certain limitations in the authors' research. Firstly, as a retrospective single-center study, the study failed to illuminate causal linkage or extend the results to participants in other regions. Moreover, acute stress and medications are two examples of missing data that could have an impact on the model but were not analyzed because of MIMIC database restrictions. Notably, the potential outcomes of these variables tend to be biased towards zero, leading to an underestimation of the linkage between HRR and mortality. Finally, since the authors only investigated short-term results and the MIMIC-IV database did not include long-term follow-up events, more studies are necessary to evaluate long-term effects.

CONCLUSION

The authors' results confirmed that HRR is an easily obtainable and cost-effective biomarker that can independently correlate with AD patients' grim prognosis. Integrating HRR into clinical risk models can improve early prognosis and guide management decisions. To clarify the underlying molecular mechanisms and validate the clinical usefulness of HRR, further investigation is necessary.

Ethics Committee Approval: Ethical approval and consent were not required as this study was based on publicly available data.

Peer-review: Externally peer reviewed.

Author Contributions: J.W. and Z.Z. contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Supplementary Table 1. Proportion of missing values

Variables	Proportion
Height	26%
Weight	4.80%
Heart Rate	0.30%
SBP	0.30%
DBP	0.30%
MBP	0.30%
Breath rate	0.30%
Temperature	27.70%
Spo2	0.70%
Anion gap	0.30%
Lactate	35.60%
Potassium	0.30%
PTT	1%
INR	1%
PT	1%
Sodium	0.30%
Po2	30.50%
Pco2	30.50%
pH	30.50%
Base excess	30.50%
ALT	44.50%
ALP	43.50%
AST	43.80%
Bilirubin	44.90%
GCS	0.30%

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO2, percutaneous oxygen saturation; PT, prothrombin time; PTT, partial thromboplastin time; INR, International Normalized Ratio; GCS, Glasgow Coma Score.

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Acute and Long-Term Outcomes After Catheter Ablation of Atrial Tachycardia: Clinical and Electrophysiological Characteristics in the Era of High-Density Mapping

ABSTRACT

Background: Atrial tachycardia (AT) is a commonly encountered rhythm disorder and most patients require catheter ablation. In this study, the aim was to evaluate the outcomes of catheter ablation in patients with symptomatic AT, define acute and long-term outcomes, and determine the clinical and electrophysiological features that affect these outcomes.

Methods: A total of 666 (mean age: 55 ± 16, gender: 344 (51.7%) female) symptomatic patients with AT were enrolled. Activation mapping was performed using 3-dimensional electroanatomical mapping as well as entrainment mapping when needed. Atrial tachyarrhythmia (ATa) recurrence was defined as the presence of atrial fibrillation or AT (≥ 30 seconds) detected by electrocardiogram, Holter, or implantable device interrogation.

Results: Macroreentry was the primary mechanism in right and left atrium (70.2% and 52.8%, respectively). Cavotricuspid isthmus dependent macroreentry was the most frequent mechanism in right ATs, whereas perimitral reentry and roof-dependent macroreentry were the most common mechanisms in left ATs. Acute procedural success was 96.3% after catheter ablation. Freedom from ATa was 72.8% after index procedure and 84.5% after multiple procedures during a mean follow-up of 39 ± 23 months. In multivariable Cox regression analysis, history of atrial fibrillation [HR: 2.43, 95% confidence interval (CI): 1.78-3.30; $P < .001$], previous cardiac surgery (HR: 1.68, 95% CI: 1.22-2.30; $P = .001$) and moderate to severe tricuspid regurgitation (HR: 1.47, 95% CI: 1.08-2.01; $P = .014$) were significant predictors of ATa recurrence.

Conclusion: The findings demonstrated that catheter ablation of tachycardia has a high acute success rate and favorable long-term outcomes in patients with symptomatic AT.

Keywords: Atrial tachycardia, catheter ablation, macroreentry

ORIGINAL INVESTIGATION

INTRODUCTION

Atrial tachycardia (AT) is a commonly encountered rhythm disorder, especially in patients with prior catheter ablation or cardiac surgery.[1,2] As anti-arrhythmic drugs (AADs) are generally ineffective in restoring sinus rhythm, radiofrequency (RF) ablation is the most commonly preferred therapeutic option in patients with symptomatic AT. The role of catheter ablation for maintaining sinus rhythm and relieving symptoms attributable to ATs has long been known; but mapping and ablation can be challenging as the underlying substrate may have complex characteristics.

Although procedural success is high in focal ATs due to its characteristic distribution arising from a single discrete site, reentrant ATs exhibit less favorable outcomes mostly related to the underlying atrial substrate.[3-5] Previous studies have provided detailed descriptions of the mechanisms and outcomes of catheter ablation, but studies evaluating the outcomes of AT mostly include specific types of tachycardia or patients with specific characteristics, such as a history of atrial fibrillation (AF) ablation or cardiac surgery.[6-10] In this study, the aim was to

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present a single-center experience regarding the acute and long-term success of catheter ablation of AT in a variety of patients with different atrial substrate characteristics using high-density mapping as well as clinical and electrophysiological characteristics predicting AT recurrence.

METHODS

Study Population

A total of 666 symptomatic patients with documented AT episodes who underwent catheter ablation between April 2014 and October 2022 were retrospectively enrolled. Atrial tachycardia was used to define organized atrial arrhythmias including focal AT, typical atrial flutter, atypical flutter, macroreentrant tachycardias, and localized reentrant tachycardias documented either by 12-lead ECG, 24-hour Holter monitoring, or intracardiac device interrogation. Baseline demographics and data about prior medical history were obtained from patients' files or electronic database of the hospital records. The study was approved by the Local Ethics Committee.

Preprocedural Management

Transthoracic echocardiography was performed in all patients prior to the ablation procedure. Transesophageal echocardiography was performed to rule out the presence of intracardiac thrombus when transseptal puncture for left AT or concomitant AF ablation was planned. Preprocedural computed tomography scan was performed, when clinically indicated, for the evaluation of left atrium (LA) and pulmonary vein (PV) anatomy and structural heart disease. Cardiac magnetic resonance imaging was also performed in selected cases.

All procedures were performed with uninterrupted oral anticoagulation with warfarin if international normalized ratio (INR) was <2.5, bridging with low molecular weight heparin (LMWH) was done when INR value was <2 on admission and LMWH was skipped on the day of the procedure. Direct oral anticoagulants were discontinued 24 hours before the procedure. All AADs were ceased 5 half-lives before the procedure except amiodarone.

Electrophysiological Study

All procedures were performed under either conscious sedation or general anesthesia. After femoral/subclavian vein punctures, a 6 Fr steerable diagnostic catheter was placed into the coronary sinus (Cs) as a reference.

All patients who were in sinus rhythm at the beginning of the procedure underwent a routine electrophysiology study. In patients who underwent catheter ablation with 3D mapping systems (CARTO, Biosense Webster or Ensite Precision/Ensite X; Abbott), voltage mapping and in some patients, isochronal late activation mapping was created. Multipolar mapping catheters [(Advisor Circular or Advisor HD Grid, Abbott), (Lasso or Pentaray, Biosense Webster)] were used for mapping, and an irrigated tip RF ablation catheter (SmartTouch, Thermocool, Biosense Webster or FlexAbility, TactiCath, Abbott) was used for ablation.

Activation Mapping

Activation mapping was done by using an atrial reference from Cs catheter and window of interest was set in order to identify critical isthmus (CI) / focus of AT, as described previously.[11] The right atrium (RA) was mapped initially when AT with a concentric Cs activation pattern was detected. Direct LA mapping was preferred in case of non-concentric Cs activation. After completion of the electroanatomical map the wavefront propagation, activation patterns, areas of slow conduction, anatomical and functional barriers and lines of the block were analyzed.[12] If left AT was detected, transseptal puncture was performed by modified Brockenbrough technique under fluoroscopic guidance. Afterwards transseptal sheath was replaced with steerable sheath (Agilis; Abbott). Unfractionated heparin boluses were administered to maintain the activated clotting time of 300-350 seconds, after LA access was obtained.

The mechanism of tachycardia was primarily determined by activation mapping data, and entrainment mapping was performed at the operator's discretion to prevent a change in the baseline AT or degeneration into another rhythm (Figure 1). Macroreentry was defined as a continuous activation sequence covering >90% of the tachycardia cycle length (TCL) with a circular type of activation pattern around a central obstacle involving >2 separate atrial segments that can be entrained in the circuit, as described elsewhere.[13] Localized reentry was defined in the case of continuous or fragmented potentials spanning approximately 50% of the TCL around a diameter of <2 cm.[14] Centrifugal activation from a distinct focal source with presystolic potentials was considered as true focal AT.[3] Critical isthmus of the reentrant ATs was defined as the narrowest pathway between scars

HIGHLIGHTS

- Catheter ablation has a high acute success rate (96.3%) and favorable long-term outcomes in patients with symptomatic atrial tachycardias (ATs).
- Reentrant ATs are associated with less favorable outcomes compared to focal ATs.
- Macroreentry is the predominant mechanism of both right- and left-sided ATs, and tachycardia mechanisms do not differ significantly between patients with or without prior ablation history.
- Cavotricuspid isthmus–dependent atrial flutter is the most common type of ATs, followed by perimitral left atrial flutter.

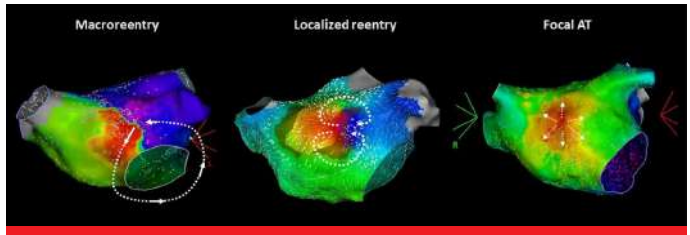

Figure 1. Mechanisms of atrial tachycardias based on activation mapping with 3D mapping systems.

and/or anatomical obstacles that had the slowest conduction based on propagation map analysis.

If the AT was not present in the beginning of the procedure, burst pacing or programmed stimulation was performed from the high right atrium, proximal and distal coronary sinus with/without intravenous isoproterenol infusion (at graded dosages from 1 to 4 μg/min, until AT developed).

Ablation Approach

Ablation strategy was primarily determined by the mechanism of AT. Radiofrequency ablation was performed using an irrigated tip contact force enabled ablation catheter with an energy setting of 25-40 W (contact force between 10 and 20 g, temperature limit <42°C, duration 20-60 seconds). These parameters were adjusted according to atrial wall thickness and the proximity to critical anatomical structures to optimize procedural safety and efficacy. A high-power short-duration ablation protocol was applied using power settings of 40-50 W delivered over short durations of 5-10 seconds in selected cases based on the operator's discretion. In focal ATs, ablation at the origin of AT was attempted. In the case of localized reentry, abnormal potentials at the isthmus of AT were completely ablated. Linear lesions aiming to connect the tachycardia isthmus with anatomical barriers or dense scar areas were attempted in the case of macroreentrant tachycardia. Phrenic nerve stimulation was performed using an ablation catheter and capture sites were tagged on the atrial wall if the ablation target is in the RA lateral wall in order to prevent phrenic nerve injury.

Procedural success was defined as termination of AT or change in reentrant circuit during RF ablation. Non-inducibility of tachycardia and abolition of abnormal electrograms were considered as procedural primary endpoints. Bidirectional block was confirmed after completion of linear lines using activation mapping and differential pacing from both sides of the ablation line, verifying absence of conduction across the ablation line in both directions. In focal or microreentrant tachycardias where linear lesions were not performed, arrhythmia termination and non-inducibility were considered procedural endpoints. Entrance and exit block in PVs were checked if concomitant or prior PV isolation was done. After ablation, non-inducibility was tested by programmed atrial stimulation with/without isoproterenol infusion in all cases. Additionally, in patients with failed endocardial ablation, epicardial mapping and ablation was performed via percutaneous subxiphoid puncture under fluoroscopic guidance.

Postprocedural Care and Follow-Up

All patients were monitored at the coronary care unit for at least 24 hours after ablation. Oral anticoagulation was started 6 hours after the procedure. Routine follow-up visits were scheduled at 1, 3, and 12 months, and every 12 months thereafter or earlier if patients had symptoms consistent with recurrence or procedure-related complications. Atrial tachyarrhythmia (ATa) was defined as the detection of AF or AT (≥30 seconds) detected by ECG, Holter, or implantable device interrogation. A 24-hour Holter monitoring was scheduled at the thirrd and 12th month after the procedure and yearly thereafter or if the patient has complaints compatible with AT. Patients remained on the AAD regimen that was prescribed before the ablation in the first 3 months after ablation, and continuation of AADs was at the discretion of the attending physician's decision.

Statistical Analysis

All statistical analysis was performed using SPSS Statistical software version 22.0. Descriptive and categorical variables were presented as counts and percentages. Normal distribution assumption was examined with detrended Q–Q plot and Kolmogorov–Smirnov test. The continuous data with normal distribution were expressed as mean ± SD and data without normal distribution were expressed as median and interquartile range. Comparisons between variables were performed by the Mann–Whitney *U*-test and independent Student's *t*-test where appropriate. To find significant predictors of ATa recurrence, Cox proportional hazard model was conducted. The Kaplan–Meier analysis was used to demonstrate freedom from ATa recurrence during the follow-up period, and the log-rank test was applied to compare recurrence-free survival across the groups. For pairwise comparisons between groups, post-hoc log-rank tests with Bonferroni correction were performed when appropriate. A 2-tailed *P* value <.05 was considered to indicate statistical significance.

RESULTS

Baseline Characteristics

A total of 666 patients [mean age: 55 ± 16; gender: 344 female (51.7%)] who underwent catheter ablation for AT were analyzed in this retrospective study. Among the study population, 478 patients [mean age: 56 ± 16; gender: 238 female (49.8%)] had no history of AF/AT ablation.

Prior catheter or surgical ablation history for AT/AF was present in 188 (28.2%) patients [mean age: 54 ± 14; gender: 106 female (56.4%)] and they underwent a redo ablation procedure in the hospital. The mean number of previous catheter ablation procedures was 0.6 ± 0.9. Among the whole study group, 219 (32.9%) patients had history of cardiac surgery [80 (12%) mitral valve replacement, 28 (4.2%) tricuspid valve surgery, 23 (3.5%) aortic valve replacement, 64 (9.6%) coronary artery bypass surgery, 44 (6.6%) atrial septal defect (ASD)/ventricular septal defect (VSD) closure, 15 (2.3%) other cardiac surgeries] and 40 (6%) of them had previous surgery for congenital heart disease. The mean LA diameter was 40.1 ± 7.2 mm and the median value of left ventricular ejection fraction (LVEF) was 60%. The baseline demographic and clinical characteristics of the study population are represented in Table 1.

Procedural Characteristics

A total of 780 procedures were performed in the whole study population. 750 (96.1%) of them were performed with 3D-electroanatomic mapping systems and in the remaining 30 procedures, AT was mapped conventionally. In 683 (87.6%) procedures, only 1 AT was recorded, whereas in the remaining 97 (12.4%) procedures, >1 ATs were documented.

Table 1. Baseline Characteristics of the Study Population (n = 666)

Age, years	55 ± 16
Gender, female, n (%)	344 (51.7)
Cardiovascular risk factors, n (%)	
Coronary artery disease	121 (18.2)
Hypertension	310 (46.5)
Diabetes mellitus	147 (22.1)
Chronic kidney disease	38 (5.7)
CHADS2-VASC2, 25th-75th percentile	2.00 (1.00-3.00)
AADs before ablation, n (%)	203 (30.4)
Echocardiographic parameters	
LA diameter, mm	40.1 ± 7.2
LVEDD, mm, 25th-75th percentile	47.0 (44-51)
Moderate to severe mitral regurgitation, n (%)	218 (32.7)
Moderate to severe tricuspid regurgitation, n (%)	284 (42.6)
LV EF, %, 25th-75th percentile	60 (50-61)
sPAP, mm Hg, 25th-75th percentile	35 (28-40)
BNP, pg/mL, 25th-75th percentile	119.5 (49.5-258.3)
History of AF, n (%)	269 (40.4)
Cardiac implantable electronic device, n (%) ICD PM CRT-D	45 (6.8) 23 (3.5) 10 (1.5)
Structural heart disease, n (%)	133 (19.9)
Previous AT/AF catheter ablation, n (%)	
Catheter ablation for AT/AF	199 (29.9)
AT Ablation	73 (11)
PVI	108 (16.2)
RF ablation	51 (7.6)
Cryoballoon	74 (11.1)
Surgical AF ablation	18 (2.7)
Cryoballoon	13 (1.9)
RF ablation	5 (0.7)
Cardiac surgery, n (%)	219 (32.9)

AADs, anti-arrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; BNP, B-type natriuretic peptide; CRT; cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; LA, left atrium; LV EDD, left ventricular end-diastolic diameter; LV EF, left ventricular ejection fraction; PM, pacemaker; PVI, pulmonary vein isolation; RF, radiofrequency; sPAP, systolic pulmonary artery pressure.

Among all procedures, 241 (30.9%) were only left ATs and 503 (64.4%) were only right ATs; whereas in 34 (4.4%) procedures both right and left ATs were detected. In 2 (0.3%) procedures, biatrial AT was detected. Patients presented to the procedure with an initial rhythm of AT (43.5%), sinus rhythm (52.1%), AF (4%), junctional rhythm (0.3%) or pacemaker rhythm (0.1%). Mean total procedure time and fluoroscopy time were 146.1 ± 49.8 minutes and 26.8 ± 14.3 minutes, respectively.

In 751 (96.3%) procedures, AT was terminated during catheter ablation, whereas ATs could not be terminated despite the prolongation in TCL in 14 patients (1.8%). In 15 (1.9%) patients, AT was degenerated into AF. In 431/780 (55.3%) procedures, only RA mapping was performed; whereas in 154/780 (19.7%) procedures, only left-sided mapping was performed. In 195/780 (25%) procedures, both right and LA were mapped. Detailed procedural characteristics are shown in Table 2.

Table 2. Procedural Characteristics of the Study Population (n = 780)

Procedure Time, minutes	146.1 ± 49.8
Flouroscopy Time, minutes	26.8 ± 14.3
Radiation dose, mGy, median, 25th-75th percentile	647.3 (320-1099.5)
Total ablation time, min, 25th-75th percentile	19.7 (12-37.7)
Median number of mapped points RA LA	 801 (338-1834) 1701 (804-4608)
Mapping atrium, n (%) RA LA RA & LA	431 (55.3) 154 (19.7) 195 (25)
Type of anesthesia during catheter ablation, n (%) General anesthesia Conscious sedation	268 (34.4) 512 (65.6)
Rhythm at the beginning of catheter ablation, n (%) AT Sinus rhythm AF Junctional rhythm Pacemaker stimulation	339 (43.5) 407 (52.1) 31 (4) 2 (0.3) 1 (0.1)
TCL of ATs, 25th-75th percentile	270 (230-335)
Acute procedural success, n (%)	96.3
Entrainment mapping, n (%)	87 (11.2)
Number of AT per procedure, n (%) 1 AT >1 AT	683 (87.6) 97 (12.4)

AF, atrial fibrillation; AT, atrial tachycardia; LA, left atrium; RA, right atrium; TCL, tachycardia cycle length.

Arrhythmia Mechanisms

The most common mechanism of AT was macroreentry in RA and LA (70.2% and 52.8%, respectively) (Figure 2). Among these, CTI-dependent macroreentry was the most frequent mechanism (58%) in right ATs, whereas perimitral reentry (29%) and roof-dependent macroreentry (16%) were the most common mechanisms in left ATs (Supplementary Figure 1).

Patients with Index Procedure

In 478 patients without a history of AF/AT ablation, 87 (18.2%) were only left ATs and 377 (78.9%) were only right ATs; whereas in 14 (2.9%) procedures both right and left ATs were detected. Macroreentry was found to be the most common mechanism for right and left ATs (67.7% and 45.4%, respectively). Cavotricuspid isthmus–dependent macroreentry was the most frequent mechanism (229/252) in right atrial macroreentrant ATs, whereas perimitral reentry (29/49) and roof-dependent macroreentry (12/49) were the most common mechanisms in left atrial macroreentrant ATs.

A total of 51 localized reentrant ATs were detected, 39 (76.4%) of them were located in the LA and anterior wall (20/39) was the most common site of ATs. Among all, 12/51 of them were detected in the right atrium and lateral wall (11/12) was the most common site for localized reentries in the right atrium.

A total of 147 focal ATs were detected and 120 (81.6%) of them originated from right atrium. Crista terminalis (63/120) and PVs (16/27) were the most common origins for focal ATs in right and LA, respectively. Dual loop reentry was detected in 6.1% (25/409) and 4.9% (6/121) of the ATs in right and LA, respectively.

Patients with Previous Ablation

In 188 patients with history of AF/AT ablation, 93 (49.5%) were only left ATs and 83 (44.1%) were only right ATs; whereas in 12 (6.4%) procedures both right and left ATs were detected. The most common mechanism of AT was macroreentry in right and LA (62.2% and 48.8%, respectively). Cavotricuspid isthmus–dependent macroreentry was the most frequent mechanism (54/66) in right atrial macroreentrant ATs, and perimitral reentry (35/61) and roof-dependent macroreentry (20/61) were the most common mechanisms in left atrial macroreentrant ATs.

Localized reentrant ATs were detected in 49 patients and 42 (85.7%) of them were located in the LA and anterior wall (13/42) and posterior wall (12/42) were the most common sites.

Focal ATs were detected in 43 patients and 28 (65.1%) of them originated from right atrium. Crista terminalis (8/28), tricuspid anulus (6/28) and PVs (9/15) were the most common origins for focal ATs in right and LA, respectively. Dual loop reentry was detected in 4.7% (5/106) and 5.6% (7/125) of the ATs in right and LA, respectively.

Follow-Up and Predictors of Recurrence

During the mean follow-up duration of 39 ± 23 months, freedom from ATa after index procedure was 82.3%, 75.9%, and 71.7% at 12, 24, and 36 months, respectively, and after multiple procedures, 84.5% of patients were free from ATa recurrence on/off AADs (Supplementary Figure 2).

In patients with index procedure, freedom from ATa was 83.2%, 76.4%, and 72.7% at 12, 24, and 36 months, respectively. In patients with history of previous ablation, freedom

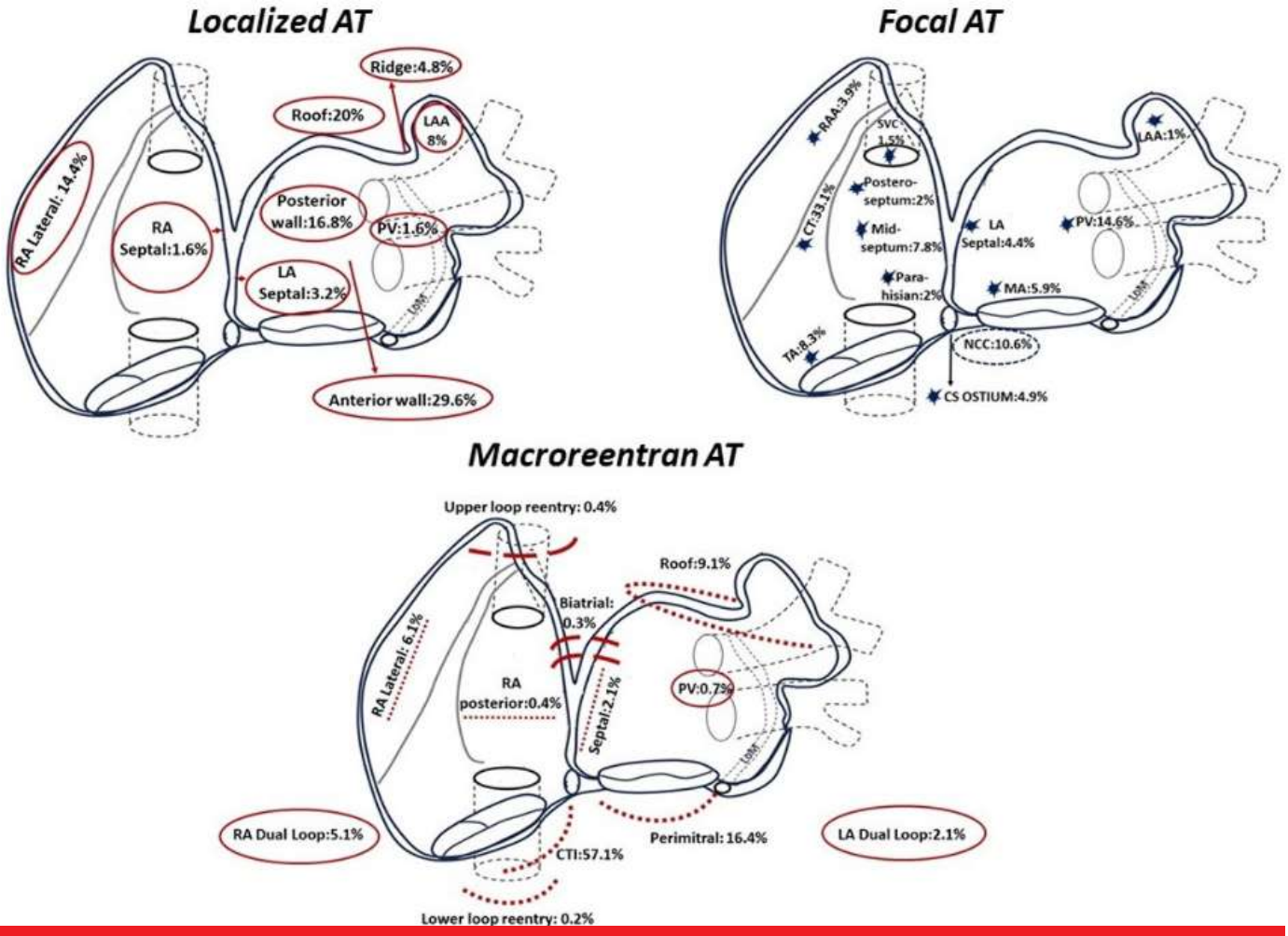

Figure 2. The distribution of atrial tachycardia types in both atria.

from ATa was 79.9%, 74.9%, and 69.3% at 12, 24, and 36 months, respectively ($P = .35$).

Patients with ATa recurrence had higher prevalence of a history of AF (55.8% vs. 34.6%, $P < .001$) or cardiac surgery (44.2% vs. 28.7%, $P < .001$) and had a significantly larger LA diameter (41.0 vs. 39.6 mm, $P = .039$) and greater baseline BNP level (150.2 vs. 105.2 pg/mL, $P < .001$) than those without recurrence (Supplementary Table 1).

Among the whole study group, 231 (34.6%) patients were on AADs for the first 3 months after ablation. In 165 (24.7%) of them, AADs were given beyond 3 months and in 58/165 of them, AADs were either escalated or switched to another AAD because of the side effects or ATa recurrence during the follow-up.

During long-term follow-up of 39 ± 23 months, 68.5%, 74.6%, and 83.6% patients were free from ATa recurrence after index procedure for macroreentrant, localized reentrant and focal ATs, respectively ($P = .001$) (Figure 3).

Univariate Cox regression analysis showed that history of cardiac surgery [HR 1.75, 95% confidence interval (CI) 1.30-2.35; $P < .001$], LA diameter (HR 1.02, 95% CI 1.00-1.04; $P = .009$), systolic pulmonary artery pressure (HR 1.02, 95% CI 1.01-1.03; $P < .001$), severity of mitral regurgitation (HR 1.20, 95% CI 0.88-1.63; $P = .24$), tricuspid regurgitation (HR 1.74, 95% CI 1.29-2.35; $P < .001$), history of previous LA ablation (HR 1.42, 95% CI 1.05-1.91; $P = .020$) and history of AF (HR 2.26, 95% CI 1. 68-3.04; $P < .001$) were associated with ATa recurrence. In multivariable Cox regression analysis, history of AF (HR 2.43, 95% CI 1.78-3.30; $P < .001$), previous cardiac surgery (HR 1.68, 95% CI 1.22-2.30; $P = .001$) and moderate to severe tricuspid regurgitation (HR 1.47, 95% CI 1.08-2.01; $P = .014$) were significant predictors of ATa recurrence; history of AF (HR 2.43, 95% CI 1.78-3.30; $P < .001$), history of cardiac surgery (HR 1.68, 95% CI 1.22-2.30; $P = .001$) and moderate to severe tricuspid regurgitation (HR 1.47, 95% CI 1.08-2.01; $P = .014$) were significant predictors of ATa recurrence.

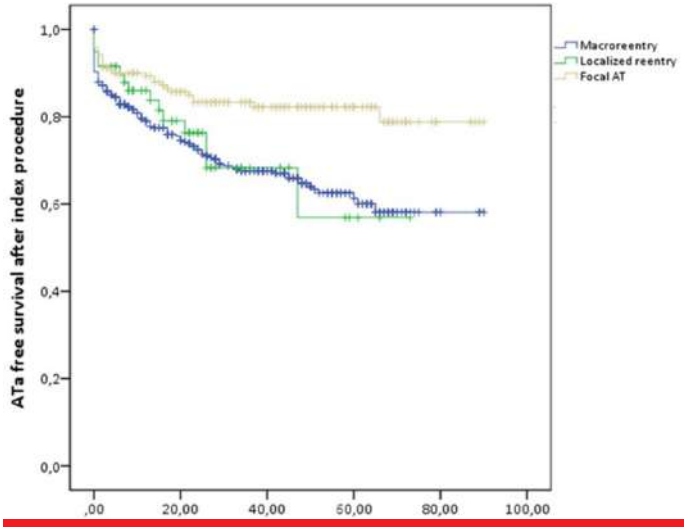

Figure 3. Freedom from atrial tachyarrhythmia after index procedure for macroreentrant, localized reentrant and focal atrial tachycardias during the mean follow-up of 39 ± 23 months.

In patients with index procedure, history of AF (HR 2.69, 95% CI 1.86-3.88; $P < .001$), history of cardiac surgery (HR 1.56, 95% CI 1.06-2.29; $P = .022$) and moderate to severe tricuspid regurgitation (HR 1.73, 95% CI 1.17-2.54; $P = .005$) were significant predictors of ATa recurrence. In patients with previous ablation, history of AF (HR 2.21, 95% CI 1.11-4.40; $P = .024$) and history of cardiac surgery (HR 1.78, 95% CI 1.02-3.10; $P = .040$) were found to be significant predictors of ATa recurrence in multivariable Cox regression analysis, history of AF (HR 2.43, 95% CI 1.78-3.30; $P < .001$), previous cardiac surgery (HR 1.68, 95% CI 1.22-2.30; $P = .001$) and moderate to severe tricuspid regurgitation (HR 1.47, 95% CI 1.08-2.01; $P = .014$) were significant predictors of ATa recurrence.

Complications

A total of 59 (7.5%) complications were observed in 780 procedures. Vascular access complications (femoral pseudoaneurysm/fistula) were the most common complications seen in 20 procedures and endovascular/surgical treatment was required in 3/20 patients. In 18 procedures, pericardial effusion was observed; only 4/18 of them necessitated pericardiocentesis. In 4 procedures, splines of the PentaRay mapping catheter were entrapped in the mechanical mitral valve prosthesis, which were freed by sheath and catheter maneuvers. Periprocedural prosthetic valve dysfunction was not observed in these patients. The details of procedural complications are given in Supplementary Table 2.

Redo Procedures

Patients with Index Procedure

In the group of 127 (26.6%) patients with recurrence, presenting rhythm was AT in 81 (63.7%) of them, whereas 45 (35.4%) patients had AF and 1 (0.9%) patient had supraventricular tachycardia (SVT). In patients with ATa recurrence, index procedure was performed in RA and LA in 6/14 (42.9%) patients, RA in 93/376 (24.8%) patients and LA in 28/87 patients (32.3%) ($P = .07$).

Repeat ablation was performed in 66 patients (58 for AT and 8 for AF). Recurrences were from previous ablation site in 33% of patients with focal AT, 41.3% of patients with macroreentrant AT, and 50% of patients with localized reentrant AT.

In 87 patients who underwent catheter ablation for left ATs in the index procedure, 28 patients (24.7%) had ATa recurrence (8 of them AF, 20 of them AT). One patient was referred for redo ablation in patients with AF recurrence. In 20 patients with AT recurrence, 14/20 patients underwent a redo ablation procedure. In 10/14 patients, recurrences were left AT, and right and left AT in 3/17 patients. In 1 patient, the recurrence AT was biatrial AT.

For patients who underwent catheter ablation for right AT in the index procedure, 93/376 patients (24.7%) had ATa recurrence (37 of them AF, 55 of them AT, 1 of them SVT). In patients with AF recurrence, 7/37 patients underwent AF ablation and 1 patient, atrioventricular (AV) node ablation

was performed. Among patients with AT recurrence, 40/55 of them underwent redo ablation procedures. In 10/40 patients, recurrences were left AT and in 30/40 patients, right AT was detected in the subsequent ablation procedure.

In 14 patients who underwent catheter ablation for right and left AT in the index procedure, 6 patients (42.9%) had AT recurrence. In 5/6 patients, left AT ablation and in 1 patient, DCCV was performed.

Patients with Previous Ablation

A total of 54 (28.7%) patients had ATa recurrence and presenting rhythm was AT in 44 (81.5%) of them, whereas 9 (16.7%) patients had AF and 1 (1.8%) patient had SVT. In patients with ATa recurrence, index procedure was performed in RA and LA in 4/12 (33.3%) patients, RA in 27/83 (32.5%) patients and LA in 23/93 patients (24.7%) (P = .65).

Repeat ablation was performed in 37 patients (33 for AT and 4 for AF). Recurrences were from previous ablation site in 50% of patients with focal AT, 40.9% of patients with macroreentrant AT, and 40% of patients with localized reentrant AT.

Of the 93 patients who underwent catheter ablation for left ATs in the index procedure, 23 (24.7%) had ATa recurrence (3 of them AF, 20 of them AT). Atrial fibrillation ablation procedure was performed in 1 patient with AF recurrence and AV node ablation in 1 patient. Redo ablation procedure was performed in 17/20 of patients with AT recurrence and AV node ablation was performed in 2 patients. Recurrences were left AT in 16/17 patients and right AT in 1/17 patient.

Among 83 patients who underwent catheter ablation for right AT in the index procedure, 27 patients (32.5%) had ATa recurrence (6 of them AF, 20 of them AT, 1 of them SVT). In patients with AF recurrence, AF ablation was performed in 3/6 patients. A redo ablation procedure was performed in 14/20 patients with AT recurrence. Recurrence was left AT in 5/14 patients, whereas in 9/14 patients, right AT was detected in the subsequent ablation procedure.

Four patients (4/12) had ATa recurrence after catheter ablation for right and left AT in the index procedure and, in 3/4 patients, left AT ablation and in 1 patient, AV node ablation was performed.

DISCUSSION

The main findings of this study were as follows: i) Catheter ablation has a high acute success rate (96.3%) and favorable long-term outcomes in patients with symptomatic ATs, ii) Reentrant ATs had less favorable outcomes compared to the patients with focal ATs, iii) Macroreentry is the major mechanism for right- and left-sided ATs. Tachycardia mechanisms did not differ between patients with or without a history of prior ablation. Cavotricuspid isthmus–dependent atrial flutter is the most common type of tachycardia followed by perimitral and roof-dependent left atrial flutter and localized reentrant ATs were predominantly determined in the left atrial anterior wall in both groups.

These findings revealed that the right atrium was the predominant origin for focal ATs with an acute procedural success rate of 99% and a low recurrence rate (16.6%) during the long-term follow-up. Moreover, anatomical sites hosting focal ATs were consistent with previous studies, where 74.1% of ATs originated from right atrium and right-sided focal ATs predominantly originated from the crista terminalis (33.1%), parahisian region-noncoronary cusp (12.6%), tricuspid annulus (8.3%), and coronary sinus ostium (4.9%). On the other hand, left-sided focal ATs mainly originated from the PVs (14.6%) and mitral annulus (5.9%). In the era of conventional mapping, the right atrium origin was found to be the only significant predictor of successful radiofrequency catheter ablation.[15] However, these findings revealed an acute procedural success of 99% for focal ATs, which did not differ between both atria. Overall freedom from ATs was 81.1% and 84.3% for left and right focal ATs during the long-term follow-up, respectively. These findings were also in line with a previous study by Whitaker and colleagues,[16] which demonstrated no statistically significant difference in recurrence rates according to the location of origin for focal ATs.

The number of studies evaluating the outcomes of catheter ablation for localized reentrant ATs in the literature is limited and data were derived from small-scale studies or subgroup analyses of patients with left/right atrial reentrant tachycardias. Almost all of the studies evaluating electrophysiological characteristics and follow-up results of catheter ablation of left atrial localized reentries included patients with history of AF ablation. In a previous study including 70 patients undergoing catheter ablation of long-lasting persistent AF, in 9 of them localized reentry was demonstrated in a repeat ablation and at 11 ± 7 months after the procedure, 8 of 9 patients (89%) were free from any arrhythmias.[17] Previously, Ju et al[18] reported that freedom from ATa was 90.9% for 11 patients with localized reentrant AT recurrence after AF ablation. An important limitation of the above-mentioned studies was having a very small sample size. On the other hand, this study includes one of the highest number of patients in the literature with an ATa freedom rate of 86% at 12 months and 76.3% at 24 months after the index procedure. Although most of the patients with localized reentry had a previous history of ATa ablation or surgery, in 18 patients de novo localized reentrant ATs were observed. Characteristics of de novo localized reentries have not yet been well defined, but recent studies provided some data about underlying pathogenesis, distribution, and ablation outcomes.[19-21] Yet, Zaidi et al[22] reported a study with 62 patients and among 85 de novo atypical flutters, contrary to previous studies, most of the tachycardias (50% of left ATs and 70% of right ATs) were localized reentries. One of the notable findings of this study is that despite high recurrence rates (66%), recurrent ATs predominantly originated from discrete sites of the atrium compared to the index ablation procedure. Therefore, high ATa/AF recurrence is attributed mainly to the progression of already existing atrial myopathy. These functional properties of the atrial substrate may play a role in the development of atrial tachyarrhythmias as well as future recurrences.

Cavotricuspid isthmus–dependent macroreentry is the primary mechanism of right-sided macroreentry; however, non-CTI-dependent ATs are also frequent and catheter ablation

had high success rates in previous studies.[23-25] In a meta-analysis including 10 719 patients, Perez et al[26] reported that freedom from ATa was 89% after CTI-dependent AT ablation during a mean follow-up of 13.8 ± 0.3 months. These findings also revealed favorable outcomes after CTI-dependent AT ablation as well as non-CTI-dependent macroreentry in the right atrium. Studies evaluating the outcomes of left atrial reentrant tachycardias mostly include patients with AT recurrence after AF ablation and perimitral and roof-dependent macroreentry are the most commonly reported mechanisms with the ratio of 4%-20%.[27] Previous studies reported that catheter ablation had an 85%-91% acute success rate and freedom from ATa was 73%-97% in long-term follow-up.[28-30] Similar to these studies, the current study's findings demonstrated freedom from ATa of 79.6% and 73.2% after the index procedure at 12th and 24th months for macroreentrant tachycardias, respectively. Recurrences were reported to be predominantly from the reconnections from prior lesions for reentrant tachycardias in previous studies.[31] Similar to these findings, in 57 patients that underwent redo ablation procedure, ATs originated from the previous ablation sites in half of the patients, whereas different tachycardia circuits were documented in the other half. These findings underscore the importance of contiguous and durable linear lesion formation to prevent future recurrences. Furthermore, new ATs originating different from index sites were not uncommon, highlighting the role of substrate progression in such patient groups despite high acute procedural success.

The large-scale single-center experience regarding AT ablation outcomes has several strengths. To the authors' knowledge, this is one of the highest volume studies presenting clinical and electrophysiological findings and overall long-term outcomes for all types of AT. These results demonstrated that focal ATs had better long-term results compared to reentrant tachycardias, and there was no statistically significant difference between recurrence rates for right- and left-sided ATs. In addition, the findings demonstrated the long-term success rate even in the case of extensive atrial remodeling or after multiple ablation procedures, which may be due to more extensive ablation. Moreover, the study findings revealed no difference in terms of AT mechanisms and outcomes in patients with or without prior ablation history. Furthermore, extensive use of high-resolution multipolar mapping catheters and contact-forced RF ablation catheters enabled accurate identification of the origin of focal ATs or CI sites of reentrant circuits, as well as areas of low voltage and slow conduction.

Study Limitations

Our study had several limitations. Firstly, this was a retrospective analysis of a single-center experience. Secondly, this center is a referral center which may limit the generalizability of these findings in routine clinical practice in terms of patient sample. Thirdly, at least one-third of the patients had history of catheter/surgical ablation or cardiac surgery, which may mitigate the generalizability of these findings to the entire patient population. Finally, the tachycardia mechanism was primarily determined based on activation mapping, and entrainment mapping was not systematically performed to confirm critical sites for reentry in all patients to prevent degeneration into another AT or AF or termination of tachycardia.

CONCLUSION

This study characterized the clinical and electrophysiological features and long-term ablation outcomes of different types and mechanisms of AT. These findings indicated that catheter ablation is an effective therapeutic option with a high acute procedural success rate and favorable long-term results, especially in focal AT patients, whereas there are moderate long-term outcomes in reentrant ATs.

Ethics Committee Approval: Hacettepe University Noninterventional Clinical Research Ethics Committee (Date: November 29, 2022; No.: 2022/20-05).

Informed Consent: Due to the retrospective nature of the study, written informed consent from patients was unattainable.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.Y., K.A.; Design – G.S.K., H.Y.; Supervision – H.Y., K.A.; Resources – G.S.K., C.Ç.; Materials – G.S.K., C.Ç.; Data Collection and/or Processing – G.S.K.; Analysis and/or Interpretation – G.S.K. C.Ç.; Literature Search – G.S.K., H.Y.; Writing –G.S.K.; Critical Review – K.A., H.Y.

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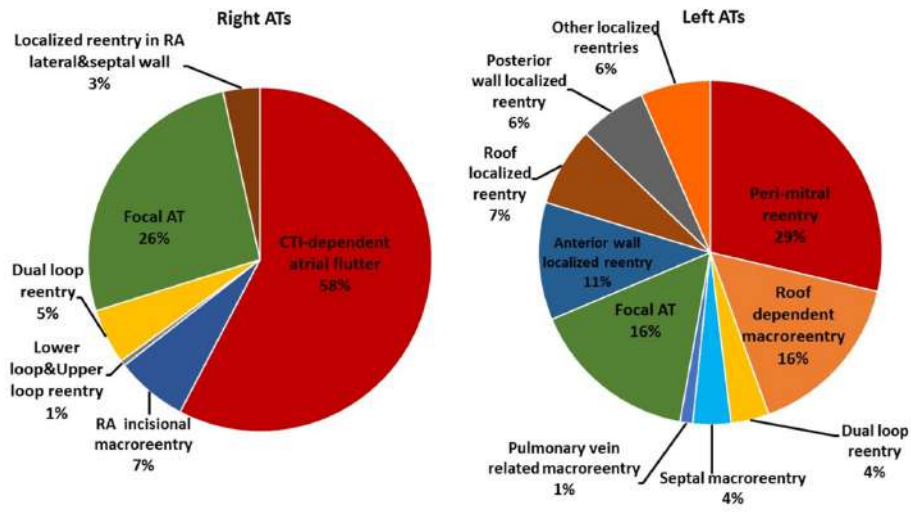
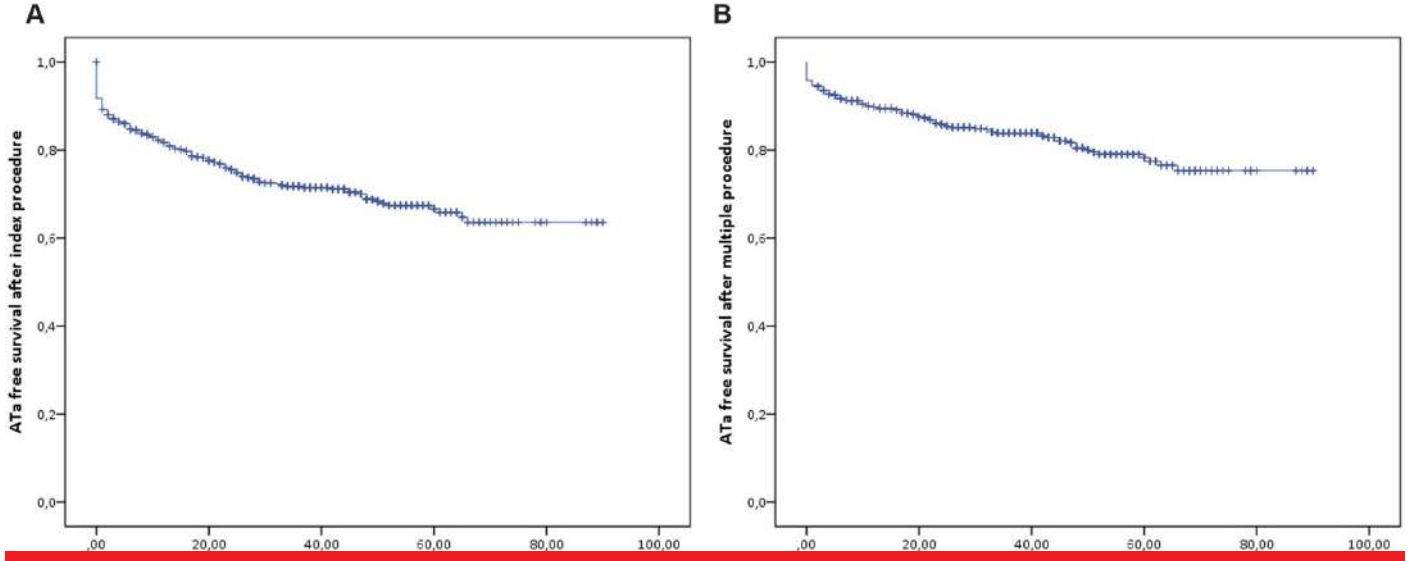


Supplementary Figure 1. The characteristics of AT mechanisms for right & left ATs.



Supplementary Figure 2. Freedom from ATa after index and multiple procedure during the mean follow-up of 39 ± 23 months.

Supplementary Table 1. Baseline characteristics of patients with or without ATa recurrence

	Patients with ATa recurrence (n=181)	Patients without ATa recurrence (n=485)	*P*
Age, years	54 ± 16	55 ± 15	0.147
Gender, female, n (%)	99 (54.7%)	245 (50.5%)	0.33
Cardiovascular Risk Factors, n (%);			
Coronary artery disease	32 (17.7%)	89 (18.4%)	0.84
Hypertension	79 (43.6%)	231 (47.6%)	0.35
Diabetes mellitus	31(17.1%)	116 (23.9%)	0.06
Chronic kidney disease	12 (6.6%)	26 (5.4%)	0.53
CHADS2-VASC2, 25th-75th percentile	2.00 (1.00-3.00)	2.00 (1.00-3.00)	0.95
Echocardiographic parameters;			
LA diameter, mm	41 ± 7.7	39.6 ± 7.04	0.039***
LVEDD, mm	48.2± 6.6	47.9 ± 6.05	0.702
LV EF, %	54.4%±11.2%	55.0% ± 11.4%	0.51
sPAP, mm Hg, 25th-75th percentile	38.8±13.6	34.9 ± 10.2	<0.001***
Mitral regurgitation			
Mild	65%	67.1%	0.61
Moderate to severe	35%	31.9%	
Tricuspid regurgitation			
Mild	46%	59.4%	0.002***
Moderate to severe	54%	40.6%	
AF, n (%)	101 (55.8%)	168 (34.6%)	<0.001***
BNP, pg/ml, 25th-75th percentile	150.2 (82.4-357.3)	105.2 (45.5-222.1)	<0.001***
Index procedure, n	127 (70.2%)	351 (72.4%)	
Redo procedure, n	54 (29.8%)	134 (27.6%)	
History of cardiac surgery, n	80 (44.2%)	139 (28.7%)	<0.001***
History of catheter ablation, n	51 (28.2%)	148 (30.5%)	0.55
History of surgical ablation, n	8 (4.4%)	10 (2.1%)	0.09***

AF, atrial fibrillation; ATa, atrial tachyarrhytmia; LA, left atrium; LV EDD, left ventricular end-diastolic diameter; LV EF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure.

Supplementary Table 2. Major and minor complications after AT ablation

Major Complications	14 (1.8%)
Tamponade	4 (0.5%)
Major vascular injury	2 (0.2%)
Hemorragic/thromboembolic cerebrovascular event	3 (0.3%)
PTE/DVT	3 (0.3%)
High grade AV block	2 (0.2%)
Minor Complications	45 (5.7%)
Vascular access complications	20 (2.5%)
Minor Pericardial effusion	13 (1.6%)
Diaphragm paralysis	2 (0.2%)
Pneumotorax	1 (0.1%)
Acute pulmonary edema	1 (0.1%)
Coronary spasm	2 (0.2%)
GI bleeding	2 (0.2%)
Mapping catheter entrapping in mechanical mitral valve prosthesis	4 (0.5%)

AV, atrioventricular; DVT, deep vein thrombosis; GI, gastrointestinal; PTE, pulmonary thromboembolism.

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Triglyceride-Glucose Index and the Risk of Calcific Aortic Valve Stenosis: A Bidirectional Mendelian Randomization Study

ABSTRACT

Background: Calcific aortic valve stenosis (CAVS), the predominant valvular heart disease in developed countries, arises primarily from metabolic and inflammatory dysregulation. The triglyceride-glucose (TyG) index, a composite biomarker of insulin resistance and systemic inflammation, has been associated with cardiovascular diseases. However, its causal association with CAVS remains unclear. This study employs bidirectional Mendelian randomization (MR) to elucidate the potential causal relationship between the TyG index and CAVS.

Methods: Genome-wide association study) summary statistics of TyG index and CAVS were obtained from UK-biobank cohort (n = 273 368) and FinnGen database (cases = 12 418 and controls = 487 930). Two-sample MR and multiple MR analyses were conducted to evaluate the association of TyG index with CAVS. The primary method was inverse variance weighted (IVW), complemented by MR-Egger, weighted median, and sensitivity analyses to ensure robustness.

Results: The MR analysis demonstrated a significant causal effect of the higher TyG index (per 1-unit increment of TyG index) on CAVS risk (odds ratio [OR] = 1.50, P = .007, 95% CI: 1.12-2.02). Similar causal relationships were observed for triglyceride and glucose levels with CAVS. Sensitivity analyses confirmed robustness with no evidence of horizontal pleiotropy (P > .05). This association remained statistically significant in multiple MR analyses after adjusting for potential confounders (OR = 1.64, P = .003, 95% CI: 1.18-2.28). No reverse causality from CAVS to the TyG index was detected.

Conclusion: This MR study provides evidence supporting the causal effect of higher TyG index on CAVS.

Keywords: Calcific aortic valve stenosis, inflammation, insulin resistance, Mendelian randomization, triglyceride-glucose index

ORIGINAL INVESTIGATION

INTRODUCTION

Calcific aortic valve stenosis (CAVS) is the most prevalent valvular heart disease in developed countries, with an incidence of 2%-3% in individuals aged >65 years.[1-4] Surgical or transcatheter valve replacement remains the primary effective therapeutic option.[5,6] Pathologically, CAVS is increasingly recognized as an active process involving inflammation, oxidative stress, and metabolic dysregulation, akin to atherosclerosis.[7,8] Among these mechanisms, metabolic disturbances, particularly insulin resistance, have emerged as a critical contributor to CAVS pathogenesis.[9,10] Insulin resistance exacerbates systemic inflammation, oxidative stress, and endothelial dysfunction, all of which are implicated in aortic valve calcification.[11-14]

The triglyceride-glucose (TyG) index, a novel and cost-effective marker of insulin resistance derived from fasting triglyceride and glucose levels, has gained attention for its clinical utility.[15-20] Unlike traditional measures such as the Homeostasis Model Assessment of Insulin Resistance, the TyG index offers greater accessibility and reflects both lipid and glucose dysregulation, key drivers of systemic inflammation and vascular calcification.[21-27] Recent studies have underscored its relevance in CAVS, with a case-control study demonstrating a significant association between the TyG index and the presence of aortic valve calcification

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(OR = 1.743, $P < .05$, 95% CI: 1.04-2.93).[28] Furthermore, retrospective cohort studies have demonstrated that a higher TyG index is linked to poor prognosis in patients with CAVS undergoing transcatheter aortic valve replacement [Hazard ratio (HR) = 5.41, $P < .001$, 95% CI: 4.01-7.32],[29] and increases all-cause mortality in severe aortic stenosis (HR = 1.622, $P = .018$, 95% CI: 1.09-2.42).[30] These findings collectively suggest a potential role of the TyG index in CAVS progression.

However, the causal relationship between the TyG index and CAVS remains unclear, necessitating robust analytical approaches such as Mendelian randomization (MR) to address potential confounding and reverse causality.[31,32] While previous MR studies have separately established robust causal associations between triglycerides, diabetes, and CAVS,[33-35] the potential causal association between the TyG index, a composite metabolic biomarker, and CAVS remains unexplored. To address this knowledge gap, bidirectional 2-sample MR and multiple MR were employed to elucidate the independent causal effect of the TyG index on CAVS.

METHODS

Study Design

This study utilized a bidirectional MR framework to assess causal relationships in both directions: (1) the effect of the TyG index on the risk of CAVS and (2) the effect of CAVS on the TyG index. The MR analysis is grounded in 3 fundamental assumptions: (1) the selected instrumental variables (IVs) must exhibit strong associations with the TyG index, triglyceride levels, and glucose levels; (2) the IVs must be independent of potential confounders; and (3) the IVs should influence CAVS exclusively through the TyG index, triglycerides, and glucose levels, but not other pathways. A schematic overview of the study design is presented in Figure 1.

Two Sample Mendelian Randomization Analysis

The 2-sample MR was adopted to investigate the causal association between TyG index and CAVS. Summary statistics were obtained from publicly available genome-wide association study (GWAS) databases, including the Integrative Epidemiology Unit Open GWAS Project (IEU-GWAS), the United Kingdom Biobank (UK Biobank), and the Finnish Genetics (FinnGen) database. In this study, single nucleotide polymorphisms (SNPs) strongly associated with the TyG index, triglyceride, and glucose levels were selected as IVs. These SNPs are randomly allocated at the time of conception, ensuring the minimal influence of environmental factors.[36] Initially, the random-effects inverse variance weighted (IVW) method was applied to estimate the causal effect of TyG index on CAVS. To enhance the robustness of the outcomes, complementary approaches such as the MR Egger, weighted median, simple mode, and weighted mode methods were applied. Furthermore, heterogeneity and pleiotropy were assessed using the IVW method and MR-Egger intercept, while leave-one-out analysis was performed to evaluate the influence of individual variants. All study procedures adhered to the STROBE-MR guidelines.[37,38]

Multiple Mendelian Randomization Analysis

To further address potential pleiotropy arising from confounding factors, multiple MR analyses were conducted, adjusting for body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), diabetes mellitus (DM), and hypertension (HTN). First, the causal effects of TyG index, triglyceride, and glucose levels on CAVS were evaluated through multiple MR analyses. Subsequently, the IVW method and the MR-Egger intercept were utilized to evaluate heterogeneity and pleiotropy. All results were visualized in forest plots for clarity and comparison.

Date Sources and Single Nucleotide Polymorphisms Selection

Genetic variants associated with the TyG index were derived from a prior GWAS based on the UK Biobank cohort,[39] which included 273368 individuals aged 40-69 years without diabetes or lipid metabolism disorders. The SNPs associated with the TyG index at genome-wide significance ($P < 5 \times 10^{-8}$) were identified using linear regression, adjusted for age, sex, and the top 5 genetic principal components to control population stratification. These SNPs were further pruned by linkage disequilibrium with $r^2 < .01$, and those that were significantly associated with triglyceride or glucose were also excluded. In total, 192 initial SNPs were selected for TyG index (Supplementary Table 1).

To ensure effectiveness of the SNPs and avoid bias, linkage disequilibrium was defined with $r^2 < 0.001$ for triglyceride and glucose levels. The Data Harmonization key steps were as follows: (1) SNPs matching and strand alignment: genetic instruments for the exposure and outcome were initially matched by their ID. The effect alleles for all SNPs were aligned to the forward strand to ensure a consistent reference framework across datasets; (2) harmonization of effect alleles: for each SNP, it was ensured that the effect allele reported in the outcome dataset corresponded to the same physical allele as the effect allele in the exposure dataset. This was achieved by flipping the sign of the beta coefficient for the outcome association when the effect alleles were complementary or mismatched, thereby aligning the direction of effect; (3) quality control and exclusion criteria: ① palindromic SNPs: all ambiguous palindromic SNPs were excluded to prevent errors caused by indeterminate strand orientation, ② allele frequency check: for non-palindromic SNPs, the effect allele frequencies were compared between the exposure and outcome samples. The SNPs with an absolute allele frequency difference > 0.08 were removed to

HIGHLIGHTS

- This study reveals a unidirectional causal relationship between elevated triglyceride-glucose (TyG) index and higher calcific aortic valve stenosis (CAVS) risk, employing bidirectional Mendelian randomization analysis.
- This study supports the involvement of insulin resistance and systemic inflammation in CAVS development.
- This study proposes the TyG index as a metabolic biomarker to stratify CAVS risk and guide prevention.

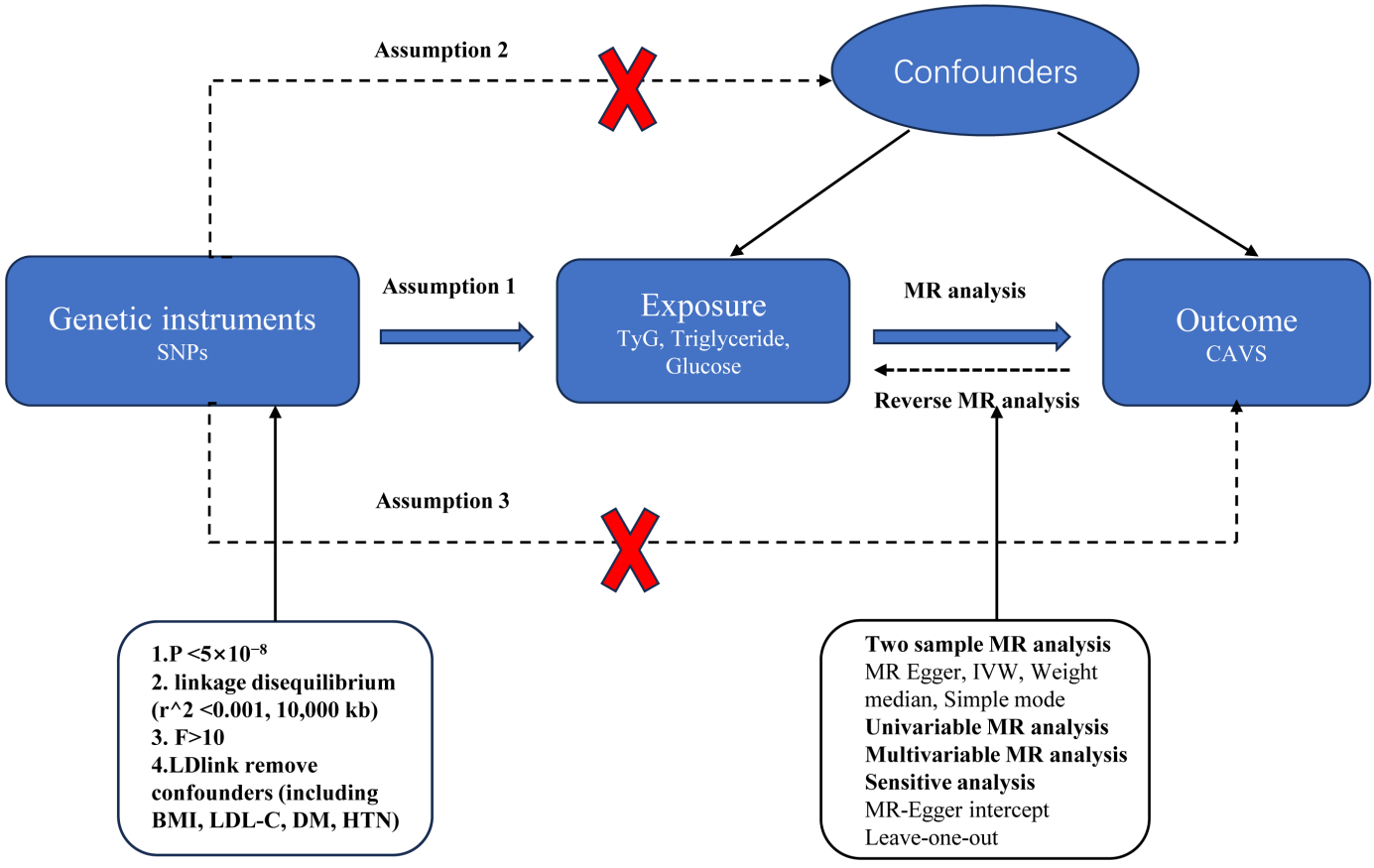

Figure 1. Study designed. BMI, body mass index; AVS, calcific aortic valvular stenosis; DM, diabetes mellitus; GWAS, genome-wide association studies; HTN, hypertension; IVW, inverse variance weighted; LDL-C, low density lipoprotein cholesterol; MR, Mendelian randomization; SNPs, single nucleotide polymorphisms.

minimize bias from potential population stratification or poor imputation quality, ③ incompatible SNPs: any SNPs with non-matching alleles (e.g., A/C in the exposure vs. G/T in the outcome) that could not be resolved through strand flipping were deemed incompatible and excluded from the analysis.

Genetic variants for triglycerides and glucose were sourced from IEU-GWAS (https://gwas.mrcieu.ac.uk/), comprising 389 562 and 314 916 participants, respectively. The CAVS outcome data were obtained from the FinnGen database (https://www.finngen.fi/en), which included 12 418 cases and 487 930 controls. Further details are provided in Table 1. All studies were reviewed and approved by local institutional review boards. Genetic variants associated with exposure were rigorously selected based on their strength of association and independence. To assess the strength of the IVs, the F-statistics was calculated. All IVs were selected for the MR analyses only if they exceeded the empirical threshold of $F > 10$.[40] Additionally, the LDlink database (https://ldlink.nih.gov/) was utilized to exclude SNPs that were significantly associated with potential confounders or other traits related to CAVS and eliminated all SNPs associated ($P < 5 \times 10^{-8}$) with the following traits. This step ensured that the selected IVs were specific to the exposures of interest (TyG index, triglycerides, and glucose) and not influenced by other metabolic factors such as BMI, LDL-C, DM, or HTN. These confounders were selected a priori based on their established associations in the existing epidemiological literature.[34,41-44]

Details on all datasets downloaded and screened are displayed in Table 1. Finally, 312 and 109 SNPs for triglyceride and glucose, respectively, were selectively obtained. In addition, 34 SNPs for CAVS were sourced from the FinnGen database for further reverse causality analysis (Supplementary Tables 2-4).

Statistical Analysis

All statistics were calculated using R software version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). The causal effect was deemed significant if the IVW *P* value was below the Bonferroni-corrected threshold ($P < .05/3 \approx .017$), while *P* values in the range of .017 to .05 were considered suggestive.

RESULTS

Two-Sample Mendelian Randomization Analysis

The 2-sample MR analysis based on the IVW method demonstrated a significant causal association between genetically predicted TyG index (n = 273 368 individuals) and CAVS (OR = 1.50, *P* = .007, 95% CI: 1.12-2.02) (Figure 2). Consistent findings were observed using the MR-Egger method (n = 500 348 individuals) (Figure 2). Furthermore, MR analysis

Table 1. Information on Data Included in the Study

Phenotypes/ID	Data Source	Population/PMID	Sample Size/Cases	Author/Year
TyG				
UK Biobank cohort[39]	UK Biobank database	European/NA	273 368	Si S/2020
Triglyceride levels				
ebi-a-GCST90014014	IEU-GWAS database	European/34017140	389 562	Mbatch J/2021
Glucose levels				
ebi-a-GCST90018955	IEU-GWAS database	European/34594039	314 916	Sakaue S/2021
CAVS				
finn_I9_CAVS_OPERATED	FinnGen database	European/NA	500 348/12 418	NA/2024
Confounders				
BMI				
ebi-a-GCST006368	IEU-GWAS database	European/30108127	315 347	Hoffmann TJ/2018
LDL-C				
ebi-a-GCST90092883	IEU-GWAS database	European/35213538	115 082	Richardson TG/2022
DM				
finn-b-E4_DIABETES	FinnGen database	European/30108127	218 792/35 607	NA/2021
Hypertension				
ebi-a-GCST90038604	IEU-GWAS database	European/33959723	484 598/129 909	Dönertas HM/2021

BMI, body mass index; CAVS, calcific aortic valvular stenosis; DM, diabetes mellitus; FinnGen, Finnish Genetics IEU-GWAS; Integrative Epidemiology Unit Open Genome-Wide Association Studies Project; LDL-C, low density lipoprotein cholesterol; TyG, triglyceride-glucose; UK Biobank: United Kingdom Biobank.

supported a causal role of triglycerides in CAVS development (OR = 1.29, $P < .001$, 95% CI: 1.15-1.45). A similar significant causal relationship was identified between glucose and CAVS (OR = 1.21, $P = .01$, 95% CI: 1.05-1.40) (Figure 2).

The IVW method was used to test for heterogeneity, and the MR-Egger intercept to test pleiotropy. Although significant heterogeneity was observed ($P < .001$), no directional pleiotropy was detected in the associations between the TyG index

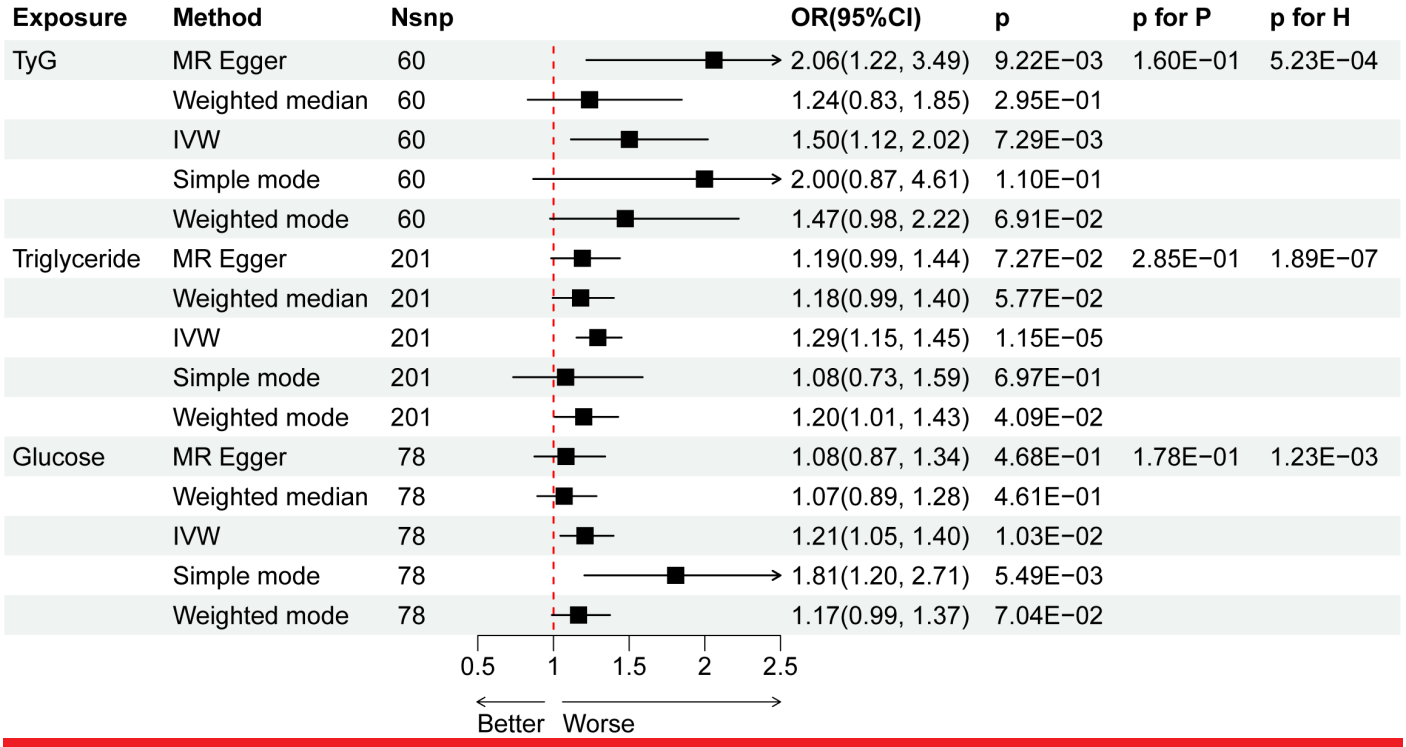

Figure 2. Two-sample MR analysis about exposures to CAVS. CAVS, calcific aortic valve stenosis; H, heterogeneity; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; P, pleiotropy; TyG, triglyceride-glucose.

and CAVS ($P = .16$) (Figure 2, Supplementary Table 5). This suggested that the IVs exert their effects through the intended pathway, supporting the validity of the causal inference. Similarly, no significant evidence of directional pleiotropy was detected for the associations of triglycerides ($P = .285$) or glucose ($P = .178$) with CAVS. The effects of TyG index on CAVS were illustrated in scatter plots (Figure 3), where each point represents a genetic variant, demonstrating the association between its effect on exposure and outcome. Sensitivity analysis employing a leave-one-out approach demonstrated that no individual SNP exerted a disproportionate influence on the causal association between the TyG index and CAVS (Supplementary Figure 2). Additional visual representations, including scatter plots for triglycerides and glucose, as well as funnel and forest plots, are shown in Supplementary Figures 1-3.

Multiple Mendelian Randomization Analysis

Univariable MR analysis supported a causal role of the TyG index in CAVS development (OR = 1.77, $P < .001$, 95% CI: 1.47-2.12). Similar causal relationships were observed for triglycerides (OR = 1.28, $P < .001$, 95% CI: 1.16-1.41) and glucose (OR = 1.20, $P = .011$, 95% CI: 1.04-1.38) (Figure 4). To further rule out the influence of confounding factors, multiple MR analysis was performed, adjusting for BMI, LDL-C, DM, and HTN. The multiple MR analysis confirmed a significant association between the TyG index and CAVS (OR = 1.64, $P = .003$, 95% CI: 1.18-2.28) (Figure 4).

Reverse 2-Sample Mendelian Randomization Analysis

The reverse 2 sample MR analysis based on the IVW method revealed no significant association between genetically predicted CAVS (n = 500 348 individuals) and triglycerides (OR = 1.01, $P = .129$, 95% CI: 1.00-1.03) (Figure 5). Similarly, MR-Egger analysis showed no association between CAVS and triglycerides (n = 389 562 individuals) (Supplementary Table 7). No significant relationship was observed between CAVS and glucose (OR=1.01, $P = .188$, 95% CI: 1.00-1.02) (Figure 5), indicating the absence of reverse causality.

No significant evidence of directional pleiotropy was detected in the association between CAVS and triglycerides ($P = .431$) (Figure 5). For glucose, there is no evidence of heterogeneity ($P = .112$) and pleiotropy ($P = .922$). The effects of CAVS on TyG index were illustrated in scatter plots (Figure 6). Sensitivity analyses, including leave-one-out, funnel, and forest plots, were presented in Supplementary Figures 4-6.

DISCUSSION

To the best of knowledge, this is the first bidirectional MR study to comprehensively assess the causal relationship between the TyG index and CAVS. Conversely, no substantial causal effect of CAVS on the TyG index was observed. These results highlight that insulin resistance, as reflected by the TyG index, contributes to CAVS pathophysiology independently of established clinical and metabolic confounders.

Previous observational studies have suggested that the TyG index, a surrogate marker of insulin resistance, may contribute to CAVS through its pro-oxidant and pro-inflammatory properties. However, the evidence remains inconsistent and limited. For instance, a case-control study involving 361 patients with aortic valve calcification and 89 controls reported a significant predictive value of the TyG index for aortic valve calcification (OR = 1.743, $P < .05$, 95% CI: 1.04-2.93).[28] Similarly, Milad et al[34] identified a significant association between triglycerides and aortic stenosis risk in an MR study (OR = 1.52, $P = .006$, 95% CI: 1.12-2.03). The Copenhagen General Population Study, encompassing 108 559 individuals, further corroborated these findings, showing that higher triglyceride levels (>5 mmol/L) were both observationally and genetically linked to an increased risk of aortic valve stenosis (OR = 1.52, $P < .001$, 95% CI: 1.02-2.27).[45] Additionally, another MR study revealed that genetically predicted type 2 diabetes was associated with increased CAVS risk (OR = 1.15, $P < .001$, 95% CI: 1.10-1.21).[43] Conversely, a cross-sectional study of 183 elderly patients with CAVS reported a negative association between the TyG index and CAVS (OR = 0.43, $P < .001$, 95% CI:

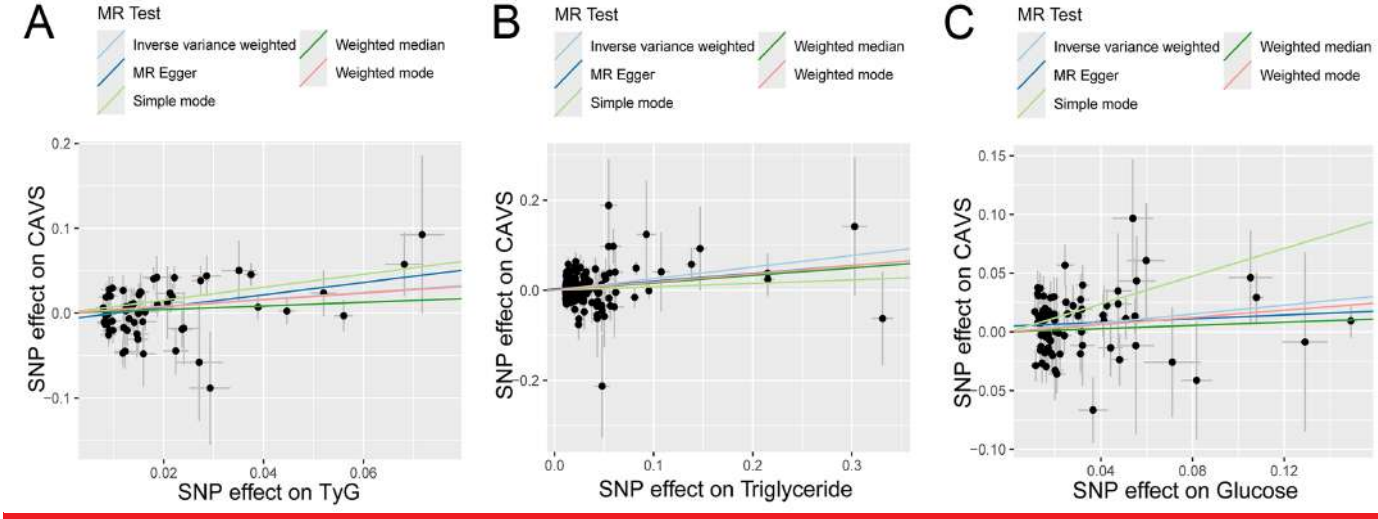

Figure 3. Scatter plots of MR analysis about exposures to CAVS. CAVS, calcific aortic valve stenosis; MR, Mendelian randomization; SNP, single nucleotide polymorphism; TyG, triglyceride-glucose.

Exposure	Method	Nsnp	OR(95%CI)	p	p for P	p for H
TyG(crude analysis)	MR Egger	150	2.18(1.60, 2.96)	1.74E−06	9.61E−02	<0.01
	Weighted median	150	1.68(1.28, 2.22)	2.06E−04		
	IVW	150	1.77(1.47, 2.12)	1.13E−09		
	Simple mode	150	1.76(0.99, 3.12)	5.48E−02		
	Weighted mode	150	1.72(1.29, 2.28)	2.79E−04		
TyG(r^2<0.001)	IVW	85	1.70(1.33, 2.17)	2.20E−05	2.23E−01	<0.01
Adjusted for BMI, LDL−C, DM, HTN	IVW	86	1.64(1.18, 2.28)	3.01E−03	9.60E−02	<0.01
Triglyceride(crude analysis)	MR Egger	245	1.28(1.09, 1.50)	3.18E−03	9.46E−01	<0.01
	Weighted median	245	1.25(1.10, 1.43)	8.54E−04		
	IVW	245	1.28(1.16, 1.41)	5.14E−07		
	Simple mode	245	1.19(0.89, 1.60)	2.35E−01		
	Weighted mode	245	1.27(1.10, 1.47)	1.56E−03		
Adjusted for BMI, LDL−C, DM, HTN	IVW	148	1.20(1.07, 1.35)	2.45E−03	5.10E−02	<0.01
Glucose(crude analysis)	MR Egger	92	1.03(0.83, 1.28)	7.71E−01	7.98E−02	<0.01
	Weighted median	92	1.07(0.89, 1.28)	4.70E−01		
	IVW	92	1.20(1.04, 1.38)	1.11E−02		
	Simple mode	92	1.65(1.08, 2.53)	2.27E−02		
	Weighted mode	92	1.12(0.96, 1.30)	1.51E−01		
Adjusted for BMI, LDL−C, DM, HTN	IVW	54	1.25(1.05, 1.49)	1.35E−02	9.37E−01	<0.01

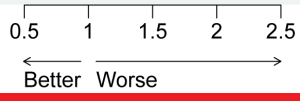

Figure 4. Multiple MR analyses about exposures to CAVS. BMI, body mass index; CAVS, calcific aortic valvular stenosis; DM, diabetes mellitus; H, heterogeneity; HTN, hypertension; IVW, inverse variance weighted; LDL-C, low density lipoprotein cholesterol; OR, odds ratio; P, pleiotropy; TyG, triglyceride-glucose index.

0.28-0.68).[46] These discrepancies likely stem from confounding factors and reverse causality, which the MR approach effectively mitigates.

In this 2-sample MR study, genetic variants were utilized as IVs to establish a robust causal association between elevated TyG index (n=273368 individuals) and increased CAVS risk (OR=1.50, *P* = .007, 95% CI: 1.12-2.02). Consistent results were observed for triglycerides and glucose levels, with complementary MR methods and sensitivity analyses confirming the robustness and reliability of these associations (*P* > .05). It was stated that while the primary sensitivity

Outcome	Method	Nsnp	OR(95%CI)	p	p for P	p for H
Triglyceride	MR Egger	25	0.99(0.93, 1.05)	6.84E−01	4.31E−01	7.20E−05
	Weighted median	25	1.00(0.99, 1.02)	7.34E−01		
	IVW	25	1.01(1.00, 1.03)	1.29E−01		
	Simple mode	25	1.00(0.97, 1.03)	8.25E−01		
	Weighted mode	25	1.00(0.98, 1.02)	8.83E−01		
Glucose	MR Egger	30	1.01(0.99, 1.03)	5.16E−01	9.22E−01	1.12E−01
	Weighted median	30	1.00(0.99, 1.01)	7.01E−01		
	IVW	30	1.01(1.00, 1.02)	1.88E−01		
	Simple mode	30	1.00(0.98, 1.02)	7.84E−01		
	Weighted mode	30	1.00(0.99, 1.02)	6.85E−01		

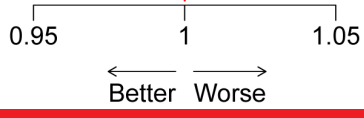

Figure 5. Reverse 2-sample MR analysis about CAVS to outcomes. CAVS, calcific aortic valve stenosis; H, heterogeneity; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; P, pleiotropy.

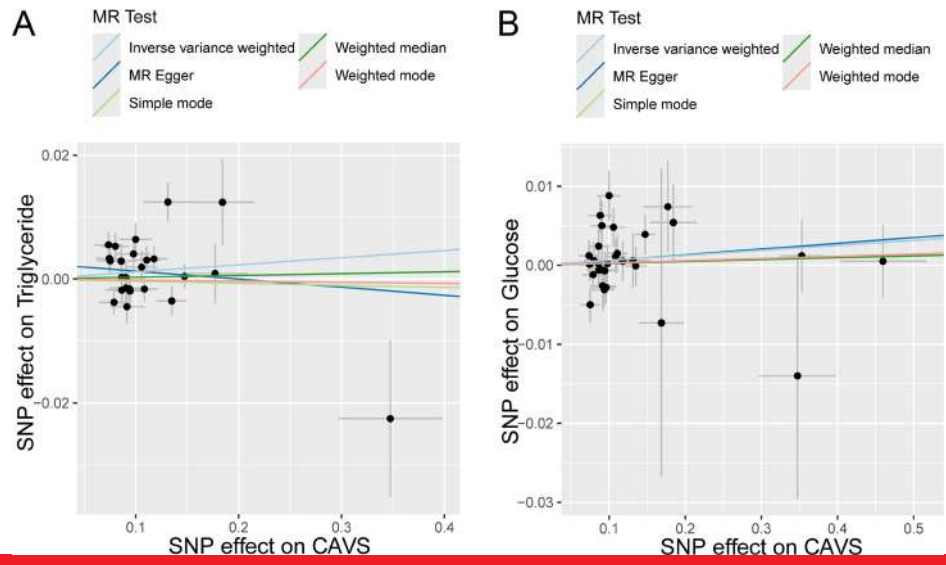

Figure 6. Scatter plots of MR analysis about CAVS to outcomes. CAVS, calcific aortic valve stenosis; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

analyses did not detect directional pleiotropy, heterogeneity might still reflect pleiotropic effects. Reverse MR analyses further excluded the possibility of reverse causality (triglycerides: OR = 1.01, *P* = .129, 95% CI: 1.00-1.03; glucose: OR = 1.01, *P* = .188, 95% CI: 1.00-1.02). Multiple MR analysis, adjusted for potential confounders, reinforced the positive association between the TyG index and CAVS (OR = 1.64, *P* = .003, 95% CI: 1.18-2.28). These findings collectively highlight a consistent causal relationship and address critical limitations inherent in observational studies, thereby advancing the understanding of the potential pathogenesis of CAVS.

Several plausible mechanisms may explain the observed positive correlation between elevated TyG index and CAVS. First, systemic inflammation plays a pivotal role. Insulin resistance, as indicated by a higher TyG index, promotes systemic inflammation through the activation of pro-inflammatory pathways, such as nuclear factor-kappaB and the NLRP3 inflammasome.[47,48] These pathways are critical in driving aortic valve calcification by inducing osteogenic differentiation of valvular interstitial cells.[49,50] Second, oxidative stress is another key contributor. Insulin resistance is associated with increased oxidative stress, which exacerbates endothelial dysfunction and lipid deposition in the aortic valve.[51,52] Oxidative stress enhances the uptake of oxidized LDL by macrophages, leading to foam cell formation and subsequent calcification.[53] Third, the TyG index, as a composite marker of triglyceride and glucose dysregulation, is closely associated with lipid metabolism abnormalities. Elevated triglyceride levels promote lipoprotein deposition within the valve leaflets, a process that can initiate calcific remodeling and contribute to the pathogenesis of CAVS.[12,35,54]

The TyG index may serve as an accessible and cost-effective biomarker for identifying individuals at high risk for CAVS. Early identification of at-risk populations could facilitate targeted preventive strategies. Further research is necessary to demonstrate the precise mechanistic pathways through which insulin resistance promotes valvular calcification, particularly the roles of inflammation, oxidative stress, and lipid metabolism.

Strengths and Limitations

This study is the first to investigate the causal relationship between the TyG index and CAVS, filling a significant gap in the literature. The bidirectional MR design provides a robust framework for assessing causality in both directions, effectively mitigating potential reverse causation. The use of genetic variants as IVs minimizes confounding and enhances causal inference. Nevertheless, several limitations should be acknowledged. First, the study population was exclusively of European ancestry, which may limit the generalizability of the findings to other ethnic groups. Genetic determinants of the TyG index and their impact on CAVS risk may vary across populations, underscoring the need for replication in more diverse cohorts. Second, while the MR approach reduces confounding, it relies on the assumption that the genetic instruments are valid, which may not hold in all cases. Although sensitivity analyses, including MR-Egger and IVW methods, were employed to address pleiotropy, residual pleiotropic effects cannot be entirely ruled out. Third, the limited GWAS data for the TyG index restricted its direct application in reverse MR analysis. Future studies with larger, more diverse populations are warranted to validate these findings.

CONCLUSION

In conclusion, the MR study demonstrates a causal association between higher TyG index and increased risk of CAVS, highlighting the important role of metabolic regulation in CAVS pathogenesis and prevention.

Data availability statement: The complete dataset produced or examined in this research is available within the manuscript and its supplementary materials. For further inquiries, please contact the corresponding author.

Ethics Committee Approval: All data used in this study were obtained from publicly available sources and are in the public domain. Thus, no ethical approval or clinical trial registration was required.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – Y.H., X.S.; Design – X.S.; Supervision – Y.H.; Resource – Y.H., X.S.; Materials – X.S., Y.H.; Date Collection – X.S., X.X.; Analysis and interpretation – X.S., X.L.; Literature Search – X.S., X.L., X.X.; Writing – X.S., Y.H.; Critical Reviews – Y.H.

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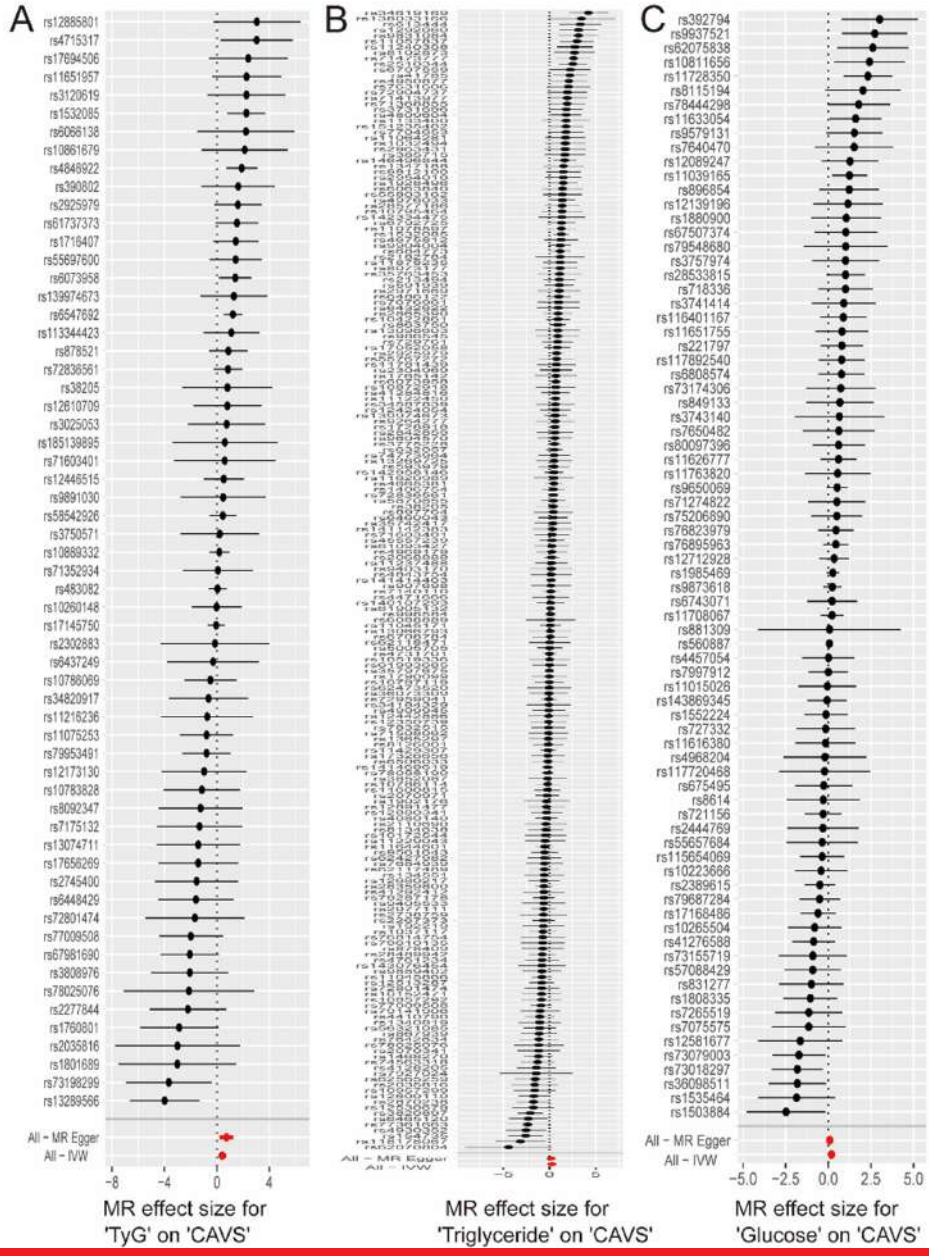
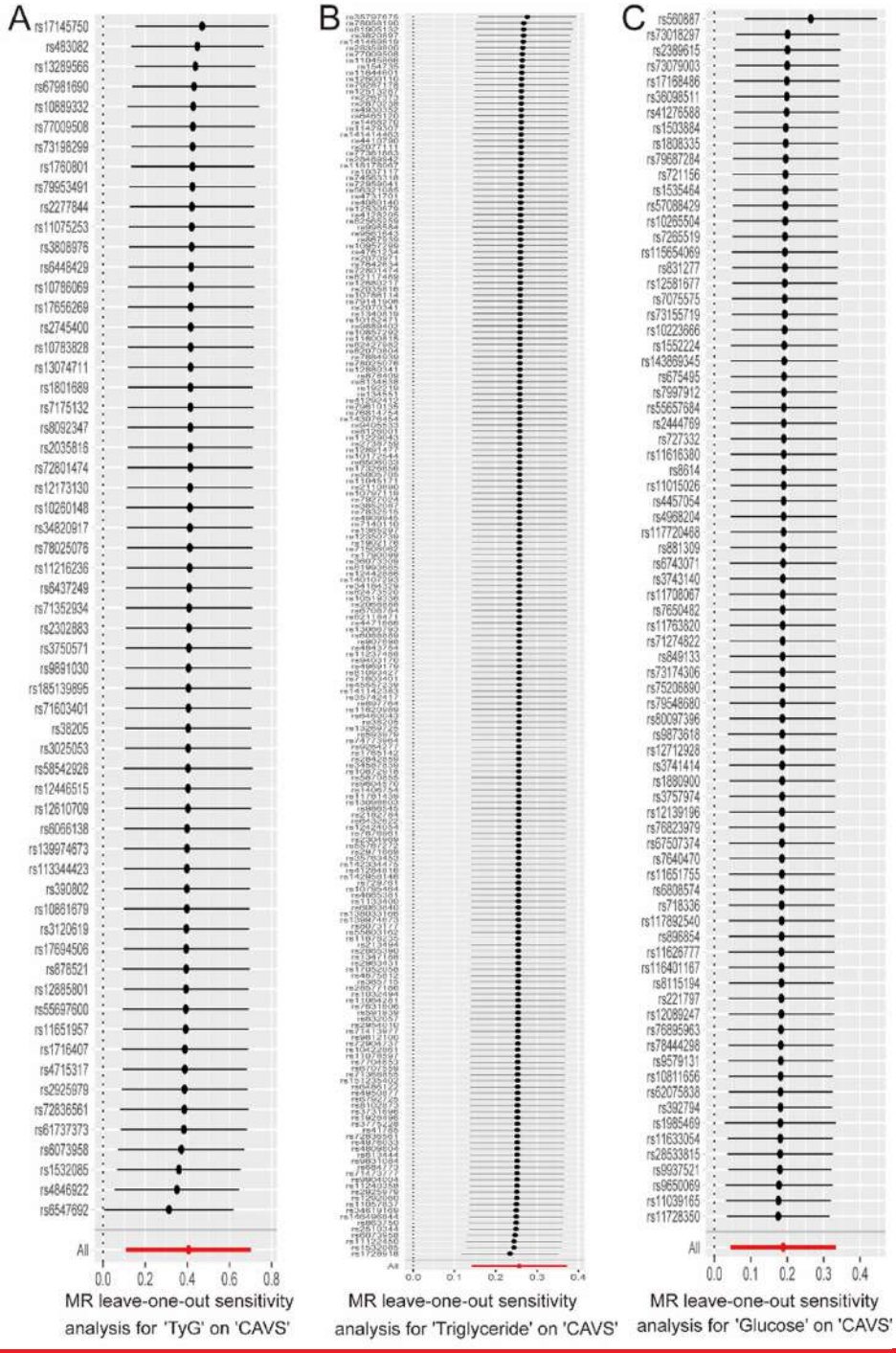
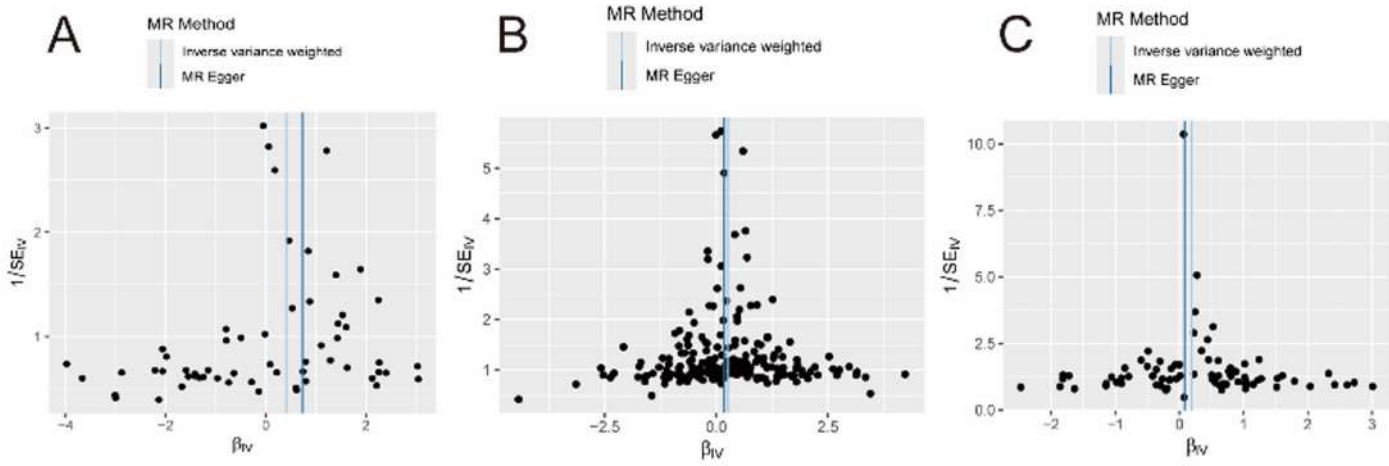


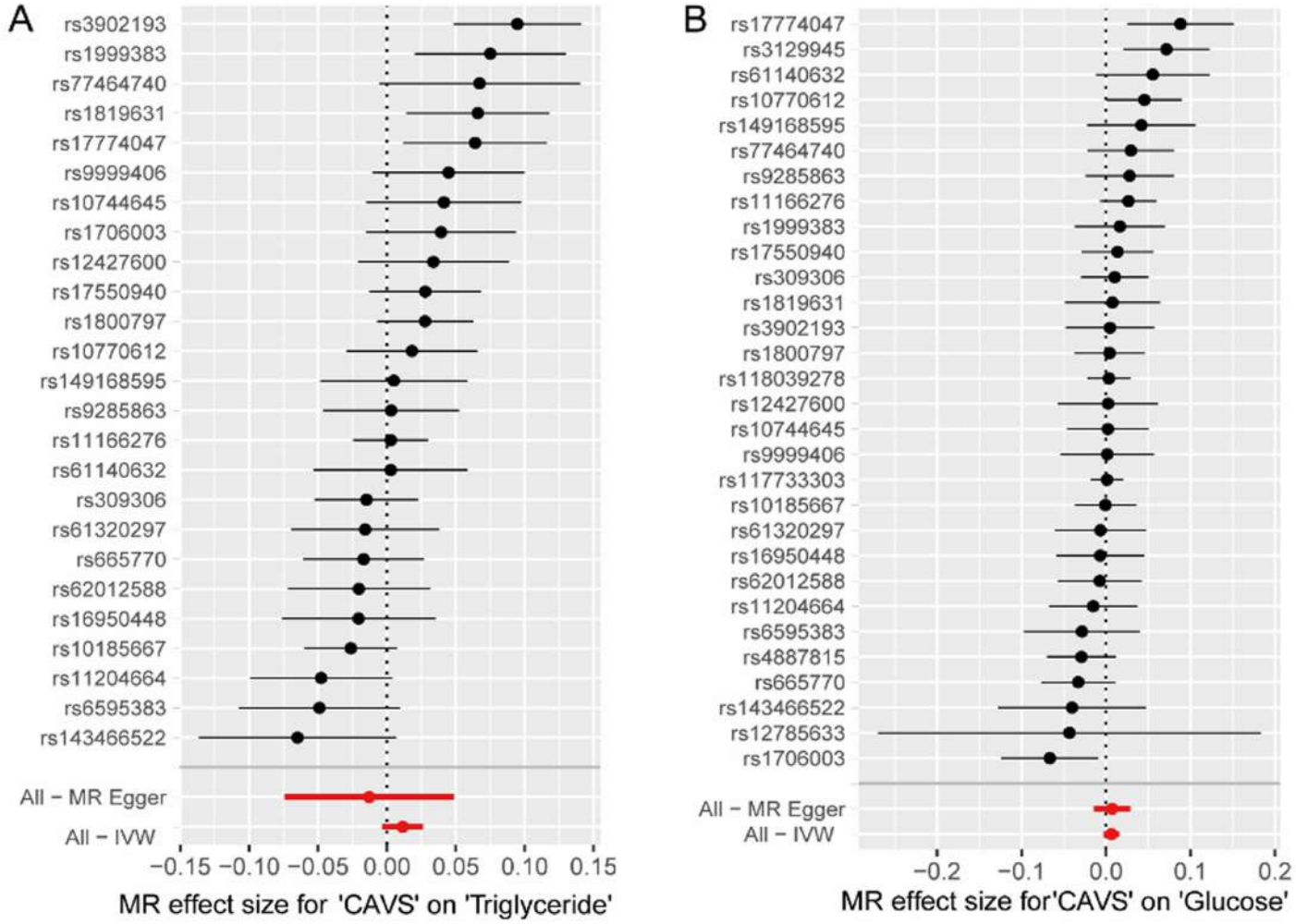
Supplementary Figure 1. Forest plots of the causal effect of SNPs of exposures on CAVS. (A)TyG index, (B)Triglyceride and (C) Glucose. MR: Mendelian randomization; TyG index: triglyceride-glucose index; CAVS: calcific aortic valve stenosis; IVW: inverse variance weighted; SNPs: Single nucleotide polymorphisms.



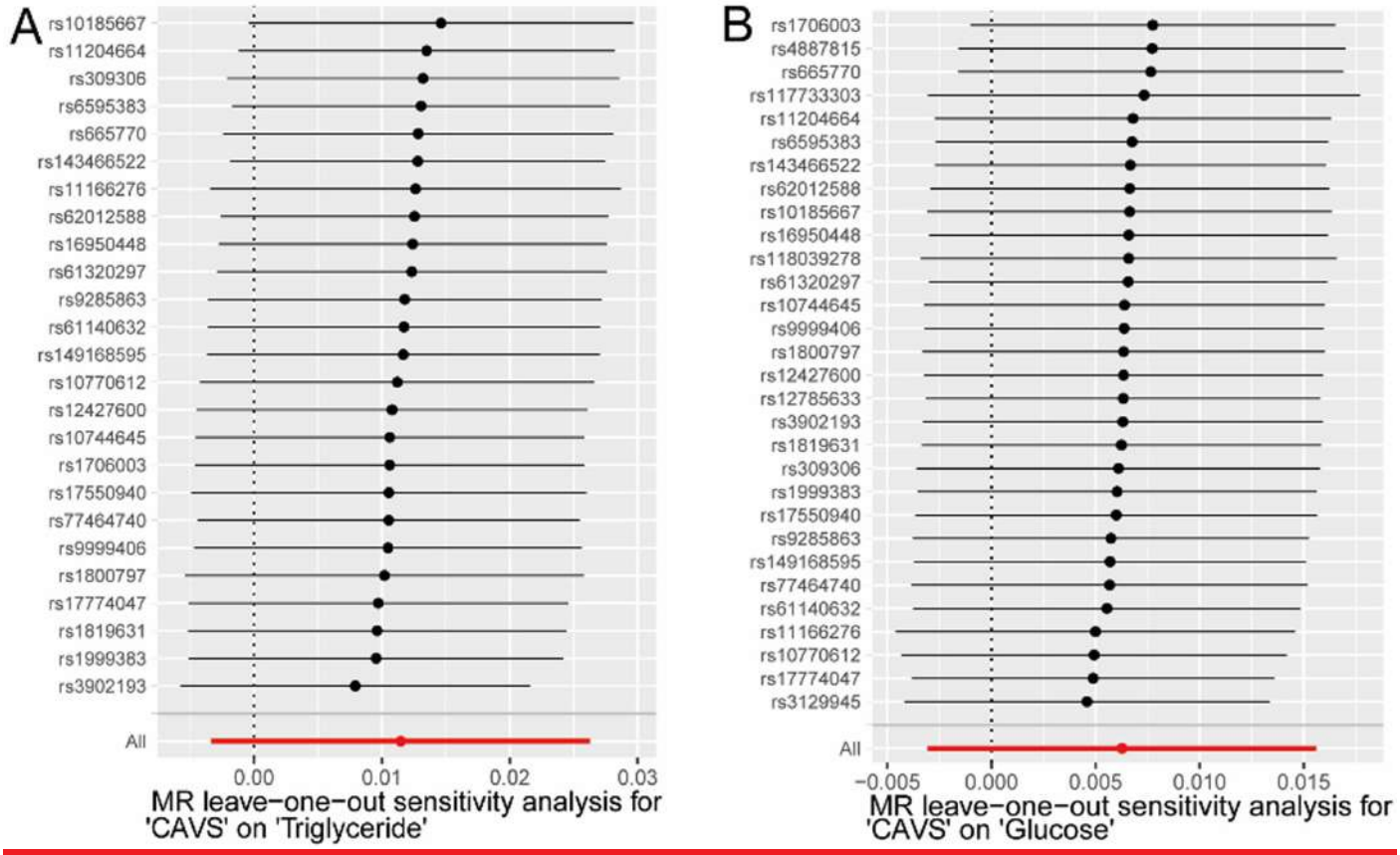
Supplementary Figure 2. Leave-one-out analysis for the effect of exposures on CAVS. (A)TyG index, (B)Triglyceride and (C) Glucose. MR: Mendelian randomization; TyG index: triglyceride-glucose index; CAVS: calcific aortic valve stenosis.



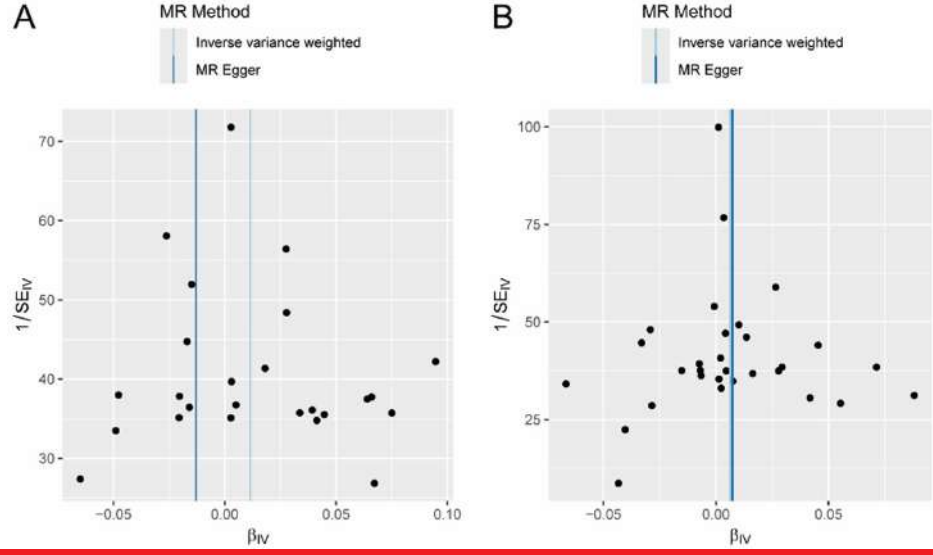
Supplementary Figure 3. Funnel plots of exposures to CAVS. (A)TyG index, (B)Triglyceride and (C)Glucose. TyG index: triglyceride-glucose index; CAVS: calcific aortic valve stenosis; MR: Mendelian randomization; SE: standard Error; IV: instrument variable.



Supplementary Figure 4. Forest plots of the causal effect of SNPs of CAVS on outcomes. (A) Triglyceride and (B)Glucose. MR: Mendelian randomization; CAVS: calcific aortic valve stenosis; IVW: inverse variance weighted; SNPs: Single nucleotide polymorphisms.



Supplementary Figure 5. Leave-one-out analysis for the effect of CAVS on outcomes. (A) Triglyceride and (B)Glucose. MR: Mendelian randomization; CAVS: calcific aortic valve stenosis.



Supplementary Figure 6. Funnel plots of CAVS to outcomes. (A) Triglyceride and (B)Glucose. CAVS: calcific aortic valve stenosis; MR: Mendelian randomization; TyG index: triglyceride-glucose index; SE: standard Error; IV: instrument variable.

Supplementary Table 1. SNPs of TyG index

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs114165349	G	C	0.04453	0.004653	1.07E-21
TyG	rs72904790	T	C	-0.01371	0.002406	1.20E-08
TyG	rs213498	T	A	-0.00803	0.001464	4.17E-08
TyG	rs10889332	C	T	-0.0389	0.00143	1.34E-162
TyG	rs72669514	C	T	0.018609	0.003207	6.53E-09
TyG	rs17656269	C	T	0.008749	0.00147	2.65E-09
TyG	rs16836630	G	C	-0.01734	0.002521	6.14E-12
TyG	rs1760801	G	A	-0.00896	0.001513	3.19E-09
TyG	rs340836	T	C	-0.0087	0.001396	4.71E-10
TyG	rs76172548	A	C	0.022814	0.003832	2.64E-09
TyG	rs3120619	G	A	0.011881	0.001803	4.45E-11
TyG	rs11118610	A	C	-0.00903	0.001389	8.09E-11
TyG	rs4846922	C	T	0.022155	0.001463	8.63E-52
TyG	rs907866	G	A	-0.00928	0.001388	2.31E-11
TyG	rs111585158	C	T	0.012113	0.002114	1.00E-08
TyG	rs144470864	A	C	0.017261	0.003078	2.05E-08
TyG	rs76384951	A	C	-0.02955	0.002524	1.16E-31
TyG	rs533617	T	C	-0.04645	0.003467	6.48E-41
TyG	rs35750610	T	C	0.018513	0.002347	3.09E-15
TyG	rs34921778	A	G	0.008426	0.00145	6.21E-09
TyG	rs12617848	C	T	0.014279	0.002006	1.09E-12
TyG	rs80216311	C	T	-0.01417	0.00239	3.05E-09
TyG	rs61737373	G	A	-0.02861	0.002929	1.57E-22
TyG	rs6547692	A	G	0.037507	0.001384	2.05E-161
TyG	rs10206462	T	C	-0.00894	0.001428	3.85E-10
TyG	rs6760053	C	G	-0.00779	0.001377	1.55E-08
TyG	rs6710938	A	C	-0.00899	0.001618	2.76E-08
TyG	rs79953491	A	G	-0.0237	0.002108	2.49E-29
TyG	rs115128825	C	A	0.026901	0.004876	3.46E-08
TyG	rs484066	T	A	-0.01592	0.001419	3.31E-29
TyG	rs17694506	T	C	0.009005	0.001419	2.19E-10
TyG	rs2943645	T	C	-0.02092	0.001432	2.40E-48
TyG	rs6437249	C	T	0.008385	0.001493	1.95E-08
TyG	rs147764624	G	C	-0.03019	0.005506	4.18E-08
TyG	rs390802	G	A	-0.01534	0.001765	3.63E-18
TyG	rs62271373	T	A	0.025359	0.003039	7.16E-17
TyG	rs13074711	T	C	0.012011	0.002185	3.86E-08
TyG	rs13108218	G	A	0.01564	0.001438	1.54E-27
TyG	rs71603401	A	G	0.012509	0.002055	1.15E-09
TyG	rs6448429	C	T	0.012675	0.001878	1.49E-11
TyG	rs1471251	A	T	0.016447	0.001408	1.56E-31
TyG	rs4134363	G	A	-0.0095	0.001702	2.37E-08
TyG	rs3822076	T	A	0.008671	0.001382	3.50E-10
TyG	rs2035816	A	G	-0.01594	0.002491	1.54E-10
TyG	rs78025076	C	T	0.027112	0.004828	1.96E-08
TyG	rs390556	T	C	-0.01327	0.002204	1.73E-09
TyG	rs72754154	G	A	-0.0214	0.003141	9.58E-12
TyG	rs3936511	A	G	0.021613	0.001747	3.69E-35
TyG	rs151913	G	A	0.00787	0.001414	2.60E-08

(*Continued*)

Supplementary Table 1. SNPs of TyG index (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs7703744	C	G	-0.01093	0.001552	1.84E-12
TyG	rs72801474	G	A	-0.01464	0.002353	4.88E-10
TyG	rs12173130	T	C	0.009711	0.001769	4.07E-08
TyG	rs11134475	G	A	-0.01694	0.001423	1.15E-32
TyG	rs2963476	A	G	0.013369	0.001699	3.58E-15
TyG	rs6923241	C	T	-0.01092	0.001547	1.67E-12
TyG	rs2745400	G	A	0.00826	0.001372	1.76E-09
TyG	rs2894211	C	A	0.017465	0.002189	1.46E-15
TyG	rs7758790	T	C	0.01428	0.001648	4.52E-18
TyG	rs55697600	A	G	0.035107	0.003604	2.05E-22
TyG	rs185139895	G	A	0.020756	0.003384	8.63E-10
TyG	rs3025053	G	A	-0.01346	0.002125	2.40E-10
TyG	rs4715317	G	T	0.009743	0.001439	1.30E-11
TyG	rs1967685	G	C	-0.01428	0.001371	2.25E-25
TyG	rs632057	G	T	0.015367	0.001421	2.94E-27
TyG	rs12208357	C	T	0.021956	0.002725	7.75E-16
TyG	rs77009508	A	G	0.022418	0.002596	5.86E-18
TyG	rs55730499	C	T	-0.01825	0.002552	8.74E-13
TyG	rs186696265	C	T	-0.04726	0.005925	1.51E-15
TyG	rs4709746	C	T	-0.01125	0.002032	3.11E-08
TyG	rs852424	C	T	0.008528	0.001463	5.55E-09
TyG	rs38205	C	A	0.007915	0.00144	3.87E-08
TyG	rs2106727	G	A	-0.01082	0.001428	3.59E-14
TyG	rs4722551	T	C	-0.01858	0.001881	5.21E-23
TyG	rs1534696	A	C	0.010737	0.001376	6.18E-15
TyG	rs2971676	G	A	0.013349	0.002398	2.61E-08
TyG	rs878521	G	A	0.021762	0.001587	8.43E-43
TyG	rs62459110	G	C	-0.02139	0.003643	4.32E-09
TyG	rs799157	C	T	0.040791	0.003402	4.05E-33
TyG	rs17145750	C	T	-0.05606	0.001856	5.28E-200
TyG	rs10260148	C	T	0.014959	0.001542	2.96E-22
TyG	rs73198299	T	C	0.012271	0.002229	3.68E-08
TyG	rs7821812	G	C	0.016336	0.001697	6.39E-22
TyG	rs904009	A	C	0.015931	0.001626	1.16E-22
TyG	rs4921914	T	C	0.019439	0.001659	1.07E-31
TyG	rs2975424	T	C	0.010605	0.001755	1.53E-09
TyG	rs1388941	G	A	0.014354	0.001459	8.01E-23
TyG	rs268	A	G	0.10865	0.005152	1.25E-98
TyG	rs117026536	G	T	-0.09518	0.002263	1.00E-200
TyG	rs57295072	G	C	-0.03049	0.004697	8.60E-11
TyG	rs17091881	T	C	0.078595	0.004274	1.82E-75
TyG	rs74444445	T	C	0.034928	0.004886	8.82E-13
TyG	rs117805502	C	T	-0.03217	0.004394	2.48E-13
TyG	rs28550053	A	G	-0.01771	0.001821	2.42E-22
TyG	rs75662196	G	C	-0.02793	0.004345	1.30E-10
TyG	rs17092008	C	T	0.020825	0.002853	2.91E-13
TyG	rs11781356	T	A	0.009932	0.001766	1.85E-08
TyG	rs2081687	C	T	0.011677	0.001454	9.63E-16
TyG	rs71525127	C	G	0.019603	0.002547	1.42E-14

(*Continued*)

Supplementary Table 1. SNPs of TyG index (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs11558471	A	G	-0.01148	0.001471	6.29E-15
TyG	rs17321515	A	G	-0.0439	0.001371	1.00E-200
TyG	rs62521590	T	G	0.014654	0.001558	5.11E-21
TyG	rs10811661	T	C	-0.00987	0.001805	4.53E-08
TyG	rs13289566	C	T	-0.01183	0.001669	1.37E-12
TyG	rs2244278	C	A	-0.01339	0.002119	2.62E-10
TyG	rs3750571	C	A	-0.01241	0.001898	6.27E-11
TyG	rs11006681	G	A	-0.01101	0.001844	2.38E-09
TyG	rs142164605	T	A	-0.01776	0.002781	1.71E-10
TyG	rs10786069	T	C	0.013098	0.001378	2.06E-21
TyG	rs113344423	G	A	0.021299	0.003018	1.70E-12
TyG	rs2792736	A	T	-0.01005	0.001538	6.40E-11
TyG	rs10832027	A	G	-0.01226	0.001482	1.37E-16
TyG	rs3808976	A	G	0.009819	0.001701	7.84E-09
TyG	rs99780	C	T	0.020203	0.001436	5.73E-45
TyG	rs35169799	C	T	0.024724	0.002833	2.61E-18
TyG	rs678614	C	A	0.009351	0.001532	1.04E-09
TyG	rs2302883	T	C	0.008865	0.001623	4.71E-08
TyG	rs187217942	G	A	0.031159	0.005403	8.06E-09
TyG	rs17119701	A	G	0.037068	0.00375	4.94E-23
TyG	rs61362984	A	G	-0.01395	0.001422	1.06E-22
TyG	rs61904855	C	A	0.023378	0.004096	1.15E-08
TyG	rs11216122	G	T	-0.01819	0.003103	4.59E-09
TyG	rs7930786	G	C	0.124688	0.002787	1.00E-200
TyG	rs56225305	G	A	0.108415	0.002786	1.00E-200
TyG	rs2075294	G	T	0.038812	0.005799	2.19E-11
TyG	rs75919952	C	T	-0.04681	0.00317	2.56E-49
TyG	rs11600380	T	C	-0.03673	0.002541	2.34E-47
TyG	rs5110	C	A	-0.01854	0.002485	8.59E-14
TyG	rs12721078	C	A	-0.03228	0.003938	2.46E-16
TyG	rs71480323	G	A	-0.01956	0.002114	2.24E-20
TyG	rs11216236	C	T	0.024039	0.003424	2.21E-12
TyG	rs187929675	C	T	-0.07679	0.006068	1.07E-36
TyG	rs11045171	A	G	-0.01166	0.001737	1.91E-11
TyG	rs67981690	A	G	0.014856	0.002075	8.09E-13
TyG	rs10783828	G	A	0.009035	0.001475	9.04E-10
TyG	rs7296326	T	C	-0.01186	0.002173	4.84E-08
TyG	rs1585705	A	C	0.008766	0.001496	4.64E-09
TyG	rs10861679	T	C	0.009354	0.001507	5.35E-10
TyG	rs1882491	T	C	-0.0135	0.001481	8.04E-20
TyG	rs1716407	A	G	-0.01506	0.001399	4.90E-27
TyG	rs7140110	T	C	0.01437	0.001508	1.61E-21
TyG	rs112740904	T	G	-0.0149	0.001958	2.76E-14
TyG	rs12885801	C	A	0.009085	0.001622	2.11E-08
TyG	rs34820917	G	A	-0.0158	0.00285	2.97E-08
TyG	rs35477346	T	C	0.009297	0.001497	5.32E-10
TyG	rs139974673	T	C	0.071769	0.00443	5.34E-59
TyG	rs72739147	A	T	-0.01212	0.002061	4.04E-09
TyG	rs1532085	G	A	0.018004	0.00141	2.64E-37

(*Continued*)

Supplementary Table 1. SNPs of TyG index (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs261334	C	G	0.026145	0.001678	9.88E-55
TyG	rs11636087	T	C	0.011653	0.001545	4.65E-14
TyG	rs8028620	T	C	-0.00898	0.001375	6.53E-11
TyG	rs7175132	A	G	-0.00812	0.001414	9.44E-09
TyG	rs8025505	C	T	0.009647	0.001584	1.13E-09
TyG	rs9935836	A	C	0.009882	0.001773	2.49E-08
TyG	rs11075253	C	A	-0.01411	0.001502	5.65E-21
TyG	rs12446515	C	T	-0.01876	0.001475	4.76E-37
TyG	rs5880	G	C	0.022114	0.002981	1.18E-13
TyG	rs12934528	T	C	0.013515	0.001958	5.15E-12
TyG	rs2925979	C	T	0.015438	0.001498	6.79E-25
TyG	rs11651957	G	A	0.018648	0.002936	2.14E-10
TyG	rs12937081	A	G	0.010884	0.001891	8.64E-09
TyG	rs72836561	C	T	0.068218	0.003899	1.69E-68
TyG	rs231539	C	T	0.013065	0.001881	3.76E-12
TyG	rs11657238	G	A	-0.00785	0.001384	1.41E-08
TyG	rs1801689	A	C	-0.02932	0.004081	6.78E-13
TyG	rs77244849	T	C	-0.00875	0.001488	4.09E-09
TyG	rs9891030	G	A	0.009938	0.001594	4.54E-10
TyG	rs71352934	A	C	-0.01631	0.002736	2.50E-09
TyG	rs8092347	A	G	0.008121	0.001411	8.69E-09
TyG	rs197156	A	G	-0.00925	0.001454	1.99E-10
TyG	rs1035941	G	A	0.011015	0.001533	6.75E-13
TyG	rs4804413	C	T	0.009485	0.001385	7.53E-12
TyG	rs116843064	G	A	-0.10888	0.004912	8.79E-109
TyG	rs57192995	G	C	-0.0199	0.003024	4.65E-11
TyG	rs58542926	C	T	-0.05205	0.002577	1.26E-90
TyG	rs188247550	C	T	-0.06447	0.006421	1.02E-23
TyG	rs62102718	A	T	0.011589	0.001527	3.22E-14
TyG	rs58895965	C	A	0.012724	0.001804	1.75E-12
TyG	rs541012177	G	T	0.024254	0.003536	6.94E-12
TyG	rs41290102	C	T	-0.03312	0.005888	1.86E-08
TyG	rs419925	G	C	-0.01304	0.001499	3.39E-18
TyG	rs483082	G	T	0.044675	0.001617	8.09E-168
TyG	rs79429216	G	A	0.037821	0.006299	1.92E-09
TyG	rs146390218	A	G	0.035524	0.004351	3.22E-16
TyG	rs62132802	C	T	-0.00912	0.001502	1.29E-09
TyG	rs12610709	G	A	0.013994	0.001833	2.24E-14
TyG	rs2207132	G	A	0.028323	0.003878	2.83E-13
TyG	rs2250900	C	T	0.008996	0.00164	4.10E-08
TyG	rs6073958	T	C	0.027409	0.001724	7.14E-57
TyG	rs4812995	T	C	0.009133	0.001617	1.64E-08
TyG	rs6066138	G	A	-0.00851	0.001523	2.36E-08
TyG	rs6090040	C	A	0.008917	0.001388	1.33E-10
TyG	rs2277844	A	G	-0.00908	0.001385	5.43E-11

SNP: single nucleotide polymorphism; TyG: triglyceride-glucose; SE: standard error.

Supplementary Table 2. SNPs of Triglyceride

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs114165349	G	C	0.084607	0.006823	2.59E-35
Triglyceride	rs880315	T	C	-0.01206	0.002176	3.01E-08
Triglyceride	rs72904737	G	A	-0.0261	0.003646	8.09E-13
Triglyceride	rs5005705	C	A	-0.0227	0.002757	1.84E-16
Triglyceride	rs12119979	C	G	0.0193	0.002058	6.77E-21
Triglyceride	rs61778883	T	C	0.019485	0.003079	2.47E-10
Triglyceride	rs10889334	C	G	-0.08094	0.002147	1.00E-200
Triglyceride	rs12749691	A	T	-0.01834	0.002263	5.25E-16
Triglyceride	rs4950877	A	G	-0.01288	0.002108	9.90E-10
Triglyceride	rs1494368	T	C	-0.01541	0.002306	2.34E-11
Triglyceride	rs11206374	G	A	0.026749	0.002456	1.25E-27
Triglyceride	rs213494	C	T	0.016422	0.00215	2.21E-14
Triglyceride	rs1365297	A	G	-0.0165	0.002646	4.54E-10
Triglyceride	rs141142383	C	T	-0.02666	0.003764	1.41E-12
Triglyceride	rs2842859	T	C	0.013303	0.002294	6.70E-09
Triglyceride	rs7539464	T	A	-0.01441	0.002071	3.49E-12
Triglyceride	rs10631642	C	CTTT	-0.01295	0.002268	1.13E-08
Triglyceride	rs907698	G	A	-0.01226	0.002091	4.60E-09
Triglyceride	rs11240358	G	A	0.013662	0.002101	7.85E-11
Triglyceride	rs11122450	T	G	-0.05017	0.002108	3.39E-125
Triglyceride	rs57929942	A	AT	0.015251	0.00265	8.70E-09
Triglyceride	rs114052230	C	T	-0.02121	0.00285	9.88E-14
Triglyceride	rs28489942	T	C	-0.02035	0.002154	3.61E-21
Triglyceride	rs6752845	G	C	-0.0144	0.00208	4.32E-12
Triglyceride	rs7424120	C	T	-0.01338	0.002107	2.15E-10
Triglyceride	rs1009360	T	C	-0.01876	0.002087	2.46E-19
Triglyceride	rs11688682	G	C	-0.0159	0.002391	2.93E-11
Triglyceride	rs3820897	T	C	0.020442	0.002703	3.91E-14
Triglyceride	rs4564803	G	T	-0.06872	0.002458	6.53E-172
Triglyceride	rs10172544	C	A	-0.01191	0.002091	1.21E-08
Triglyceride	rs6708784	A	G	-0.01345	0.002061	6.72E-11
Triglyceride	rs6432622	A	G	-0.01126	0.002057	4.32E-08
Triglyceride	rs2110690	A	G	0.011262	0.002059	4.50E-08
Triglyceride	rs4128205	A	C	0.012509	0.002072	1.56E-09
Triglyceride	rs13389219	C	T	-0.03812	0.002103	2.01E-73
Triglyceride	rs2943645	C	T	0.039947	0.002151	5.33E-77
Triglyceride	rs4675812	G	A	-0.01437	0.002088	5.78E-12
Triglyceride	rs1728918	A	G	-0.0823	0.00232	1.00E-200
Triglyceride	rs78058190	G	A	0.080843	0.005276	5.44E-53
Triglyceride	rs4665381	A	C	0.027301	0.002059	3.95E-40
Triglyceride	rs17326656	G	T	0.019274	0.002422	1.77E-15
Triglyceride	rs138033166	A	G	0.054578	0.008525	1.53E-10
Triglyceride	rs7563812	C	G	-0.0133	0.002171	9.05E-10
Triglyceride	rs3731696	A	G	0.022579	0.003151	7.74E-13
Triglyceride	rs6707559	C	T	-0.01287	0.002095	8.02E-10
Triglyceride	rs57074291	C	G	-0.0145	0.002343	6.07E-10
Triglyceride	rs9812100	G	A	-0.0141	0.00205	6.02E-12
Triglyceride	rs9831084	T	C	-0.01231	0.002056	2.14E-09
Triglyceride	rs13098603	G	A	0.011714	0.00213	3.82E-08

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs76824303	A	C	-0.02015	0.003515	9.81E-09
Triglyceride	rs13066793	A	G	-0.01965	0.003574	3.86E-08
Triglyceride	rs7642634	T	C	-0.01767	0.003043	6.35E-09
Triglyceride	rs6792725	A	G	-0.01758	0.002284	1.39E-14
Triglyceride	rs79287178	G	A	0.056335	0.00618	7.86E-20
Triglyceride	rs1899951	C	T	-0.02806	0.003123	2.63E-19
Triglyceride	rs62271373	T	A	0.04357	0.004403	4.33E-23
Triglyceride	rs11919048	C	T	0.021181	0.002956	7.74E-13
Triglyceride	rs79141906	A	C	-0.01274	0.002187	5.63E-09
Triglyceride	rs17052058	A	G	-0.03007	0.002655	9.63E-30
Triglyceride	rs684773	A	C	0.030154	0.002419	1.16E-35
Triglyceride	rs7631606	T	G	-0.01291	0.002331	3.04E-08
Triglyceride	rs12513287	C	T	0.028639	0.002784	8.05E-25
Triglyceride	rs144586415	G	GTT	0.016549	0.002415	7.25E-12
Triglyceride	rs3775228	C	T	0.035561	0.002096	1.52E-64
Triglyceride	rs3852087	A	C	-0.01574	0.00284	2.96E-08
Triglyceride	rs10857292	A	C	-0.01345	0.002136	2.98E-10
Triglyceride	rs13108218	A	G	-0.03123	0.002124	6.10E-49
Triglyceride	rs13101719	T	A	0.01883	0.002462	2.06E-14
Triglyceride	rs7676961	T	C	-0.01146	0.002048	2.20E-08
Triglyceride	rs77361663	C	A	-0.01184	0.002172	4.92E-08
Triglyceride	rs78025076	C	T	0.050198	0.007183	2.78E-12
Triglyceride	rs385715	T	C	0.012966	0.002234	6.51E-09
Triglyceride	rs1902176	T	G	0.012027	0.002146	2.09E-08
Triglyceride	rs986545	T	C	-0.01127	0.002049	3.84E-08
Triglyceride	rs2870238	C	T	0.014209	0.002046	3.83E-12
Triglyceride	rs2035816	A	G	-0.02999	0.003726	8.31E-16
Triglyceride	rs457134	G	C	-0.01145	0.002071	3.18E-08
Triglyceride	rs1347188	A	G	0.013482	0.002382	1.52E-08
Triglyceride	rs71603401	A	G	0.026049	0.003017	5.86E-18
Triglyceride	rs7684939	G	A	-0.01297	0.002045	2.25E-10
Triglyceride	rs7666808	G	C	-0.01147	0.00209	4.07E-08
Triglyceride	rs181193678	C	T	-0.01507	0.002155	2.68E-12
Triglyceride	rs154735	G	A	0.024538	0.004215	5.84E-09
Triglyceride	rs192219	T	C	-0.01275	0.002273	2.03E-08
Triglyceride	rs7735249	C	G	0.025774	0.00325	2.19E-15
Triglyceride	rs11429307	G	GT	0.044123	0.002612	4.98E-64
Triglyceride	rs142047875	A	T	-0.01327	0.00209	2.14E-10
Triglyceride	rs4976033	A	G	0.018966	0.002114	2.90E-19
Triglyceride	rs7704653	A	G	0.015927	0.002312	5.62E-12
Triglyceride	rs10519336	G	A	0.012829	0.002333	3.82E-08
Triglyceride	rs5870855	A	AT	-0.02131	0.002322	4.51E-20
Triglyceride	rs72801474	G	A	-0.02933	0.003522	8.32E-17
Triglyceride	rs2963431	C	T	0.015838	0.002413	5.25E-11
Triglyceride	rs62397245	C	G	0.015346	0.002473	5.49E-10
Triglyceride	rs6882076	T	C	0.035833	0.002124	7.62E-64
Triglyceride	rs593979	T	C	-0.01584	0.002111	6.31E-14
Triglyceride	rs61093427	C	T	-0.01587	0.002453	9.88E-11
Triglyceride	rs970069	C	T	0.018388	0.002502	1.98E-13

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs998584	C	A	0.040704	0.002055	2.42E-87
Triglyceride	rs2077111	A	G	-0.01971	0.002083	3.03E-21
Triglyceride	rs945890	A	T	0.013332	0.002273	4.50E-09
Triglyceride	rs186696265	C	T	-0.10902	0.008497	1.11E-37
Triglyceride	rs28359800	CAA	C	0.029221	0.002268	5.63E-38
Triglyceride	rs9353320	C	G	-0.01198	0.002091	1.00E-08
Triglyceride	rs72959041	G	A	0.06177	0.004752	1.22E-38
Triglyceride	rs73025562	G	A	0.014648	0.002389	8.70E-10
Triglyceride	rs35742417	C	A	-0.01595	0.002632	1.36E-09
Triglyceride	rs28383314	T	C	0.039203	0.002115	1.08E-76
Triglyceride	rs1064173	G	A	-0.0261	0.002373	3.83E-28
Triglyceride	rs9405533	A	G	-0.01181	0.002157	4.36E-08
Triglyceride	rs4710938	A	G	-0.01348	0.002054	5.38E-11
Triglyceride	rs28752924	T	C	0.031231	0.002133	1.48E-48
Triglyceride	rs707931	A	G	0.027323	0.004328	2.73E-10
Triglyceride	rs35834134	G	GA	-0.0154	0.002759	2.41E-08
Triglyceride	rs9264277	T	C	0.013956	0.002132	5.88E-11
Triglyceride	rs729761	T	G	0.016742	0.002282	2.19E-13
Triglyceride	rs62427982	C	T	-0.01465	0.002198	2.64E-11
Triglyceride	rs9480889	C	G	0.017568	0.002486	1.58E-12
Triglyceride	rs632057	T	G	-0.02933	0.002118	1.40E-43
Triglyceride	rs9403170	T	G	-0.01407	0.002547	3.31E-08
Triglyceride	rs77009508	A	G	0.048113	0.003882	2.77E-35
Triglyceride	rs38205	A	C	-0.01531	0.002134	7.15E-13
Triglyceride	rs4722551	T	C	-0.03778	0.002807	2.62E-41
Triglyceride	rs55896322	T	G	0.018535	0.003343	2.95E-08
Triglyceride	rs112182225	C	T	0.015304	0.002685	1.20E-08
Triglyceride	rs4731701	C	T	-0.03468	0.002057	9.54E-64
Triglyceride	rs56321085	G	A	0.021147	0.003699	1.08E-08
Triglyceride	rs34184329	C	T	0.018423	0.003093	2.58E-09
Triglyceride	rs852386	A	G	0.014142	0.002489	1.34E-08
Triglyceride	rs17138358	G	C	0.014704	0.002099	2.48E-12
Triglyceride	rs35797675	T	G	-0.09524	0.002507	1.00E-200
Triglyceride	rs6460043	T	C	-0.1076	0.008679	2.66E-35
Triglyceride	rs6465120	A	G	-0.01273	0.00205	5.28E-10
Triglyceride	rs2070971	G	T	0.026306	0.002989	1.36E-18
Triglyceride	rs183115140	T	A	0.079322	0.010382	2.17E-14
Triglyceride	rs12530679	A	G	-0.01145	0.002084	3.90E-08
Triglyceride	rs41785	C	A	-0.01435	0.002084	5.65E-12
Triglyceride	rs1406754	G	T	-0.02156	0.002105	1.24E-24
Triglyceride	rs2971669	C	T	0.016183	0.00249	8.08E-11
Triglyceride	rs4410790	T	C	0.017181	0.002132	7.73E-16
Triglyceride	rs62473520	T	C	-0.02193	0.003938	2.56E-08
Triglyceride	rs112206063	T	C	0.019665	0.002612	5.13E-14
Triglyceride	rs13269725	A	G	0.034846	0.003828	8.88E-20
Triglyceride	rs4500049	A	T	-0.0269	0.00207	1.29E-38
Triglyceride	rs1495743	G	C	-0.03779	0.002473	1.01E-52
Triglyceride	rs6999158	T	A	-0.08727	0.002276	1.00E-200
Triglyceride	rs12680217	T	C	-0.02555	0.004485	1.22E-08

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs2081687	T	C	-0.02688	0.002184	8.24E-35
Triglyceride	rs13255619	T	C	-0.01306	0.002095	4.58E-10
Triglyceride	rs35859536	C	T	-0.01378	0.002231	6.58E-10
Triglyceride	rs7832515	A	G	-0.01685	0.002666	2.62E-10
Triglyceride	rs2035889	T	A	-0.03918	0.002269	8.19E-67
Triglyceride	rs10957299	T	G	-0.01139	0.002085	4.71E-08
Triglyceride	rs11461788	G	GT	0.014574	0.002571	1.45E-08
Triglyceride	rs11781439	C	A	0.01555	0.002642	3.98E-09
Triglyceride	rs2954010	A	C	-0.01349	0.002072	7.45E-11
Triglyceride	rs4537315	A	G	0.048164	0.002116	1.03E-114
Triglyceride	rs2980858	T	C	-0.08437	0.002247	1.00E-200
Triglyceride	rs1567353	C	G	0.014137	0.002222	1.98E-10
Triglyceride	rs613444	G	A	0.012245	0.0022	2.62E-08
Triglyceride	rs28712486	C	A	-0.02108	0.00244	5.60E-18
Triglyceride	rs550057	C	T	-0.01878	0.002347	1.21E-15
Triglyceride	rs581080	G	C	0.015668	0.002663	3.99E-09
Triglyceride	rs12350739	G	A	-0.01314	0.002111	4.86E-10
Triglyceride	rs10797119	T	C	0.016317	0.002062	2.52E-15
Triglyceride	rs62565259	C	T	-0.01717	0.002721	2.79E-10
Triglyceride	rs1800978	C	G	-0.02816	0.003129	2.26E-19
Triglyceride	rs34619169	G	A	0.013699	0.002218	6.53E-10
Triglyceride	rs10795464	G	A	0.011804	0.002108	2.16E-08
Triglyceride	rs2068888	G	A	-0.03136	0.002055	1.49E-52
Triglyceride	rs2773469	A	G	-0.01819	0.002326	5.30E-15
Triglyceride	rs71508062	G	A	0.044793	0.007146	3.66E-10
Triglyceride	rs71473777	A	G	0.020412	0.003157	1.01E-10
Triglyceride	rs75398587	C	G	-0.02776	0.00401	4.38E-12
Triglyceride	rs55767272	A	C	-0.0302	0.004135	2.80E-13
Triglyceride	rs10882098	C	T	-0.01281	0.002088	8.54E-10
Triglyceride	rs74563318	C	A	-0.04301	0.005574	1.20E-14
Triglyceride	rs1133400	A	G	0.013433	0.002461	4.78E-08
Triglyceride	rs10786114	C	T	-0.02884	0.003091	1.06E-20
Triglyceride	rs140107293	A	G	-0.02471	0.002823	2.04E-18
Triglyceride	rs10822163	C	G	-0.03076	0.002051	7.55E-51
Triglyceride	rs878409	G	A	-0.01145	0.002061	2.71E-08
Triglyceride	rs1765142	C	A	-0.01217	0.002175	2.21E-08
Triglyceride	rs12294913	C	G	0.056257	0.004972	1.12E-29
Triglyceride	rs4930352	G	T	-0.01199	0.002109	1.30E-08
Triglyceride	rs61905132	C	T	0.215164	0.006632	1.00E-200
Triglyceride	rs7927024	T	C	-0.04307	0.006504	3.54E-11
Triglyceride	rs6486122	C	T	0.019915	0.002239	5.75E-19
Triglyceride	rs118178067	C	T	0.024242	0.004198	7.68E-09
Triglyceride	rs11030102	C	G	0.01746	0.002348	1.03E-13
Triglyceride	rs10750766	C	A	0.020306	0.002287	6.78E-19
Triglyceride	rs61905077	C	A	-0.27794	0.007271	1.00E-200
Triglyceride	rs76814754	C	T	-0.0476	0.007236	4.76E-11
Triglyceride	rs79610135	T	C	-0.03763	0.005486	6.90E-12
Triglyceride	rs142958146	A	G	0.3028	0.012621	3.33E-127
Triglyceride	rs4080140	G	A	-0.05493	0.007794	1.82E-12

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs141469619	A	G	0.33102	0.010872	1.00E-200
Triglyceride	rs11600815	G	A	-0.03257	0.00475	7.09E-12
Triglyceride	rs10838681	G	A	-0.028	0.002333	3.62E-33
Triglyceride	rs11229043	C	T	0.016726	0.003055	4.35E-08
Triglyceride	rs174574	A	C	-0.05084	0.002168	1.28E-121
Triglyceride	rs11237488	C	T	-0.01782	0.003143	1.43E-08
Triglyceride	rs45557239	C	T	-0.04759	0.00767	5.51E-10
Triglyceride	rs4909945	T	C	0.015415	0.002236	5.45E-12
Triglyceride	rs7117115	A	G	-0.01219	0.002109	7.33E-09
Triglyceride	rs141414463	C	T	0.214919	0.006915	1.00E-200
Triglyceride	rs74773964	T	C	-0.05154	0.007453	4.65E-12
Triglyceride	rs149137426	T	A	0.134098	0.008659	4.28E-54
Triglyceride	rs35192698	T	C	-0.06375	0.00777	2.31E-16
Triglyceride	rs142334475	G	A	-0.09266	0.009656	8.28E-22
Triglyceride	rs11057837	C	T	0.021433	0.003389	2.54E-10
Triglyceride	rs11064281	T	G	0.015914	0.002716	4.64E-09
Triglyceride	rs11045171	A	G	-0.0273	0.002585	4.48E-26
Triglyceride	rs11045866	A	C	0.025952	0.002885	2.38E-19
Triglyceride	rs36073309	G	A	-0.01307	0.002181	2.06E-09
Triglyceride	rs4760254	G	C	-0.02902	0.002384	4.19E-34
Triglyceride	rs12424054	G	A	0.020528	0.002418	2.08E-17
Triglyceride	rs76895963	T	G	-0.08957	0.007926	1.30E-29
Triglyceride	rs1032494	A	G	-0.01227	0.00222	3.23E-08
Triglyceride	rs1790099	C	T	0.015504	0.002262	7.15E-12
Triglyceride	rs4930724	T	C	-0.02631	0.002177	1.22E-33
Triglyceride	rs35763453	T	C	0.029112	0.004455	6.36E-11
Triglyceride	rs4761234	T	C	-0.01445	0.002053	1.95E-12
Triglyceride	rs863750	C	T	0.030684	0.002098	1.86E-48
Triglyceride	rs2182784	C	A	0.013591	0.00246	3.30E-08
Triglyceride	rs9561643	A	C	0.018173	0.002206	1.73E-16
Triglyceride	rs7140110	T	C	0.029471	0.002239	1.45E-39
Triglyceride	rs1340819	A	C	-0.01206	0.00215	2.03E-08
Triglyceride	rs41284816	G	T	-0.06123	0.007583	6.79E-16
Triglyceride	rs9604570	A	G	-0.02289	0.00264	4.26E-18
Triglyceride	rs1928496	C	T	0.018051	0.002336	1.09E-14
Triglyceride	rs10872918	C	A	0.015759	0.00289	4.96E-08
Triglyceride	rs12880341	T	C	0.022136	0.002814	3.65E-15
Triglyceride	rs2070341	C	T	0.011849	0.002092	1.47E-08
Triglyceride	rs61993685	T	C	-0.02531	0.003807	2.96E-11
Triglyceride	rs12891477	C	T	0.012957	0.002126	1.10E-09
Triglyceride	rs71413977	T	C	-0.0151	0.002573	4.37E-09
Triglyceride	rs11620989	A	G	0.012199	0.002102	6.47E-09
Triglyceride	rs1037117	G	A	0.019607	0.002361	1.01E-16
Triglyceride	rs7170463	A	G	-0.01508	0.002213	9.43E-12
Triglyceride	rs12442886	T	C	0.013672	0.002385	9.87E-09
Triglyceride	rs10152471	G	A	-0.01244	0.002107	3.55E-09
Triglyceride	rs139974673	T	C	0.146821	0.006565	8.95E-111
Triglyceride	rs1532085	A	G	-0.03201	0.002103	2.49E-52
Triglyceride	rs261334	G	C	-0.04617	0.002498	2.61E-76

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs12591786	C	T	-0.01912	0.002849	1.92E-11
Triglyceride	rs62012775	A	T	0.023199	0.002693	7.00E-18
Triglyceride	rs2925979	T	C	-0.03225	0.002231	2.36E-47
Triglyceride	rs4471666	T	G	-0.02343	0.004106	1.16E-08
Triglyceride	rs28577186	G	A	-0.0142	0.002179	7.11E-11
Triglyceride	rs143076454	G	A	0.04289	0.007584	1.56E-08
Triglyceride	rs11644601	T	C	-0.02834	0.002242	1.31E-36
Triglyceride	rs3814883	C	T	0.015661	0.002054	2.46E-14
Triglyceride	rs247617	C	A	-0.03271	0.002188	1.62E-50
Triglyceride	rs2937124	C	T	-0.01847	0.002183	2.58E-17
Triglyceride	rs34682685	G	A	0.033122	0.003349	4.55E-23
Triglyceride	rs12600110	T	C	-0.01617	0.00211	1.84E-14
Triglyceride	rs4843754	A	G	0.012403	0.002052	1.50E-09
Triglyceride	rs8073177	T	C	-0.01592	0.002454	8.89E-11
Triglyceride	rs591939	A	G	0.020038	0.002364	2.33E-17
Triglyceride	rs1801689	A	C	-0.06139	0.006022	2.09E-24
Triglyceride	rs11078597	T	C	0.020974	0.002625	1.34E-15
Triglyceride	rs9904004	A	G	0.041163	0.004285	7.52E-22
Triglyceride	rs1468270	C	T	-0.01981	0.002563	1.08E-14
Triglyceride	rs60856912	G	T	0.025474	0.002789	6.59E-20
Triglyceride	rs9889402	G	A	0.014576	0.002309	2.75E-10
Triglyceride	rs4969179	T	G	-0.01707	0.002094	3.63E-16
Triglyceride	rs2304969	G	T	-0.01663	0.002937	1.50E-08
Triglyceride	rs72836561	C	T	0.138147	0.005812	6.78E-125
Triglyceride	rs12601665	C	G	-0.01481	0.002082	1.11E-12
Triglyceride	rs1292060	A	G	0.013757	0.002247	9.16E-10
Triglyceride	rs62070804	C	T	0.048037	0.007728	5.11E-10
Triglyceride	rs4121765	G	A	-0.01245	0.002227	2.25E-08
Triglyceride	rs867939	G	A	-0.01329	0.002079	1.61E-10
Triglyceride	rs2510344	T	C	-0.01677	0.002046	2.43E-16
Triglyceride	rs41292412	C	T	0.060419	0.009438	1.54E-10
Triglyceride	rs6506033	C	T	-0.02348	0.00396	3.07E-09
Triglyceride	rs34690548	C	CAAA	0.020392	0.00357	1.12E-08
Triglyceride	rs58542926	C	T	-0.1056	0.003891	3.58E-162
Triglyceride	rs12891	G	C	-0.01165	0.002083	2.22E-08
Triglyceride	rs55803162	C	T	-0.01318	0.002186	1.64E-09
Triglyceride	rs483082	G	T	0.088813	0.002416	1.00E-200
Triglyceride	rs5112	C	G	0.069518	0.002206	1.00E-200
Triglyceride	rs739320	T	C	-0.02195	0.00215	1.76E-24
Triglyceride	rs8102873	C	T	0.011841	0.002083	1.32E-08
Triglyceride	rs11878235	G	A	-0.01417	0.002115	2.07E-11
Triglyceride	rs116843064	G	A	-0.22586	0.007469	1.00E-200
Triglyceride	rs62117489	C	A	-0.04352	0.004525	6.70E-22
Triglyceride	rs188247550	C	T	-0.13795	0.009323	1.53E-49
Triglyceride	rs71368855	C	T	0.026048	0.003236	8.27E-16
Triglyceride	rs62112763	C	G	0.020101	0.002076	3.64E-22
Triglyceride	rs62118471	T	C	0.042229	0.006727	3.45E-10
Triglyceride	rs10422861	C	T	-0.02122	0.002182	2.33E-22
Triglyceride	rs897764	T	C	0.025428	0.004151	9.05E-10

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs74698119	A	T	0.067123	0.008029	6.26E-17
Triglyceride	rs4809604	T	G	0.016007	0.002084	1.57E-14
Triglyceride	rs2738759	A	G	0.020959	0.003733	1.97E-08
Triglyceride	rs34587839	G	A	0.016788	0.002834	3.13E-09
Triglyceride	rs6063840	G	A	0.013111	0.002216	3.29E-09
Triglyceride	rs8126001	C	T	-0.01595	0.002052	7.82E-15
Triglyceride	rs151235402	C	T	0.05455	0.008279	4.42E-11
Triglyceride	rs6088889	C	A	0.01562	0.002861	4.76E-08
Triglyceride	rs2865390	T	C	0.016561	0.002085	2.00E-15
Triglyceride	rs146496844	G	A	0.059334	0.008471	2.48E-12
Triglyceride	rs6073958	T	C	0.055684	0.002567	2.40E-104
Triglyceride	rs8134638	T	C	0.013671	0.00211	9.32E-11
Triglyceride	rs5755799	C	G	0.012303	0.002055	2.13E-09
Triglyceride	rs2071887	T	A	0.016384	0.002153	2.75E-14
Triglyceride	rs140287	G	A	-0.0128	0.002085	8.18E-10
Triglyceride	rs134551	C	T	-0.01342	0.002167	5.89E-10
Triglyceride	rs2267373	C	T	0.02173	0.002074	1.11E-25
Triglyceride	rs9626823	G	A	0.023428	0.003254	6.07E-13

SNP: single nucleotide polymorphism; SE: standard error.

Supplementary Table 3. SNPs of Glucose

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Glucose	rs481443	G	C	0.021	0.0031	7.80E-12
Glucose	rs78444298	G	A	0.054	0.009	2.21E-09
Glucose	rs348330	G	A	-0.0159	0.0022	2.80E-13
Glucose	rs12139196	G	T	-0.015	0.0025	1.75E-09
Glucose	rs12089247	G	A	-0.0157	0.0023	1.04E-11
Glucose	rs3176447	T	A	-0.0186	0.0034	2.90E-08
Glucose	rs41276588	G	A	0.0222	0.0024	3.38E-20
Glucose	rs79687284	G	C	0.0818	0.0068	1.29E-33
Glucose	rs1260326	T	C	0.0362	0.002	7.50E-70
Glucose	rs115654069	C	T	0.0712	0.0124	9.67E-09
Glucose	rs12712928	G	C	0.041	0.0024	5.26E-64
Glucose	rs881309	C	A	0.0208	0.0033	2.59E-10
Glucose	rs2444769	C	A	-0.017	0.0028	1.33E-09
Glucose	rs560887	T	C	0.1491	0.0026	1.00E-200
Glucose	rs6743071	T	G	-0.0414	0.0041	1.18E-23
Glucose	rs143869345	A	G	0.1291	0.0099	3.75E-39
Glucose	rs2389615	T	C	0.0482	0.0037	6.50E-38
Glucose	rs7640470	G	A	0.0113	0.0021	4.47E-08
Glucose	rs9873618	G	A	-0.0549	0.0023	1.22E-124
Glucose	rs6808574	T	C	0.0196	0.0026	1.73E-14
Glucose	rs73174306	A	T	0.0475	0.0062	1.69E-14
Glucose	rs7650482	A	G	-0.0125	0.0021	5.24E-09
Glucose	rs11708067	A	G	-0.0509	0.0029	7.96E-70
Glucose	rs75206890	A	C	-0.0476	0.0058	4.13E-16
Glucose	rs73079003	G	A	-0.0208	0.0037	2.76E-08
Glucose	rs73018297	A	G	-0.0366	0.0065	1.76E-08
Glucose	rs11728350	A	G	0.0244	0.0037	3.24E-11
Glucose	rs376109082	G	GGTT	0.0169	0.0026	3.91E-11
Glucose	rs116401167	T	C	-0.0312	0.0036	6.61E-18
Glucose	rs1503884	T	G	0.0116	0.0021	2.55E-08
Glucose	rs4457054	G	C	-0.0203	0.0026	1.47E-14
Glucose	rs10476553	G	C	-0.0316	0.0028	1.76E-30
Glucose	rs6887717	A	T	0.0158	0.0025	2.37E-10
Glucose	rs392794	C	T	0.0125	0.0023	3.39E-08
Glucose	rs10223666	G	C	-0.0181	0.0024	4.50E-14
Glucose	rs9371670	C	G	0.0151	0.0021	6.28E-13
Glucose	rs693906	G	C	0.0202	0.003	3.34E-11
Glucose	rs727332	A	G	-0.0172	0.0024	1.13E-12
Glucose	rs57088429	G	A	-0.0169	0.0024	3.51E-12
Glucose	rs76823979	C	T	-0.0301	0.0032	2.28E-21
Glucose	rs7766070	C	A	0.027	0.0022	7.60E-35
Glucose	rs675495	C	T	-0.0161	0.0021	2.86E-14
Glucose	rs80097396	A	G	-0.0318	0.0046	3.13E-12
Glucose	rs188745922	C	T	0.038	0.0021	1.83E-71
Glucose	rs849133	C	T	-0.0131	0.0021	1.03E-09
Glucose	rs11763820	T	G	0.0138	0.0021	2.52E-11
Glucose	rs117892540	C	T	-0.0556	0.0082	1.36E-11
Glucose	rs221797	A	C	0.0279	0.0036	7.89E-15
Glucose	rs10265504	A	G	-0.0171	0.0022	2.47E-14
Glucose	rs76323047	A	G	0.0364	0.003	1.25E-33

(*Continued*)

Supplementary Table 3. SNPs of Glucose (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Glucose	rs1985469	A	T	0.1079	0.0032	1.00E-200
Glucose	rs17168486	C	T	0.0311	0.0024	2.28E-38
Glucose	rs718336	C	A	-0.0598	0.0082	3.99E-13
Glucose	rs3757974	A	G	0.0148	0.0021	2.14E-12
Glucose	rs9987289	A	G	-0.0442	0.0042	3.42E-26
Glucose	rs896854	T	C	-0.0148	0.0021	7.89E-13
Glucose	rs9650069	C	T	-0.0427	0.0021	4.66E-88
Glucose	rs10811656	C	T	0.0127	0.0021	1.57E-09
Glucose	rs28533815	T	C	0.0248	0.0025	8.02E-23
Glucose	rs12335452	G	C	-0.0485	0.0081	2.21E-09
Glucose	rs115478735	A	T	0.0288	0.003	3.92E-22
Glucose	rs4237150	G	C	0.0211	0.002	7.93E-25
Glucose	rs10811660	G	A	-0.03	0.0024	3.28E-36
Glucose	rs831277	A	T	0.0184	0.0026	3.41E-12
Glucose	rs11257655	C	T	0.0231	0.0023	2.52E-23
Glucose	rs7075575	A	G	0.0136	0.0024	1.67E-08
Glucose	rs12244654	C	T	-0.0525	0.0043	1.36E-33
Glucose	rs34872471	T	C	0.0508	0.0026	2.75E-85
Glucose	rs11015026	G	C	-0.0216	0.0032	1.87E-11
Glucose	rs174600	T	C	-0.0185	0.0021	3.61E-18
Glucose	rs3750952	G	C	-0.0156	0.0021	2.41E-13
Glucose	rs11039165	A	G	-0.0321	0.0027	1.51E-31
Glucose	rs117720468	G	C	0.0553	0.0081	9.31E-12
Glucose	rs5215	C	T	-0.0166	0.0021	1.97E-15
Glucose	rs1552224	A	C	-0.0241	0.0032	5.13E-14
Glucose	rs3842753	T	G	-0.0245	0.0026	1.70E-20
Glucose	rs2237897	C	T	-0.0409	0.0036	6.31E-30
Glucose	rs721156	C	T	-0.0443	0.0053	5.88E-17
Glucose	rs12581677	A	G	-0.0201	0.0036	3.34E-08
Glucose	rs36098511	A	T	0.0162	0.0024	9.62E-12
Glucose	rs76895963	T	G	-0.1053	0.0095	2.56E-28
Glucose	rs71274822	C	CT	-0.0198	0.0025	4.38E-15
Glucose	rs3741414	C	T	-0.0163	0.0029	1.76E-08
Glucose	rs55657684	A	T	0.032	0.0053	1.94E-09
Glucose	rs7997912	T	C	0.0316	0.0028	8.70E-30
Glucose	rs9579131	A	G	-0.0196	0.0025	6.81E-15
Glucose	rs11616380	G	T	-0.0161	0.0022	9.01E-13
Glucose	rs11626777	T	C	-0.0255	0.0023	1.74E-27
Glucose	rs1535464	G	A	-0.0144	0.0026	2.14E-08
Glucose	rs79548680	G	C	0.0144	0.0025	1.55E-08
Glucose	rs189400382	A	G	0.0174	0.0025	7.00E-12
Glucose	rs67507374	T	A	-0.0172	0.0025	1.04E-11
Glucose	rs11633054	A	G	0.0181	0.0022	6.44E-17
Glucose	rs3743140	G	A	0.0153	0.0028	4.58E-08
Glucose	rs2239741	T	C	-0.026	0.0032	1.05E-15
Glucose	rs9937521	C	T	0.0136	0.0021	2.55E-10
Glucose	rs8614	C	A	-0.0168	0.0023	8.22E-13
Glucose	rs62076542	C	T	0.0178	0.0025	9.83E-13
Glucose	rs62075838	C	T	0.0124	0.0021	3.82E-09

(*Continued*)

Supplementary Table 3. SNPs of Glucose (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Glucose	rs11418239	G	GA	0.0272	0.0036	2.15E-14
Glucose	rs4968204	C	T	-0.014	0.0024	7.83E-09
Glucose	rs1880900	T	C	-0.0128	0.002	3.89E-10
Glucose	rs11651755	C	T	-0.0172	0.0021	7.82E-17
Glucose	rs1808335	A	G	-0.019	0.0022	2.82E-17
Glucose	rs1964272	G	A	-0.0167	0.0025	2.08E-11
Glucose	rs3833331	A	AG	-0.0365	0.0036	1.35E-23
Glucose	rs8115194	C	T	-0.015	0.0026	8.00E-09
Glucose	rs7265519	C	T	-0.0156	0.0025	2.52E-10
Glucose	rs73155719	A	G	0.0139	0.0025	3.59E-08

SNP: single nucleotide polymorphism; SE: standard error.

Supplementary Table 4. SNPs of CAVS

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
CAVS	rs1999383	A	G	-0.07351	0.013426	4.38E-08
CAVS	rs11166276	C	T	0.147265	0.013215	7.64E-29
CAVS	rs11204664	T	C	0.078853	0.014272	3.29E-08
CAVS	rs17550940	A	C	0.110605	0.013547	3.23E-16
CAVS	rs665770	G	A	0.09374	0.013421	2.85E-12
CAVS	rs3902193	C	A	0.131192	0.023733	3.24E-08
CAVS	rs309306	C	T	-0.10839	0.013382	5.52E-16
CAVS	rs10185667	C	T	-0.13494	0.014772	6.57E-20
CAVS	rs1706003	G	T	-0.07507	0.013323	1.75E-08
CAVS	rs9999406	T	C	0.074275	0.013264	2.14E-08
CAVS	rs61320297	G	A	0.090625	0.016123	1.90E-08
CAVS	rs9285863	T	C	-0.08617	0.014395	2.15E-09
CAVS	rs6595383	C	T	-0.09136	0.016644	4.05E-08
CAVS	rs3129945	G	A	0.08831	0.015158	5.68E-09
CAVS	rs1819631	G	T	-0.08008	0.013359	2.04E-09
CAVS	rs7804522	G	C	0.075625	0.013252	1.15E-08
CAVS	rs1800797	A	G	-0.11771	0.013237	5.97E-19
CAVS	rs99780	C	T	-0.09828	0.013426	2.48E-13
CAVS	rs12785633	T	C	0.168577	0.029699	1.38E-08
CAVS	rs10744645	T	C	0.097806	0.016684	4.56E-09
CAVS	rs10770612	A	G	-0.10568	0.015928	3.25E-11
CAVS	rs149168595	G	T	-0.17707	0.032278	4.12E-08
CAVS	rs12427600	T	C	0.085846	0.01498	1.00E-08
CAVS	rs17774047	C	T	-0.09985	0.01584	2.91E-10
CAVS	rs62012588	G	A	0.094335	0.014331	4.63E-11
CAVS	rs186779791	C	T	0.17143	0.029004	3.41E-09
CAVS	rs4887815	A	C	0.096026	0.013416	8.22E-13
CAVS	rs9896030	C	G	-0.10855	0.016069	1.43E-11
CAVS	rs16950448	G	A	0.086428	0.015781	4.34E-08
CAVS	rs61140632	G	A	-0.09039	0.014823	1.08E-09
CAVS	rs143466522	G	A	0.347348	0.050515	6.15E-12
CAVS	rs77464740	C	T	0.184277	0.030735	2.03E-09

SNP: single nucleotide polymorphism; CAVS: calcific aortic valve stenosis; SE: standard error.

Supplementary Table 5. Statistical analysis results of exposures associated with CAVS

Exposure	Method	Nsnp	OR (95% CI)	*p*	*p* for H	MR Egger_intercept	*p* for P
TyG	MR Egger	60	2.06 (1.22, 3.49)	9.22E-03	5.23E-04	-7.39E-03	1.60E-01
	Weighted median	60	1.24 (0.83, 1.85)	2.95E-01			
	IVW	60	1.50 (1.12, 2.02)	7.29E-03			
	Simple mode	60	2.00 (0.87, 4.61)	1.10E-01			
	Weighted mode	60	1.47 (0.98, 2.22)	6.91E-02			
Triglyceride	MR Egger	201	1.19 (0.99, 1.44)	7.27E-02	1.89E-07	2.60E-03	2.85E-01
	Weighted median	201	1.18 (0.99, 1.40)	5.77E-02			
	IVW	201	1.29 (1.15, 1.45)	1.15E-05			
	Simple mode	201	1.08 (0.73, 1.59)	6.97E-01			
	Weighted mode	201	1.20 (1.01, 1.43)	4.09E-02			
Glucose	MR Egger	78	1.08 (0.87, 1.34)	4.68E-01	1.23E-03	4.80E-03	1.78E-01
	Weighted median	78	1.07 (0.89, 1.28)	4.61E-01			
	IVW	78	1.21 (1.05, 1.40)	1.03E-02			
	Simple mode	78	1.81 (1.20, 2.71)	5.49E-03			
	Weighted mode	78	1.17 (0.99, 1.37)	7.04E-02			

TyG: triglyceride-glucose index; OR: Odds ratio; IVW: Inverse variance weighted; CAVS: calcific aortic valve stenosis; P: pleiotropy; H: heterogeneity.

Supplementary Table 6. MVMR statistical analysis results of exposures associated with CAVS

Exposure	Method	Nsnp	OR (95% CI)	*p*	*p* for H	MR Egger_intercept	*p* for P
TyG	MR Egger	150	2.18 (1.60, 2.96)	1.74E-06	9.75E-05	-4.98E-03	9.61E-02
(crude analysis)	Weighted median	150	1.68 (1.28, 2.22)	2.06E-04			
	IVW	150	1.77 (1.47, 2.12)	1.13E-09			
	Simple mode	150	1.76 (0.99, 3.12)	5.48E-02			
	Weighted mode	150	1.72 (1.29, 2.28)	2.79E-04			
(r^2<0.001)	IVW	85	1.70 (1.33, 2.17)	2.20E-05	2.46E-04	-5.17E-03	2.23E-01
Adjusted for confounders	IVW	86	1.64 (1.18, 2.28)	3.01E-03	0.00E-00	-1.00E-02	9.60E-02
Triglyceride	MR Egger	245	1.28 (1.09, 1.50)	3.18E-03	3.87E-10	1.50E-04	9.46E-01
	Weighted median	245	1.25 (1.10, 1.43)	8.54E-04			
	IVW	245	1.28 (1.16, 1.41)	5.14E-07			
	Simple mode	245	1.19 (0.89, 1.60)	2.35E-01			
	Weighted mode	245	1.27 (1.10, 1.47)	1.56E-03			
Adjusted for confounders	IVW	148	1.20 (1.07, 1.35)	2.45E-03	0.00E-00	-3.00E-03	5.10E-02
Glucose	MR Egger	92	1.03 (0.83, 1.28)	7.71E-01	2.46E-05	6.23E-03	7.98E-02
	Weighted median	92	1.07 (0.89, 1.28)	4.70E-01			
	IVW	92	1.20 (1.04, 1.38)	1.11E-02			
	Simple mode	92	1.65 (1.08, 2.53)	2.27E-02			
	Weighted mode	92	1.12 (0.96, 1.30)	1.51E-01			
Adjusted confounders	IVW	54	1.25 (1.05, 1.49)	1.35E-02	0.00E-00	0.00E-00	9.37E-01

TyG: triglyceride-glucose index; OR: Odds ratio; IVW: Inverse variance weighted; MVMR: multivariable mendelian randomization; CAVS: calcific aortic valve stenosis; P: pleiotropy; H: heterogeneity.

Supplementary Table 7. Reverse statistical analysis results of CAVS associated with outcomes

Outcome	Method	Nsnp	OR (95% CI)	*p*	*p* for H	MR Egger_intercept	*p* for P
Triglyceride	MR Egger	25	0.99 (0.93, 1.05)	6.84E-01	7.20E-05	2.56E-03	4.31E-01
	Weighted median	25	1.00 (0.99, 1.02)	7.34E-01			
	IVW	25	1.01 (1.00, 1.03)	1.29E-01			
	Simple mode	25	1.00 (0.97, 1.03)	8.25E-01			
	Weighted mode	25	1.00 (0.98, 1.02)	8.83E-01			
Glucose	MR Egger	30	1.01 (0.99, 1.03)	5.16E-01	1.12E-01	-1.25E-04	9.22E-01
	Weighted median	30	1.00 (0.99, 1.01)	7.01E-01			
	IVW	30	1.01 (1.00, 1.02)	1.88E-01			
	Simple mode	30	1.00 (0.98, 1.02)	7.84E-01			
	Weighted mode	30	1.00 (0.99, 1.02)	6.85E-01			

OR: Odds ratio; IVW: Inverse variance weighted; CAVS: calcific aortic valve stenosis; P: pleiotropy; H: heterogeneity.

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Perennial Parameter for Intravenous Iron Therapy in Heart Failure: Reticulocyte Crisis

ABSTRACT

Background: Managing comorbidities alongside guideline-directed medical therapy is essential in heart failure (HF) treatment. Intravenous (IV) iron therapy is recommended for HF patients with left ventricular ejection fraction (LVEF) <50% to correct iron deficiency. Traditional markers such as ferritin and transferrin saturation (TSAT) are affected by inflammation and have delayed responses, limiting their clinical utility. This study aimed to evaluate early response to IV iron therapy by monitoring reticulocyte counts, a parameter unaffected by inflammation.

Methods: Hospitalized HF patients with LVEF <50% meeting CONFIRM-HF criteria for IV iron therapy were included. Reticulocyte counts were measured at admission and 72-120 hours post treatment. Associations with hemoglobin (Hb) increase at 1 month, hospital stay duration, emergency department (ED) readmissions, and mortality were assessed.

Results: Patients with ≥1 g/dL Hb increase at 1 month had higher reticulocyte levels at admission (2.0% vs. 1.5%, $P = .04$) and 72-120 hours post treatment (2.2% vs. 1.3%, $P = .004$). A ≥9% reticulocyte increase at 72-120 hours predicted Hb rise ≥1 g/dL with 90% specificity (area under the curve: 0.79, $P = .002$). Those with higher reticulocyte increases had shorter hospital stays (7 vs. 10 days, $P = .023$) and fewer ED readmissions (24% vs. 66%, $P = .004$). Higher reticulocyte and Hb levels correlated with reduced mortality over 2 years.

Conclusion: Reticulocyte increase within 72-120 hours after IV iron therapy offers an early, inflammation-independent marker of treatment response in HF patients, outperforming ferritin and TSAT. Elevated baseline reticulocytes may indicate active bone marrow and predict therapeutic benefit.

Keywords: Ferritin, heart failure, inflammation, iron deficiency, reticulocyte crisis

ORIGINAL INVESTIGATION

INTRODUCTION

Although substantial progress has been made in reducing hospitalizations and mortality through advancements in guideline-directed medical therapy and the increased adoption of cardiac resynchronization therapy, morbidity and mortality rates among patients with heart failure (HF) continue to be substantial.[1-3] This highlights the necessity of addressing comorbid conditions associated with HF management and underscores the need for alternative therapeutic approaches.[4]

Iron deficiency (ID) as a modifiable determinant is observed in 55% of patients with chronic HF and 80% of patients with acute heart failure (AHF). Current guidelines recommend regular anemia and ID screening in all HF patients. In symptomatic patients with HF with reduced ejection fraction and HF with mildly reduced ejection fraction, intravenous (IV) iron supplementation is recommended to alleviate HF symptoms and enhance quality of life and decrease hospital admissions.[5,6] Notably, it takes 4-10 weeks for hemoglobin (Hb) levels to return to normal after oral iron replacement and 3 months to correct erythrocyte parameters. However, the reticulocyte crisis that occurs 3-7 days after oral therapy has long been used as a parameter to assess early treatment response in children with ID anemia.[7-9] Reticulocytes need at least 3-4 days to mature from their synthesis in the bone marrow to become mature red blood cells (RBCs), with half of that time spent in the peripheral blood. Consequently, reticulocyte analysis and diagnosis of the iron levels can be facilitated by using the blood sample.

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Studies testing the efficacy of IV iron therapy frequently relied on surrogate markers, which require a longer time window.[10,11] Besides, it is well recognized that inflammation also affects markers utilized in therapy indication and response, such as ferritin and transferrin saturation (TSAT).[12]

In hospitalized patients with acute decompensated HF, the reticulocyte response—unaffected by inflammation—was evaluated following IV iron therapy as an early surrogate marker of Hb response.

METHODS

Study Population

Between January 1, 2020, and December 31, 2022, 251 hospitalized patients with acute decompensated HF and a left ventricular ejection fraction (LVEF) below 50% were screened after receiving IV iron therapy for iron deficiency anemia. IV iron therapy was administered according to the 2021 guidelines recommendations, specifically to patients with an LVEF of less than 50% with serum ferritin values below 100 ng/mL, or when serum ferritin values were between 100 and 299 ng/mL with TSAT below 20%.[3,4] Iron carboxymaltose was the only IV iron preparation available during that window. The treatment protocol was adjusted according to the CONFIRM-HF study. Since all of the HF cases had Hb <12 g/dL, a loading dose of 1000 mg was administered to all patients. For subjects <70 kg with Hb <10 g/dL at presentation, an additional dose of 500 mg was given at week 6, whereas for subjects ≥70 kg with Hb <10 g/dL, 1000 mg was administered at week 6, and 500 mg was given if Hb ≥10 g/dL as per recommended.[13]

Out of 251 eligible HF patients for IV therapy, 183 were excluded due to missing baseline or follow-up laboratory data or the absence of clinical follow-up data at the center. The remaining 68 HF patients with all available iron parameters, including ferritin, TSAT, Hb levels, and reticulocyte levels at baseline and 72-120 hours after IV iron therapy, along with clinical follow-up data, were considered.

The baseline data included demographic characteristics, iron parameters, brain natriuretic peptide (BNP), electrocardiogram, LVEF measured by Simpson's in transthoracic echocardiography, and C-reactive protein (CRP) as a marker of inflammation. Among the parameters, the reticulocyte measurement was specified as the percentage of reticulocytes, a portion of the total number of RBCs in the blood sample. The typical reticulocyte count spans from 0.5% to 2.5% in adults.[14] The primary endpoint was an increase in Hb levels in the first month. Secondary endpoints included duration of hospital stay, post-discharge emergency department (ED) or outpatient visits for worsening HF during 2-year follow-up and all-cause mortality. Worsening HF was defined as ED or outpatient visits for HF accompanied by elevated BNP levels and the presence of exacerbation of HF symptoms (dyspnea, orthopnea, and signs of congestion) according to the contemporary reports.[15] The institutional electronic health records system and the national mortality database were utilized to ascertain survival status and the date of death. The follow-up period was defined as the duration between the date of the initial administration and either the date of death or the last clinical visit.

The institutional ethics committee approved this analysis and followed the rights specified in the Declaration of Helsinki (2023/05-07, February 22, 2023). The written and verbal consent was obtained from the subjects.

Statistical Analysis

The statistical analysis was performed with SPSS version 29 (SPSS Inc., Chicago, IL, USA). Histograms and the Kolmogorov–Smirnov test validated the normal distribution of continuous variables. The continuous data are shown as median (interquartile range) and means ± SDs. Where suitable, 3 tests were utilized to assess differences between groups: the chi-square, Mann–Whitney *U*, and Student's *t*-test. The efficacy of reticulocyte crisis in forecasting Hb level elevation was assessed using receiver operating characteristic curves. The area under the curve (AUC) values were calculated, and statistical significance was determined with a threshold of $P < .05$.

RESULTS

Prospectively enrolled 68 following cases who received IV iron therapy with HF were considered. The average follow-up period was 2 years. The mean age of the patients was 69.5 ± 14 years, and 39% (n = 27) were female. Regarding the baseline characteristics, 58% (n = 39) had coronary artery disease, 77% (n = 52) had hypertension, 40% (n = 27) had diabetes mellitus, and 52% (n = 35) had chronic kidney disease. The mean LVEF was 43% ± 13. The median Hb value at presentation was 10 g/dL (8.4-10.9), and at the end of the first month, the median Hb was 11 g/dL (9.8-12). At the end of the first month following IV iron therapy, 82% (n = 55) yielded increased Hb levels by more than 1 g/dL. The median reticulocyte value at presentation was 1.8% (1.3-2.4), and the reticulocyte level at 72-120 hours was 2.1% (1.4-2.7) (Table 1).

During the 2-year follow-up, 15 patients (22%) died. Subjects were classified into 2 subsets based on whether they had an Hb increase of more than 1 g/dL in the first month. Compared to patients without an increase in Hb, those with an Hb increase had substantially lower mortality during the 2-year follow-up [9 out of 55 (16%) vs. 6 out of 13 (46%), $P = .011$], and significantly fewer ED visits due to worsening HF [13 out of 55 (24%) vs. 8 out of 13 (66%), $P = .004$]. Furthermore,

HIGHLIGHTS

- Reticulocyte count may serve as an early indicator of treatment response to intravenous iron therapy in patients with heart failure (HF).
- Although recent studies have failed to demonstrate a mortality benefit of intravenous iron in HF, reticulocyte levels may be associated with long-term mortality outcomes in this population.
- As a well-known yet underutilized parameter, reticulocyte count is unaffected by inflammation and responds rapidly, making it a potentially valuable tool in monitoring iron therapy efficacy in HF patients.

Table 1. Baseline Characteristics of the Patients

Baseline Characteristic	
Age, years, ±SD	69.5 ± 14
Sex, male, n (%)	41 (61)
Coronary artery disease, n (%)	39 (58)
Hypertension, n (%)	52 (77)
Diabetes mellitus, n (%)	27 (40)
Chronic kidney disease, n (%)	35 (52)
Malignancy, n (%)	3 (4.5)
Hb at admission, g/dL	10 (8.4-10.9)
Hb at 1st month, g/dL	11 (9.8-12)
Increased Hb >1 g/dL, n (%)	55 (82)
Ferritin at admission, µg/L	73 (22-163)
Ferritin at 1st month, µg/L	240 (121-453)
Reticulocyte at admission, 10^9/L	1.8 (1.3-2.4)
Reticulocyte at 48-72 hours, 10^9/L	2.1 (1.4-2.7)
Delta Reticulocyte >9%, n (%)	48 (71)
TSAT at admission, %	8.8 (5.5-15)
TSAT at 1st month, %	16.2 (10.4-24.5)
BNP at admission, pg/mL	619 (273-1568)
BNP at 1st month, pg/mL	396 (273-547)
TTE-LVEF (%)	43 ± 13
ECG, sinus rhtym, n (%)	26 (38)
Admission to the ED with AHF, n (%)	21 (31)
GFR, mL/min/1.73 m^2	60 ± 29
CRP, mg/L	20 (11.5-47)

AHF, acute heart failure; BNP, brain natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiogram; ED, emergency department; GFR, glomerular filtration rate; Hb, hemoglobin; LVEF, left ventricular ejection fraction; TSAT, transferrin saturation; TTE, transthoracic echocardiography.

in patients with an Hb increase, both the initial reticulocyte level [2.0 ± 0.9 vs. 1.5 ± 0.7, *P* = .040] and the reticulocyte level at 72-120 hours [2.2 ± 0.9 vs. 1.3 ± 0.7, *P* = .004] were significantly higher.

When comparing patients with and without Hb increase, no statistically significant difference was found in ferritin levels at pretreatment [66 ng/mL (22-63) vs. 144 ng/mL (31-163), *P* = .39] and at the end of the first month [234 ng/mL (120-420) vs. 359 ng/mL (185-898), *P* = .091]. Similarly, no statistical difference was observed in TSAT levels in the first month. However, in patients with a Hb increase, the baseline TSAT level was statistically significantly lower [7.9% (5.4-15) vs. 12% (8.5-21), *P* = .038] (Table 2). No notable statistical variation was detected between CRP levels, an alternative indicator of inflammation, and reticulocyte levels. Similarly, no significant disparity in CRP levels was found between patients with and without Hb increase.

Our study checked the difference between the reticulocyte count at 72-120 hours and the basal reticulocyte count as the "delta reticulocyte." Receiver operating characteristic curve analysis revealed that a delta reticulocyte level >9% at 72-120 hours significantly predicts a 1 g/dL increase in Hb at 1 month with 90% specificity (AUC: 0.79, CI: 0.67-0.91, *P* = .002) (Figure 1). Among patients with versus without <1 g/ dL Hb increase, those with >1 g/dL Hb increase had a higher frequency of delta reticulocyte levels greater than 9% [44 (80%) vs. 4 (33%), *P* = .001].

Similarly, patients with delta reticulocyte >9% had a statistically significant shorter hospital stay [10 days (6-17) vs. 7 days (3-10), *P* = .023]. Nevertheless, no statistically meaningful association was observed between the length of hospital stay and Hb levels (*P* = .110).

Worsening HF during follow-up was significantly less common in HF patients, with a 1-gr-Hb increase during the 2-year follow-up [13 (24%) vs. 8 (66%), *P* = .004] (Table 2).

All cause mortality was lower in HF subjects with delta reticulocyte >9% or 1-gr-Hb increase during the follow-up [delta reticulocyte >9%: 8 (53%) vs. 41 (78%), *P* = .015; Hb increase >1 g/dL: 9 (15%) vs. 46 (88%), *P* = .011].

Table 2. Comparison of Patients with and Without a ≥1 g/dL Hemoglobin Increase at the End of the First Month

	Hemoglobin Increase >1 g/dL (n = 54)	Without Hemoglobin Increase >1 g/dL (n = 12)	*P*
Mortality 2 years follow-up, n (%)	9 (16)	6 (50)	**.011**
Admission to the ED with AHF-2 years follow-up, n (%)	13 (24)	8 (66)	**.004**
Hb at 1st month, g/dL	11 ± 1.6	10 ± 1.3	**.040**
Ferritin at admission, µg/L	66 (22-63)	144 (31-163)	.390
Ferritin at 1st month, µg/L	234 (120-420)	359 (185-898)	.091
Reticulocyte at admission, 10^9/L	2.0 ± 0.9	1.5 ± 0.7	**.040**
Reticulocyte at 72 hours, 10^9/L	2.2 ± 0.9	1.3 ± 0.7	**.004**
Delta reticulocyte >9%, n (%)	44 (80)	4 (33)	**.001**
TSAT at admission, %	7.9 (5.4-15)	12 (8.5-21)	.038
TSAT at 1st month, %	15.6 (10.5-27)	20.2 (11-23.8)	.420
BNP at admission, pg/mL	554 (257-1340)	959 (332-3094)	.130
BNP at 1st month, pg/mL	378 (209-524)	475 (340-3506)	.180

AHF, acute heart failure; BNP, brain natriuretic peptide; ED, emergency department; Hb, hemoglobin; TSAT, transferrin saturation. *P*-values that reached statistical significance are highlighted in bold.

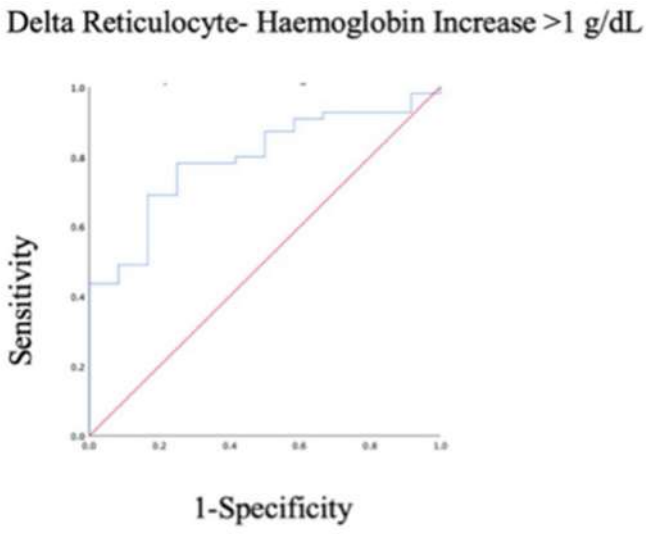

Figure 1. Receiver operating characteristic curve analysis: Delta reticulocyte-hemoglobin increase >1 g/dL. This study checked the difference between the reticulocyte count at 72-120 hours and the basal reticulocyte count, which is known as the "delta reticulocyte." Receiver operating characteristic curve analysis revealed that a delta reticulocyte level >9% at 72-120 hours significantly predicts a 1 g/dL increase in Hb at 1 month with 90% specificity (AUC: 0.79, CI: 0.67-0.91, *P* = .002).

A subgroup analysis was conducted on patients with a baseline TSAT of less than 20% (n = 59), for whom IV iron administration was indicated independently of ferritin levels. Among these patients, those who exhibited an Hb increase of >1 g/dL (n = 50) were compared to those who did not achieve this increase (n = 9), with a focus on the frequency of delta reticulocyte >9%. The group with increased Hb demonstrated a higher frequency of delta reticulocyte >9% [42 (84%) vs. 2 (22%), *P* < .001].

When comparing patients who experienced mortality (n = 15) and those who did not (n = 41) within this cohort, the group without mortality had a significantly greater occurrence of delta reticulocyte >9% [37 (82%) vs. 7 (50%), *P* = .016].

In a comparison between patients with baseline TSAT below and above 20%, no statistically significant variation was observed between the groups in terms of Hb increase (*P* = .120), reticulocyte increase (*P* = .110), mortality (*P* = .470), or hospital admissions due to AHF (*P* = .710) following IV iron therapy.

DISCUSSION

This study compared HF patients with or without a 1 g/dL Hb increase in the first month following IV iron therapy. It is well-known that Hb increase following iron therapy typically occurs between the 4th and 10th weeks.[16] When evaluating the reticulocyte levels, which is the main hypothesis of this study, the baseline reticulocyte levels were significantly frequent in cases with increased Hb (*P* = .04). It is assumed that the standard lifespan of a RBC is 120 days and that the duration of reticulocytes in peripheral blood is 1 day. From this, it can be inferred that in a person in a steady state, the reticulocytes at any given time would constitute 1/120th, or 0.8%, of all RBCs. The normal percentage ranges from 0.5% to 2%. The percentage of reticulocytes in peripheral blood indicates the RBC turnover rate if the patient is stable. The number of reticulocytes released into the blood reflects the erythropoiesis on a given day and can indicate active bone marrow.[17-19]

Based on the reticulocyte crisis observed during oral iron replacement, the control reticulocyte levels measured 72-120 hours after IV iron therapy were also statistically significantly frequent in cases with an Hb increase >1 g/dL. In the analysis of patients with a TSAT level <20%, delta reticulocyte levels were higher in patients who had an increase in Hb and in those who did not experience mortality during follow-up (*P* = .001, *P* = .016). The reticulocyte crisis may also be an appropriate parameter for assessing treatment response in patients with low TSAT. According to these results, reticulocyte levels could be an important parameter for assessing the early response to treatment (at 72-120 hours) without waiting for iron parameters at 12 weeks, which inflammation and infection may affect. The easily calculable delta reticulocyte level can also predict Hb increase with 90% specificity.

Low serum ferritin and TSAT levels in healthy individuals are reliable parameters for diagnosing ID. Still, ferritin, an acute-phase reactant, fluctuates in inflammatory conditions along with hepcidin levels. HF has long been associated with inflammation and inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1, and interleukin-6. This process complicates the diagnosis of functional ID. Therefore, in clinical studies related to HF, parameters used in the literature related to chronic kidney disease have been applied to define ID, such as ferritin levels <100 ng/mL or ferritin levels between 100 and 299 ng/mL with TSAT <20%. These criteria, first used in the FAIR-HF trial in 2008, have since become widely accepted for assessing ID in HF patients in subsequent studies.[20]

However, in a study conducted by Grote Beverborg and colleagues involving 42 HF patients undergoing coronary artery bypass surgery, these standards were evaluated against bone marrow iron staining results, which are regarded as the gold standard for diagnosing ID anemia. The study demonstrated that the FAIR-HF criteria exhibited a sensitivity of 82.4%, specificity of 72.0%, positive predictive value of 66.7%, and negative predictive value of 85.7%. Based on the FAIR-HF criteria, one-third of patients diagnosed with iron deficiency were found to have normal bone marrow iron stores.[21] Furthermore, it was shown that ferritin, as per the FAIR-HF criteria, was not associated with mortality, and evidence suggested that serum iron indices in HF could fluctuate and return to normal spontaneously without needing exogenous iron supplementation.[22,23]

These findings indicate that the currently recommended parameters may not accurately reflect ID anemia and may not be suitable for evaluating treatment responses.

Reticulocyte levels, which are less affected by these processes and directly reflect bone marrow activity, could be a more appropriate parameter.

This study's patient enrollment was based on the currently accepted FAIR-HF criteria. In this work, worsening HF events were less frequent in the group with >1 g/dL Hb increase. When comparing the results to other studies, the IRONMAN study evaluated composite outcomes of HF-related hospitalizations and cardiovascular death over an average follow-up of 2.7 years [risk ratio (RR): 0.82, 95% CI: 0.66-1.02; $P = .070$].[10] Similarly, the AFFIRM AHF study showed that hospitalizations for HF were less frequent in the group receiving IV iron therapy (RR: 0.74; 95% CI: 0.58-0.94, $P = .013$).[8] In addition, a meta-analysis by Graham et al[23], which incorporated 10 studies, revealed that IV iron therapy lowered the combined outcome of total HF hospitalizations and cardiovascular mortality (RR: 0.75, 95% CI: 0.61-0.93; $P < .01$).

In contrast to these studies, which compared IV iron treatment with usual care, the current work differentiated between patients who responded to IV iron therapy and those who did not. All-cause mortality during follow-up was also lower in the subgroup with >1 g/dL Hb increase ($P = .011$). However, in the IRONMAN and AFFIRM AHF studies, there was no statistically significant difference in cardiovascular mortality among patients who administered IV iron and those who did not.[10,11] This lack of benefit might be linked to negligence of the pathobiological response of IV iron therapy, as in the presence of a pathobiological link in the form of Hb increase, it seems there is a benefit.

It is recommended that ferritin and TSAT levels be monitored at 12, 24, and 36 weeks following the initiation of iron therapy.[24] In the CONFIRM-HF study, the treatment response was defined by increased ferritin levels to over 100 µg/L, or if ferritin levels were between 100 and 300 µg/L, a TSAT level above 20%.[13] Although different studies set varying targets, the parameters used remain consistent. However, no statistically significant differences were noted in the study's baseline and 1-month ferritin levels between patients with and without increased Hb ($P = .39$, $P = .091$). This could be attributed to ferritin acting as an acute-phase reactant. During malignancy and infection, ferritin concentrations rise to decrease the availability of unbound iron for tumor cells or pathogens, respectively, and are upregulated by pro-inflammatory cytokines. Inflammatory conditions increase ferritin levels while reducing transferrin levels, a negative acute-phase protein that carries iron. Ferritin sequesters iron and prolonged inflammation or malignancy can lead to anemia or chronic disease. Therefore, ferritin may not be a reliable marker for ongoing monitoring.[25,26]

Another parameter, TSAT levels, was lower in the group with a Hb increase ($P = .038$). However, there was no difference in TSAT values at the end of the first month ($P = .42$). This result may also be due to the influence of inflammation and infection on TSAT levels, similar to ferritin.[27,28]

Strengths and Limitations

The main strength of this work is based on an easily measurable but perennial parameter, i.e., the reticulocyte level, which, as a novel metric in this field, seems to work for

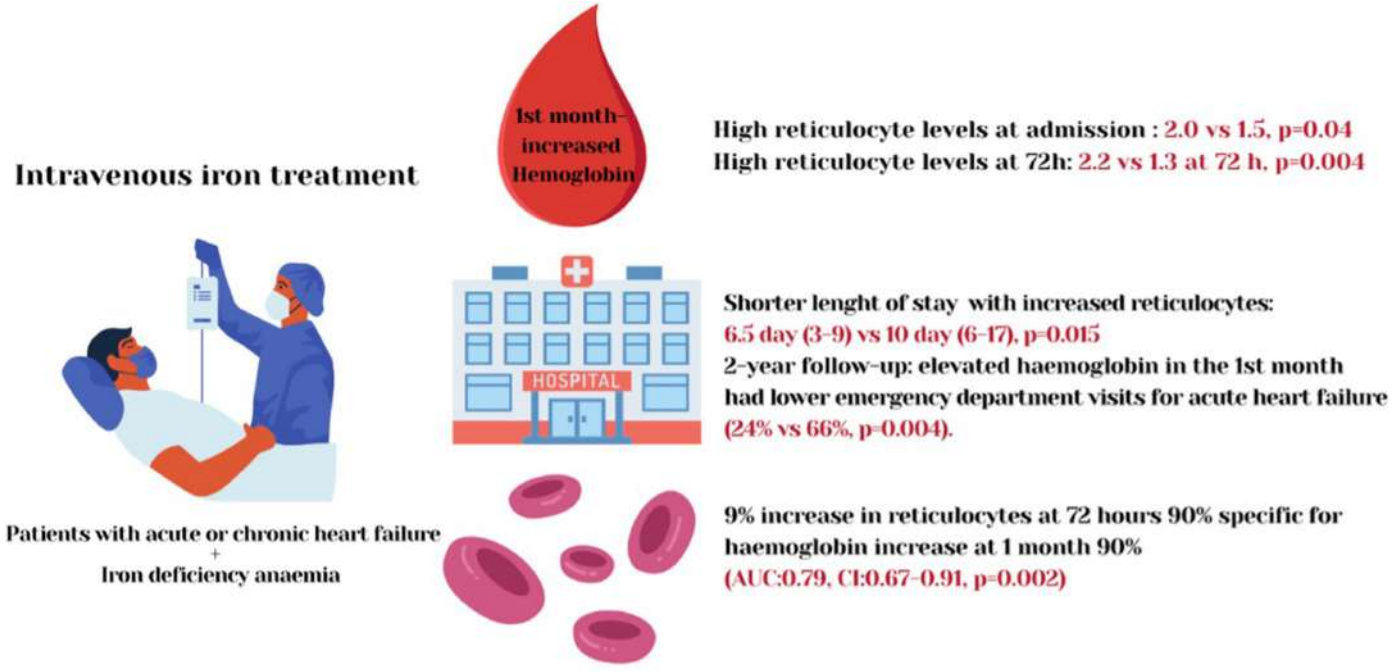

Figure 2. Central illustration. The central illustration summarizes the key findings: In patients receiving IV iron therapy for heart failure, those who exhibited increased Hb levels at 1 month had significantly higher reticulocyte levels at baseline and at 72 hours. Patients with an increase in reticulocyte levels had a shorter hospital stay. Over a 2-year follow-up period, those with increased Hb levels had significantly lower rates of heart failure-related hospitalizations. A delta reticulocyte level >9% was identified as 90% specific for predicting an increase in Hb at 1 month (AUC: 0.79, CI: 0.67-0.91, $P = .002$).

assessing the response to IV iron therapy in HF patients. This parameter, assessed at a very early stage, such as between 72 and 120 hours, remains unaltered by inflammation and predicts an increase in Hb by the end of the first month. It can be easily used in HF patients, where clinical progression is highly variable and patient monitoring is crucial.

The primary limitations of this work include the small sample size of a single-center experience and the unequal distribution of groups. Hence, only 68 patients could be included, as they were required to return for follow-up evaluations between 72 and 120 hours upon administration. While the sample size is limited for making definitive conclusions, power analysis indicated a sufficient power of 92% when comparing reticulocyte levels between patients with an Hb increase greater than 1 g/dL and those with an increase of less than 1 g/dL. Cardiovascular mortality could not be assessed to prevent the misclassification of deaths. Due to the small sample size, this study cannot establish a true causal relationship. Nevertheless, these findings may be a preliminary study showcasing the importance of reticulocyte levels in evaluating the response to IV iron therapy in HF patients. Other limitations of this study include potential laboratory errors in reticulocyte measurements, the absence of a defined cut-off value for Hb, the evaluation of increases relative to baseline, and the relatively short follow-up period. Nonetheless, this study found that a delta reticulocyte >9% was associated with 90% specificity in predicting Hb increase > 1 g/dL by the end of the first month.

CONCLUSION

This current study is among the first preliminary reports assessing reticulocyte levels and the response to IV iron therapy in HF. It is widely recognized that TSAT, ferritin, and Hb levels should be assessed before administering IV iron therapy. However, these variables are influenced by various conditions, such as inflammation and infection. They respond to treatment after 4-12 weeks. However, the reticulocyte level, which is unaffected by these factors, increases at 72-120 hours after treatment and can be used to evaluate the treatment response of patients in the early period. In addition, high reticulocyte levels on admission may indicate which patients will benefit from treatment as an indicator of active bone marrow (Figure 2).

Ethics Committee Approval: The Ethics Committee of Dokuz Eylül University approved this analysis and followed the rights specified in the Declaration of Helsinki (2023/05-07, February 22, 2023).

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

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Author Contributions: Concept - Z.K., Design: Z.K., Supervision - M.B.Y., Resource - Z.K., H.U., Materials - Z.K., H.U., Data Collection and Processing - Z.K., H.U., Analysis and Interpretation - Z.K., M.B.Y., Literature Search - Z.K., H.U., Writing - Z.K., M.B.Y., Critical Reviews - Z.K., M.B.Y.

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Turkish Real-Life Atrial Fibrillation in Clinical Practice: 2-Year Clinical Outcomes of the TRAFFIC Study

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ABSTRACT

Background: Atrial fibrillation (AF) is a major public health issue associated with thromboembolism and mortality. Real-world data from Türkiye are limited despite expanding use of non-vitamin K antagonist oral anticoagulants (NOACs). The Turkish Real Life Atrial Fibrillation in Clinical Practice (TRAFFIC) study aimed to characterize the demographic features, risk profiles, treatment patterns, and 2-year clinical outcomes of patients with non-valvular AF (NVAF) in Türkiye.

Methods: TRAFFIC was a national, prospective, multicenter, observational registry enrolling 1659 NVAF patients from 36 centers with 6-monthly follow-up for 24 months. Baseline data included demographics, comorbidities, CHA_2DS_2-VASc, HAS-BLED, AF subtype, European Heart Rhythm Association (EHRA) score, and antithrombotic therapy. Outcomes were ischemic stroke/systemic embolism (SE), major bleeding, and all-cause mortality. Predictors of mortality were evaluated using adjusted Cox regression, and associations of risk scores were explored using univariate Cox models with restricted cubic splines.

Results: Median age was 70 years, 48% female, with intermediate CHA_2DS_2-VASc (most 2-5) and low-to-intermediate HAS-BLED scores (most 0-2). Permanent AF was the most common subtype (48%). Antithrombotic therapy largely reflected risk profiles, with NOACs being the dominant treatment (65%). Over 2 years, all-cause mortality was 8.9%, ischemic stroke/SE 2.4%, and major bleeding 1.3%. In adjusted analysis, age, congestive heart failure, and diabetes mellitus were independent predictors of mortality. Both CHA_2DS_2-VASc and HAS-BLED scores showed threshold effects for mortality and thromboembolic risk but not for bleeding.

Conclusion: TRAFFIC provides contemporary Turkish NVAF data, showing lower event rates than historical cohorts. Outcomes are comparable with international registries; persistent mortality burden highlights the need for AF care beyond anticoagulation.

Keywords: Atrial fibrillation, NOAC, registries, TRAFFIC registry, Türkiye

INTRODUCTION

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia in the general population, imposes a significant global public health burden.[1] Beyond substantially increasing the risk of thromboembolic events, particularly ischemic stroke, AF is associated with heart failure, impaired quality of life, and increased mortality.[2,3] Large-scale studies in the literature have shown that the rates of cardiovascular and non-cardiovascular death in patients diagnosed with AF are considerable, and stroke is not the sole determinant of mortality.[4-6] Management strategies for AF, including thromboprophylaxis, rate- and rhythm-control approaches, and the management of associated comorbidities, have evolved significantly in recent years. Notably, the shift from vitamin K antagonists (VKAs) to direct oral anticoagulants (NOACs) for stroke prevention has altered treatment paradigms.[7]

Previous important data regarding the prevalence, incidence, and outcomes of AF in Türkiye were derived from the TEKHARF study, which included follow-up data until 2006-2007.[8] However, since then, developments in diagnostic and

therapeutic approaches and the widespread introduction of NOACs have necessitated the collection of contemporary real-world data. At the international level, large prospective registry studies like GARFIELD-AF have played a crucial role in elucidating the characteristics, treatment patterns, and clinical outcomes of AF patients in real-world settings.[9] These registries have demonstrated current practice variations and levels of guideline adherence across different geographies and care settings. Data from GARFIELD-AF, for instance, highlighted that the highest event rates (stroke, bleeding, mortality) occur in the early period after diagnosis and that mortality is a more frequent outcome than stroke.[10]

In this context, there was a need for a national, prospective, real-world registry to evaluate the current demographic characteristics, risk profiles, treatment patterns, and clinical outcomes of the contemporary AF patient population in Türkiye, reflecting the impact of evolving diagnostic and therapeutic approaches. The TRAFFIC (Turkish Real Life Atrial Fibrillation in Clinical Practice) study aims to prospectively examine the current management and 2-year clinical outcomes of NVAF patients across Türkiye. This study seeks to reveal the current state of AF management practice in Türkiye, provide a benchmark for comparison with international real-world data, and establish a foundation for future clinical practice and research.

METHODS

Study Design and Participants

The TRAFFIC study is a national, prospective, multicenter, observational registry conducted across Türkiye. The study protocol was reviewed and approved by an independent ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki.[11] Written informed consent was obtained from all participating patients.[12]

The study population comprised consecutive patients diagnosed with non-valvular atrial fibrillation (NVAF) aged 18 years and older, enrolled from 36 cardiology centers in 25 different cities across Türkiye between July 2020 and October 2022. The diagnosis of NVAF was confirmed by ECG or 24-hour Holter recording at the time of enrollment or within the preceding 6 weeks, or included patients with a medical history of AF who were currently receiving treatment. Patients with valvular AF (rheumatic mitral stenosis, mechanical or bioprosthetic heart valves), AF due to transient or reversible causes, and those with a life expectancy of less than 6 months that would preclude study participation were excluded. Only patients who attended at least the 6-month follow-up visit, thus allowing outcome assessment, were included in the final analysis. The selection of centers aimed to represent different geographical regions of Türkiye (according to the NUTS-2 classification).[13]

Data Collection

Patient data were collected prospectively through face-to-face clinical visits at baseline and subsequently at 6, 12, 18, and 24 months. During the data collection process, patients' demographic information, medical history (including comorbidities and risk factors), vital signs, AF symptoms (EHRA score), ECG and echocardiographic findings, CHA_2DS_2-VASc and HAS-BLED risk scores, applied interventional treatments (cardioversion, catheter ablation, etc.), and current antithrombotic and antiarrhythmic medications were recorded. Event data (ischemic stroke, systemic embolism [SE], major bleeding, all-cause mortality, cardiovascular death, non-cardiovascular death, and hospitalizations) were ascertained during follow-up visits and confirmed from medical records. Data were entered into web-based electronic case report forms (eCRFs).

Definitions and Endpoints

The definitions used in the study were based on standard clinical guidelines. CHA_2DS_2-VASc and HAS-BLED scores were used to assess patients' thromboembolic and bleeding risks, respectively.[14,15] The primary endpoints were defined as all-cause death, systemic thromboembolism (ischemic stroke/SE), and major bleeding. The definition and classification of events were based on relevant international standards.[14,15] Major bleeding was defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria as any fatal bleeding and/or symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) and/or a fall in hemoglobin ≥2 g/dL and/or transfusion of ≥2 units of blood.[16]

Statistical Analysis

Baseline characteristics and demographic data are presented using descriptive statistics. Continuous variables are expressed as median and interquartile range (IQR), while categorical variables are presented as counts and percentages.

Event rates for ischemic stroke/SE, major bleeding, and all-cause mortality over the 2-year follow-up period were calculated. Independent predictors for all-cause mortality were assessed using an adjusted Cox proportional hazards regression model. Factors considered in this model included age, congestive heart failure, diabetes mellitus, AF subtype (paroxysmal, persistent, newly diagnosed, long-standing persistent, permanent), and baseline antithrombotic treatment strategy (NOAC, VKA, antiplatelet alone, no therapy). Analysis results are presented with hazard ratios (HRs), 95% CIs, and statistical significance levels (*P*-value). The importance of each predictor's contribution to the model is reflected by the corresponding chi-square

HIGHLIGHTS

- Contemporary real-world Turkish NVAF data from the TRAFFIC registry show NOACs as the predominant antithrombotic strategy and overall low 2-year event rates.
- Two-year outcomes were favorable (mortality 8.9%, ischemic stroke/SE 2.4%, major bleeding 1.3%) and broadly comparable to international registries.
- Mortality was independently associated with age, heart failure, and diabetes, highlighting residual risk and the need for comprehensive AF care beyond anticoagulation.

statistic. Univariate associations between CHA_2DS_2-VASc and HAS-BLED scores and all-cause mortality, ischemic stroke/SE, and major bleeding were also investigated using Cox regression analyses. In these analyses, to model potential non-linear relationships between risk scores and endpoints, CHA_2DS_2-VASc and HAS-BLED scores were included in the model as restricted cubic splines with 3 knots. The results of these analyses are presented with HRs and 95% CIs, and changes in event risk across different values of the risk scores are evaluated. Statistical analyses were performed using R statistical software (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). A two-sided *P*-value of < .05 was considered statistically significant for all analyses.

RESULTS

From July 2020 to October 2022, a total of 1659 patients were prospectively enrolled with NVAF across 36 centers in 25 Turkish cities. However, in this study, only patients who completed at least the 6-month follow-up visit, enabling outcome assessment, were included in the analysis, resulting in a final cohort of 1442 patients. At baseline, the current cohort of 1659 patients (median age 70 years, IQR 62-77; 48% female) exhibited a wide spectrum of thromboembolic and bleeding risk, AF phenotypes, and symptom burden. CHA_2DS_2-VASc scores clustered between 2 and 5 (≈75% of patients), while HAS-BLED scores were predominantly 0-2 (≈86%). Across both risk scales, NOACs were the dominant therapy (~60%-80%), with VKAs and antiplatelets used infrequently and untreated rates dropping below 5% at higher CHA_2DS_2-VASc levels (Figure 1). Atrial fibrillation subtype was heterogeneous: nearly half (48%) had permanent AF, 23% paroxysmal, 19% newly diagnosed, 4.9% persistent, and 4.3% long-standing persistent. Symptom burden, measured by the EHRA score, also spanned the full spectrum: 14% were asymptomatic (EHRA I), 39% had mild symptoms not affecting daily life (EHRA IIa), 33% mild but troublesome symptoms (EHRA IIb), 13% marked limitation (EHRA III), and 1.4% severe symptoms at rest (EHRA IV). Valvular disease was present in one-quarter of patients: mitral regurgitation affected 50% (predominantly mild in 57%, moderate in 36%, severe in 6.7%), while aortic regurgitation was seen in 21% (82% mild, 17% moderate, 1.4% severe). Stenotic lesions were less common—mitral stenosis in 2.5% and aortic stenosis in 2.5%—but when present were mostly mild. Antithrombotic therapy reflected these risk profiles: 65% received a NOAC (32% rivaroxaban, 22% edoxaban, 19% apixaban, 3.2% dabigatran), 8.5% a VKA, 5.0% antiplatelet alone, and 11% no therapy. At the index admission, no patient had a prior history of left atrial appendage closure, whereas during follow-up 9 patients underwent the procedure. Rate control dominated management (77%), with rhythm-control interventions—pharmacological or electrical cardioversion, catheter ablation—applied in 15% of patients (Table 1).

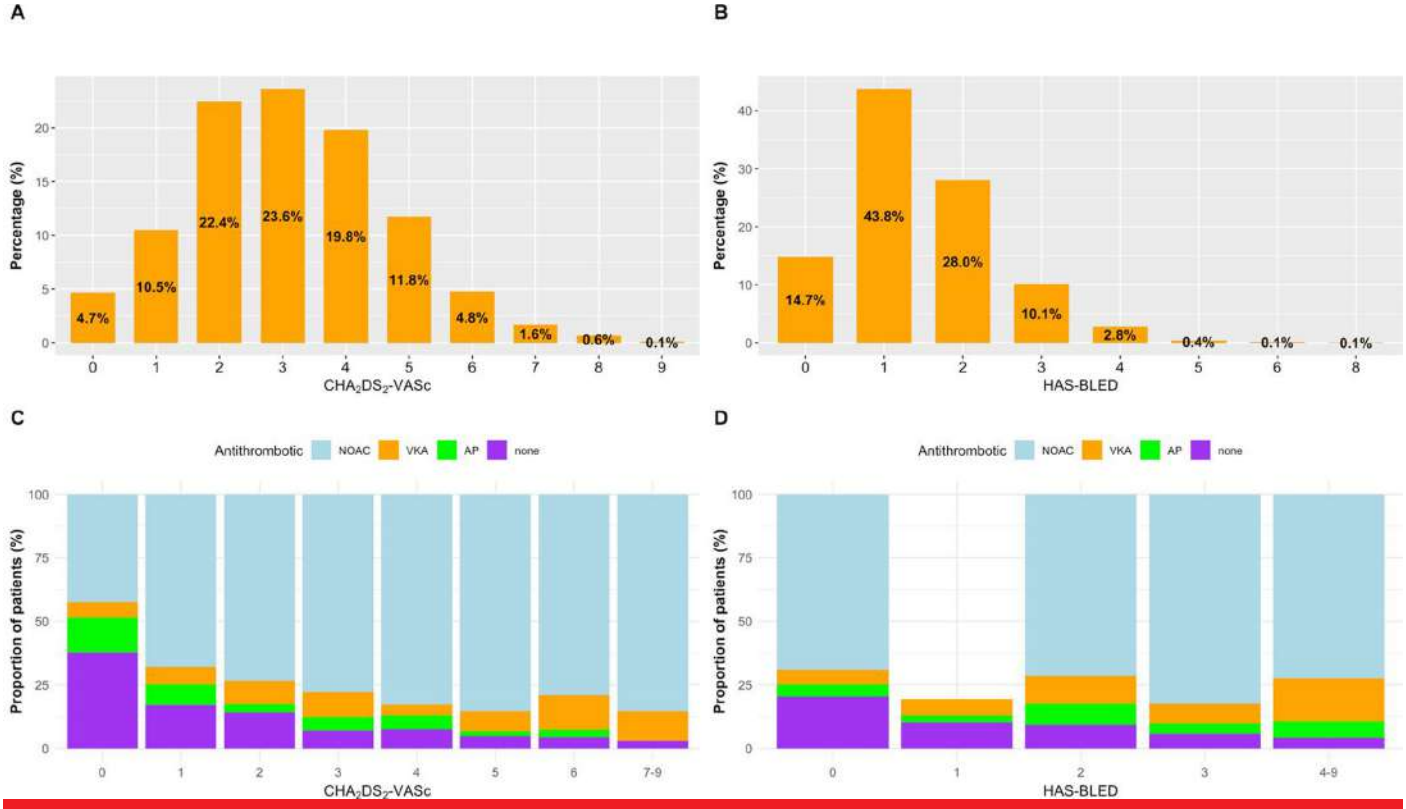

Figure 1. Distribution of risk scores and antithrombotic treatment patterns: (A) Distribution of CHA_2DS_2-VASc scores across the cohort. (B) Distribution of HAS-BLED scores across the cohort. (C) Proportion of patients receiving different antithrombotic treatments (NOAC, VKA, Antiplatelet (AP), or no treatment) according to CHA_2DS_2-VASc score categories. (D) Proportion of patients receiving different antithrombotic treatments according to HAS-BLED score categories.

Table 1. Baseline Clinicial Characteristics

Characteristic		Mortality (Yes) n = 126	Mortality (No) n = 1232	*P*
Age (years), median (quartiles)	70 (62, 77)	75 (69, 82)	70 (62, 76)	<.001
Age ≥ 75, n (%)	449 (32)	66 (52)	364 (30)	<.001
Age between 65 and 74, n (%)	526 (37)	39 (31)	471 (38)	.11
Age ≥ 65, n (%)	975 (69)	105 (83)	835 (68)	<.001
Gender (Female), n (%)	669 (48)	53 (42)	597 (49)	.2
Antithrombotics, n (%)				.004
None	152 (11)	23 (18)	127 (10)	
Antiplatelets	70 (5.0)	2 (1.6)	65 (5.3)	
Apixaban	263 (19)	19 (15)	228 (19)	
Dabigatran	45 (3.2)	3 (2.4)	42 (3.4)	
Edoxaban	314 (22)	26 (21)	281 (23)	
Rivaroxaban	448 (32)	38 (30)	393 (32)	
VKA	120 (8.5)	15(12)	96 (7.8)	
Coronary artery disease, n (%)	592 (42)	55 (44)	515 (42)	.7
Myocardial infarction, n (%)	206 (15)	20 (16)	181 (15)	.7
Peripheral artery disease, n (%)	41 (2.9)	5 (4.0)	36 (2.9)	.6
Rheumatic heart disease, n (%)	13 (0.9)	1 (0.8)	12 (1.0)	>.9
Dyslipidemia, n (%)	247 (18)	10 (7.9)	228 (19)	.003
Hyperthyroidism, n (%)	59 (4.2)	4 (3.2)	54 (4.4)	.5
Congestive heart failure, n (%)	254 (18)	43 (34)	194 (16)	<.001
Hypertension, n (%)	1010 (72)	87 (69)	838 (68)	.9
Systolic blood pressure >160 mm Hg, n (%)	217 (15)	29 (23)	182 (15)	.016
Diabetes mellitus, n (%)	454 (32)	47 (37)	393 (32)	.2
Previous stroke/systemic embolism, n (%)	131 (9.3)	12 (9.5)	112 (9.1)	.9
Vascular pathology, n (%)	299 (21)	31 (25)	254 (21)	.3
Abnormal kidney function, n (%)	124 (8.8)	24 (19)	96 (7.8)	<.001
Abnormal liver function, n (%)	15 (1.1)	2 (1.6)	13 (1.1)	.6
Bleeding history or diathesis, n (%)	62 (4.4)	6 (4.8)	53 (4.3)	.8
Unstable INR, n (%)	49 (3.5)	3 (2.4)	46 (3.8)	.6
Alcohol, n (%)	26 (1.9)	2 (1.6)	23 (1.9)	>.9
Use of bleeding-risk medications, n (%)	448 (32)	45 (36)	395 (32)	.4
Hemoglobin (g/dL)	13.4 (12.0, 14.6)	11.8 (10.6, 14.0)	13.5 (12.2, 14.6)	<.001
Platelet count (10^3/μL)	236 (197, 284)	222 (177, 272)	239 (200, 286)	.067
Creatinine (mg/dL)	0.91 (0.77, 1.11)	1.09 (0.85, 1.27)	0.90 (0.76, 1.10)	<.001
LDL (mg/dL)	101 (80, 130)	81 (64, 105)	102 (81, 130)	.004
Left atrial diameter (mm)	45 (40, 50)	47 (43, 51)	44 (40, 49)	<.001
LVEF (%)	55 (50, 60)	55 (40, 60)	57 (50, 60)	.001
Previous AF related treatment, n (%)				
Rhythm control	201 (15)	8 (6.6)	189 (16)	.008
Rate control	1065 (77)	88 (73)	927 (77)	.3
Electrical cardioversion	67 (4.9)	5 (4.1)	61 (5.1)	.7
Pharmacological cardioversion	147 (11)	9 (7.4)	131 (11)	.2
Catheter ablation	42 (3.0)	3 (2.5)	38 (3.2)	>.9
Device therapy	25 (1.8)	2 (1.7)	22 (1.8)	>.9

Eighty-four patients with unknown vital status were not included in the table.
AF, atrial fibrillation; VKA, vitamin K antagonist.

During the 2-year follow-up, 126 patients (8.9%) died—17 (1.2%) from cardiovascular causes, 51 (3.6%) from non-cardiovascular causes, and 58 (4.1%) of undetermined etiology. Ischemic stroke occurred in 26 (1.8%), Ischemic stroke/SE in 34 (2.4%), and major bleeding in 18 (1.3%). In the adjusted Cox model, each interquartile-range increase in age (from the 25th

to the 75th percentile, 62.3-77.3 years) was associated with a more than 2-fold higher hazard of death (HR 2.33; 95% CI 1.74-3.13; *P* < .001), and its chi-square statistic (31.4) reflected the greatest variable importance. Congestive heart failure (HR 2.62; 95% CI 1.76-3.88; *P* < .001; chi-square 22.9) and diabetes mellitus (HR 1.73; 95% CI 1.16-2.58; *P* = .007; chi-square 7.2) were the next most influential predictors. In contrast, sex, hypertension, vascular pathology, prior stroke/SE, and past bleeding showed no independent association with mortality. Among AF subtypes, persistent AF carried the highest risk relative to permanent AF (HR 2.26; 95% CI 1.17-4.37; *P* = .033; chi-square 10.5), whereas newly diagnosed, paroxysmal, and long-standing persistent forms did not significantly alter risk. Finally, antithrombotic strategy ranked fourth in importance (chi-square 13.4; *P* = .031 overall): lack of anticoagulation (HR 2.22; 95% CI 1.25-3.92) and VKA use (HR 1.92; 95% CI 1.09-3.37) were each linked to higher mortality compared with NOAC therapy (Table 2).

To explore unadjusted associations, it was found that both CHA_2DS_2-VASc and HAS-BLED scores exhibit threshold effects for mortality and thromboembolic risk, but not for bleeding. In the upper row (panels A–C), CHA_2DS_2-VASc points below approximately 2 carry minimal change in hazard, whereas an interquartile-range increase in score (from the 25th to the 75th percentile) corresponds to a 36% higher unadjusted risk of all-cause death (HR 1.36; 95% CI 1.08-1.71; *P* = .002) and an 81% higher risk of stroke or SE (HR 1.81; 95% CI 1.04-3.14; *P* = .021). By contrast, the bleeding curve remains essentially flat across the same CHA_2DS_2-VASc range (HR 1.04; 95% CI 0.58-1.87; *P* = .947), indicating no clear relationship. In the lower row (panels D-F), a similar pattern emerges for HAS-BLED: an interquartile rise from score 1 to 2 predicts a 47% increase in mortality risk (HR 1.47; 95% CI 1.21-1.79; *P* < .001) and a 47% increase in stroke/SE risk (HR 1.47; 95% CI 1.02-2.12; *P* = .037), yet again without a significant uptick in major bleeding (HR 1.05; 95% CI 0.68-1.62; *P* = .778) (Figure 2).

Table 2. Factors Associated with All-Cause Mortality

Variables	HR	Lower 95% CI	Upper 95% CI	*P*	Chi-square
Age (from 62.3 to 77.3 years)	2.33	1.74	3.13	<.001	31.4
Gender (female sex)	0.89	0.61	1.30	.543	0.37
Diabetes (yes)	1.73	1.16	2.58	.007	7.2
Hypertension (yes)	0.74	0.48	1.13	.161	1.96
Congestive heart failure (yes)	2.62	1.76	3.88	<.001	22.9
Vascular pathology (yes)	0.98	0.63	1.51	.912	0.01
Previous Stroke/SE (yes)	0.83	0.44	1.54	.556	0.35
Past bleeding (yes)	1.24	0.54	2.87	.608	0.26
AF type (ref: Permanent)				.033	10.5
Newly diagnosed	1.89	1.16	3.11		
Paroxymal	1.18	0.66	2.08		
Persistent	2.26	1.17	4.37		
Long-standing persistent	1.28	0.51	3.22		
Antithrombotic (ref: NOAC)				.031	13.4
None	2.22	1.25	3.92		
Antiplatelets	0.40	0.09	1.66		
VKA	1.92	1.09	3.37		

AF, atrial fibrillation; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism; VKA, vitamin K antagonist.

DISCUSSION

This prospective nationwide cohort study provides contemporary data on the demographic characteristics, risk profiles, treatment patterns, and clinical outcomes of 1659 Turkish patients with NVAF enrolled between July 2020 and October 2022. The current findings reflect a broad spectrum of thromboembolic and bleeding risks, diverse AF phenotypes, and varying symptom burdens, aligning closely with international registries while highlighting distinct regional trends.[17-19]

Our cohort exhibited intermediate event rates compared with historical national data and recent international registries.[8,9,19] Specifically, the 1-year stroke/TIA rate (~2%) was notably lower than the earlier Turkish TRAF study (~6.9%) yet remained higher compared to recent European EORP-AF registry (~0.7%).[20,21] This improvement likely stems from increased adherence to guideline-driven anticoagulation practices, particularly the rising use of non-vitamin K antagonist oral anticoagulants (NOACs). Nonetheless, the persistent gap with contemporary European cohorts underscores ongoing opportunities for optimizing stroke prevention through improved risk-factor management and enhanced adherence to anticoagulation regimens.

Similarly, the all-cause mortality rate (~6-7% annually) observed in this cohort occupies an intermediate position—lower than historical Turkish data (TRAF, 11.5%) but higher compared to recent European data (EORP-AF, 5.2%).[20,21] Factors such as differences in patient age, comorbid conditions, and healthcare delivery models may account for this disparity. Importantly, these results reinforce the protective effect of NOAC use over VKAs, as patients on NOAC therapy exhibited better outcomes, a finding consistent with international observations, including GARFIELD-AF and EORP-AF registries.[9,21]

Regarding major bleeding events (~2% per year), these findings are broadly similar to both historical national (TRAF, 2.0%) and recent European data (EORP-AF, 2.3%), indicating that modern anticoagulation strategies in Türkiye effectively manage bleeding risks at acceptable levels.[20,22] Notably, the timing of events revealed a higher incidence during the initial 6 months post-enrollment, underscoring the necessity for intensified patient monitoring and support during the early treatment phase.

Treatment patterns in the current cohort strongly reflected current European Society of Cardiology (ESC) guidelines, with widespread anticoagulant use among high-risk patients, predominantly NOACs.[14] This

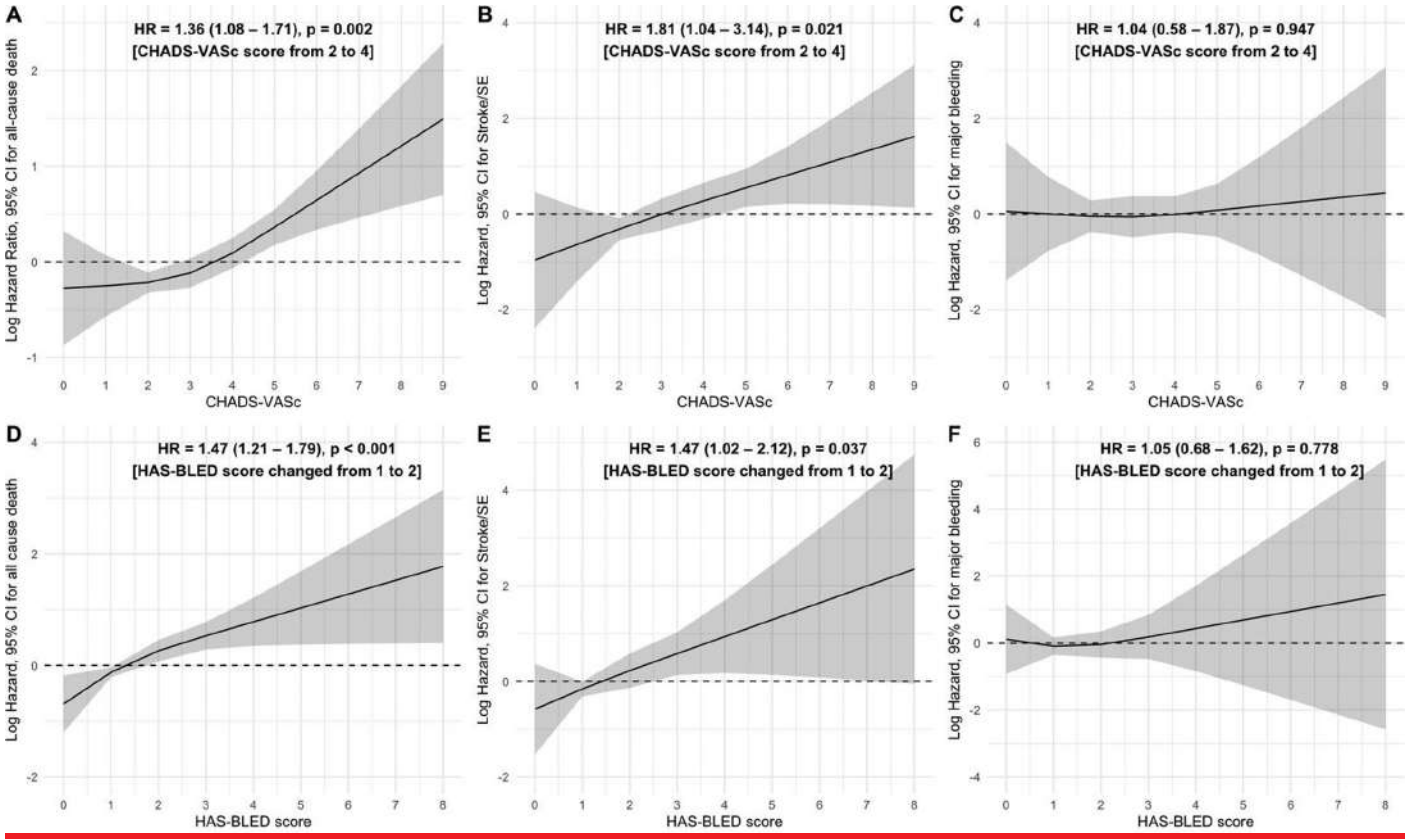

Figure 2. Association between risk scores and clinical outcomes: (A) Hazard ratio (HR) and 95% CI for all-cause mortality with changes in CHA_2DS_2-VASc score from 2 to 4. (B) HR and 95% CI for stroke/systemic embolism with changes in CHA_2DS_2-VASc score from 2 to 4. (C) HR and 95% CI for major bleeding with changes in CHA_2DS_2-VASc score from 2 to 4. (D) HR and 95% CI for all-cause mortality with changes in HAS-BLED score from 1 to 2. (E) HR and 95% CI for stroke/systemic embolism with changes in HAS-BLED score from 1 to 2. (F) HR and 95% CI for major bleeding with changes in HAS-BLED score from 1 to 2.

represents a significant shift from earlier practices dominated by VKAs, underscoring an evolution toward safer and more effective therapies. Compared to EORP-AF (2017-2018), where NOAC use was 33%, this study reported a much higher rate (65%), highlighting improved guideline adherence and increased NOAC availability in Türkiye.[23] This transition likely contributed to the observed reduction in thromboembolic events. Furthermore, the current analysis reaffirmed the prognostic importance of AF subtypes. Persistent and permanent AF were associated with higher morbidity and mortality compared to paroxysmal AF, aligning with findings from EORP-AF and other international registries.[24-26] Thus, AF subtype should continue to inform risk stratification and management strategies beyond standard risk scores. Risk stratification tools—CHA_2DS_2-VASc and HAS-BLED scores—demonstrated moderate predictive value, effectively identifying patients at very low risk of events, thus validating their continued use per ESC guidelines.[14]

Clinical implications of this study highlight the tangible benefits of modern NVAF management strategies, particularly widespread anticoagulation with NOACs, in reducing stroke risk. However, the notable residual annual mortality (~6%-7%) emphasizes that comprehensive AF care must extend beyond anticoagulation to include rigorous risk-factor modification, symptom management, and targeted rhythm or rate control interventions.

Strengths of this study include its large sample size, nationwide scope covering diverse geographic regions, and a rigorous prospective design with a comprehensive data collection strategy over a substantial 2-year follow-up period. These factors enhance the generalizability and relevance of these findings. Nevertheless, the current study has several limitations. First, its observational nature precludes definitive causal conclusions. Additionally, the 2-year follow-up, while informative, may not fully capture long-term outcomes. Potential biases arising from center selection and variability in data adjudication could influence results, limiting generalizability. Detailed socio-economic and educational factors influencing treatment adherence and outcomes were not extensively captured. These considerations underline the importance of cautious interpretation and the need for continued, longer-term research.

CONCLUSION

In conclusion, the large-scale, multicenter Turkish cohort demonstrates significantly improved outcomes compared to historical national data, aligning closely with international registries, driven predominantly by increased NOAC utilization and guideline-concordant practices. However, residual

morbidity and mortality highlight the need for continued emphasis on comprehensive AF management strategies. These findings provide a valuable benchmark for Türkiye and contribute to global efforts toward evidence-based NVAF care optimization.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Republic of Turkey Ministry of Health and the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (29/03/2021-HNEAH-KAEK 2019/KK/150).

Informed Consent: All subjects gave their informed consent for inclusion before they participated in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.Y.K., I.H.T.; Design – C.Y.K., I.H.T.; Supervision – M.A.A., F.V.A.; Resources – A.S.Y., G.A.; Materials – U.U., B.Ş.; Data Collection and/or Processing – A.O.A., F.Ö.; Analysis and/or Interpretation – İ.H.T.; Literature Search – B.C.K., Ü.G.; Writing – İ.H.T., C.Y.K.; Critical Review – M.A.A., F.V.A.

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Ventricular Tachycardia Caused by Moderator Band in a Patient with Thalassemia Major

CASE REPORT

INTRODUCTION

Heart failure and arrhythmias associated with cardiac iron overload are known to occur in patients with thalassemia major.[1] Among arrhythmia cases, atrial and ventricular tachycardia (VT) cases have been previously reported.[1,2] This case presents a rare type of VT originating from the right ventricular moderator band.

CASE REPORT

A 27-year-old female patient diagnosed with thalassemia major, who was taking deferasirox 1 × 1440 mg, presented to the emergency department with palpitations. Ventricular tachycardia was observed on the electrocardiogram (ECG) in the emergency department (Figure 1). Rhythm control could not be maintained with intravenous 10 mg metoprolol and intravenous 300 mg amiodarone. Synchronized electrical cardioversion with 100 J was done, and sinus rhythm was provided (Figures 2 and 3). The patient was administered amiodarone 200 mg 3 × 1 and metoprolol 50 mg 2 × 1. The patient's blood tests showed hemoglobin 9.5 g/dL, iron 177 µg/dL, iron-binding capacity 30 µg/dL, total iron-binding capacity 207 µg/dL, and ferritin 7484 µg/L. An echocardiogram performed on the patient showed a left ventricular ejection fraction of 50%, second-degree tricuspid regurgitation, and a systolic pulmonary artery pressure of 35 mmHg. Cardiac magnetic resonance imaging revealed a myocardial T2* time of 2.5 milliseconds and severe iron accumulation (Figure 4). The patient underwent implantation of a ventricular chamber implantable cardioverter defibrillator. Follow-up device recordings showed ongoing VT episodes, and the patient underwent three-dimensional mapping. Right ventricular mapping performed with ECG-guided pace mapping demonstrated VT with a right ventricle (RV) moderate band morphology, 95% consistent with the mapping (Figures 5 and 6, Videos 1 and 2). These areas were ablated with 50 W radiofrequency (RF) ablation energy to achieve homogenization. No VT episodes were observed in the patient during follow-up.

DISCUSSION

Cardiac side effects are seen in patients with thalassemia major due to iron accumulation. While heart failure is the most common cause of death among these patients, it is known that deaths due to QT prolongation, ventricular arrhythmia, and torsades de pointes related to iron accumulation are also seen.[1,3] Arrhythmias are usually reentrant tachycardias.[1] Studies in patients with thalassemia major have found that patients with iron loading <10 milliseconds on the T2 sequence of cardiac MRI have a high risk of ventricular arrhythmia and a high risk of developing heart failure.[1,4] In this patient, the T2 sequence duration was less than 10 milliseconds on the MRI, and a VT episode was present.

In the literature, no patient has been reported with both thalassemia major and VT caused by a moderator band. This patient is unique in this point. The moderator band is a structure extending from the septum to the anterior papillary muscle of the right ventricle. It can cause ventricular arrhythmias, ventricular extrasystoles, VT, and ventricular fibrillation.[5,6] It has been demonstrated in animal experiments

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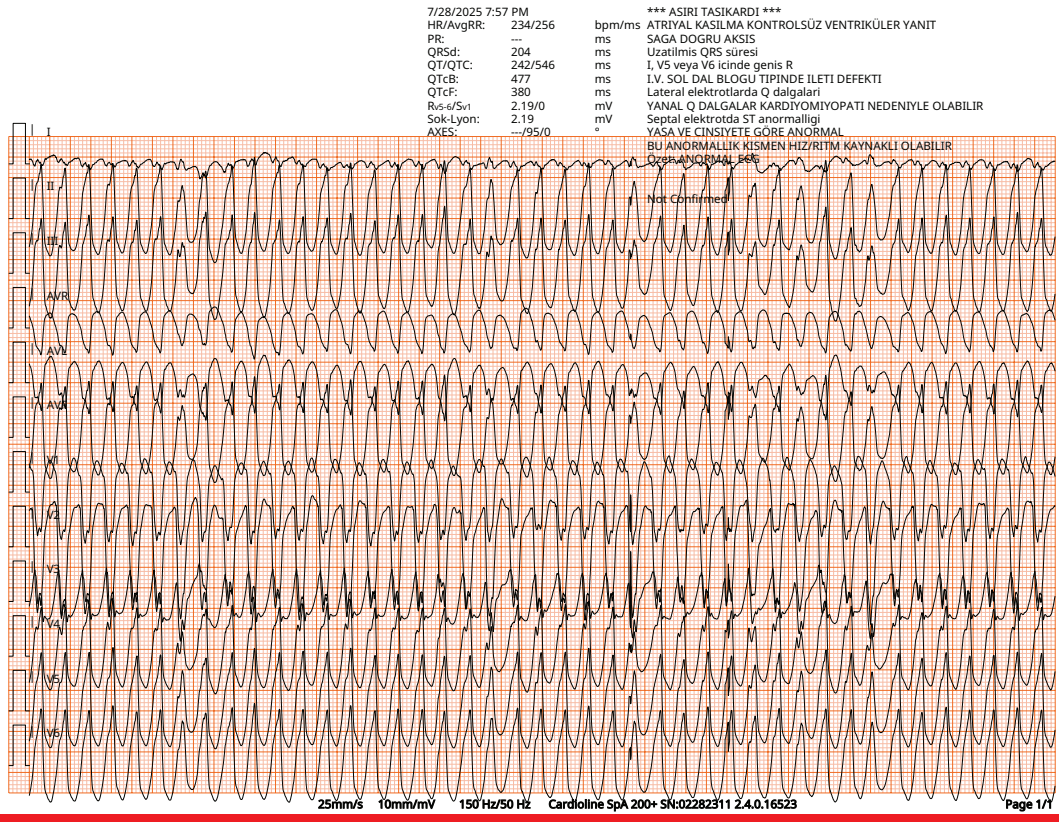

Figure 1. Patient's electrocardiogram with ventricular tachycardia.

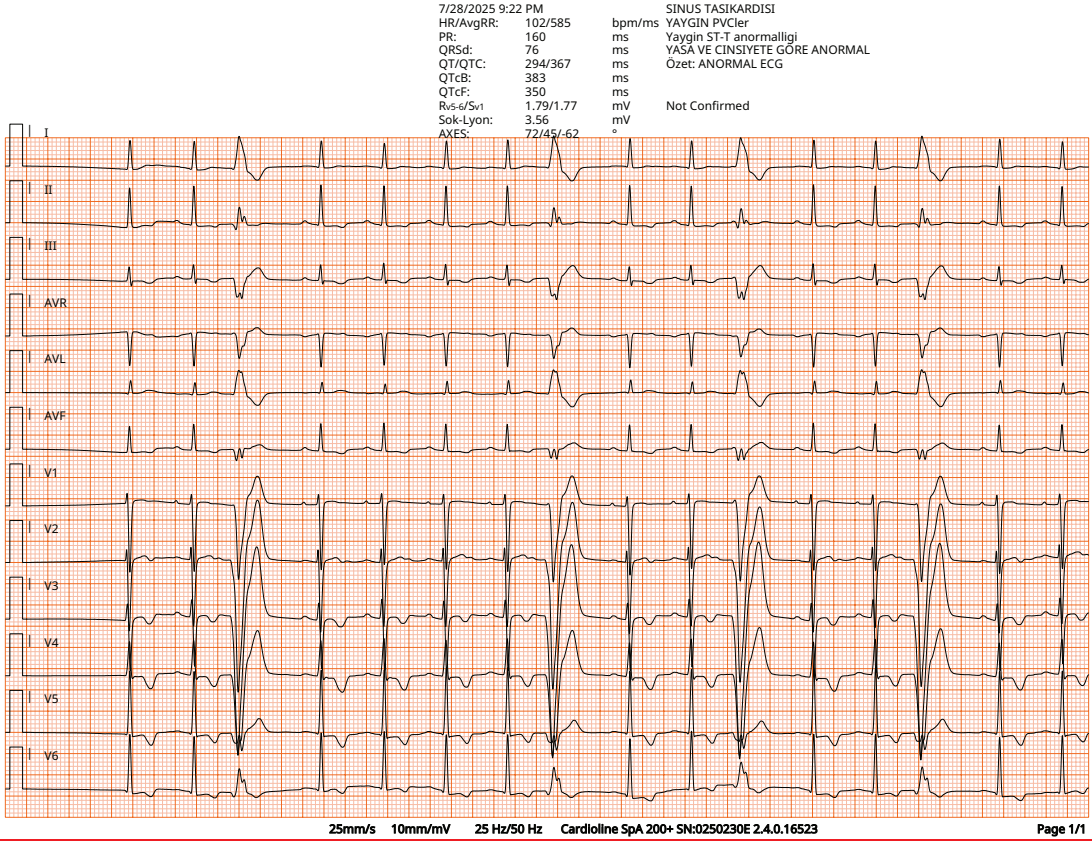

Figure 2. Patient's electrocardiogram with ventricular extrasystoles in sinus rhythm.

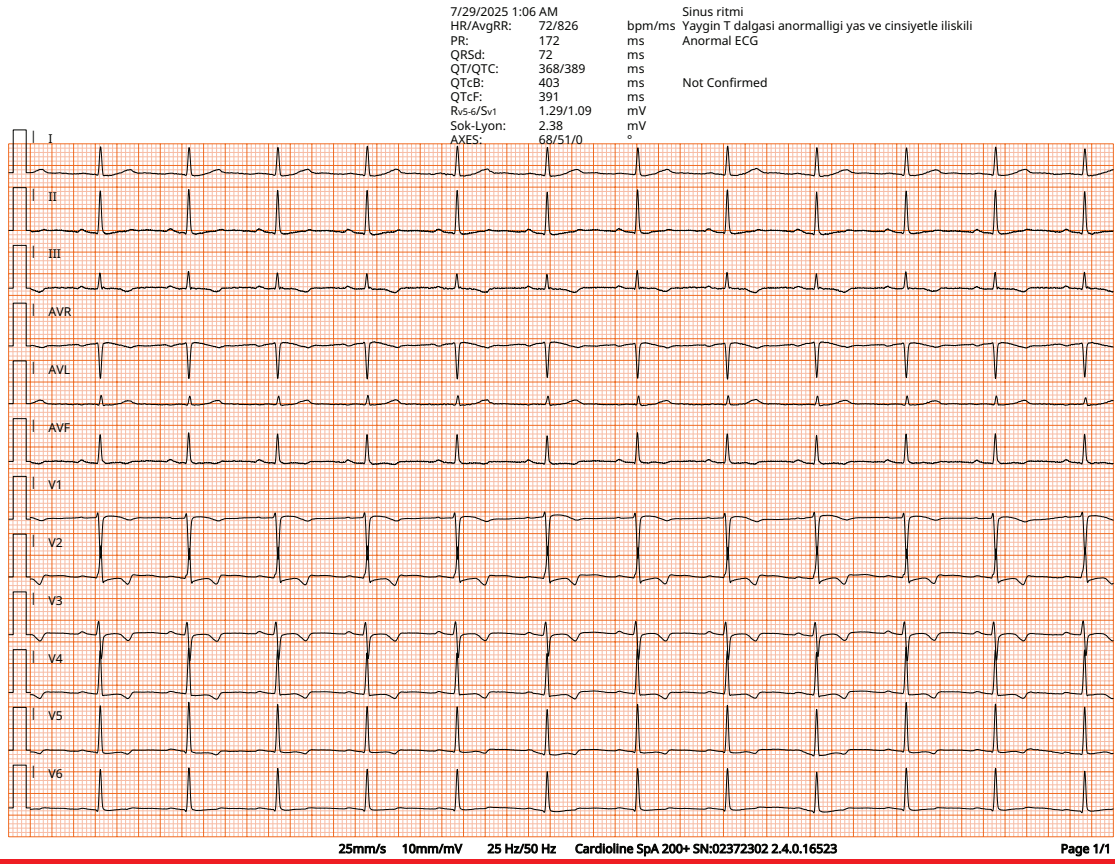

Figure 3. Patient's electrocardiogram in sinus rhythm.

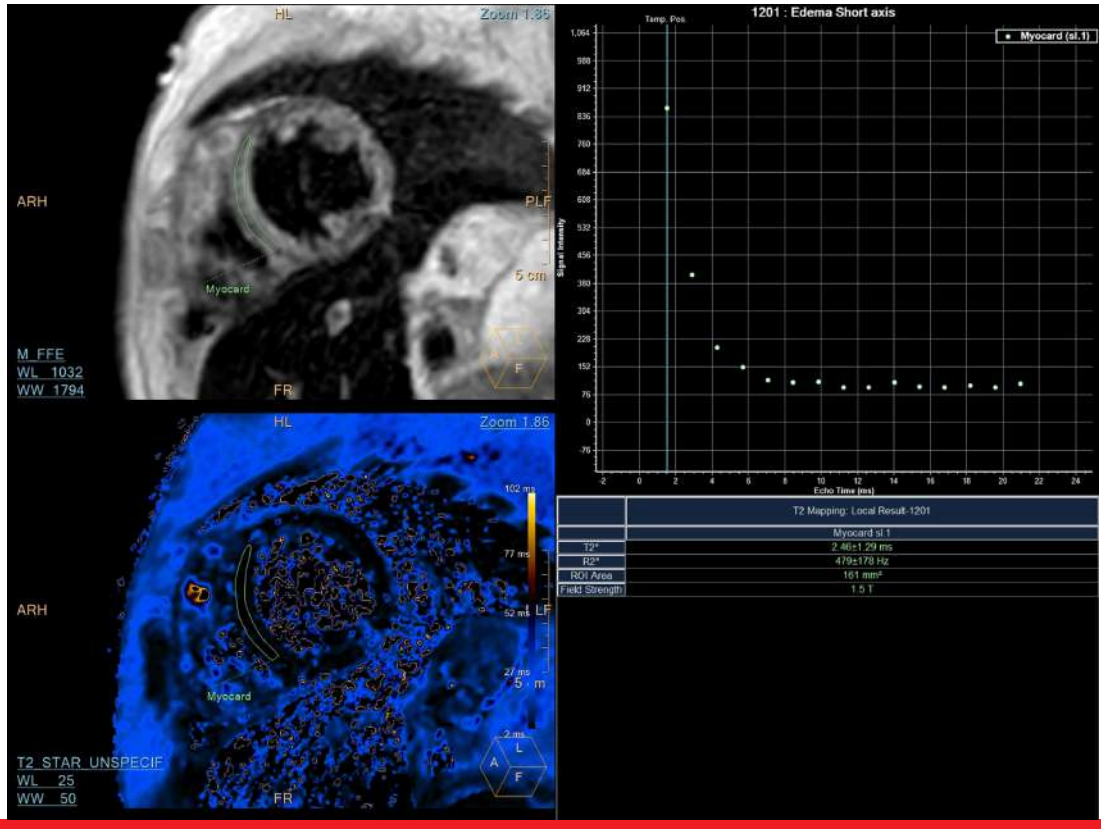

Figure 4. Cardiac magnetic resonance imaging T2 star sequence.

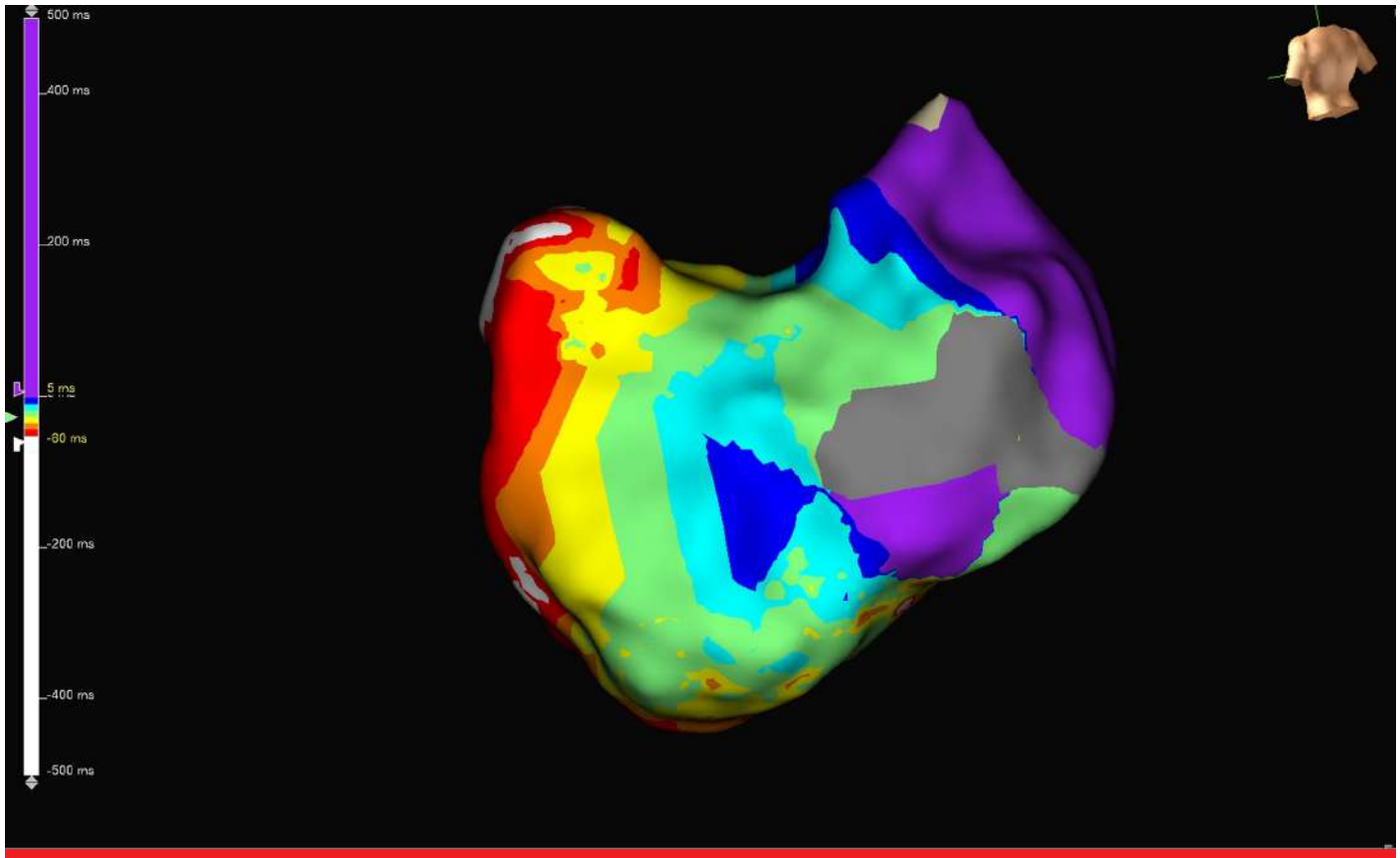

Figure 5. Local activation time map during the patient's 3D mapping.

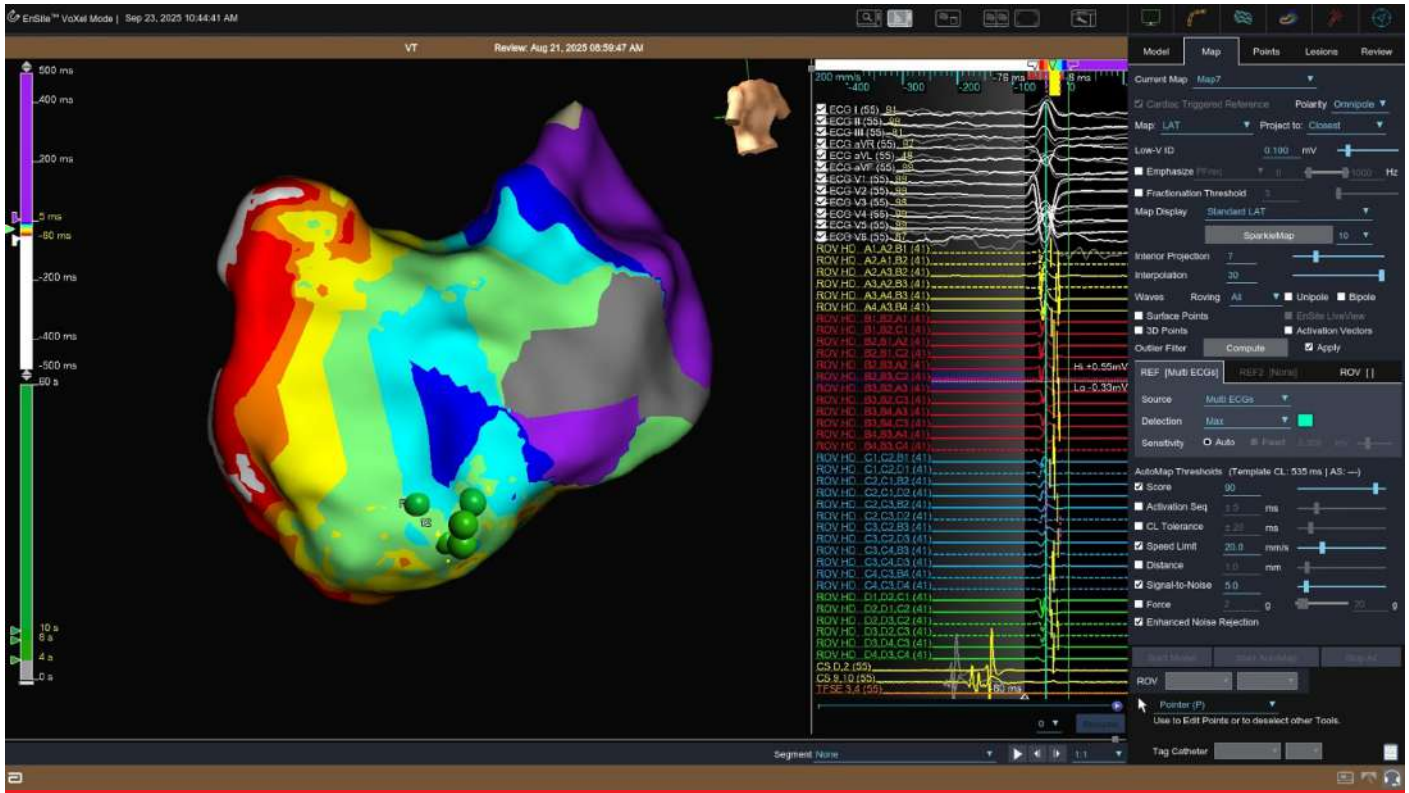

Figure 6. Locations where the RF application was applied to the patient.

that this shortens the right ventricular free wall and septum, leading to ventricular reentrant arrhythmias.[6] If RF ablation is unsuccessful in the ablation of moderator band-related ventricular arrhythmias, cryoballoon ablation can be adjuvantly performed to minimize contact problems.[7,8] RF ablation alone was effective in controlling arrhythmias in this patient.

CONCLUSION

Patients with thalassemia major are a group that requires close monitoring for arrhythmia. Monitoring patients' T2 times with cardiac MRI and performing rhythm Holter monitoring are important for early diagnosis, while particular care should be taken with reentrant tachycardias in these patients. The use of pace mapping will be helpful in identifying anatomical structures that could cause reentrant tachycardia.

Informed Consent: The informed consent was obtained from the patient for this study.

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

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Video 1: Mapping during pacing.

Video 2: Local Activation Time (LAT) activation map.

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The Increase in Pediatric Postural Orthostatic Tachycardia Syndrome During the Pandemic May be due to Autonomic Neuropathy as a Complication of SARS-CoV-2 Infection

LETTER TO THE EDITOR

To the Editor,

We read with interest the article by Bilen et al[1] on a retrospective study of the frequency and severity of postural orthostatic tachycardia syndrome (POTS) before and during the SARS-CoV-2 pandemic in pediatric patients recruited between January 2018 and December 2023 at a tertiary center in Türkiye.[1] It was found that the incidence of POTS increased during the pandemic, which was attributed to less physical activity, high screen time, and an increased incidence of anxiety with palpitations.[1] It was concluded that POTS was more common in children during the pandemic due to lifestyle changes and psychosocial stress rather than malnutrition.[1] The study is noteworthy, but some points should be discussed.

The first point is that a retrospective design was used.[1] Retrospective designs have several disadvantages.[2] Since they are based on the evaluation of medical records that were not originally designed for the collection of data for research purposes, some information is inevitably missing. Selection and recall errors can also influence the results.[2]

The second point is that the prevalence of POTS and changes in its prevalence can only be assessed by examining and comparing a representative sample of the healthy population in the area from which the patients were recruited.

The third point is that small fiber neuropathy (SFN) was not considered a cause of POTS in the analyzed cohort.[1] The SFN predominantly affects A-delta and C fibers, which are components of the peripheral autonomic nervous system (ANS). Since autonomic neuropathy can be a cause of POTS,[3] it would have been crucial to test all included patients for the presence of SFN. Tests for diagnosing SFN include not only the tilt table test but also QSART, Sudoscan, sympathetic skin response, laser-evoked potentials, confocal corneal microscopy, and skin biopsy. Were any of the included patients tested for the presence of SFN?

The fourth point is that the number of patients infected with SARS-CoV-2 prior to the onset of POTS during the pandemic has not been reported.[1] Knowledge of the SARS-CoV-2 infection rate is crucial, as SARS-CoV-2 infection can be complicated by SFN neuropathy of the ANS.[4] The SFN is one of the most common causes of peripheral POTS, and patients may not show symptoms during the acute phase of infection but could have developed SFN as a manifestation of post-COVID syndrome.[5]

The fifth point is that the included patients were not tested for autonomic disorders other than POTS. Since SFN can affect more than just the fibers supplying the heart and arteries, we should know how many of the patients had pupil

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abnormalities, sicca syndrome, endocrine abnormalities, respiratory impairments, gastrointestinal motility disorders, or urogenital problems.

The sixth point is that anxiety was assessed but not systematically quantified using a standardized questionnaire or psychiatric examination. Therefore, anxiety should be excluded from the analysis.

Overall, SFN as a complication of SARS-CoV-2 infection should be considered a cause of pediatric POTS.

Declaration of Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Reply to Letter to the Editor: "The Increase in Pediatric Postural Orthostatic Tachycardia Syndrome During the Pandemic May be due to Autonomic Neuropathy as a Complication of SARS-CoV-2 Infection"

LETTER TO THE EDITOR
REPLY

To the Editor,

We would like to thank the author(s)[1] for their interest in and valuable comments on our study entitled "Increased Diagnosis Rates and Clinical Characteristics of Pediatric Postural Orthostatic Tachycardia Syndrome During the COVID-19 Pandemic", published in *The Anatolian Journal of Cardiology*.[2] We greatly appreciate their contribution, which has allowed us to further clarify the quality, comprehensiveness, and limitations of our work.

1. Study design
It is true that retrospective studies have certain limitations such as missing data and recall bias. We explicitly addressed this limitation in the discussion section of our article. We applied the most objective methods possible during patient selection. By implementing well-defined inclusion and exclusion criteria, we ensured the most reliable data collection possible. Under the constraints of the pandemic, the retrospective design enabled the evaluation of a relatively large patient group over an extended time period.

2. Population representativeness
Our study included all consecutive patients presenting with syncope or orthostatic intolerance symptoms to a tertiary pediatric cardiology center. Therefore, while it may not fully represent the general pediatric population, it reflects real-world experience and referral patterns at a major reference center. Accordingly, the observed prevalence rates may be higher than expected, a point we explicitly acknowledged as a study limitation.

3. Small fiber neuropathy (SFN)
We agree that SFN may contribute to the pathophysiology of postural orthostatic tachycardia syndrome (POTS). However, advanced diagnostic tools such as skin biopsy, corneal confocal microscopy, or Sudoscan are not routinely available at our center. Therefore, SFN assessment could not be incorporated into our study. Nonetheless, in both the introduction and discussion sections, we emphasized that viral infections such as SARS-CoV-2 may trigger autoimmune and autonomic dysfunction mechanisms.

4. History of COVID-19 infection
During the pandemic, it was not possible to access patient SARS-CoV-2 PCR records due to the confidentiality policies of the Ministry of Health. Therefore, a direct assessment of prior infection in patients diagnosed with POTS could not be performed. However, in our discussion, we specifically addressed the potential role of viral infections and autoimmune mechanisms in the development of POTS. While knowledge of patients' PCR results would undoubtedly have provided more reliable data to associate our findings with the pandemic, this was not legally permissible within the regulations governing our institution.

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5. Evaluation of other autonomic disorders

As the primary aim of our study was to compare the frequency and clinical characteristics of POTS, it was not feasible to comprehensively evaluate all autonomic system disorders. Nevertheless, we acknowledge that future prospective studies should also investigate multisystemic autonomic involvement. We consider research into all potential contributing etiological factors highly valuable.

6. Assessment of anxiety

As correctly noted, due to the retrospective design, we could not employ standardized questionnaires or psychiatric evaluations. Anxiety-related findings were recorded based on patient and family reports. This limitation was explicitly mentioned in the discussion section of our study.

In conclusion, our study demonstrated a significant increase in pediatric POTS diagnoses during the pandemic. While lifestyle changes and psychosocial stress were among the primary contributing factors, we also believe the possible impact of viral infections should be considered. We once again thank the authors for their insightful contributions.

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Clarification Needed on Methodological Aspects of TAVR Outcomes Across Flow-Gradient and Ejection Fraction Profiles

LETTER TO THE EDITOR

To the Editor,

We read with interest the recent article by Yamashita et al[1] examining outcomes after transcatheter aortic valve replacement (TAVR) across distinct flow-gradient and ejection fraction profiles. The study addresses an important clinical question; however, several methodological issues may affect interpretation and merit clarification.

First, cardiovascular (CV) death is designated a primary endpoint, with outcome definitions stated to align with STS/TVT and VARC-3 criteria.[1,2] However, the manuscript does not detail how CV deaths were ascertained or adjudicated. This is particularly important given the discrepancy between Table 3 and Supplementary Table 1. In Table 3, the adjusted hazard ratio for CV death in the LF-LG with reduced ejection fraction (rEF) group is not significant (HR: 1.04, 95% CI: 0.50-2.16), whereas Supplementary Table 1 reports a significant association (HR: 1.94, 95% CI: 1.19-3.18).[1] Clarification regarding this divergence would be helpful.

Second, the study does not report post-TAVR use of heart failure guideline-directed medical therapy (GDMT) or atrial fibrillation (AF) therapies. Without these data, it is difficult to assess whether differences in medical management influenced outcomes, particularly in groups with reduced EF or high AF prevalence. Both GDMT- and AF-directed treatments are known to impact CV death, heart failure hospitalization, and stroke risk.[3,4]

Third, AF was excluded from final models despite prevalence as high as 71% in some subgroups; Supplementary Table 1 lists AF as "not selected" across all endpoints.[1] Atrial fibrillation's exclusion may thus confound phenotype-outcome associations and introduce measurement bias in flow-dependent groupings. Specifically, the left ventricular outflow tract time-velocity integral was averaged over five cardiac cycles in AF and three in sinus rhythm, introducing greater variability in stroke volume index among patients with AF.[1]

The small LF-HG with rEF cohort (n = 50) also limits precision for CV death estimates, as reflected in wide confidence intervals (Table 3). This imprecision likely contributes to the discrepancy between Table 3 and Supplementary Table 1.

These issues are central to interpreting the study's conclusions. We respectfully encourage the authors to clarify CV death adjudication methods, report GDMT and AF therapy use where available, and consider sensitivity analyses that force AF into the covariate set. These steps would enhance transparency and strengthen the study's contribution to clinical practice.

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Concerns Regarding Impedance Cardiography's Reliability in Pulmonary Arterial Hypertension Assessment

LETTER TO THE EDITOR

To the Editor,

I read with interest the article by Zhang et al,[1] titled "Impedance Cardiography Is a Potent Non-Invasive Method in Cardiac Output Measurement and Pulmonary Arterial Hypertension Risk Assessment" (*Anatol J Cardiol*. 2025;29(7):347-354).[1] The study's exploration of impedance cardiography (ICG) as a non-invasive alternative for measuring cardiac output (CO) and stroke volume (SV) in pulmonary arterial hypertension (PAH) is commendable. However, I noted several inconsistencies, gaps, and discrepancies with the literature that merit discussion, and I pose questions to the authors to clarify these points.

The study reports a moderate correlation between CO measured by ICG and thermodilution (COTD) ($r = 0.49$, $P < .001$), with a Bland-Altman analysis showing a bias of 0.52 L/min, limits of agreement (LoA) from −1.76 to 2.80 L/min, and a high percentage error of 49.89%.[1] This wide LoA and error rate question ICG's reliability as a substitute for right heart catheterization (RHC). How do the authors justify the clinical acceptability of this variability, and what measures could enhance ICG's accuracy? Additionally, the weaker correlation in chronic thromboembolic pulmonary hypertension (CTEPH) patients compared to Group 1 PAH patients is noted (Supplementary Figures 1 and 2),[1] but the reasons are underexplored. Could CTEPH-specific vascular pathology or right heart geometry contribute, and what are ICG's limitations in this subgroup?

The lack of simultaneous ICG and RHC measurements is a significant limitation, given the rapid hemodynamic changes in PAH.[1] How was the impact of this time gap assessed, and what steps minimized its effect? Previous studies, such as Yung et al[2] and Tonelli et al,[3] reported lower ICG accuracy in PAH. Despite claiming "acceptable correlation," the high error rates (49.89% for CO, 54.38% for SV) align with these concerns.[1] How do the authors reconcile this, and are further validation studies planned? The study also suggests ICG-derived cardiac index (CIICG) and stroke volume index (SVIICG) for PAH risk stratification,[1] yet the 2022 European Society of Cardiology/European Respiratory Society guidelines recommend RHC or cardiac magnetic resonance imaging.[4,5] Can additional data support ICG's reliability here? No predictors of ICG accuracy were identified despite examining factors like skin condition or thoracic morphology.[1] Are further analyses planned to explore right heart volume or pulmonary artery dilation's impact on thoracic impedance? The ROC analysis for clinical deterioration (AUC 0.76 for CIICG, 0.81 for SVIICG) relies on a small cohort (n = 54).[1] Are larger studies planned to validate these findings? Given the high error rate, in which clinical scenarios (e.g., low-risk patient follow-up) is ICG most suitable?

I suggest simultaneous ICG and RHC measurements to reduce time-related errors, a broader literature review under the new PAH criteria (mean pulmonary arterial pressure > 20 mm Hg),[4] subgroup analyses for CTEPH, and extended follow-up with larger cohorts to validate ICG's prognostic value. The study highlights ICG's potential, but high error rates and wide LoA, especially in CTEPH, limit its clinical

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utility. Clarifications could enhance its relevance. I look forward to the authors' responses.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Soldier's Heart and a Gifted Mind: Additional Considerations for Atatürk's Cardiac Symptoms

LETTER TO THE EDITOR

To the Editor,

This letter offers additional considerations regarding the article "Atatürk's (1881–1938) Heart Disease: A Qualitative Research."[1] Its purpose is to re-examine the diagnostic interpretation of Atatürk's cardiac symptoms and propose a plausible functional explanation. Retrospective medical analyses of historically significant figures enhance understanding of both the individual and their era, and such inquiry is particularly meaningful for Gazi Mustafa Kemal Atatürk, founder of the Republic of Türkiye and among the foremost leaders of the early 20th century.

The article examined two cardiac episodes Atatürk experienced in 1923 and 1927, concluding that they likely represented acute coronary syndromes. These events, characterized by chest pain and fatigue, appeared self-limiting and uncomplicated, except for fever noted in the latter. However, available records document no cardiac symptoms before 1923, between these two episodes, or after 1927 until his death. Current evidence indicates that cardiac symptoms and antecedent events are highly prevalent before acute coronary syndromes and frequently recur thereafter.[2,3] Despite persistent risk factors such as tobacco use and the absence of any specific cardiac treatment, Atatürk remained symptom-free thereafter. From a clinical standpoint, survival under such conditions—without intervention or risk modification—would generally be improbable, and long-term recovery exceptional. These observations suggest that alternative, non-ischemic explanations should be considered.

A plausible candidate is Da Costa syndrome, or "soldier's heart," a functional cardiovascular disorder described in 19th-century soldiers and associated with chest pain, palpitations, dyspnea, and fatigue in the absence of structural heart disease.[4] In modern terms, it may represent a stress-related autonomic dysfunction. Atatürk's life was defined by prolonged combat—from 1905 through the War of Independence (1922)—and recurrent exposure to severe stress and injury, including a nonpenetrating chest wound during the Battle of Dardanelles. After the war, new political and ideological pressures replaced the physical strain of battle. Notably, his cardiac episodes coincided with the proclamation of the Republic and the resolution of major political crises. This temporal pattern resembles the "letdown effect," in which illness occurs following relief from intense stress. Lipton et al[5] showed that sudden reductions in stress may precipitate migraine attacks through autonomic shifts; a similar mechanism may plausibly have contributed to Atatürk's post-stress cardiac symptoms.

In a previous article, I underscored intellectual giftedness as a key developmental trait shaping Atatürk's character.[6] Gifted individuals often display heightened autonomic reactivity and experience profound inner tension, existential questioning, and uncompromising dedication to ideals—all evident in Atatürk's life. This dimension should inform any assessment of the extraordinary psychological stress he endured.

Finally, the "Atatürk's Consultation Report" warrants brief comment. The persistence of auscultatory rales in the lower left lung for about a year represents a clinically concerning finding, and the absence of appropriate evaluation reflects

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the diagnostic limitations of early 20th-century medicine. Likewise, given the restricted reliability of laboratory methods of the time, the alleged gonorrheal infection should be regarded as uncertain and unreliable. It is also notable that no forensic medical evaluation was performed during his cardiac events, despite his status as a national leader.

In summary, these reflections help us appreciate how a great leader followed his heart in devotion to his nation and to humanity, and how this extraordinary effort ultimately resonated within his own heart.

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Primary Cardiac Myxosarcoma Invading the Mitral Valve

A 32-year-old woman presented with a 1-year history of palpitations and worsening exertional chest tightness. Cardiac auscultation revealed a moderate diastolic murmur and a grade 3/6 systolic murmur in the apical region. Transthoracic echocardiography (TTE) showed a hypoechoic mass measuring 2.8 cm × 2.3 cm attached to the atrial side of the anterior mitral valve leaflet (Figure 1A and B), prolapsing into the left ventricle during diastole causing mitral valve stenosis (Figure 1C), a peak flow velocity of 3.2 m/s, mean trans-mitral gradient of 41 mm Hg (Figure 1D), and severe mitral regurgitation in systole (Figure 1E). Cardiac computed tomography (CT) confirmed that the soft tissue mass was isolated to the mitral valve with no extension into other chambers or vessels (Figure 1F and G). The patient underwent surgical mass resection and mitral valve replacement;

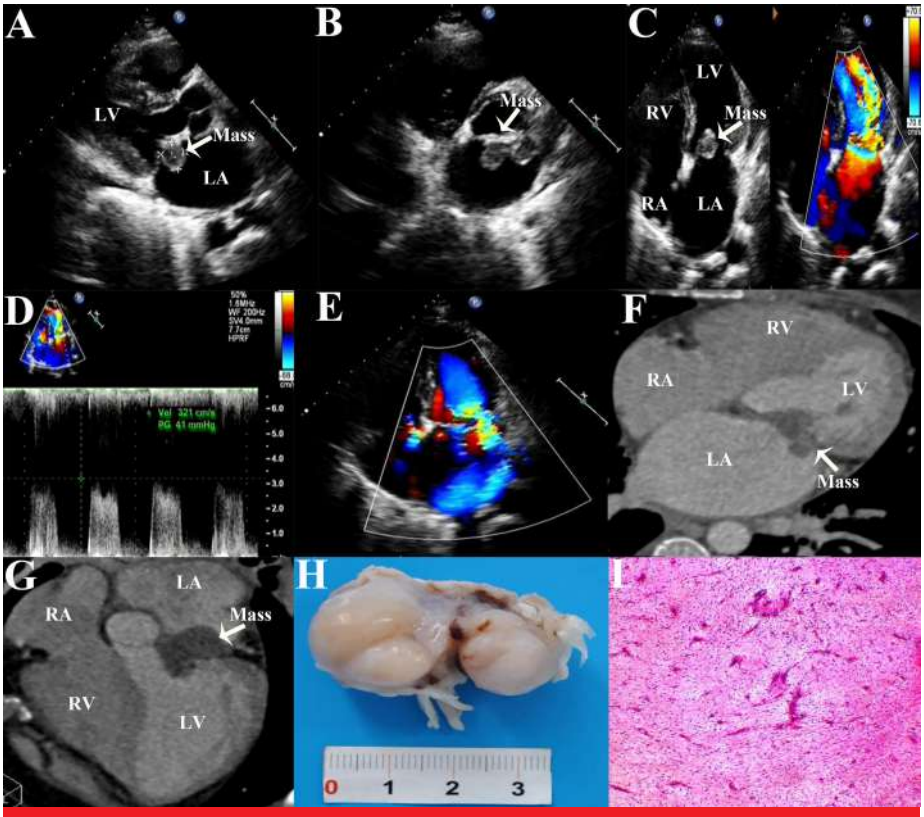

Figure 1. (A-E) Transthoracic echocardiography shows a hypoechoic mass attached to the atrial side of the anterior mitral valve leaflet (A and B), prolapsing into the left ventricle during diastole, causing mitral valve stenosis (C), a peak flow velocity of 3.2 m/s, mean trans-mitral gradient of 41 mm Hg (D), and severe mitral regurgitation in systole (E). (F and G) Cardiac CT confirms that the soft tissue mass is isolated to the mitral valve with no extension into other chambers or vessels. (H and I) Histopathology confirmed the diagnosis of myxosarcoma. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

E-PAGE ORIGINAL IMAGE

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the gross and histopathological examination confirmed the diagnosis of myxosarcoma (Figure 1H and I). The postoperative adjuvant chemotherapy with pazopanib hydrochloride was given. At 12 months of follow-up, there were no signs of local recurrence or metastases.

Primary cardiac myxosarcoma is a rare condition that most commonly originates in the left atrium. It is frequently involved in the pulmonary artery, pericardium, or pleura, and may also lead to distant metastasis.[1] Myxosarcomas that invade the mitral valve are extremely rare and are difficult to differentiate from the more common benign myxomas. The multimodality imaging technique, including TTE, transesophageal echocardiography (TEE), cardiac CT, cardiac magnetic resonance imaging (CMR), and ^{18}F-fluorodeoxyglucose positron emission CT, can provide important preliminary diagnostic information on the tumor size, boundary, location, and infiltration status, which is necessary to plan the treatment. The first-line imaging technique for classifying cardiac masses according to their size and border is TTE. Additionally, it offers details on ventricular function, abnormal pericardial thickness, valve involvement, and cardiac hemodynamics. A non-septal origin, extension into the pulmonary vein, multiple masses, extensive attachment to the left atrial wall, and a semisolid mass consistency within the left atrium are all possible characteristics of malignant lesions. When characterizing cardiac masses and surrounding structures, TEE is superior to TTE. The TEE is an intrusive test, though, so it might not be appropriate for every patient. Cardiac CT offers a high-resolution picture of the cancerous tumors and their surroundings. It is acknowledged as the best method for assessing extracardiac involvement in cardiac metastases. The CMR provides comprehensive details on the location of the tumor in relation to adjacent structures, motility, tissue characteristics, vascularization, and whether the tumor contains fibrous or necrotic tissue. It is also possible to employ PET-CT to identify distant metastases and differentiate between benign and malignant tumors.[2] Nevertheless, histopathologic and immunohistochemical examinations are required to confirm a diagnosis of cardiac myxosarcoma.[3] Early diagnosis and a multidisciplinary approach, including cardiac surgeons, oncologists, and critical care specialists, are crucial in the management of this disease.[4] At present, surgery is the preferred treatment option for cardiac myxosarcoma. Radiotherapy and chemotherapy may play a positive role in improving prognosis.

Informed Consent: The informed consent was obtained from the patient for this study.

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

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Mitral Valve Leaflet Dissection and Aneurysm Secondary to Bicuspid Aortic Valve Regurgitation

An asymptomatic 47-year-old male with bicuspid aortic valve (BAV) was referred for a transesophageal echocardiogram (TEE) to assess aortic regurgitation. The patient had no notable medical history. Transesophageal echocardiogram revealed a BAV with fusion of the left and right coronary leaflets (Figure 1A) (Supplementary Video 1), but 3 sinuses of Valsalva, and moderate aortic regurgitation [Vena Contracta (VC) 5 mm, 3-dimensional VC area 0.3 cm^2, PISA Effective Regurgitant Orifice Area 0.1 cm^2, Regurgitant Volume 16 mL, without holo-diastolic flow reversal in the descending thoracic aorta]. Concomitantly, trivial mitral valve regurgitation was diagnosed. The mitral valve annulus and the coaptation line had normal size, location, and function. However, the A2 scallop of the anterior leaflet was aneurysmal and dissected (Figure 1D and E) (Supplementary Videos 2 and 3). Noteworthy, the regurgitant jet of the BAV was directed toward the A2 scallop of the anterior mitral valve leaflet, generating the hypothesis that the high-velocity eccentric jet of aortic regurgitation impinging the area of the anterior mitral valve leaflet generated the leaflet dissection and aneurysm (Figure 1B and C) (Supplementary Videos 4-6). The billowing height of the A2 scallop aneurysm was measured at 6.9 mm. In the literature, only a few cases of mitral valve prolapse associated with BAV have been described; however, none of those reported dissection of the mitral valve. This case highlights the relevance of eccentric aortic regurgitation due to BAV leading to the mechanical complication of the dissection and aneurysm of the anterior mitral valve leaflet diagnosed by 3-dimensional TEE, which may hold significant implications for its etiology, prognosis, and surgical management.

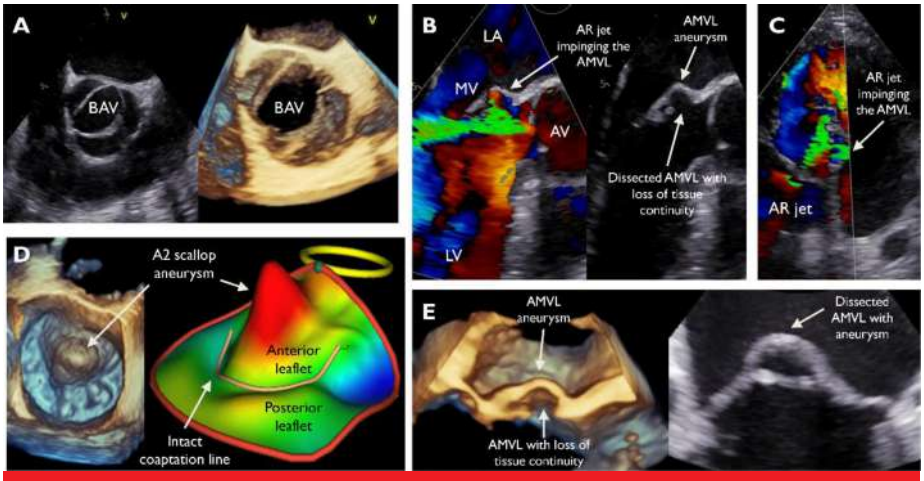

Figure 1. Transesophageal echocardiographic assessment of a bicuspid aortic valve. Mitral valve leaflet dissection and aneurysm secondary to bicuspid aortic valve regurgitation.

E-PAGE ORIGINAL IMAGE

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Data Availability Statement: The imaging data and other materials supporting the findings of this submission are available from the corresponding author upon reasonable request.

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

Supplementary Video 1: 3D TEE imaging of the aortic valve revealing a bicuspid morphology with left-right coronary cusp fusion.

Supplementary Video 2: 3D TEE imaging of the mitral valve, viewed from the left atrial side (surgical perspective), revealing an aneurysmal and dissected A2 scallop of the anterior mitral leaflet.

Supplementary Video 3: 3D TEE imaging of the mitral valve with color Doppler demonstrating trivial mitral valve regurgitation.

Supplementary Video 4: TEE midesophageal long-axis view of mitral and aortic valves.

Supplementary Video 5: TEE midesophageal long-axis view with color Doppler demonstrating a high-velocity eccentric jet of aortic regurgitation impinging the area of the anterior mitral valve leaflet, generated the leaflet dissection and aneurysm.

Supplementary Video 6: A deep transgastric TEE view with color Doppler, demonstrating an eccentric aortic regurgitation jet directed towards A2 scallop of the anterior mitral leaflet.