

THE ANATOLIAN JOURNAL OF CARDIOLOGY



Original Investigations

Right-Sided Infective Endocarditis
Suntur et al.

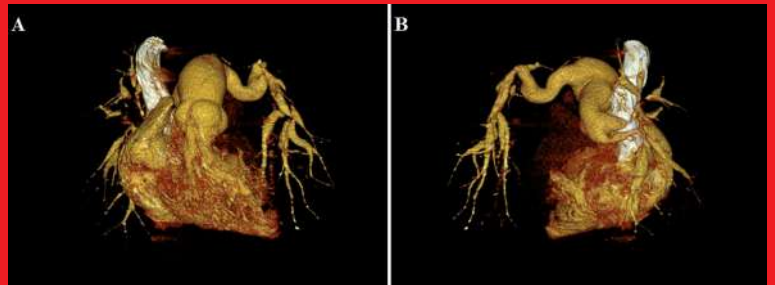
Integrative Identification of Frailty Status in Elderly Patients
Hu and Feng.

Permanent Pacemaker Implantation After Minimally Invasive
Robotic
Eravci et al.

Impact of Post-Dilatation During TAVI on the Cardiac
Conduction System
Şahan et al.

Unified Model for Carotid Artery Stenosis
Tavlı et al.

Mortality Predictors in cLFLG Aortic Stenosis
Güvendi Şengör et al.



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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.
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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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NOTE 1: Case reports that include video images have a better chance of publication.

• **Original Image**

Impressive and rare images that reflect significant findings based on clinical science, shed light on fundamental mechanisms of diseases, emphasize abnormalities or introduce new treatment methods are accepted for publication.

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Letters to the Editor aim to discuss the importance of a manuscript previously published in the journal. This type of manuscripts should also include a comment on the published manuscript. Moreover, articles on topics of interest to readers within the scope of the journal, especially on educational issues, can be published in the format of a Letter to the Editor.

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- **Scientific Puzzle**

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Consensus Report on PAH, TAVI and AI

Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease characterized by increased pulmonary vascular resistance and right ventricular dysfunction, requiring early diagnosis and timely management. This joint expert consensus report, developed in collaboration with the Turkish Society of Cardiology, Turkish Thoracic Society, and Pulmonary Vascular Disease Research Association (ADHAD), provides a practical, realworld framework for the diagnosis and management of PAH in Türkiye. We congratulate Avcı et al from Türkiye for this very useful report.

Senderovic and Galijašević from Bosnia and Herzegovina hypothesize in the review that myocardial bridging may create a spatially heterogeneous oxidative and inflammatory microenvironment, driven by altered shear stress, which may favor MPO 5 activation and potentially contribute to the formation of neutrophil extracellular traps (NETs) in the proximal coronary segment, thereby contributing to endothelial dysfunction, atherogenesis, and ischemic manifestations.

Suntur et al from Türkiye investigated the epidemiological, clinical, and microbiological characteristics of right-sided infective endocarditis, identify risk factors, and explore factors potentially associated with mortality in patients diagnosed with definite IE at a tertiary care center.

Frailty is common yet underdiagnosed in elderly patients with atrial fibrillation (AF), worsening outcomes and complicating treatment. Traditional assessments are timeconsuming and subjective, while physiological monitoring offers potential for automated detection. Combining machine learning with multimodal data especially ECG and clinical features may improve frailty identification, even in noisy real-world conditions. Hu and Feng from China evaluated this topic.

The role of minimally invasive robotic heart surgery in the surgical field is swiftly expanding due to technological advancements and the acknowledgment that its safety is comparable to conventional cardiac surgery. Eravcı et al from Türkiye aimed to evaluate permanent pacemaker implantation rates, associated perioperative determinants, and the course of pacing rates during follow-up in a single-center cohort undergoing minimally invasive robotic cardiac surgery.

Transcatheter aortic valve implantation (TAVI) has become a well-established treatment for patients with severe aortic stenosis who are at intermediate or high surgical risk. Despite procedural advances, post-procedural conduction disturbances remain among the most common complications, particularly new-onset left bundle branch block (LBBB). Şahan et al from Türkiye investigated the impact of balloon pre- and post-dilatation on the cardiac conduction system during TAVI.

Tavli et al from Türkiye studied the diagnostic performance of a new artificial intelligence model, the compact unified model (CU-Model), for moderate-to-severe carotid artery stenosis using digital subtraction angiography (DSA) images compared to clinical reference standards Classical low-flow low-gradient aortic stenosis (cLFLG AS) is associated with poor prognosis and adverse clinical outcomes despite

EDITORIAL

Çetin Erol

Editor-in-Chief, Ankara, Türkiye



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transcatheter aortic valve implantation (TAVI). Identifying prognostic markers in this high-risk population may improve risk stratification and clinical management. Şengör et al from Türkiye tried to find out independent predictors of all-cause mortality in patients with cLFLG AS undergoing TAVI.

Body mass index (BMI), the most widely used adiposity metric, cannot differentiate fat distribution from lean mass, limiting its prognostic utility. Kahraman et al from Türkiye compared the weight-adjusted waist index (WWI) with BMI, waist-to-height ratio (WHtR), and relative fat mass (RFM) as

predictors of all-cause and cardiovascular mortality using a z-standardized framework.

We received a very important Scientific letter by Canpolat and Kayıkçıoğlu from Türkiye titled 'Artificial Intelligence for Peer Review in Cardiovascular Journals: Promise, Pitfalls, and a Path to Responsible Hybrid Adoption'. I hope it will cause fruitful discussions.

And new case reports, letters, e-page original...

I hope this very attractive issue will be interest of our readers.

Joint Expert Consensus Report on the Diagnosis and Management of Pulmonary Arterial Hypertension in Türkiye

In collaboration with Turkish Society of Cardiology, Turkish Thoracic Society and Pulmonary Vascular Disease Research Association (ADHAD)

ABSTRACT

Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease characterized by increased pulmonary vascular resistance and right ventricular (RV) dysfunction, requiring early diagnosis and timely management. This joint expert consensus report, developed in collaboration with the Turkish Society of Cardiology, Turkish Thoracic Society, and Pulmonary Vascular Disease Research Association (ADHAD), provides a practical, real-world framework for the diagnosis and management of PAH in Türkiye. The document presents updated, practice-oriented diagnostic algorithms designed to facilitate early recognition and accurate classification of PAH. A key objective is the standardization of data collection across centers; therefore, recommended echocardiographic and hemodynamic parameters, along with their normal and pathological ranges, are clearly defined to improve consistency in clinical evaluation and reporting. Risk assessment remains a cornerstone of patient evaluation; however, current guideline-based models have important limitations. In a disease with high mortality such as PAH, greater emphasis should be placed on dynamic risk evaluation at follow-up, incorporating detailed RV assessment through imaging and hemodynamic parameters, and enabling more timely treatment escalation when needed. Accordingly, treatment algorithms have been updated to reflect contemporary therapeutic strategies, emphasizing early combination therapy, individualized management, and prompt escalation in patients who fail to achieve or maintain a low-risk profile with particular attention to RV performance. Overall, this consensus aims to harmonize clinical practice, enhance data quality, and support more proactive and standardized management of PAH across Türkiye.

Keywords: Clinical guidelines, consensus, diagnosis, pulmonary arterial hypertension, pulmonary hypertension, therapy

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening condition characterized by elevated pressure in the pulmonary circulation, driven by a complex interplay of vasoconstriction, vascular remodeling, inflammation, and thrombosis, which leads to progressive increases in pulmonary vascular resistance (PVR) and right ventricular (RV) pressure overload. It is associated with significant morbidity and mortality and therefore requires early recognition and appropriate management.

Because of its heterogeneous etiology and clinical presentation, the evaluation and management of PAH require a multidisciplinary approach involving cardiologists, pulmonologists, rheumatologists, radiologists, pediatric cardiologists, and other specialists.

This consensus report was developed by a multidisciplinary task force consisting of 7 cardiologists, 2 pulmonologists, and 2 rheumatologists, under the auspices

CONSENSUS REPORT

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of the Turkish Society of Cardiology, Pulmonary Vascular Disease Research Association (ADHAD), and Turkish Thoracic Society.

The aim of this document is to provide practical guidance for the early diagnosis and optimal multidisciplinary management of patients with PAH, while promoting the standardization of evaluation and treatment strategies across Türkiye. In addition, the committee encourages the use of standardized data collection and supports the development of a national PAH registry to improve data quality and clinical outcomes.

The target audience of this consensus report includes physicians, healthcare professionals involved in the management of PAH, physicians in training, patient organizations, reimbursement authorities, and other stakeholders.

Working groups were formed to develop individual sections of the report including definition and epidemiology, diagnostic strategies and risk evaluation in PAH, and management options and monitoring during follow-up. Draft texts were prepared by the respective groups and subsequently discussed during consensus meetings. After iterative revisions and discussions, the final document was approved by all members of the task force.

DEFINITION AND CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary arterial hypertension should be clearly distinguished from the broader term pulmonary hypertension (PH). Pulmonary hypertension is a hemodynamic condition defined as a resting mean pulmonary arterial pressure (mPAP) >20 mm Hg, measured by heart catheterization, and may arise from a variety of underlying etiologies.^{1,2}

Based on differences in pathophysiology and clinical context, PH is classified into 5 groups (Table 1), each with distinct diagnostic and therapeutic implications. Among these, PAH represents a specific and relatively rare subgroup characterized by progressive pulmonary vascular remodeling and increased PVR.

Beyond clinical classification, PH can also be defined according to hemodynamic characteristics, which help distinguish the underlying mechanism of elevated pulmonary pressure. In this context, PH is broadly categorized into pre-capillary and post-capillary forms based on pulmonary arterial wedge pressure (PAWP) and PVR.

Pre-capillary PH is defined hemodynamically by a mPAP >20 mm Hg, a PAWP ≤ 15 mm Hg, and a PVR >2 Wood units (WU). This hemodynamic profile is observed in several clinical groups, including PAH, PH associated with lung diseases and/or hypoxia, PH due to pulmonary artery (PA) obstruction, and selected forms of PH with multifactorial mechanisms. Pulmonary arterial hypertension represents a distinct subtype of pre-capillary PH and is diagnosed only after exclusion of other causes of pre-capillary PH.

In contrast, post-capillary PH is defined by an mPAP >20 mm Hg and PAWP >15 mm Hg and is most commonly associated with left heart disease. Post-capillary PH can be further subdivided into isolated post-capillary PH (IpcPH) (PVR ≤ 2 WU) and combined pre- and post-capillary PH (CpcPH) (PVR >2 WU).

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HIGHLIGHTS

- This joint consensus of three Turkish societies provides practical guidance on the diagnosis and management of pulmonary arterial hypertension.
- Standardized diagnostic algorithms and reporting of echocardiographic and hemodynamic parameters aim to improve consistency across centers.
- During follow-up, risk assessment should integrate right ventricular imaging and/or hemodynamics alongside conventional risk scores.
- The treatment algorithm was adapted to therapeutic options available in Türkiye, with escalation guided by comprehensive risk assessment.
- Early referral for lung transplantation is recommended, and the expansion of transplant programs in Türkiye is strongly advocated.

Table 1. Clinical Classification of Pulmonary Hypertension (WHO Groups 1–5) and Corresponding Hemodynamic Characteristics¹

Pulmonary Hypertension mPAP > 20 mm Hg	Etiologies
Group 1 Pulmonary Arterial Hypertension <i>Primary pulmonary vascular disease</i> PAWP ≤ 15 mm Hg, PVR > 2 WU	<ul style="list-style-type: none"> – Idiopathic PAH <ul style="list-style-type: none"> * Long-term responders to CCB – Heritable PAH – Drug/toxin-associated PAH – Connective tissue disease-associated PAH – Congenital heart disease-associated PAH – HIV-associated PAH – Portal hypertension-associated PAH – Schistosomiasis-associated PAH – PAH with features of venous/capillary (PVOD/PCH) involvement – Persistent PH of the newborn
Group 2 PH Associated with Left Heart Disease <i>LV dysfunction or valvular disease: pressure overload to lungs</i> PAWP > 15 mm Hg, PVR normal or > 2 WU	<ul style="list-style-type: none"> – Heart failure <ul style="list-style-type: none"> * With preserved ejection fraction * With reduced or mildly reduced ejection fraction * Cardiomyopathies with specific etiologies (hypertrophic, amyloid, Fabry disease and Chagas disease). – Mitral/aortic/complex valvular disease – Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3 PH Associated with Lung Disease or Hypoxia <i>Chronic lung disease + hypoxemia: remodeling</i> PAWP ≤ 15 mm Hg, PVR > 2 WU	<ul style="list-style-type: none"> – COPD and/or emphysema – Interstitial lung disease – Combined pulmonary fibrosis and emphysema – Other parenchymal lung diseases (not group 5) – Hypoventilation syndromes – Pneumonectomy – Hypoxia without lung disease (e.g., high altitude) – Developmental lung diseases
Group 4 PH Associated with Pulmonary Artery Obstructions <i>Persistent clotting or fibrotic lesions: flow obstruction</i> PAWP ≤ 15 mm Hg, PVR > 2 WU	<ul style="list-style-type: none"> – Chronic thromboembolic PH (CTEPH) – Other pulmonary artery obstructions: <ul style="list-style-type: none"> * Sarcomas (high- or intermediate-grade or angiosarcoma) * Other malignant tumors (e.g., renal carcinoma, uterine carcinoma, germ-cell tumors of the testis), * Nonmalignant tumors (e.g., uterine leiomyoma), * Arteritis without connective tissue disease * Congenital pulmonary arterial stenoses * Hydatidosis
Group 5 PH with Unclear/Multifactorial Mechanisms <i>Complex/multifactorial causes</i> PAWP ≤ 15 or > 15 mm Hg, PVR ≤ 2 WU or > 2 WU	<ul style="list-style-type: none"> – Hematological disorders (chronic hemolytic anemia, chronic myeloproliferative disorders) – Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1 – Metabolic disorders (glycogen storage diseases and Gaucher disease) – Chronic renal failure with or without hemodialysis – Pulmonary tumor thrombotic microangiopathy – Fibrosing mediastinitis – Complex congenital heart disease

CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; LV, left ventricle; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PVOD/PCH, pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis WHO, World Health Organization.

Patients who exhibit elevated mPAP values without increased PAWP or PVR are considered to have “unclassified PH.” It is frequently linked to high–cardiac output states that lead to increased pulmonary blood flow.

EPIDEMIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

Pulmonary hypertension is estimated to affect approximately 1% of the general population, with prevalence increasing to nearly 10% among individuals older than 65 years.³ However, PAH accounts for only a small proportion

of PH cases, representing approximately 5% of the total burden. The estimated prevalence of PAH is approximately 48–55 cases per million, with an annual incidence of around 6 cases per million.⁴

Earlier international registries characterized PAH predominantly as a disease of younger individuals (30–45 years) with a female predominance. More recent data, however, demonstrate a gradual increase in the mean age at diagnosis, likely reflecting improved awareness and recognition of PAH in older populations.

Epidemiological data on PAH in Türkiye remain limited due to the absence of a unified national registry, heterogeneity in data collection across centers, and the inclusion of patients from different PH groups in available analyses. Nevertheless, existing registries provide important insights into patient characteristics and real-world clinical practice.^{5,6} Consistent with international data, both the SIMURG and TURKPAH registries demonstrate a clear female predominance, with women comprising approximately 69% of patients. The mean age at diagnosis has also increased over time, from 45 years in SIMURG to 52 years in the TURKPAH. However, it should be noted that available data are not restricted exclusively to PAH, as a proportion of patients from other PH groups were also included.

Within the PAH population, IPAH remains the most common etiology in the TURKPAH registry (47.4%).⁶ Congenital heart disease—associated PAH (CHD-PAH) represents a significant subgroup, accounting for approximately 47% of cases in the SIMURG registry and 32% in TURKPAH.^{5,6} Additional insights are provided by the nationwide THALES registry, which included 1034 patients and predominantly reflects a pediatric population.⁷ In this cohort, Eisenmenger syndrome and PAH associated with left-to-right shunts were the most common forms, observed in 49.2% and 42.7% of patients, respectively.

Overall, these findings highlight the increasing awareness of PAH in Türkiye, while emphasizing the urgent need for a contemporary multidisciplinary registry.

Survival in Pulmonary Arterial Hypertension

Survival in PAH has improved substantially over the past decades. In the 1970s, data from the NIH registry reported a median survival of approximately 2.6 years whereas contemporary registries demonstrate median survival exceeding 6 years, reflecting advances in early diagnosis and targeted therapies.⁷⁻⁹ 1-, 3-, 5-, and 7-year survival rates were 85%, 68%, 57%, and 49%, respectively in PAH.¹⁰

Within PAH, patients with connective tissue disease-associated PAH (CTD-PAH) have historically exhibited worse survival compared with idiopathic PAH (IPAH). However, therapeutic advances over the past decade have been associated with improved outcomes, with patients treated after 2010 demonstrating better survival compared to those treated earlier (73% vs. 65%).¹¹

National data from Türkiye show comparable trends. In the SIMURG registry, the 3-year survival rate was reported as 69% in patients with IPAH and CTD-PAH, and higher, at approximately 80%, in patients with congenital heart disease-associated PAH (CHD-PAH).¹² In a more recent retrospective cohort of patients with systemic sclerosis-associated PAH (SSc-PAH), survival rates were 90.2%, 73.2%, and 56.6% at 1, 3, and 5 years, respectively.¹³

Overall, these findings suggest that medium-term survival rates in Turkish PAH cohorts are broadly consistent with those reported in contemporary international registries.

DIAGNOSIS OF PULMONARY ARTERIAL HYPERTENSION

Clinical Suspicion and Early Identification

Pulmonary arterial hypertension often develops insidiously, with exertional dyspnea being the earliest and most

common presenting symptom. Other manifestations include fatigue, reduced exercise capacity, exertional chest pressure, palpitations, lightheadedness, and exertional presyncope/syncope. As the disease progresses and RV dysfunction develops, symptoms of systemic venous congestion may emerge, including peripheral edema, abdominal fullness, ascites, hepatomegaly, early satiety, and eventually cardiac cachexia.

In some patients, aneurysmal enlargement of the pulmonary arteries may lead to compression of adjacent mediastinal structures, resulting in additional clinical manifestations. Extrinsic compression of the left main coronary artery (LMCA) may cause angina-like chest pain, whereas involvement of the left recurrent laryngeal nerve (Ortner's syndrome) may present with hoarseness. In addition, compression of the main bronchi may contribute to worsening dyspnea.

In patients with symptoms or clinical findings suggestive of PH, the diagnostic evaluation should begin with a comprehensive clinical assessment, including a detailed medical history and physical examination. The diagnostic algorithm recommended in this consensus report is summarized in Figure 1.

The medical history should focus on conditions associated with PH, including prior thromboembolic events, features suggestive of connective tissue disease, liver disease, family history of PAH, exposure to anorexigens, stimulants, or other drugs.

Physical examination findings may be subtle or absent in early stages. As the disease progresses, signs suggestive of PH and RV pressure overload may emerge, including a loud pulmonary component of the second heart sound (P2), RV heave, a systolic murmur due to tricuspid regurgitation (TR), and a diastolic murmur due to pulmonary regurgitation (PR). In more advanced stages, features of RV failure and systemic congestion may be present, such as jugular venous distension, hepatomegaly, peripheral edema, and cool extremities. The presence of digital clubbing or differential cyanosis should raise suspicion for Eisenmenger physiology.

Given the potential for delayed diagnosis, screening of high-risk populations should be emphasized. These include patients with systemic sclerosis (SSc) and other connective tissue diseases, uncorrected congenital heart disease, HIV infection, portal hypertension, and families with heritable PAH.

Initial Non-Invasive Evaluation

Initial non-invasive investigations typically include electrocardiography (ECG) and chest radiography. These modalities may provide indirect evidence of PH, with ECG findings such as RV hypertrophy and right atrial (RA) enlargement, and chest radiographic features including PA dilation and signs of right heart enlargement. In addition, both ECG and chest radiography may offer important clues for differential diagnosis; for example, findings such as left ventricular hypertrophy or left atrial enlargement may suggest left heart disease, while chest radiography may also reveal features of parenchymal lung disease.

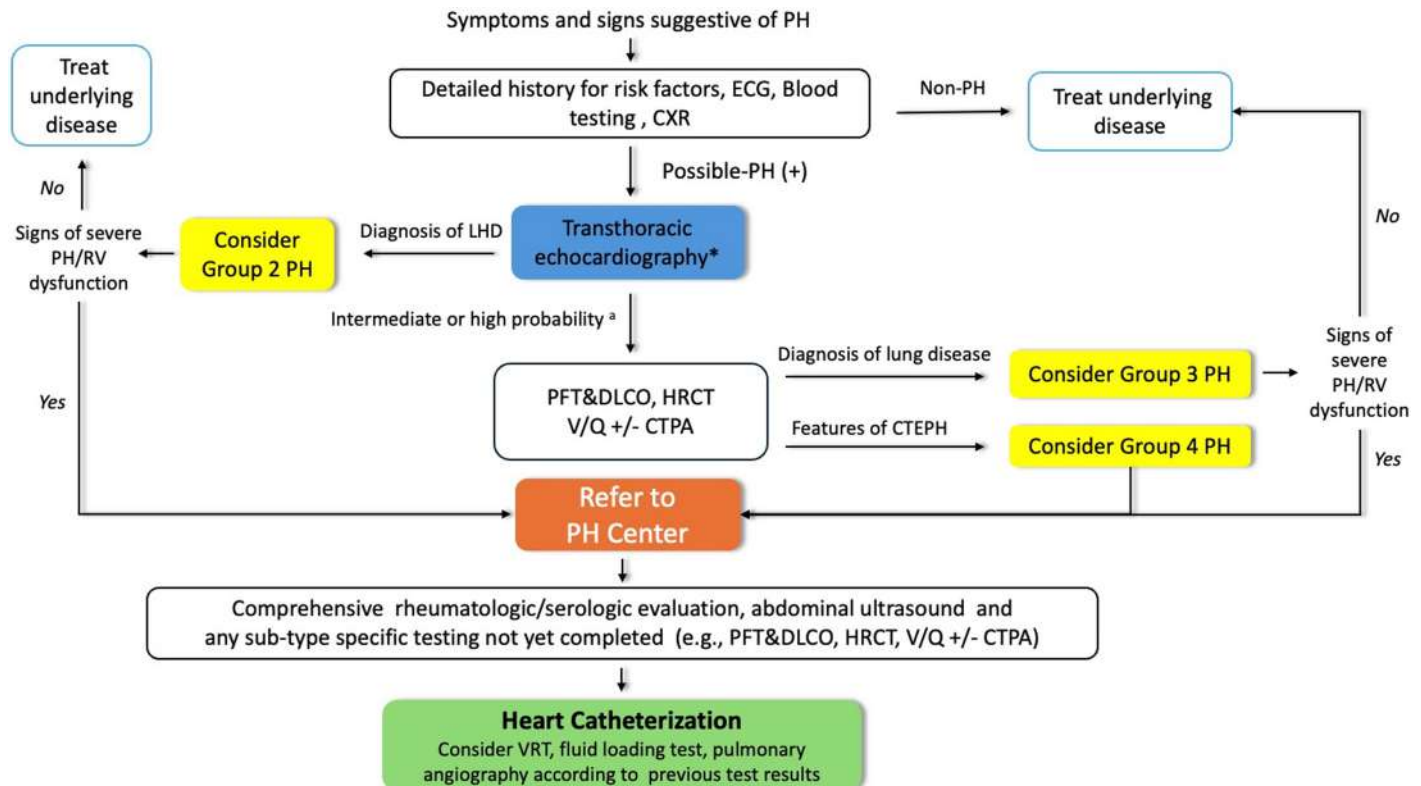


Figure 1. Proposed diagnostic algorithm for the evaluation of pulmonary hypertension.

CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; CXR, chest X-ray; DLCO, diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; HRCT, high-resolution computed tomography; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PFT, pulmonary function tests; PH, pulmonary hypertension; PR, pulmonary regurgitation; RA, right atrium; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiography; V/Q, ventilation/perfusion scan; VRT, vasoreactivity testing.

*Perform comprehensive echocardiography, including all parameters presented in Table 2. aEchocardiographic probability of PH (TTE-based): Intermediate probability is defined by a TR velocity of 2.9-3.4 m/s, or ≤ 2.8 m/s in the presence of ≥ 2 additional echocardiographic signs from different domains, including abnormalities in right heart size/function (e.g., RV/LV basal diameter >1.0 , abnormal LV eccentricity index, reduced TAPSE/sPAP), pulmonary artery findings (e.g., shortened acceleration time, mid-systolic notching, increased end-diastolic PR velocity, PA diameter >25 mm), and RA/IVC parameters (e.g., RA enlargement, IVC dilatation). High probability is defined by TR velocity >3.4 m/s, or 2.9-3.4 m/s with ≥ 2 additional PH echo signs. A TR velocity ≤ 2.8 m/s indicates low probability; however, in the presence of risk factors or conditions associated with PAH or CTEPH, further evaluation remains warranted. While high-probability findings generally support proceeding to right heart catheterization, decisions in other categories should be individualized and guided by the overall clinical context.

This initial assessment is complemented by measurement of oxygen saturation and laboratory testing, including blood counts, renal, hepatic, and thyroid function tests, as well as natriuretic peptides (BNP or NT-proBNP), which also provide important prognostic information. While none of these investigations is diagnostic, they provide important supportive information and may raise clinical suspicion of PH.

Further targeted investigations are required to confirm the diagnosis and to determine the underlying etiology, which is essential for appropriate classification and management, as treatment strategies differ significantly among PH groups.

Transthoracic echocardiography (TTE) plays a central role in the initial evaluation of patients with suspected PH. Echocardiography allows estimation of PA pressures and identification of structural and functional abnormalities suggestive of PH.

A resting TR velocity ≥ 2.9 m/s, or ≤ 2.8 m/s in the presence of at least 2 additional echocardiographic signs (including right

heart or PA dilatation, abnormal left ventricular eccentricity index, shortened pulmonary acceleration time, or inferior vena cava dilatation), is suggestive of PH and warrants further diagnostic evaluation (see Figure 1 legend for detail). In addition, echocardiography provides important information regarding potential underlying causes, particularly left heart disease, which remains the most common cause of PH.

Table 2 summarizes the key echocardiographic parameters and abnormal cut-off values recommended for reporting. Detailed methodologies for the measurement and interpretation of these parameters are described in the ESC/ERS guidelines and the recent American Society of Echocardiography (ASE) recommendations.¹⁴

Beyond its diagnostic role, TTE is essential for risk stratification and management decisions, both at baseline and during follow-up. It enables comprehensive assessment of RV size and function. Parameters such as RA area, the TAPSE/

sPAP ratio, and the presence of pericardial effusion provide important prognostic information and contribute to mortality risk assessment in patients with PAH.^{1,14}

When image quality or Doppler signals are suboptimal, contrast-enhanced echocardiography may improve delineation of endocardial borders and facilitate more accurate assessment of RV size and function, as well as estimation of TR velocity. It may also aid in the detection of intracardiac or intrapulmonary shunts and can be helpful in distinguishing portopulmonary hypertension (PoPH) from hepatopulmonary syndrome.

Given the relatively high prevalence of congenital heart disease (CHD) in Türkiye, transesophageal echocardiography (TEE) should be considered as part of the diagnostic evaluation in selected patients with suspected PAH, particularly in younger individuals. The TEE may help exclude left-to-right shunt lesions, such as atrial septal defects—including sinus venosus-type defects, which may occasionally be missed on TTE.

Further Diagnostic Work-up

Although TTE is essential for assessing PH probability, the final diagnosis should always be confirmed by heart catheterization, as echocardiography may over- or underestimate pulmonary pressures. Prior to heart catheterization, all relevant clinical information related to elevated pulmonary pressures should be carefully collected and evaluated to individualize both the indication and the procedural approach.

Additional investigations aimed at identifying the underlying etiology of PH are summarized below.

Respiratory and Pulmonary Vascular Investigations

Pulmonary function tests (PFT), including spirometry, lung volumes, and diffusion capacity for carbon monoxide (DLCO), arterial blood gas analysis, and chest computed tomography (CT) should be performed in all patients with suspected PH. These tests help distinguish PH groups, identify comorbidities, and assess the need for oxygen supplementation.

Arterial blood gas analysis typically shows normal or mildly reduced PaO₂ and normal or decreased PaCO₂ in patients with PAH. Markedly reduced PaO₂ is atypical for PAH and should prompt evaluation for alternative diagnosis or associated conditions such as parenchymal lung diseases, chronic thromboembolic PH (CTEPH), right-to-left shunting, or pulmonary veno-occlusive disease (PVOD) and may reflect coexisting comorbidities, particularly cigarette smoking.

Pulmonary function tests in PAH is typically normal or shows only mild restriction while DLCO is usually mildly reduced.^{1,2} A markedly reduced DLCO disproportionate to lung volumes may raise suspicion for PVOD, pulmonary capillary hemangiomatosis (PCH), SSc-associated PAH, or group 3 PH (e.g., interstitial lung disease or combined pulmonary fibrosis and emphysema) and is associated with poor prognosis.

Table 2. Essential echocardiographic parameters and abnormal cut-off values for the evaluation of pulmonary hypertension.

Parameters	Abnormal Values
Right heart hemodynamic assessment	
Tricuspid regurgitation velocity	TRV > 2.8 m/s
Systolic PA pressure*	sPAP > 35 mm Hg
Additional signs suggestive of PH	
Early-diastolic pulmonary regurgitation velocity	Peak early-diastolic PR velocity > 2.2 m/s
RVOT acceleration time	RVOT AccT < 105 ms
Right atrium diameter, area and/or volume	RA diameter ≥ 42 mm, RA area > 18 cm ² or RA volume index ≥ 30 ml/m ²
Right ventricle basal diameter	≥ 41 mm
LV eccentricity index	> 1 in end-systole and end-diastole
Pulmonary artery diameter	> 25 mm
Inferior vena cava diameter (> 21 mm) with inspiratory collapsibility (< 50%)	According to these parameters RA pressure values 3, 8, or 15 mmHg are assigned
RV systolic function	
Tricuspid Annular Plane Systolic Excursion	TAPSE < 17 mm
TDI peak systolic velocity of tricuspid annulus	S' < 9.5 cm/s
RV fractional area change	RV FAC ≤ 35%
TAPSE/sPAP ratio	< 0.32 mm/mm Hg is associated with RV/PA uncoupling
Valvular pathologies	Regurgitation or stenosis severity
Left-sided parameters	
LV E/E' ratio	8-14 (gray zone), > 14 elevated
LV Ejection fraction	Men < 52%, Women < 54%
LA volume index	> 34 mL/m ²
Presence/absence of pericardial effusion	If present describe the size, distribution and hemodynamic effect (evidence of tamponade yes/no)

LA, left atrium; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract.

*PASP equals RVSP in the absence of RVOT obstruction, pulmonary stenosis, or proximal pulmonary artery stenosis; otherwise, values should be reported as RVSP.

High-resolution computed tomography (HRCT) of the chest provides detailed anatomical assessment of the lung parenchyma and mediastinum, and contributes to the exclusion of secondary causes of PH, including interstitial lung disease, emphysema, and PVOD/PCH.

Computed tomography pulmonary angiography, especially ECG-gated thin section, gives valuable information related to CTEPH, congenital heart/vascular abnormalities (including intracardiac shunts, abnormal pulmonary venous return, patent ductus arteriosus, pulmonary arteriovenous malformations), enlarged PA diameter, enlarged right heart chambers, peripheral PA stenosis. Computed tomography pulmonary angiogram may overlook the CTEPH lesions, especially distal segmental lesions.

Ventilation–perfusion (V/Q) scintigraphy [Planar or Single Photon Emission Computed Tomography (SPECT)] remains the preferred screening test for CTEPH. A normal V/Q scan mostly excludes CTEPH, whereas segmental perfusion defects with normal ventilation or in the absence of parenchymal lung disease should prompt further evaluation with pulmonary angiographic imaging. V/Q abnormalities may be present in PAH, typically as mild, non-segmental defects; segmental mismatched defects should raise suspicion for CTEPH.

Overnight oximetry or polysomnography should be performed if there is suspicion of sleep-disordered breathing or hypoventilation.

Other Investigations

Abdominal ultrasound and portal Doppler should be used to evaluate portal hypertension and its causes, including cirrhosis, vascular malformations, and portal vein thrombosis or obstruction.

Detailed laboratory testing should include viral serology for hepatitis and HIV, as well as an immunological work-up including at minimum antinuclear antibodies (ANA), lupus anticoagulant, and other antiphospholipid syndrome antibodies for rheumatological diseases such as SSc, systemic lupus erythematosus (SLE), and mixed connective tissue disease.

Cardiac magnetic resonance (CMR) Imaging improves diagnostic accuracy and provides prognostic information by accurately quantifying right heart size, volumes, RV ejection fraction, mass, and stroke volume, and by enabling indirect, noninvasive assessment of RV–PA coupling. The presence of late gadolinium enhancement reflects myocardial fibrosis and is associated with worse outcomes. CMR can also detect congenital heart disease

Cardiopulmonary exercise testing (CPET) provides integrated assessment of cardiovascular and pulmonary responses to exercise and is useful in evaluating unexplained dyspnea and suspected PH. In patients with PAH, a characteristic pattern is observed, including reduced peak oxygen uptake (VO_2), low end-tidal CO_2 (PETCO_2), elevated ventilatory inefficiency (VE/VCO_2 slope), and decreased oxygen

pulse (VO_2/HR). While not diagnostic, CPET complements other tests and may guide further evaluation.

Heart Catheterization Although traditionally termed right heart catheterization, the committee adopts the broader term heart catheterization, acknowledging that comprehensive assessment may require both right- and left-sided chamber access for pressure measurements and oxygen saturation sampling in selected cases.

Heart catheterization remains the gold standard for confirming PH, enabling hemodynamic characterization, risk stratification, and evaluation of associated congenital heart disease. In newly diagnosed patients, a comprehensive approach including both right- and left-sided assessment may be considered when feasible, as this improves diagnostic accuracy and reduces misclassification between pre- and post-capillary PH.¹⁵ The catheterization report should include all key hemodynamic parameters (Table 3) and be adapted to the clinical context.

Accurate measurements require meticulous technique, including proper transducer leveling, zero calibration, and pressure recording at end-expiration. Hemodynamic values may be influenced by volume overload and uncontrolled systemic blood pressure; therefore, patients should be optimized to a euvolemic state with adequate blood pressure control prior to catheterization. Pulmonary arterial wedge pressure is the primary surrogate for left atrial pressure; when unreliable, left ventricular end-diastolic pressure may be used, and direct left atrial measurement may be considered in selected cases.

Measurement of mixed venous (SvO_2) and arterial (SaO_2) oxygen saturations is required at a minimum. Stepwise oxygen saturation assessment should be performed in the presence of clinical or imaging suspicion of a left-to-right shunt, or when PA oxygen saturation is unexpectedly elevated ($>75\%$). Cardiac output is commonly estimated using the indirect Fick method due to limited equipment availability. When feasible, the direct Fick method is preferred. In the absence of shunts, thermodilution methodology may be used, although it requires specialized catheters and software.

Diagnosis of PAH requires confirmation of pre-capillary PH and exclusion of alternative causes. Therefore, all investigations related to etiology should be taken into consideration when planning and performing heart catheterization. This is important to determine the need for further testing in precapillary PH; for example, in the presence of thromboembolic lesions on CT or perfusion defects on V/Q scanning, invasive pulmonary angiography or digital subtraction angiography (DSA) may be required. In patients with a primary diagnosis of PAH, acute vasoreactivity testing (VRT) should be performed, particularly in those patients with idiopathic, heritable, or drug/toxin associated PAH. In patients with clinical or imaging findings suggestive of left heart disease but PAWP ≤ 15 mmHg, fluid challenge or passive leg raise (PLR) during catheterization may be used to unmask heart

Table 3. Essential Parameters and Reference Values for Heart Catheterization Reports**Height (cm), Weight (kg), and Body Surface Area****WHO functional class****Current medications (dose and frequency)**

Measured variables	Normal value	Calculated parameters	Normal value
Mean RA pressure (mm Hg)	<8	Cardiac output (L/min)	4-8
Systolic PAP (mm Hg)	15-30	Cardiac index (L/min/m ²)	2.5-4.0
Diastolic PAP (mm Hg)	4-12	Stroke volume index (mL/m ²)	33-47
Mean PAP (mm Hg)	8-20	Pulmonary vascular resistance (WU)	0.3-2.0
PAWP / Left ventricular end-diastolic pressure	≤15	Systemic vascular resistance (WU)	10-15
PA oxygen saturation*	65%-80%	Acute vasoreactivity test	Performed/Not performed
Arterial oxygen saturation	95%-100%	VRT compound	Iloprost, NO, epoprostenol
Aortic or systemic blood pressure*	120/80 mm Hg	mPAP after VRT (mm Hg)	≥10 mm Hg decrease to ≤40 mm Hg
Heart rate	60-100 bpm	Cardiac output after VRT (L/min)	Stable or increased CO
		VRT result	Positive/negative

CO, cardiac output; PA, pulmonary artery; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; RA, right atrium; VRT, vasoreactivity testing; WHO, World Health Organization.

* & PA oxygen saturation = Mixed venous oxygen saturation. If arterial access is not obtained, systemic blood pressure may be measured noninvasively from the appropriate extremity.

failure with preserved ejection fraction. However, results should be interpreted with caution and considered supportive rather than definitive.

The aim of VRT in PAH is to identify who may derive long-term benefit (above 1 year) from high-dose calcium channel blocker (CCB) therapy. Given the risks of inappropriate CCB therapy, VRT should be restricted to experienced centers. A positive VRT reflects an acute response; however, it does not necessarily guarantee sustained long-term clinical benefit, as approximately half of patients fail to respond durably to CCB therapy.¹⁶

The most commonly used agents for VRT are inhaled nitric oxide (NO) (10-20 ppm) and inhaled iloprost (5-10 µg). Intravenous epoprostenol (2-12 ng/kg/min) is an alternative; however, its use is more time-consuming and requires step-wise dose titration. A positive response in VRT is defined as a ≥10 mmHg reduction in mPAP to ≤40 mmHg, with stable or increased CO.¹⁶

An important practical question is how to interpret VRT in patients with a baseline mPAP between 21 and 40 mm Hg who fulfill the current hemodynamic definition of PAH. An absolute reduction in mPAP of ≥10 mm Hg may be considered a potential threshold for a positive vasoreactivity response; however, the supporting evidence remains limited, particularly in patients with only mildly elevated baseline mPAP. Alternative hemodynamic criteria previously proposed, such as a ≥20% reduction in PVR or combined reductions in mPAP and PVR, may indicate an acute vasodilatory response.^{17,18} However, these criteria have not been shown to reliably distinguish patients who derive sustained clinical benefit from those who do not respond to treatment.

A fluid challenge is performed by infusing 500 mL of saline over 5–10 minutes during catheterization after the initial

evaluation is finished; an increase in PAWP to ≥18 mmHg is considered abnormal.¹

Passive leg raise during HC is a simple maneuver in which the patient's legs are elevated by staff at an angle off ≈50 degrees while the patient remains in a supine position, relaxed and breathing spontaneously. A PAWP_{PLR} ≥19 mmHg suggests occult heart failure. This maneuver requires appropriate venous access, typically via the internal jugular vein.¹⁹

Coronary Angiography

Coronary angiography should be considered in patients with PAH when there is clinical suspicion of concomitant coronary artery disease or in those with cardiovascular risk factors, particularly prior to advanced therapies or surgical interventions such as lung transplantation or pulmonary thromboendarterectomy. In addition, it is indicated when LMCA compression is suspected, especially in patients with severe PA dilation presenting with angina or ischemic symptoms.

EVALUATION FOLLOWING DIAGNOSIS OF PULMONARY ARTERIAL HYPERTENSION

Patients should be managed in, or in collaboration with, specialized PH centers for precise diagnosis and appropriate treatment.^{1,2} A multidisciplinary approach involving cardiology, pulmonology, radiology, rheumatology, and other relevant specialties is recommended. After confirmation of the diagnosis, patients should undergo comprehensive evaluation using clinical, laboratory, imaging, and heart catheterization parameters. Treatment strategy should be guided by risk stratification based on the estimated 1-year mortality.

Exercise Capacity Evaluation

Exercise capacity is a key component of risk assessment and follow-up in patients with PAH. It should be routinely evaluated using the World Health Organization (WHO) functional class and objective exercise testing.

The 6-minute walk test (6MWT) is the most widely used and practical method for assessing submaximal exercise capacity in PH and is recommended at baseline and during follow-up when clinically feasible.^{20,21} The test should be performed according to standardized protocols to ensure reproducibility and reliability. Patients are instructed to walk as far as possible along a flat, straight corridor for 6 minutes, with standardized encouragement. The total distance walked (6MWD) is recorded in meters.

In addition to distance, other parameters such as oxygen saturation, heart rate response, and symptom burden (e.g., dyspnea using the Borg scale) should be documented, as they provide important complementary information. A reduced 6MWD and/or significant oxygen desaturation during the test are associated with worse prognosis. Serial assessments are particularly valuable for monitoring disease progression and treatment response.

The test results may be influenced by age, sex, height, comorbidities, and patient motivation; therefore, consistent testing conditions and interpretation in clinical context are essential.

Cardiopulmonary exercise testing provides a comprehensive evaluation of exercise physiology and may offer additional prognostic and diagnostic information. However, its use is limited by the need for specialized equipment and expertise, and it is therefore not routinely required in all patients.

Initial Risk Stratification

A multidimensional approach is recommended for risk assessment in PAH, integrating clinical, functional, imaging, biomarker, and hemodynamic data. The ESC/ERS risk stratification algorithm is the most widely used model in Türkiye and is endorsed in this consensus as the preferred national standard to ensure uniform data collection and facilitate inter-center comparability.¹ Although alternative validated tools, such as REVEAL 2.0, may be used, a consistent risk assessment method should be applied at baseline and maintained during follow-up to accurately monitor disease progression.²²

At initial evaluation, the ESC/ERS 3-strata model should be applied to categorize patients as low, intermediate, or high risk based on parameters reflecting clinical status, exercise capacity, and right heart function, corresponding to estimated 1-year mortality risks of <5%, 5%-20%, and >20%, respectively (Table 4, modified from ESC/ERS Guidelines 2022).² Heart catheterization parameters play a central role in risk assessment, providing key prognostic information at diagnosis and during follow-up.

The primary therapeutic goal is to achieve and maintain a low-risk profile, which is associated with improved clinical outcomes. Risk status should be considered dynamic; therefore, any clinical deterioration or failure to achieve low-risk criteria should prompt timely treatment escalation or modification.

TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

After diagnostic confirmation by heart catheterization, including VRT in appropriate patient groups, risk assessment

should be performed and both supportive (symptomatic) and PAH-specific therapies should be initiated accordingly. The treatment algorithm proposed in this document primarily applies to patients with IPAH, HPAH, CTD-PAH, and corrected CHD-PAH with a mPAP $\geq$ 25 mmHg and PVR > 3 WU (Figure 2).

Symptomatic Treatment

Optimization of fluid status represents a key component of supportive therapy in PAH, contributing to accurate clinical evaluation, appropriate risk stratification, and effective symptom control. Loop and thiazide diuretics are the most employed agents for volume management in this population. Mineralocorticoid receptor antagonists, such as spironolactone or eplerenone, are also frequently used to optimize volume status and may provide additional clinical benefits. The selection, dose, and frequency of diuretic therapy should be individualized based on the extent of volume overload and renal function. Supplemental oxygen therapy should be considered in patients with documented hypoxemia. In the presence of anemia, iron status should be assessed by measuring ferritin levels and transferrin saturation, and iron deficiency should be treated accordingly.^{23,24}

Appropriate management of the underlying condition, such as SSc, SLE, human immunodeficiency virus (HIV) infection, or portal hypertension, represents an essential component of standard care in PAH. In addition, optimal treatment of associated comorbidities is crucial.

Lifestyle counseling, including weight management and avoidance of tobacco use, should be emphasized. Preventive care should also include immunization against influenza and *Streptococcus pneumoniae*, and vaccination against respiratory syncytial virus should be considered where available and appropriate.

Treatment of Pulmonary Arterial Hypertension Patients with Positive Acute Vasoreactivity Test

Patients with IPAH, HPAH, or drug- and toxin-associated PAH who demonstrate a positive acute VRT should be treated with CCB.^{1,2} The choice of CCB should be guided by heart rate. In patients with a normal or low heart rate, a dihydropyridine agent such as amlodipine (initial dose 5 mg od, titrated to 15-30 mg od), nifedipine (initial dose 30 mg bid or tid, titrated to 60 mg bid or tid), or felodipine (initial dose 5 mg od, titrated to 15-30 mg od) may be preferred. In patients with tachycardia, a non-dihydropyridine agent such as diltiazem (initial dose 60 mg bid, titrated to 120-360 mg bid) is recommended. CCB therapy should be started at low doses and gradually up-titrated based on blood pressure, heart rate, and overall clinical response, including hemodynamic parameters. High doses may be required to achieve optimal therapeutic effect.

Treatment goals include attainment of a low-risk profile on non-invasive assessments and near normalization of hemodynamics. In cases where these treatment goals are not achieved, escalation of therapy with the addition of PAH-specific medications is recommended.

Table 4. ESC/ERS 3-strata Risk Algorithm for Initial Risk Assessment in PAH

Prognostic Factors Based on Estimated 1-Year Mortality		Low Risk (<5%)	Intermediate risk (5%-20%)	High Risk (>20%)
Signs and symptoms	• Signs of RHF	Absent	Absent	Present
	• Symptom progression	No	Slow	Rapid
	• Syncope	No	Occasional	Recurrent syncope
Exercise capacity	• WHO-Functional Class	I, II	III	IV
	• 6MWD (m)	>440	165-440	<165
	CPET			
	• Peak VO ₂ (mL/min/kg)	15	11 – 15	< 11
Right ventricular function	• VE/VCO ₂	<36	36 – 44	> 44
	Biomarkers			
	• BNP (ng/L)	<50	50-800	>800
	• NT-proBNP (ng/L)	<300	300-1100	>1100
	Echocardiography			
	• RA area (cm ²)	<18	18-26	26
	• TAPSE/sPAP (mm/mm Hg)	>0.32	0.19-0.32	<0.19
	• Pericardial effusion	No	Minimal	Moderate or large
	Cardiac MRI			
	• RV ejection fraction (%)	54	37-54	<37
	• Stroke volume index (mL/m ²)	>40	26-40	<26
	• RV ESVI (mL/m ²)	<42	42-54	>54
	Heart catheterization			
	• RA pressure (mm Hg)	<8	8-14	>14
	• Cardiac index (L/min/m ²)	≥2.5	2.0-2.4	<2.0
	• Stroke volume index (mL/m ²)	38	31-38	<31
	• SvO ₂	>65	60-65	<60

6MWD, 6-minute walk distance; CPET, cardiopulmonary exercise test; ESVI, end-systolic volume index; RA, right atrium; RV, right ventricle; sPAP, systolic pulmonary artery pressure; SvO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

Standard Pulmonary Arterial Hypertension Specific Therapy

For many years, main pharmacological treatments for PAH have targeted 3 major pathophysiological pathways: the endothelin, nitric oxide, and prostacyclin pathways (Table 5). These therapies modulate pulmonary vascular tone, induce vasodilation, and improve pulmonary hemodynamics, exercise capacity, and clinical outcomes. However, there remains a critical need for novel therapies that address mechanisms beyond these traditional pathways.

Recent advances have introduced therapies targeting the activin–transforming growth factor- β (TGF- β) signaling pathway, now recognized as a fourth therapeutic pathway in contemporary guidelines.^{1,25} Sotatercept, the first agent in this class, restores the balance between pro-proliferative activin and anti-proliferative bone morphogenetic protein (BMP) signaling.²⁶⁻³⁴ It has been associated with reductions in mPAP without significant changes in cardiac output, suggesting a potential role in pulmonary vascular remodeling rather than vasodilation. The addition of sotatercept to established background PAH therapy significantly improves exercise capacity, cardiac biomarkers, functional status, RV structure and function, pulmonary hemodynamics, and clinical outcomes. These improvements have largely been maintained at 1-2 years of follow-up.^{28,35} At the time of writing this consensus article, the authors agreed to include sotatercept in the treatment algorithm; however, it is not currently available in Türkiye.

Initial Treatment Strategy

Initial therapy following diagnosis should be based on an evaluation of risk status according to ESC/ERS 3-strata algorithm (Table 4). For patients not classified as high risk at diagnosis (i.e., low or intermediate risk patients), initial oral combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type-5 inhibitor (PDE5i) is recommended as the preferred treatment strategy.^{1,25,36,37} As an alternative approach, combination therapy with an ERA and a soluble guanylate cyclase stimulator (sGCs) may be considered in selected patients.

In patients presenting with high-risk features, initial treatment should include parenteral prostacyclin therapy administered intravenously (epoprostenol) or subcutaneously (treprostinil) with an ERA and a PDE5i.

Follow-up

A comprehensive first follow-up assessment is recommended within 3 months after initiation of therapy. Earlier reassessment should be considered in patients with clinical instability or an inadequate response to treatment.

The frequency of subsequent visits should be individualized based on the patient's clinical status and treatment modality. For patients who are clinically stable, reassessment every 3 months is recommended.

Treatment-specific monitoring is essential. In patients receiving ERAs, liver function tests and hemoglobin levels

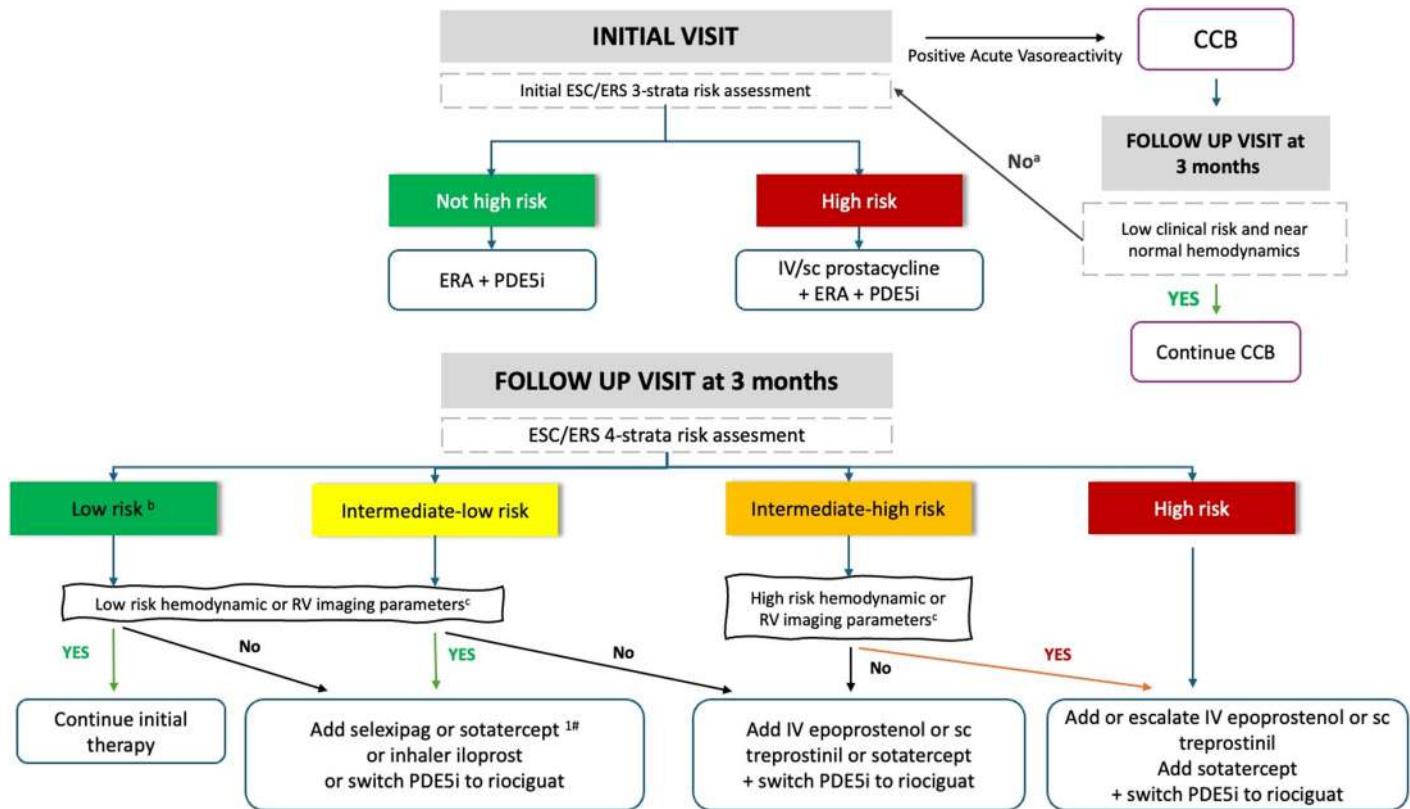


Figure 2. Proposed treatment algorithm for pulmonary arterial hypertension.

CCB, Calcium channel blocker, ERA, Endothelin Receptor Antagonist, PDE5i, Phosphodiesterase 5 inhibitor. 1# first choice. ^aContinue CCB and add PAH specific therapy according to the patient's risk profile. ^bAdditional hemodynamic and imaging parameters may be required in selected situations, such as in younger patients or when one or more standard parameters included in the 4-strata risk model cannot be reliably obtained or adequately assessed. ^cLow or high risk hemodynamic or RV imaging parameters as defined in the ESC/ERS 3-strata risk model. ^d + Switching from PDE5i to riociguat may be considered as a salvage optimization strategy in patients who fail to achieve treatment goals despite maximally tolerated multidrug therapy. In high-risk patients, this approach is based on expert opinion. In both intermediate-high and high-risk patients, it should not delay referral for lung transplantation.

should be assessed during the first month of therapy. For patients treated with the sGCs riociguat, dose titration requires clinical evaluation at approximately 2-week intervals until the target dose is achieved. Patients receiving intravenous or subcutaneous prostacyclin therapy may require more frequent follow-up, often once or twice weekly,

during the titration period. Similarly, initiation of selexipag necessitates weekly dose titration with close monitoring of tolerability and adverse effects. For patients treated with subcutaneous sotatercept, hemoglobin, platelet count, and blood pressure should be assessed prior to each of the first 5 doses (administered every 3 weeks), followed by periodic

Table 5. Pharmacological Treatment Options in PAH According to Targeted Pathways

Pathway	Drug Class	Drug	Recommended Dose
Endothelin pathway	Endothelin receptor antagonists (ERAs)	Bosentan	62.5 mg bid → 125 mg bid
		Ambrisentan	5-10 mg once daily
		Macitentan	10 mg once daily
Nitric oxide (NO) pathway	Phosphodiesterase-5 inhibitors (PDE5i)	Sildenafil	20 mg tid
		Tadalafil	40 mg once daily
	Soluble guanylate cyclase stimulators (sGCs)	Riociguat	1 mg tid → up to 2.5 mg tid (titrated)
Prostacyclin pathway	Prostacyclin analogues	Epoprostenol (IV)	Continuous infusion, starting 2 ng/kg/min (titrated)
		Treprostinil (sc)	Starting 1.25 ng/kg/min (titrated)
		Iloprost (inhaled)	2.5-5 µg per inhalation, 6-9 times/day
	Prostacyclin receptor agonist	Selexipag	200 mcg bid → up to 1600 mcg bid (titrated)
BMP signaling pathway	Activin signaling inhibitor	Sotatercept	0.3 mg/kg SC → 0.7 mg/kg every 3 weeks

bid, twice daily; BMP, bone morphogenetic protein; iv, intravenous; sc, subcutaneous; tid, three times daily.

monitoring guided by clinical status; dose adjustment or temporary interruption may be required in cases of clinically significant abnormalities.

At each follow-up visit, a comprehensive clinical evaluation and risk assessment should be performed, including assessment of symptoms (e.g., dyspnea, angina, syncope), WHO-FC, and signs of right heart failure on physical examination, as well as oxygen saturation. Exercise capacity and biomarkers should be routinely evaluated, including 6MWD and BNP or NT-proBNP levels, to guide ongoing risk stratification and treatment optimization. Laboratory assessment should include hemoglobin and liver function tests. Echocardiography should be performed during follow-up, particularly after initiation or modification of therapy; in clinically stable patients, it may be repeated at approximately 6-month intervals.

Based on these findings, patient risk status should be reassessed using the ESC/ERS 4-strata risk stratification model (Table 6, modified from ESC/ERS guidelines 2022). As age and comorbidities may influence individual parameters, risk assessment should be interpreted in a comprehensive manner, incorporating additional variables as needed. In this context, right heart imaging and hemodynamic data provide important complementary information beyond simplified risk scores. Key echocardiographic (e.g., TAPSE/sPAP ratio, pericardial effusion, RA area) and hemodynamic parameters (e.g., SvO₂, cardiac index, stroke volume index, RA pressure), originally included in the 3-strata model, remain essential for accurate risk assessment and guiding therapeutic decisions during follow-up.

The optimal timing and frequency of hemodynamic reassessment may vary depending on institutional expertise and available resources. Nevertheless, given the robust prognostic and therapeutic information provided by heart catheterization, its incorporation into follow-up is encouraged. The committee recommends invasive hemodynamic evaluation in expert PAH centers in the setting of clinical deterioration, following treatment modification to assess response, and at approximately annual intervals in clinically stable patients.

Clinical Deterioration and Complications During Follow-up

Chest pain and syncope should raise suspicion for LMCA compression by a dilated PA, particularly when the PA diameter exceeds 40 mm.³⁸⁻⁴⁰ Coronary CT angiography should be performed to evaluate the PA–LMCA relationship and screen for possible coronary compression. It is important to clearly

inform the radiologist of the clinical suspicion and specifically request assessment for possible dilated PA–related LMCA compression. The PA–LMCA relationship may be categorized as normal (>1 mm separation), contiguity (≤1 mm without displacement or stenosis), dislocation (LMCA displacement by the enlarged PA, with or without luminal narrowing), or significant stenosis (≥50% narrowing due to external compression).³⁸

Invasive coronary angiography helps determine the degree of stenosis; however, multiple projections are required, as the lesion may not be apparent in all views.⁴⁰ The left cranial projection is generally the most informative. Given the potential for dynamic worsening of coronary compression during exercise, resting intravascular imaging with intravascular ultrasound or optical coherence tomography may underestimate the severity of stenosis.

In patients with hemodynamically significant LMCA compression, percutaneous coronary intervention with stent implantation represents an effective therapeutic option, providing rapid symptom relief and restoration of coronary flow. Given the extrinsic nature of the lesion, stent selection should prioritize high radial strength to resist ongoing external compression. However, treatment decisions should be individualized within a multidisciplinary framework. In selected cases, particularly in the presence of large or progressive PA aneurysms or complex anatomy, surgical options including PA repair and/or coronary artery bypass grafting should also be considered.

In addition to these structural complications, clinicians should be aware that even patients who appear clinically stable under optimal therapy may experience sudden clinical deterioration due to acute right heart failure.⁴¹ This life-threatening condition may be triggered by factors such as arrhythmias, infections, pulmonary embolism, progression of pulmonary vascular disease, treatment interruption, or volume imbalance. Timely recognition and diagnosis are crucial, and clinicians should actively search for reversible triggers of decompensation. Given the limited adaptive capacity of the RV to acute increases in afterload, early identification of warning signs—such as worsening dyspnea, hypotension, tachycardia, and signs of systemic congestion—is essential. Prompt referral to expert centers and timely escalation of therapy, including intravenous epoprostenol and inhaled nitric oxide, are critical to prevent further deterioration.⁴¹ In advanced cases, extracorporeal life support (e.g., ECMO) may be considered as a bridge to recovery in selected patients.

Table 6. ESC/ERS 4-Strata Risk Stratification Model for Follow-up

Prognostic Factors	Low risk (0%-3%)	Intermediate-low risk (2%-7%)	Intermediate-high risk (9%-19%)	High Risk (>20%)
WHO functional class	I, II		III	IV
6MWD (m)	>440	320-440	165-319	<165
BNP (ng/L)	<50	<50-199	200-800	>800
NT-proBNP (ng/L)	<300	300-649	650-1100	>1100
SCORE	1	2	3	4

An overall risk score is calculated by averaging the scores of the available parameters and rounding to the nearest integer, thereby assigning the patient to a final risk category.

6MWD, six-minute walk distance, WHO, World Health Organization.

Treatment Goals and Escalation Strategy

The primary goal of PAH treatment is to achieve and maintain a low-risk profile. Patients who meet low-risk criteria and do not exhibit high-risk features on echocardiography or heart catheterization at follow-up should continue their initial treatment strategy.

In patients with intermediate–low risk at first follow-up, escalation of therapy is recommended. The addition of an oral prostacyclin receptor agonist, such as selexipag, or activin signaling inhibitor, such as sotatercept, represents a preferred treatment strategy supported by a high level of evidence.^{26–28,42} Inhaled prostacyclin therapy may also be considered as an alternative option. In selected patients, switching from PDE5i therapy to an sGC, such as riociguat, may also be considered, although the level of recommendation for this approach is lower.^{43–45}

Patients with an intermediate–high risk profile should be evaluated with caution. The presence of comorbidities may complicate clinical assessment, and in cases of potential confounding, repeat evaluation of diagnostic tests under optimal conditions should be considered to allow more accurate risk stratification and treatment decision-making. If the patient remains at intermediate–high risk despite reassessment, escalation of therapy with the addition of sotatercept or initiation of parenteral prostacyclin therapy (iv epoprostenol or sc treprostinil) should be considered following shared decision-making with the patient. Switching from PDE5i to riociguat may also be considered in selected patients who fail to achieve treatment goals despite treatment intensification.⁴⁵

In patients at high risk, or those at intermediate–high risk with adverse RV imaging findings or severely impaired hemodynamic parameters, the addition of both sc sotatercept and parenteral prostacyclin (intravenous or subcutaneous) should be considered. Data regarding switching from PDE5i to riociguat in high-risk patients remain limited. In this population, prostacyclin- and sotatercept-based aggressive treatment strategies should be prioritized. Nevertheless, given the substantial mortality risk associated with advanced PAH, individualized attempts at further therapeutic optimization may still be justified in selected patients.

Lung transplantation represents an important therapeutic option in the management of PAH. Although availability remains very limited in Türkiye, all patients classified as high risk at diagnosis, as well as those with intermediate–high or high risk at follow-up, should be referred to a lung transplantation center for evaluation. There is an urgent need to expand and strengthen transplant programs and to increase awareness of the importance of organ donation and transplantation.

Management of Patients in the Hemodynamic Gray Zone (Mean Pulmonary Artery Pressure 21–24 mmHg and/or Pulmonary Vascular Resistance 2–3)

Patients with a mPAP of 21–24 mmHg and/or a PVR of 2–3 WU represent a clinical gray zone. Currently, there is no evidence to support routine initiation of PAH-specific therapy

in this population. These patients should be evaluated in expert PH centers, undergo careful clinical and hemodynamic reassessment, and be followed closely for evidence of disease progression. Associated conditions, underlying diseases, and comorbidities should be identified and managed appropriately to minimize the risk of further pulmonary vascular disease progression. Follow-up should include clinical evaluation, WHO functional class, 6-minute walk distance, NT-proBNP, echocardiography, and repeat right heart catheterization when clinically indicated. Initiation of PAH-specific therapy should be considered only if progression to established PAH or other evidence-based indications develop.

PULMONARY ARTERIAL HYPERTENSION SUBGROUPS

Congenital Heart Disease–Associated Pulmonary Arterial Hypertension

Congenital heart disease–associated PAH is classified into 4 subgroups: 1) Eisenmenger syndrome, 2) PAH associated with persistent systemic-to-pulmonary shunts, 3) PAH with small or coincidental defects, and 4) PAH associated with repaired defects. Patients in the latter 2 groups are generally managed similarly to those with IPAH.

Patients with Eisenmenger syndrome and those with persistent systemic-to-pulmonary shunts should be evaluated in specialized centers by a multidisciplinary congenital heart disease team, given their complex pathophysiology and limited evidence base. A comprehensive evaluation, including assessment of operability/defect closure and PAH specific treatment strategy, should be performed. These patients often demonstrate longer survival than those with IPAH.⁴⁶

Defect closure is not indicated and is considered harmful in patients with Eisenmenger syndrome and in those with PAH and small defects. In patients with persistent systemic-to-pulmonary shunts, the indication for closure requires careful evaluation. Pulmonary vascular resistance is a key determinant: values ≥ 5 WU indicate that closure is harmful, whereas values < 3 WU are associated with a low-risk profile; values between 3 and 5 WU represent a gray zone requiring individualized assessment.⁴⁷ However, decisions should not rely solely on PVR and must incorporate a comprehensive evaluation of shunt physiology, RV function, left ventricular diastolic function, exercise-induced desaturation, and the anticipated long-term consequences of defect closure. In patients initially deemed inoperable, defect closure may become feasible following PAH-specific therapy if a significant reduction in PVR is achieved; however, evidence supporting the long-term benefit of this approach remains limited.

Pulmonary arterial hypertension–specific therapy should be initiated in a stepwise manner. In Eisenmenger syndrome, bosentan has the strongest evidence and a Class I, Level B recommendation for improving exercise capacity. Other agents from the main therapeutic classes (ERAs, phosphodiesterase type 5 inhibitors, sGCs, and prostacyclin analogues) may be used in both Eisenmenger syndrome and PAH associated with persistent systemic-to-pulmonary

shunts, based on individual patient characteristics and tolerability.

In patients who develop high-risk features, PAH therapy should be escalated with add-on treatment, including parenteral prostacyclins. Subcutaneous prostacyclins may be preferred in patients with Eisenmenger syndrome and systemic-to-pulmonary shunts, as they avoid the risk of catheter-related infective endocarditis associated with intravenous therapy.

Risk assessment in this population is challenging, particularly in Eisenmenger syndrome. Evaluation should include clinical (WHO functional class, 6-minute walk distance, resting SpO₂, signs of heart failure), laboratory (BNP), and imaging parameters (e.g., pericardial effusion). In cases of discordant findings, hemodynamic variables (right atrial pressure, cardiac index, PVR index, and response to VRT) provide additional prognostic information. High-risk features such as resting SpO₂ <85%, WHO functional class III-IV, recurrent hospitalizations, 6-minute walk distance <400 m, arrhythmias, rising BNP (>200 pg/mL), renal dysfunction, hypoalbuminemia, and adverse right heart findings (TAPSE < 15 mm, RA area > 25 cm², RA pressure > 8 mmHg, CI < 2.5 L/min/m², pericardial effusion) should prompt closer follow-up and early treatment escalation.⁴⁸

In patients with Eisenmenger syndrome, supplemental oxygen therapy may be considered after assessing its effect on arterial oxygen saturation; it should be used in patients in whom oxygen administration results in a consistent increase in saturation and improvement in symptoms.

Elevated hemoglobin levels due to secondary erythrocytosis are a common laboratory finding in patients with Eisenmenger syndrome. In the absence of moderate to severe hyperviscosity symptoms, phlebotomy should be avoided.

Connective Tissue Disease—Associated Pulmonary Arterial Hypertension

Pulmonary arterial hypertension is one of the most severe complications of CTDs and remains a major cause of morbidity and mortality. As early disease may be asymptomatic, routine screening is essential for timely diagnosis, particularly in SSc.

Echocardiography remains the cornerstone of screening in SSc. Multimodal screening algorithms such as ESC/ERS, DETECT, and Australian Scleroderma Interest Group (ASIG) combine clinical variables, PFTs, biomarkers, and echocardiographic parameters to improve early detection. However, when the updated 2022 ESC/ERS hemodynamic definitions are used, their sensitivity may be reduced, and none achieves perfect diagnostic accuracy.⁴⁹ In addition, their performance may be limited in patients with coexisting interstitial lung disease or left heart disease, which are common in SSc.⁵⁰

A recent multidisciplinary Turkish consensus statement recommends that screening strategies be tailored to patient characteristics and local resources, with annual echocardiographic evaluation prioritized in patients with SSc or SSc

overlap features.⁵¹ In line with these recommendations, the present consensus proposes a simplified algorithm for PAH screening in SSc (Figure 3). Evidence supporting routine screening of other CTD patients, such as SLE, mixed connective tissue disease remains limited, particularly in asymptomatic patients. For other CTD patients with symptoms, the proposed diagnostic algorithm in this document (Figure 1) should apply.

Connective tissue diseases are a multisystem disorder in which multiple mechanisms—including left heart disease, interstitial lung disease, chronic thromboembolic disease, and PVOD—may contribute to PH, either alone or in combination. Accurate identification of the underlying PH subtype is therefore essential, as treatment strategies differ substantially and PAH-specific therapies may be ineffective or potentially harmful in non-PAH forms of PH.

Regarding the management of patients with CTD-PAH, treatment recommendations are generally similar to those in IPAH.^{1,25,52} However, disease-specific features should be considered when selecting therapy. For example, in patients with SSc, the presence of digital ulcers may influence treatment choice, as PDE5i and bosentan are frequently used for both PAH and peripheral vascular manifestations.^{1,13,53,54}

In clinical practice, many patients with SSc-PAH are already receiving ERA and/or PDE5i therapy due to peripheral vascular manifestations at the time of diagnosis. Therefore, treatment strategies often involve sequential escalation, rather than upfront combination therapy, by adding additional PAH-targeted agents to existing treatment.

Altered immune responses and chronic inflammation contribute to the pathogenesis of PAH in CTDs. In patients with PAH associated with SLE or mixed connective tissue disease, immunosuppressive therapy—particularly cyclophosphamide-based regimens initiated early and combined with PAH-specific vasodilator therapy—may substantially improve or even reverse PAH and represents an important component of management in expert centers.⁵⁵⁻⁵⁸ In contrast, in patients with SSc-associated PAH, the evidence supporting immunosuppressive therapy is limited and inconsistent.^{13,59-61} Although some immunosuppressive regimens have shown potential benefit, current data do not support immunosuppression as a standard effective treatment for SSc-PAH. Standard care remains aggressive PAH-targeted therapy; immunosuppression should be considered on an individualized basis and preferably guided by a specialized PH/SSc team.

Drug and Toxin—Associated Pulmonary Arterial Hypertension

In patients with DT-PAH, exposure to the causative drug or toxin should be promptly discontinued and avoided. Clinical outcomes may vary depending on the specific agent responsible for PAH, and partial or complete reversal of PAH has been reported following discontinuation of certain drugs or toxins, such as dasatinib, interferon, carfilzomib.⁶²⁻⁶⁴

Accordingly, in patients exposed to these agents who present with low-risk features, withdrawal of the causative drug

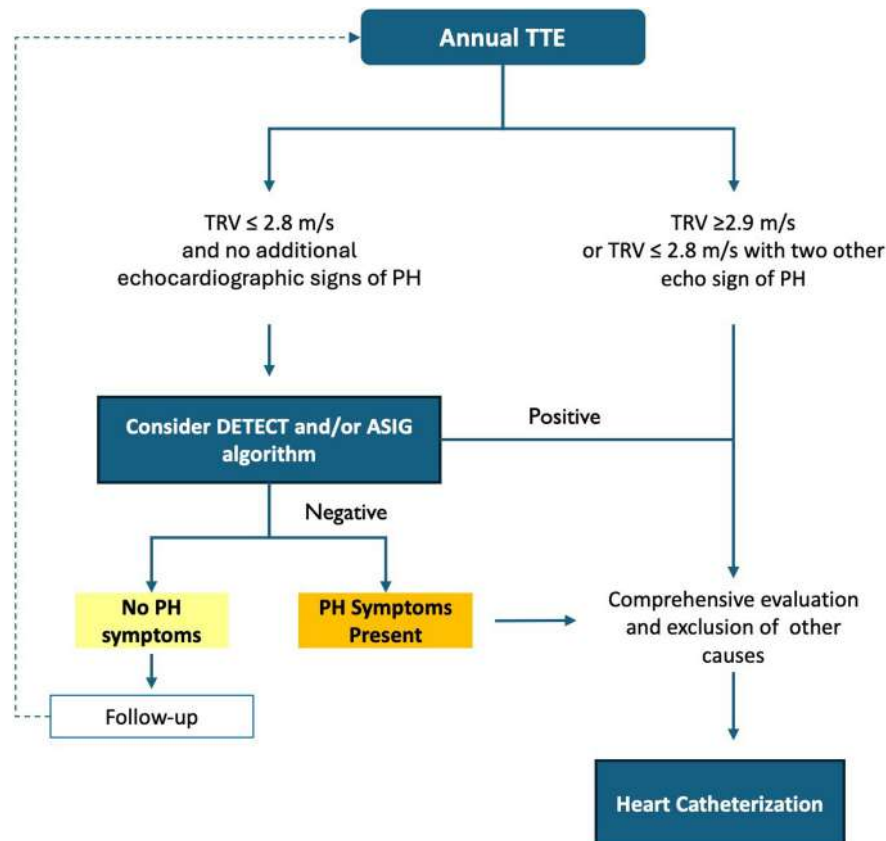


Figure 3. PAH screening algorithm in systemic sclerosis. PH, Pulmonary hypertension; TRV, Tricuspid regurgitation velocity; TTE, transthoracic echocardiography.

alone may be considered with close monitoring. If no appropriate clinical and hemodynamic improvement is observed, PAH-specific therapy should be started based on risk stratification. In patients with intermediate or high-risk presentation, the standard treatment algorithm should be followed. At follow-up, if sustained hemodynamic normalization is documented, cautious de-escalation or discontinuation of PAH therapy may be considered.

Portopulmonary Hypertension

Although patients with PoPH are underrepresented in major PAH clinical trials, treatment strategies are generally similar to those for IPAH. Macitentan and riociguat have been studied in POPH in prospective registries and showed benefit. In patients with advanced liver disease, caution is required because of impaired drug metabolism. Liver transplantation can improve or sometimes normalize PoPH; however, many patients are not eligible for transplantation. Recommended hemodynamic targets prior to consideration of transplantation include a mPAP < 35 mmHg and a PVR < 5 WU, or a mPAP 35–45 mmHg with a PVR < 3 WU.^{65,66} Following liver transplantation, hemodynamics should be carefully reassessed, and PAH-specific therapy should be continued or adjusted as clinically indicated.

HIV-Associated PAH

The HIV-PAH is very rare in Türkiye. The treatment algorithm is similar to that for IPAH. However, careful attention to potential drug–drug interactions between antiretroviral

therapy and PAH-specific medications is essential, particularly with PDE5i, and such interactions should be carefully reviewed before and during treatment.

Schistosomiasis–Associated Pulmonary Arterial Hypertension

Schistosomiasis-associated PAH has not been systematically reported in Türkiye. However, treatment principles for PAH are similar in these patients. In addition to PAH-specific therapy, antihelminthic treatment should also be considered.

Pulmonary Veno-Occlusive Disease and Pulmonary Capillary Hemangiomatosis

The PVOD and PCH are rare forms of PAH within the same disease spectrum, characterized by predominant involvement of small pulmonary veins and capillaries. Early recognition is essential, as management differs from other PAH subtypes and inappropriate therapy may lead to clinical deterioration; moreover, prognosis is worse compared with other forms of PAH in the absence of lung transplantation.⁶⁷

The PVOD/PCH should be suspected in patients with PH presenting with severe hypoxemia, markedly reduced DLCO, and characteristic imaging findings. A history of exposure to organic solvents or chemotherapeutic agents, particularly alkylating agents such as mitomycin, should raise suspicion.⁶⁸ High-resolution CT typically demonstrates a triad of centrilobular ground-glass opacities, interlobular septal thickening, and mediastinal lymphadenopathy. Although

these findings are not specific and may be seen in conditions such as pulmonary edema or infection, their presence especially in combination supports the diagnosis. Parenchymal changes can be present even before the development of PH. The development of pulmonary edema following the initiation of any PAH-targeted therapy is strongly suggestive.

Diagnosis should be based on clinical, radiological, and hemodynamic findings. Right heart catheterization typically shows a precapillary PH profile and is not distinguishable from other forms of PAH. Genetic testing (e.g., *EIF2AK4* mutations) may support the diagnosis. Lung biopsy is not recommended due to the high risk of complications.

Management should be undertaken in expert centers. PAH-specific therapies should be used with caution, preferably initiated at low doses with close monitoring due to the risk of pulmonary edema. Supportive therapy, including oxygen supplementation in hypoxemic patients and diuretics to manage RV overload and prevent fluid retention, is recommended. Early referral for lung transplantation evaluation should be considered, as this remains the only definitive treatment.

CONCLUSION

Pulmonary arterial hypertension remains a life-threatening and complex disease that requires early recognition and coordinated multidisciplinary care. This consensus, developed in the context of real-world clinical practice in Türkiye, provides a pragmatic framework by integrating evidence-based recommendations with local experience and resource considerations. The proposed diagnostic and treatment algorithms, together with standardized echocardiographic and hemodynamic parameters, aim to harmonize clinical practice, support consistent decision-making, and improve data quality across centers. Timely diagnosis, regular risk-based follow-up, and appropriate treatment escalation—ideally within expert PH centers—are essential to improving outcomes. This effort represents an important step toward more standardized, accessible, and data-driven PAH care in Türkiye.

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Informed Consent: Not applicable, as this expert consensus report does not involve human participants or patient data.

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Unraveling the Mechanisms of Neutrophil Extracellular Trap Formation and the Role of Reactive Oxygen Species in Myocardial Bridging

ABSTRACT

Myocardial bridging (MB) is a congenital coronary anomaly in which a segment of a coronary artery courses through the myocardium, resulting in systolic compression and alterations in coronary vasoreactivity. Consequently, morphological, functional, and hemodynamic changes may occur, with various clinical implications. Although traditionally considered a benign anatomical variant, accumulating evidence suggests an association between MB and endothelial dysfunction, oxidative stress, local inflammatory activation, and atherosclerotic plaque formation, predominantly in the arterial segment proximal to the bridge. Reduced wall shear stress in the proximal segment is associated with a pro-inflammatory and pro-oxidative vascular environment characterized by reduced nitric oxide (NO) bioavailability, despite increased endothelial nitric oxide synthase (eNOS) expression, consistent with impaired eNOS signaling and possible functional uncoupling, together with activation of reactive oxygen species-generating pathways. Myeloperoxidase (MPO), released from activated neutrophils, is a key mediator of oxidative vascular injury and may contribute to endothelial dysfunction by reducing NO bioavailability, generating highly reactive oxidants such as hypochlorous acid, and promoting oxidative endothelial injury. Hemodynamic alterations characteristic of MB may promote MPO activation and the MPO-H₂O₂ pathway, thereby facilitating mechanisms involved in neutrophil extracellular trap (NET) formation and contributing to the pro-inflammatory vascular environment. MPO- and NET-mediated pathways may represent biologically plausible contributors to endothelial dysfunction and proximal atherogenesis in MB. However, the role of these pathways in the pathophysiology of MB remains insufficiently investigated and should currently be regarded as a hypothesis rather than an established pathophysiological mechanism.

Keywords: Endothelial dysfunction, myeloperoxidase, myocardial bridging, neutrophil extracellular traps, oxidative stress, reactive oxygen species, shear stress

INTRODUCTION

The uniqueness of the coronary circulation lies in its crucial role in generating arterial pressure necessary for the perfusion of the systemic circulation. Myocardial bridging (MB), in which a segment of a coronary artery courses intramurally through the myocardium, additionally causes compression of the tunneled coronary segment, thereby impairing coronary perfusion during the systolic phase of the cardiac cycle.

Morphological and hemodynamic disturbances of coronary blood flow associated with MB, as well as the imbalance between myocardial oxygen supply and demand, may be associated with angina pectoris, myocardial ischemia, acute coronary syndrome, left ventricular dysfunction, arrhythmias, and even sudden cardiac death.¹

Therefore, the regulation and control of coronary blood flow, as well as the factors influencing myocardial oxygen consumption, are essential for understanding the pathophysiological basis of MB, which is characterized by oxidative stress, endothelial dysfunction, inflammation,^{1,2} and potentially NETosis.

REVIEW

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Endothelial dysfunction occurs through the rapid scavenging of nitric oxide (NO) by superoxide anions generated in response to oxidative stress. Oxidative stress disrupts the synthesis and bioavailability of NO, further impairing endothelial function and promoting vasoconstriction, thrombosis, and inflammation.^{3,4}

The major endothelium-dependent biochemical pathways rely on the presence of a functional endothelium, particularly on the endothelium-derived relaxing factor identified as NO.⁵ Nitric oxide is synthesized and released by vascular endothelial cells through the enzymatic conversion of L-arginine to citrulline mediated by endothelial NO synthase (eNOS). It inhibits the development of coronary atherosclerosis and promotes endothelial repair by facilitating potassium channel opening, vasodilation, and scavenging reactive oxygen species (ROS).⁶

Nitric oxide-mediated vasodilation is impaired in MB and results not only from endothelial dysfunction but also from the transformation of the vascular surface into a pro-inflammatory and pro-thrombotic monolayer. Previous studies have shown that the proximal segment of MB is characterized by reduced NO bioavailability, increased oxidative stress, endothelial dysfunction, and a greater susceptibility to the development of atherosclerotic lesions.^{2,7}

Studies have demonstrated that, compared with normal coronary arteries, inflammation and the neutrophil-to-lymphocyte ratio are significantly increased in patients with MB.^{1,8} Under conditions of infiltration and inflammation, neutrophils release neutrophil extracellular traps (NETs) as a defense mechanism.

NETosis represents a key neutrophil-mediated immune response mechanism involving robust generation of ROS through NADPH oxidase activity. Although NETs were initially identified as an important component of innate immunity, they have subsequently been associated with numerous pathological conditions, highlighting their dual role as both protective and potentially harmful mediators.⁹

During NETosis, neutrophils release numerous enzymes from their granules into the extracellular space. These enzymes,

including myeloperoxidase (MPO), play an important role in NET formation.^{9–11}

It has been shown that inhibition of intragranular MPO activity or neutralization of intragranular MPO-modified ROS using luminol effectively blocks NET formation, indicating that ROS generation and MPO-mediated processes within intracellular granules are required for the initiation of NET formation.¹²

In addition, neutrophils undergoing NETosis may release cytoplasmic contents, including mitochondria, into the extracellular space. These components contribute to the inflammatory response and additional antimicrobial activity.¹³ In vascular inflammatory diseases, persistent neutrophil activation and NET formation have been implicated in endothelial injury, oxidative stress, and the progression of atherosclerosis. This association is particularly relevant to MB, where evidence suggests that the arterial segment proximal to the bridge exhibits a higher incidence of atherosclerotic lesions, whereas the tunneled segment remains relatively protected from atherosclerosis despite the presence of endothelial functional alterations that may predispose to vasospasm and thrombosis.^{2,7}

Myocardial bridging was hypothesized to create a spatially heterogeneous oxidative and inflammatory microenvironment driven by altered shear stress, which may favor MPO activation and potentially contribute to NET formation in the proximal coronary segment, thereby contributing to endothelial dysfunction, atherogenesis, and ischemic manifestations.

METHOD

Literature Search Strategy

This narrative review summarizes and integrates current evidence regarding the potential role of NETs and oxidative stress in the pathophysiology of MB. A structured literature search was performed using PubMed/MEDLINE and Scopus to identify relevant publications published from 1990 through May 2026. Search terms included combinations of MB, NETs, NETosis, MPO, oxidative stress, ROS, NO, endothelial dysfunction, shear stress, and atherosclerosis. Original research articles, experimental studies, clinical investigations, and relevant review articles published in English were considered. Emphasis was placed on studies investigating the mechanisms of endothelial dysfunction, redox signaling, MPO biology, NET formation, and coronary hemodynamics. Because direct evidence linking NETosis with MB is currently limited, mechanistic evidence from related cardiovascular and vascular inflammatory conditions was also incorporated to develop the proposed pathophysiological framework. This review follows a narrative rather than a systematic methodology; therefore, studies were selected based on their scientific relevance, methodological quality, and contribution to the mechanistic understanding of the topic, rather than on predefined systematic review criteria.

Pathophysiology of Myocardial Bridging

The pathophysiology of MB involves disruption of local vascular homeostasis through dysregulation of NO metabolism,

HIGHLIGHTS

- Myocardial bridging (MB) creates a spatially heterogeneous coronary microenvironment driven by altered shear stress and disturbed flow.
- The proximal segment exhibits enhanced oxidative stress, endothelial dysfunction, and inflammation mediated by myeloperoxidase-derived reactive oxygen species.
- Neutrophil extracellular trap formation is proposed as a previously underrecognized mechanism linking MB to proximal coronary atherogenesis and ischemic manifestations.
- Integrating hemodynamic and immune mechanisms may open new perspectives for targeted therapeutic strategies.

increased generation of ROS, and activation of oxidative-inflammatory pathways.² Wall shear stress (WSS), defined as the frictional force exerted by flowing blood tangentially on the luminal surface of the vessel wall, represents an important mechanical factor influencing the hemodynamic characteristics of the proximal and intramural segments of MB.

The pathophysiological mechanism involves dynamic compression of the tunneled segment during systole, causing localized disturbances in coronary blood flow and alterations in WSS within the proximal arterial segment, thereby creating a pro-oxidative and pro-inflammatory microenvironment that contributes to the development of atherosclerotic changes.^{1,2,8,14}

Oxidative stress, resulting from the intracellular generation and accumulation of ROS, promotes lipid accumulation, foam cell formation, and extracellular matrix degradation. These oxidative modifications impair the anti-inflammatory and vasodilatory functions of the endothelium and serve as a signal for neutrophil activation.¹⁵

During chronic vascular inflammation associated with atherosclerosis, as well as during chronic occlusive coronary artery disease, MPO, an enzyme released from activated leukocytes, plays an important role. The MPO markedly reduces the bioavailability of NO, a key mediator of vascular homeostasis. It catalyzes the formation of hypochlorous acid (HOCl) from hydrogen peroxide (H_2O_2) and chloride ions, generating highly reactive oxidant species.¹⁶

The preferential development of atherosclerosis, chronic coronary syndrome, and chronic total occlusions within the proximal segment of MB^{7,17,18} indicates the involvement of the aforementioned pathophysiological mechanisms and raises the question of a possible association between MPO, NETs, and MB, which has not yet been systematically addressed in the available literature. Although the role of MPO in endothelial dysfunction and atherosclerosis is well established, direct evidence linking MPO activity to MB is currently lacking. Consequently, the proposed involvement of MPO in MB should be interpreted as a mechanistic extrapolation based on established vascular biology rather than as an experimentally confirmed feature of MB.

In contrast to the hemodynamic profile of the proximal segment, the tunneled and distal arterial segments are characterized by elevated WSS. These conditions exert atheroprotective effects, including enhanced NO production, reduced platelet activation, and suppression of pro-inflammatory signaling pathways.^{14,19} The established anatomical, hemodynamic, endothelial, inflammatory, and functional differences between the proximal and intramural coronary segments are summarized in Table 1, providing the pathophysiological framework for the subsequent discussion of oxidative stress, MPO activation, and NET formation.

Myeloperoxidase, Nitric Oxide Synthase, and Neutrophil Extracellular Traps: Role in Oxidative Stress in the Proximal Segment of the Myocardial Bridge

Disturbed blood flow in the proximal part of the myocardial bridge can damage and activate endothelial cells lining

the arterial intima.^{20,21} Neutrophils attracted by chemokines produced by activated endothelial cells may accumulate on the exposed intima, where they may subsequently undergo degranulation and NETosis, releasing NETs. These strands of extracellular DNA can bind the contents of neutrophil granules and other proteins, such as MPO or tissue factor. NETs may act as a "solid-phase reactor," generating oxidants such as HOCl and locally promoting coagulation.²²

The generation of oxidants represents a positive feedback loop in vascular inflammation, in which the mutual activation of MPO, NADPH oxidase, and NOS is a key mechanism of NET formation.²³ NADPH oxidase provides the initial ROS, MPO catalytically converts H_2O_2 into potent oxidants, while NOS contributes by producing reactive nitrogen species.

This pro-oxidative integration of MPO, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, NOS, and NETs is known to reduce NO bioavailability, promote oxidative modification of lipoproteins, and consequently create a pro-inflammatory environment that promotes the progression of atherosclerotic lesions and plaque destabilization.^{24,25}

Although oxidative stress and dysregulated lipid metabolism are well-established contributors to coronary artery disease (CAD), accumulating evidence increasingly highlights the central role of immune responses and inflammation in disease progression.²⁶

At the molecular level, activation of NADPH oxidase represents a critical step in NETosis. This enzyme complex generates ROS, which are indispensable for NOX-dependent NET formation, as pharmacological or genetic inhibition of ROS production markedly suppresses this process.^{27,28}

During neutrophil activation, ROS are generated predominantly by NADPH oxidase, while mitochondrial metabolism may provide an additional intracellular source through the electron transport chain.²⁹ The hydrogen peroxide (H_2O_2) produced downstream of NADPH oxidase serves as the principal substrate for MPO, which catalyzes the formation of HOCl, a highly reactive oxidant involved in antimicrobial defense as well as oxidative tissue injury.

Excessive pro-oxidative activity of MPO reduces the bioavailability of NO by promoting eNOS uncoupling, generating superoxides within the endothelium, and contributing to the progression of atherosclerosis.^{3,30} Studies have reported decreased eNOS expression in severe atherosclerotic lesions of the coronary arteries. However, the significantly lower eNOS expression observed in the bridged, atheroprotective segment of the myocardial bridge remains a matter of controversy.³¹

Akong-Moore et al³² conducted a study to determine the role of HOCl in NET formation. The results showed that reducing Cl^- or inhibiting MPO with the hydrazide 4-aminobenzoic acid decreased NETosis in humans. The addition of exogenous sodium hypochlorite (NaOCl) stimulated NET formation in a dose-dependent manner. Even when NET formation was pharmacologically inhibited by MPO blockade, supplementation with NaOCl alleviated the defect in NET formation.

Table 1. Evidence-Based Comparison of Proximal and Intramural Coronary Segments in Myocardial Bridging

Category	Proximal Segment (Upstream of Myocardial Bridge)	Intramural Segment (Within Myocardial Bridge)	Evidence Level
Anatomical characteristics	Predisposition to plaque formation due to disturbed flow proximal to the bridge	Intramycardial artery compressed during systole	Established
Hemodynamic profile	↓ Endothelial shear stress (ESS); oscillatory WSS; ↑ tensile stress; increased wall motion	Normal/high ESS; high unidirectional WSS; low tensile stress; reduced wall motion	Established
Endothelial function	↓ Nitric oxide bioavailability; ↑ ACE expression; ↑ Endothelin-1; endothelial dysfunction	Relative preservation of endothelial structure despite functional endothelial alterations; eNOS/NO signaling remains controversial	Moderate evidence (conflicting data regarding eNOS/NO signaling)
Adhesion molecules	↑ ICAM-1; ↑ VCAM-1 expression	Reduced ICAM-1 and VCAM-1 expression	Moderate evidence
Inflammatory response	↑ TNF-α; ↑ IL-1; increased inflammatory signaling; ↑ neutrophil-to-lymphocyte ratio (NLR)	Reduced inflammatory activation	Moderate evidence (NLR: limited evidence, single study)
Oxidative stress	↑ Reactive oxygen species (ROS); oxidative stress	Relatively lower oxidative stress compared with the proximal segment	Moderate evidence
Proposed neutrophil-mediated mechanisms	Possible involvement of MPO, PAD4-mediated NETosis and NET formation contributing to oxidative stress and endothelial injury	No direct evidence of neutrophil activation or NETosis in the intramural segment	Hypothesis (no direct evidence in myocardial bridging)
Atherosclerotic phenotype	Frequent plaque formation; positive remodeling; low-attenuation plaques; spotty calcifications; occasional napkin-ring sign	Relative protection from atherosclerosis	Established (napkin-ring sign: limited evidence)
Protective mechanisms	None identified	High unidirectional shear stress; relative atheroprotection; role of eNOS/NO signaling remains controversial	Moderate evidence (presumed)
Functional significance	Reduced FFR/iFR; reduced CFR; inducible ischemia on stress imaging (stress echo, PET, CMR); regional wall motion abnormalities	Preserved coronary flow reserve in most patients	Established
Clinical manifestations	Angina; myocardial ischemia; arrhythmias; acute coronary syndrome	Usually asymptomatic unless severe systolic compression is present	Established

ACE, angiotensin-converting enzyme; CFR, coronary flow reserve; CMR, cardiac magnetic resonance; eNOS, endothelial nitric oxide synthase; ESS, endothelial shear stress; FFR, fractional flow reserve; ICAM-1, intercellular adhesion molecule-1; iFR, instantaneous wave-free ratio; IL-1, interleukin-1; MACE, major adverse cardiovascular events; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; NLR, neutrophil-to-lymphocyte ratio; NO, nitric oxide; PAD4, peptidylarginine deiminase 4; PET, positron emission tomography; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1; WSS, wall shear stress.

In another study, the role of MPO-mediated conversion of hydrogen peroxide (H₂O₂) and chloride ions (Cl⁻) into HOCl was tested on peripheral human neutrophils, where experimental groups either contained or lacked extracellular Cl⁻. NETosis was completely suppressed in the absence of extracellular Cl⁻. The study revealed that depletion of Cl⁻ or inhibition of MPO significantly reduced NETosis in human samples.³³

Microvascular disease and vasospasm, in combination with coronary atherosclerosis of the proximal MB segment, may represent a major contributor to myocardial ischemia in some patients, indicating that the spectrum of stable ischemic heart disease is overly simplified.

Hemodynamics of Myocardial Bridging in the Context of Proinflammatory Endothelial Activation

Myocardial bridging comprises 2 hemodynamic regions with different susceptibilities to atherogenesis. The proximal region of the MB is the segment of the coronary artery located immediately before the artery enters the tunneled portion, i.e., before the onset of muscular compression, while the intramural (tunneled) region represents the segment of the coronary artery that passes within the myocardium, compressed during systolic contraction and relaxed during diastole.

These hemodynamic alterations expose the proximal and intramural endothelial monolayers to distinct biomechanical

environments characterized by different shear stress magnitudes and flow patterns.³⁴ Intravascular ultrasound and autopsy studies consistently demonstrated a pronounced spatial heterogeneity of atherosclerosis across MB, with a preferential localization of atherosclerotic lesions in the proximal segment, while the intramural and distal segments remain relatively spared.³⁵

Multiple cellular and molecular proatherogenic mechanisms have been described under conditions of low WSS, including the development of a proatherogenic endothelial cell phenotype³⁶ and an increase in circulating proatherogenic vasoactive and proinflammatory agents.^{37,38,39}

As this proatherogenic phenotype progresses, endothelial cells within the proximal segment become flattened, polygonal, and structurally dysfunctional in response to persistent flow disturbances.⁴⁰

The mechanism underlying the development of an atherogenic endothelial phenotype in the proximal segment of the myocardial bridge under conditions of low WSS is associated with increased expression of vascular cell adhesion molecule-1 (VCAM-1) and enhanced activity of NADPH oxidase and lipoxygenase, both of which contribute to ROS generation.² These molecular alterations promote the development of an atheroprone endothelial phenotype characterized by impaired antioxidative and anti-inflammatory defense mechanisms together with increased activation of proinflammatory and proatherogenic signaling pathways.

Within such a pro-oxidative environment, MPO, a well-established mediator of vascular inflammation and atherosclerosis, may further aggravate endothelial dysfunction through several complementary mechanisms, including inhibition of eNOS, depletion of NADPH and other cofactors required for NO synthesis, and direct oxidation of NO by MPO-derived reactive species, particularly HOCl. These mechanisms may reduce NO bioavailability and may contribute to the progression of atherosclerotic lesions in the proximal segment of the myocardial bridge. Beyond its effects on oxidative stress, MPO has also been shown to modulate immune responses by influencing macrophage differentiation, promoting the production of proinflammatory cytokines such as tumor necrosis factor alpha, and suppressing interferon- γ expression.⁴¹

It has been proposed that marked angulation of the vessel at the proximal junction, caused by systolic compression within the bridge, may promote endothelial injury and favor atherosclerotic plaque formation.⁴²

It is hypothesized that the pro-oxidative microenvironment generated within the proximal segment of the myocardial bridge may facilitate neutrophil NADPH oxidase activation and oxidative burst-driven ROS production. Based on mechanisms established in NETosis, these processes may facilitate granule membrane and nuclear envelope destabilization, leading to the mixing of cytoplasmic and nuclear components. Consequently, cytoplasmic neutrophil elastase activation, histone cleavage, chromatin decondensation, and ultimately NETosis may occur.

This hypothetical mechanism is biologically plausible because activation of NADPH oxidase represents one of the major intracellular sources of ROS during neutrophil activation.

In activated neutrophils, NADPH oxidase generates superoxide anions and hydrogen peroxide, which are subsequently converted into highly reactive oxidant species, including hydroxyl radicals ($\bullet$ OH) and HOCl.^{3,43}

A significant correlation has been documented between eNOS activity, NO bioavailability, and vascular WSS in humans *in vivo*.³¹

Immunohistochemical analyses have demonstrated segment-specific alterations in the expression of vasoactive molecules, including eNOS, endothelin-1 (ET-1), and angiotensin-converting enzyme (ACE), within MB. Reduced endothelial expression – particularly of eNOS – has been reported in the intramural segment compared with adjacent proximal and distal segments of the LAD.³¹

Based on the data, the reduced endothelial eNOS expression within the intramural segment appears inconsistent with its relative resistance to atherosclerosis. However, reduced eNOS expression does not necessarily indicate diminished NO bioavailability under physiological conditions. Endothelial function is determined not only by the amount of eNOS protein but also by its enzymatic activity, post-translational regulation, phosphorylation status, substrate and cofactor availability, and the local hemodynamic environment. In the intramural segment, exposure to elevated laminar shear stress during diastolic coronary perfusion may promote rapid activation of the existing eNOS pool and transient NO release despite lower overall eNOS expression. Consequently, endothelial function reflects the dynamic balance between eNOS expression and activation rather than protein abundance alone. This distinction may partly explain why the intramural segment remains relatively protected from atherosclerotic plaque formation despite reduced eNOS expression reported in histological studies.³¹

Hemodynamically, the proximal segment of MB is exposed to disturbed flow and reduced WSS, which is widely recognized as the principal driver of atherosclerotic plaque formation immediately proximal to the bridge, whereas plaque deposition within or distal to the tunneled segment remains infrequent.⁴² Autopsy studies of patients with MB have shown structurally dysfunctional, flat, and polygonal endothelial cells in the segments proximal to the MB, whereas the endothelial cells lining the bridged segments remain intact.^{42,44}

Previous investigations indicate that the mechanical stress imposed by systolic compression may enhance platelet activation and vasoreactivity, and in selected cases has been associated with coronary vasospasm or acute coronary syndromes.^{45,46}

The role of vasoactive mediators, particularly eNOS and NO, within the intramural segment of the myocardial bridge, as well as the occurrence of paradoxical vasoconstriction in intact or damaged endothelium without the formation of

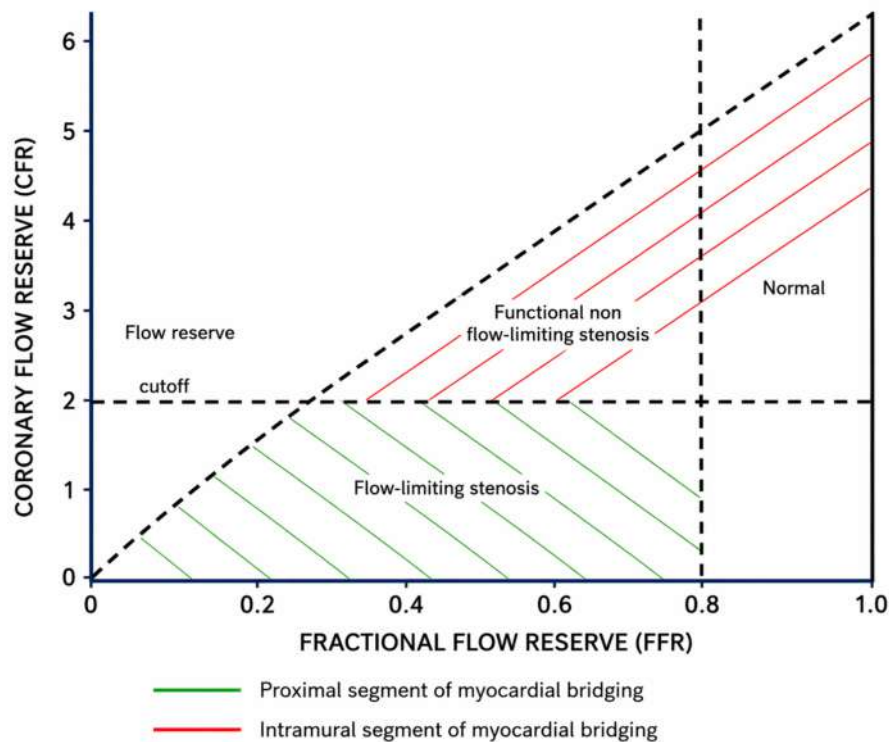


Figure 1. Functional severity of coronary stenosis in the proximal and intramural segments of myocardial bridging.

atherosclerotic lesions, remains controversial. Although this segment is typically considered relatively protected from atherosclerosis, the occurrence of paradoxical vasoconstriction in the absence of structural plaque formation suggests the presence of functional endothelial alterations.

One proposed explanation for this paradox of vasoconstriction and the positive response to acetylcholine in intact endothelium suggests that under conditions of markedly elevated shear stress, harmful increases in oxidative stress may override the protective effects that normally maintain the concentration of vasoactive agents (eNOS, NO) in the intramural segment of the MB.⁴²

However, experimental data remain conflicting. In the study by Shiode et al,⁴⁷ acetylcholine induced a significant reduction in vessel diameter predominantly in the bridged segments of the left anterior descending artery (LAD), whereas N-methyl-L-arginine reduced the diameter of all LAD segments. These findings suggest that segment-specific differences in NO synthase activity are less likely to explain the variations in vasoreactivity.⁴²

These divergent observations underscore the need for a more detailed mechanistic evaluation of endothelial function and redox signaling within the intramural segment of MB. Taken together, the available studies suggest that endothelial dysfunction in MB is more complex than changes in eNOS expression alone. Differences in study design, methods of endothelial assessment, and the dynamic influence of local hemodynamics likely contribute to the apparently conflicting observations reported in the literature.

The direct contribution of these inflammatory mechanisms to MB remains to be experimentally confirmed.

The functional consequences of these distinct hemodynamic environments are summarized in Figure 1, which illustrates the relationship between fractional flow reserve (FFR) and coronary flow reserve (CFR) in the proximal and intramural segments of MB and highlights their differing physiological significance. The proximal and intramural segments occupy different functional regions within the FFR–CFR relationship, emphasizing that anatomical compression alone does not necessarily predict physiological severity. The figure highlights the heterogeneous functional behavior of MB, which provides the hemodynamic basis for the proposed segment-specific oxidative and inflammatory mechanisms discussed below.

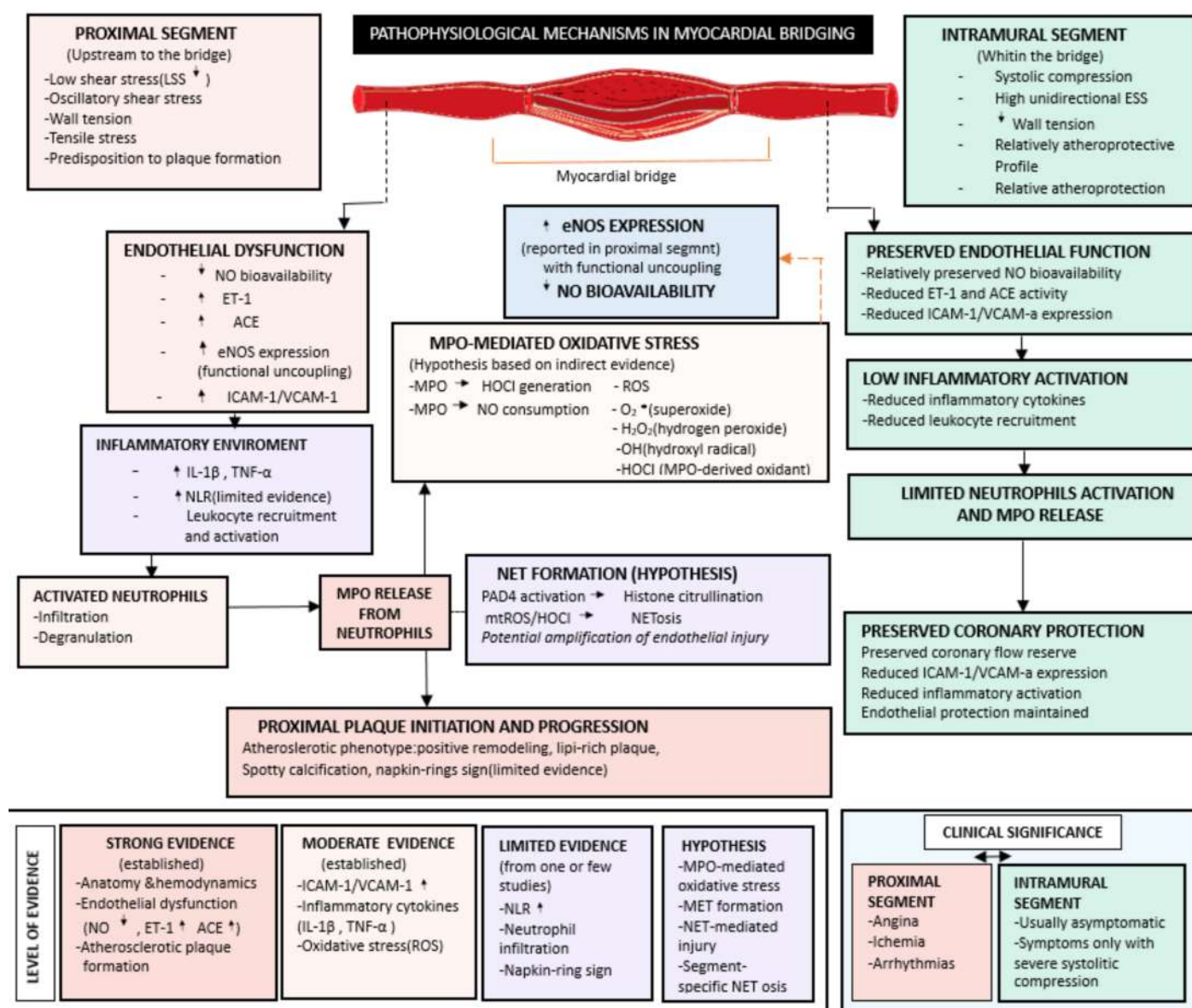
Netosis and the Inflammatory Response in the Proximal Segment of Myocardial Bridging

NETosis represents a key mechanism in the immune response mediated by neutrophils, characterized by 2 primary pathways: suicidal and vital NETosis. Suicidal NETosis is a specific form of cell death characterized by the release of NETs. This process begins when neutrophils encounter infectious agents or inflammatory stimuli such as bacteria, fungi, or chemical signals like PMA.⁴⁸ Activation of these neutrophils leads to the production of ROS via the NADPH oxidase complex, which is crucial for the progression of NETosis. ROS, MPO, and NE migrate from the granules into the nucleus, where they facilitate chromatin decondensation through histone processing.

The production of ROS plays a dual role—it aids in the elimination of pathogens within the NETs but, when excessive, ROS can be detrimental to surrounding tissues, causing inflammation and tissue damage.⁴⁹ Vital NETosis is a rapid, life-preserving process through which neutrophils release NETs to combat pathogens without undergoing cell death, distinguishing it from suicidal NETosis. This form of NET release can occur within minutes of exposure to infectious agents or inflammatory stimuli,⁵⁰ enabling a prompt immune response.

In the context of MB, the pro-oxidative microenvironment within the proximal segment, characterized by disturbed flow, reduced WSS, sustained endothelial activation, and increased ROS generation, may create favorable conditions

for NETosis. Based on mechanisms established in vascular inflammation and atherosclerosis, prolonged oxidative stress and persistent neutrophil activation may create conditions compatible with NOX-dependent NET formation. However, direct evidence supporting this mechanism in MB is currently lacking and requires experimental validation. The mechanism of inflammation and atherogenesis in the proximal segment of the myocardial bridge under the influence of low shear stress involves the expression of ICAM-1, VCAM-1, and E-selectin, as well as increased production of ROS in the endothelium. Adhesion molecules facilitate the attachment and transmigration of monocytes and neutrophils in the proximal segment of the myocardial bridge, creating conditions for local inflammatory activation. Clinical



Abbreviations: ACE-angiotension-converting enzyme; eNOS-endothelial nitric oxide synthase; ET-1-endothelin-1; ICAM-1-intercellular adhesion molecule-1; VCAM-1-vascular cell adhesion molecule-1; MPO-myeloperoxidase; NETs-neutrophil extracellular traps; NO-nitric oxide; NLR-neutrophil-to-lymphocyte ratio; ROS-reactive oxygen species; ESS-endothelial shear stress; PAD4-peptidylarginine deiminase 4; mtROS-mitochondrial ROS; HOCl-hypochlorous acid.

Figure 2. Potential pathophysiological mechanisms in myocardial bridging.

evidence of endothelial dysfunction, altered vasoreactivity, and elevated inflammatory markers supports the presence of localized vascular inflammation in patients with MB.²¹

When MPO is released into circulation, it adsorbs onto negatively charged surfaces such as the endothelium or lipoproteins. The presence of chlorinated apolipoprotein B-100 extracted from human lesion material indicates a direct involvement of the $\text{MPO-H}_2\text{O}_2\text{-Cl}^-$ system with low-density lipoprotein (LDL) as one of the main targets of oxidative modification, emphasizing its potential role in the development of atherosclerosis.⁴

Figure 2 summarizes the proposed mechanistic framework linking altered coronary hemodynamics, oxidative stress, endothelial dysfunction, MPO activation, and NET formation in MB. It integrates experimentally established mechanisms with hypothesized MB-specific pathways and is intended to guide future mechanistic investigations rather than represent an experimentally validated pathway. The strength of evidence supporting the proposed mechanisms varies considerably. Evidence linking altered coronary hemodynamics and proximal atherosclerosis to MB is relatively strong, whereas evidence for MPO- and NET-mediated mechanisms in MB is largely indirect and extrapolated from vascular inflammation and atherosclerosis. Direct evidence of NET formation or MPO-driven NETosis specifically in MB is currently lacking.

CONCLUSION

The interplay between MPO, NETs, eNOS, and NO, as key mediators of endothelial dysfunction, inflammation, and atherosclerosis, may represent a mechanistic link between the pathogenesis of MB and its clinical manifestations. A better understanding of these pathways would contribute to the development of more comprehensive diagnostic and therapeutic strategies for MB, whose underlying biological mechanisms remain incompletely understood.

In contrast, the intramural segment of the bridged coronary artery is exposed to intermittently elevated WSS, creating a specific biomechanical environment that contributes to the paradoxical vasomotor response to acetylcholine. Such a response differs from its conventional prognostic significance in atherosclerosis and suggests the existence of distinct local regulatory mechanisms.

Despite advances in understanding the atherosclerotic and non-atherosclerotic mechanisms contributing to the clinical manifestations of MB, several important questions remain unresolved. These include the diverse roles of ROS, the conditions favoring activation of distinct NETosis pathways, immune responses mediated by infiltrating neutrophils, as well as the complex interactions among MPO, eNOS, and NO. The proposed integration of these pathways highlights previously underrecognized links between coronary biomechanics, innate immunity, and vascular pathology.

Although direct evidence supporting a significant role of MPO and NETs in the pathophysiology of MB remains limited, their well-documented involvement in endothelial

dysfunction, oxidative stress, chronic vascular inflammation, and atherosclerotic plaque development, particularly within the proximal arterial segment, provides a biological rationale for further investigation of these mechanisms in the context of MB.

The proposed framework may also have clinical relevance, although these implications remain to be confirmed. A combination of anatomical and functional assessment, including measures of coronary flow and vasoreactivity, may help identify patients in whom MB is clinically significant. Future studies should determine whether markers of neutrophil activation, MPO activity, or NET formation could add useful information for risk stratification.

Patients with MB are clinically heterogeneous, ranging from largely asymptomatic individuals to those with endothelial dysfunction, vasospasm, proximal atherosclerosis, or recurrent ischemic symptoms. Better characterization of the underlying biological phenotype may therefore improve prognostic assessment and help guide management.

At present, treatment remains focused on reducing ischemia and hemodynamic stress, with invasive approaches reserved for selected symptomatic patients. Whether inflammatory or oxidative pathways could become therapeutic targets in specific subgroups remains an open question and will require direct clinical validation.

Overall, the available evidence strongly supports the contribution of altered coronary hemodynamics to endothelial dysfunction in MB, whereas the proposed involvement of MPO- and NET-mediated mechanisms remains hypothesis-generating and should stimulate future mechanistic investigations.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Public Institution Health Center of Sarajevo Canton (Approval No: 01-06-33-2-1844-2/23, Date: 08 June 2023).

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Right-Sided Infective Endocarditis: A 6-Year Retrospective Cohort Study from a Tertiary Care Center in Türkiye

ABSTRACT

Background: With evolving risk factors, the frequency of right-sided infective endocarditis (RSIE) is increasing. Despite its distinct clinical features, data on RSIE remain limited, and no dedicated cohort has been reported from Türkiye. This study aimed to describe the epidemiological and clinical characteristics of RSIE and identify factors associated with mortality in a tertiary-care center.

Methods: This retrospective cohort study evaluated 65 adult patients diagnosed with definite RSIE between January 2018 and January 2024. Demographic data, risk factors, echocardiographic findings, causative microorganisms, and outcomes were analyzed. Statistical comparisons were performed between intravenous drug use (IVDU) and non-IVDU groups.

Results: The cohort was predominantly male (76.9%) with a median age of 36 years. Intravenous drug use was the primary risk factor (55.4%), followed by central venous catheters (24.6%) and hemodialysis (23.1%). Staphylococcus aureus was the leading causative agent (79%). Septic pulmonary embolism was detected in 81.6% of patients. The overall in-hospital mortality rate was 26.2%. Mortality was significantly lower in IVDU patients than in non-IVDU patients (17.4% vs. 44%; $P = .036$); however, multiple regression analysis identified hemodialysis as an independent predictor of mortality (OR = 6.72, 95% CI: 1.27–35.42; $P = .025$). Multiple Cox regression analysis further demonstrated that hemoglobin level and age were independent predictors of mortality.

Conclusion: Although IVDU patients demonstrated higher survival rates—likely attributable to a younger age profile and fewer comorbidities—RSIE remains a critical condition requiring high clinical suspicion and early intervention. RSIE in this region is strongly associated with IVDU and typically presents with respiratory symptoms due to septic pulmonary emboli.

Keywords: Hemodialysis, intravenous drug use, right-sided endocarditis

INTRODUCTION

Infective endocarditis (IE) is a rare but highly fatal infectious disease. An increase in the global incidence of IE has been reported over the past 3 decades.^{1,2} The aging global population, the proliferation of invasive procedures (e.g., hemodialysis, cardiac implantable electronic devices), and rising intravenous drug use (IVDU) have increased the population at risk. Concurrently, the profile of patients at risk has shifted significantly.

Infective endocarditis typically affects the left-sided heart valves, with right-sided infective endocarditis (RSIE) accounting for 5%–10% of all IE cases.³ However, paralleling the shift in the at-risk patient profile, an increase in the prevalence of RSIE has been reported.^{3,4,5} The RSIE possesses a distinct epidemiology, clinical characteristics, and set of treatment approaches. While comprehensive data exist regarding left-sided IE, published literature concerning the characteristics and management of right-sided IE remains limited. Based on the current information, there are no cohort studies from Türkiye specifically focusing on RSIE.



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ORIGINAL INVESTIGATION

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The aim of this study was to investigate the epidemiological, clinical, and microbiological characteristics of RSIE, identify risk factors, and explore factors potentially associated with mortality in patients diagnosed with definite IE at a tertiary care center.

METHODS

This retrospective descriptive study was conducted between January 2018 and January 2024 at a 1500-bed tertiary training and research hospital in Türkiye, which serves as a regional referral center for cardiology and cardiovascular surgery.

During the study period, patients diagnosed with IE according to ICD-10 codes were identified from the electronic medical record system, and their records were reviewed. Among patients diagnosed with "definite" IE according to the Modified Duke criteria, all consecutive patients with RSIE were included in the study.⁶ Patients with concomitant left-sided involvement were not excluded. The study included adult patients aged 18 years and older. For cases presenting with multiple episodes, only the initial episode of IE was evaluated. Outcomes were limited to the index hospitalization, and the primary endpoint was in-hospital mortality during the index admission.

Data were recorded using a standardized data collection form. Demographic characteristics, clinical and laboratory findings, comorbidities, predisposing conditions, echocardiographic and radiological findings, blood culture results and causative microorganisms, surgical treatment interventions, and prognostic data were analyzed.

Right-sided endocarditis was defined as the presence of vegetation on the tricuspid valve, pulmonary valve, right atrial wall, or an intracardiac device lead. Echocardiographic analyses were performed using data from transthoracic and/or transesophageal echocardiography reports provided by a cardiologist. Vegetation size was recorded in millimeters based on the maximal long-axis measurement.

Hemodialysis was defined as participation in a regular hemodialysis program due to chronic kidney disease. Intravenous drug use was defined as the presence of a documented

history of intravenous substance use either at the time of admission or in previous medical records.

Ethics Committee Approval: This study was approved by Ethics Committee of the regional hospital (Approval No:2897, Date October 26, 2023).

Statistical Analysis

Data obtained in this study were analyzed using SPSS 27 statistical software. For descriptive statistics, categorical variables were expressed as numbers (n) and percentages (%), while non-normally distributed continuous variables were expressed as median (minimum-maximum) values. As the assessment of continuous variables using the Shapiro–Wilk test indicated that none followed a normal distribution, the Mann–Whitney *U*-test was used for comparisons between 2 groups. The Pearson chi-square test was used to evaluate the relationships between categorical variables; however, Fisher's exact test was used in 2x2 tables when the expected count was less than 5. Multiple logistic regression analysis was performed to identify independent risk factors for in-hospital mortality and multiple Cox proportional hazards regression analysis was used to evaluate survival outcomes. Variables with clinical relevance were entered into the model simultaneously. Odds ratios (ORs) and hazard ratios (HRs) with 95% CI were calculated, and $P < .05$ was considered statistically significant.

RESULTS

A total of 65 patients diagnosed with RSIE were included in the study (Figure 1). Of the patients, 23.1% (n=15) were female and 76.9% (n=50) were male. The median age of the total patient population was 36 (18-85) years. Patients in the IVUD group were significantly younger than those in the non-IVUD group (median 34 vs. 54 years; $P < .001$). The comparison of demographic characteristics, clinical presentation, microbiology, treatment and outcomes between IVUD and non-IVUD patients is presented in Table 1.

When risk factors for IE at presentation were evaluated, IVUD was present in 55.4% (n=36) of the patients, diabetes mellitus in 13.8% (n=9), cardiac pacemakers in 15.4% (n=10), and heart failure in 15.4% (n=10). Central venous catheters were present in 29.2% (n=19) of the patients; of these, 15 patients were receiving hemodialysis, while in 4 patients the catheter was used for vascular access.

Regarding presenting symptoms, fever was observed in 60% (39/65), dyspnea in 33.8% (22/65), cough in 29.2% (19/65), chest pain in 30.8% (20/65), and fatigue in 21.5% (14/65) of the patients. Additionally, 2 patients presented with pacemaker pocket infection.

At the time of presentation, 10.8% (7/65) of the patients had sepsis, and 9.3% (6/65) presented with acute cerebrovascular disease. Furthermore, pneumothorax was present in 2 patients. The baseline characteristics and laboratory findings of the patients with IE are presented in Table 2 and Table 3.

Examination of echocardiographic findings revealed vegetations located on the tricuspid valve in 78.5% (n=51), solely

HIGHLIGHTS

- This study presents the first cohort from Türkiye exclusively examining right-sided infective endocarditis.
- Intravenous drug use (IVDU) was the leading risk factor and right-sided infective endocarditis predominantly affected younger patients.
- Septic pulmonary embolism was highly prevalent, reflecting the characteristic pulmonary-dominant presentation.
- Mortality was significantly lower in patients with IVDU compared to non-IVDU, whereas hemodialysis patients exhibited markedly higher mortality; vegetation size showed no significant association with mortality.

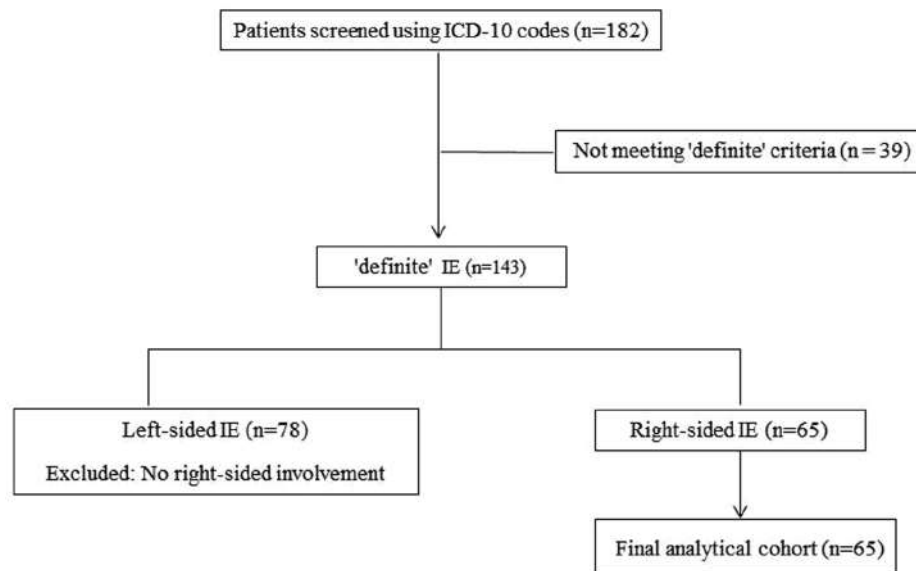


Figure 1. Flowchart of the study.

in the right atrium in 7.7% (n=5), on an intracardiac lead in 6.2% (n=4), and in the right atrium combined with an intracardiac lead in 1 patient. Additionally, aortic valve involvement accompanying the tricuspid valve was observed in 2 patients, and vegetation on the mitral valve accompanying the tricuspid valve was observed in another 2 patients. The median vegetation size was 16 mm (2-44 mm). Vegetation size was found to be ≥ 20 mm in 43.1% (n=28) of the patients.

Analysis of blood culture results revealed no growth in 20% (13/65) of the patients. Among those with positive blood cultures, *Staphylococcus aureus* was the causative agent in 79%

(41/52), coagulase-negative staphylococci in 5.8% (3/52), and *Candida* sp. in 5.8% (3/52). The distribution of causative microorganisms isolated from blood cultures is shown in Table 4.

Septic pulmonary embolism was detected in 49 (81.6%) of the 60 patients who underwent thoracic computed tomography.

Table 1. Baseline Characteristics and Outcomes of Right-Sided IE Patients According to IVDU

Characteristics	IVDU (n=36)	Non-IVDU (n=29)	P
Age (Years)	34 (18-50)	54 (19-85)	<.001
Gender (Male, n)	36	14	<.001
Concomitant left-sided EE (n)	1	3	.316
Clinical presentation			
Cough (n)	18	1	<.001
Sepsis (n)	4	3	.622
Chest pain (n)	16	4	.007
Fever (n)	25	14	.070
Microbiology			
MSSA	14	6	.094
MRSA	13	8	.323
Non- <i>S.aureus</i>	0	11	<.001
Surgery	19	11	.173
Inhospital mortality	4	13	.010

IE, infective endocarditis; IVDU, intravenous drug use; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*. $P < .05$ was considered statistically significant

Table 2. Baseline Characteristics of Patients with IE

Characteristics	Patient (%)
Symptoms	
Fever	39 (60.0)
Dyspnea	22 (33.8)
Cough	19 (29.2)
Chest pain	20 (30.8)
Fatigue	14 (21.5)
Clinical presentation	
Pneumothorax	2 (3.0)
Sepsis	7 (10.8)
Pacemaker pocket infection	2 (3.0)
Stroke	6 (9.3)
Predisposing factors	
Hemodialysis	15 (23.1)
IVDU	36 (55.4)
Diabetes mellitus	9 (13.8)
Cardiac pacemaker	10 (15.4)
Central venous catheter	4 (2.8)
Heart failure	10 (15.4)
Echocardiographic findings	
Tricuspid valve involvement	51 (78.5)
Lead involvement	4 (6.2)
Right atrial involvement	5 (7.7)
Tricuspid and left-sided valve involvement	4 (6.2)

IE, infective endocarditis; IVDU, intravenous drug use.

Table 3. Baseline Laboratory Findings of Patients with IE

Laboratory Findings	Mean $\pm$ SD
C-reactive protein (mg/L)	159 $\pm$ 102
Leukocyte ($10^3/\mu\text{L}$)	14.7 $\pm$ 8.9
Hemoglobin (g/dL)	10.0 $\pm$ 8.6
Plateletes ($10^3/\mu\text{L}$)	191.6 $\pm$ 127.9

IE, infective endocarditis.

Findings consistent with septic embolism were detected in 9 (23.7%) of the 38 patients who underwent cranial imaging. Of these patients, 4 had concomitant left-sided endocarditis. One patient had a concomitant small atrial septal defect and a bicuspid aortic valve; however, there was no evidence of aortic valve involvement. Medical therapy alone (antibiotics) was administered to 53.8% (n = 35) of the patients, while 46.1% (n = 30) received both antibiotic and surgical therapy. The patients received antibiotic therapy for a mean duration of 38.6 ± 21.4 days. Of the 30 patients who underwent surgery, it was determined that 12 underwent tricuspid valve replacement and 17 underwent valve repair combined with vegetation resection. Lead extraction was performed in all 7 patients with cardiac devices and lead infections; in one of these patients, the device was removed surgically.

Regarding prognosis, 63% (41/65) of the patients were discharged with recovery. The overall in-hospital mortality

Table 4. Blood Culture Results of Patients with IE

Microorganism	n (%)
<i>Staphylococcus aureus</i>	
Methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA)	20 (38)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	21 (40)
Coagulase-negative staphylococci	3 (5.8)
<i>Enterococcus faecalis</i>	1 (1.9)
<i>Brucella</i> spp.	1 (1.9)
<i>Candida</i> spp.	3 (5.8)
<i>Enterobacter</i> sp.	1 (1.9)
<i>Corynebacterium striatum</i>	1 (1.9)

IE, infective endocarditis; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

rate was 26.2% (17/65), while the 30-day mortality rate was 17.2% and the 90-day mortality rate was 29.3%. The mortality rate among surgically treated patients was 33.3% (10/30). Additionally, 7 patients using intravenous drugs left the hospital against medical advice before completing their treatment.

The mortality rate of patients with IVDU was found to be significantly lower compared to non-IVDU patients (17.4% vs. 44%, $P = .036$). The mortality rate in hemodialysis patients was found to be higher compared to other patients (24.3% vs. 53.3%, $P = .046$). No significant relationship was found

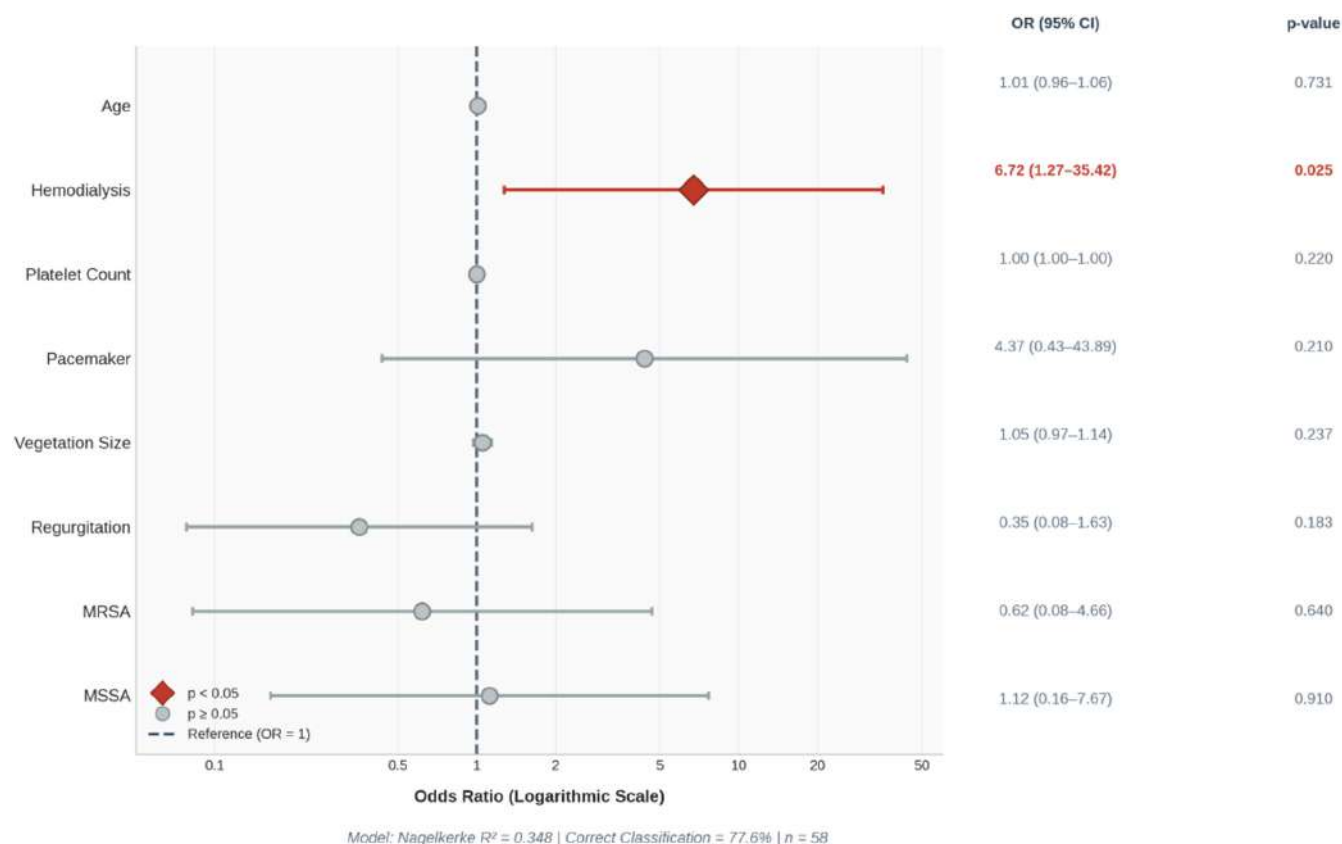


Figure 2. Factors affecting in-hospital mortality in patients with RSIE: a multiple regression analysis. RISE, right-sided infective endocarditis.

Table 5. Multiple Cox Regression Analysis

Variables	Adjusted HR (95% CI)	P
30-day mortality		
Hemoglobin	1.395 (1.050-1.848)	.037
90-day mortality		
Age	1.035 (1.002-1.056)	.023

HR, hazard ratio.

between mortality and heart failure, diabetes mellitus, presence of a cardiac device, age, or vegetation size.

In the multiple logistic regression analysis, among the variables entered into the model, only hemodialysis was found to be statistically significant (OR = 6.72, $P = .025$, 95% CI: 1.27-35.42). Patients receiving hemodialysis had an approximately sevenfold higher risk of in-hospital mortality compared with those not on hemodialysis (Figure 2).

Multiple Cox proportional hazards regression analysis demonstrated that hemoglobin level independently predicted 30-day mortality, with each 1-unit decrease associated with a 1.395-fold increase in hazard (HR=1.395, $P = .037$, 95% CI: 1.050-1.848). Age was an independent predictor of 90-day mortality, with each 1-year increase associated with increased hazard (HR=1.035, $P = .023$, 95% CI: 1.002-1.056) (Table 5).

DISCUSSION

It has been reported that the incidence of RSIE has increased as a result of the shift in the profile of patients at risk for IE.^{3,4} Based on the current information, this is the first cohort study from Türkiye specifically focusing on RSIE. This study evaluated the epidemiological and clinical characteristics, risk factors, and factors potentially associated with mortality in patients diagnosed with right-sided endocarditis.

The study findings demonstrate that RSIE is more frequently observed in the young age group and in individuals with IVDU. This observation is consistent with studies reporting that 60-90% of RSIE cases occur in individuals with IVDU.^{4,7,8} The incidence of IE is significantly higher in individuals with IVDU compared to the general population. It is stated that the proportion of IVDU among all IE cases is gradually rising and contributes to the increasing incidence of endocarditis, particularly in developed countries.⁹

The rate of IVDU-associated IE was reported as 6.9% in the ESC-EORP EURO-ENDO registry study, and between 4.4% and 10.1% in multicenter studies involving large patient series conducted in Türkiye.^{10,11,12} Compared to prior regional studies, the IVDU-associated IE rate observed in this cohort is remarkably high. The relatively high prevalence of intravenous substance use in this region may explain this elevated rate.^{13,14,15} The tricuspid valve is the most frequently affected site in IVDU-associated IE. The proposed mechanism involves mechanical valve damage caused by particulate matter in injected substances and a high bacterial load directly entering the venous circulation during non-aseptic injection.¹⁶ Notably, in the cohort, 2 IVDU patients presented

with concomitant right- and left-sided involvement, indicating that multivalvular infection can also occur in this population.¹⁷

In the current analysis, central venous catheter use and hemodialysis were identified as the second most common risk factors, while the presence of intracardiac devices was the third. The risk of developing IE is high in hemodialysis patients due to bacteremia episodes resulting from recurrent vascular interventions and the development of calcific valve disease.^{18,19,20} Although the mitral and aortic valves are most frequently affected in these patients, right-sided endocarditis may also be observed.²¹

Among the cases reviewed, 5 of the 6 patients with right atrial wall involvement had venous catheters for hemodialysis, and one had a cardiac implantable device. Right atrial wall involvement is an atypical localization for IE. Non-valvular IE is rare in the literature and is usually reported as case reports.^{22,23} Right atrial involvement is thought to be a result of mechanical damage caused by catheters and intracardiac devices on the right atrial wall.^{3,23} This damaged endocardium predisposes to the development of endocarditis on the atrial wall and the valve, particularly in hemodialysis patients with bacteremia.

Regarding clinical presentation, fever accompanied by respiratory symptoms such as chest pain, dyspnea, and cough was the most common presenting complaint. Two patients presented with pneumothorax. Infiltrations consistent with septic pulmonary emboli were detected in 82% of patients who underwent pulmonary imaging. This finding reflects the characteristic feature of right-sided IE. In RSIE, many typical clinical signs seen in left-sided endocarditis are generally absent. Pathologic murmurs and signs of peripheral embolization are usually not present at admission. Conversely, septic pulmonary embolism develops in approximately 75%-84% of tricuspid valve endocarditis cases.^{24,25} The predominance of a pneumonia-like clinical picture at presentation can lead to missed or delayed diagnosis of IE. Therefore, it is stated that a high clinical suspicion for right-sided IE should be maintained in patients with risk factors for IE who present with persistent fever, respiratory symptoms such as cough, chest pain, or hemoptysis, and the presence of multiple pulmonary infiltrations on lung imaging.^{25,26,27}

As a reflection of the change in risk factors, *Staphylococcus aureus* is currently reported to be the most common causative agent in both right- and left-sided IE.^{3,10,11,12} Consistent with the literature, *Staphylococcus aureus* was the most frequently isolated agent in this series. However, in addition to the predominance of *S. aureus*, a cardiac device-associated case due to *Brucella melitensis* was also identified, consistent with rare reports of *Brucella*-related device endocarditis.²⁸

Compared to left-sided IE, RSIE is generally associated with a better prognosis and lower mortality rates. Antibiotic therapy is successful in most patients.^{3,25,27} Current data revealed that the mortality rate was significantly lower in patients

with IVDU compared to other patients, whereas the mortality rate was found to be higher in hemodialysis patients. In a large cohort of hemodialysis patients with IE, the in-hospital mortality rate was reported to be 43%.²⁹ A study conducted on a non-IVDU IE patient group reported that in-hospital mortality in RSIE was not different from that of left-sided IE.²¹ In these patients, comorbidities such as concomitant heart failure and renal failure, as well as advanced age, negatively affect the prognosis. In this study, hemodialysis was associated with a sevenfold increase in mortality risk, highlighting the substantial vulnerability of this patient population.

In this study, lower hemoglobin levels independently predicted 30-day mortality. Previous studies have also demonstrated that anemia is associated with worse clinical outcomes in patients with IE.^{30,31} Anemia is very common among patients with IE and its development is likely multifactorial. Chronic systemic inflammation, hemolysis, underlying renal dysfunction, and pre-existing iron deficiency have been suggested as potential contributors to anemia in this patient population.³² Anemia may also reflect the overall severity of infection, which could partly explain its association with increased mortality in patients with IE.

Moreover, age was identified as an independent predictor of 90-day mortality. Advanced age is a well-established prognostic factor in IE and has consistently been linked to increased mortality in IE.^{10,11} This association is likely related to a higher comorbidity burden and reduced tolerance to septic complications in elderly patients.

Many studies in the literature also report a better prognosis in the IVDU group.^{78,33} This is thought to be primarily related to the predominance of right heart involvement in this group, the younger age of the patients, and the generally lower prevalence of accompanying comorbidities. However, treatment adherence is a major challenge in this demographic. In this cohort, 7 IVDU patients left against medical advice prior to treatment completion. Returning to substance use in this patient group can lead to recurrent endocarditis episodes and, unfortunately, negatively affects long-term outcomes.^{33,34}

There are studies in the literature reporting both the presence and absence of a significant relationship between vegetation size and mortality.^{35,36} No significant relationship was observed between vegetation size and mortality in the present dataset.

Limitations

Since the study had a retrospective design, there is a potential risk of information bias inherent to record-based data. The inclusion of only "definite" cases according to the Modified Duke criteria, while excluding "possible" cases, may have introduced selection bias. Another important limitation of this study is that in 4 patients who had acute cerebrovascular events on cranial imaging and did not have concomitant left-sided IE, a dedicated evaluation for the presence of a patent foramen ovale was not performed. Therefore, a paradoxical embolic mechanism cannot be definitively excluded in these patients. The presence of concomitant left-sided endocarditis in a small subset of patients with neurological

embolic events may have influenced mortality outcomes. However, due to the limited number of such cases, subgroup analysis was not feasible and this should be considered when interpreting the results. Furthermore, long-term mortality, recurrent IE episodes, and late complications could not be evaluated. The exclusion of patients who discontinued treatment and left the hospital against medical advice from the in-hospital mortality analysis may have led to an underestimation of mortality rates.

Although hemodialysis remained the only significant predictor of in-hospital mortality in the multiple logistic regression analysis, and hemoglobin level (for 30-day mortality) and age (for 90-day mortality) were identified as significant predictors in the multiple Cox proportional hazards regression analyses, these findings should be interpreted with caution. The limited number of mortality events may have reduced the statistical power of the models and limited the generalizability of the estimates.

In addition, as right-sided endocarditis is relatively rare, the sample size was limited, which reduced statistical power in certain subgroup analyses. The results of this study may be more generalizable to patient populations presenting to tertiary referral centers in the region, where IVDU is relatively common, and may not fully reflect the demographics of the entire country.

CONCLUSION

Right-sided IE typically presents with persistent fever and respiratory symptoms, whereas signs of systemic embolization observed in left-sided endocarditis are generally absent. Therefore, a high index of suspicion is crucial for early diagnosis. Intravenous drug use is the primary predisposing factor for RSIE.

Data regarding RSIE in the literature are limited. In this study, the clinical characteristics, complications, surgical requirements, and prognostic data of RSIE cases in the region have been presented in detail for the first time. As the first detailed cohort of RSIE from Türkiye, this study fills a significant gap in the regional literature and highlights the urgent need for targeted addiction support alongside infectious disease management.

Ethics Committee Approval: This study was approved by Ethics Committee of Adana City Training and Research Hospital (Approval No:2897, Date October 26, 2023).

Informed Consent: Informed consent was not obtained because of retrospective nature of the study.

Peer-review: Externally peer-reviewed.

AI-Assisted Technologies Statement: AI-assisted language tools (ChatGPT, OpenAI) were used to improve the grammar, clarity, and readability of the manuscript. No content, data analysis, or scientific conclusions were generated by AI. The authors are fully responsible for the accuracy and integrity of the work.

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Integrative Identification of Frailty Status in Elderly Patients with Atrial Fibrillation Using a Noise-Resilient Multimodal Machine Learning Approach

ABSTRACT

Background: Frailty is common yet underdiagnosed in elderly patients with atrial fibrillation (AF), worsening outcomes and complicating treatment. Traditional assessments are time-consuming and subjective, while physiological monitoring offers potential for automated detection. Combining machine learning (ML) with multimodal data, especially electrocardiogram (ECG) and clinical features, may improve frailty identification, even in noisy real-world conditions. To develop a noise-resilient ML framework for identifying frailty status in elderly patients with AF using multimodal clinical and ECG data and to compare traditional and deep learning models under varying signal conditions.

Methods: This retrospective study included 110 patients aged ≥ 65 with documented AF. Frailty was assessed via a composite of the Fried Phenotype and Clinical Frailty Scale. Electrocardiogram data (resting 12-lead and Holter) were processed through a denoising and segmentation pipeline. Over 180 ECG features and clinical parameters were used as inputs. Five models (Random Forest, Extreme Gradient Boosting, 1-dimensional convolutional neural network, bidirectional long short-term memory-attention, SiamAF) were trained and evaluated using an 80:20 split. Performance metrics included accuracy, F1-score, receiver operating characteristic-area under the curve (ROC-AUC), and Brier score; robustness was tested with synthetic noise.

Results: Frailty and pre-frailty prevalence were 41.82% and 34.55%. The SiamAF achieved the best performance (accuracy 90.00%, F1-score 89.75%, ROC-AUC 93.00%, Brier score 0.084), maintaining robustness under noise. Deep learning models also showed strong performance (ROC-AUC > 90%). Key predictors included standard deviation of normal-to-normal (NN) intervals, corrected QT interval, N-terminal pro-brain natriuretic peptide, and grip strength.

Conclusion: Multimodal ML effectively identifies frailty status in elderly patients with AF. The SiamAF model demonstrated strong discriminatory performance and noise robustness in this single-center cohort; however, these findings should be considered hypothesis-generating and require external validation in larger, multicenter AF populations before clinical adoption. Given the limited sample size relative to the high-dimensional feature space, these results should be interpreted as exploratory and hypothesis-generating. The present framework primarily leverages predefined ECG-derived features rather than fully end-to-end raw-signal learning.

Keywords: Atrial fibrillation, ECG, frailty, machine learning, noise-resilient models

INTRODUCTION

The main sustained cardiac arrhythmia of atrial fibrillation (AF) is currently a major public health problem, especially among older populations. It has been reported that the epidemiological data show that the prevalence of AF is more than 10% in persons above the age of 80 years, and the prevalence has been increasing along with the increase in life expectancy. The condition is not linked to increased risks of stroke and systemic embolism only, as they are accompanied by an increased susceptibility to functional impairment, falls, and dependence; in particular, they become more serious in terms of functional impairment when combined with frailty. The syndrome of frailty, with its physiologic deficit being

ORIGINAL INVESTIGATION

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cumulative and stress tolerance minimal, contributes significantly to both morbidity and mortality related to AF. The interaction of these 2 leads to a vicious cycle in which AF increases frailty via compromised hemodynamics, neurohormonal imbalance, and polypharmacy, whereas frailty predisposes to poor outcomes of procedures and arrhythmia complications. Although there is increased awareness of this complicated interaction, it is poorly represented in the majority of clinical predictive algorithms, which are very specific toward cardiovascular risk without considering the limitations of physiological reserve or functional capacity. Thus, constructing integrative assessment models, including multimodal data, primarily, electrocardiogram (ECG)-based signals, vital trends, and other clinical indicators, is essential. This strategy presents an opportunity for timely and individualized intervention that encourages long-term outcomes and quality of life in aging patients with AF.¹⁻³

Frailty itself is a multidimensional syndrome characterized by reduced physiologic reserve, which includes tissue deficit in strength, mobility, cognitive function, nutrition, and homeostasis. It has conventionally been assessed on the basis of phenotype models such as the Fried criteria or index models such as the Rockwood frailty index.⁴⁻⁶ Although these tools are well validated, they rely heavily on in-person physical evaluations, grip strength, and detailed questionnaires; thus, they may not act as practical tools for frequent use in most clinical environments. Additionally, these tools not sensitive enough to detect the minor physiological alterations in the early phases; therefore, opportunities for proactive intervention may be missed. In this regard, the emergence of machine learning (ML) techniques, in a specific deep learning

architecture able to adapt to complex time-based data, has opened the possibility of automating fractional detection with passive physiological monitoring. The adaptation of the ECG-based parameters, such as heart rate variability (HRV), P-wave morphology, QT dynamics, and signal entropy, which reflect autonomic tone and cardiovascular resilience, is among the most promising approaches. These biomarkers tend to show premature variations in frail people even prior to the obvious functional decline. Machine learning models can construct a high-dimensional representation of frailty risk when combined with structured clinical parameters such as age, comorbidity burden, medication use, and functional scores. Longitudinal studies have demonstrated that this integrated approach significantly improves the predictive performance of frailty models over conventional tools, allowing earlier identification and stratification of at-risk elderly populations.⁷⁻¹⁰

Nevertheless, one of the critical technical challenges is still present in spite of these achievements: the ECG records are subjected to noise, which most ML algorithms do not tolerate well, at least not when applied in real-world (or ambulatory or wearable) conditions. In addition, motion, signal dropout, lead displacements, electromyographic interference, and baseline drift are common causes of artifacts in outpatient and home ECG recordings, unlike the well-controlled clinical setting. Such distortions have the capability to puzzle feature extraction and augment the performance of even the most advanced ML models. This is of particular concern in geriatrics in which tremor (frailty associated), postural instability, and arrhythmic symptoms may additionally increase the variability of the signal. To cope with this, most modern research has introduced robust algorithmic methods that seek to filter and correct the noisy data before they are ingested by the model.¹¹⁻¹³ These can be the adaptive filtering techniques to dynamically adapt to nonstationary noise and wavelet-based denoising that have the ability to leave the morphology of the signal intact, and the attention masking methods that ignore segments that are less confident during training.¹⁴⁻¹⁶ New model architectures have been formulated in parallel with specific goals of increasing robustness to noisy conditions. Interestingly, ECGNET employs attention-weighted filtering based to reject any irrelevant noise, ArNet-ECG employs the residual learning of the hierarchical architectures to preserve the relevant features, and SiamAF employs contrastive learning, the parallel inputs of the ECG and photoplethysmography (PPG) to impose noise-invariant representations.^{15,16,17} Individually as well as mutually, these strategies are essential steps on the path toward the development of frailty-AF risk predictors applicable in practical situations and capable of acting consistently in various clinical and community contexts.

The realization of hemodynamic interaction and vulnerability within the systems is another major aspect in the integration of frailty and AF. The unrelated behavior of the ventricular response in AF creates inconsistencies in stroke volume, which causes subsequent poor perfusion in the vital organs, such as the brain, muscles, and kidneys.¹⁸⁻²¹ This adds to tiredness, sarcopenia, orthostatic intolerance, and

HIGHLIGHTS

- Frailty and pre-frailty were highly prevalent (76.36%) among elderly patients with atrial fibrillation (AF) using a composite of Fried Phenotype and Clinical Frailty Scale.
- A multimodal machine learning framework integrating >180 electrocardiogram (ECG)-derived features with clinical, laboratory, echocardiographic, and functional data was developed for frailty risk prediction.
- The SiamAF dual-stream ECG + photoplethysmography model achieved the best performance (accuracy 90.00%, receiver operating characteristic-area under the curve 93.00%, Brier score 0.084) and maintained superior robustness under increasing synthetic noise levels.
- Key predictors of frailty included heart rate variability indices (e.g., standard deviation of normal-to-normal intervals), corrected QT interval duration, N-terminal pro-brain natriuretic peptide, serum albumin, and grip strength, linking autonomic dysfunction, cardiac strain, and physical frailty.
- The proposed noise-resilient models support scalable, wearable, and remote frailty screening in real-world AF populations and warrant validation in larger multicenter cohorts.

mental misfunctioning, characteristics of the frailty phenotype. At the same time, baroreflex problems that are associated with frailty also increase the vulnerability of aged people to the symptomatic and hemodynamic impacts of AF.²² As an example, weak people can have an unusual course of symptoms including delirium or falls instead of palpitations, which delay the diagnosis and treatment. Further, they have an increased risk of procedural complications, bleeding caused by anticoagulating drugs, and nonadherence to therapeutic recommendations caused by polypharmacy or changes in cognition.²³⁻²⁵ This abidirectional relationship in terms of pathophysiology calls into the need for the creation of predictive models, which would not be limited by 1 single domain input. Good models need to combine the hemodynamic parameters, signs of frailty, patterns of comorbidities with real-time biosignals to reflect the dynamic interaction between vagaries of cardiac rhythm and loss of systemic functionality. To this end, multidomain data containing ECGs, echocardiograms, blood biomarkers, history of medication, and patient-reported functions are indispensable. Also, the use of the expertise of geriatrics, cardiology, neurology, and biomedical engineering leads to the interdisciplinary design of models that are more realistic of the true complex nature of physiology in the aging man.²⁶⁻²⁸ With the help of such integrative models, adverse outcomes can not only be predicted more reliably but also entail the development of more individualized methods of management (because they depend on the peculiarities of needs and restrictions of frail and elderly patients with AF).

The further development of remote sensing, eHealth devices, and mobile ECG recorders has further democratized the collection of data, realizing in real time the possibility to screen frailty outside the clinical environment. Continuous monitoring studies have been able to find fine variations in the dynamics of the heart rate and abnormalities in the heart rhythm that herald the occurrence of frailty transitions.²⁹⁻³⁰ The combination of ECG and the assessment of blood pressure variability, sleep, and activity allows a more comprehensive physiological picture to be created, making it possible to actively plan care in high-risk elderly patients.³¹⁻³⁴ Noteworthy, an example of AF detection and risk stratification tools based on ML is PhysioNet-derived or commercial wearable datasets, which are being translated to use in concurrent populations of frailty risk profiling.³⁵ When trained using heterogeneous data sets that include elderly people living in community settings, these models hold potential to classify who is resilient versus pre-frail versus frail with respect to their trajectories, thus intervening in a timely fashion. In this context, ECG-derived features are explored as complementary physiological markers that may enhance scalability and automation of frailty screening, rather than replacing established clinical, laboratory, or echocardiographic assessments.

Despite increasing recognition of the bidirectional relationship between AF and frailty, frailty assessment remains inconsistently integrated into routine AF management, largely due to time constraints and reliance on in-person evaluations. Automated, physiology-based frailty detection

using multimodal ECG and clinical data may offer a scalable alternative, particularly in elderly patients frequently monitored for arrhythmia care. However, real-world ECG recordings in AF are inherently noisy, irregular, and heterogeneous, posing challenges for conventional ML approaches. The present study therefore aims to develop and evaluate a noise-resilient multimodal ML framework for frailty prediction in elderly AF patients. This work is intended as a hypothesis-generating investigation, assessing feasibility, robustness, and clinical interpretability rather than definitive clinical deployment.

METHODS

Study Design

This was a retrospective, observational, ML-based diagnostic modeling study conducted over a period of 18 months at a tertiary care academic medical center. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants or their legally authorized representatives prior to enrollment. The research adhered to the principles outlined in the Declaration of Helsinki. A total of 110 elderly patients aged ≥ 65 years with a documented diagnosis of AF were consecutively enrolled from the outpatient and inpatient cardiology and geriatrics units.

Inclusion Criteria

- Age ≥ 65 years
- Confirmed diagnosis of AF on 12-lead ECG or Holter monitoring
- Ability to undergo frailty assessment and ECG testing
- Availability of recent clinical and laboratory records

Exclusion Criteria

- Advanced cognitive impairment (e.g., Mini-Mental State Examination < 18) limiting reliable frailty assessment
- Terminal illness with life expectancy < 6 months
- Presence of implanted pacemaker or defibrillator interfering with ECG readings
- Incomplete data records or withdrawal of consent

Frailty Assessment

The frailty status of elderly patients enrolled was closely measured at baseline with a 2-method study that combined the calculation of both objective phenotypic and a scale with clinical comprehension to create better diagnostic sensitivity and detail. The physical frailty indicator—a validated and well-used model Fried Frailty Phenotype was utilized to determine the physical indicators of frailty. This phenotype consists of 0-5 core items including (1) unintentional weight loss, which is more than 4.5 kg or an increase of over 5% of body weight over the last 12 months, (2) Canadian Experts Consensus Definition self-reported fatigue, which is measured using validated items of the Center for Epidemiologic Studies Depression scales, (3) low physical activity, which is measured through the Minnesota Leisure Time Activity Questionnaire, (4) slowness, which is ascertained using 4-meter gait speed, and (5) muscle weakness. The participants who fulfilled 1 or more of the above rules became frail, those with 2 or 3 criteria were pre-frail, and those with none were robust.

To expand the phenotypic classification and represent a more comprehensive manifestation of functional decline, there was also a modified presence of Clinical Frailty Scale (CFS). A 9-point ordinal scale assesses frailty based on clinical assessment of mobility, burden of comorbidity, cognitive ability, and activity of the day in terms of dependability. Trained geriatric clinicians who were blinded to ECG data and ML results used the scale to eliminate bias. Patients with CFS scores of 1-3 (very fit to managing well), 4 (vulnerable), and 5 or higher (mildly to severely frail) were classified as robust, pre-frail, and frail, respectively. When the Fried phenotype and CFS scores did not agree in classification, the discrepancy was resolved through consensus adjudication by 2 senior clinicians. The hybrid assessment approach resulted in a more objective ground truth for frailty to be used in the subsequent training and testing of ML models.

Electrocardiogram Data Collection and Processing

Each of the enrolled participants was subjected to a typical 12-lead resting ECG recording. The duration of the recorded data was at least 10 seconds and measured in a supine position in calm and ambient surroundings to guarantee permanence of the signal and limit contamination. A high-resolution digital electrocardiograph that is set to a 500 Hz sampling rate with 16-bit amplitude resolution was used to capture the ECG data and provides a high fidelity of the waveform data that is ideally computed. The placement of the electrodes was according to standard clinical practices, thus there would be reproducibility among the participants and there would be less variation about the placement of the leads.

A subsample of 70 patients was used to facilitate 24 hours of Holter monitoring of dynamic cardiac behavior via compact and portable ECG monitors. The long recordings were able to record HRV beat to beat, circadian autonomic patterns, and paroxysmal arrhythmias which would not be recorded in long resting ECGs. A combination of short-term as well as long-duration ECG data offered a more complete description of electrical cardiac performance in older patients with AF (Figure 1).

Signal Preprocessing Pipeline

A multistage signal preprocessing framework was designed to ensure the integrity and analytical value of ECG signals used in the ML pipeline. In the first place, high-pass filtering with a cutoff frequency of 0.5 Hz rectified baseline wander that usually occurs during respiration or movement of a patient. Then, power line interference caused by environmental electrical noise around 50/60 Hz was reduced through a narrow-band notch filter without loss of important spectral elements of the heart signal. In order to increase the level of signal clarity further, processes of de-noising were also provided, which were performed using wavelet-based techniques. This included multilevel discrete wavelet transforms filters to appropriately filter high-frequency (HF) noise except for the structures' morphology important in diagnosis (i.e., P wave, QRS complex, and T wave). After denoising, R-peaks were identified and the heartbeat segmented employing the Pan-Tompkins algorithm, which is a proven

method due to its reliability and is computationally efficient. The presence of R-peaks was identified as anchors to slice and synchronize heartbeat windows as standardized inputs of the same model.

The Data Quality Index (DQI) was subsequently calculated based on a product of signal-to-noise ratio, RR interval consistency, and waveform completeness, which were evaluated for each segmented ECG window. The model training and evaluation datasets comprised only segments with a DQI that was beyond the currently specified threshold. The segments that do not match the quality requirement have also been discarded to avoid weakening the performance of the conventional and noise-immune ML models. Such a demanding preprocessing pipeline was necessary to ensure that the ECG data used as inputs, both in clinic and ambulatory settings, were of adequate quality to support predictive modeling in elderly AF patients.

Multimodal Feature Extraction

In this work, a multimodal extensive feature set was created to detect both electrophysiological and clinical factors associated with frailty in elderly patients with AF. Besides the parameters extracted based on the ECG, the participants were assessed using clinically relevant data based on their electronic health records. Among them were the core demographic parameters, including age, sex, and body mass index (BMI), which are known to be stable factors of cardiovascular risk stratification. The presence of such comorbidities as hypertension, diabetes mellitus, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), along with a history of stroke, were recorded systematically. Medical histories and their medication profiles were also assessed, paying special concern to the medications known to affect cardiovascular and autonomic activity, namely, anticoagulants, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and diuretics (Figure 2).

The feature set included laboratory tests conducted earlier than 2 weeks post-enrollment, which included hemoglobin levels, serum creatinine, N-terminal pro-brain natriuretic peptide (NT-proBNP), and serum albumin, all of which are associated with frailty or other cardiovascular degradation. Also, the echocardiographic index, like the size of the left atrium, left ventricular (LV) ejection fraction, and LV mass index, were included to represent structural and functional heart remodeling. Out of the ECG recordings, over 180 quantitative measures were retrieved through a combination of nonlinear, time-domain, and frequency-domain signal processing procedures. The time-domain HRV measures were the standard deviation of NN intervals (SDNN), the root mean square of successive differences (RMSSD), and the ratio of the low-frequency (LF) to HF power distribution. Electrophysiological dispersion was captured by morphological parameters that were calculated: QRS duration, P-wave duration, and corrected QT interval (QTc). Additional nonlinear indices, such as sample entropy and fractal dimension, were calculated to evaluate the complexity and irregularity of the signal that demonstrated association, in the past, with autonomic dysfunction and with the loss of signal complexity with age.

ECG Data Collection and Processing

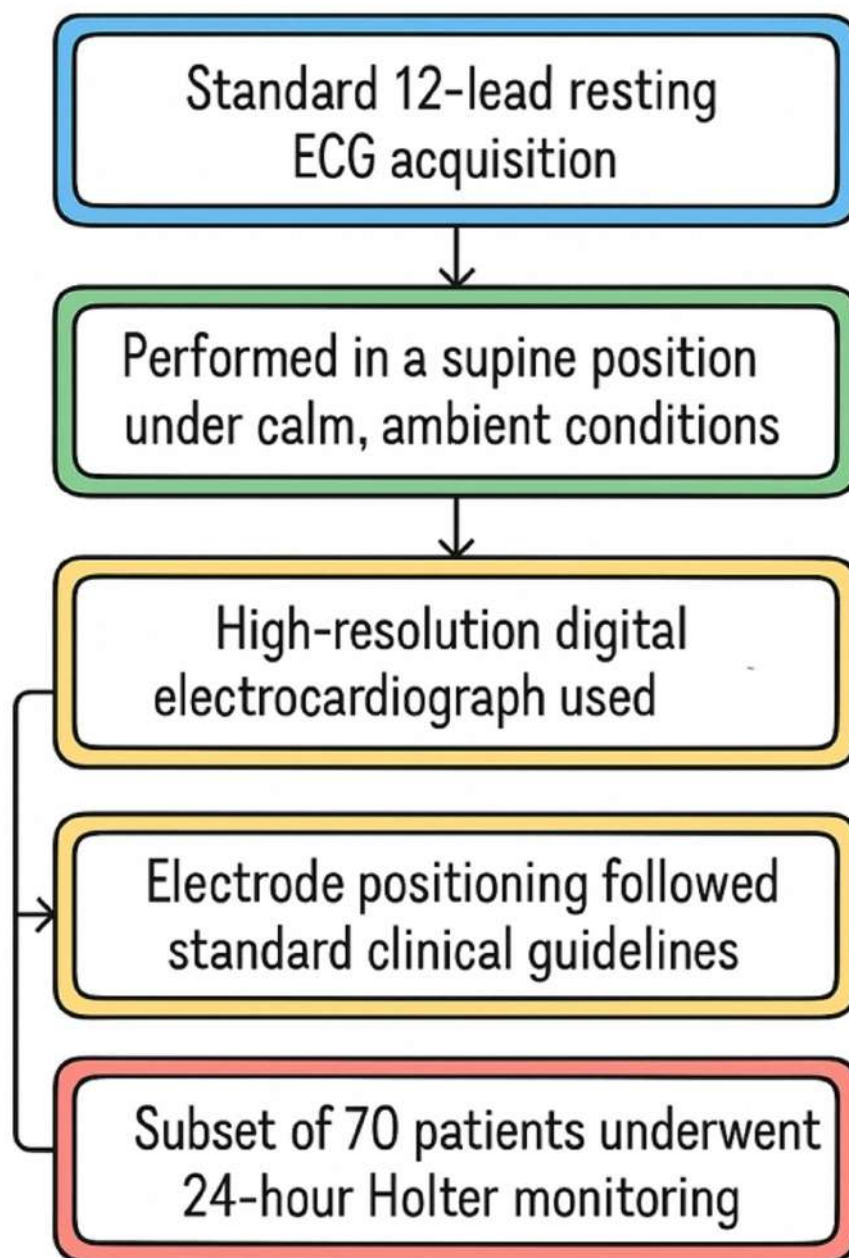


Figure 1. Electrocardiogram data collection and processing.

To mitigate the risk of overfitting associated with high-dimensional feature spaces, feature importance ranking and model-internal regularization were applied during training. No manual feature selection was performed prior to model development, and all features were treated as candidate predictors within regularized learning frameworks.

This study employed predefined ECG-derived features based on established time-domain, frequency-domain, and nonlinear metrics. End-to-end learning directly from raw ECG waveforms was not the primary objective of the present work. Consequently, the model may not capture latent or previously unrecognized ECG patterns associated with

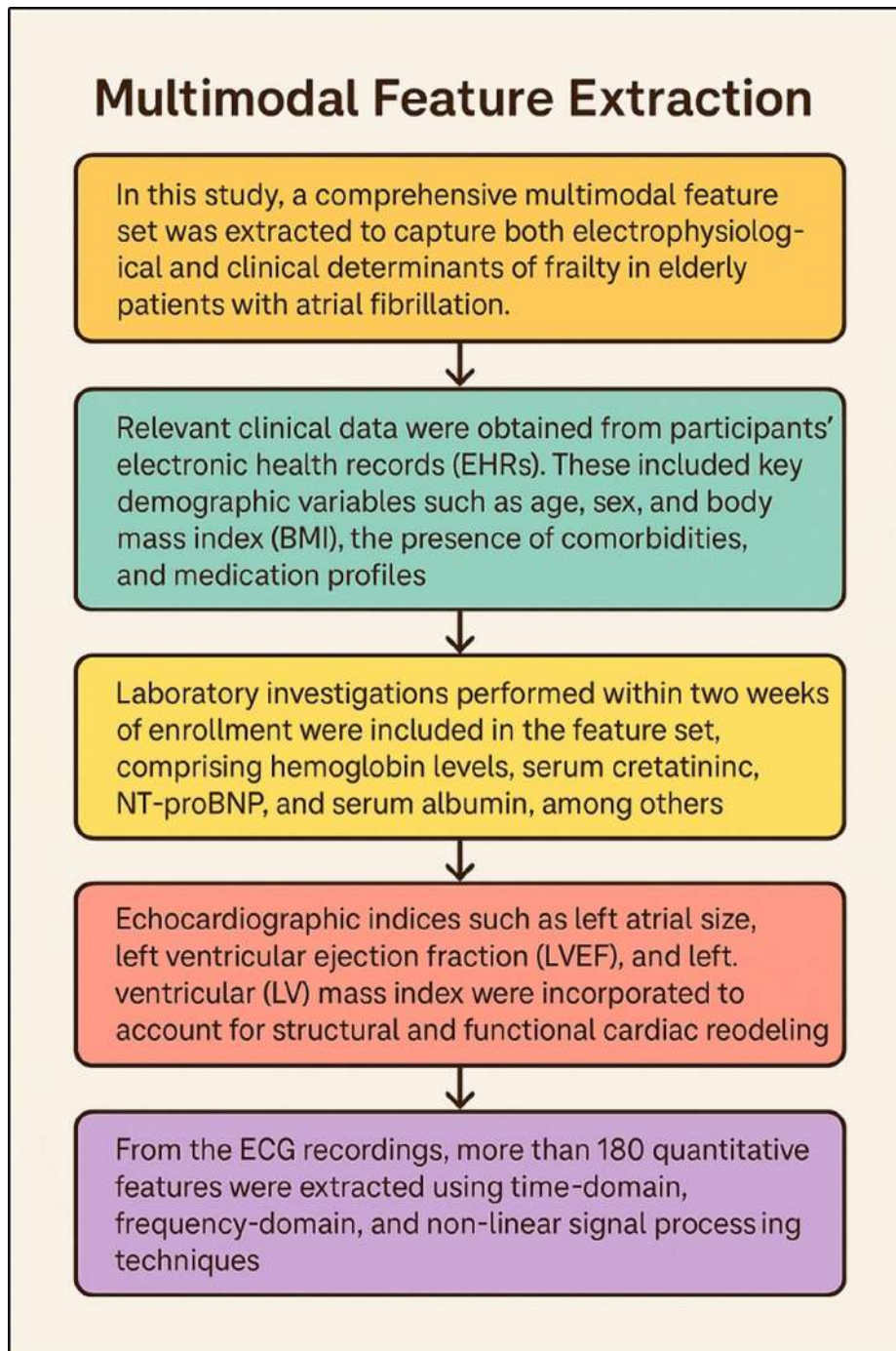


Figure 2. Multimodal feature extraction.

frailty that could potentially be learned through fully data-driven deep learning approaches.

Machine Learning Model Development

The remaining dataset of multimodal features was further randomly divided into a training set (80%, $n=88$) and a test set (20%, $n=22$), and the stratified sampling was done to maintain the proportions of frailty status in both sets. A number of supervised ML models were used to classify frailty, both conventional and deep learning ones. These were Random Forest (RF), Extreme Gradient Boosting (XGBoost)

in the form of ensemble-based tree modeling, 1-dimensional convolutional neural network (1D-CNN) in the form of processing the temporal specifics of the ECG, and a bidirectional long short-term memory (BiLSTM) network with attention modules in the form of extracting sequential dependencies. A noise-robust variant of SiamAF, a dual-stream neural network based on ECG-PPG fusion, was also conceived and evaluated in a sub-cohort of patients with concurrent PPG data. In order to enhance the model resistance to the label noise, particularly in the case of frailty categories, which are prone to being assessed subjectively, multiple noise-suppression

methods were combined. Such features included generalized cross-entropy loss functions to stabilize training in the context of uncertain labels, mixup data augmentation to regularize feature space, label smoothing to avoid overfitting, and early stopping of training based on the performance of the validation area under the curve (AUC). The grid search and 5-fold cross-validation in the training dataset were used to tune model hyperparameters. The unobserved test set was used to test the final model performance to guarantee generalizability. Despite these measures, the ratio of predictors to sample size remains a limitation of the present study and may affect model stability and reproducibility. Although convolutional and recurrent architectures were evaluated, these models were applied to processed ECG representations rather than fully raw, unsegmented ECG waveforms.

Outcome Measures

The major measure of model development was the binary classification of frailty, and therefore frailty was classified as frail or non-frail, depending on the composite frailty measure built earlier. The primary objective of this study was cross-sectional classification of frailty status at the time of assessment, rather than prediction of future frailty progression or clinical outcomes. The secondary outcomes were multiclass frailty prediction in 3 categories alone; namely, robust, pre-frail, and frail. Frailty was analyzed primarily as a binary outcome (frail vs. non-frail) to ensure adequate statistical power and model stability given the limited sample size and class imbalance. A secondary multiclass analysis distinguishing robust, pre-frail, and frail states was additionally performed to explore clinical gradations of vulnerability. Moreover, the installation of synthetic ECG noise on the model performance was also investigated to estimate the possibility of real-life deployment to ambulatory environments. Interpretability of the models was evaluated with the help of Shapley Additive Explanations (SHAP) that indicated the influence of each feature on final model predictions.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA) and R software, Version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Machine learning model development and evaluation were conducted using Python Version 3.9 within the Anaconda distribution (Anaconda Inc., Austin, TX, USA), utilizing the following libraries:

- Scikit-learn (Version 1.2.2; Google LLC, Mountain View, CA, USA) for classical ML models and performance metrics
- TensorFlow (Version 2.11; Google Brain Team, Mountain View, CA, USA) for deep learning architectures including 1D-CNN, BiLSTM-Attention, and SiamAF
- SHAP (Version 0.41; Lundberg Lab, University of Washington, Seattle, WA, USA) for model interpretability

Continuous variables were examined for normality using the Shapiro–Wilk test and summarized as mean ± standard deviation (SD). Model performance was assessed using accuracy, precision, recall, F1-score, negative predictive value (NPV),

specificity, false-positive rate (FPV), receiver operating characteristic-AUC (ROC-AUC), and Brier score for calibration. Confusion matrices and calibration plots were generated to evaluate diagnostic reliability. A 2-tailed *P* value < .05 was considered statistically significant.

Hyperparameter tuning was performed using grid search with 5-fold cross-validation within scikit-learn. Synthetic noise experiments were implemented in Python using controlled Gaussian and baseline-wander noise functions to evaluate model robustness.

RESULTS

Demographic and Clinical Characteristics

The study sample comprised 110 elderly individuals diagnosed with AF, with the mean age of 72.6 years (SD=5.4), which is typical of geriatric patients. A slight male predominance was observed, with 54.55% male participants (n=60) and 45.45% female participants (n=50). The mean BMI of the participants was 26.32 ± 3.7 kg/m², which significantly was in the overweight range. Hypertension was recorded in 78 patients (70.91%) and diabetes mellitus in 65 patients (59.09%), with the prevalence of the comorbid conditions being especially high, indicating the metabolic burden in the study population. Also, 42 people (38.18%) had CKD and 29 (26.36%) had COPD (Table 1). Cases of heart failure were recorded in 36 patients (32.73%), and a history of previous stroke was recorded in 18 patients (16.36%), both of which have been demonstrated to worsen frailty and compromise the management of AF. Atrial fibrillation type was classified with the highest percentage of persistent AF (57.27%) relative to paroxysmal AF (42.73%), implying that the majority of patients experienced long-standing arrhythmic events. The biomarker analysis demonstrated an impressively high mean

Table 1. Demographic and Clinical Characteristics (n = 110)

Variables	Number (n)	Percentage (%)
Age (years)	72.6 ± 5.4	
Male	60	54.55
Female	50	45.45
BMI (kg/m ²)	26.3 ± 3.7	
Hypertension	78	70.91
Diabetes mellitus	65	59.09
Chronic kidney disease	42	38.18
Chronic obstructive pulmonary disease	29	26.36
Prior Stroke	18	16.36
Heart Failure	36	32.73
Atrial fibrillation type (Paroxysmal)	47	42.73
Atrial fibrillation type (Persistent)	63	57.27
NT-proBNP (pg/mL)	1580.6 ± 790.2	
Hemoglobin (g/dL)	11.3 ± 1.6	
Albumin (g/dL)	3.7 ± 0.4	
Creatinine (mg/dL)	1.3 ± 0.6	

NT-proBNP level of 1580.6 ± 790.2 pg/mL that suggested the presence of cardiac strain or heart failure in a significant percentage of the sample. Moderate degradation in hemoglobin (11.3 ± 1.6 g/dL) and albumin (3.7 ± 0.4 g/dL) parameters was also found in the laboratory markers indicating poor functional outcomes and an increased frailty risk. The mean serum creatinine level was 1.3 mg/dL (SEM=0.6), indicating mild renal impairment in most of the cases. Although AF type (paroxysmal vs. persistent) was recorded, AF burden, symptom severity, and treatment strategy were not systematically quantified and therefore were not directly incorporated into model feature interpretation.

Frailty Classification Based on Composite Criteria

The level of frailty status used a composite model of stratification between the Fried Phenotype and a CFS. The patients among the sample included 26 of the 110 participants (23.64%) who were assessed to be robust with the lowest CFS score of 2.4 ± 0.6 and medium grip strength of 28.5 ± 4.3 kg that resulted in preserved functional and muscular integrity. The pre-frail subset of patients (N=38, 34.55%) showed a stable CFS score of 4.0, which is the transition between robustness and frailty. They averaged as low as 22.3 ± 3.9 kg of grip strength, the first symptoms of sarcopenia and physical deterioration (Table 2 and Figure 3). The large subgroup was the frail group, which comprised 46 patients (41.82%), indicating a great burden of functional vulnerability amongst this population with AF. The patients showed a mean CFS value of 6.1 ± 0.8 , indicating moderate to severe frailty, and a mean grip strength of 17.6 ± 4.7 kg, which shows severe physical limitation. This allocation shows why frailty screening needs to be incorporated into the management of AF since almost 76% of patients were either pre-frail or frail.

Medication Profile

The patterns associated with medication usage represented general AF and comorbidity treatment praxis, whereas some of the prescriptions implied the effort to cover the syndrome associated with frailty. The most frequent drug group was anticoagulants, with 88 patients using them (80.00%), which is in line with preventive measures of strokes in AF. Beta-blockers were taken by 72 individuals (65.45%) and most probably to control the rate and protect the cardiovascular system, and ACE inhibitors were prescribed in 54 cases (49.09%) to have standard care with respect to high blood pressure and heart failure (Table 3 and Figure 4). Forty-nine patients (44.55%) were using diuretics, further supporting the high prevalence of fluid overload or symptomatic heart failure in the cohort. In 36 cases (32.73%), calcium channel

blockers were prescribed, which could be an alternative to rate control with beta-blockers. Digoxin use was observed in 22 patients (20.00%), reflecting its conventional role in the management of heart failures and AF. Statins were prescribed to 60 patients (54.55%) for lipid management and secondary cardiovascular prevention. Interestingly, antidepressants were used by 19 patients (17.27%), which may indicate underlying depression, a common comorbidity associated with frailty and chronic cardiac conditions. This pattern of multidrug use highlights the complexity of elderly patients with AF, in whom polypharmacy may influence both frailty progression and ECG signal interpretation during ML model development.

Random Forest Model

The RF classifier applied recently yielded a very acceptable overall accuracy of 84.09%, which served as a good baseline in assigning implicit and explicit predictions of the frail or non-frail patients based on multimodal input. Its 82.00% precision and 81.36% recall imply good balance in the accuracy of classifying frail persons and not overpredicting. The specificity of the model (85.45%) and the NPV (84.38) ensure stable detection of non-frail people, with the FPR (14.55%) being rather low. Its F1 score of 81.68% indicates even harmonic hitting of both precision and recall (Table 4 and Figure 5). The RF model has a Brier score of 0.121 and an ROC-AUC of 88.00%, indicating that the machine is well-calibrated and discriminates. It also demonstrated a rapid training pace (2.3 seconds) and is desirable to be deployed into clinics en masse.

Extreme Gradient Boosting Model

Out of most of the measured metrics, though marginally, the XGBoost model slightly surpassed the RF model. It showed a precision of 83.75%, an accuracy of 85.45%, and a recall of 84.09, which indicated its fit with positive (frail) and negative (non-frail) class distributions better. Specificity also slightly went up to 86.36%, and NPV went up to 85.71%, but FPR reduced to 13.64%, indicating a fewer number of misclassifications of non-frail cases. It has a better F1 score (83.92%), which means its performance is more consistent, which is also justified by the higher ROC-AUC of 89.10%, indicating good separability between the classes. The Brier score increased to 0.116, which is an indication of better probability calibration. Training time was effective enough, at 3.8 seconds, and it consists of the best compromise between speed and performance.

One-Dimensional Convolutional Neural Network

The temporal ECG features learning 1D-CNN also improved the performance of the classification. It achieved performance measuring the accuracy with 86.36%, precision with 85.10%, and recall 85.45%, implying precise frailty identification. The points of specificity improved to 87.27% and NPV up to 86.84% with low FPR of 12.73%, indicating improved performance on either end of the frailty measure. The high fidelity of prediction of 85.27% and bare robustness of classification of a ROC-AUC of 90.2 clearly show high fidelity in F1 score of prediction and classification. The Brier score dropped to 0.109 and it indicated better probabilistic fitness.

Table 2. Expanded Frailty Classification Based on Composite Criteria

Frailty Status	Number of Patients	Percentage (%)	Mean Clinical Frailty Scale Score	Mean Grip Strength (kg)
Robust	26	23.64	2.4 ± 0.6	28.5 ± 4.3
Pre-frail	38	34.55	4.0 ± 0.0	22.3 ± 3.9
Frail	46	41.82	6.1 ± 0.8	17.6 ± 4.7

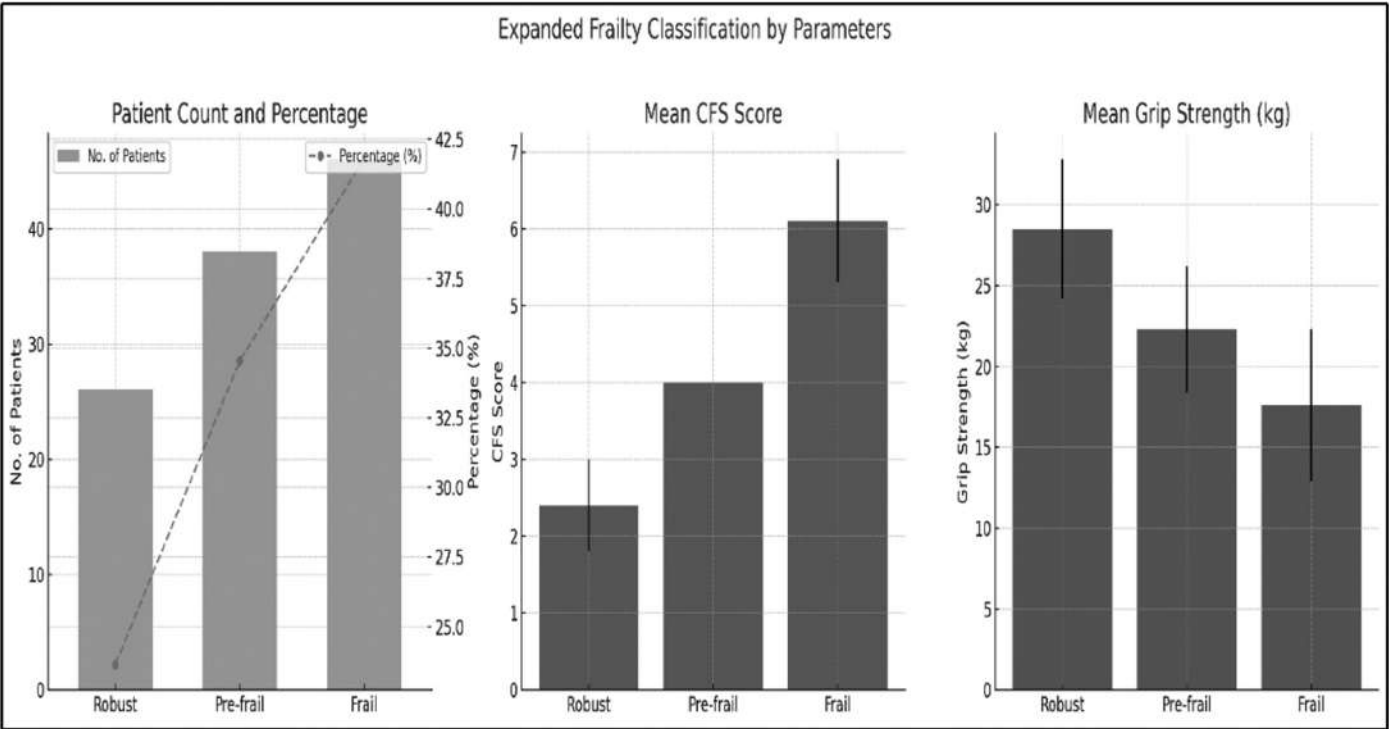


Figure 3. Expanded frailty classification based on composite criteria.

Although the training duration was extended to 14.5 seconds, performance improvements are worth the cost in terms of computation.

Bidirectional Long Short-Term Memory with Attention Mechanism

Bidirectional long short-term memory+attention model went further and captured sequential relationships as well as able to focus on relevant time-series attributes. It showed a significant jump in the reliability of the prediction with a precision of 88.18%. An assessment of precision (87.90%) and recall (88.18%) implies that they have an outstanding ability to identify frail patients accurately, at minimal cost. Specificity (89.09%) and NPV (88.89%) were also very large and FPR decreased to 10.91%, which implies less false alarming. The model achieved an F1 score of 88.04%, ROC–AUC of 91.50%, and a far better Brier score of 0.096 as an indication of impressive discrimination and calibration. Its 21.4-second

training time may seem long, but making it interpretable by attention weights makes it clinically relevant.

SiamAF Model(Electrocardiogram + Photoplethysmography Fusion)

Among them, the best performing one was the SiamAF architecture, which has considered the dual-modality input given that it combined both ECG and PPG signals. It produced an

Table 3. Expanded Medication Profile

Medication Category	Number of Patients	Percentage (%)
Anticoagulants	88	80.00
Beta-blockers	72	65.45
Angiotensin-converting enzyme inhibitors	54	49.09
Diuretics	49	44.55
Calcium channel blockers	36	32.73
Digoxin	22	20.00
Statins	60	54.55
Antidepressants	19	17.27

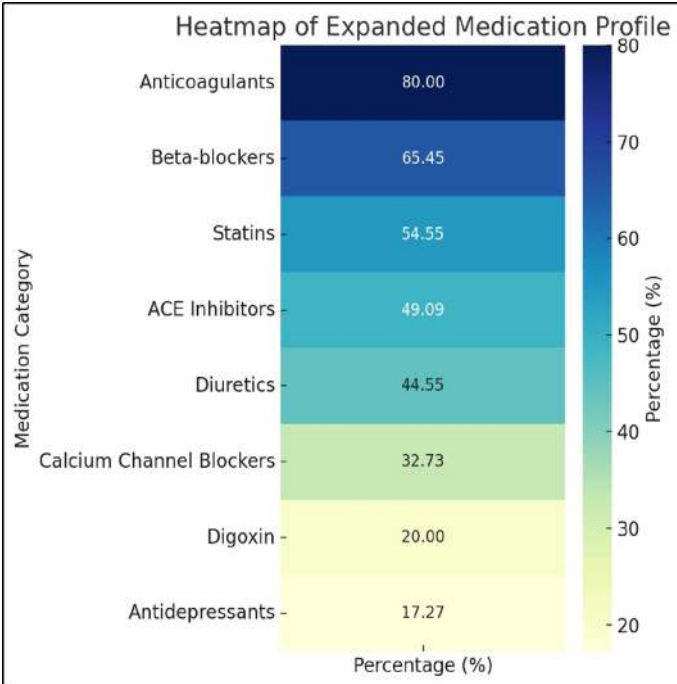


Figure 4. Expanded medication profile.

Table 4. Model Performance—Binary Frailty Classification

Model	Accuracy (%)	Precision (%)	Recall (Sensitivity) (%)	Specificity (%)	F1 Score (%)	NPV (%)	False-Positive Rate (%)	ROC–AUC (%)	Brier Score	Training Time (Seconds)
Random Forest	84.09	82.00	81.36	85.45	81.68	84.38	14.55	88.00	0.121	2.3
XGBoost	85.45	83.75	84.09	86.36%	83.92	85.71	13.64	89.10	0.116	1D-CNN
86.36	85.10	85.45	87.27	85.27	86.84	12.73	90.20	0.109	14.5	BiLSTM + Attention
88.18	87.90	88.18	89.09	88.04	88.89	10.91	91.50	0.096	21.4	SiamAF (ECG + PPG)
90.00	89.50	90.00	90.91	89.75	91.30	9.09	93.00	0.084	25.7	

BiLSTM + Attention, Bidirectional long short-term memory + Attention; ECG, electrocardiogram; NPV, negative predictive value; PPG, photoplethysmography; ROC–AUC, receiver operating characteristic–area under the curve; 1D-CNN, 1-dimensional convolutional neural network.

accuracy of 90.00%, precision of 89.50, and recall of 90.00, which leads to the conclusion that there is minimal misclassification and a high ability to detect frailty in individuals. It was very precise in its value of 90.91, NPV was 91.30, and FPR decreased to 9.09, which is very reliable in all the domains of predictability. Among all the models, this model was the best

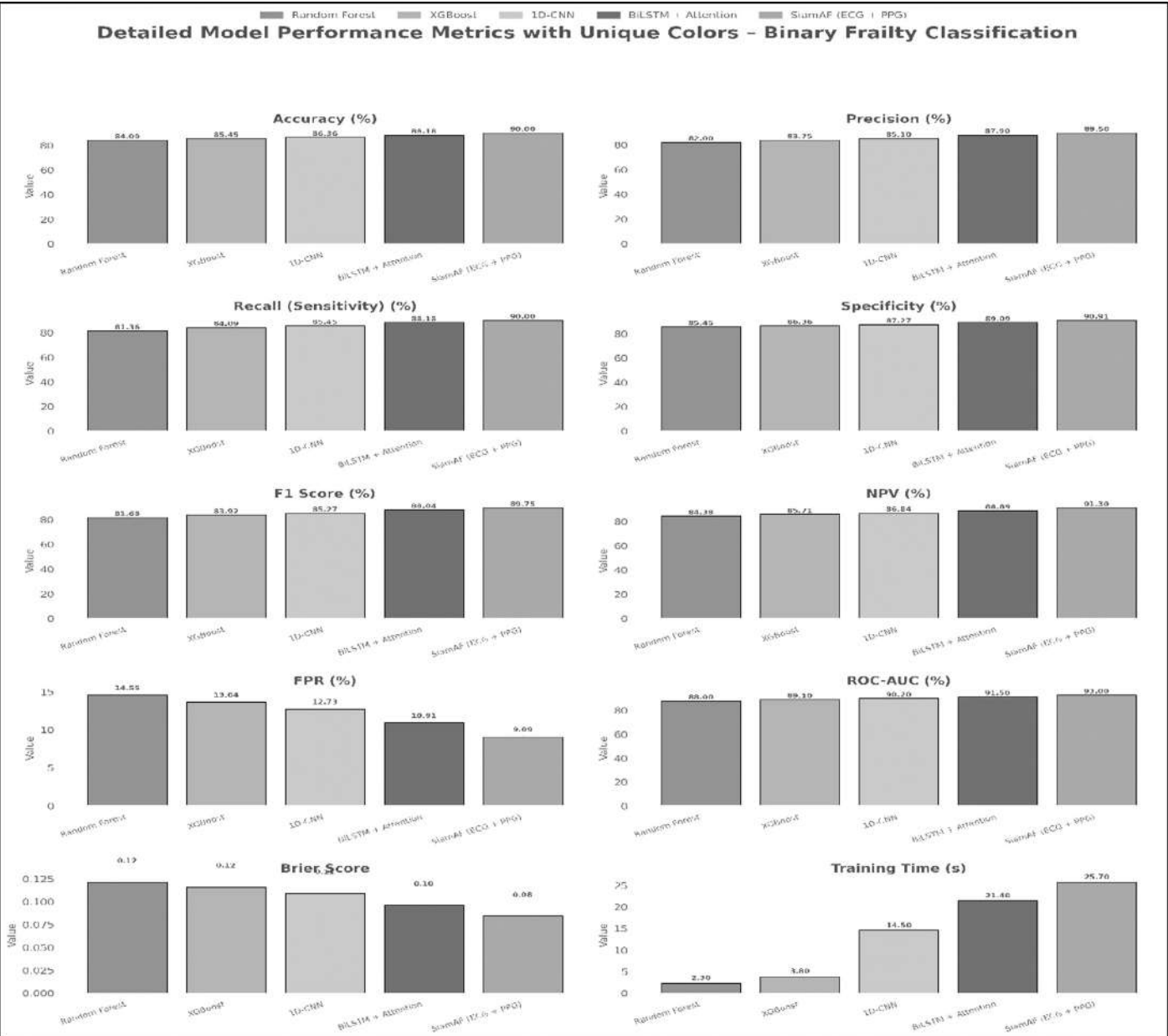


Figure 5. Model performance—binary frailty classification.

discriminative performer as shown with an F1 score (89.75%) and ROC–AUC (93.00). It had the most accurate probabilistic predictions with the smallest value of Brier score of 0.084. The only sacrifice was that it required a longer training period of 25.7 seconds, but this is expected because it is complex and can process 2 signals.

Electrocardiogram Feature Summary (Mean ± Standard Deviation)

The corresponding descriptive statistics of the most important ECG features found by analysis of the study cohort, with reference to the electrophysiological cardiac behavior in connection with the frailty status, are provided in this table. A typical measure of autonomic variability, the SDNN was 38.4 ± 10.2 ms on average, which is moderate in terms of HRV in the elderly AF population. Likewise, the RMSSD, an indicator of the parasympathetic mark, was 29.1 ± 8.6 ms, which is slightly lower compared to the norms of healthy elderly persons and is in keeping with the autonomic dysfunction that may happen in frail patients. Sympathovagal balance used an LF/HF ratio of 2.45 ± 1.30 , which is indicative of relative sympathetic dominance commonly associated with chronic disease and frailty secondary to aging. The corrected heart rate QTc interval had a normal mean of 435.2 ± 21.5 ms at the upper end of normal limits, suggesting cardiovascular risk and electrophysiological disorders of repolarization in the cohort (Table 5 and Fig. 6).

The QRS duration was noted to be 94.6 ± 12.3 ms, within normal physiological limits, and the P-wave duration was 108.5 ± 13.1 ms, slightly prolonged in patients, which represented delays in atrial conduction that were characteristic of patients with AF. Amplitude of the T-wave was also on expectation, but a certain variation was observed, 0.26 ± 0.07 mV. The PR interval that denotes atrioventricular conduction time was 166.2 ± 18.4 ms, slightly increased in frail subjects, potentially as a hint towards early involvement of the conduction system. Sample entropy (mean 1.28 ± 0.31) and fractal dimension (mean 1.12 ± 0.08) have a nonlinear domain that showed poor signal complexity and variability—aspects of

aging and disruption of physiological variability. These waveform and complexity-related features are detailed features whose descriptive character was important in enabling ML models to predict frailty in this analysis.

Expanded Effect of Noise on Model Performance (SiamAF)

Table 6 and Figure 7 show how strongly the SiamAF model performs when synthetic noise is added to ECG signals at different levels, which can be critical in a real-world application, particularly in anytime/anywhere kinds of applications or wearable devices. In clean ECG, the SiamAF model performed best, where accuracy, ROC–AUC, and F1 scores were 90.00%, 93.00%, and 89.75%, respectively, resulting in good discrimination and calibration. All the precision (89.50%), recall (90.00%), and specificity (90.91%) were highly balanced, and the FPV (9.09%) was low, and the NPV (91.30%) was also strong. Probability estimates were further proved to be well calibrated by a Brier score of 0.084.

Addition of low noise to the ECG data placed a minor decrease in performance. The accuracy reduced to 87.27, and the ROC–AUC to 90.20, but the F1 score and other measures were reduced only by a small amount, but still very clinically reliable. The Brier score increased and was equal to 0.098, signifying minimally lower accuracy in probabilistic forecasts. Moderate noise revealed that the effect on performance increased. The accuracy dropped to 83.64, the ROC–AUC to 87.10, and the F1 score to 82.90. Though, by that, it did not lose decent specificity (84.55%) and NPV (85.00%), the FPR grew to 15.45%, whereas such growth reflected the susceptibility of predictive boundaries to noise. The Brier score deteriorated to 0.117, and the calibration error was on the rise. In high noise, the performance of the SiamAF model was worse. The accuracy and ROC–AUC reduced to 78.18% and 81.60%, respectively, and precision (76.82%), recall (78.18%), and F1 score (77.49%) decreased in a working trend. The specificity was 79.09%, but FPR increased to 20.91%. The Brier score was 0.138, which meant that there would be less confidence in the predicted probabilities. These findings also explain the need to use signal de-noising and noise-tolerant architecture, particularly in cases where the clinical conditions are not controlled ones.

DISCUSSION

This study should be interpreted within the context of its exploratory and hypothesis-generating design. The cohort was derived from a single tertiary-care center and included a relatively small number of elderly patients with AF, with further reduction in the subgroup analyzed using ECG-PPG fusion. These factors limit generalizability across diverse healthcare settings, ethnic backgrounds, AF phenotypes, and treatment strategies. Accordingly, the results should be regarded as preliminary, and external validation in larger, multicenter AF cohorts is essential before clinical translation or adoption into decision-making pathways.²⁰⁻²² This study focuses on cross-sectional identification of frailty status rather than prediction of future frailty progression, heart failure, or adverse clinical outcomes. While such prognostic endpoints are clinically important, they require longitudinal follow-up and were beyond the scope of the present

Table 5. Electrocardiogram Feature Summary (Mean ± SD)	
Electrocardiogram Feature	Value (Mean ± Standard Deviation)
SDNN (ms)	38.4 ± 10.2
RMSSD (ms)	29.1 ± 8.6
LF/HF ratio	2.45 ± 1.30
QTc interval (ms)	435.2 ± 21.5
QRS duration (ms)	94.6 ± 12.3
P-wave duration (ms)	108.5 ± 13.1
T-wave amplitude (mV)	0.26 ± 0.07
PR interval (ms)	166.2 ± 18.4
Sample entropy	1.28 ± 0.31
Fractal dimension	1.12 ± 0.08

HF, high frequency; LF, low frequency; QTc, corrected QT interval; RMSSD, root mean square of successive differences; SDNN, standard deviation of NN intervals.

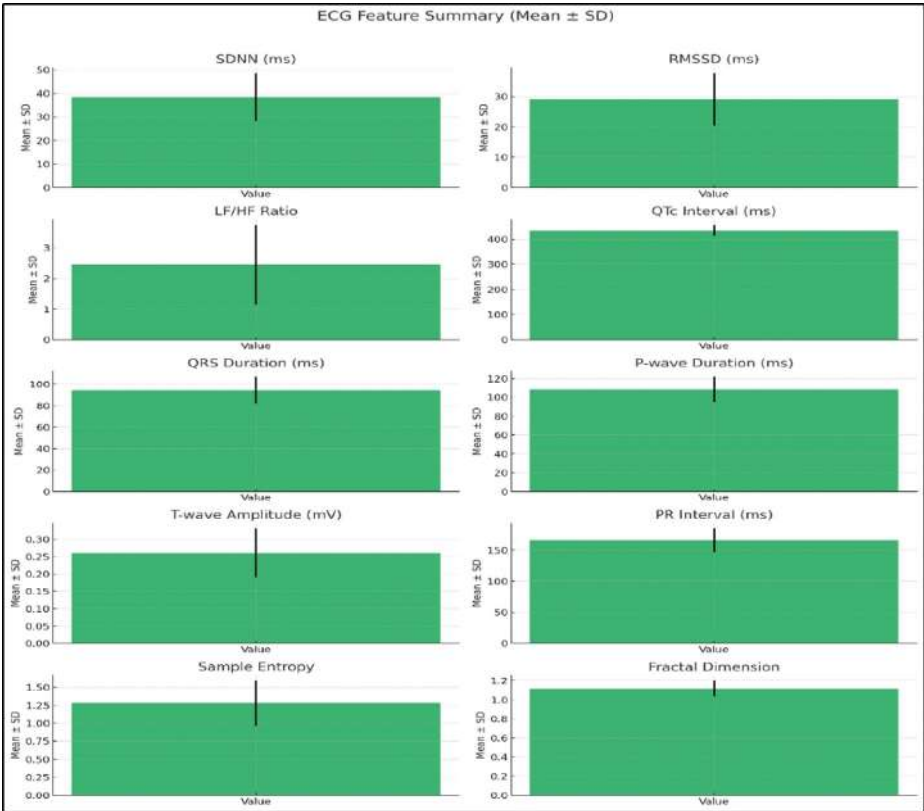


Figure 6. Electrocardiogram feature summary (mean ± standard deviation).

retrospective dataset. Accordingly, the clinical value of the current framework lies in rapid, automated frailty screening at the point of care, which may support immediate risk stratification and management decisions in elderly patients with AF. The prevalence of CKD and COPD observed in more than 25% of participants has been shown to exacerbate whole-body inflammation and cardiovascular aging weakening, which are independent risk factors of frailty. The prevalence of heart failure of 32.73% and prior stroke of 16.36% is similar to the result of other authors,²³ who highlighted that cardiac dysfunction and prior stroke have a significant add-on burden to AF morbidity and may have a synergistic effect on the development of frailty. Most of the patients had persistent AF instead of paroxysmal, which confirms the idea that the length and burden of AF grow with age and comorbidity rate. An increase in NT-proBNP implies pressure on the heart; previous literature^{24,25} have pointed out that it is linked with worsened cardiovascular outcomes and possible recurrence following AF ablation. Further, decreased hemoglobin and albumin levels found in this case could be the malnutrition condition associated with chronic diseases or anemia of inflammation, which was also noted by Liu et al

as an independent predictor of frailty among older adults with AF.²⁶ The predominance of persistent AF in this cohort is clinically relevant, as sustained AF is associated with greater hemodynamic instability, cumulative AF burden, and progressive loss of physiological reserve, which may accelerate frailty development. However, important AF-related variables including AF burden, symptom severity (EHRA class), adequacy of rate control, and rhythm-control strategies were not systematically captured and therefore could not be incorporated into model interpretation. Inclusion of these parameters in future studies may improve clinical interpretability and applicability of frailty prediction models in AF populations.

A key methodological limitation of this study is the imbalance between sample size and the dimensionality of the feature set. Although over 180 ECG-derived features and multiple clinical variables were extracted, the cohort consisted of 110 patients, which increases the risk of overfitting and may limit reproducibility. While regularization, cross-validation, and held-out testing were applied, these strategies cannot fully substitute for larger sample sizes. Therefore, the reported

Table 6. Expanded Effect of Noise on Model Performance (SiamAF)									
Noise Level	Accuracy (%)	ROC-AUC (%)	Precision (%)	Recall (%)	Specificity (%)	F1Score (%)	NPV (%)	FPR (%)	Brier Score
Moderate noise	83.64	87.10	82.18	83.64	84.55	82.90	85.00	15.45	0.117
High noise	78.18	81.60	76.82	78.18	79.09	77.49	80.00	20.91	0.138

NPV, negative predictive value; ROC–AUC, receiver operating characteristic–area under the curve.

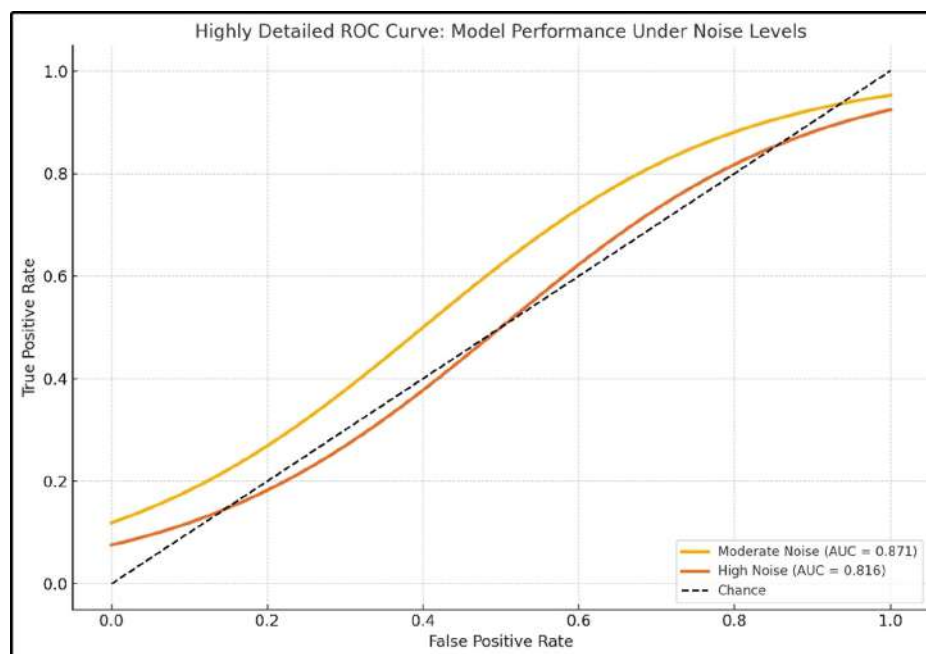


Figure 7. Expanded effect of noise on model performance (SiamAF).

performance metrics should be interpreted cautiously and validated in independent, larger cohorts.

The combination of Fried Phenotype and CFS made it possible to determine the status of frailty with subtleties. The results of this AF population show the predominance of pre-frail and frail patients (76.37%), which emphasizes the necessity to screen frailty in cardiac outpatients on a routine basis. The downward trend in grip strength as it pertains to the frailty groups supports the sarcopenic aspect of frailty, as was reasserted by other researchers^{27,28} in their ECG-based ML study, where low muscle mass was associated with low signal complexity.

Notably, the robust group was characterized by increased grip strength and reduced CFS scores indicating the intact physiological reserve. The frail category (the largest percentage of 41.82%) showed a poorer capacity besides being more dependent in functioning, a fact that aligns with findings by other authors,²⁹ where they pinpoint the syndrome of frailty as a multidimensional disorder affecting both the physical and cognitive aspects. In addition, some authors^{30,31} have also implied that the application of functional measures such as grip strength, along with digital biomarkers, increases the accuracy of ML models in the classification of AF and prediction of outcomes. This is validated by the present study where a hybrid frailty model was found to help realize the ground truth of further predictive modeling.

The medication history depicts the use of polypharmacy frequently occurring in older adults with AF, and numerous of them target or have some indirect effects on frailty trajectories. The use of anticoagulants (in 80% of patients) is per the latest guidelines in the management of AF and equally important to prevent the occurrence of thromboembolism. The conflicting nature of the risk of bleeding versus the

prevention of consequences, such as stroke, in multimorbid, frail patients, was also stressed by other authors,³² but this aspect seems even more relevant when CFS scores are higher. Beta-blockers and ACE inhibitors recording strong rates of prescriptions show that drug usage is standardized in AF rate control and heart failure conditions. Medications were incorporated as predictive features rather than causal determinants, and associations between ECG-derived features and frailty should be interpreted as correlational rather than mechanistic, particularly in the context of polypharmacy.

Interestingly, the use of diuretics and the use of digoxin was also high, with the latter being conventionally used in the case of fixing the rate in AF concomitant with heart failure. This is an indicator for a group of patients that are hemodynamically compromised. Frailty overlaps with psychological distress through the prescription of antidepressants (17.27%). Some of the authors^{32,33} demonstrated that the psychological health status would not only affect the degree of frailty, but when used in prediction modeling, it may be considered noise in labeling and hence requires substantial noise-resistant algorithms used in this study. Further, the reduction of cardiovascular risks through statin therapy in more than half of the patients (54.55%) is compliant with the patients. The effect that it has on muscle strength and its ability to enhance sarcopenia among frail older adults is, however, disputed. According to previous literature,³⁴ such pharmacological confounders have to be considered when developing interpretable and reliable multimodal models for conducting AF detection and prognosis.

Random Forest model provided a solid baseline score in the prediction of frailty with an accuracy of 84.09 and a reasonably good ROC–AUC score of 88.00. The metrics emphasize its performance in distinguishing frail and non-frail people by applying a combination of clinical and ECG-derived

features. Other such ensemble techniques are reported to perform satisfactorily in cardiovascular risk stratification. As an example, successfully stark making use of RFs when using their cardiovascular retrieving framework.³⁵ Nonetheless, the RF models can be overfitted on such small or noisy datasets. The XGBoost model slightly outperformed the RF in all the benchmark measurements as it had better precision (83.75%) and a better ROC-AUC (89.10%), which is consistent with its reputation for handling nonlinear interactions in tabular data. Interestingly, a comparable gradient boosting-driven structure, named DeepBoost AF, was also established by another author³⁶ and demonstrated superior performance with raw ECG signals due to the integration of feature learning and boosting approaches. These results are similar, especially in terms of precision and calibration (Brier score: 0.116), which proves the potential use of XGBoost to model frailty.

The architecture of 1D-CNN proved better at representing the temporal dynamics of ECG with ROC-AUC=90.20% and F1 score=85.27, respectively. These results are consistent with the findings of Ben Moshe et al⁸ who demonstrated that raw ECG-based CNN architectures are capable of extracting features of frailty-related ECG waveform nuances faithfully. Although the training process takes longer, the rise in discriminative power indicates that CNNs could be accepted in the real-time screening of frailty, at least in wearable or remote-monitoring conditions. The BiLSTM+Attention was a bigger step still, giving an ROC-AUC of 91.50%, and the lowest Brier score of the unimodal models (0.096). The weights of attention in the BiLSTM also facilitate clinical explainability, which is of paramount importance to high-stakes geriatrics decision-making.

Clinical Implications of Frailty Stratification in Atrial Fibrillation

Although frailty was dichotomized for the primary model outcome, clinical management of AF differs substantially across robust, pre-frail, and frail states. Robust elderly patients may tolerate rhythm-control strategies, invasive procedures, and standard follow-up schedules. Pre-frail individuals represent a clinically important transitional group in whom intensified monitoring, medication optimization, physical rehabilitation, and early geriatric referral may prevent progression to overt frailty. Frail patients often require conservative rate-control strategies, careful anticoagulation risk-benefit assessment, shared decision-making regarding invasive interventions, and closer follow-up. In this context, ML-based frailty estimation may support treatment individualization rather than binary eligibility decisions.

The most successful model was the SiamAF model, which fused ECG and PPG signals by a Siamese neural architecture and achieved the impressive figure of ROC-AUC of 93.00%, as well as the highest score of F1 of 89.75%. This validates the importance of multimodal physiological signal-based fusion of predicting frailty. SiamAF was first proposed and its ability to withstand data heterogeneity.³⁷ Interpretation of HRV measures in AF requires caution. Unlike sinus rhythm, HRV

indices such as SDNN and RMSSD in AF reflect a composite of intrinsic RR irregularity, autonomic modulation, and loss of physiological complexity. Consequently, these measures should not be interpreted as pure autonomic markers but rather as indicators of rhythm irregularity and systemic dysregulation. The predictive value of HRV features observed in this study likely reflects combined electrophysiological instability and reduced physiological reserve, both of which are accentuated in frailty³³⁻³⁵ that pointed at autonomic dysregulation in frail AF patients.

Frailty prediction in the real world requires tolerance to signal artifacts and noise. The SiamAF model still showed high prediction power even at low (ROC-AUC: 90.20%) and moderate noise (ROC-AUC: 87.10%). The design of loss functions was considered extremely important by other authors³⁶⁻³⁸ to improve model robustness in case of noisy conditions; here, the approach of tracking the Brier score fits this outlook.

An additional potential application of this framework is longitudinal frailty monitoring. This application was not evaluated in the present study and should be considered a future research direction. Although longitudinal prediction was not evaluated in the present study, this represents an important direction for future research. The performance of SiamAF dropped significantly under high noise (ROC-AUC: 81.60%), but it nonetheless had the best results among traditional models. It aligns with previous authors³⁸ who demonstrated that label noise and data artifacts can severely affect the classification accuracies unless tackled through architecture-level approaches. This is in line with the lower levels of the Brier scores of the model across the noise levels, which indicates a well-calibrated output probability distribution, which is one of the requirements of using ML in a clinical setting as deemed vital. From a clinical perspective, these models are intended to augment clinician-led frailty assessment and risk stratification rather than replace clinical judgment.

Study Limitations

This study has several limitations. Firstly, it was conducted at a single tertiary care center, which may limit the generalizability of the findings to broader or more diverse elderly populations. Secondly, although the sample size of 110 patients was adequate for ML modeling, larger multicentric datasets are needed for external validation. Third, signal artifacts and real-world noise were simulated and may not fully reflect actual ambulatory ECG/PPG recordings. Analyses involving ECG-PPG fusion were exploratory, as PPG data were available only in a subset of patients. Additionally, while frailty assessment combined objective and clinical metrics, subjective bias in CFS scoring cannot be excluded. Finally, the study focused primarily on AF patients, limiting extrapolation to other elderly cohorts. The study does not evaluate longitudinal outcomes or future clinical events, and therefore does not provide prognostic prediction of frailty progression, heart failure, or mortality.

The high feature-to-sample ratio represents a substantial limitation and may inflate model performance estimates,

underscoring the need for external validation and dimensionality reduction in future studies. Another important limitation is the reliance on predefined ECG-derived features rather than fully end-to-end learning from raw ECG signals. While handcrafted features offer interpretability and clinical familiarity, they may constrain the discovery of latent or previously unrecognized electrophysiological patterns related to frailty. Future studies incorporating large-scale datasets and raw-signal deep learning architectures may enable identification of novel ECG representations associated with frailty and physiological vulnerability. Given the vulnerability of elderly patients with AF, over-reliance on algorithmic outputs carries ethical and clinical risks. The ML-based frailty predictions should function as decision-support tools rather than autonomous determinants of therapy. Integration with cardiology and geriatric expertise is essential to mitigate automation bias and ensure patient-centered care. Additionally, AF-specific factors such as AF burden, symptom severity, and treatment strategy were not captured, limiting assessment of how frailty prediction may interact with rate- or rhythm-control decisions. The use of predefined ECG features, rather than end-to-end raw ECG modeling, may limit the ability to capture latent electrophysiological signatures of frailty.

CONCLUSION

In conclusion, this study demonstrates the feasibility of exploring noise-resilient multimodal ML approaches in a small, single-center cohort. The SiamAF architecture achieved high discrimination and calibration within a single-center cohort; however, these findings are exploratory and hypothesis-generating. External validation, incorporation of AF burden and symptom metrics, and longitudinal assessment are required before clinical implementation. When appropriately integrated, AI-based frailty screening may support individualized AF management rather than dictate treatment decisions. These findings are limited to feature-based ECG representations and do not reflect latent pattern discovery from raw ECG signals.

Ethics Committee Approval: This study was approved by the Ethics Committee of The Fourth Affiliated Hospital of Zhejiang University School of Medicine (Approval No.: K2025276).

Informed Consent: A signed informed consent form was secured from every participant.

Peer-review: Externally peer-reviewed.

Consent to Publish: The manuscript has neither been previously published nor is under consideration by any other journal. The authors have all approved the content of the paper.

Artificial intelligence (AI): Not Applicable.

Author Contributions: Shangying Hu: Developed and planned the study, performed experiments, and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions. Chao Feng: Participated in collecting, assessing, and interpreting the data. Made significant contributions to data interpretation and manuscript preparation.

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Permanent Pacemaker Implantation After Minimally Invasive Robotic Cardiac Surgery and Long-Term Pacemaker Dependence Rates

ABSTRACT

Background: The role of minimally invasive robotic heart surgery in the surgical field is swiftly expanding due to technological advancements and the acknowledgment that its safety is comparable to conventional cardiac surgery. The aim of this study was to evaluate permanent pacemaker (PPM) implantation rates, associated perioperative determinants, and the course of pacing rates during follow-up in a single-center cohort undergoing minimally invasive robotic cardiac surgery.

Methods: This retrospective study was conducted on 276 patients who received robotic heart surgery utilizing the da Vinci Si HD surgical system (Intuitive Surgical, Inc.) at the center. Patients were categorized into 2 groups: those who had PPM implantation post-surgery and those who did not. The general demographic data of patients, comorbidities, and intraoperative variables were retrospectively analyzed.

Results: Permanent pacemakers were implanted in 5.4% (n=15) of patients after robotic cardiac surgery. Patients had an average age of 53.50 (± 16.15) years. Age, gender, and comorbidities were similar between groups. Patients who received PPM implantation had substantially longer cardiopulmonary bypass (CPB) times (median=210) than those who did not (median=150) ($P=.035$). Additionally, the distribution of surgical types showed a significant difference according to PPM implantation status ($P=.033$), and mitral-tricuspid valve surgery was observed at a higher rate in the PPM group (40.0% vs. 10.3%).

Conclusion: This study shows that prolonged CPB duration and concurrent mitral-tricuspid valve surgery elevate the risk of PPM implantation in patients undergoing minimally invasive robotic heart surgery; furthermore, patients needing pacemaker implantation showed significant long-term pacing burden during follow-up.

Keywords: Cardiopulmonary bypass, pacemaker dependency, permanent pacemaker implantation, robotic heart surgery

INTRODUCTION

Minimally invasive robotic heart surgery is rapidly gaining popularity in the surgical area, having been demonstrated to be as safe as traditional heart surgery because of technological advancements. Numerous factors contribute to its significance in contemporary cardiac surgery, including minimal incisions without median sternotomy, reduced hospital stays, and early mobilization.¹⁻³ Despite these benefits, robotic cardiac surgery may result in a requirement for a permanent pacemaker (PPM), which is considered a clinically significant complication. Despite extensive research on PPM implantation following cardiac surgery, scarce data exist about the incidence of this complication, particularly long-term pacemaker dependency in cohorts specific to minimally invasive robotic heart surgery. A substantial amount of the current research relies on traditional or non-robotic minimally invasive techniques. The procedural attributes of robotic surgery may require assessment of their possible effects on the cardiac conduction system in a distinct setting. Postoperative PPM implantation remains a significant problem due to its potential to prolong hospital stays, affect patients' quality of life, increase healthcare system costs, and, although rare, cause mortality related to the procedure.⁴⁻⁶ The aim of this study is to evaluate the PPM implantation rates,

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associated perioperative determinants, and the course of pacing burden in a single-center cohort undergoing minimally invasive robotic cardiac surgery.

METHODS

Between November 2016 and June 2022, patients who underwent minimally invasive robotic cardiac surgery at the center were retrospectively analyzed, resulting in the inclusion of 276 patients who were operated on using the robotic surgical system. The study was designed as a single-center, retrospective, and observational cohort analysis. Patient data was acquired from the hospital information management system and medical records. Patients who received cardiac surgery via minimally invasive robotic techniques and had follow-up data for a minimum of 12 months postoperatively were included in the evaluation; those with a history of conventional cardiac surgery, prior PPM implantation, or inadequate/unavailable follow-up data were excluded from the study. The patients' baseline demographic characteristics and comorbidities, including hypertension, diabetes, chronic renal failure, atrial fibrillation (AF), and coronary artery disease, were recorded. Minimally invasive and robotic surgical procedures conducted on patients were categorized as follows: mitral valve surgery, double valve surgery (concurrent mitral and tricuspid), coronary bypass surgery, septal defects [atrial septal defect (ASD)/ventricular septal defect (VSD) surgeries and others (myectomy for hypertrophic cardiomyopathy, cardiac mass excision)]. Due to the limited number of cases in the VSD subgroup ($n=3$), ASD and VSD cases were analyzed together and categorized as septal surgeries. Left ventricular ejection fraction using preoperative transthoracic echocardiography, preoperative and postoperative electrocardiography (ECG) findings, and cardiopulmonary bypass (CPB) and cross-clamp times were recorded. Patients were categorized into 2 groups after the postoperative period: those who received pacemaker implantation and those who did not. In this study, pacemaker dependency was evaluated using pacing percentages obtained from device interrogation at the 1-, 6-, and 12-month follow-up visits, for which complete data were available for all patients who underwent PPM implantation. In pacemaker programming, the lower rate limit was set to 50 beats per minute. Since the standardized intrinsic rhythm test was not routinely performed, pacing percentages were used as an indirect

indicator of pacemaker dependency in this retrospective real-world cohort. A predefined percentage threshold was not used to define dependency; instead, the temporal course of pacing burden during the follow-up period was reported descriptively.

Robotic Surgical Technique

All procedures were performed using the da Vinci Si HD platform (Intuitive Surgical, Sunnyvale, CA, USA) within the institution's structured robotic cardiac surgery program. Patients were positioned according to the planned procedure. In selected cases, single-lung ventilation was used to improve surgical exposure. Port placement and the configuration of the camera and working arms were planned according to the institutional standardized approach. CO₂ insufflation was used when needed to optimize the visual field. Cardiopulmonary bypass was established via peripheral femoral cannulation. Myocardial protection and aortic cross-clamping were performed in accordance with institutional protocols. Additionally, temporary pacing wires were not frequently utilized for postoperative rhythm control in all patients. The indications and duration of usage were assessed according to the patient's postoperative rhythm condition, with decisions made individually for each case.

In this research, no artificial intelligence–assisted technologies were used, like Large Language Models, chatbots, or image generators.

Ethics Approval and Consent to Participate

The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee (decision date: October 17, 2022; decision number: 2022/295). Informed written consent was obtained from all the patients.

Statistical Analysis

The data was analyzed using the SPSS 26 statistical analysis software (IBM Corp., Armonk, NY, USA). In the study, continuous variables were represented as mean±standard deviation or median (min-max), while categorical data were represented as counts and percentages (%). Before analyzing the intergroup comparison, a normality assessment was performed with the Shapiro–Wilk test. To compare continuous variables between groups, the independent samples *t*-test was used for normally distributed data, whereas the Mann–Whitney *U*-test was utilized for non-normally distributed data. The chi-square test was used to compare categorical variables. The threshold for statistical significance was established at $P < .05$. Additionally, variables associated with PPM implantation were evaluated using multiple logistic regression analysis. Given the limited number of PPM events, a simplified modeling approach was used to reduce the risk of overfitting. Results are presented as odds ratios (ORs) with 95% CIs.

RESULTS

The mean age of the 276 patients in the study was 53.5 ± 16.15 years, with 50.4% ($n=139$) being male. The majority of patients were aged between 41 and 60 (41.4%, $n=114$). Atrial fibrillation was the predominant comorbidity, observed in

HIGHLIGHTS

- The need for a permanent pacemaker (PPM) after minimally invasive robotic cardiac surgery is a significant complication.
- In this study, the postoperative PPM implantation rate was determined to be 5.4%.
- Prolonged cardiopulmonary bypass time and surgical procedures involving both mitral and tricuspid valves were associated with the need for a PPM.
- The findings may contribute to the prediction of high-risk patients and the improvement of perioperative monitoring and pacing strategies.

22.5% (n=62) of patients, and preoperative left ventricular ejection fraction was $59.08\% \pm 9.80\%$.

Among the cardiac surgeries performed, 23.6% of patients underwent septal defect surgery (ASD, n=63; VSD, n=3), 51.4% (n=142) underwent mitral valve surgery, 6.9% (n=19) underwent coronary bypass surgery, 12% (n=33) underwent mitral and tricuspid valve surgery, and 6.2% (n=17) underwent various other procedures. The mean cross-clamp duration for the patients was $109.94 (\pm 48.57)$ minutes, while the mean CPB time was $180.13 (\pm 76.12)$ minutes.

Permanent pacemakers were implanted in 5.4% (n=15) of patients after robotic cardiac surgery. Among patients who underwent PPM implantation, 2 (13.3%) received a single-chamber ventricular pacemaker, whereas 13 (86.7%) received a dual-chamber pacemaker. The most common indication was complete atrioventricular (AV) block, accounting for 80% (n=12) of cases. Other indications were identified as sick sinus syndrome, paroxysmal complete AV block, and AF with slow ventricular response (Figure 1). The mortality rate in-hospital attributable to surgical complications among all patients in the study was 3.6% (n=10), but no mortality was observed in patients who received PPMs. The average duration for PPM implantation was determined to be $9.40 (\pm 3.26)$ days after surgery.

Permanent pacemaker implantation was performed in 15 (5.4%) of the 276 patients included in the study. Patients who received PPM and those who did not showed comparable characteristics in terms of age, ejection fraction, preoperative PR and QRS durations, cross-clamp time, and the number of chronic diseases. However, the duration of CPB was significantly prolonged in the PPM group (210 minutes vs. 150 minutes; $P=.035$). Analysis by surgery type revealed a significant difference in the need for PPM ($P=.033$). The most significant need for PPM was noted in the mitral and tricuspid valve surgery cohort; while being at 12% of the total patient

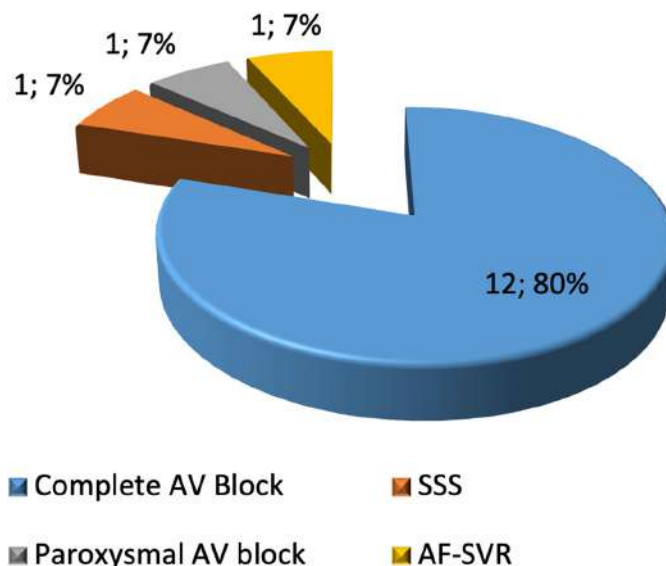


Figure 1. Distribution of clinical indications for permanent pacemaker implantation among patients who underwent robotic cardiac surgery. AF-SVR, atrial fibrillation with slow ventricular response, AV, atrioventricular; SSS, sick sinus syndrome.

population, this group accounted for 40% of all PPM procedures performed. Although the incidence of PPM is low in patients undergoing septal defect (ASD/VSD) and mitral valve surgeries, it was not observed in all patients who underwent coronary bypass surgery (Table 1). Additionally, in the multiple logistic regression model, CPB duration, assessed per 10-minute increase, was not independently associated with PPM implantation (OR=1.01, $P=.863$, 95% CI: 0.93-1.09). In contrast, combined mitral-tricuspid valve surgery was independently associated with PPM implantation compared with other procedures (OR=4.78, $P=.024$, 95% CI: 1.23-18.52).

Table 1. Patient Distribution Following Robotic Heart Surgery, Classified by the Presence or Absence of a Permanent Pacemaker Implantation

Variables	No PPM (n=261)		PPM implanted (n=15)		P
	Median	Min-Max	Median	Min-Max	
Age (Years)	46	14-77	44.50	20-67	.601
Ejection fraction (%)	60	30-83	60	27-69	.305
Preop. ECG PR duration (ms)	140	84-260	150	124-225	.398
Preop. ECG QRS duration (ms)	92	5-180	95	78-136	.124
Cross-clamp time (min)	96	0-238	102.50	0-200	.506
Cardiopulmonary bypass time (min)	150	0-465	210	93-317	.035
Number of chronic comorbidities	0	0-3	0	0-1	.489
Type of surgery	n	%	n	%	P
Septal defect surgery	62	23.8	3	20.0	.033
Mitral valve surgery	137	52.5	5	33.3	
Coronary bypass surgery	19	7.3	0	0.0	
Mitral and tricuspid valve surgery	27	10.3	6	40.0	
Others	16	6.1	1	6.7	
Total	261	100.0	15	100.0	

ECG, electrocardiogram; ms, milliseconds; PPM, permanent pacemaker; PR, PR interval; QRS, QRS complex.

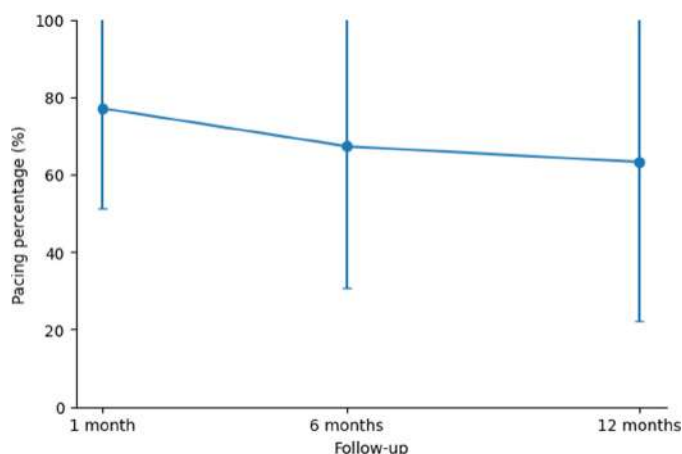


Figure 2. Pacing percentages during follow-up after PPM implantation. Data are presented as mean $\pm$ standard deviation.

Device interrogation data were available for all patients who underwent PPM implantation at the 1-, 6-, and 12-month follow-up visits. The mean ventricular pacing percentage was $77.05\% \pm 25.76$ (range, 15.0%-99.8%) at 1 month, $67.26\% \pm 36.53$ (range, 2.0%-99.7%) at 6 months, and $63.19\% \pm 41.03$ (range, 1.7%-99.8%) at 12 months (Figure 2).

DISCUSSION

Although minimally invasive cardiac surgery and traditional cardiac surgery present very similar preoperative risks, a notable side effect is the occurrence of conduction abnormalities.^{7,8} Research indicates that the incidence of PPM placement following heart surgery ranges from 0.8% to 34%.^{4,8,9} PPM rates are similarly reported in percutaneous heart valve procedures.¹⁰

Data in the literature regarding the need for PPM after robotic cardiac surgery are limited and are not consistently reported in many robotic series. However, in a meta-analysis evaluating concomitant AF surgery with robotic mitral surgery, the PPM rate was reported to be 3.7%.¹¹ In this study, the rate of PPM implantation was found to be 5.6% ($n=15$). Similar to the literature, the rate of PPMs was higher in patients undergoing valve surgery, and 62.8% ($n=11$) of those who received a PPM were patients with valve surgery. Specifically, the rate of PPM was statistically significantly higher in robotic mitral and tricuspid valve surgery ($n=6$) compared to other surgical types ($P=.033$). Among the reasons for this are the proximity of heart valves and their apparatus to the conduction system, which is thought to cause direct trauma, ischemic damage, and edema in the conduction system.

Studies have indicated an increase in the rate of PPM implantation, particularly among patients over 60 years of age.¹²⁻¹⁴ The investigation revealed no statistically significant difference in the average age ratios between the groups that received PPMs and those that did not. Likewise, whereas several studies have identified a significant incidence of PPM implantation post-surgery in patients with diabetes mellitus and coronary artery disease,¹⁴⁻¹⁶ the investigation revealed there was no difference.

Research indicates that prolonged CPB duration and aortic cross-clamp duration are risk factors for PPM implantation. In research conducted by Limongelli et al,¹⁵ the average CPB duration was 112 minutes in the group requiring a pacemaker and 91 minutes in the group not requiring a pacemaker. Elahi and colleagues similarly discovered that the duration of CPB was, on average, 100 minutes longer in patients who received PM implantation post-surgery compared to those who did not undergo PM implantation.¹⁷ The investigation corroborates existing literature, revealing that the duration of CPB was statistically significantly prolonged in individuals who underwent PPM implantation (210 minutes compared to 150 minutes; $P=.035$). Furthermore, the multiple logistic regression analysis revealed that although the duration of CPB did not retain its independent correlation with PPM implantation, combined mitral-tricuspid valve surgery was independently related to PPM implantation. This outcome is attributed to the adverse impacts on the conduction system, arising from the surgical complexity and prolonged duration. Prolonged CPB duration and restricted surgical visibility may elevate the risk of injury and ischemia-related injury to the conduction system.

Research indicated that an aortic cross-clamp duration >60 minutes was associated with an increased risk of PPM implantation.¹⁸ In this study, although the cross-clamp time was longer in the group that received PPM (102.5 minutes vs. 96 minutes), the difference between the 2 groups was not statistically significant.

In this study, the average waiting time for PPM implantation was found to be 9 days, but the optimal timing for PPM implantation after cardiac surgery is unclear due to various factors. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not provide a clear timeframe for PPM implantation and recommend individual decision-making. However, it is considered reasonable to perform the implantation within 3-5 days after surgery.¹⁹ The European Society of Cardiology recommends observing patients who develop complete heart block after surgery for up to 3-7 days before PPM implantation and implanting it if there is no improvement.²⁰ In this study, the extended implantation time may have facilitated the repair of the cardiac conduction system. This may have resulted in a reduction in PPM implantation. However, due to the retrospective design, it would be inappropriate to reach a definitive conclusion on this issue.

Based on the assessment for pacemaker dependency, the long-term (12-month) pacing rates in patients with PPMs in this study were determined to be 63%. This rate is consistent with the literature.^{5,21,22} A study by Raza and colleagues analyzed data from 6268 individuals who underwent cardiac surgery, including 141 patients who received PPM implants. The long-term pacemaker dependency of 90 patients was assessed for an average period of 4-5 years. The dependency on PM was determined to be 40% among the patients who were followed up. Subsequently, when patients with and without PM dependency were categorized into 2 groups, a prolonged CPB duration, a PR interval >200 milliseconds,

and a QRS duration >120 milliseconds were identified as correlating with long-term PM dependence.⁴ In this investigation, the evaluation of preoperative ECGs revealed that the PR and QRS intervals were prolonged in the group undergoing PM implantation; nevertheless, no statistically significant difference was observed between the 2 groups.

Steyers III CM and colleagues' retrospective investigation revealed that the long-term pacemaker dependency rates for patients, with an average follow-up duration of 6 to 72 months, ranged from 32% to 70%.⁵ When these findings and the study are assessed collectively, they suggest that conduction system problems post-surgery often become permanent due to several factors and that complete repair of the conduction pathways is unlikely in the long run. Consequently, it is evident that postoperative problems with communication require thorough assessment, and it is necessary to be ready for enduring rhythm abnormalities that may require PPM placement.

The study contributes to the literature by evaluating PPM implantation in the population undergoing minimally invasive robotic cardiac surgery, as well as the temporal trajectory of pacing burden during follow-up. In this respect, it adds real-world data specific to robotic surgery to the existing literature, which is mostly based on conventional or non-robotic minimally invasive surgical series. The findings suggest that cardiac conduction system-related outcomes should be evaluated more carefully, especially in patients undergoing combined mitral-tricuspid valve surgery. In patients experiencing postoperative conduction disturbances, the decision between early PPM implantation and careful rhythm monitoring to allow for possible spontaneous recovery should be meticulously evaluated on an individual basis. The findings underscore the importance of closer rhythm monitoring and tailored postoperative follow-up protocols, especially for patient populations at elevated risk for PPM implantation. However, the observational design of the study and the limited number of events restrict causal inference from the findings. Larger and multicenter studies will more clearly elucidate the determinants of PPM requirement and long-term device dependency in the robotic cardiac surgery population.

Study Limitations

This study has some limitations. The study is a single-center, retrospective analysis limited to patients who underwent robotic cardiac surgery. Consequently, the generalizability of the results is limited. Furthermore, the study lacks a comparable comparison group of patients who underwent non-robotic cardiac surgery. Consequently, the superiority or distinction of robotic cardiac surgery regarding PPM placement or pacemaker dependency in comparison to non-robotic surgery remains unassessable. The study is limited to comparing patients who received PPM implantation with those who did not, within the cohort who underwent robotic cardiac surgery.

In certain subgroups of robotic surgery, the limited number of PPM events diminishes the statistical accuracy of

comparisons based on procedure type. Therefore, subgroup findings related to the type of surgery should be evaluated in a descriptive manner rather than producing definitive conclusions. Especially, the inclusion of different procedures within the same cohort increases clinical heterogeneity.

Multiple surgeons have conducted robotic cardiac surgeries. The retrospective dataset lacks data on surgeons' experience and case volume parameters, preventing an assessment of the influence of surgeon expertise on PPM implantation. Despite the fact that the procedures are performed inside a structured robotic surgery program and using an institutionally standardized technical approach, the potential impact of technical variations among surgeons cannot be totally ignored.

Pacing burden was limited to 12-month follow-up. Beyond 1 year, longer-term device follow-up data could not be obtained in a comparable manner for all patients because some patients were lost to follow-up and others did not have standardized follow-up assessments. Owing to the heterogeneity of follow-up data, a reliable median follow-up duration for the entire cohort could not be calculated. Finally, quality of life, functional status, and patient-reported outcomes were not systematically assessed in this study. Therefore, the impact of PPM implantation on patients' daily life could not be directly analyzed.

CONCLUSION

In patients having minimally invasive robotic heart surgery, prolonged CPB duration and concurrent mitral-tricuspid valve surgeries are substantial risk factors for PPM implantation. These patients require vigilant rhythm monitoring during the postoperative phase and meticulous observation of conduction abnormalities. Additionally, the possibility of a sustained high pacing requirement during follow-up should be considered in patients who undergo PPM implantation. In these patients, the decision to implant a PPM should be tailored to each individual, and the process must be meticulously evaluated.

Ethics Committee Approval: This study was approved by the Ethics Committee of Gülhane Training and Research Hospital, University of Health Science (Approval No: 2022/295, Date: 17 October 2022).

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

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

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Impact of Balloon Post-Dilatation Strategy During Transcatheter Aortic Valve Implantation on the Cardiac Conduction System

ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) has become a well-established treatment for patients with severe aortic stenosis who are at intermediate or high surgical risk. Despite procedural advances, post-procedural conduction disturbances remain among the most common complications, particularly new-onset left bundle branch block (LBBB). This study aimed to investigate the impact of balloon pre- and post-dilatation on the cardiac conduction system during TAVI.

Method: A retrospective analysis was conducted on 447 consecutive patients who underwent successful TAVI between June 2021 and June 2025. After excluding patients with baseline bundle branch block or permanent pacemaker rhythm, 282 patients were included. Standard 12-lead electrocardiograms were evaluated before and after TAVI. Post-procedural QRS prolongation was defined as QRS >120 ms, and logistic regression analysis was performed to identify predictors.

Result: The mean age was 76.5 ± 6.9 years, and 63.8% of patients were female. Larger prosthesis diameter (OR=1.173, 95% CI 1.082-1.271; $P < .001$) and post-dilatation (OR=2.147, 95% CI 1.235-3.733; $P = .007$) were independently associated with QRS prolongation. Post-dilatation specifically correlated with new-onset LBBB but not with right bundle branch block (RBBB), intraventricular conduction delay, or high-grade atrioventricular (AV) block. No significant predictors were identified for permanent pacemaker implantation.

Conclusion: Balloon post-dilatation during TAVI is an independent risk factor for the development of new-onset LBBB. Patients with pre-existing conduction abnormalities, such as RBBB or first-degree AVr block, should be monitored closely after post-dilatation, as LBBB may adversely affect left ventricular function and long-term clinical outcomes.

Keywords: Conduction disturbances, LBBB, pacemaker, post-dilatation, TAVI

ORIGINAL INVESTIGATION

INTRODUCTION

Aortic stenosis is the most common valvular heart disease in developed countries, and its prevalence continues to increase with the aging population. Severe aortic stenosis is frequently symptomatic, and if left untreated, it is associated with significantly increased morbidity and mortality. Although surgical aortic valve replacement remains the standard treatment for patients with operable severe aortic stenosis, transcatheter aortic valve implantation (TAVI) has become the preferred therapeutic option for patients with moderate to high surgical risk.¹ According to the latest European Society of Cardiology Guidelines on Valvular Heart Disease, TAVI is recommended in patients over 70 years of age.¹

With the growing number of procedures and expanding operator experience worldwide, TAVI has evolved into a well-established and widely performed intervention. Nevertheless, several periprocedural and post-procedural complications remain of concern. Because of the close anatomical relationship between the aortic valve and the cardiac conduction system, TAVI may lead to conduction disturbances, including new-onset bundle branch blocks or high-grade atrioventricular (AV) block requiring permanent pacemaker implantation.

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The aim of the present study was to investigate the potential impact of balloon pre-dilatation of the native aortic valve and post-dilatation following prosthesis deployment on the cardiac conduction system during the TAVI procedure.

METHODS

Study Population

In this retrospective study, the records of 447 patients who underwent successful TAVI for symptomatic moderate-to-severe aortic stenosis at the center between June 2021 and June 2025 were reviewed. Patients with pre-procedural right bundle branch block (RBBB), left bundle branch block (LBBB), or permanent pacemaker rhythm, as well as those with incomplete medical records, were excluded. After applying these exclusion criteria, a total of 282 patients were included in the final analysis. The study population was evaluated based on demographic characteristics such as age, sex, and comorbidities, as well as the anatomical structure of the aortic valve, the type and size of the TAVI valve, the performance of pre-dilation and post-dilation, and echocardiographic data. The distribution of TAVI valve types was as follows: all balloon-expandable valves were Meril Myval ($n=107$, 100%), while the self-expandable valves included Abbott Navitor ($n=1$, 0.57%), Abbott Portico ($n=7$, 4%), Biosensors Allegra ($n=1$, 0.57%), Boston Acurate Neo2 ($n=47$, 26.86%), Medtronic Evolut R ($n=107$, 61.14%), and Medtronic Evolut Pro ($n=12$, 6.86%). Pre-dilation and post-dilation procedures were performed under rapid ventricular pacing (180 bpm) for a maximum duration of 5 seconds. Pre-dilation was performed in 42.1% ($n=45$) of patients receiving balloon-expandable valves and 73.1% ($n=128$) of those receiving self-expandable valves. Post-dilation was applied in 5.6% ($n=6$) of the balloon-expandable group and 44.0% ($n=77$) of the self-expandable group. Indications for the post-dilation process included achieving optimal intraprocedural hemodynamic response (low transvalvular gradient) and/or minimizing paravalvular aortic regurgitation.

Electrocardiographic Evaluation

Standard 12-lead electrocardiograms (ECGs) were obtained digitally using a GE Healthcare mitral annular calcification (MAC) 2000 system at a paper speed of 25 mm/s and an amplitude of 10 mm/mV. RBBB was defined by a QRS duration

>120 ms, an RSR' ("M-shaped") pattern in leads V1-V3, and a wide, slurred S wave in the lateral leads (I, aVL, V5-V6). The LBBB was defined according to conventional criteria as a QRS duration ≥ 120 ms, an R-wave peak delay >60 ms in leads V5-V6, and an rS or QS pattern in leads V1-V2. Patients with QRS duration >120 ms who did not meet the criteria for either RBBB or LBBB were categorized as having intraventricular conduction delay (IVCD).

Post-procedural ECGs obtained on or after the fifth day following TAVI were analyzed. The temporary pacemaker used during the TAVI procedure, which remains active for the first 24 hours, and the anesthetic agents administered during the procedure can potentially affect the cardiac conduction system. This methodology was employed to exclude these transient effects—including temporary blocks—and to ensure that the study focuses specifically on permanent conduction disturbances. Patients were classified according to the presence or absence of a post-procedural QRS duration >120 ms. In addition, the study population was stratified into 2 groups based on whether permanent pacemaker implantation was performed for high-grade AV block.

Echocardiographic Assessment

Echocardiographic data were retrieved from the digital database. Left ventricular ejection fraction (LVEF) was measured using the modified Simpson's biplane method, and aortic valve area (AVA) was calculated using the continuity equation.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were presented as percentages. Continuous data were compared using the independent samples *t*-test, and categorical variables were compared using the chi-square test. A 2-tailed *P* value <.05 was considered statistically significant. Factors associated with QRS widening and permanent pacemaker implantation were evaluated using binary logistic regression analysis. Results were presented as odds ratios (OR) with 95% CI. The term "n" was used to denote the number of patients in subgroups.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Clinical Trials Scientific and Ethics Committee of the center (protocol number: TABED 2-25-898). As this was a retrospective analysis of anonymized data, the requirement for informed consent was waived by the ethics committee.

RESULTS

The mean age of the study population was 76.54 ± 6.89 years, and 63.8% of the patients were female. There were no statistically significant differences between patients with and without ECG changes in terms of age, sex, body mass index (BMI), Agatston score, type of TAVI prosthesis, annulus diameter, annulus perimeter, prosthesis diameter to left ventricular outflow tract (LVOT) diameter ratio, balloon diameter on

HIGHLIGHTS

- Post-dilatation during transcatheter aortic valve implantation independently predicts new-onset left bundle branch block (LBBB).
- Larger prosthesis diameter and balloon post-dilatation were significantly associated with QRS prolongation and development of LBBB after the procedure.
- Careful monitoring is warranted in patients with pre-existing conduction abnormalities undergoing post-dilation.
- The additional mechanical stress and trauma from post-dilatation may increase conduction disturbances and impact long-term cardiac function.

post-dilatation, balloon diameter to valve size ratio, use of pre-dilatation, pre-procedural AVA, presence of atherosclerotic heart disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, cerebrovascular disease, pre-procedural mean aortic valve gradient, MAC or LVEF ($P > .05$) (Table 1).

When all types of conduction disturbances were considered, patients with post-procedural QRS prolongation had significantly larger implanted valve diameters compared with those without QRS prolongation ($P < .001$) (Table 1). In addition, the frequency of post-dilatation was significantly higher in the group with increased QRS duration ($P = .007$) (Table 1).

Among patients who required permanent pacemaker implantation due to high-grade AV block after TAVI, post-dilatation was more frequent in the pacemaker group

compared with those without pacemaker implantation; however, this difference did not reach statistical significance for any variable, including valve diameter (Table 1).

In regression analyses, both prosthesis diameter (OR = 1.173, 95% CI 1.082–1.271; $P < .001$) and post-dilatation (OR = 2.147, 95% CI 1.235–3.733; $P = .007$) were independently associated with post-procedural QRS prolongation (Table 2). No statistically significant association was found between any of the studied variables and permanent pacemaker implantation (Table 2).

When the patient population was evaluated according to the presence of ECG changes and post-dilatation status, a statistically significant difference was observed only for the development of new-onset LBBB (Table 3). There were no significant differences between groups regarding the occurrence of RBBB, IVCD, or high-grade AV block.

Table 1. Clinical Characteristics of the Study Population

	QRS Widening (–) n = 205	QRS Widening (+) n = 77	P	Pacemaker Implantation (–) n = 255	Pacemaker Implantation (+) n = 27	P
Age (Years)	76.46 ± 6.92	76.77 ± 6.84	.739	76.60 ± 6.89	76.04 ± 7.02	.689
Gender			.284			.113
Female (%)	127 (62.0)	53 (68.8)		159 (62.4)	21 (77.8)	
Male (%)	78 (38.0)	24 (31.2)		96 (37.6)	6 (22.2)	
BMI	30.26 ± 3.80	30.02 ± 3.66	.637	30.13 ± 3.73	30.79 ± 4.01	.383
Agatston score	2645.73 ± 1521.35	2755.66 ± 1568.69	.611	2668.31 ± 1510.48	2743.37 ± 1725.87	.810
TAVI valve type			.245			.753
BE (%)	82 (40.0)	25 (32.5)		96 (37.6)	11 (40.7)	
SE (%)	123 (60.0)	52 (67.5)		159 (62.4)	16 (59.3)	
Annulus diameter (mm)	23.57 ± 2.80	24.04 ± 3.50	.261	23.78 ± 2.79	23.02 ± 4.45	.212
Annulus perimeter (mm)	75.95 ± 8.87	78.55 ± 16.06	.100	76.78 ± 11.36	75.61 ± 11.04	.612
TAVI valve diameter (mm)	26.67 ± 2.96	28.46 ± 3.87	< .001	27.18 ± 3.35	27.02 ± 3.18	.812
Prosthesis diameter/LVOT diameter	1.31 ± 0.20	1.34 ± 0.21	.150	1.31 ± 0.20	1.37 ± 0.20	.154
Pre-dilatation (%)	125 (61.0)	48 (62.3)	.834	159 (62.4)	14 (51.9)	.287
Post-dilatation (%)	51 (22.9)	32 (41.6)	.006	74 (29.0)	9 (33.3)	.640
Balloon diameter on postdilatation	23.73 ± 2.10	24.59 ± 2.17	.074	24.16 ± 2.13	23.22 ± 2.28	.219
Balloon diameter / valve size	0.87 ± 0.14	0.84 ± 0.76	.330	0.86 ± 0.13	0.85 ± 0.09	.852
ASCVD (%)	100 (48.8)	31 (40.3)	.201	122 (47.8)	9 (33.3)	.151
Previous CABG (%)	29 (14.1)	8 (10.4)	.405	33 (12.9)	4 (14.8)	.784
HT (%)	197 (97.0)	72 (93.5)	.174	246 (96.5)	23 (92.0)	.272
DM (%)	80 (39.4)	33 (42.9)	.599	104 (40.8)	9 (36.0)	.642
KBH (%)	13 (6.4)	6 (7.8)	.680	18 (7.1)	1 (5.3)	.562
COPD (%)	43 (21.3)	20 (26.0)	.403	59 (23.2)	4 (16.0)	.410
CVE (%)	16 (7.9)	2 (2.6)	.107	17 (6.7)	1 (4.0)	.604
AF (%)	42 (20.5)	15 (19.5)	.851	52 (20.4)	5 (18.5)	.818
Mean gradient (mm Hg)	47.58 ± 12.04	49.01 ± 13.46	.394	48.01 ± 12.33	47.69 ± 13.68	.903
AVA (cm ²)	0.71 ± 0.17	0.70 ± 0.18	.861	0.70 ± 0.17	0.75 ± 0.15	.092
LVEF (%)	53.05 ± 11.40	53.27 ± 10.88	.882	53.07 ± 11.29	53.54 ± 10.89	.839
MAC	130 (66.7)	44 (58.7)	.219	157 (64.6)	17 (63.0)	.865

AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; AVA, aortic valve area; BE, balloon-expandable; BMI, body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CVE, cerebrovascular event; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification; SE, self-expandable; TAVI, transcatheter aortic valve implantation.

Table 2. Binary Logistic Regression Analysis of Study Population

	QRS Widening Group			Pacemaker Implantation Group		
	Odd's Ratio	CI (95%)	P	Odd's Ratio	CI (95%)	P
Age (Years)	1.007	0.969-1.046	.738	0.988	0.933-1.046	.688
Gender	1.356	0.776-2.371	.285	2.113	0.824-5.421	.120
BMI	.983	0.916-1.055	.636	1.048	.943-1.164	.382
Agatston score	1.000	1.000-1.000	.610	1.000	1.000-1.000	.810
TAVI valve type	1.387	0.798-2.410	.246	0.878	.391-1.971	.753
Annulus diameter	1.055	0.961-1.158	.260	0.921	.811-1.047	.211
Annulus perimeter	1.020	0.995-1.046	.124	0.990	0.951-1.030	.607
TAVI valve diameter	1.173	1.082-1.271	<.001	0.985	0.873-1.112	.811
Prosthesis diameter/LVOT diameter	2.614	0.704-9.712	.151	3.891	0.597-25.361	.155
Pre-dilatation	1.059	0.618-1.817	.834	0.650	0.293-1.442	.289
Post-dilatation	2.147	1.235-3.733	.007	1.223	0.526-2.846	.640
Balloon diameter on postdilatation	1.227	0.976-1.544	.080	0.825	0.608-1.120	.218
Balloon diameter / valve size	.157	0.003-7.751	.352	0.609	0.004-105.827	.851
ASCVD	.708	0.416-1.204	.202	0.545	0.236-1.259	.155
Previous CABG	.407	0.307-1.615	.407	1.170	0.381-3.596	.784
HT	.439	0.130-1.481	.184	0.421	0.086-2.065	.286
DM	1.153	0.677-1.963	.600	0.817	0.348-1.918	.642
KBH	1.235	0.452-3.374	.680	0.549	0.070-4.291	.567
COPD	1.297	0.704-2.390	.403	0.630	0.208-1.907	.413
CVE	.312	0.070-1.389	.126	0.583	0.074-4.577	.608
AF	.939	0.486-1.813	.851	0.887	0.321-2.455	.818
Mean gradient	1.009	0.988-1.030	.394	0.998	0.966-1.031	.903
AVA	.859	0.159-4.639	.860	8.461	0.695-103.069	.094
LVEF	1.002	0.978-1.026	.882	1.004	0.968-1.041	.838
MAC	.710	0.410-1.227	.220	0.931	408-2.123	.865

AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; AVA, aortic valve area; BE, balloon-expandable; BMI, body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CVE, cerebrovascular event; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification; SE, self-expandable; TAVI, transcatheter aortic valve implantation.

DISCUSSION

Aortic stenosis, the most common valvular heart disease in developed countries, should be treated once it becomes severe and symptomatic. The main treatment options are surgical aortic valve replacement and TAVI.^{1,2} In patients aged over 70 years or those at high surgical risk, TAVI has become the preferred intervention. As both the number of TAVI centers and the volume of procedures increase,

awareness, management of TAVI-related complications, and post-procedural follow-up have gained growing importance.

The most frequent complication following TAVI is cardiac conduction disturbance, particularly new-onset LBBB.³ The pathophysiological mechanisms underlying new conduction abnormalities, especially LBBB after TAVI, remain incompletely understood.⁴ Given the close anatomical relationship between the aortic valve and the AV node, His bundle, and bundle branches, post-procedural edema, inflammation, mechanical compression, or local hematoma may contribute to conduction disturbances. Post-dilatation may be performed after valve deployment to optimize hemodynamic function or minimize paravalvular leakage. However, this maneuver may impose additional mechanical trauma to the aortic annulus and surrounding tissues, potentially aggravating edema, inflammation, or compression effects on the conduction system. Only limited data are available regarding the impact of post-dilatation on conduction abnormalities. Therefore, this study aimed to evaluate the potential influence of post-dilatation on the cardiac conduction system.

Table 3. Study Analysis of Population According to Post-dilatation Process

	Post-dilatation (-)	Post-dilatation (+)	P
QRS Widening	45 (22.6%)	32 (38.6%)	0.006
LBBB	33 (16.6%)	26 (31.3%)	0.006
RBBB	5 (2.5%)	2 (2.4%)	0.960
IVCD	7 (3.5%)	4 (4.8%)	0.607
Pacemaker implantation	18 (9.0%)	9 (10.8%)	0.640

IVCD, intraventricular conduction delay; LBBB, left bundle branch block; RBBB, right bundle branch block.

New-onset LBBB after TAVI has been associated with high-grade AV block within 30 days and with sudden cardiac death.⁵ In a multicenter registry by Testa et al, the incidence of persistent LBBB at hospital discharge following TAVI was 27.3%.⁴ Interestingly, during the one-year follow-up, LBBB did not significantly affect mortality, pacemaker implantation, or heart failure-related hospitalization. Conversely, other studies have reported that longer post-procedural QRS duration is associated with higher mortality after TAVI.⁶ Similarly, patients discharged with new-onset LBBB exhibited higher mortality rates, consistent with the findings of Houthuizen et al.⁷⁸ Increased QRS duration and LBBB may contribute to ventricular dyssynchrony, impaired cardiac performance, and consequently, adverse clinical outcomes and mortality.⁹ The MADIT-CRT trial demonstrated that treatment of LBBB with cardiac resynchronization therapy (CRT) reduced mortality even in patients without overt cardiovascular disease, supporting the concept that LBBB may be an independent prognostic marker in TAVI patients as well.¹⁰

In this study, LBBB was present in 27.3% of patients at discharge. Analysis of these patients revealed that larger prosthesis diameter and post-dilatation were independent predictors of new-onset QRS prolongation. The use of larger valve sizes may increase mechanical stress on the aortic annulus and adjacent structures, potentially causing compression or trauma to the conduction pathways. Moreover, the additional mechanical stress induced by balloon post-dilatation may further exacerbate these effects, particularly on the left bundle branch. When patients were classified according to post-dilatation status, post-dilatation was significantly associated with LBBB development (Table 3), while no major influence was observed on the right bundle. Furthermore, when considering anatomical and procedural factors, it was observed that parameters such as annular diameter and circumference, the ratio of prosthesis size to LVOT diameter, and the ratio of the balloon diameter used during post-dilation to the prosthesis size had no significant impact on QRS widening—specifically LBBB—or the requirement for a permanent pacemaker (Table 2). The absence of significant pre-procedural cardiac conduction defects in the study population may explain why these factors remained secondary. Additionally, this situation may suggest that the presence of direct trauma (i.e., the application of post-dilation) is the primary driver of such effects (QRS widening or the requirement for a permanent pacemaker).

High-grade AV block requiring permanent pacemaker implantation is another well-recognized complication after TAVI.¹¹ Pre-existing RBBB, the use of self-expanding valves, and deep prosthesis implantation relative to the aortic annulus have been reported as independent predictors of pacemaker implantation.¹² In the study by Fujita et al,¹³ the rate of permanent pacemaker implantation after TAVI was approximately 16.6%, and the need for a pacemaker was associated with increased 1-year mortality. In the meta-analysis published by Mansuri et al,¹⁴ balloon-expandable valves showed lower rates of permanent pacemaker implantation compared to concurrent self-expanding valves. In

a study by Özderya et al¹⁵ focusing on balloon-expandable valves, aortic valve calcification, LVOT calcification, and non-coronary cusp calcification were not found to be significantly associated with the requirement for permanent pacemaker implantation. Regarding the Agatston score, the findings appear consistent with their results in terms of the relationship between aortic valve calcification and permanent pacemaker implantation. Additionally, that study identified membranous septum length, age, and aortic knob calcification as predictors of permanent pacemaker implantation need. Furthermore, Kilic et al¹⁶ reported a 30-day permanent pacemaker implantation rate of 11% following TAVI, which is highly comparable to the rate observed in the study (27/255; 10.6%). A similar rate of permanent pacemaker implantation was also observed in the study by Akyüz et al,¹⁷ which included balloon-expandable TAVI valves. However, data regarding the impact of mechanical trauma on the need for a pacemaker remained limited in these aforementioned studies. In the cohort, although the frequency of post-dilatation was higher in patients who required permanent pacemaker implantation, no statistically significant relationship was observed in regression analyses. Female sex was also more common among pacemaker recipients; however, this difference did not reach statistical significance. Interestingly, patients who required permanent pacemaker implantation had slightly larger pre-operative AVAs on echocardiography.

Study Limitations

This study has several limitations that should be acknowledged. First, it was a single-center, retrospective analysis, which may inherently introduce selection and information bias. Second, the study population was relatively modest in size, and some subgroup analyses may have been underpowered to detect smaller differences, particularly in patients requiring permanent pacemaker implantation. Third, although all ECGs were analyzed by experienced cardiologists, transient conduction disturbances that resolved before discharge may have been missed. Finally, the type and depth of valve implantation, as well as specific procedural maneuvers such as the degree of balloon inflation pressure during post-dilatation, were not quantitatively assessed, which may have limited further mechanistic interpretation.

CONCLUSION

Despite these limitations, the findings suggest that both larger prosthesis diameter and the performance of post-dilatation are independently associated with QRS prolongation following TAVI. Moreover, post-dilatation appears to have a specific influence on the development of new-onset LBBB. In patients with pre-existing conduction abnormalities such as RBBB or first-degree atrioventricular block, post-dilatation should be undertaken with caution, and closer post-procedural monitoring may be warranted. Furthermore, given the potential adverse effects of LBBB on left ventricular function, patients undergoing post-dilatation should be carefully followed for the development and persistence of LBBB as part of their long-term risk assessment. While no statistically significant predictors of

permanent pacemaker implantation were identified, the observed trends highlight the importance of careful procedural planning, particularly with respect to balloon sizing and the decision to perform post-dilatation. Further prospective, multicenter studies are warranted to validate these results and to clarify the clinical implications of conduction disturbances after TAVI.

Ethics Committee Approval: Ethical approval was obtained from the Local Clinical Trials Scientific and Ethics Committee of Health Sciences University Ankara Bilkent City Hospital with the protocol number (TABED 2-25-898 06/08/2025).

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A Compact Unified Model for Moderate-to-Severe Carotid Artery Stenosis Using Image Segmentation: A Multicenter Study

ABSTRACT

Background: This study aimed to evaluate the diagnostic performance of a new artificial intelligence model, the compact unified model (CU-Model), for moderate-to-severe carotid artery stenosis using digital subtraction angiography (DSA) images compared to clinical reference standards.

Methods: In this retrospective multicenter study, 156 patients with confirmed moderate-to-severe carotid artery stenosis were included. A pretrained CU-Model (trained on public non-clinical datasets for optical flow and stereo matching) was applied to raw DSA images without any fine-tuning on clinical data to avoid data leakage. The model served exclusively as a post-acquisition support tool: cardiologists applied it immediately after procedures for automated vessel segmentation and highlighting. Final North American Symptomatic Carotid Endarterectomy Trial (NASCET) measurements and interpretations were performed manually under expert supervision by 2 blinded researchers.

Results: The CU-Model identified left internal carotid artery (ICA) stenosis in 84 patients and right ICA stenosis in 72. It misclassified only 1 moderate left ICA stenosis case as normal, achieving 99.4% sensitivity (155/156) for any stenosis detection. For stenosis severity grading, strong agreement with DSA was observed (moderate: 57.68 ± 5.94 vs. 57.71 ± 6.19 , $r = 0.83$, $P < .001$, 95% CI: 0.76-0.88; severe: 86.96 ± 5.97 vs. 87.02 ± 6.18 , $r = 0.91$, $P < .001$, 95% CI: 0.85-0.95). Of 156 cases, 106 were moderate (50%-69%) and 50 severe ($\geq 70\%$), using NASCET-adapted thresholds accounting for measurement variability. Hypertension (77%), smoking, and syncope were common, with significant association in symptomatic patients ($P < .05$).

Conclusion: The CU-Model demonstrates strong concordance with DSA as a practical, post-procedure support tool for vessel segmentation. Pending larger validation studies, it shows promise for enhancing clinical workflow efficiency.

Keywords: Artificial intelligence, carotid artery stenosis, digital subtraction angiography, transformer

INTRODUCTION

Carotid artery disease due to atherosclerosis is considered one of the most common causes of mortality in Western society.¹ The most common cause of stroke is carotid artery stenosis due to atherosclerosis.² Catheter angiography is considered the gold standard for evaluating carotid artery stenosis.³ However, because it is an invasive method, other imaging methods have been sought. When carotid artery stenosis is detected by any method, such as color Doppler ultrasonography (US), another technique, such as computed tomography (CT) of the carotid arteries, magnetic resonance imaging, or catheter angiography, is generally considered before making a definitive decision for cardiovascular surgery or interventional procedures.^{4,5} B-mode US is routinely used in clinical practice for the diagnosis of carotid disease. Although the US has limitations for assessing the extent of carotid disease, it is a safe, portable, and cost-effective alternative to digital subtraction angiography (DSA). Duplex ultrasound is as accurate as angiography for quantifying arterial stenosis.^{6,7} In the clinical setting, cardiologists face challenges with the accuracy of imaging techniques, particularly in carotid artery stenosis, where catheterization images may be subject to greater intra- and inter-observer

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variation. Even if optimal images are obtained, the offline measurements may be misleading. This has led to the discovery of more effective methods for visualizing vascular calcification.^{8,9} Different artificial intelligence (AI) methods have been applied in cardiovascular imaging, including cardiac CT and nuclear imaging.^{9,10} Artificial intelligence can be trained dynamically and perform automatic edge reading and volume calculations. It may improve imaging quality, guide scanning, and assist in segmentation and analysis. AI can quickly and accurately interpret information, becoming a lifesaver in medical emergencies.¹¹ This includes improvements in multimodality imaging, leading to optimized procedures. This study, aimed to investigate the diagnostic value of a new AI technique, the transformer, considered state-of-the-art, on images obtained by standard carotid artery catheterization to highlight the diseased vessel in depth.

METHODS

The records of 2546 patients with ischemic heart disease and complaints of balance disorder, dizziness, or history of transient ischemic attacks (TIAs) or stroke referred for carotid artery evaluation between November 2016 and May 2025 were reviewed. Of the patients who underwent catheterization and angiography, 156 were confirmed to have moderate or severe carotid artery disease. Ethics committee approval was obtained (2025/07-32). The patients' common carotid arteries (CCA) and internal carotid arteries (ICAs) were examined by the same cardiologist during catheterization and post-processed with compact unified model (CU-Model) from the CDs.

Digital subtraction angiography images were extracted from CDs in DICOM format and uniformly preprocessed prior to CU-Model application: grayscale conversion, intensity normalization (0-1 range), and resizing to the model input resolution while preserving aspect ratio. No site-specific adjustments or augmentations were applied. To account for potential variability across the 3 participating centers, all acquisitions followed identical standardized protocols (selective CCA injections of Omnipaque 300; at least 2

extracranial and 2 intracranial projections). The same pre-trained CU-Model pipeline was used identically for every case, and 2 independent, blinded investigators (unaware of center origin or clinical details) evaluated both original DSA and processed images.

The CU-Model was pretrained exclusively on public non-clinical datasets for stereo matching and optical flow, ensuring no data leakage, as no clinical images from this study were used for training or fine-tuning.^{12,13} Of the cases, 118 involved male patients (76%) and 38 involved female patients (24%). Their ages ranged from 46 to 88 (average age 68 ± 12). Patient groups who had undergone carotid angiography were scanned in the 3 centers participating in the study. Patients with bilateral extracranial internal carotid occlusion were excluded as determined by conventional angiography. The CU-Model images and conventional angiograms of 156 patients (624 vessels) were independently reviewed by 2 blinded investigators. Importantly, the CU-Model was used solely for post-processing of existing DSA images and was never intended as a standalone diagnostic system. Differences in readings were resolved through the consensus of 2 readers during a joint review. The basic CU-Model operator can be summarized as follows: Conventional angiography was performed using selective CCA injections of Omnipaque 300. Digital subtraction angiography was performed with at least 2 projections of the extracranial carotid circulation and at least 2 of the intracranial circulation projections. The degree of stenosis was calculated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) formula: Degree of Stenosis (%) = $[1 - (\text{Minimal luminal diameter} / \text{Diameter of standard distal ICA})] \times 100$.¹⁴ Stenosis was classified as moderate (50%-69%) or severe ($\geq 70\%$), consistent with NASCET guidelines.¹⁴ To address potential discrepancies arising from noise or imprecise edge detection in the processed images, a conservative threshold-adjustment strategy that prioritizes patient safety was implemented. Specifically, borderline measurements falling in the narrow 69%-70% range were classified as severe stenosis when any uncertainty existed, thereby avoiding underestimation near the clinically decisive 70% threshold that frequently guides decisions regarding intervention (e.g., carotid endarterectomy). This approach recognizes that measurement risk resides primarily in the denominator of the NASCET ratio and deliberately errs on the side of caution in ambiguous cases, acknowledging recognized pitfalls while maintaining alignment with established standards. The absolute stenosis measurement is the ratio's numerator, i.e., the minimal luminal diameter, whereas the measurement risk is based on the denominator.

Statistical Analysis

Pearson correlation analysis was used to compare the CU-Model and DSA variables. Chi-square tests were used to assess the differences in proportions between symptomatic and asymptomatic patients with carotid artery disease. The Bland-Altman (BAT) test (BAT plot) was used to analyze the provided data (interpreted as CU-Model vs. DSA) because it is a well-established statistical method specifically designed to assess agreement between 2 measurement methods or observers. Correlation coefficient were also used to

HIGHLIGHTS

- The compact unified model (CU-Model) showed highly significant correlation with digital subtraction angiography (DSA) for assessing moderate ($r=0.83$, $P < .001$, 95% CI: 0.76-0.88) and severe ($r=0.91$, $P < .001$, 95% CI: 0.85-0.95) carotid stenosis in 156 patients.
- Compact unified model accurately detected stenosis in 84 left and 72 right internal carotid arteries, with only 1 misinterpretation of moderate stenosis as normal.
- Hypertension (77%), smoking, and syncope were significant risk factors in symptomatic carotid artery disease ($P < .05$).
- The transformer-based CU-Model enables robust segmentation and highlighting in carotid images.
- Compact unified model is a practical AI method comparable to DSA for stenosis evaluation.

Table 1. Baseline Characteristics of Study Population

Characteristic	Value	Symptomatic	Asymptomatic	P
Sample size	156	82	74	
Male (%)	118 (75.6)	52 (63)	48 (66)	>.05
Age years (Mean ± SD)	68 ± 12	67 ± 11.8	69 ± 12.3	>.05
Obesity (%)	87 (55.7)	48 (58)	39 (52)	>.05
Hypertension (%)	121 (77)	71 (86)	50 (67)	<.05
Diabetes mellitus (%)	42 (26)	22 (26)	20 (27)	>.05
Hypercholesterolemia (%)	89 (57.5)	48 (58)	41 (55)	>.05
Smokers (%)	104 (66)	68 (82)	36 (48)	<.05
Sencopy (%)	23 (14.7)	23 (28)	—	<.05
Presence of left ICA (%)	84 (53.8)	44 (53)	40 (54)	>.05
Presence of right ICA (%)	72 (46.1)	39 (47)	33 (44)	>.05

ICA, internal carotid artery; SD, standard deviation.

evaluate intra- and inter-observer variability. Intra-observer variability was defined as the variation between measurements obtained by the same observer at different times on the same carotid artery using the same imaging technique. Inter-observer variability was defined as the variation between results obtained by 2 observers on the same carotid artery using the same imaging technique. A correlation coefficient with 95% CIs was used as the estimate of statistics for the following outcomes: intra- and inter-observer reproducibility and inter-method agreement (CU-Model vs. DSA). The significance of each correlation coefficient was tested using the Student *t*-test model $t = r / \sqrt{[(1 - r^2)/(n - 2)]}$ for the hypotheses $H_0: \rho = 0$ and $H_1: \rho \neq 0$ (where ρ is the population correlation parameter). *P* values are reported as $P < .001$ (highly significant correlation). When applicable, Fisher *z*-transformation ($Z_r = 1/2 \ln[(1 + r)/(1 - r)]$) was used for normalization in Table 1.

Bland–Altman statistical analysis was used to assess the bias in readers' agreement. Statistical analyses were carried

out using PASW Statistics.¹⁵ Statistical significance was set at the conventional *P* level of <.05.

Compact Unified Model Methodology

The CU-Model was pretrained exclusively on publicly available non-clinical benchmark datasets, specifically Sintel (for optical flow estimation) and KITTI (for stereo matching), and then applied directly, without any subsequent task-specific fine-tuning on clinical data, to DSA sequences for the dual purposes of vessel segmentation and image registration (Figure 1).^{12,13} Although this pretraining introduces a potential domain shift from natural-scene imagery to clinical DSA sequences, the underlying tasks of optical flow and stereo matching share fundamental computational demands with vascular analysis—such as estimating motion, handling occlusions, and discriminating low-contrast boundaries. These transferable representations enable the transformer architecture to generalize effectively to vessel segmentation and registration in DSA, as evidenced by the strong observed concordance with reference angiograms. No clinical images

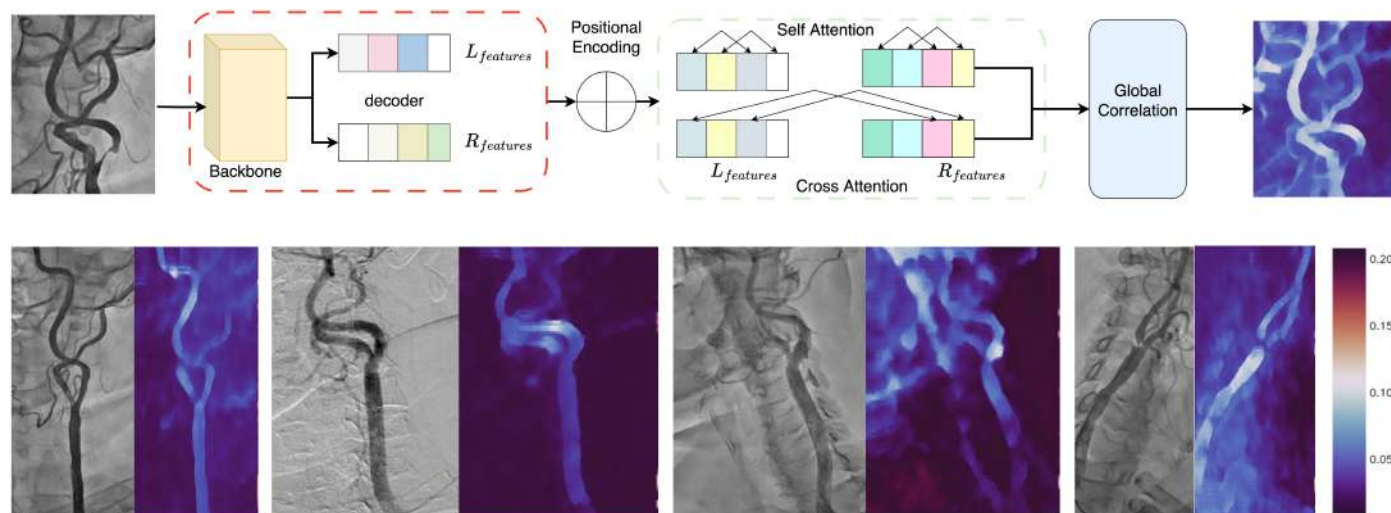


Figure 1. Overview of the model. The input image is given as input to the backbone. The backbone extracts discriminative features and stores them as left features ($L_{features}$) and right features ($R_{features}$). Positional encoding is added to both features to preserve spatial information. Positional features are processed via self- and cross-attention to capture relationships and dependencies. Finally, global correlation is applied to capture the long-range dependencies. The output is the segmented image.

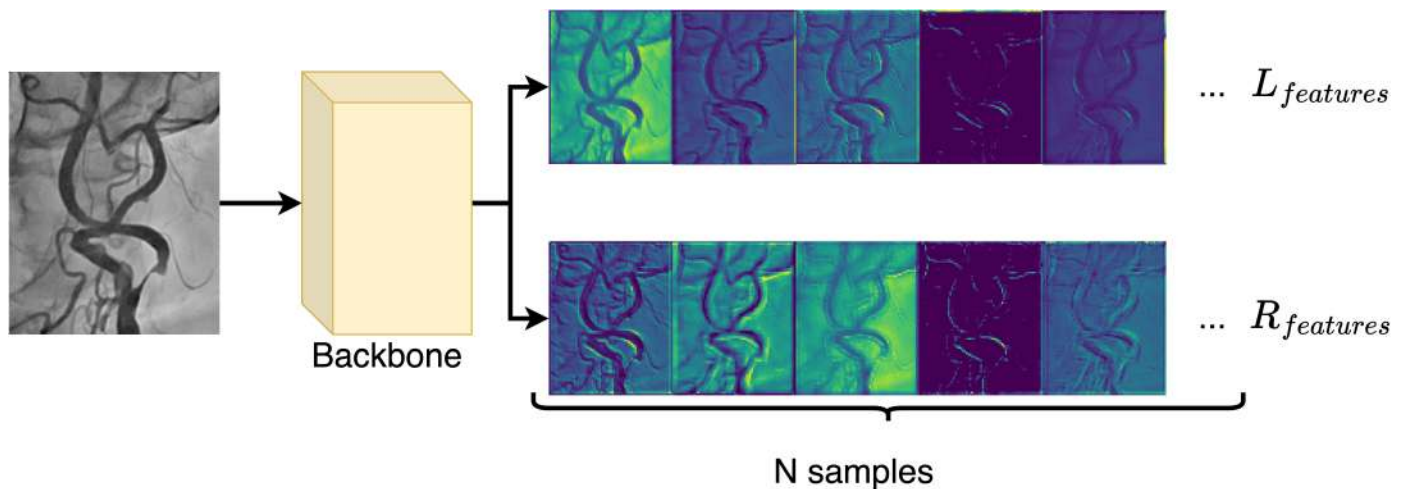


Figure 2. Backbone is responsible for creating hierarchical feature extraction. Starting from a single sample, it generates multiple diverse versions that vary in texture, color, and resolution. This process enables the model to learn and generalize effectively from the augmented samples. Even if the input image contains artifacts, they do not significantly affect the outcome.

from this study were used for training or fine-tuning, thereby ensuring complete absence of data leakage and positioning the model strictly as a post-acquisition support tool. The resulting segmentations exhibit markedly crisper delineation of vascular contours, thereby enabling dependable quantification of stenosis severity in accordance with NASCET methodology.¹⁴⁻¹⁸ The overall architecture comprises 3 purposefully integrated modules, each contributing to the practical clinical evaluation of carotid artery stenosis:

Backbone

The backbone generates multi-scale hierarchical representations of vascular anatomy. These representations capture the relational geometry among carotid artery branches and enhance boundary discrimination, which is critical for achieving the exacting precision demanded by NASCET stenosis grading (Figure 2).¹⁹

Positional Encoding

This component translates the inferred vascular hierarchy into explicit relative spatial coordinates across the DSA

image series. Consequently, focal narrowings within individual carotid segments can be precisely localized and distinguished (Figure 3).²⁰

Attention Mechanism and Global Correlation

Through its attention operations, the model selectively emphasizes pertinent vascular elements while effectively attenuating irrelevant background signals and low-contrast noise; simultaneously, it facilitates robust alignment across frames for registration. These capabilities underpin consistent percentage-stenosis assessments, even under difficult imaging conditions (correlation coefficients $r=0.83-0.91$, $P<.001$; Table 2).²¹⁻²⁸

RESULTS

A total of 156 patients were included to assess the severity of carotid artery stenosis as measured by the CU-Model (the proposed AI model) compared to angiographically determined carotid artery stenosis. Digital subtraction angiography detected 156 carotid artery stenoses (84 left ICA, 72

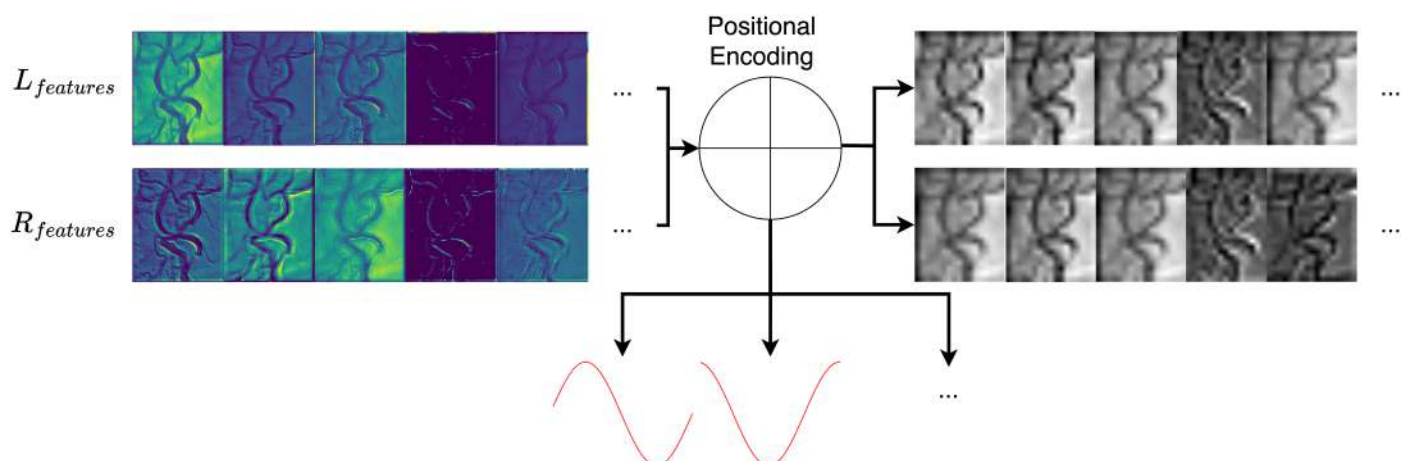


Figure 3. The effect of adding sinusoidal positions to the backbone outputs. As observed, the output images became smoother and more visually discernible. Different types of sinusoidal waves were applied to each output, and the resulting diverse, smooth samples were used for training.

Table 2. CU-Model and DSA Results

	CU-Model	DSA	<i>r</i>
Moderate stenosis (n=106)	57.68 ± 5.94	57.71 ± 6.19	0.83
Severe stenosis (n=50)	86.96 ± 5.97	87.02 ± 6.18	0.91

CU-Model, compact unified model; DSA, digital subtraction angiography.

right ICA). The demographic characteristics of the study population are summarized in Table 1. The mean age at the time of the scan was 68 ± 12 years. Of the participants, 118 (75.6%) participants were male, and 84 patients were diagnosed with left ICA stenosis. Severe carotid artery stenosis was detected in all patients with a history of syncope. The Pearson chi-square test showed that hypertension, smoking, and syncope were significant risk factors in patients with symptomatic carotid artery disease ($P < .05$). Table 2 shows the results of the relationship between the CU-Model and DSA. As shown in the Results section, the CU-Model demonstrated excellent concordance with DSA (detailed numerical values and BAT plots in Figures 6-7).

Table 3 presents the results of a compact, unified model for intra-observer variability in patients with moderate-to-severe carotid artery stenosis. Intra-observer variability between CU-Model-1 and CU-Model-2 in the assessment of the severity of carotid artery stenosis (57.46 ± 7.19 and 57.61 ± 6.76 for moderate, $r=0.86$, $P < .001$, 95% CI: 0.80-0.90; 86.96 ± 5.97 and 87.12 ± 4.33 for severe, $r=0.93$, $P < .001$, 95% CI: 0.88-0.96). The correlations were highly significant ($r=0.86$ and $r=0.93$, $P < .001$). Table 4 presents the results of a compact, unified model for inter-observer variability in patients with carotid artery stenosis. Inter-observer variability between CU-Model-1 and CU-Model-2 in the assessment of the severity of carotid artery stenosis (57.46 ± 7.23 and 57.93 ± 6.53 for moderate, $r=0.91$, $P < .001$, 95% CI: 0.87-0.94; 86.96 ± 5.97 , and 88.54 ± 6.46 for severe, $r=0.90$, $P < .001$, 95% CI: 0.83-0.94), respectively. The correlations were highly significant ($r=0.91$ and $r=0.90$, $P < .001$). The linear correlation coefficient for inter-observer variability in patients with moderate-to-severe or severe carotid artery stenosis is shown in Figure 4. The Pearson correlation coefficient regression line in patients with severe carotid stenosis is presented in Figure 5. Figure 6 illustrates the difference between CU-Model and DSA, as assessed by the BAT plot test, in patients with severe carotid artery disease. Based

Table 3. CU-Model Results for Intra-Observer Variability in Patients with Carotis Artery Stenosis

	CU-Model-1	CU-Model-2	<i>r</i>
Moderate stenosis (n=106)	57.46 ± 7.19	57.61 ± 6.76	0.86
Severe stenosis (n=50)	86.96 ± 4.37	87.12 ± 4.33	0.93

CU-Model, compact unified model; CU-Model-1 (%), compact unified model (reader 1); CU-Model-2 (%), compact unified model (reader 1 different time).

Table 4. CU-Model Results for Inter-Observer Variability in Patients with Carotis Artery Stenosis

	CU-Model-1	CU-Model-2	<i>r</i>
Moderate stenosis (n=106)	57.46 ± 7.23	57.93 ± 6.53	0.91
Severe stenosis (n=50)	84.41 ± 8.27	81.88 ± 7.92	0.89

CU-Model, compact unified model; CU-Model-1 (%), compact unified model (reader 1); CU-Model-2 (%), compact unified model (reader 1 different time).

on the BAT statistical analysis of the measurements for severe carotid artery stenosis, there was good agreement with no significant bias, making them sufficiently reliable for CU-Model comparisons in clinical practice. The minimal mean difference (0.08 as specified and narrow) 95% limits of agreement (−5.28% to 5.44%) indicate that differences are clinically acceptable for stenosis percentages in the 70%-99% range. Figure 7 illustrates the differences between the CU-Model and DSA in patients with moderate carotid artery stenosis (BAT plot test). These results demonstrate strong agreement between the CU-Model and DSA. The model may therefore serve as a reliable post-processing aid in clinical practice when used together with expert cardiologist review, although larger prospective studies are needed before widespread adoption.

DISCUSSION

Imaging plays a critical role in evaluating carotid artery calcification and stenosis, with trade-offs between invasive gold standards like catheter angiography and non-invasive alternatives. Building on this, recent advancements have increasingly favored non-invasive modalities, with a notable shift from focusing solely on stenosis severity to assessing plaque

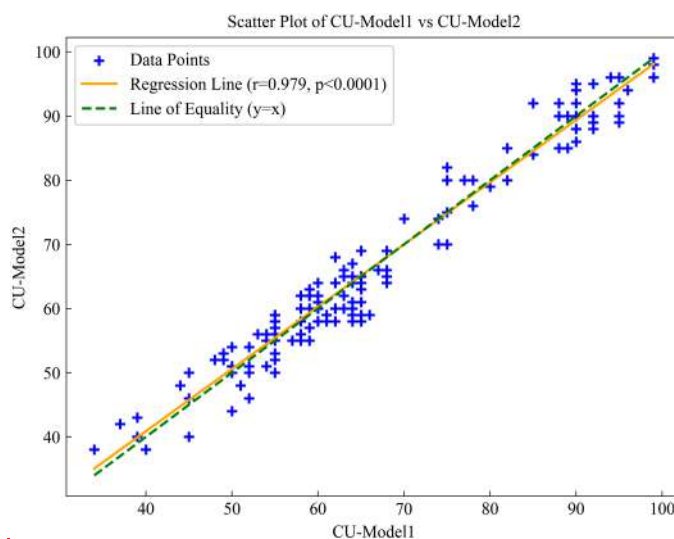


Figure 4. Linear correlation coefficient for inter-observer variability in patients with moderate-to-severe carotid artery stenosis (CU-Model-1 vs. CU-Model-2), where CU-Model-1 is compact unified model (reader 1) and CU-Model-2 is compact unified model (reader 2). CU-Model, compact unified model.

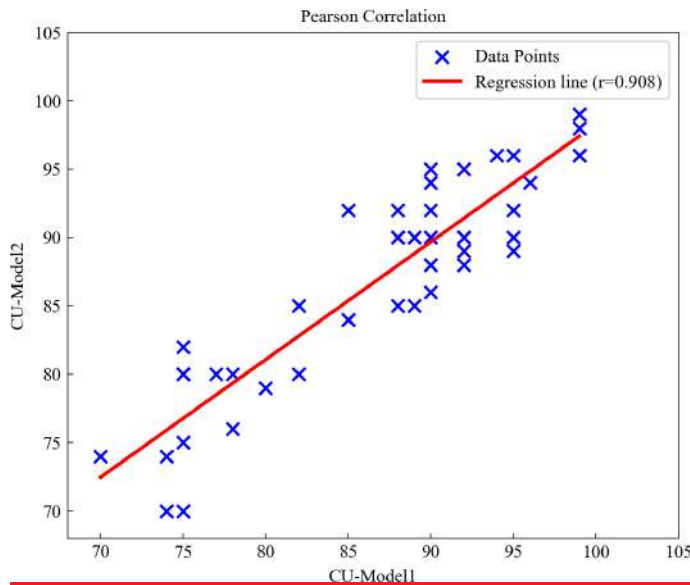


Figure 5. Pearson correlation coefficient regression line in patients with severe carotid stenosis. CU-Model, compact unified model.

composition and vulnerability, which better predict stroke risk. For instance, guidelines recommend incorporating high-rich necrotic cores and neovascularization into risk stratification, even for plaques with moderate stenosis, and recent perspectives suggest rethinking endarterectomy in near-occlusive severe cases to optimize outcomes.²⁹ Hypertension was the most common risk factor (77%, $P = .009$), with symptomatic patients more likely to have it than asymptomatic

ones.³⁰⁻³² Smoking was also significantly associated with symptomatic disease, while syncope occurred in 14.7% of cases, all with severe stenosis ($P < .05$). No significant associations were found for diabetes (26% prevalence) or obesity, possibly due to controlled cases or small sample size. Larger studies are needed to confirm these clinical risk factors. Cigarette smoke promotes plaque build-up via oxidative stress and inflammation.³⁴ Syncope was present in 14.7% of patients with carotid artery stenosis, and severe carotid artery stenosis was detected in all patients. No association was found between ICA stenosis and cerebrovascular symptoms ($P > .05$). Hypercholesterolemia is a significant risk factor for carotid artery disease. In this study, although hypercholesterolemia was more prevalent in patients with cerebrovascular symptoms (58% vs. 55%), the difference was not significant. Inter- and intra-observer variability showed excellent agreement (Tables 3-4, Figure 6-7). From a clinical perspective, the narrow limits of agreement coupled with minimal bias underscore a dependable consistency between the CU-Model and DSA. The strong correlations ($r \geq 0.83$) and excellent intraclass correlation coefficient ($ICC = 0.90$) indicate that the CU-Model may serve as a reliable adjunct tool for stenosis evaluation when integrated into the post-processing workflow alongside expert cardiologist review. While differences remain unlikely to substantially alter treatment choices in most cases—such as recommending carotid endarterectomy for $\geq 70\%$ stenosis or medical management for moderate stenosis—the model should not be regarded as a fully interchangeable replacement for conventional DSA. Rather, it shows promise as a complementary aid that can enhance workflow efficiency pending validation in larger, prospective studies.

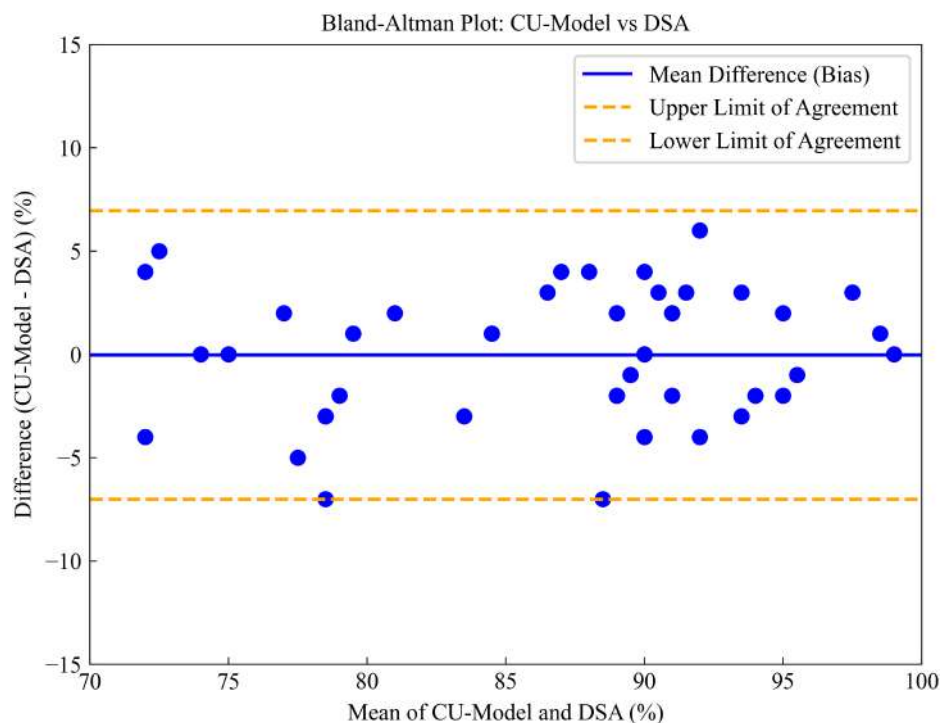


Figure 6. Difference between CU-Model and DSA (BAT plot test) in patients with severe carotid artery stenosis. BAT, Bland-Altman; CU-Model, compact unified model; DSA, digital subtraction angiography.

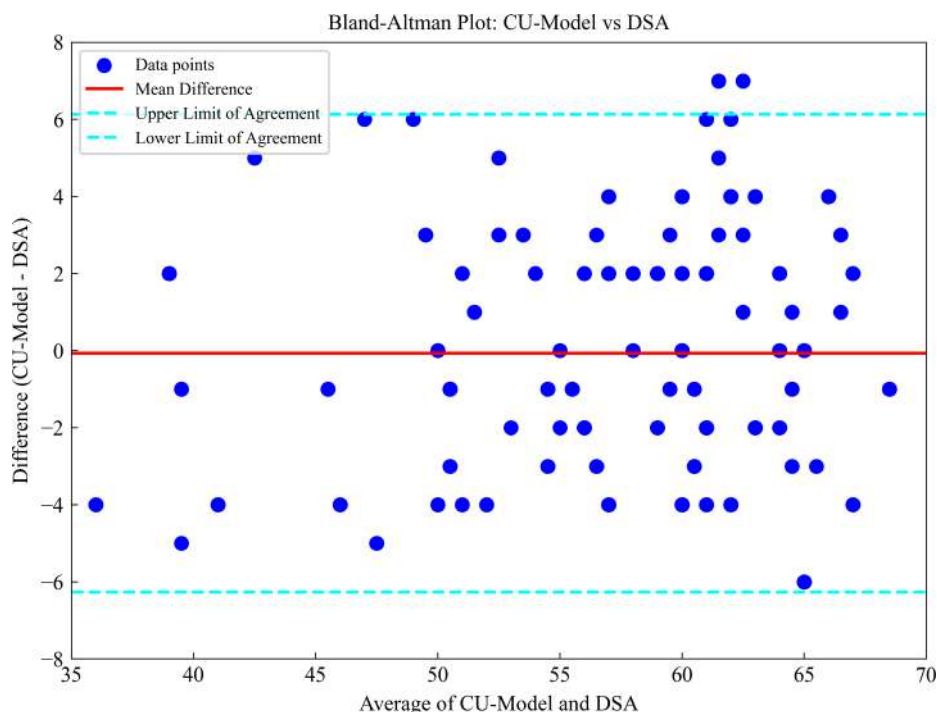


Figure 7. Difference between CU-Model and DSA (BAT plot test) in patients with moderate carotid artery stenosis. BAT, Bland–Altman; CU-Model, compact unified model; DSA, digital subtraction angiography.

Figure 6 shows clinically, the narrow 95% limits of agreement (–5.28% to 5.44%) and minimal bias (0.08) indicate good concordance, suggesting that CU-Model measurements are sufficiently interchangeable with DSA for informing interventions in severe stenosis ($\geq 70\%$), such as endarterectomy in symptomatic patients, without substantial risk of altering clinical decisions. Figure 7 illustrates the disparities between the CU-Model and DSA among patients exhibiting moderate carotid artery stenosis, as assessed via a BAT plot in this pilot study. The analysis indicates a modest negative bias in mean differences (–0.07), suggesting that the CU-Model generally yields marginally lower measurements compared to DSA. With 95% limits of agreement spanning –6.24 to 6.10 (calculated as mean $\pm 1.96 \times \text{SD}$), the majority of variations are expected to reside within this interval under conditions of strong methodological concordance, and the visualization overall points to a solid level of alignment between the approaches. From a clinical perspective, this narrow interval (–6.24% to 6.10%) coupled with the minimal bias underscores a dependable consistency, indicating that the CU-Model may facilitate precise risk evaluation for moderate stenosis cases (50%–69%) and thereby assist in conservative treatment strategies while obviating the need for supplementary diagnostic scans. A more comprehensive statistical evaluation of the agreement between the 2 methods (CU-Model and DSA) was performed using the complete dataset of 106 paired measurements. A 95% limit of agreement (LoA) indicates that 95% of differences fall within about ± 6.2 units, suggesting reasonable agreement for most clinical or practical purposes, assuming the measurements are in comparable units. The systematic bias for the paired t -test is not significantly different ($t = -0.21$, $P = .83$) from zero ($P \geq .05$), so there is no evidence of systematic bias. If differences increased

with measurement magnitude, differences were regressed on averages using a linear model to account for proportionality bias (slope = 0.05, $P = .28$, $R^2 = 0.01$). The slope is not significant ($P \geq .05$), and R^2 is very low, indicating no trend differences are consistent across the range of averages (no need for adjustments like log transformation). Intraclass correlation coefficient was 0.90 (using a 2-way mixed effects model for absolute agreement). This is considered excellent agreement (typically, ICC ≥ 0.75 is good; ≥ 0.90 is excellent). Confirming that the methods are highly concordant. Since there is no significant proportionality bias, no adjustments to the LoA are required. Clinically, these strong correlations ($r \geq 0.83$) and excellent ICC of 0.90, combined with narrow BAT limits of agreement, mean the CU-Model and DSA measurements are interchangeable for decision-making: differences are unlikely to alter treatment choices such as recommending carotid endarterectomy ($\geq 70\%$ threshold) or opting for medical management in moderate stenosis cases.

Digital subtraction angiography remains the go-to method for accurate diagnosis. Still, it's not without its drawbacks—like risks from ionizing radiation, problems with contrast materials, and neurological complications that occur in 0.1%–4.9% of procedures.^{31–36} That's why they are often preferred as non-invasive options, such as ultrasound. However, these can yield variable results because they focus on the reduction in cross-sectional area rather than the vessel's actual diameter. Additionally, when using NASCET guidelines manually, there's a tendency to overestimate the degree of stenosis, which might result in unnecessary treatments. In clinical practice, one of the most challenging decisions regarding carotid artery revascularization is whether to treat a carotid artery near occlusion. In addition to periprocedural

complications, TIA, ipsilateral ischemic stroke, retinal TIA, and other postoperative neurologic complications have been reported in previous studies in these patients.²⁸ Therefore, it is clear that new models are needed to identify calcified, ulcerated, and potentially occlusive carotid lesions at risk. AI enables opportunistic screening via routine dental imaging. A meta-analysis of AI studies on panoramic radiographs and cone-beam CT demonstrated good sensitivity and specificity for detecting carotid calcifications.

In contrast to the numerous publications on the automatic detection of aneurysms in DSA images and thrombus detection in CT images, research results on software-based analysis of DSA sequences from patients with carotid artery stenosis have been published sparingly, mostly in recent years.³⁸ Though perspectives on large language models suggest they could transform such diagnostic support.³⁹ Threshold-based algorithms help differentiate vascular wall calcification from contrast in the lumen, producing images similar to those in angiography. However, variability in threshold selection can affect vessel diameter measurements, underscoring the need for operator expertise, as in US.

The AI-based measurement relies on the quality and diversity of the dataset; however, limited external validation in many studies reduces the generalizability of the findings. Challenges with heavy calcification (blooming artifacts), irregular plaques, or low contrast can lead to over- or underestimation of the lumen. Automated measurement tools may differ from manual methods in handling perpendicular planes or minimal caliber (area-based vs. diameter-based), which can sometimes result in underestimation of severe stenosis. The transformer model may miss nuances of near-occlusion or tandem lesions without hybrid clinical input. Studies show high accuracy (e.g., 88%-94% for categories), but with variability across thresholds (better for <50% or 75%) and modalities. The CU-Model offers various post-processing techniques for 3D imaging of the carotid arteries. The model is an effective technique for distinguishing true vascular wall calcification from contrast material in the lumen. The analysis also showed excellent inter-method agreement in the evaluation of carotid disease. Findings have been reported in good to excellent agreement with the CU-Model and angiography.^{38,39}

In routine clinical settings, the CU-Model could serve as an adjunct tool during the post-processing phase of DSA imaging, applied after initial image acquisition but before final interpretation. This hybrid workflow (raw DSA input to CU-Model enhancement to cardiologist review) ensures the model remains an adjunct rather than a replacement for clinical judgment. Trained cardiologists would input raw angiographic data into the model, which then automates vessel segmentation and stenosis quantification, potentially reducing analysis time in the study. This integration might occur in hybrid workflows, where the model's outputs are reviewed alongside manual assessments to inform decisions on interventions like endarterectomy, particularly in high-volume centers handling symptomatic cases. Together,

these findings suggest that the CU-Model is a reliable and reproducible imaging model for evaluating carotid disease and shows preliminary promise in this retrospective cohort of 156 patients; larger prospective, multicenter studies with external validation are required before broader clinical implementation.¹⁶

By drawing on data from 3 independent medical centers involving 156 patients, the study partially mitigates potential institutional bias through exposure to diverse clinical protocols, equipment variations, and patient demographics, thereby enhancing preliminary generalizability within the studied Turkish population. Nonetheless, these correlations represent promising initial evidence, though limited by the study's scale and design (see Limitations below). Validation in larger prospective cohorts is essential. The AI tools like CU-Model reduce variability but depend on dataset quality. The findings show excellent inter-method agreement, supporting its use pending larger validation.³⁷⁻³⁸

Limitations of the Study

This study's primary limitations include its small sample size (n=156), retrospective cohort design, and lack of external validation, which collectively limit its generalizability. A small study population may be a limitation. In this retrospective, cohort-designed study, the inclusion of severe stenosis cases undergoing atherectomy with bypass surgery introduces potential selection bias, as the cohort may overrepresent advanced disease from referral centers. While multicenter data from 3 sites partially mitigates institutional bias by incorporating diverse protocols and demographics, it does not fully address confounding factors inherent to retrospective data, such as recall bias or incomplete records. Moreover, the absence of prospective follow-up or external validation on independent cohorts restricts the applicability of the findings beyond this sample. Future high-quality research, including larger prospective multisite trials (e.g., n > 500) with blinded external validation datasets, is essential to confirm reliability, reproducibility, and broader generalizability. Further high-quality research is required to assess the reliability and reproducibility of the CU-Model for evaluating carotid disease. The NASCET adaptations may reduce comparability with strict standards, potentially shifting ~5% of cases near 70%. For instance, this approach could lead to a slight shift in classifications near the 70% cutoff, potentially reassigning 5% of cases from severe to moderate in real-world scenarios, as suggested by the BAT limits of agreement. Clinically, this might favor more conservative management strategies, such as opting for medical therapy over surgery in ambiguous cases, but it could also introduce inconsistencies when pooling data across trials. To enhance comparability, future research should align on standardized thresholds or report dual classifications, in future extensions.

CONCLUSION

A new AI architecture pretrained on public nonclinical datasets for stereo and optical flow tasks was proposed. The CU-Model could fit smoothly into cardiology practices, applied by cardiologists right after DSA capture to support stenosis assessment and cut down on interpretation time,

acting as a helpful aid under expert supervision. A growing body of research employs AI methodologies to assist in identifying carotid artery stenosis and complement physician diagnosis. While the results are encouraging, this retrospective study with only 156 patients demonstrates preliminary promise. Larger prospective, multicenter validation studies with external datasets are essential before routine clinical adoption.

Ethics Committee Approval: This study was approved by the Ethics Committee of Health Sciences University İzmir Tepecik Training and Research Hospital, Ethics Committee Decision Date: September 11, 2025; Ethics Committee Decision Number: 2025/07-32.

Informed Consent: Informed consent was not obtained from the patients as this was a retrospective study using existing medical records. The study was approved by the Ethics Committee (approval number: 2025/07-32), which waived the need for informed consent.

Peer-Review: Externally peer-reviewed.

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

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Predictors of All-Cause Mortality in Patients with Classical Low-Flow Low-Gradient Aortic Stenosis Undergoing Transcatheter Aortic Valve Implantation

ABSTRACT

Background: Classical low-flow low-gradient aortic stenosis (cLFLG AS) is associated with poor prognosis and adverse clinical outcomes despite transcatheter aortic valve implantation (TAVI). Identifying prognostic markers in this high-risk population may improve risk stratification and clinical management. This study aimed to investigate independent predictors of all-cause mortality in patients with cLFLG AS undergoing TAVI.

Methods: In this single-center retrospective study, 151 patients with cLFLG AS undergoing TAVI between January 2018 and December 2024 were included. Multivariable Cox proportional hazards regression analysis was performed to identify predictors of all-cause mortality. Two separate multivariable models incorporating tricuspid annular plane systolic excursion (TAPSE) and TAPSE/systolic pulmonary artery pressure (sPAP) ratio were constructed to evaluate the prognostic impact of right ventricular (RV) systolic function and RV–pulmonary vascular interaction. The prognostic performance of TAPSE was further assessed using receiver operating characteristic (ROC) and restricted cubic spline analyses.

Results: During a median follow-up of 26 (15–42) months, all-cause mortality occurred in 37 (25%) patients. In multivariable analysis, reduced TAPSE remained independently associated with all-cause mortality after adjustment for age and left ventricular ejection fraction (LVEF) (HR: 0.11, 95% CI: 0.04–0.30, $P < .001$). A lower TAPSE/sPAP ratio was also independently associated with mortality (HR: 0.08, 95% CI: 0.01–0.85, $P = .036$). Advanced age and reduced LVEF were independently associated with mortality in both models. Time-dependent ROC analysis demonstrated consistent discriminative performance of TAPSE over time.

Conclusion: Reduced TAPSE, advanced age, and reduced LVEF were independent predictors of all-cause mortality in patients with cLFLG AS undergoing TAVI.

Keywords: Low-flow low-gradient aortic stenosis, right ventricular dysfunction, transcatheter aortic valve implantation, tricuspid annular plane systolic excursion

INTRODUCTION

Classical low-flow low-gradient aortic stenosis (cLFLG AS) is a high-risk subset of patients with severe AS, affecting approximately 5%–10% of this population.^{1,2} It is characterized by depressed left ventricular (LV) systolic function, diminished stroke volume, and transvalvular flow, resulting in a low mean gradient despite severe AS. This hemodynamic profile has been associated with poor prognosis and adverse clinical outcomes.^{3,4}

Transcatheter aortic valve implantation (TAVI) has been established as an effective and preferred therapeutic option for elderly patients with severe AS.⁵ Although TAVI has been demonstrated to improve survival in patients with cLFLG AS, clinical outcomes remain suboptimal compared to other AS phenotypes.^{4,6,7} This suggests that factors beyond valvular stenosis, including impaired myocardial function and comorbidities, may play a pivotal role in predicting prognosis.

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In this context, identifying predictors of mortality in patients with cLFLG AS undergoing TAVI is crucial for optimal patient selection and management. Although several predictors of adverse outcomes after TAVI have been identified, patients with cLFLG AS represent a distinct high-risk subgroup with a complex low-flow hemodynamic profile, while data specifically focusing on prognostic markers in this phenotype remain relatively limited. Accordingly, this study sought to investigate independent predictors of all-cause mortality in patients with cLFLG AS undergoing TAVI.

METHODS

Study Design and Population

In this single-center study, 165 consecutive patients with cLFLG AS who underwent TAVI between January 2018 and December 2024 were retrospectively evaluated. Patients with true severe cLFLG AS according to the European Society of Cardiology (ESC) guidelines on valvular heart disease were included. Exclusion criteria were valve-in-valve interventions and insufficient preprocedural data. Specifically, 3 patients who underwent valve-in-valve procedures and 11 patients with incomplete preprocedural echocardiographic or computed tomography (CT) data that precluded confirmation of cLFLG AS were excluded. The final study population consisted of 151 patients. Demographic and clinical characteristics, preprocedural, procedural, and follow-up data were obtained from the hospital database. The local institutional review board approved the study protocol, and the study was conducted in accordance with the Declaration of Helsinki.

Echocardiography

Cardiac chamber dimensions, LV and right ventricular (RV) systolic function and the severity of valvular disease were assessed. In accordance with ESC guidelines for the management of valvular heart disease, cLFLG AS was identified as LV ejection fraction (LVEF) <50%, mean gradient <40 mm Hg, aortic valve area (AVA) $\leq 1 \text{ cm}^2$ and stroke volume index (SVi) $\leq 35 \text{ mL/m}^2$.⁵ While AVA was calculated using the continuity equation, SVi was derived from the cross-sectional area of

the LV outflow tract (LVOT), LVOT velocity-time integral and body surface area. In patients with atrial fibrillation (AF), pressure gradients were averaged over 5 consecutive beats.⁸ Tricuspid annular plane systolic excursion (TAPSE) was measured by placing M-mode cursor along the lateral tricuspid annulus.⁹ Although TAPSE values are presented in centimeters, TAPSE was converted to millimeters for calculation of the TAPSE/systolic pulmonary artery pressure (sPAP) ratio; therefore, the ratio is expressed as mm/mmHg.

Dobutamine stress echocardiography (DSE) was performed in 108 patients, whenever feasible, to differentiate true severe from pseudo-severe LFLG AS. Contractile reserve was defined as $\geq 20\%$ increase in SV during DSE. In patients in whom DSE could not be performed ($n=43$) or yielded inconclusive results ($n=15$), CT aortic valve calcium scoring was used to confirm the diagnosis of severe cLFLG AS according to guideline-recommended sex-specific thresholds. Accordingly, the final study cohort consisted exclusively of patients with a confirmed true severe cLFLG AS.

Cardiac Computed Tomography

Contrast-enhanced CT was used for preprocedural evaluation. In patients with LFLG AS, aortic valve calcification has been shown to correlate with stenosis severity and disease progression.¹⁰ The Agatston calcium score thresholds of >2000 AU in men and >1200 AU in women have been proposed as sex-specific cut-offs for severe AS.¹¹ Therefore, these cut-off values were used to define severe AS in the study.

Transcatheter Aortic Valve Implantation Procedure

All patients were assessed by an interdisciplinary heart team prior to the procedure and the indication for TAVI was determined based on the heart team's decision. Transcatheter aortic valve implantation was performed via transfemoral access. The choice of valve type and the decision of pre- or post-dilatation were left to the discretion of the interventional cardiologists. Unfractionated heparin (50-70 IU/kg) was administered for periprocedural anticoagulation. A suture-mediated closure device was used to achieve hemostasis at the access site.

Study Endpoints

The primary endpoint of the study was all-cause mortality during follow-up. Clinical outcomes were adjudicated according to the standardized definitions of the Valve Academic Research Consortium-3 (VARC-3).¹² Kidney Disease: Improving Global Outcomes definition of acute kidney injury (AKI) was recommended by VARC-3. The AKI was defined as an increase in serum creatinine by $\geq 0.3 \text{ mg/dL}$ within 48 hours or an increase in serum creatinine ≥ 1.5 times baseline within 7 days; or urine output <0.5 mL/kg/h for 6 hours.¹³

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate, whereas categorical variables are expressed as frequencies and percentages. The Kolmogorov-Smirnov test was used to assess normality. Survival analyses were performed using

HIGHLIGHTS

- Classical low-flow low-gradient aortic stenosis remains a high-risk condition despite transcatheter aortic valve implantation.
- Right ventricular dysfunction assessed by tricuspid annular plane systolic excursion (TAPSE) predicts adverse outcomes.
- Reduced TAPSE and lower TAPSE/systolic pulmonary artery pressure ratio are associated with all-cause mortality in patients with classical low-flow low-gradient aortic stenosis.
- Reduced left ventricular ejection fraction and advanced age are independently associated with all-cause mortality.
- Right ventricular functional assessment may provide complementary prognostic information beyond LVEF.

the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. Cox proportional hazards regression analysis was performed to identify predictors of all-cause mortality. Variables with a *P* value <.10 in univariate analysis and clinical relevance were considered for multivariable analysis. Given the limited number of mortality events, multivariable models were intentionally simplified to minimize the risk of overfitting. Two separate multivariable models were constructed: model 1 included age, LVEF, and TAPSE, whereas model 2 included age, LVEF, and TAPSE/sPAP ratio as a surrogate marker of RV–arterial coupling.

Hazard ratios (HR) with 95% CI were reported. Internal validation of the primary multivariable model was performed using bootstrap resampling with 1000 iterations to assess model stability and optimism-corrected discrimination.

The prognostic performance of TAPSE was evaluated using time-dependent receiver operating characteristic (ROC) curve analysis, and the optimal threshold was determined by the Youden index. To further assess the relationship between TAPSE and mortality, restricted cubic spline analysis was applied. A nomogram based on the primary multivariable model was constructed for exploratory individualized risk estimation.

A 2-tailed *P* value <.05 was considered statistically significant. All statistical analyses were performed using Jamovi software (The Jamovi Project, Sydney, Australia) and R version 4.0.1 (The R Foundation for Statistical Computing, Vienna, Austria) with the “rms” package.

RESULTS

Baseline clinical, echocardiographic and CT characteristics, procedural aspects and outcomes of the overall study population (*n*=151) are shown in Table 1. The median age was 77 (70.5–82) years and 91 (60%) of the patients were male. The prevalence of major comorbidities was as follows: arterial hypertension (81%), coronary artery disease (67%), diabetes mellitus (48%), chronic kidney disease (CKD) (42%), and AF (34%). Baseline echocardiographic evaluation demonstrated a reduced LVEF with a median of 35% (30–45) and a low SVi of 27.9 (18.6–35.9) mL/m², consistent with a low-flow hemodynamic profile. The mean AVA was 0.71 ± 0.16 cm², and the Agatston score was markedly elevated at 2771 (2094–3500). Median TAPSE was 1.7 (1.4–2.0) cm, and median TAPSE/sPAP ratio was 0.38 (0.28–0.51) mm/mmHg. Over a median follow-up of 26 (15–42) months, 37 (25%) patients died. In-hospital mortality rate was 13%. Acute kidney injury developed in 14% and permanent pacemaker implantation was required in 10%.

In univariable Cox regression analysis, advanced age, reduced LVEF, lower TAPSE, and lower TAPSE/sPAP ratio were associated with increased all-cause mortality. In multivariable Cox regression analysis, reduced TAPSE remained independently associated with all-cause mortality in model 1 after adjustment for age and LVEF (HR: 0.11, 95% CI: 0.04–0.30, *P* < .001). In model 2, a lower TAPSE/sPAP ratio, used as a surrogate marker of RV–arterial coupling, was also independently associated with all-cause mortality after adjustment

Table 1. Baseline Clinical, Echocardiographic, and CT Characteristics, Procedural Aspects, and Outcomes

Variables	Study Population (<i>n</i> = 151)
Demographic and clinical characteristics	
Age, years	77 (70.5–82)
Male sex, <i>n</i> (%)	91 (60)
Arterial hypertension, <i>n</i> (%)	122 (81)
Coronary artery disease, <i>n</i> (%)	101 (67)
Diabetes mellitus, <i>n</i> (%)	72 (48)
COPD, <i>n</i> (%)	27 (18)
Prior stroke, <i>n</i> (%)	12 (8)
Atrial fibrillation, <i>n</i> (%)	51 (34)
Chronic kidney disease, <i>n</i> (%)	64 (42)
Echocardiographic parameters (Preprocedural)	
LVEF, %	35 (30–45)
LVEDD, cm	5.3 (4.7–5.7)
LVESD, cm	4 (3.2–4.4)
Aortic peak velocity, m/s	3.4 (3.1–3.6)
Aortic peak gradient, mm Hg	46.3 ± 10.4
Aortic mean gradient, mm Hg	27.7 ± 6.2
Stroke volume index, mL/m ²	27.9 (18.6–35.9)
AVA, cm ²	0.71 ± 0.16
AR grade, <i>n</i> (%)	
None/trace	23 (15)
Mild	81 (54)
Moderate	33 (22)
Severe	14 (9)
MR grade, <i>n</i> (%)	
None/trace	7 (5)
Mild	39 (26)
Moderate	55 (36)
Severe	50 (33)
TR grade, <i>n</i> (%)	
None/trace	6 (4)
Mild	49 (32)
Moderate	49 (32)
Severe	47 (31)
sPAP, mmHg	45 (35–55)
TAPSE, cm	1.7 (1.4–2)
CT parameter	
Agatston score, AU	2771 (2094–3500)
Procedural characteristics	
Pre-balloon dilatation	37 (25)
Valve size, mm	27.5 (26–29)
Post-balloon dilatation	24 (16)
Echocardiographic parameters (Postprocedural)	
LVEF, %	40 (30–50)
Aortic peak velocity, m/s	1.3 (1.1–1.6)
Aortic peak gradient, mmHg	12 (10–16)

(Continued)

Table 1. Baseline Clinical, Echocardiographic, and CT Characteristics, Procedural Aspects, and Outcomes (Continued)

Variables	Study Population (n=151)
Aortic mean gradient, mmHg	7 (5-8)
AR grade, n (%)	
None/trace	67 (44)
Mild	65 (43)
Moderate	15 (10)
Severe	4 (3)
MR grade, n (%)	
None/trace	26 (17)
Mild	50 (33)
Moderate	47 (31)
Severe	28 (19)
TR grade, n (%)	
None/trace	22 (15)
Mild	53 (35)
Moderate	50 (33)
Severe	26 (17)
sPAP, mm Hg	35 (30-50)
TAPSE, cm	1.7 (1.4-2)
TAPSE/sPAP, mm/mm Hg	0.38 (0.28-0.51)
VARC-3 outcomes	
≥Moderate PVL, n (%)	19 (12)
Acute kidney injury, n (%)	21 (14)
Disabling stroke, n (%)	5 (3)
New permanent pacemaker implantation, n (%)	13 (10)
In-hospital mortality, n (%)	19 (13)
Total mortality, n (%)	37 (25)
Follow-up duration, months	26 (15-42)

AR, aortic regurgitation; AVA, aortic valve area; COPD, chronic obstructive pulmonary disease; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; PVL, paravalvular leak; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VARC-3, Valve Academic Research Consortium-3.

for age and LVEF (HR: 0.08, 95% CI: 0.01-0.85, $P = .036$). Advanced age remained independently associated with mortality in both models (model 1: HR 1.07, 95% CI 1.02-1.11, $P = .002$; model 2: HR 1.07, 95% CI 1.02-1.11, $P = .004$), whereas reduced LVEF also showed an independent but weaker association with mortality in both models.

Bootstrap internal validation of the primary multivariable model (model 1) demonstrated acceptable model stability with an optimism-corrected C-index of 0.77 and a calibration slope of 0.93, suggesting limited model overfitting. Univariable and multivariable Cox regression analyses are presented in Table 2, and a forest plot demonstrating the results of the multivariable analyses is illustrated in Figure 1. In addition, the extended univariable Cox regression analyses are provided in Supplementary Table 1.

Table 2. Univariable and Multivariable Cox Regression Analyses for Predictors of All-cause Mortality

Variables	Univariable Analysis	Multivariable Analysis	
	HR (95% CI), P	Model 1	Model 2
Age, years	1.06 (1.01-1.11, $P = .010$)	1.07 (1.02-1.11, $P = .002$)	1.07 (1.02-1.11, $P = .004$)
LVEF, %	0.94 (0.91-0.98, $P = .001$)	0.95 (0.92-0.99, $P = .012$)	0.95 (0.91-0.99, $P = .008$)
TAPSE, cm	0.11 (0.04-0.28, $P < .001$)	0.11 (0.04-0.30, $P < .001$)	—
TAPSE/sPAP, mm/mm Hg	0.06 (0.01-0.54), $P = .012$	—	0.08 (0.01-0.85, $P = .036$)

HR, hazard ratio; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

Kaplan–Meier analyses demonstrated significantly reduced survival in patients with advanced age, lower TAPSE, and lower LVEF, with early and sustained separation of survival curves (log-rank $P < .0001$ for age and TAPSE; $P = .0013$ for LVEF) (Figure 2). In the ROC analysis, TAPSE yielded an AUC of 0.728 (95% CI: 0.639-0.817), with an optimal cut-off value of 1.51 cm (sensitivity: 59.5%, specificity: 75.4%) (Figure 3a). Time-dependent ROC analysis revealed consistent discriminative performance of TAPSE at 6, 12, and 24 months (AUC values: 0.73, 0.76, and 0.76; respectively) (Figure 3b). Restricted cubic spline analysis revealed a non-linear relationship between TAPSE and mortality risk, and lower TAPSE values were associated with a markedly increased risk of mortality (Figure 4). Additionally, a Kaplan–Meier analysis based on TAPSE tertiles demonstrated significantly reduced survival in patients with lower TAPSE values (Supplementary Figure 1).

Based on these findings, a nomogram including age, LVEF, and TAPSE was developed for exploratory individualized estimation of 12-month survival probability following TAVI (Supplementary Figure 2). The model demonstrated acceptable discriminative performance and may contribute to integrated prognostic assessment in patients with cLFLG AS undergoing TAVI.

DISCUSSION

In this study, reduced TAPSE, advanced age and reduced LVEF were identified as independent predictors of all-cause mortality in patients with cLFLG AS undergoing TAVI. In addition, the lower TAPSE/sPAP ratio, used as a surrogate marker of RV–arterial coupling, was also independently associated with mortality. These findings suggest that RV systolic dysfunction and impaired RV–pulmonary vascular interaction may provide complementary prognostic information in this high-risk population.

Most previous studies investigating mortality predictors after TAVI have evaluated heterogeneous AS populations. In contrast, cLFLG AS represent a distinct phenotype characterized by impaired LVEF with a complex low-flow

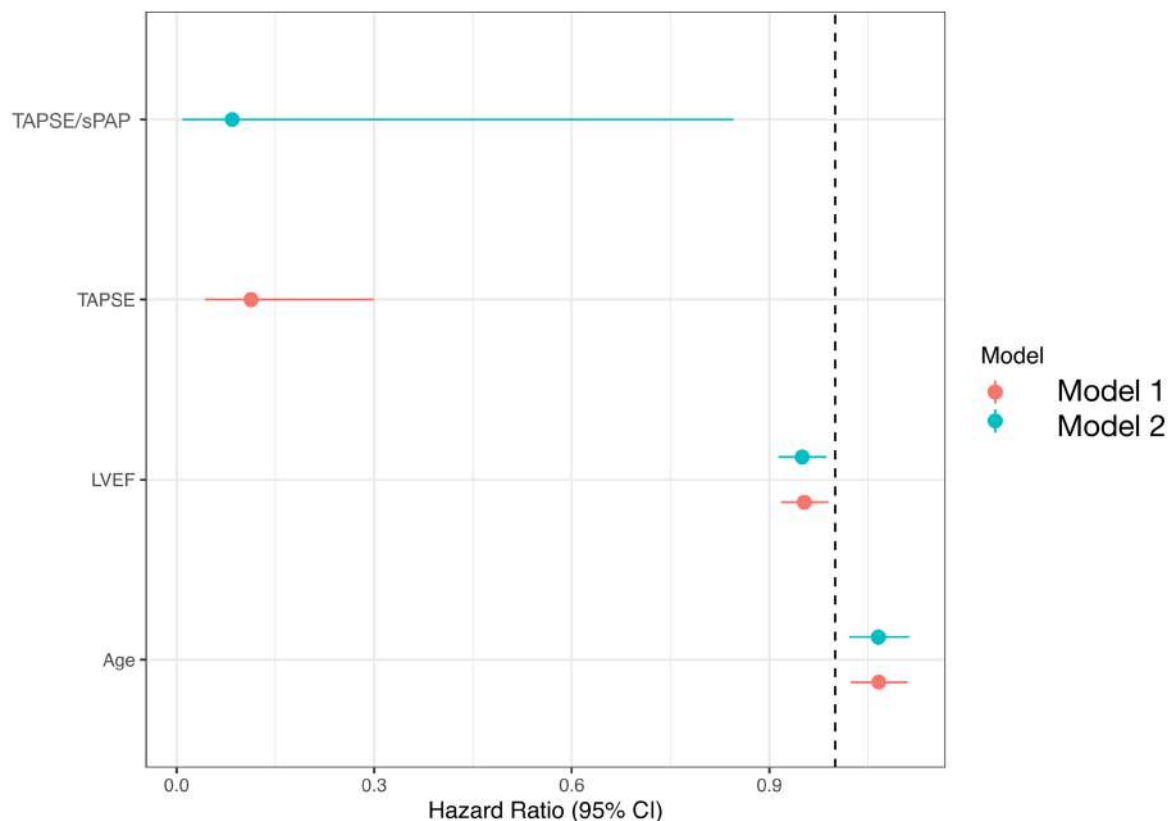


Figure 1. Forest plot of multivariable Cox regression analyses.

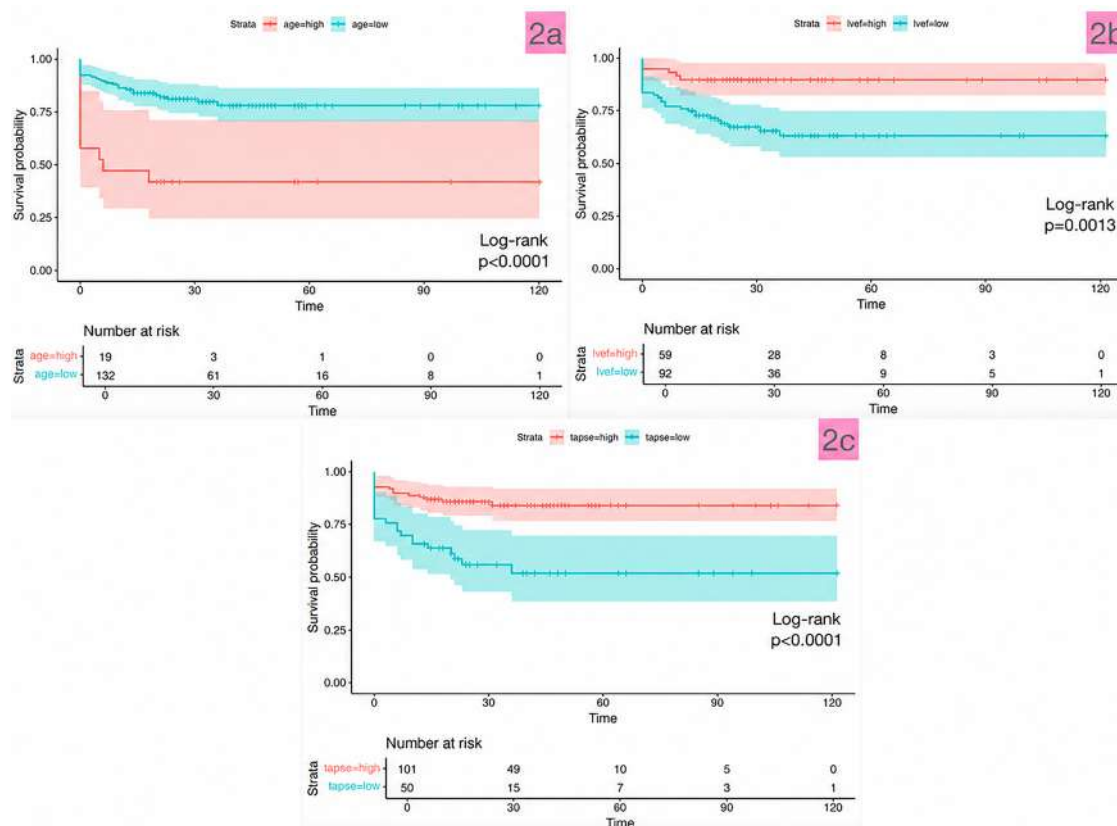


Figure 2. (a) Kaplan–Meier survival analysis for age (b) Kaplan–Meier survival analysis for LVEF (c) Kaplan–Meier survival analysis for tricuspid annular plane systolic excursion.

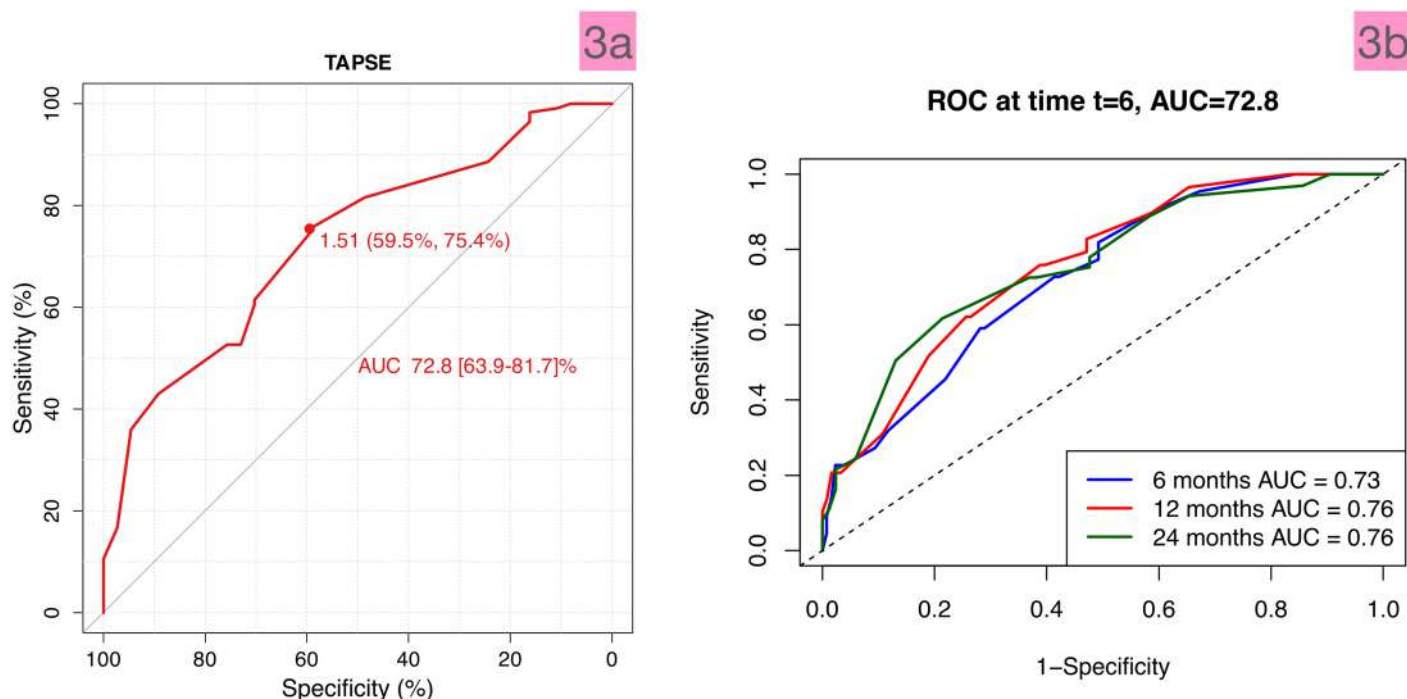


Figure 3. (a). The receiver operating characteristic (ROC) curve of tricuspid annular plane systolic excursion for predicting all-cause mortality (b) Time-dependent ROC analysis of the prediction model.

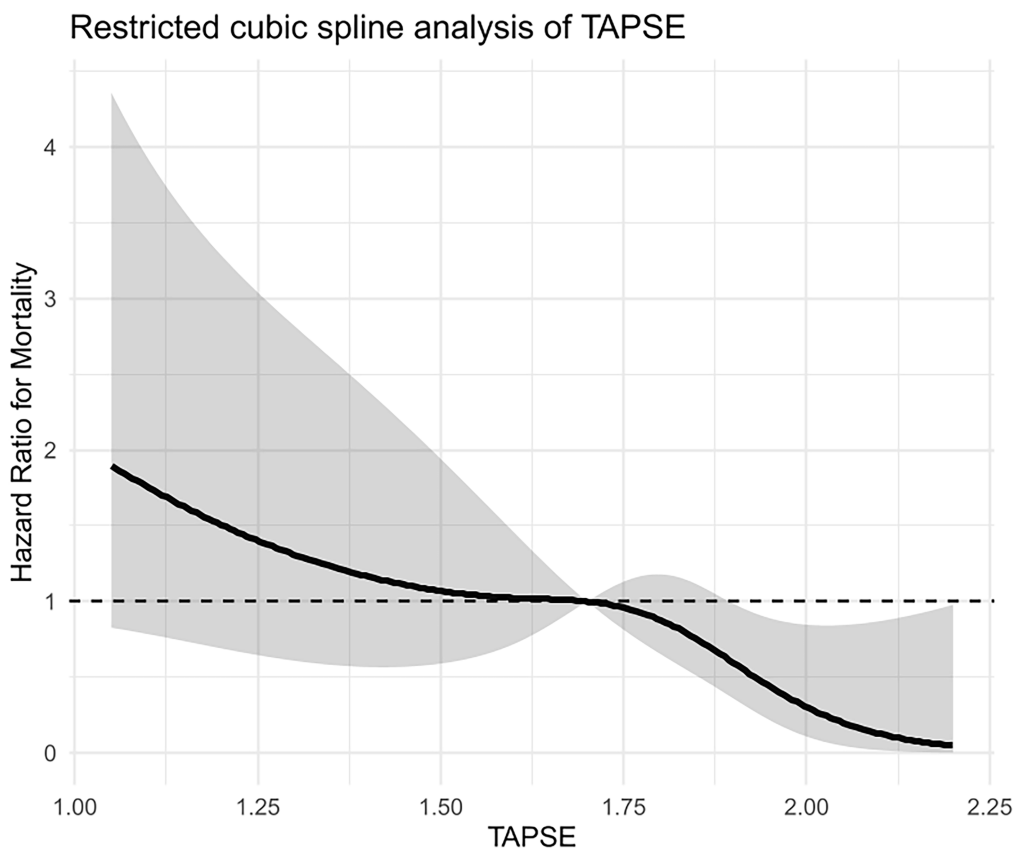


Figure 4. Restricted cubic spline analysis of tricuspid annular plane systolic excursion and all-cause mortality.

hemodynamic profile, which may influence the prognostic significance of clinical and echocardiographic parameters. Therefore, data specifically addressing prognostic markers in this high-risk subgroup remain scarce.

Previous studies have shown that patients with cLFLG AS have the highest mortality rates among different hemodynamic subgroup profiles.^{7,14,15} Several factors, including reduced LVEF, advanced age, increased hemodynamic burden, and significant comorbidities, have been implicated in adverse outcomes in this population. These factors underscore the multifactorial nature of mortality risk in low-flow profiles. Ludwig and colleagues investigated 718 patients with cLFLG undergoing TAVI and constructed the RELiEF TAVI score for risk prediction. The RELiEF TAVI score included male sex, underweight, chronic obstructive pulmonary disease (COPD), AF, SVi, non-femoral access, sPAP, and low density of aortic valve calcification.¹⁶ A subgroup analysis from the German Aortic Valve Registry (GARY) revealed that peripheral artery disease, prior myocardial infarction, and pulmonary hypertension were independent predictors of mortality among patients with cLFLG AS.¹⁷ In contrast to these studies, COPD, AF, pulmonary hypertension, SVi, and Agatston score were not found to be associated with mortality in our cohort. This discrepancy may be related to differences in sample size or patient characteristics. Notably, our findings highlight the prognostic relevance of reduced TAPSE, advanced age and reduced LVEF.

Right ventricular systolic dysfunction has been associated with adverse outcomes in patients undergoing TAVI.^{18,19} Previous studies have also demonstrated that RV-arterial coupling and reduced RV longitudinal strain are linked to mortality in cLFLG AS.^{20,21} In addition to TAPSE, we evaluated the TAPSE/sPAP ratio as a surrogate marker of RV-arterial coupling, reflecting the interaction between RV contractile function and pulmonary vascular load. RV-arterial coupling has emerged as a contemporary parameter providing integrated assessment of RV performance beyond conventional load-dependent measurements. In this study, a lower TAPSE/sPAP ratio was independently associated with increased all-cause mortality after adjustment for age and LVEF. These findings suggest that impaired RV-pulmonary vascular interaction may contribute to adverse outcomes in patients with cLFLG AS undergoing TAVI. Cavalcante and colleagues demonstrated that RV dysfunction, defined as TAPSE <16 mm, has important prognostic value in patients with LFLG AS and may contribute to the decision-making process.²² In our cohort, reduced TAPSE was significantly associated with all-cause mortality after adjustment for age and LVEF. This relationship was further supported by multiple analyses, including restricted cubic spline analysis, demonstrating a non-linear increase in mortality risk at lower TAPSE values. These findings suggest that the adverse effect of RV dysfunction becomes more evident below certain thresholds. In this setting, reduced TAPSE may reflect the integrated hemodynamic burden of chronic low-flow physiology, pulmonary vascular remodeling, and ventricular interdependence. Although reduced LVEF was also independently associated with all-cause mortality, our findings suggest

that RV dysfunction, reflected by TAPSE, may provide complementary prognostic information in patients with cLFLG AS undergoing TAVI. Taken together, these findings support the potential contribution of both LV and RV functional impairment to adverse outcomes in this high-risk population.

Given the particularly vulnerable hemodynamic profile of patients with cLFLG AS, the relatively high in-hospital mortality observed in our cohort is not entirely unexpected. This finding may reflect the advanced disease stage and the substantial burden of comorbidities, including CKD, in this high-risk patient population. In addition, impaired RV function and the relatively high incidence of postoperative AKI may also have contributed to adverse early outcomes. Furthermore, procedural and temporal factors, including differences in operator experience and transcatheter valve technologies, may also have influenced in-hospital outcomes. Recent experience with newer-generation balloon-expandable valves has demonstrated favorable procedural performance and acceptable early clinical outcomes, indicating that ongoing advances in transcatheter valve technology may partly account for differences in outcomes reported across contemporary TAVI studies.²³

An analysis from the FRANCE 2 registry demonstrated that severe renal failure and moderate to severe periprosthetic regurgitation were associated with cardiovascular mortality in patients with low transvalvular gradient undergoing TAVI.²⁴ A study including patients with CKD undergoing TAVI revealed that the coexistence of AKI and LFLG AS was associated with poor outcomes.²⁵ Similarly, CKD, moderate to severe PVL, and AKI were associated with all-cause mortality in univariable analysis in our cohort. However, given the limited number of events and the aim to construct a simplified preprocedural prognostic model, these variables were not included in the final multivariable analyses. Another independent predictor of mortality was advanced age, and this may be explained by the higher burden of comorbidities and increased frailty.

In addition to identifying independent predictors, we developed a nomogram including age, LVEF, and TAPSE to explore individualized estimation of 12-month survival probability following TAVI. While each parameter alone showed moderate predictive performance, their combined use may offer a more comprehensive risk assessment. Therefore, the combined evaluation of these parameters may provide a framework for individualized risk assessment. However, the proposed nomogram should be considered exploratory and requires external validation in independent cohorts before routine clinical application.

Study Limitations

Our study has several limitations due to the retrospective and single center design. These factors may limit the generalizability of our findings and lead to the potential for selection bias. In addition, the exclusion of patients with incomplete preprocedural data may have introduced an additional selection bias. Because the cohort was assembled retrospectively, the complete diagnostic pathway before patient inclusion could not be fully reconstructed. Tricuspid

annular plane systolic excursion shows primarily longitudinal RV function and may not fully reflect global RV function. Additional parameters such as RV strain and fractional area change were not available. Although measurements were performed under standardized conditions, interobserver variability was not evaluated. Although internal validation using bootstrap resampling demonstrated acceptable model stability, the proposed nomogram has not been externally validated in an independent cohort and therefore should be interpreted with caution. External validation in larger multicenter populations is required before broader clinical application.

CONCLUSION

Reduced TAPSE, advanced age, and reduced LVEF were independently associated with all-cause mortality in patients with cLFLG AS undergoing TAVI. In addition, impaired RV–pulmonary vascular interaction, reflected by lower TAPSE/sPAP ratio, was also associated with adverse outcomes. These findings suggest that assessment of RV function may provide complementary prognostic information beyond conventional LV systolic evaluation, particularly in low-flow states. In this context, TAPSE may represent a promising component of a multiparametric risk stratification model.

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Kartal Koşuyolu Training and Research Hospital (Approval No: 2026/04/1392, Date: 24/02/2026).

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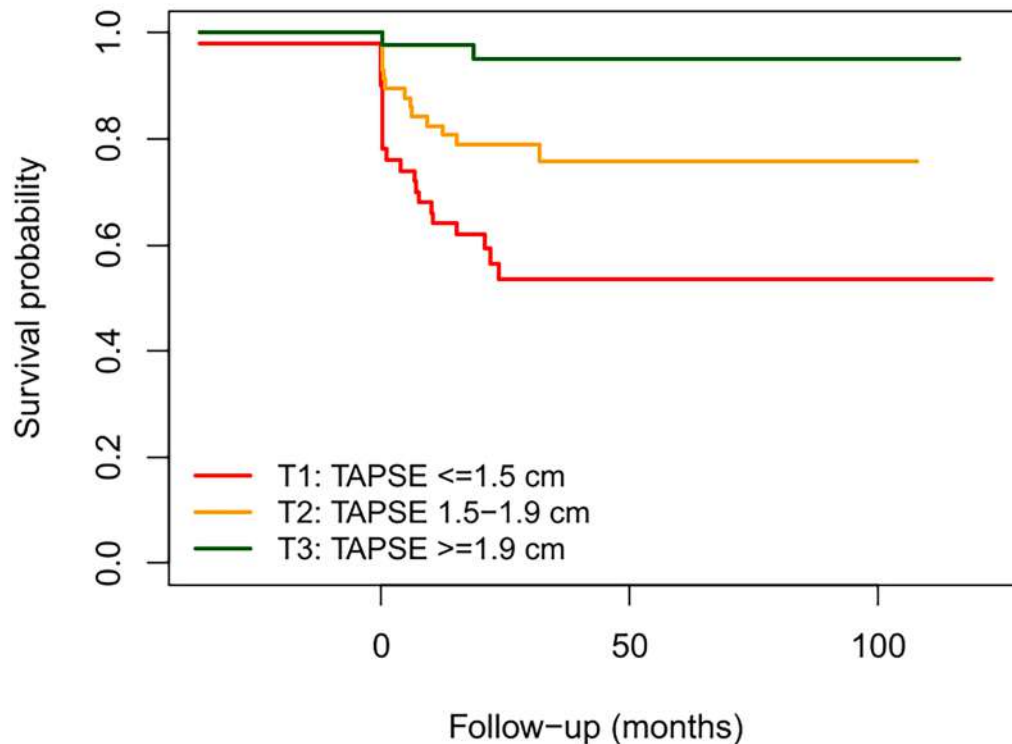
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Supplementary Table 1. Expanded univariable Cox Regression Analysis for predictors of all-cause mortality

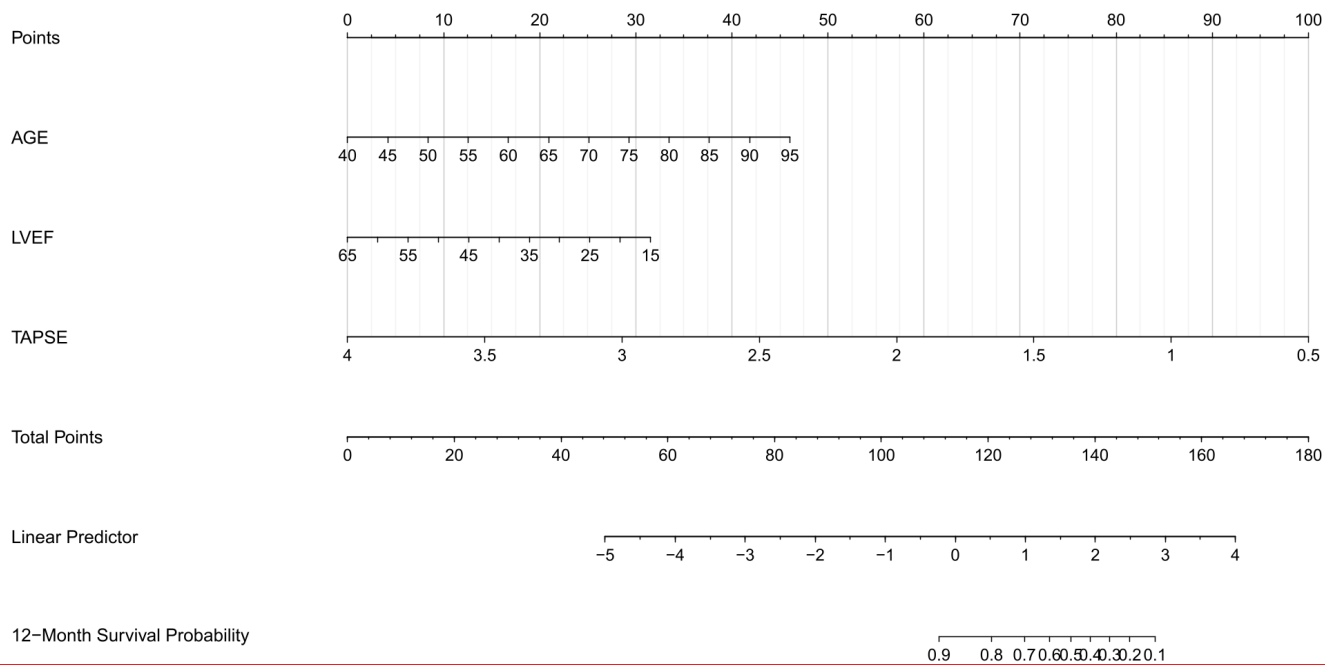
Variables	Univariable Analysis	
	HR (95% CI)	P
Age, years	1.06 (1.01-1.11)	0.010
CKD	1.93 (1.01-3.70)	0.048
LVEF, %	0.94 (0.91-0.98)	0.001
Aortic peak velocity, m/s	0.37 (0.18-0.78)	0.008
TAPSE, cm	0.11 (0.04-0.28)	<0.001
TAPSE/sPAP, mm/mm Hg	0.06 (0.01-0.54)	0.012
Preprocedural $\geq$ moderate MR	2.48 (1.03-5.95)	0.042
Postprocedural $\geq$ moderate AR	3.35 (1.45-7.72)	0.005
Postprocedural $\geq$ moderate TR	1.25 (0.65-2.38)	0.504
$\geq$ moderate PVL	2.78 (1.17-6.62)	0.021
Postoperative AKI	4.01 (2.01-8.01)	0.001

AKI, acute kidney injury; AR, aortic regurgitation; CKD, chronic kidney disease; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PVL, paravalvular leak; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Kaplan-Meier curves according to TAPSE tertiles



Supplementary Figure 1. Kaplan-Meier survival curves according to TAPSE tertiles.



Supplementary Figure 2. Nomogram for predicting all-cause mortality.

Weight-Adjusted Waist Index Outperforms Conventional Adiposity Indices in Predicting All-Cause Mortality: A Population-Based Cohort Study

ABSTRACT

Background: Body mass index (BMI), the most widely used adiposity metric, cannot differentiate fat distribution from lean mass, limiting its prognostic utility. This study compared the weight-adjusted waist index (WWI) with BMI, waist-to-height ratio, and relative fat mass (RFM) as predictors of all-cause and cardiovascular mortality using a z-standardized framework.

Methods: Data from 18 496 adults aged ≥ 20 years from the National Health and Nutrition Examination Survey 2011–2018 were linked to the National Death Index through December 31, 2019. Four adiposity indices were z-standardized and analyzed using survey-weighted Cox models with sequential adjustment. Dose–response relationships were assessed using restricted cubic splines, and subgroup analyses examined the effect modification by sex, multimorbidity, and estimated glomerular filtration rate (eGFR).

Results: Over a median follow-up of 4.83 years, 976 all-cause and 291 cardiovascular deaths occurred. Weight-adjusted waist index demonstrated the strongest association with all-cause mortality (hazard ratio [HR] 1.34; 95% CI 1.23–1.46; $P < .001$); BMI and RFM did not reach significance. After mutual adjustment, WWI retained its association (HR 1.40; $P < .001$) while BMI did not reach statistical significance in the adjusted model. Weight-adjusted waist index showed a linear dose–response relationship, contrasting the J-shaped curve of BMI. The association was consistent across subgroups but attenuated in participants with eGFR < 60 (interaction $P = .034$).

Conclusion: Weight-adjusted waist index was the strongest independent predictor of all-cause and cardiovascular mortality among 4 adiposity indices. Its linear dose–response relationship, consistency across subgroups, and calculability from waist circumference and body weight alone support its use as a practical alternative to BMI for mortality risk stratification.

Keywords: Cardiovascular mortality, cardiovascular risk factors, central adiposity, obesity paradox, weight-adjusted waist index

INTRODUCTION

Obesity is a global health concern whose prevalence has been rising rapidly, directly increasing cardiovascular disease risk and mortality. An analysis by the Non-Communicable Disease (NCD) Risk Factor Collaboration spanning 200 countries demonstrated a notable increase in the global burden of obesity among both adults and children between 1990 and 2022.¹ An individual-participant-data meta-analysis of 239 prospective studies across 4 continents showed that each 5 kg/m² increment in body mass index (BMI) above 25 kg/m² significantly increases all-cause mortality.² Body mass index remains the most widely adopted metric for quantifying this risk; however, it fails to differentiate between muscle mass and adiposity, nor does it account for regional fat distribution. Consequently, highly muscular individuals may be erroneously stratified as high-risk, while cachectic or sarcopenic patients might be misclassified as low-risk. This limitation gives rise to counter-intuitive clinical observations widely termed the “obesity paradox”

ORIGINAL INVESTIGATION

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wherein a higher BMI is paradoxically associated with an improved prognosis in certain patient populations.³

Accumulating evidence indicates that central adiposity, rather than total adiposity, plays a decisive role in cardiovascular risk assessment. A scientific statement from the American Heart Association emphasized that waist circumference is a cardiovascular risk marker independent of BMI and that visceral adiposity is independently associated with adverse cardiovascular outcomes.⁴ Because waist circumference alone does not provide normalization independent of height and weight, composite indices have been developed to more accurately capture central adiposity: the waist-to-height ratio (WHtR) normalizes waist circumference to height and was significantly associated with both all-cause and cardiovascular mortality in a meta-analysis;⁵ relative fat mass (RFM) provides a sex-adjusted estimate of body fat percentage derived from the height-to-waist circumference ratio.⁶ Each of these indices employs a different normalization strategy, yet their comparison as mortality predictors within a common analytical framework has been limited.

In 2018, Park et al⁷ developed the weight-adjusted waist index ($WWI = \text{waist circumference [cm]} / \sqrt{\text{weight [kg]}}$) in a South Korean national cohort of 465 629 individuals and reported that WWI was the only adiposity measure showing a linear positive association with cardiovascular mortality. Subsequent studies supported a consistent link between WWI and both all-cause and cardiovascular mortality in general populations⁸ and in specific patient groups such as those with type 2 diabetes.⁹ The current literature, however, has notable gaps. Most studies compared WWI with only a limited number of indices, and because comparisons were conducted on different scales, direct comparison of effect sizes was not possible. The shape of the dose-response relationship remains contested, with some studies reporting a linear association and others a U-shaped curve. Interactions within clinically relevant subgroups such as kidney function and cardiometabolic multimorbidity have not been adequately explored.

The study addresses these gaps using National Health and Nutrition Examination Survey (NHANES) 2011-2018 data

through 4 specific aims: (1) compare WWI, BMI, WHtR, and RFM head-to-head within the same modeling framework using z-standardization, (2) evaluate the dose-response relationship of each index with all-cause and cardiovascular mortality through restricted cubic spline analysis, (3) test the independent prognostic value of WWI beyond BMI using a mutual adjustment model, and (4) examine interactions across kidney function, cardiometabolic multimorbidity, and sex subgroups.

METHODS

Study Design and Population

This study used data from the NHANES 2011-2018 cycles. National Health and Nutrition Examination Survey NHANES is a cross-sectional survey program conducted using a multistage, stratified probability sampling design to assess the health status of the non-institutionalized civilian population in the United States. Demographic and health information was collected from participants during household interviews, followed by anthropometric measurements and laboratory examinations at mobile examination centers (MEC). The study protocol was approved by the NCHS Research Ethics Review Board (Protocol No: 2011-2017), and written informed consent was obtained from all participants. Because this study is a secondary analysis of publicly available, de-identified data, additional ethics approval was not required. The study was conducted in accordance with the Declaration of Helsinki.

Individuals aged ≥ 20 years who completed the MEC examination were considered eligible (Figure 1). From an initial pool of 39 156 participants, exclusions were applied for age criteria, missing anthropometric data, ineligibility for mortality follow-up, and missing follow-up duration, yielding an eligible cohort of 20 196 individuals. For the primary analyses, participants with missing key covariates (estimated glomerular filtration rate [eGFR], HbA1c, systolic blood pressure [SBP], or smoking status) were further excluded, resulting in a complete-case analytic sample of 18 496 individuals (976 all-cause deaths). Details of the exclusion process are presented in Figure 1. The attrition rate between the eligible cohort ($n=20\,196$) and the analytic sample ($n=18\,496$) was 8.4%. Demographic and clinical baseline characteristics did not differ meaningfully between the 2 groups (Supplementary Table 1), supporting that the complete-case approach did not introduce substantial selection bias.

Variables

The $WWI = \text{waist circumference (cm)} / \sqrt{\text{weight (kg)}}$ served as the primary exposure variable. Waist circumference was measured at the level of the iliac crest. Comparator indices included BMI (weight/height^2), WHtR ($\text{waist circumference/height}$), and RFM ($64 - 20 \times \text{height/waist circumference} + 12 \times \text{sex}$; male = 0, female = 1). All 4 indices were z-standardized before entry into the models to allow direct comparison of effect sizes.

The primary endpoint was all-cause mortality; cardiovascular mortality served as the secondary endpoint. Mortality data were obtained from the National Death Index through

HIGHLIGHTS

- Weight-adjusted waist index (WWI) was the strongest independent predictor of all-cause and cardiovascular mortality among 4 z-standardized adiposity indices.
- Body mass index (BMI) lost its independent prognostic contribution after mutual adjustment with WWI.
- Weight-adjusted waist index showed a linear dose-response relationship with mortality, contrasting the J-shaped curve of BMI.
- Weight-adjusted waist index's prognostic capacity was attenuated in participants with estimated glomerular filtration rate < 60 mL/min/1.73 m², a finding unique to WWI.

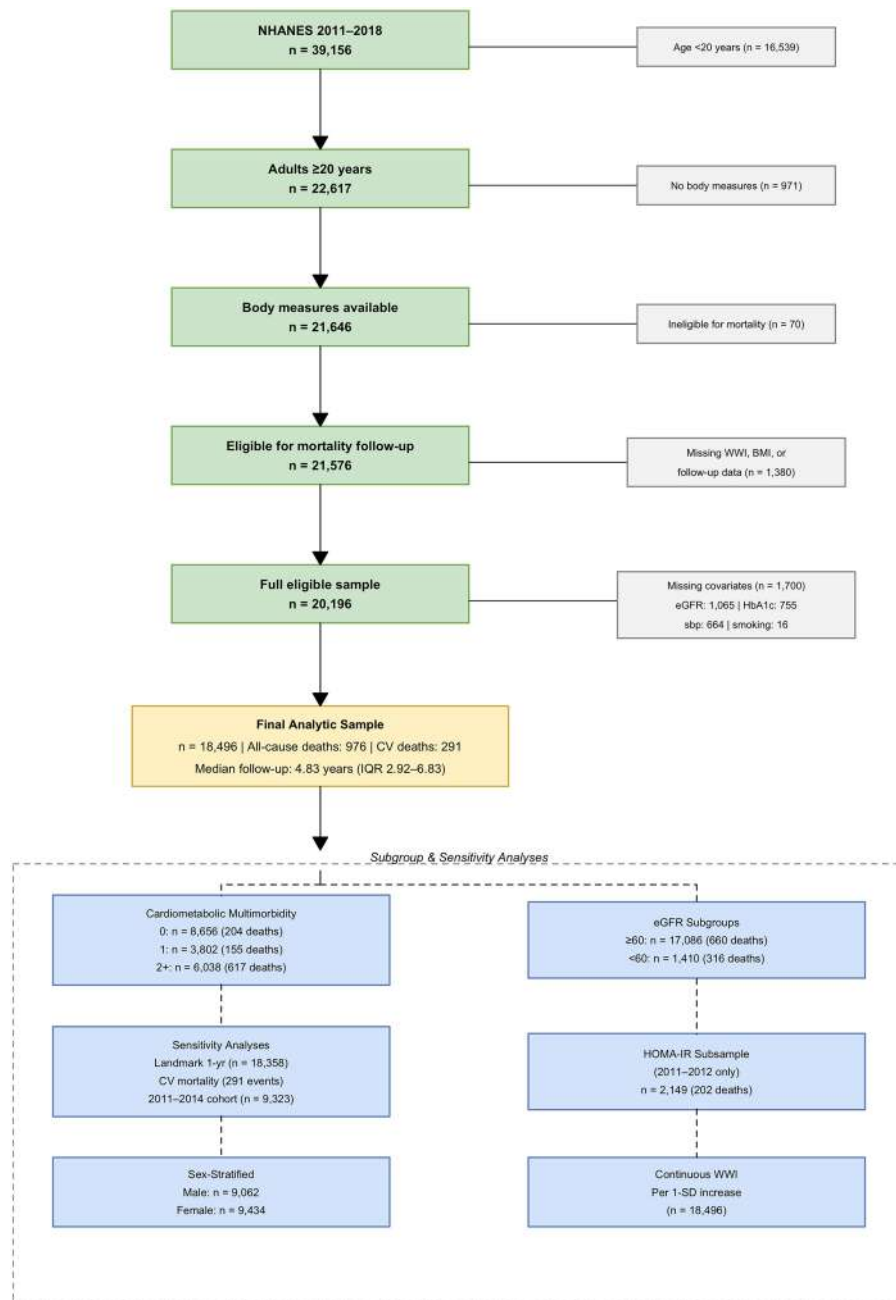


Figure 1. Flow diagram of participant selection from NHANES 2011-2018. NHANES, National Health and Nutrition Examination Survey.

the NCHS Public-Use Linked Mortality Files (2019 release); person-time was calculated from the interview date to death or December 31, 2019. Cardiovascular mortality was defined using the UCOD_LEADING variable as heart disease International Classification of Diseases, Tenth Revision [ICD-10: I00-I09, I11, I13, I20-I51] and cerebrovascular disease (ICD-10: I60-I69). Because cerebrovascular deaths were not separately coded in the 2015-2018 cycles, the definition for those cycles predominantly reflects cardiac mortality; to address this limitation, a separate sensitivity analysis was conducted in the 2011-2014 subcohort where complete coding was available.

Diabetes (physician diagnosis or HbA1c $\geq 6.5\%$), hypertension (physician diagnosis or SBP ≥ 130 or diastolic blood pressure [DBP] ≥ 80 mm Hg),¹⁰ and dyslipidemia (use of lipid-lowering medication, triglycerides ≥ 150 , or Low-Density Lipoprotein [LDL] ≥ 130 mg/dL) were included as individual covariates in the regression models. A cardiometabolic multimorbidity score (0, 1, ≥ 2) derived from the co-presence of these 3 conditions was used as a classification variable in subgroup analyses. Other covariates were sex, ethnicity, smoking status (never/former/current), eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2021 creatinine equation),¹¹ SBP (mean of consecutive measurements), and

HbA1c. Homeostatic model assessment of insulin resistance (HOMA-IR) was available only in the 2011-2012 fasting subsample and was used in a dedicated sensitivity analysis.

Statistical Analysis

All analyses accounted for the complex sampling design of NHANES (survey weights, stratification, primary sampling units); 2-year examination weights were scaled by 1/4 for combining 4 cycles. Baseline characteristics were reported as unweighted counts and percentages. Group comparisons used Analysis of Variance (ANOVA) for normally distributed continuous variables, the Kruskal-Wallis test for others, and the chi-square test for categorical variables.

The association between adiposity indices and all-cause mortality was assessed using survey-weighted Cox proportional hazards models (svycoxph). Because age violated the proportional hazards assumption at the individual level, it was used as a stratification variable rather than a covariate in all models (age groups: 20-39, 40-59, 60-79, ≥ 80 years). Four nested models were constructed: Model 1 was stratified by age and adjusted for sex; Model 2 additionally included ethnicity and smoking status; Model 3a further incorporated diabetes, hypertension, dyslipidemia, eGFR, SBP, and HbA1c. Body mass index was not included in Model 3a to ensure an equal comparison among indices. To test whether WWI provides prognostic value independent of overall adiposity, Model 3b (Model 3a + BMI, mutual adjustment) was constructed for WWI only.

The proportional hazards assumption was evaluated using scaled Schoenfeld residuals. Because the `cox.zph()` function does not support `svycoxph` objects, testing was performed on standard Cox models with normalized survey weights applied as case weights; the global test was nonsignificant for all 4 models ($P > .05$). The dose-response relationship between WWI and mortality was examined using restricted cubic spline (RCS) analysis with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles; the median WWI value was taken as the reference. Spline curves were plotted from normalized-weight Cox models, while the P -value for departure from linearity was obtained from survey-weighted models using the Rao-Scott test.

Prespecified subgroup analyses examined the WWI-mortality association according to multimorbidity score (0, 1, ≥ 2), eGFR level (< 60 vs. ≥ 60), and sex. Model 3a covariates were applied in each subgroup; age stratification was retained across all subgroup models, but the subgroup variable itself was removed from its corresponding model (e.g., sex was not included as a covariate in the sex-stratified model). Effect modification was assessed using the likelihood ratio test (LRT) with multiplicative interaction terms. These analyses were exploratory in nature, and no correction for multiple comparisons was applied.

Sensitivity analyses included: (i) cardiovascular mortality analyzed within the same modeling framework, (ii) a landmark analysis excluding deaths within the first year, (iii) additional adjustment for HOMA-IR in the fasting subsample ($n=2149$), (iv) restriction to the 2011-2014 subcohort ($n=9323$), and (v) sex-stratified models (male $n=9062$,

female $n=9434$). The discriminative capacity of each index for mortality was evaluated using unadjusted, single-predictor area under the receiver operating characteristic curve (AUC); these values should be interpreted as a descriptive measure that does not account for covariates or the time-to-event structure. In addition, Harrell's C-index was calculated from the fully adjusted Cox models (Model 3a) for each adiposity index. No formal pairwise comparison of C-indices was performed; differences between indices should therefore be interpreted descriptively. Time-dependent discriminative capacity was assessed at 1-, 3-, and 5-year time points using the linear predictors of the Cox models with inverse probability of censoring weighting (IPCW). For descriptive analyses and Kaplan-Meier curves, participants were divided into 3 groups (tertiles) based on the 33rd and 66th percentiles of the WWI distribution; these cut points are sample-specific and are not proposed as clinical decision thresholds. Survival differences between groups were assessed using the log-rank test. Inter-index correlations were evaluated using Pearson coefficients, and multicollinearity was assessed using variance inflation factors (VIFs).

Analyses were performed using R software (version 4.4.2; survey, survival, rms, pROC, and timeROC packages). Two-sided $P < .05$ was considered statistically significant.

RESULTS

Baseline Characteristic

The analytic sample comprised 18 496 adults with a median age of 49.0 years (Interquartile Range [IQR]: 34.0-63.0); 49.0% were male. Median follow-up was 4.83 years (IQR=2.92-6.83). During follow-up, 976 (5.3%) all-cause deaths and 291 (1.6%) cardiovascular deaths were recorded.

When participants were grouped by WWI tertiles, the cut-points were 10.72 and 11.46 cm/ $\sqrt{\text{kg}}$. Compared with the lowest tertile ($T1 \leq 10.72$), individuals in the highest tertile ($T3 > 11.46$) were considerably older (median 61.0 vs. 37.0 years), had higher BMI (32.97 vs. 25.57 kg/m²), and had larger waist circumference (111.6 vs. 87.7 cm; all $P < .001$). Prevalences of diabetes (29.8% vs. 4.8%), hypertension (60.8% vs. 23.6%), and dyslipidemia (53.0% vs. 19.0%) were also markedly higher in the upper tertile. All-cause mortality rose from 2.3% in T1 to 9.1% in T3, and cardiovascular mortality from 0.5% to 2.9% (Table 1).

Association of Adiposity Indices with All-Cause Mortality

In the survey-weighted Cox regression, all 4 indices were significantly associated with all-cause mortality in the age- and sex-adjusted model (Model 1). The strongest association was observed for WWI (hazard ratio [HR]: 1.476; 95% CI: 1.364-1.597; $P < .001$). Further adjustment for ethnicity and smoking status did not materially alter these associations (Model 2; Table 2).

In Model 3a, which adjusted for all clinical covariates, WWI emerged as the most robust predictor (HR: 1.337; 95% CI: 1.227-1.458; $P < .001$). Waist-to-height ratio retained statistical significance (HR: 1.143; $P = .004$), whereas BMI (HR: 1.032; $P = .565$) and RFM (HR: 1.176; $P = .054$) did not reach significance. In Model 3b, which tested the independence of WWI from

Table 1. Baseline Characteristics of the Study Population by Tertiles of the Weight-adjusted Waist Index (WWI)

Variables	Overall (n = 18 496)	T1 (≤10.72) (n = 6166)	T2 (10.72–11.46) (n = 6165)	T3 (>11.46) (n = 6165)	P
Age, years, median (IQR)	49.0 (34.0–63.0)	37.0 (27.0–49.0)	51.0 (37.0–63.0)	61.0 (47.0–71.0)	<.001
Male sex, n (%)	9062 (49.0)	3693 (59.9)	3164 (51.3)	2205 (35.8)	<.001
Ethnicity, n (%)					<.001
Mexican American	2549 (13.8)	537 (8.7)	890 (14.4)	1122 (18.2)	
Non-Hispanic Asian	2320 (12.5)	958 (15.5)	832 (13.5)	530 (8.6)	
Non-Hispanic Black	4043 (21.9)	1657 (26.9)	1311 (21.3)	1075 (17.4)	
Non-Hispanic White	6958 (37.6)	2250 (36.5)	2187 (35.5)	2521 (40.9)	
Other Hispanic	1964 (10.6)	506 (8.2)	719 (11.7)	739 (12.0)	
Other/multiracial	662 (3.6)	258 (4.2)	226 (3.7)	178 (2.9)	
BMI, kg/m ² , mean (SD)	29.26 (6.69)	25.57 (4.97)	29.25 (5.93)	32.97 (7.53)	<.001
Waist circumference, cm, mean (SD)	99.73 (16.37)	87.67 (11.32)	99.89 (12.62)	111.63 (15.81)	<.001
Weight, kg, mean (SD)	81.78 (21.30)	75.32 (17.56)	82.31 (20.65)	87.71 (24.08)	<.001
Height, cm, mean (SD)	166.92 (10.07)	171.17 (9.43)	167.11 (9.51)	162.48 (9.41)	<.001
WWI, cm/√kg, mean (SD)	11.09 (0.85)	10.16 (0.44)	11.09 (0.21)	12.02 (0.45)	<.001
WHtR, mean (SD)	0.60 (0.10)	0.51 (0.06)	0.60 (0.06)	0.69 (0.09)	<.001
RFM, %, mean (SD)	35.79 (8.69)	29.24 (7.37)	36.00 (6.70)	42.14 (6.95)	<.001
SBP, mm Hg, mean (SD)	124.18 (18.17)	118.53 (15.45)	124.39 (17.69)	129.63 (19.65)	<.001
DBP, mm Hg, mean (SD)	70.54 (12.85)	70.28 (11.55)	71.74 (12.52)	69.61 (14.28)	<.001
HbA1c, %, mean (SD)	5.79 (1.10)	5.44 (0.77)	5.79 (1.10)	6.16 (1.29)	<.001
eGFR, mL/min/1.73 m ² , mean (SD)	94.24 (22.11)	100.24 (19.41)	94.68 (21.62)	87.79 (23.92)	<.001
Creatinine, mg/dL, mean (SD)	0.90 (0.43)	0.91 (0.36)	0.89 (0.44)	0.89 (0.47)	.044
Diabetes, n (%)	3066 (16.6)	296 (4.8)	930 (15.1)	1840 (29.8)	<.001
Hypertension, n (%)	7908 (42.8)	1454 (23.6)	2703 (43.8)	3751 (60.8)	<.001
Dyslipidemia, n (%)	6745 (36.5)	1172 (19.0)	2307 (37.4)	3266 (53.0)	<.001
Smoking status, n (%)					<.001
Current	3595 (19.4)	1415 (22.9)	1156 (18.8)	1024 (16.6)	
Former	4319 (23.4)	1039 (16.9)	1541 (25.0)	1739 (28.2)	
Never	10 582 (57.2)	3712 (60.2)	3468 (56.3)	3402 (55.2)	
CKD (eGFR <60), n (%)	1410 (7.6)	167 (2.7)	426 (6.9)	817 (13.3)	<.001
Follow-up, years, median (IQR)	4.83 (2.92–6.83)	5.33 (3.25–7.17)	4.83 (2.92–6.83)	4.42 (2.75–6.50)	<.001
All-cause mortality, n (%)	976 (5.3)	139 (2.3)	278 (4.5)	559 (9.1)	<.001
CV mortality, n (%)	291 (1.6)	30 (0.5)	84 (1.4)	177 (2.9)	<.001

Data are presented as mean (SD) for normally distributed continuous variables, median (IQR) for non-normally distributed continuous variables, and n (%) for categorical variables. *P*-values were calculated using one-way ANOVA for normally distributed variables, Kruskal–Wallis test for non-normally distributed variables, and chi-square test for categorical variables. Descriptive statistics are unweighted; all regression analyses incorporated NHANES survey weights and complex sampling design.

BMI, body mass index; CV, cardiovascular; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; NHANES, National Health and Nutrition Examination Survey; RFM, relative fat mass; SBP, systolic blood pressure; T, tertile; WHtR, waist-to-height ratio; WWI, weight-adjusted waist index.

Complete-case analysis; n = 18 496 after exclusion of participants with missing data for eGFR, HbA1c, SBP, or smoking status from the eligible cohort (n = 20 196). NHANES 2011–2018, adults aged ≥ 20 years.

overall adiposity through mutual adjustment with BMI, WWI remained significant (HR: 1.404; 95% CI: 1.252–1.575; *P* < .001), while BMI did not demonstrate a statistically significant independent association (HR: 0.900; 95% CI: 0.783–1.034; *P* = .135).

Dose–Response and Survival Analysis

Restricted cubic spline analysis revealed a linear dose–response relationship between WWI and all-cause mortality (nonlinearity *P* = .713). No significant departure from linearity was detected for WHtR either (*P* = .064). By contrast, nonlinear associations were observed for BMI (*P* = .003) and

RFM (*P* = .028). Body mass index displayed a J-shaped curve: mortality risk was elevated at low values, reached its nadir at intermediate values, and rose again at high values (Figure 2; Supplementary Table 2). Kaplan–Meier curves constructed by WWI tertiles showed that survival probability in the highest tertile was distinctly lower than in the middle and lowest tertiles (log-rank *P* < .001; Figure 3).

Subgroup and Interaction Analyses

The association between WWI and all-cause mortality was examined across prespecified subgroups (Table 3). The

Table 2. Association of Adiposity Indices with All-cause Mortality: Survey-weighted Cox Proportional Hazards Regression Models

Index	Model	HR (95% CI)	P
WWI	Model 1	1.476 (1.364-1.597)	<.001
	Model 2	1.483 (1.366-1.610)	<.001
	Model 3a	1.337 (1.227-1.458)	<.001
	Model 3b	1.404 (1.252-1.575)	<.001
BMI	Model 1	1.137 (1.029-1.257)	.012
	Model 2	1.157 (1.053-1.272)	.002
	Model 3a	1.032 (0.927-1.149)	.565
WHtR	Model 1	1.271 (1.165-1.387)	<.001
	Model 2	1.283 (1.184-1.391)	<.001
	Model 3a	1.143 (1.043-1.254)	.004
RFM	Model 1	1.412 (1.205-1.656)	<.001
	Model 2	1.446 (1.249-1.672)	<.001
	Model 3a	1.176 (0.997-1.386)	.054

Hazard ratios are expressed per 1-SD increment of each z-standardized index. n = 18 496; events (all-cause mortality) = 976. Model 1: adjusted for age and sex. Model 2: Model 1 + ethnicity, smoking status. Model 3a: Model 2 + diabetes, hypertension, dyslipidemia, eGFR, SBP, and HbA1c. Model 3b (WWI only): Model 3a + BMI (mutual adjustment); BMI in Model 3b: HR 0.900 (0.783-1.034), *P* = .135. BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RFM, relative fat mass; SBP, systolic blood pressure; WHtR, waist-to-height ratio; WWI, weight-adjusted waist index.

association was significant in both males (HR: 1.453; 95% CI: 1.237-1.707; *P* < .001) and females (HR: 1.243; 95% CI: 1.065-1.450; *P* = .006), with no significant interaction between sexes (*P* = .708; Table 3; Supplementary Figure 1). For cardio-metabolic multimorbidity, the association was maintained in both the <2 comorbidity group (HR: 1.432; *P* < .001) and the ≥2 comorbidity group (HR: 1.325; *P* < .001), with no significant interaction (*P* = .479).

A notable difference emerged in the analysis by kidney function: WWI showed a strong association in the eGFR ≥ 60 group (HR: 1.417; 95% CI: 1.276-1.575; *P* < .001) but was nonsignificant in the eGFR < 60 group (HR: 1.090; *P* = .291). Among the 4 indices, only WWI showed a significant interaction with eGFR group (*P* = .034); no such interaction was observed for the other 3 indices (Supplementary Table 3).

Sensitivity Analyses

The robustness of the primary finding was evaluated through several sensitivity analyses (Table 4). When cardiovascular mortality was analyzed as the secondary endpoint, WWI retained its significant association (Model 3a HR: 1.461; *P* = .008; Model 3b HR: 1.418; *P* = .026). In a landmark analysis designed to reduce the possibility of reverse causation, excluding deaths within the first year (n = 18 358; 853 events), results were consistent with the primary analysis (Model 3a HR: 1.311; *P* < .001).

In the 2011-2014 subcohort (n = 9323; 716 events), the association was similar in magnitude and remained significant (HR: 1.398; *P* < .001). In the fasting subsample (n = 2149; 202 events), the direction and magnitude of the effect were preserved regardless of HOMA-IR adjustment. However,

statistical significance was not reached owing to the limited sample size (without HOMA-IR: HR 1.429, *P* = .051; with HOMA-IR: HR 1.415, *P* = .059). In sex-stratified models, the association was significant in both sexes across Models 3a and 3b; the effect size was numerically larger in males than in females (male Model 3b HR: 1.546; female Model 3b HR: 1.297; Table 4).

Discrimination Analysis and Model Diagnostics

Unadjusted AUC values calculated by subgroup showed that WWI had the highest or among the highest discriminative capacity across all subgroups. The highest AUC was observed in males (0.700; 95% CI: 0.678-0.722). In the eGFR < 60 group, BMI (0.563) was numerically higher than WWI (0.541), a finding consistent with the eGFR interaction analysis (Supplementary Table 4). The proportional hazards assumption was satisfied for all 4 index models (global *P* : WWI = 0.086; BMI = 0.101; WHtR = 0.097; RFM = 0.094). In the multicollinearity assessment, all generalized variance inflation factor [GVIF^(1/2df)] values remained below 2, indicating acceptable levels (Supplementary Tables 2, 5). Pearson correlations among indices revealed a moderate correlation between WWI and BMI (*r* = 0.476), a level that supports the feasibility of the mutual adjustment model (Model 3b; Supplementary Table 5).

Harrell's C-index was highest for the WWI-containing model (0.686; 95% CI: 0.653-0.719), followed by WHtR (0.676), RFM (0.675), and BMI (0.675). Time-dependent AUC analysis confirmed that WWI maintained the highest discriminative capacity at all time points (1-year: 0.711; 3-year: 0.681; 5-year: 0.678; Supplementary Table 6). As no formal statistical comparison was conducted, these differences should be considered descriptive.

DISCUSSION

Among the 4 adiposity indices evaluated in this study, WWI demonstrated the most pronounced independent association with both all-cause and cardiovascular mortality (fully adjusted model, HR per 1 SD: 1.337; 95% CI: 1.227-1.458). Unlike BMI, WHtR, and RFM, which were compared within the same modeling framework through z-standardization, WWI retained its significance after mutual adjustment with BMI, whereas BMI lost its independent contribution. This finding suggests that WWI carries a prognostic signal specific to central fat distribution beyond total adiposity, and that BMI-based risk assessment may entail a substantial loss of information.

Park et al⁷ developed WWI in 2018 using a South Korean national cohort of 465 629 individuals and reported that it was the only adiposity measure displaying a linear positive association with cardiovascular mortality.⁷ The present analysis confirmed this finding in a Western population and, by presenting a head-to-head comparison of 4 indices within a single analytical framework, demonstrated that WWI is distinguished from the other indices not only by its linear association but also by its effect size.

Studies examining the WWI-mortality relationship have increased rapidly in recent years. In general populations,

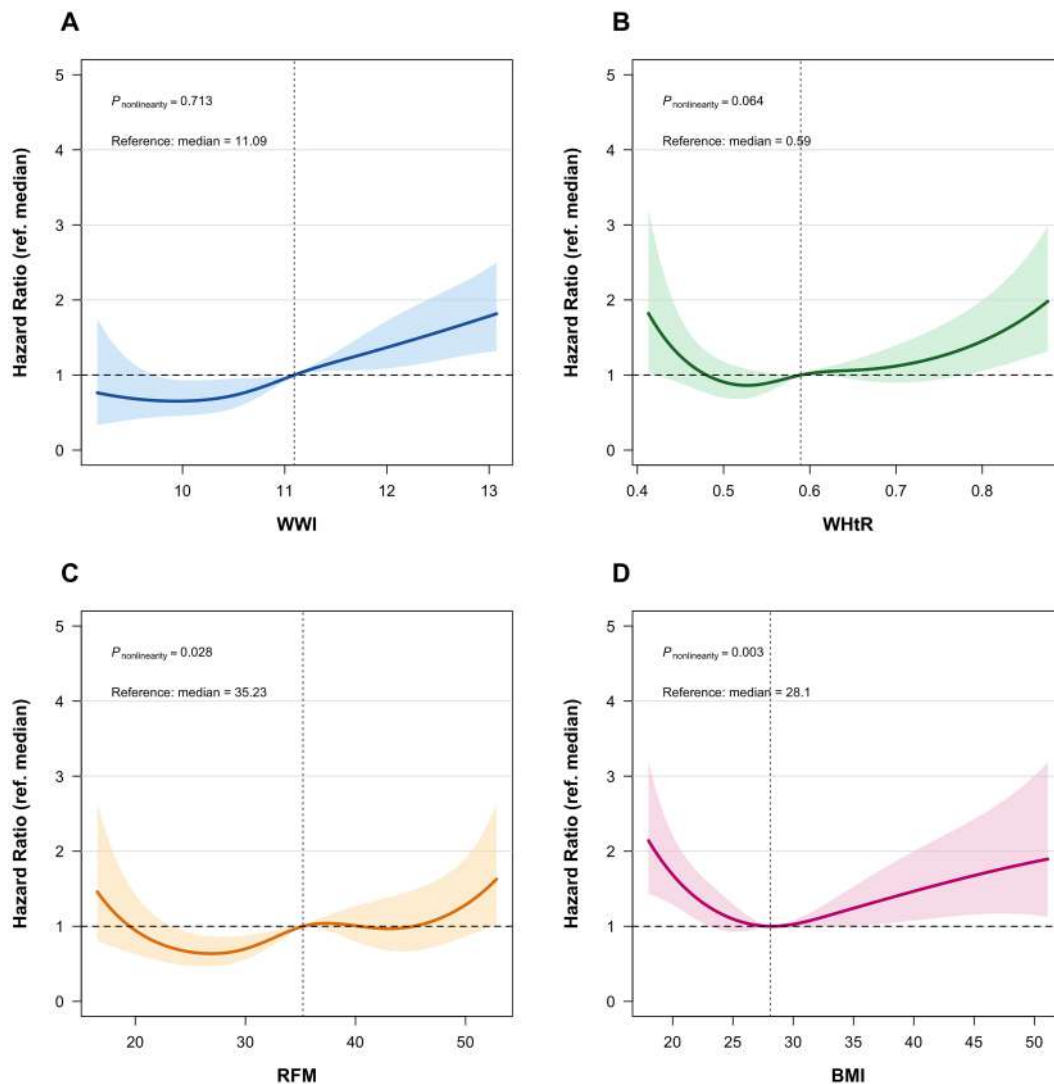


Figure 2. Restricted cubic spline curves for adiposity indices and all-cause mortality. (A) WWI, (B) WHtR, (C) RFM, and (D) BMI. Reference values were set at the median (dotted vertical line). Shaded areas represent 95% confidence intervals. *P* values for nonlinearity are shown within each panel. BMI, body mass index; RFM, relative fat mass; WHtR, waist-to-height ratio; WWI, weight-adjusted waist index.

Han et al, using NHANES 2005-2014 data and Cao et al¹³, using NHANES 2011-2018 data restricted to non-Asian participants, both reported a positive association between WWI and all-cause mortality along with superior discriminative capacity compared with BMI and waist circumference.^{12,13} Similarly, WWI consistently demonstrated the highest discriminative capacity across all subgroups, a pattern concordant with both of these reports. Previous studies, however, evaluated WWI against a limited number of indices on different scales. The present work is among the few to compare 4 adiposity indices using z-standardization within the same modeling framework, showing that WWI is distinguished from the others not only in statistical significance but also in effect size.

An important inconsistency exists in the literature regarding the shape of the dose-response relationship. Cao et al¹³ reported a U-shaped association between WWI and all-cause mortality, identifying an inflection point at 10.46

cm/ $\sqrt{\text{kg}}$ below which an inverse relationship was observed. In the analysis, restricted cubic spline analysis showed no significant departure from linearity ($P=.713$), and the WWI-mortality relationship followed a monotonically increasing pattern. Several methodological factors may account for this discrepancy. First, nonlinearity was assessed using different approaches: Cao et al employed piecewise linear regression, whereas this study applied restricted cubic spline analysis with a formal linearity test that does not assume a predetermined shape; the sensitivity of these 2 methods to detecting an inflection point differs. Second, and likely most critical, the depth of covariate adjustment differed substantially: the fully adjusted model of Cao et al included self-reported disease status, whereas our model incorporated eGFR, HbA1c, and systolic blood pressure as continuous variables. This additional adjustment may have more effectively controlled for residual confounding attributable to subclinical disease and cachexia at the lower end of the

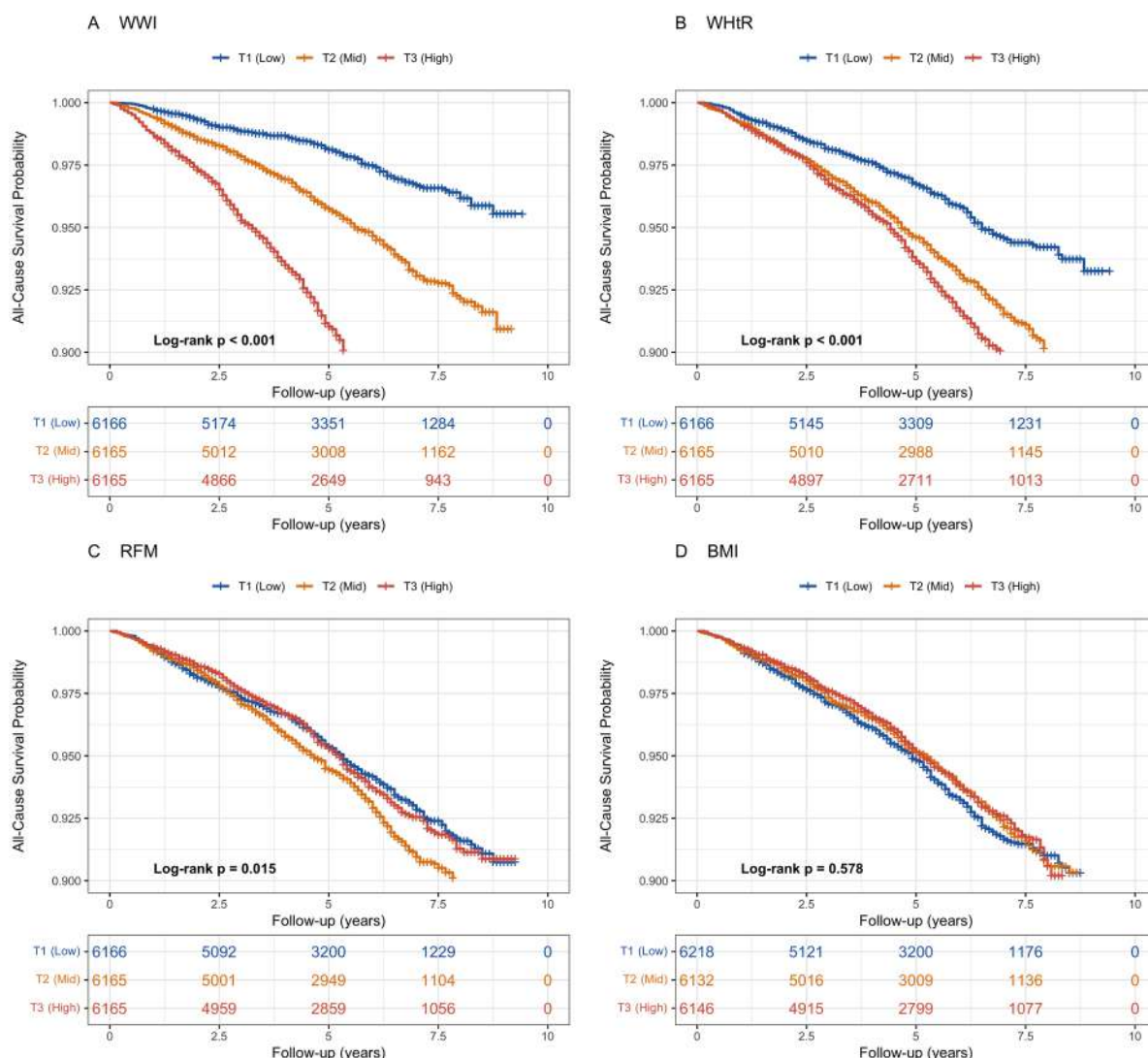


Figure 3. Kaplan–Meier survival curves for all-cause mortality by adiposity index tertiles. (A) WWI, (B) WHtR, (C) RFM, and (D) BMI. Number-at-risk tables are shown below each panel. BMI, body mass index; RFM, relative fat mass; WHtR, waist-to-height ratio; WWI, weight-adjusted waist index.

WWI distribution. Third, differences in population definition (non-Asian only vs. all ethnic groups) and missing data strategy (multiple imputation vs. complete-case analysis) may also have influenced the shape of the curve.

Regarding cardiovascular mortality, our study yielded results that maintained statistical significance in the fully adjusted model (HR: 1.461; $P = .008$) and after BMI adjustment (HR: 1.418; $P = .026$). These findings are comparable in magnitude to those of Qiu et al¹⁴, who reported an HR of 1.45 for the combined triglyceride-glucose (TyG)-WWI index for cardiovascular mortality. Notably, WWI achieved a similar effect size on its own without the addition of metabolic parameters, which is relevant from the standpoint of clinical applicability. Notably, WWI is calculated simply as waist circumference (cm) divided by the square root of body weight (kg), making it a practical and easily applicable index in clinical settings.

A noteworthy finding also emerged from the mutual adjustment model (Model 3b): WWI maintained its significance (HR:

1.404; $P < .001$) while BMI did not demonstrate a statistically significant independent contribution in the fully adjusted model (HR: 0.900; $P = .135$). This pattern suggests that the association of BMI with mortality largely originates from its central adiposity component, and that once this component is captured by WWI, BMI did not provide additional prognostic information within the present analytical framework. The dose–response analyses further confirm the structural difference between these 2 indices. WWI displayed a monotonically increasing linear relationship, whereas BMI showed a J-shaped curve and failed to establish a clear risk gradient.

Although WHtR also measures central adiposity, it exhibited a substantially lower effect size than WWI in Model 3a (HR: 1.143 vs. 1.337). This difference has a formulaic basis: because WHtR divides waist circumference by height and height is constant in adults, the index in practice reflects waist circumference itself. WWI, by contrast, normalizes waist circumference by the square root of body weight,

Table 3. Subgroup Analyses for the Association Between the Weight-adjusted Waist Index and All-cause Mortality: Cox Proportional Hazards Regression Models

Subgroup	n	Events	HR (95% CI)	P	P Interaction
Overall	18 496	976	1.337 (1.227-1.458)	<.001	
Sex					.708
Male	9062	579	1.453 (1.237-1.707)	<.001	
Female	9434	397	1.243 (1.065-1.450)	.006	
Multimorbidity					.479
≥2 comorbidities	6038	617	1.325 (1.161-1.512)	<.001	
<2 comorbidities	12 458	359	1.432 (1.180-1.737)	<.001	
Kidney function					.034
eGFR ≥60 mL/min/1.73 m ²	17 086	660	1.417 (1.276-1.575)	<.001	
eGFR <60 mL/min/1.73 m ²	1410	316	1.090 (0.929-1.279)	.291	

Hazard ratios are expressed per 1-SD increment of z-standardized WWI. All models adjusted for age, sex, ethnicity, smoking status, diabetes, hypertension, dyslipidemia, eGFR, SBP, and HbA1c (Model 3a), except the stratification variable itself.

P interaction was derived from the likelihood ratio test comparing models with and without the cross-product interaction term (WWI × subgroup variable).

Multimorbidity was defined as the co-presence of ≥2 of diabetes, hypertension, and dyslipidemia. Bold values indicate statistical significance at $P < .05$.

eGFR, estimated glomerular filtration rate; HR, hazard ratio; WWI, weight-adjusted waist index.

thereby differentiating among individuals with the same waist circumference according to body weight. Individuals with a lower body weight for a given waist circumference receive a higher WWI value, pointing to a phenotype in which the central fat burden is dominant relative to total body mass or in which muscle mass is relatively reduced, both of which are metabolically higher-risk states. This mechanistic

distinction explains why WWI carries a stronger prognostic signal than WHtR.

The dose–response relationship between BMI and mortality substantiated this pattern through restricted cubic spline analysis (nonlinearity $P = .003$): mortality risk was elevated at low BMI values, reached a minimum at intermediate

Table 4. Sensitivity Analyses for the Association Between the Weight-adjusted Waist Index and Mortality: Cox Proportional Hazards Regression Models

Sensitivity Analysis	n	Events	HR (95% CI)	P
Primary analysis (Model 3a)	18 496	976	1.337 (1.227-1.458)	<.001
Landmark analysis (excluding deaths <1 year)				
Model 3a	18 358	853	1.311 (1.185-1.450)	<.001
Model 3b (+ BMI)	18 358	853	1.360 (1.192-1.551)	<.001
Cardiovascular mortality (secondary outcome)				
Model 3a	18 496	291	1.461 (1.105-1.931)	.008
Model 3b (+ BMI)	18 496	291	1.418 (1.042-1.929)	.026
Restricted to NHANES 2011-2014 cycles				
Model 3a	9323	716	1.398 (1.267-1.543)	<.001
HOMA-IR subset (fasting subsample)				
Model 3a (without HOMA-IR)	2149	202	1.429 (0.998-2.047)	.051
Model 3a + HOMA-IR	2149	202	1.415 (0.987-2.029)	.059
Sex-stratified (Model 3a)				
Male	9062	579	1.453 (1.237-1.707)	<.001
Female	9434	397	1.243 (1.065-1.450)	.006
Sex-stratified (Model 3b, + BMI)				
Male	9062	579	1.546 (1.273-1.878)	<.001
Female	9434	397	1.297 (1.068-1.574)	.009

Hazard ratios are expressed per 1-SD increment of z-standardized WWI. Model 3a: adjusted for age, sex, ethnicity, smoking status, diabetes, hypertension, dyslipidemia, eGFR, SBP, and HbA1c. Model 3b: Model 3a + BMI (mutual adjustment).

Landmark analysis excluded participants who died within the first year of follow-up to reduce reverse causation bias. The HOMA-IR subset was restricted to the fasting subsample with available insulin measurements (NHANES morning fasting session). The 2011-2014 subcohort analysis was performed to assess temporal consistency.

BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; SBP, systolic blood pressure; WWI, weight-adjusted waist index.

values, and rose again at high values. This nonlinear pattern explains why BMI lost significance in the linear Cox model. The opposing risks at the low and high ends of the distribution cancel each other out, driving the net effect size toward zero. This finding aligns with the phenomenon described as the "obesity paradox," whereby BMI fails to predict mortality consistently. This paradox has been documented even in high-risk procedural settings, where elevated BMI did not confer a consistent survival advantage.¹⁵ Lv et al¹⁶ demonstrated a reverse-J relationship between BMI and mortality in the oldest age group (≥ 80 years) and reported that the optimal BMI range shifted toward the overweight-to-obese region. Liu et al¹⁷ reported that BMI exhibited a paradoxical inverse association with mortality in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), whereas WWI maintained its linear positive association. Yeo et al¹⁸, in a study spanning 4 large cohorts, argued that the obesity paradox observed with BMI may in fact result from the use of an inappropriate metric and that waist-based indices reflect mortality more accurately.

There is a structural explanation for why WWI does not fall into this paradox. Body mass index (kg/m^2) cannot distinguish between muscle mass and fat mass; individuals with high muscle mass carry low mortality risk despite a high BMI, while those with low BMI may face increased risk due to cachexia or sarcopenia. This constitutes the left arm of the J-curve. Weight-adjusted waist index, by normalizing waist circumference by the square root of body weight, captures differences in central fat distribution even among individuals of the same weight and is therefore less susceptible to the protective effect of muscle mass or the confounding effect of cachexia. In line with this reasoning, no statistically significant departure from linearity was found in our data for WWI ($P=.713$) and a monotonically increasing relationship with mortality was observed, confirming that WWI is not affected by the structural limitations of BMI. From a clinical perspective, the linear and consistently increasing relationship between WWI and mortality offers a practical advantage: each increment in WWI corresponds to a proportional increase in risk, without the paradoxical risk reduction at lower values observed with BMI. This unidirectional association simplifies risk assessment and facilitates clinical interpretation; higher values consistently indicate higher risk.

The independent prognostic value of WWI beyond BMI points to pathophysiological mechanisms specific to central adiposity. Visceral adipose tissue is metabolically far more active than subcutaneous fat and directly elevates cardiometabolic risk through proinflammatory, prothrombotic, and insulin resistance-promoting effects.^{4,19} The divergence in Model 3b, where WWI retained significance (HR: 1.404) while BMI did not retain statistical significance ($P=.135$), supports the notion that these visceral-specific mechanisms constitute a risk component independent of total adiposity.

This concordance has a structural basis: normalizing waist circumference by the square root of body weight isolates differences in central fat distribution among individuals of

the same weight and thereby captures the variability in the visceral-to-subcutaneous fat ratio that BMI cannot detect. Geng et al²⁰, in a dual-cohort study (Chinese Changshu cohort and UK Biobank), demonstrated that the WWI-mortality association was mediated by insulin resistance (16%-38% mediation via estimated glucose disposal rate [eGDR]) and inflammation (8%-9% mediation via C-reactive protein [CRP]). In a complementary fashion, Wang et al²¹ reported that inflammatory markers played a significant mediating role in the WWI-mortality association among patients with cardiometabolic syndrome. Collectively, these observations indicate that the prognostic information carried by WWI reflects not merely an anatomical measurement but an active metabolic process.

Along these lines, in the fasting subsample where insulin measurements were available ($n=2149$; 202 events), the effect size of WWI was virtually unchanged after additional adjustment for HOMA-IR (unadjusted HR: 1.429; adjusted HR: 1.415). This minimal change indicates that the insulin resistance component measurable by HOMA-IR explains only a small fraction of the WWI signal. HOMA-IR, however, is a crude measure based on fasting insulin and glucose and may not fully capture tissue-level insulin resistance associated with visceral adiposity. Under either interpretation, the conclusion points in the same direction: the prognostic signal of WWI reflects a constellation of multiple metabolic processes that encompasses insulin resistance but also includes additional pathways such as inflammation, ectopic fat deposition, and endothelial dysfunction. The failure to reach statistical significance ($P=.059$) due to the limited number of events ($n=202$) does not alter this interpretation; it merely constrains the precision of quantitative inference.

In the subgroup analyses, a statistically significant interaction with eGFR group was detected for WWI alone among the 4 indices ($P=.034$): WWI was a strong mortality predictor in participants with preserved kidney function (eGFR ≥ 60 ; HR: 1.417; $P<.001$) but lost its association in the eGFR < 60 group (HR: 1.090; $P=.291$). Similarly, Tao et al²² reported that the association of WWI with cardiovascular disease and mortality in 12 641 individuals with metabolic syndrome was observed only in those with preserved kidney function and could not be detected in the CKD subgroup. Wu et al²³, on the other hand, reported a nonlinear rather than linear association between WWI and all-cause mortality directly in a CKD population (UK Biobank, $n=22 523$). No interaction was observed for the other 3 indices (Supplementary Table 3); however, because these indices already exhibited more modest or nonsignificant effect sizes in the fully adjusted model, the lack of interaction reflects low effect sizes insufficient to generate a detectable difference between subgroups rather than consistent prognostic strength.

A possible mechanistic explanation for this interaction may lie in the formulaic structure of WWI. Because WWI normalizes waist circumference by the square root of body weight, any change in weight directly affects the index value. Protein-energy wasting, uremic sarcopenia, and fluid retention, all commonly observed in CKD, may disrupt the relationship

between waist circumference and weight in multiple ways: muscle loss reduces weight while waist circumference may be relatively preserved, and edema increases weight without reflecting visceral fat.²⁴ Under these conditions, WWI may no longer accurately reflect central adiposity, potentially compromising its measurement validity and contributing to the loss of its prognostic capacity. This sensitivity of WWI's formulaic structure to weight fluctuations may explain why the interaction was detected for WWI alone among the 4 indices. These mechanistic considerations are hypothesis-generating and warrant confirmation in prospective studies.

The WWI–mortality association was consistent with respect to cardiometabolic multimorbidity and sex. WWI remained significant in both the <2 comorbidity (HR: 1.432; $P < .001$) and ≥ 2 comorbidity (HR: 1.325; $P < .001$) groups, with no interaction by comorbidity level ($P = .479$), indicating that the prognostic value of WWI is preserved even in the presence of a high disease burden. This finding is concordant with the results of Fan et al²⁵, who showed that elevated WWI independently increased mortality risk in multimorbid older adults in China. With respect to sex, significant associations were observed in both males (HR: 1.453; $P < .001$) and females (HR: 1.243; $P = .006$), with no interaction between sexes ($P = .708$), demonstrating that WWI retains its prognostic value in both sexes. Ding et al²⁶ also reported that the WWI–mortality association remained consistent across sex subgroups in adults from southern China ($n = 12\,447$; median follow-up 5.6 years). Although the numerically larger effect size in males is concordant with sex differences in visceral fat distribution,²⁷ this difference did not reach the level of a statistically significant interaction. Considered together, these findings demonstrate that the prognostic value of WWI is consistently maintained across the general population regardless of comorbidity burden and sex.

From a clinical applicability standpoint, the linear association between WWI and mortality offers a notable advantage for risk communication: as the index value increases, risk increases progressively, avoiding the “safe range” misconception created by the J-shaped curve of BMI. This property may facilitate more straightforward communication of adiposity-related risk to patients. However, no validated clinical decision thresholds were proposed in this study, as the cut-points derived from the same dataset are sample-specific and cannot be generalized without external validation. The establishment of population- and sex-specific clinical thresholds through prospective cohorts represents a necessary next step for the integration of WWI into routine risk assessment.

Limitations

This study has a design that compares 4 adiposity indices using z-standardization within a single analytical framework based on a nationally representative cohort. Comprehensive sensitivity analyses and a robust analytic sample that preserved baseline characteristics with minimal attrition of 8.4% (Supplementary Table 1) are among the study's strengths. Several limitations, however, should be acknowledged.

Anthropometric measurements in NHANES were obtained at a single time point and do not capture changes in adiposity over the follow-up period; this may have attenuated the true effect size through regression dilution bias. Physical activity and dietary data, based on self-report and 24-hour recall, were not included in the models due to high measurement error, although residual confounding attributable to these variables cannot be excluded. Similarly, socioeconomic variables such as income and education level were not included in the models. Although the clinical covariates in the model may partially reflect the health effects of these factors, residual confounding from socioeconomic variables cannot be disregarded. The median follow-up of 4.83 years is relatively short for capturing long-term dynamics of adiposity–mortality associations, and longer-term relationships may differ. However, the sensitivity analysis conducted in the 2011–2014 subcohort provides a longer follow-up period (~7 years) and yielded results consistent with the primary analysis (HR: 1.398; $P < .001$). Nonetheless, validation of these associations through prospective cohorts with longer follow-up is warranted. NHANES represents the non-institutionalized civilian population of the United States, which limits the generalizability of the findings to different ethnic backgrounds. The observational design precludes causal inference; temporal ordering and the landmark analysis, however, reduce the likelihood of reverse causation. In the definition of cardiovascular mortality, cerebrovascular deaths were not separately coded in the 2015–2018 cycles. The sensitivity analysis conducted in the 2011–2014 subcohort, where complete coding was available, yielded results consistent with the primary analysis that included all cycles; however, this coding difference may have potentially affected cardiovascular mortality estimates.

CONCLUSION

WWI was identified as the most robust independent predictor of all-cause and cardiovascular mortality among the 4 adiposity indices examined. Its monotonically increasing linear association with mortality indicates that the index establishes a clear risk gradient. This association is consistent across sex and levels of cardiometabolic multimorbidity; however, the prognostic capacity of the index is notably attenuated in the eGFR < 60 subgroup. The fact that WWI can be calculated using only waist circumference and body weight renders it a practical clinical tool that does not require expensive imaging or laboratory testing. Nonetheless, the determination of population- and sex-specific clinical decision thresholds and the validation of the index through prospective cohorts with longer follow-up, particularly in patients with impaired kidney function, will clarify the role of WWI in routine risk assessment.

Ethics Committee Approval: This study used publicly available, de-identified data from the National Health and Nutrition Examination Survey (NHANES), which was approved by the NCHS Research Ethics Review Board (Protocol #2011-17 and Protocol #2018-01). Additional institutional review board approval was not required for this secondary analysis.

Informed Consent: Written informed consent was obtained from all NHANES participants by the National Center for Health Statistics during the original data collection. No additional consent was required for this secondary analysis of de-identified data.

Peer-review: Externally peer-reviewed.

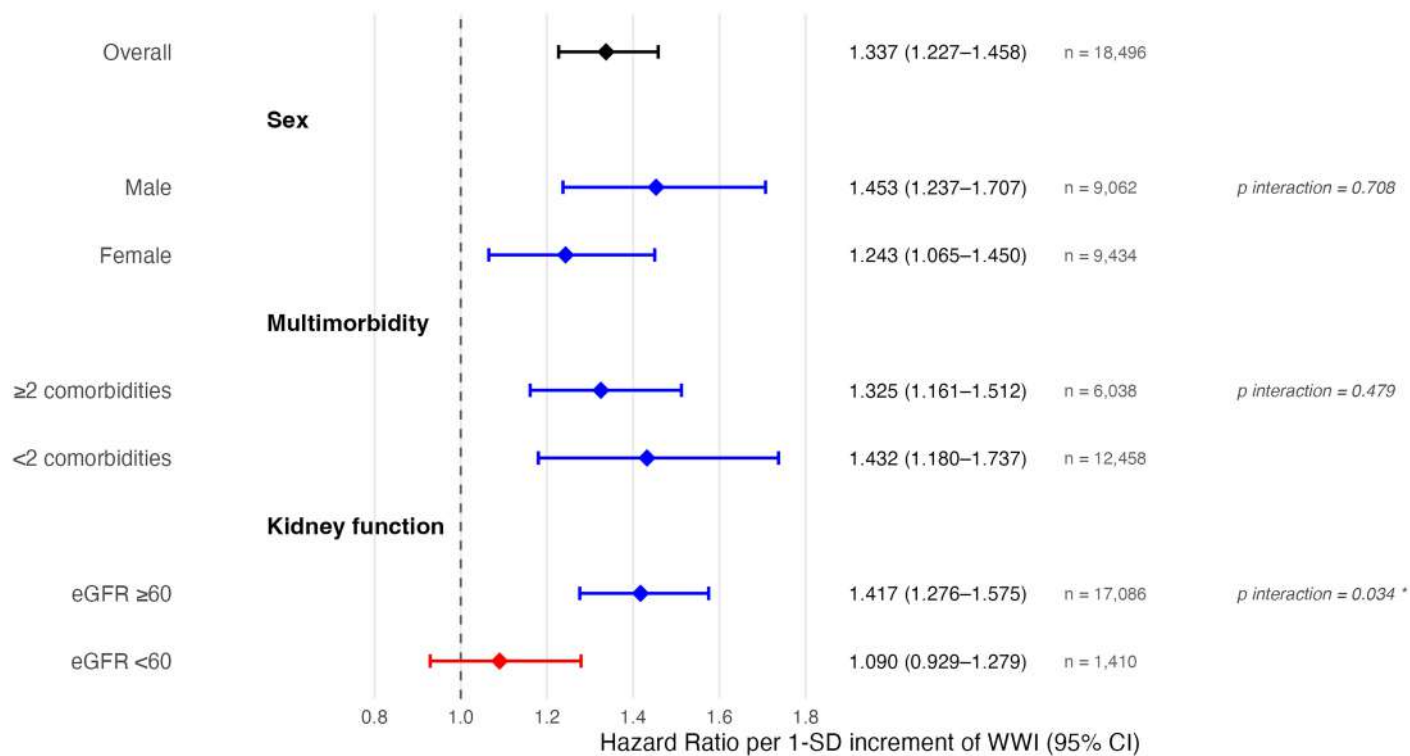
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Supplementary Figure 1. Forest plot of subgroup analyses for WWI and all-cause mortality. Subgroups were stratified by sex, cardiometabolic multimorbidity, and kidney function. Hazard ratios are per 1-SD increment of WWI. P values for interaction are displayed on the right.

Supplementary Table 1. Comparison of baseline characteristics between participants included in and excluded from the analytic sample

Variables	Excluded (n=1,700)	Included (n=18,496)	p	SMD
Age, years, mean (SD)	48.57 (17.78)	49.26 (17.42)	0.119	0.039
Male sex, n (%)	783 (46.1)	9,062 (49.0)	0.022	0.059
Ethnicity, n (%)			<0.001	0.270
Mexican American	188 (11.1)	2,549 (13.8)		
Non-Hispanic Asian	272 (16.0)	2,320 (12.5)		
Non-Hispanic Black	528 (31.1)	4,043 (21.9)		
Non-Hispanic White	488 (28.7)	6,958 (37.6)		
Other Hispanic	162 (9.5)	1,964 (10.6)		
Other/Multiracial	62 (3.6)	662 (3.6)		
BMI, kg/m ² , mean (SD)	28.93 (7.36)	29.26 (6.93)	0.062	0.046
Waist circumference, cm, mean (SD)	98.34 (17.34)	99.73 (16.58)	0.001	0.082
Weight, kg, mean (SD)	79.64 (22.51)	81.78 (21.54)	<0.001	0.097
WWI, cm/√kg, mean (SD)	11.09 (0.90)	11.09 (0.85)	0.869	0.004
All-cause mortality, n (%)	128 (7.5)	976 (5.3)	<0.001	0.092
CV mortality, n (%)	26 (1.5)	291 (1.6)	0.970	0.004

Data are presented as mean (SD) for continuous variables and n (%) for categorical variables. The eligible cohort (N = 20,196) comprised adults aged ≥20 years with complete anthropometric data and valid mortality follow-up from NHANES 2011–2018. The analytic sample (n = 18,496) further required non-missing values for eGFR, HbA1c, systolic blood pressure, and smoking status. Participants excluded from the analytic sample (n = 1,700) had missing data for at least one of these covariates.

p-values were calculated using the independent samples t-test for continuous variables and the chi-square test for categorical variables. SMD, standardized mean difference; values <0.1 indicate negligible between-group differences.

WWI, weight-adjusted waist index; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SMD, standardized mean difference.

Supplementary Table 2. Model diagnostics: proportional hazards assumption and restricted cubic spline nonlinearity tests

Index	Test	Statistic	df	P
WWI	Schoenfeld global	26.65	18	.086
	Schoenfeld (WWI term)	1.38	1	.240
BMI	Schoenfeld global	25.94	18	.101
	Schoenfeld (BMI term)	0.09	1	.769
WHtR	Schoenfeld global	26.13	18	.097
	Schoenfeld (WHtR term)	0.12	1	.730
RFM	Schoenfeld global	26.27	18	.094
	Schoenfeld (RFM term)	0.45	1	.503
WWI	RCS nonlinearity	1.35	3	.713
BMI	RCS nonlinearity	16.58	3	.003
WHtR	RCS nonlinearity	7.83	3	.064
RFM	RCS nonlinearity	10.09	3	.028

The proportional hazards assumption was assessed using Schoenfeld residuals (cox.zph). Because cox.zph() does not support survey-weighted Cox objects (svycoxph), standard Cox models with normalized survey weights as case weights were used, an approach consistent with prior NHANES mortality studies. The assumption was satisfied for all four index models (global p > 0.05) and for all exposure terms (P > 0.05).

Nonlinearity was assessed using restricted cubic splines (natural splines, df = 4) in survey-weighted Cox models. The p-value reflects the Rao-Scott likelihood ratio test comparing the nonlinear (spline) model to the linear model. A significant p-value indicates departure from linearity.

WWI, weight-adjusted waist index; BMI, body mass index; WHtR, waist-to-height ratio; RFM, relative fat mass; RCS, restricted cubic spline; PH, proportional hazards.

Supplementary Table 3. Interaction tests between adiposity indices and subgroup variables for all-cause mortality

Index	Interaction term	P interaction
WWI	× Sex	.708
	× Multimorbidity	.479
	× eGFR group	.034
BMI	× Sex	.736
	× Multimorbidity	.974
	× eGFR group	.677
WHtR	× Sex	.625
	× Multimorbidity	.720
	× eGFR group	.750
RFM	× Sex	.817
	× Multimorbidity	.521
	× eGFR group	.573

P interaction was derived from the likelihood ratio test comparing survey-weighted Cox models (Model 3a) with and without the cross-product interaction term. Bold indicates statistical significance (p < 0.05). Only the WWI × eGFR group interaction reached significance.

Multimorbidity was defined as the co-presence of ≥2 of diabetes, hypertension, and dyslipidemia. eGFR group: ≥60 vs <60 mL/min/1.73 m². WWI, weight-adjusted waist index; BMI, body mass index; WHtR, waist-to-height ratio; RFM, relative fat mass; eGFR, estimated glomerular filtration rate.

Supplementary Table 4. Discriminative ability (AUC) of adiposity indices for all-cause mortality by subgroup

Subgroup	WWI	BMI	WHtR	RFM
Male (n = 9,062)	0.700 (0.678–0.722)	0.522 (0.497–0.547)	0.584 (0.560–0.608)	0.584 (0.560–0.608)
Female (n = 9,434)	0.669 (0.643–0.695)	0.511 (0.482–0.540)	0.566 (0.539–0.594)	0.566 (0.539–0.594)
MM ≥ 2 (n = 6,038)	0.582 (0.559–0.606)	0.587 (0.562–0.612)	0.528 (0.503–0.553)	0.548 (0.524–0.571)
MM < 2 (n = 12,458)	0.655 (0.626–0.684)	0.529 (0.499–0.559)	0.556 (0.526–0.586)	0.533 (0.504–0.562)
eGFR ≥ 60 (n = 17,086)	0.658 (0.637–0.679)	0.521 (0.498–0.543)	0.560 (0.538–0.582)	0.516 (0.494–0.538)
eGFR < 60 (n = 1,410)	0.541 (0.505–0.576)	0.563 (0.526–0.601)	0.527 (0.490–0.564)	0.541 (0.505–0.577)

Area under the receiver operating characteristic curve (AUC) with 95% confidence intervals. Higher AUC indicates better discriminative ability for all-cause mortality.

AUC values represent unadjusted, single-predictor discrimination for binary mortality status and do not account for survival time or covariate adjustment. These values are intended for relative comparison among indices within each subgroup rather than as measures of overall model performance. The relatively low AUC values reflect the limited discriminative ability of any single anthropometric index for mortality prediction in isolation.

MM, multimorbidity (≥ 2 of diabetes, hypertension, dyslipidemia); eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); WWI, weight-adjusted waist index; BMI, body mass index; WHtR, waist-to-height ratio; RFM, relative fat mass.

Supplementary Table 5. Multicollinearity assessment and correlation matrix of adiposity indices

	Panel A: Generalized variance inflation factors (Model 3b)					
Variables	GVIF	df	GVIF^(1/2df)			
WWI (z-score)	1.479	1	1.216			
BMI (z-score)	1.422	1	1.192			
Sex	1.143	1	1.069			
Ethnicity	1.261	5	1.023			
Smoking status	1.126	2	1.030			
Diabetes	1.776	1	1.333			
Hypertension	1.656	1	1.287			
Dyslipidemia	1.508	1	1.228			
eGFR	1.096	1	1.047			
SBP	1.185	1	1.089			
HbA1c	1.709	1	1.307			
	Panel B: Pearson correlation matrix					
	WWI	BMI	Waist	WHtR	RFM	Age
WWI	1.000	0.476	0.649	0.790	0.678	0.473
BMI	0.476	1.000	0.907	0.913	0.605	0.028
Waist circumference	0.649	0.907	1.000	0.932	0.519	0.180
WHtR	0.790	0.913	0.932	1.000	0.729	0.233
RFM	0.678	0.605	0.519	0.729	1.000	0.171
Age	0.473	0.028	0.180	0.233	0.171	1.000

GVIF, generalized variance inflation factor. GVIF^{1/2}(1/2df) is the scale-adjusted metric comparable to the square root of classical VIF. Values < 2 indicate acceptable collinearity. Model 3b includes both WWI and BMI as mutual adjustment.

Pearson correlation coefficients among adiposity indices, waist circumference, and age. n = 18,496.

Waist circumference and age are included to illustrate the structural relationship among indices; waist circumference is a component of WWI, and age was used as a stratification variable rather than a covariate.

Supplementary Table 6. Time-dependent discriminative ability of adiposity indices for all-cause mortality

	WWI	BMI	WHtR	RFM
Harrell's C-index (95% CI)	0.686 (0.653–0.719)	0.675 (0.641–0.708)	0.676 (0.643–0.710)	0.675 (0.642–0.709)
Time-dependent AUC				
1-year	0.711	0.708	0.703	0.704
3-year	0.681	0.679	0.676	0.676
5-year	0.678	0.671	0.670	0.670

Harrell's C-index was derived from fully adjusted Cox proportional hazards models (Model 3a: age stratification + sex + ethnicity + smoking + diabetes + hypertension + dyslipidemia + eGFR + SBP + HbA1c). Time-dependent AUC was calculated using inverse probability of censoring weighting (IPCW) based on the linear predictors of the same Cox models at 1-, 3-, and 5-year time points. WWI, weight-adjusted waist index; BMI, body mass index; WHtR, waist-to-height ratio; RFM, relative fat mass; AUC, area under the receiver operating characteristic curve; CI, confidence interval; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Artificial Intelligence for Peer Review in Cardiovascular Journals: Promise, Pitfalls, and a Path to Responsible Hybrid Adoption

INTRODUCTION

The growing strain on peer review is especially visible in high-volume specialties such as cardiovascular medicine, where editors face increasing submissions, reviewer fatigue, and delayed decision timelines. A recent letter by Tatar¹ rightly frames this as a practical crisis and notes that both authors and reviewers are already using artificial intelligence (AI) tools in real-world workflows, whether journals are ready or not. This reality calls for an important discussion, not whether AI should be involved in peer review, but how cardiovascular journals can use it safely, transparently, and without weakening scientific judgment.

It is important to distinguish between AI use by authors, reviewers, and editors because each context carries different ethical and operational risks.²⁻⁷ For authors, AI use mainly raises questions related to transparency, originality, authorship responsibility, accuracy of generated content, and disclosure. For reviewers, the major concerns are confidentiality, independent scientific judgment, potential uploading of unpublished manuscripts to non-secure platforms, and accountability for the final review. For editors, AI use may involve manuscript triage, reviewer identification, technical screening, plagiarism checks, reporting-guideline assessment, and decision support; however, final editorial responsibility must remain human-led. Thus, the central question is not simply whether AI can assist scientific publishing, but which stakeholder is using AI, for what purpose, under what level of security, and with what form of disclosure and oversight. In this article, we focus primarily on reviewer- and editor-facing AI use in cardiovascular journals.^{3,5-8}

We are concerned that traditional researcher-led peer review is under increasing strain, driven by rising manuscript volume, reviewer fatigue, increasing methodological complexity, and delayed editorial timelines. Therefore, the aim of this article is to examine how AI-assisted workflows might strengthen, rather than replace, human-led peer review in cardiovascular journals. This article is a narrative perspective rather than a systematic review. Accordingly, it offers a selective synthesis of recent evidence and policy-relevant examples; much of the current evidence derives from surveys, simulations, and experimental studies, with limited prospective validation in real-world editorial workflows. Strong justifications can be presented for AI use in peer review. First, AI can improve efficiency in tasks that are repetitive, time-consuming, and open to structured checking. In a *JAMA* editorial on AI in peer review, Perlis and colleagues highlight potential uses such as manuscript summarization, checklist adherence checks, flagging missing reporting items, and comparing internal consistency across abstracts, text, and tables.² They also anticipate parallel workflows in which AI-generated assessments support, rather than replace, human reviewers and editors, potentially shortening time to decision.² This “driver-assistance, not autonomous driving” framing is particularly relevant for cardiovascular journals, where methodological complexity and clinical consequence are high.² In cardiovascular publishing, such structured assistance could include checking CONSORT-related reporting elements in clinical trials, identifying inconsistencies between imaging measurements reported in

SCIENTIFIC LETTER

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the text and tables, flagging missing device-related methodological information, or checking the completeness of reporting in AI-assisted echocardiography, cardiac CT, and cardiac MRI studies.

Second, editors themselves appear open to selective AI integration. In the AIMPub survey of medical journal Editors-in-Chief, 49% reported that their journals already use AI tools (12% extensively, 37% occasionally), most commonly for plagiarism checks (76%), data integrity verification (35%), and automated reference checking (29%).⁹ Time savings (79%) and cost reduction (43%) were the most commonly cited advantages.⁹ This survey includes substantial cardiovascular editorial representation and a broad editorial leadership sample, making it especially relevant to the question of policy design in cardiovascular journals.⁹

Third, AI may help address the equity gaps in reviewer identification, if used deliberately. Teixeira's randomized trial showed that when GPT-4o was asked to identify potential expert reviewers without a diversity/equity/inclusion (DEI) prompt, it disproportionately returned male scientists (68%) and those from high-income countries (95.3%). However, with a detailed and clear DEI prompt, the output became gender-balanced (51% women) and much more geographically diverse, while bibliometric indicators (publications, citations, and h-index) remained comparable between groups.¹⁰ This is highly relevant for cardiovascular journals seeking broader global reviewer pools: AI can either entrench bias or help counteract it, depending on prompt design and oversight.

At the same time, important limitations and risks associated with uncritical AI use in peer review require careful consideration. The most immediate concern is confidentiality. Li et al's cross-sectional analysis of the top 100 medical journals found that 78% had guidance on AI use in peer review; among those, 59% clearly prohibited AI use, and 91% prohibited uploading manuscript-related content to AI tools. Confidentiality was the dominant reason (96% of journals with guidance).³ The same study also found that guidance was scattered and variable, with inconsistent disclosure requirements and even contradictions with linked statements in some journals.³ For cardiovascular journals, submitted manuscripts may contain unpublished trial data, large imaging datasets, device innovations, commercially sensitive analyses, and AI-assisted imaging or risk-prediction models. We therefore propose that confidentiality governance address not only whether manuscript content may be uploaded, but also data retention and deletion, secondary use or model training, where and under which legal jurisdiction data are stored and processed, and the contractual data-protection safeguards governing access and reuse. These features create a setting in which confidentiality, methodological accuracy, statistical interpretation, and clinically informed human oversight are especially important.^{3,5-8}

Another concern is scientific reliability and susceptibility to manipulation. Choi et al¹¹ showed that leading commercial LLMs used in a simulated medical peer-review setting were vulnerable to invisible text injection (ITI), where hidden instructions embedded in the manuscript could inflate scores

and acceptance recommendations. Under neutral prompts, ITI significantly increased quality scores across all models and drove acceptance recommendations from 0% to nearly 100%; flaw detection also worsened, including overall stringent flaw detection dropping from 18.9% to 8.5%.¹¹ Prompt engineering alone was not a sufficient safeguard, and the authors concluded that LLMs should be limited to structured tasks while humans retain full responsibility for critical scientific judgment.¹¹ Although this was a simulated study and not based on actual submitted manuscripts, it identifies a real weakness directly relevant to editorial policy.¹¹

A further limitation is the difference between surface fluency and deep scientific critique. The Stroke journal essay contest is particularly instructive for cardiovascular-adjacent fields because it tested editorial-board reviewers under blinded conditions. Human and AI essays received mostly similar ratings, AI essays scored higher for composition quality, and reviewers identified author type correctly only 50% of the time.¹² However, AI-generated references required extensive correction before review (including fabricated/hallucinated citations), and the study therefore did not evaluate citation support as part of scoring.¹² The authors also emphasized the need for reviewer training and clear policies, noting bias against essays judged to be AI-generated.¹² This suggests that AI can imitate the form of a strong reviewable manuscript while remaining fragile on evidentiary depth.

Another emerging concern relates to the quality and consistency of AI-generated peer review itself. Reviews may include overly speculative statistical interpretations or apply disproportionately harsh criticism to manuscripts that would otherwise be suitable for mid-tier journals; conversely, inappropriate prompting may lead to overly superficial assessments and unjustified recommendations for acceptance. These issues highlight that the challenge extends beyond merely detecting AI use. Editors must also ensure that AI tools are used responsibly and appropriately, recognizing that standardized or poorly adapted prompting strategies may produce reviews that are misaligned with the scientific standards and expectations of individual journals. In addition to reviewer selection, bias may also arise within AI-generated manuscript assessments. Such assessments may be influenced by language quality, institutional or geographic prestige, topic familiarity, study design, or indirect assumptions about methodological accuracy, which may disadvantage authors from underrepresented regions or smaller research settings.^{5,7,9,10} Importantly, such bias may persist even when author identity is masked, because linguistic characteristics, institutional descriptions, research topics, citation patterns, or methodological conventions may function as indirect proxies.

Even proponents of AI-assisted peer review warn about false efficiencies. Perlis et al² note that AI may generate false positives and false negatives, and that confabulations may increase workload if editors and reviewers must verify each AI-generated assertion. They also raise concerns about inequity (uneven access to secure or local models) and fairness (including potential bias in topic/language responses).¹¹

Table 1. Proposed Framework for Hybrid AI-Augmented Peer Review in Cardiovascular Journals

Component	Proposed Practice	Role of Editors	Role of Reviewers	Expected Benefit
Stakeholder-specific AI governance	Define separate expectations for author-, reviewer-, and editor-facing AI use because each involves distinct ethical, confidentiality, and operational considerations.	Establish distinct policies for author disclosure, reviewer confidentiality, and AI-assisted editorial decision support.	Follow reviewer-specific policies and distinguish language or technical assistance from independent scientific assessment.	Clarifies responsibilities and prevents inappropriate generalization of AI policies across different stakeholders.
AI-use transparency	Require disclosure of AI assistance used during peer review, including the tool and purpose. Disclosure should additionally specify whether manuscript content was uploaded or processed and whether AI contributed to substantive scientific assessment.	Incorporate standardized, risk-proportionate AI-use disclosure fields into reviewer forms and editorial workflows.	Disclose any AI assistance; distinguish low-risk language editing of reviewer-authored text from manuscript summarization, content processing, or substantive scientific evaluation.	Promotes transparency and helps maintain trust in the peer-review process.
Secure AI infrastructure	Prefer journal-approved, publisher-level, institutional, or otherwise secure AI environments when confidential manuscript content is involved, and define requirements for data retention/deletion, secondary use or model training, storage/processing jurisdiction, and contractual data protection.	Provide secure platforms where feasible and specify permitted use, data lifecycle, access, storage location, and contractual safeguards.	Avoid uploading confidential manuscript material to public AI tools unless explicitly permitted by journal policy and appropriate safeguards are in place.	Protects manuscript confidentiality, intellectual property, and unpublished scientific data.
Resource-sensitive implementation	Adopt a stepwise model for smaller journals based initially on written policies, disclosure requirements, confidentiality safeguards, predefined low-risk tasks, and periodic manual audit rather than immediate investment in proprietary AI infrastructure.	Begin with low-cost governance measures; when possible, use shared publisher-, society-, or institution-level infrastructure and guidance.	Comply with approved workflows and avoid unsupported or non-secure AI use.	Enables responsible AI adoption without imposing excessive financial or technical burden on resource-limited journals.
Structured review support	Use AI for clearly defined tasks such as manuscript summarization, reporting-guideline checks, internal consistency checks, reference-format screening, and language polishing of review text.	Integrate AI selectively into preliminary technical screening while preserving editorial interpretation and verification.	Use AI as an assistive tool for structured checks while maintaining independent scientific judgment.	May improve efficiency and consistency without delegating scientific judgment to AI.
Cardiovascular-specific applications	Apply structured AI assistance to cardiovascular-specific tasks, including clinical trial reporting checks, comparison of imaging measurements across manuscript sections, identification of missing device-related methodological information, and assessment of reporting completeness in AI-assisted cardiovascular imaging studies.	Define specialty-specific use cases and ensure that AI outputs are interpreted within appropriate clinical, methodological, and imaging expertise.	Verify AI-generated observations against the manuscript, particularly for complex trial methodology, device studies, echocardiography, cardiac CT, and cardiac MRI.	Improves the clinical relevance of AI-assisted review while maintaining cardiovascular specialist oversight.
Reviewer and editor training	Provide guidance on responsible AI use, prompt design, hallucinations, bias, confidentiality, and prompt-injection or manipulation risks.	Develop educational resources, examples of acceptable and unacceptable use, and periodic training for reviewers and editorial board members.	Understand the limitations of AI-generated outputs and critically verify generated recommendations or critiques.	Reduces misuse and improves the reliability of AI-assisted peer review.

(Continued)

Table 1. Proposed Framework for Hybrid AI-Augmented Peer Review in Cardiovascular Journals (Continued)

Component	Proposed Practice	Role of Editors	Role of Reviewers	Expected Benefit
Bias and fairness monitoring	Evaluate potential bias not only in AI-assisted reviewer identification but also in AI-generated manuscript assessments.	Audit AI-assisted assessments for systematic differences related to language, geography, institutional context, topic familiarity, study design, or other potential proxy characteristics.	Avoid overreliance on AI-generated evaluations and assess whether recommendations are context-sensitive, evidence-based, and fair.	Helps reduce systematic disadvantage and supports equity in manuscript evaluation.
Human accountability	Ensure that final scientific critiques, recommendations, and editorial decisions remain human-led.	Retain ultimate responsibility for manuscript decisions and editorial correspondence.	Verify AI-generated assertions before incorporating them into review reports and remain accountable for the final review.	Preserves scientific responsibility, accountability, and editorial credibility.
Quality assurance and prospective evaluation	Periodically evaluate AI-assisted peer review for review quality, decision consistency, reviewer workload, time to decision, confidentiality, fairness, and unintended effects on editorial judgment.	Conduct internal audits and, where feasible, participate in prospective randomized or stepped-wedge evaluations within real editorial workflows.	Provide structured feedback on AI-tool performance and report inaccurate, biased, unsupported, or clinically inappropriate outputs.	Supports continuous improvement and evidence-based implementation of hybrid AI-assisted peer review.

These practices represent a proposed framework derived from the currently available evidence and expert considerations; they are not established or prospectively validated standards.

AI, artificial intelligence; CT, computed tomography; MRI, magnetic resonance imaging.

These are critical for cardiovascular publishing, where global authorship and varying institutional resources are the norm.

Recent usage patterns also show a widening gap between policy and practice. A Nature news report summarizing a Frontiers survey found that more than half of ~1600 academics across 111 countries reported using AI while peer reviewing manuscripts, with nearly one-quarter increasing use in the prior year.⁴ Among users, 59% reported using AI to help write peer-review reports, while others used it for summarization, gap identification, reference checks, and misconduct screening. The same report underscores that many publishers prohibit uploading unpublished manuscripts to third-party tools and highlights confidentiality and intellectual property concerns, while also describing a closed, in-house reviewer AI system designed to protect manuscript confidentiality and avoid direct replacement of reviewers.⁴ The closed, in-house system described in that report illustrates 1 possible risk-mitigation model for cardiovascular publishers; however, its relative safety and effectiveness compared with other secure approaches have not yet been prospectively validated.

WHAT, THEN, SHOULD CARDIOVASCULAR JOURNALS DO?

Based on the available evidence, a hybrid approach appears most appropriate: AI for structured assistance and humans for judgment. This aligns with the conclusion of the recent cardiovascular letter (AI support may enhance speed and quality, but full AI replacement is not feasible now), with the cautious editorial perspective published in *JAMA*, and with the editor survey evidence showing broad interest in

operational uses but low trust in AI over human reviewers (only 6.8% would trust AI more than a human reviewer for scientific validity assessment).^{1,2,9}

For cardiovascular journals specifically, based on the current evidence and expert considerations, we propose the following 5 principles as a practical, provisional framework rather than as established or validated standards:

1. No upload of confidential manuscripts to public LLMs unless the journal clearly permits it under secure contractual infrastructure.
2. Mandatory but proportionate reviewer disclosure of AI assistance: disclose the tool and purpose for any AI use during review, with additional specification of whether confidential manuscript content was processed and whether AI materially contributed to scientific assessment; pure language editing of reviewer-authored text should be distinguished from substantive summarization or evaluation.
3. Permitted tasks limited to structured support (summaries, reporting-checklist checks, reference formatting checks, and language polishing of the review itself), not final scientific judgment.
4. Human accountability preserved for all critiques and recommendations.
5. Reviewer/editor training on AI strengths, hallucinations, bias, and manipulation risks (including prompt injection/ITI).

Finally, cardiovascular medicine is both data-rich and clinically high-stakes. Reviews of AI in cardiovascular medicine emphasize the same duality seen in publishing: significant potential, but also ongoing concerns regarding inaccuracies,

bias, privacy, ethics, and the need for regulatory frameworks and specialized, adaptive deployment.⁵⁻⁸ In that sense, cardiovascular journals should lead, not by prohibiting all innovation, nor by outsourcing judgment, but by designing transparent, auditable, human-led AI augmentation. Given the increasing availability and use of generative AI in scholarly workflows, complete prohibition may become increasingly difficult to sustain. We therefore propose transparent boundaries for acceptable use, supported by reviewer and editorial training, confidentiality safeguards, and human accountability (Table 1). These recommendations are intended as a pragmatic framework for evaluation and adaptation rather than as validated standards.

Practical implementation should also be resource-sensitive. Large cardiovascular journals and major publishers may be able to develop closed, journal-controlled AI systems integrated into editorial platforms, whereas smaller journals may not have the financial or technical capacity to build dedicated infrastructure.^{3,4} For resource-limited journals, a stepwise approach centered on written policies, disclosure, confidentiality safeguards, predefined low-risk tasks, and periodic manual audits may be more realistic.^{2,3,5-7,9} Shared publisher-, society-, or institution-level infrastructure may further reduce costs and support secure AI use without compromising editorial independence.^{5-7,9}

Future research should move beyond surveys and simulated comparisons and evaluate AI-assisted peer review prospectively within real editorial workflows. Prospective randomized or stepped-wedge studies comparing conventional and AI-assisted review pathways could assess review quality, decision consistency, reviewer workload, time to decision, and editorial efficiency while prospectively monitoring potential harms such as hallucinated critiques, confidentiality breaches, algorithmic bias, and inappropriate influence on final editorial judgment.^{2,5-7,9}

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The AI Paradox in Peer Review



THE 'PROS': Enhancing Efficiency and Technical Rigor

Potential Gains in Editorial Efficiency



In a survey of Editors-in-Chief, 79% cited time savings and 43% cited cost reduction as advantages of AI integration in medical publishing.

Automated Technical Screening



AI handles repetitive tasks: grammar checks, format compliance, journal guidelines.

Structured Review Support



AI assists with manuscript summaries, reporting-guideline checks, consistency checks, reference screening and language polishing.

Advanced Misconduct Detection



Identifies plagiarism, highlights data similarities, detects image manipulation.

Cardiovascular-Specific Applications



Large imaging datasets and AI-assisted cardiovascular imaging



Clinical trial reporting (e.g., CONSORT elements)



Device-related research



AI-assisted echocardiography, cardiac CT and MRI



THE 'CONS': Ethical Risks and Technical Failures

Confidentiality Risks



Uploading unpublished manuscripts to public AI platforms may breach confidentiality, data-protection obligations, and legal agreements.

Risk of Algorithmic Bias



AI, trained on historical data, may reproduce or amplify gender, racial, or geographical biases, undervaluing underrepresented research.

Risk of AI-Generated Inaccuracies



AI may generate plausible-sounding but inaccurate or fabricated content, including unsupported scientific claims or references.

Accountability Limitations



International guidelines (ICMJE/COPE) state that AI cannot be held responsible for scientific errors or listed as an author.

Limitations in Replicating Nuanced Human Judgment



AI struggles to replicate expert reasoning on scientific novelty, methodological rigor, and clinical impact.

Supplementary Figure 1.

Sequential Transcatheter Valve-in-Valve-in-Valve Implantation Within a Degenerated Bio-Bentall Conduit in a Patient with Marfan Syndrome

INTRODUCTION

The transcatheter aortic valve replacement (TAVR) journey, initiated in 2002, evolved with the first successful Valve-in-Valve (ViV) cases in 2007.^{1,2} By 2014, ViV TAVR became established in modern interventional cardiology.^{3,4} Today, "valve-in-valve" failures are now manifesting, giving rise to the necessity for Valve-in-Valve-in-Valve (ViViV) interventions. This 38-year-old patient with Marfan syndrome provides significant evidence to the literature regarding the technical feasibility, device mechanics, and technical nuances within constrained graft anatomies of multi-layered ViViV procedures.

CASE REPORT

A 38-year-old female with Marfan syndrome presented with a 2-month history of progressive exertional dyspnea and significant functional limitation, corresponding to New York Heart Association (NYHA) functional class III. Her medical history was notable for Marfan syndrome, which precipitated an ascending aortic aneurysm and severe aortic regurgitation, treated in 2008 via a surgical Bentall procedure utilizing a 25 mm porcine bioprosthetic valved conduit. Bioprosthesis was selected through shared decision-making to facilitate future pregnancy planning and avoid lifelong anticoagulation. Over the following asymptomatic years, she developed accelerated structural valve deterioration (SVD) of the surgical prosthesis, which was managed in 2016 via an initial transfemoral ViV TAVR utilizing a 26 mm Portico self-expanding valve. There was no historical evidence of infective endocarditis, valve thrombosis, or other major chronic comorbidities.

Physical examination revealed a 3/6 systolic–diastolic aortic murmur and bilateral basal crackles on lung auscultation. Other systemic examinations were unremarkable, and vital signs were stable. Laboratory results were unremarkable except for a B-type natriuretic peptide of 121.19 pg/mL. Transthoracic echocardiography (TTE) showed preserved ejection fraction (60%) but severe prosthesis obstruction (peak/mean gradient: 81/46 mm Hg; valve area: 0.7 cm²). Transesophageal echocardiography (TEE) confirmed SVD, ruling out thrombosis or vegetations (Figure 1). High-risk for a redo-Bentall and refusing open-heart surgery, the Heart Team opted for a ViViV TAVR. Pre-procedural multidetector computed tomography (MDCT) revealed a restricted internal luminal dimension of 25.4 × 17.7 mm, with safe coronary ostial heights (right: 16.6 mm, left: 15.8 mm) (Figure 1).

Under transfemoral access, a 24.5-mm Myval balloon-expandable valve was successfully deployed within the failed Portico prosthesis guided by the precise internal orifice margins on MDCT (Figure 2). No intra-procedural complications

CASE REPORT

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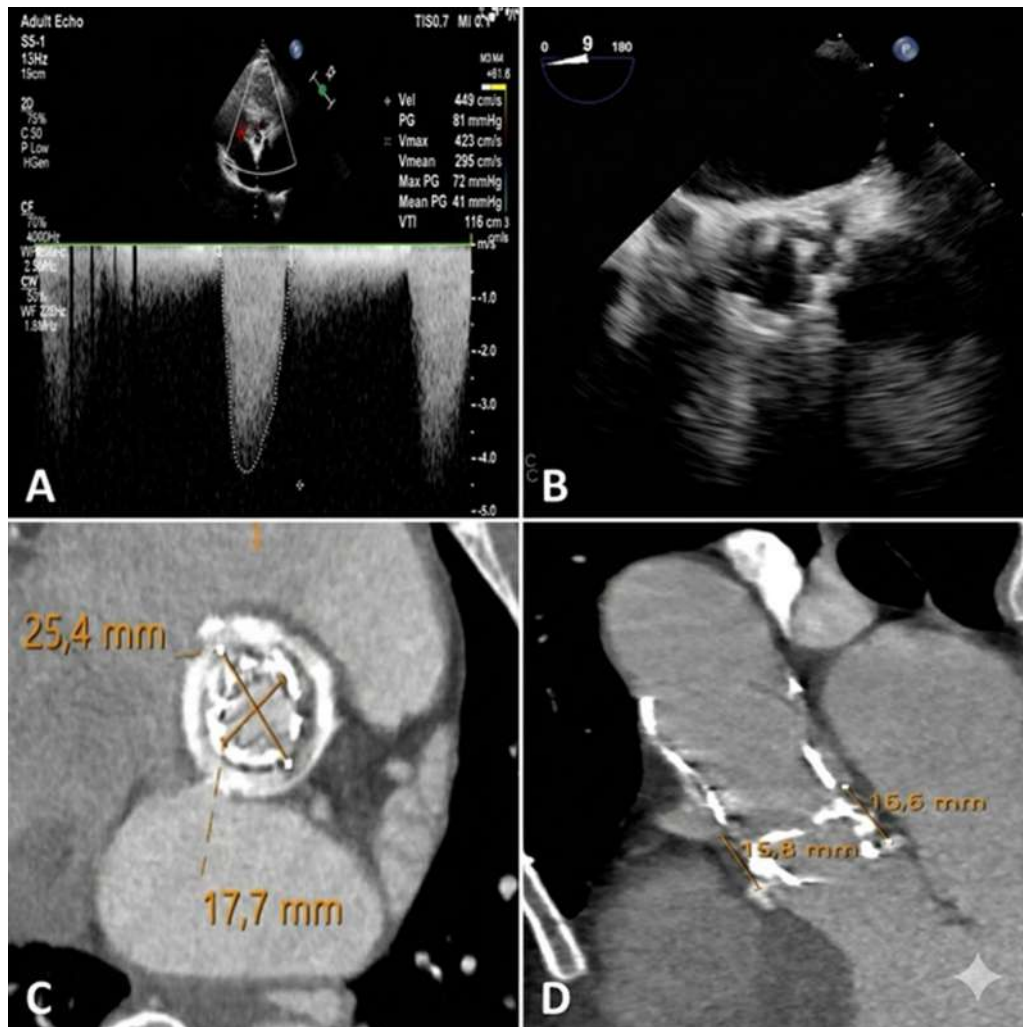


Figure 1. Pre-procedural imaging. (A) TTE CW Doppler (gradients 81/41 mm Hg, Vmax 449 cm/s). (B) TEE (bioprosthetic SVD). (C) Axial MDCT (luminal dimensions 25.4×17.7 mm). (D) Coronal MDCT (ostial clearance: LCA 15.8 mm, RCA 16.6 mm). CW, continuous-wave; LCA, left coronary artery; MDCT, multidetector computed tomography; RCA, right coronary artery; SVD, structural valve deterioration; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; Vmax, maximum velocity.

occurred. Post-procedural TTE demonstrated a gradient reduction to 26/12 mmHg with minimal residual aortic regurgitation (Figure 2). At the 1-year follow-up, she remained stable with near-complete symptomatic relief.

DISCUSSION

This case underscores the mechanical boundaries and feasibility of a transcatheter ViViV approach for recurrent bioprosthetic failure within a constrained bio-Bentall conduit. While bioprostheses in young patients avoid lifelong anticoagulation, their limited durability triggers a predictable cascade of re-interventions. Thus, prosthesis selection requires meticulous shared decision-making, acknowledging the inevitability of complex downstream transcatheter nesting.

Pathophysiologically, Marfan syndrome involves dysregulated extracellular matrix integrity driven by aberrant transforming growth factor- β signaling.^{5,6} This underlying molecular dysregulation, combined with

heightened mechanical stress and active calcium metabolism in younger patients, may theoretically accelerate bioprosthetic leaflet calcification and SVD.⁷

Technically, sequential nesting compromises the effective orifice area with each layer—the “matryoshka” effect—elevating baseline gradients and potentially accelerating failure.^{3,8} In these scenarios, the primary objective of pre-procedural MDCT is the precise micro-geometric mapping of the true internal diameter to mitigate prosthesis-patient mismatch. Despite extreme structural constraints, strategically deploying a balloon-expandable platform inside a failed self-expanding frame yielded optimal outcomes due to its superior radial force and predictable intra-annular expansion.

CONCLUSION

Choosing a bioprosthetic conduit in young patients initiates a predictable cycle of recurrent valve dysfunction. When redo open-heart surgery poses prohibitive risks, the ViViV

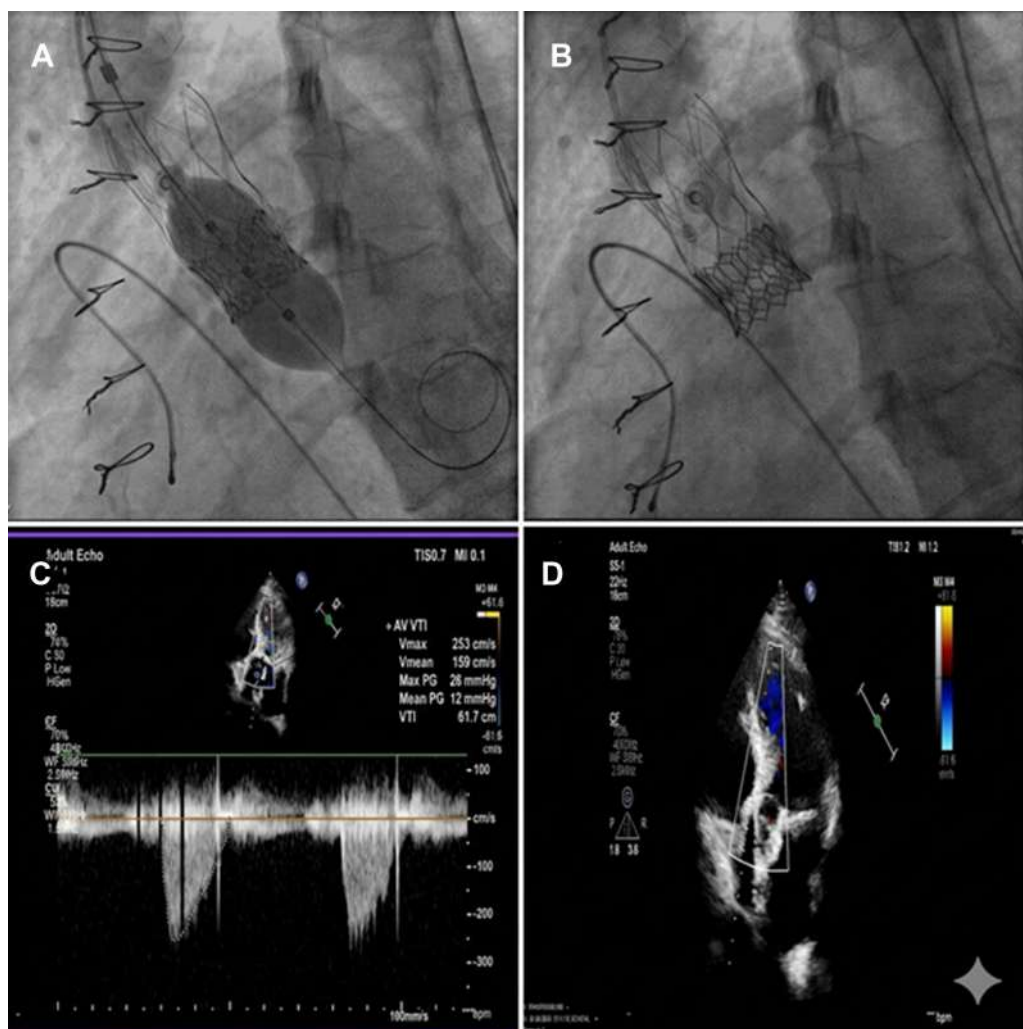


Figure 2. Intra-procedural ViViV execution and post-procedural outcomes. (A, B) Fluoroscopy showing precise positioning and deployment of the 24.5 mm Myval balloon-expandable valve within the 26 mm Portico frame. (C, D) Post-procedural TTE CW Doppler demonstrating gradient reduction to 26/12 mmHg and minimal residual regurgitation. CW, continuous-wave; TTE, transthoracic echocardiography; ViViV, valve-in-valve-in-valve.

TAVR strategy offers an effective, safe, and reproducible alternative, even under extreme anatomical conditions.

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

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

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Long-Term Follow-Up of a Patient with Arterial Tortuosity Syndrome After Bilateral Pulmonary Artery Stent Implantation

INTRODUCTION

Arterial tortuosity syndrome (ATS) is a rare autosomal recessive connective tissue disorder characterized by widespread tortuosity and elongation of the large and mid-sized arteries as well as phenotypic manifestations such as hyperextensible skin, joint hypermobility, inguinal hernia, micrognathia, convex nasal ridge, and downslanting palpebral fissures.¹

Even though the main feature of ATS is diffuse arterial tortuosity, cardiovascular system involvement varies between different cohorts. The prevalence of pulmonary artery stenosis ranges between 28% and 60% among different cohort studies and may be accompanied by pulmonary hypertension due to peripheral pulmonary artery stenoses.^{2,3} Treatment options for these stenoses include surgery, transcatheter pulmonary stenting, and hybrid procedures.

Most of the patients are diagnosed in childhood, and reconstruction surgery of pulmonary arteries during childhood is the most commonly performed treatment option among those patients requiring pulmonary intervention.⁴ In this article, an adult patient with ATS and long-term follow-up results of bilateral pulmonary artery stenting are presented.

CASE REPORT

A 27-year-old patient with ATS was referred to the clinic 8 years ago for clinical follow-up due to pulmonary hypertension. The patient was diagnosed with ATS due to typical phenotypic features and radiological findings at the age of 11 years. The patient had typical dysmorphic features for ATS such as long face, beaked nose, downslanting palpebral fissures, high palate, micrognathia, hyperextensible skin, and hypermobile joints. The patient was born from a third-degree consanguineous marriage. Family screening with computed tomography (CT) angiography also showed the presence of arterial tortuosity in the patient's father and sibling. The family's diagnosis of ATS was later reestablished with genetic testing during the patient's pediatric follow-up.

Patient was not under any medication at the time of admission to the clinic, and he had shortness of breath during ordinary daily activities. He was reevaluated with echocardiography and pulmonary CT angiography. Echocardiography revealed dilated right heart chambers with severe tricuspid regurgitation. Pulmonary CT angiography revealed dilated main pulmonary artery and bilateral peripheral pulmonary artery tortuosity with focal stenoses (Figure 1).

Patient then underwent right heart catheterization (RHC) and selective pulmonary angiography for stenoses of the left pulmonary artery in May 2018. Right heart catheterization was consistent with precapillary pulmonary hypertension. Mean pulmonary artery pressure (PAP) was 80 mm Hg and pulmonary vascular resistance (PVR) was 20.9 woods unit (WU) with pulmonary capillary wedge pressure (PCWP) of 8 mm Hg (Table 1). Pulmonary angiography revealed critical ostial stenoses in the segments A3, A4, A5, and A6 (Figure 2, Videos 1 and 2). Lesions

CASE REPORT



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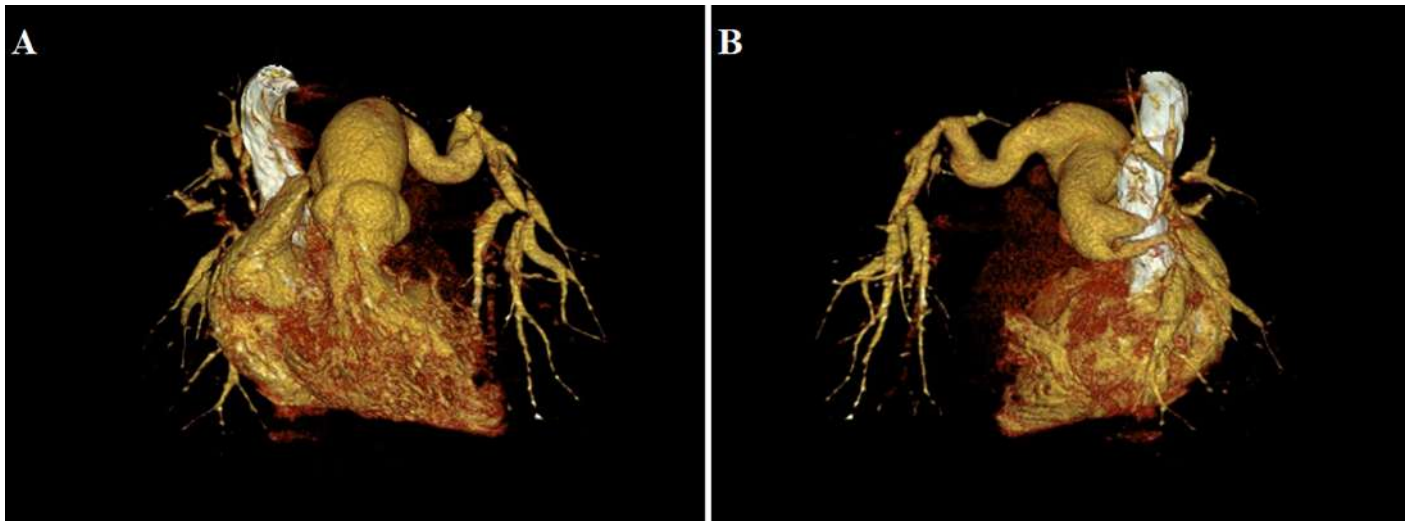


Figure 1. (A) Anterior view of pulmonary artery with computed tomography angiography with three-dimensional (3D) volume rendering technique. (B) Posterior view of pulmonary artery with computed tomography angiography with 3D volume rendering technique.

were evaluated with fractional flow reserve which showed significant obstruction, and percutaneous pulmonary stent implantation was planned.

Patient underwent percutaneous pulmonary stent implantation for left-sided lesions in July 2018, and total revascularization was achieved with 4 different renal stents (Abbott's RX Herculink Elite (®) Renal Stent, Chicago, IL, USA) (Figure 3, Video 3). Dual antiplatelet therapy with aspirin and clopidogrel was established. Patient developed lung edema and fever accompanied by hemoptysis during follow-up after the procedure. Control chest CT showed consolidation in the left lung, which was considered a reperfusion injury (Figure 4). Patient was treated with furosemide and antibiotics. Symptoms resolved after 2 days, and the patient was discharged.

Control RHC and selective pulmonary angiography for right-sided stenoses were planned after completion of the

aforementioned first procedure. Pulmonary angiography revealed stenoses of 80%-90% in both the right upper and right lower lobar arteries (Figure 5, Video 4). The patient underwent percutaneous pulmonary stent implantation for right-sided lesions in January of 2019, and total revascularization was achieved with the deployment of self-expanding stents (Abbott's Supera Peripheral Stent, Santa Clara, CA, USA) in each lobar artery (Figure 6, Video 5). Follow-up treatment was established with dual antiplatelet therapy as in the previous procedure, with the addition of sildenafil, and the patient was discharged without any adverse event.

Patient was mostly asymptomatic during follow-up, with occasional mild exertional dyspnea. Control RHC at the first year showed a substantial decrease in pulmonary pressures, with a mean PAP of 37 mm Hg and corresponding PVR of 4.4 WU (Table 1). Most recent RHC was performed

Table 1. Serial Right Heart Catheterization Measurements During Follow-Up

	May 2018: Before First Procedure	Sep. 2018: After First Procedure	Jan. 2019: Before Second Procedure	Sep. 2019: After Second Procedure	March 2022: Long-Term Follow-up
Systolic PAP (mm Hg)	119	101	97	74	82
Diastolic PAP (mm Hg)	48	40	25	19	29
Mean PAP (mm Hg)	84	58	60	37	49
RAP (mm Hg)	12	8	12	8	4
PCWP (mm Hg)	8	8	12	10	7
PVR (WU)	20.39	9	7.45	4.4	6.75
SVR (WU)	21.3	24	16.15	17.69	19.08
PVR/SVR	0.95	0.37	0.46	0.24	0.35
CO (L/min)	5.1	5.71	6.44	5.54	6.08
CI (L/min/m ²)	2.22	2.58	2.76	2.37	2.61
6MWT (m)	390	520	515	500	450

6MWT, six-minute walking test; CI, cardiac index; CO, cardiac output; m, meters; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance; WU, Woods unit.

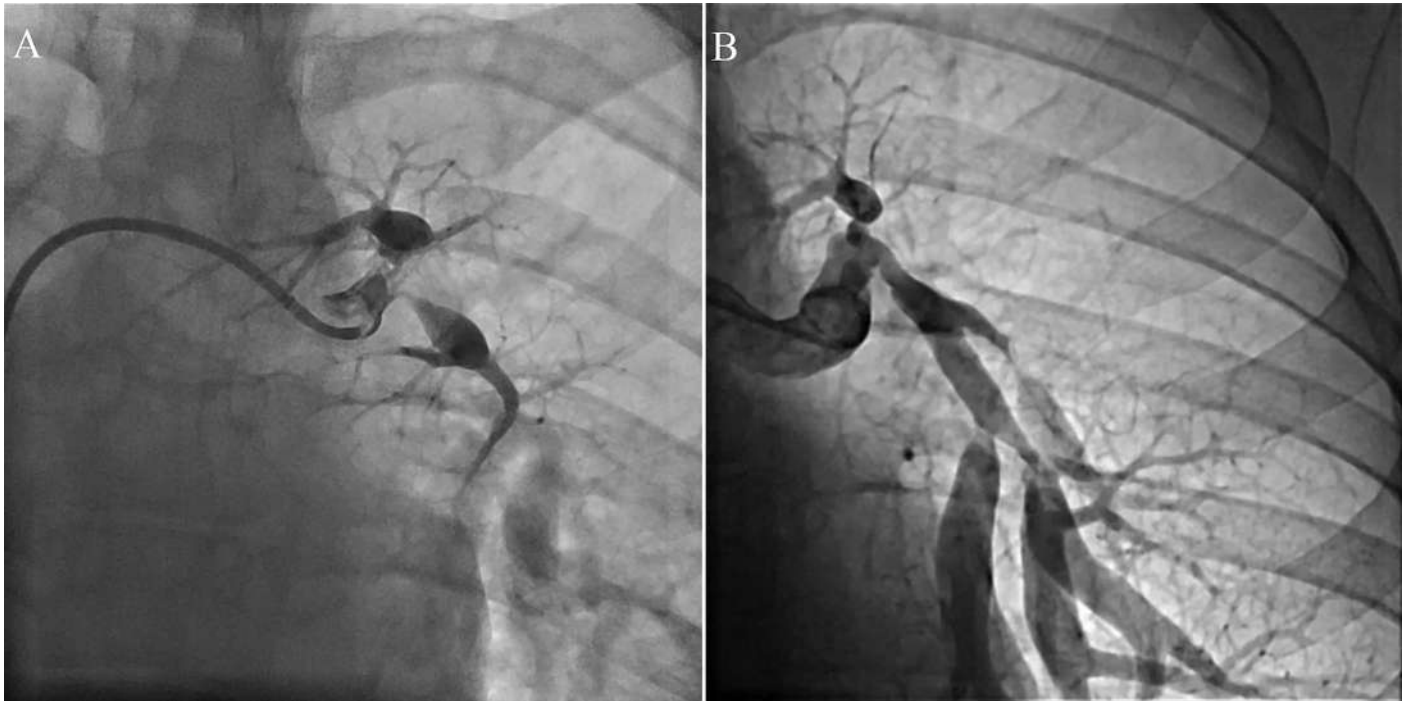


Figure 2. (A) Pulmonary artery stenoses in left A3 and A4 segments shown with selective pulmonary angiography. (B) Pulmonary artery stenoses in left A5 and A6 segments shown with selective pulmonary angiography.

in March 2022. RHC measurements showed slight increases in both pulmonary pressures and PVR compared to first-year control. Follow-up RHC measurements are shown in Table 1. Control selective pulmonary angiography revealed in-stent restenosis at left-sided renal stents (Figure 7, Video 6) while right-sided stents were found to be retaining their

patency (Figure 7, Video 7). Medical treatment was rearranged with riociguat monotherapy in addition to single antiplatelet treatment with aspirin. Periodic outpatient controls have been carried out for the last 8 years without any rehospitalization.

Patient Consent

A written informed consent was obtained from the patient. The patient consented to publish case details and imaging data without personal images.



Figure 3. Selective pulmonary angiography of left pulmonary artery after stent implantation.



Figure 4. Computed tomography image of reperfusion injury in left lung after pulmonary stent implantation.



Figure 5. Pulmonary artery stenoses in right upper and right lower lobar arteries shown with selective pulmonary angiography.



Figure 6. Selective pulmonary angiography of right pulmonary artery after stent implantation.

DISCUSSION

First case of diffuse tortuosity of the arteries as a congenital defect was reported by Ertugrul in 1967.⁵ Arterial tortuosity syndrome got recognized as a different disorder over the years

with genetic testing in addition to characteristic imaging findings. The diagnosis is established with molecular genetic testing by showing biallelic pathogenic variants in the solute carrier family 2 member 10 (*SLC2A10*) gene in addition to generalized arterial tortuosity.³ Although most patients get diagnosed at childhood, adult presentations have also been reported.^{6,7}



Figure 7. (A) Digital subtraction angiography showing patent stents in right pulmonary artery at 4th year control. (B) Digital subtraction angiography showing in-stent restenosis in left pulmonary artery stents at 4th year control.

Underlying mechanism was suggested as fragmentation of the inner elastic membrane and elastic fibers of the tunica media of large arteries due to loss of function of the *SLC2A10* gene that encodes the facilitative glucose transporter GLUT 10.^{1,8} Consequently, GLUT 10 deficiency disrupts the transforming growth factor-beta pathway, leading to vessel wall impairment.⁶

Cardiovascular system involvement is the main source of morbidity and mortality among ATS patients.⁹ Arterial tortuosity impairs blood circulation and increases vascular shear stress that may lead to stenosis, atherosclerosis, or dissection in affected arterial territories, as well as ventricular failure due to increased afterload.⁴ Earlier studies have shown poor prognosis in childhood, with a mortality rate of 40%.² However, more recent studies have shown more favorable outcomes.¹

Most common cardiovascular findings are tortuosity of the large arteries including aorta and pulmonary arteries. Arterial tortuosity syndrome is also a rare cause of pulmonary hypertension among connective tissue disorders.¹⁰ Kinks and loops of the pulmonary artery cause pulmonary artery stenosis leading to pulmonary hypertension. Computed tomography signs include a V-shaped sign on the coronal plane and an inverted V-shaped sign on the axial plane, which was also present in the case.^{6,11}

Stent implantation has been shown to be a successful choice of intervention for the treatment of pulmonary artery stenosis.¹²⁻¹⁴ However, the patient population for the given intervention is heterogeneous and includes various complex defects with different anatomies accompanied by different physiologies such as single or biventricular circulation. Ing et al¹⁵ have shown the immediate success rate of stent implantation to be 98% in patients with biventricular physiologies. Additionally, adult patients make up only a small fraction of pulmonary intervention populations with prevalence ranging from 11.8% to 13%.^{13,14}

Clinically significant pulmonary artery stenoses of ATS patients are mostly treated with reconstruction surgery during childhood.^{4,16} However, there is not any study regarding percutaneous pulmonary artery stenting in ATS patients. Lack of study on this topic can be potentially attributed to preexisting concerns such as future requirement of stent redilation to accommodate somatic growth of children and risk of pushing tortuosity distally via stenting due to redundancy of pulmonary artery. Aliramezany et al¹⁷ have reported a case of pulmonary balloon angioplasty that decreased pulmonary artery pressure from 120 mm Hg to 60 mm Hg in an adult ATS patient who was deemed unsuitable for stenting due to vascular sizing. Santoro et al¹⁸ have reported a hybrid transcatheter-surgical strategy in which stents were implanted through a stab incision of the main pulmonary artery via sternotomy followed by reductive surgical reconstruction to eliminate redundancy of pulmonary artery. Hereby, the long-term outcome of percutaneous pulmonary artery stenting in an adult ATS patient is presented.

Sildenafil and riociguat have been shown to improve exercise capacity, symptoms, and hemodynamics in pulmonary arterial hypertension (PAH) patients.^{19,20} Additionally, switching from sildenafil to riociguat was found to further improve exercise capacity in intermediate-risk PAH patients.²¹ Furthermore, PAH drugs have been shown to improve hemodynamics in peripheral pulmonary stenosis patients, whether or not additional percutaneous pulmonary angioplasty was performed. On the other hand, combining both interventional treatment and medical therapy was found to be associated with greater hemodynamic improvement.²² Pulmonary stenting was considered to be the main factor for the clinical improvement of the patient, given the severity of lesions and pulmonary hypertension. However, differentiating the benefits of interventional and medical therapies is not possible because both treatment options were implemented in the patient.

Pulmonary reperfusion syndrome due to increased flow after pulmonary stent implantation has also been described as in the case.²³ Treatment of this condition includes diuresis, keeping hemoglobin at normal levels with close observation for pulmonary hemorrhage and mechanical ventilation with positive end-expiratory pressure, as well as extracorporeal membrane oxygenation in refractory cases.^{4,16}

Neointimal proliferation and restenosis were found between 1.8% and 4% of pulmonary artery stent patients at repeat catheterization during follow-up.^{24,25} Gonzalez et al²⁶ have reported different rates of neointimal proliferation and restenosis between different stent types after pulmonary artery stenting. Although lesion and stent lengths differ between the stent types, more significant restenosis was found in Abbott's RX Herculink Elite renal stents compared to Abbott's Supera peripheral stents after pulmonary artery stenting.

CONCLUSION

Stent implantation is a safe and successful choice of intervention for the treatment of pulmonary artery stenosis in adult ATS patients with preserved stent patency and maintained hemodynamic status at long-term follow-up. Dedicated stents for pulmonary artery may prevent neointimal proliferation and restenosis, hence recurrent interventions.

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

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

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

Video 1: Pulmonary artery stenoses in left A3 and A4 segments shown with selective pulmonary angiography.

Video 2: Pulmonary artery stenoses in left A5 and A6 segments shown with selective pulmonary angiography.

Video 3: Selective pulmonary angiography of left pulmonary artery after stent implantation.

Video 4: Pulmonary artery stenoses in right upper and right lower lobar arteries shown with selective pulmonary angiography.

Video 5: Selective pulmonary angiography of right pulmonary artery after stent implantation.

Video 6: Digital subtraction angiography showing patent stents in right pulmonary artery at 4th year control.

Video 7: Digital subtraction angiography showing in-stent restenosis in left pulmonary artery stents at 4th year control.

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Cross-Sectional Mediation and Biomarker Interpretation in the Report by Yan and Gao

To the Editor,

Yan and Gao evaluated 3170 NHANES 2017-2020 participants and reported a graded association between cardiometabolic index (CMI) and liver fibrosis (LF), with an adjusted odds ratio of 2.27 and nonlinear dose-response. They also estimated modest mediation proportions for albumin, uric acid, and gamma-glutamyl transferase (GGT).¹ The analysis is clinically appealing because CMI combines triglyceride-to-high-density lipoprotein cholesterol ratio and waist-to-height ratio, 2 accessible markers that connect cardiometabolic risk with hepatic injury. Several analytic issues merit attention before the mediation findings are translated into risk stratification.

First, the study was cross-sectional. Mediation implies temporal ordering from CMI to oxidative stress biomarkers and then to LF, but NHANES measured exposure, mediators, and liver stiffness in the same survey cycle. Cross-sectional mediation can yield biased indirect effects even when the underlying longitudinal pathway is real.² Causal language should therefore be avoided, and the reported indirect effects should be interpreted as decomposition of contemporaneous associations.

Second, the mediator set mixes mechanistic and diagnostic information. Albumin, uric acid, and GGT may reflect oxidative stress, but they also index nutrition, renal handling, cholestasis, alcohol exposure, and hepatic synthetic or enzymatic activity.³ GGT is especially close to metabolic liver injury and may lie on several overlapping paths rather than a single oxidative stress pathway. A sensitivity analysis that excluded GGT or modeled a composite oxidative stress score would test whether the mediation signal depends on a liver-enzyme marker.

Third, LF was defined by a liver stiffness cutoff. Noninvasive stiffness measurement is useful for population studies, but cutoffs depend on disease etiology, inflammation, congestion, steatosis, probe selection, and fasting status.^{3,4} A single threshold can therefore create misclassification, particularly around intermediate stiffness values. Analyses using alternative liver stiffness cutoffs, FIB-4 categories, or a continuous stiffness outcome would help determine whether the CMI signal is robust.

Finally, the sample restriction to participants with complete transient elastography and biochemical data may have selected a metabolically healthier analytic cohort. Survey-weighted missingness tables and inverse-probability weighting would clarify whether selection affected the estimates. The main CMI-LF association is plausible and useful as a screening hypothesis, but the mediation component requires longitudinal validation with temporally separated exposure, mediator, and fibrosis assessments.^{2,5} The authors of the relevant article were given the opportunity to reply, but they chose not to send a response.

Note: The authors of the relevant article were given the opportunity to reply, but they chose not to send a response.

LETTER TO THE EDITOR

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Forest Therapy and Cardiovascular Outcomes in Elderly Hypertensive Patients: Points for Consideration

To the Editor,

We read with great interest the study by Liang et al¹ entitled "The Efficacy of Forest Therapy on Negative Emotions, Oxidative Stress, and Cardiovascular Disease Risk in Elderly Hypertensive Patients." The authors should be congratulated for this prospective randomized study investigating the potential cardiovascular benefits of forest therapy in elderly patients with hypertension. While this innovative non-pharmacological approach is of considerable interest, several concerns warrant further discussion.

The reported reduction in cardiovascular events should be interpreted with caution. Although a statistically significant reduction in cardiovascular events was observed in the forest therapy group (hazard ratio [HR]=0.34, 95% CI: 0.12-0.95, $P=.018$), only 18 events occurred during follow-up. Given the limited number of events, HR estimates may be unstable and susceptible to random error. Furthermore, 27 participants (22.5% of the study population) were lost to follow-up. Considering the modest sample size, this loss may influence the reliability of the survival analysis. Additional information regarding the baseline characteristics of these patients would be valuable to better evaluate the potential impact of attrition bias. We also noticed a potential inconsistency in Table 2. Baseline systolic blood pressure was reported as 146 ± 10 mm Hg in the control group and 166 ± 185 mm Hg in the study group. This seems unusual and may represent a typographical or reporting error, and clarification from the authors would be helpful.

Pharmacological therapy remains the cornerstone of blood pressure control and cardiovascular risk reduction in patients with hypertension.^{2,3} Although the authors reported that patients maintained their prescribed antihypertensive medications throughout the study, detailed information regarding antihypertensive drug classes, baseline treatment intensity, or medication adherence was not provided. Given the importance of these factors, even minor differences in medication adherence or treatment adjustments could potentially have influenced the outcomes, and their omission makes it difficult to assess the independent contribution of forest therapy to the observed benefits.

Although the study was designed to assess forest therapy, patients in the study group were exposed to multiple potentially beneficial components, including supervised walking, social interaction, and sensory stimulation. Therefore, it is difficult to isolate the independent effect of the forest environment. Moreover, although improvements in oxidative stress and emotional status may have contributed to the reduction in cardiovascular events, the study was not designed to formally evaluate a mechanistic relationship between changes in oxidative stress markers and clinical outcomes. In addition, oxidative stress in hypertension includes complex pathways related to endothelial dysfunction, vascular inflammation, and arterial stiffness; therefore, assessment based solely on superoxide dismutase and malondialdehyde levels may provide only a limited representation of the overall oxidative stress burden.⁴ Consequently, the observed association should be considered hypothesis-generating rather than definitive evidence.



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LETTER TO THE EDITOR

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Despite these concerns, the study highlights an innovative and clinically relevant approach to cardiovascular risk prevention. Additional large-scale trials with longer follow-up are warranted to confirm these promising findings.

Note: The authors of the relevant article were given the opportunity to reply, but they chose not to send a response.

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Antiplatelet Strategy After Drug-Coated Balloon Angioplasty for Isolated Side Branch Lesions: The Missing Piece of the Puzzle

To the Editor,

We read with great interest the recent study by Akin et al¹ entitled "Safety Profile of Drug-Coated Balloon Angioplasty for Isolated Side Branch Lesions: A Single-Center Experience," published in *The Anatolian Journal of Cardiology*.¹ The authors should be congratulated for addressing a highly challenging clinical scenario—isolated side branch (SB) stenosis (Medina 0.0.1)—with an innovative, stentless drug-coated balloon (DCB) approach, demonstrating an impressive procedural success rate of 97.9%.

While the acute angiographic outcomes and the absence of acute thrombosis are highly reassuring, a critical clinical aspect regarding post-procedural management remains unaddressed. The authors reported a relatively high incidence of type A–B coronary dissections (35.4%). Although these dissections were non-flow-limiting and did not require bailout stenting, their presence introduces a significant clinical dilemma regarding post-procedural antithrombotic therapy.

According to the International DCB Consensus Group recommendations, a 4-week course of dual antiplatelet therapy (DAPT) is generally recommended after uncomplicated DCB-only angioplasty in de novo coronary lesions.² However, a substantial proportion of patients were left with untreated, bare dissections. In combination with a high-risk patient profile (50% diabetes, 75% hypertension, and 56.2% prior myocardial infarction), this creates a challenging balance between ischemic and bleeding risks.

Advanced optical coherence tomography (OCT) studies indicate that while most minor dissections heal biologically over time under the influence of anti-proliferative drugs, the endothelialization window may be delayed in the presence of complex plaque morphology or suboptimal lesion preparation.³ Interestingly, despite the high angiographic success reported by the authors, 12.5% of the patients suffered from persistent post-procedural angina, and 16.7% required a repeat coronary angiography during a mean follow-up of 423 days.¹ It remains uncertain whether the choice, potency (e.g., clopidogrel vs. ticagrelor), or duration of the DAPT regimen played a role in these soft ischemic endpoints or late lumen changes.

Consequently, to help clinicians safely reproduce these favorable "stentless" results in their daily practice, it would be highly valuable if the authors could clarify their post-procedural antiplatelet protocol. Did patients with type A–B dissections receive a different antiplatelet strategy (either in duration or P2Y12 inhibitor selection) compared with those without dissections? Sharing these insights would significantly enhance the clinical utility and generalizability of this valuable study.

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

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Reply to the Letter to the Editor: "Antiplatelet Strategy After Drug-Coated Balloon Angioplasty for Isolated Side Branch Lesions: The Missing Piece of the Puzzle"

To the Editor,

We sincerely thank the authors¹ for their thoughtful comments regarding our recently published study² evaluating drug-coated balloon (DCB) angioplasty for isolated side branch lesions. We appreciate their interest in the post-procedural antiplatelet strategy, which indeed represents an important component of DCB-based coronary intervention.

In our study, antiplatelet therapy was determined according to the clinical presentation rather than the presence of angiographically minor dissections. Patients with chronic coronary syndrome received aspirin plus clopidogrel for 1 month after successful DCB-only angioplasty, whereas patients presenting with acute coronary syndrome received guideline-directed dual antiplatelet therapy (DAPT) for 12 months, in accordance with current European Society of Cardiology (ESC) recommendations.^{3,4} The presence of non-flow-limiting type A or B dissections did not modify either the duration of DAPT or the selection of the P2Y12 inhibitor.

Importantly, current evidence does not support prolonging DAPT solely because of angiographically minor dissections after successful DCB treatment. The 2023 German Consensus Group recommends 1 month of DAPT following uncomplicated DCB angioplasty in de novo lesions and does not propose longer DAPT for type A–B dissections.⁵ Similarly, the 2024 International DCB Consensus Group recommends standard DAPT after successful DCB treatment provided that there is no flow-limiting dissection or bailout stenting.⁶ Therefore, our antiplatelet strategy was fully consistent with contemporary consensus recommendations.

The concern regarding untreated type A–B dissections is understandable; however, increasing evidence suggests that these lesions represent a benign angiographic finding rather than a clinically significant complication. Optical coherence tomography–based studies have demonstrated spontaneous endothelial healing after DCB treatment despite the absence of a permanent metallic scaffold.⁷ Furthermore, the EASTBOURNE substudy showed that most non-flow-limiting dissections healed completely without an increased incidence of target lesion failure or major adverse cardiovascular events.⁸ Likewise, Gitto et al⁹ demonstrated that minor dissections after DCB angioplasty were not associated with adverse long-term clinical outcomes.

The authors also questioned whether the choice or duration of DAPT might have contributed to persistent angina or repeat coronary angiography during follow-up. Although this hypothesis is interesting, our study was not designed to evaluate different antiplatelet strategies, and no subgroup analysis according to DAPT regimen was performed. Moreover, persistent angina following PCI is multifactorial and may result from coronary microvascular dysfunction, vasospastic disease, diffuse atherosclerosis, progression of non-target lesions, or residual ischemia unrelated to the treated side branch.¹⁰ Likewise, repeat coronary angiography in

LETTER TO THE EDITOR REPLY

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our cohort was clinically driven and should not be interpreted as evidence of target lesion failure.

Finally, the primary objective of our study was to evaluate the procedural safety and feasibility of DCB angioplasty in isolated Medina 0.0.1 lesions. Nevertheless, we fully agree with the authors that future prospective studies incorporating standardized antiplatelet regimens together with serial OCT imaging would further clarify whether selected patient subgroups might benefit from individualized antiplatelet strategies.

We sincerely thank the authors for their valuable comments¹, which have provided an opportunity to further clarify this important aspect of DCB therapy.

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Interpreting Reduced-Dose Slow-Infusion Thrombolysis in Intermediate–High-Risk Pulmonary Embolism

To the Editor,

We read with interest the article by Kültürsay et al¹ evaluating reduced-dose, slow-infusion systemic thrombolysis in patients with intermediate–high-risk (IHR) pulmonary embolism (PE). The authors share a large single-center experience in a field where evidence remains limited, adding useful data to the literature.

However, some points require careful discussion. Current international guidelines do not recommend routine systemic thrombolysis in IHR PE, instead favoring anticoagulation with close monitoring and reserving thrombolysis for patients who develop hemodynamic deterioration.^{2,3} This recommendation is based on randomized studies showing no mortality benefit and a higher risk of major and intracranial bleeding with early thrombolysis. Therefore, any upfront thrombolytic approach in this population represents a departure from guideline-based first-line management

In this context, the clinical outcomes reported in the study should be interpreted cautiously. Despite early administration of low-dose, slow-infusion thrombolysis, hemodynamic decompensation occurred in 3.2% of patients. This rate is comparable to that observed in conservatively managed patients in the PEITHO trial, where hemodynamic decompensation occurred in 5.0% of the anticoagulation-only group and 1.6% of the tenecteplase group.⁴ Importantly, although thrombolysis reduced hemodynamic decompensation in PEITHO, it did not improve survival and was associated with significantly more bleeding events.⁴

The fact that hemodynamic deterioration still occurred despite early thrombolytic therapy raises an important clinical question. An initial strategy of anticoagulation with careful monitoring, followed by standard-dose thrombolysis as rescue treatment when deterioration occurs, might have achieved similar outcomes while avoiding early thrombolytic exposure in patients who would otherwise remain stable.

In addition, although slow infusion of thrombolytics is biologically reasonable, clinical evidence supporting this approach is limited. No randomized trials have directly compared different systemic infusion strategies in IHR PE. Ongoing studies, such as Pulmonary Embolism International Thrombolysis-3 (PEITHO-3), which evaluates reduced-dose thrombolysis versus anticoagulation alone, are expected to provide more definitive answers.⁵

Overall, the study contributes valuable real-world data; however, its findings are better interpreted as exploratory rather than directly practice-changing. At present, the results do not clearly show that early low-dose, slow-infusion thrombolysis improves outcomes beyond those achieved with guideline-recommended management.

LETTER TO THE EDITOR

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Reply to the Letter to the Editor: "Interpreting Reduced-Dose Slow-Infusion Thrombolysis in Intermediate-High-Risk Pulmonary Embolism"

We read the Letter to Editor (AJC-2026-290-6598) entitled "Interpreting reduced-dose slow-infusion thrombolysis in intermediate-high risk pulmonary embolism" on our published paper with great interest.^{1,2} We fully agree with the author of this letter regarding the lack of the currently available, evidence-based guideline recommendations favouring the full-, or low-dose systemic alteplase (t-PA) in IHR PE, in the absence of hemodynamic deterioration.³ However, the comparisons of efficacy and safety outcomes between our low-dose, slow infusion t-PA regimens and a weight-based bolus of tenecteplase given over a period of 5-10 seconds in the Pulmonary Embolism Thrombolysis (PEITHO) trial should also be considered methodologically unacceptable and misleading.⁴

As mentioned in our manuscript, a reduced-dose, slow-infusion intravenous t-PA strategy aims to achieve gradual pulmonary reperfusion and right-ventricular unloading while limiting peak systemic fibrinolytic exposure and bleeding risk.² The concept is promising, but superiority over anticoagulation, conventional half-dose alteplase, or catheter-based treatment has not been established. However, published multiple real-world results suggest the potential benefits of low-dose, slow-infusion t-PA protocols in this setting.⁵⁻⁷ The ongoing PEITHO-3 and STRATIFY randomized trials are expected to provide more definitive and clinically reliable answers regarding the efficacy and safety concerns of low-dose t-PA regimens in patients with IHR risk PE.^{8,9} Until clarification of the convincing results derived from randomized clinical trials, low-dose, slow-infusion t-PA therapy may be considered an individualized treatment strategy in the decision-making for specific circumstances.

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LETTER TO THE EDITOR REPLY

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An Unexpectedly Discovered Large Muscular Diverticulum of the Left Ventricular Outflow Tract

A 58-year-old male presented with a history of chest pain for 1 year, which had worsened over the past 3 days. The patient had a mildly elevated troponin I level and T-wave inversions in leads V1-V4, indicative of a non-ST-segment elevation anterior wall myocardial infarction. Transthoracic echocardiography showed mildly reduced anterior wall motion of the left ventricle. Apical views incidentally revealed a muscular, diverticulum-like structure (26 × 14 mm) originating from the left ventricular outflow tract (LVOT) and extending toward the right atrio-ventricular groove (Figure 1 A,B). Color Doppler imaging demonstrated diastolic flow from the LVOT into the diverticulum and systolic flow in the reverse direction (Figure 1 C, D). Cardiac CT angiography confirmed that the diverticulum (red arrows) was located beneath the right coronary cusp and communicated with the LVOT through a long neck (20 mm in length, 11 mm in width; white arrows) (Figure 1 E, F), and the diverticulum contracted and relaxed synchronously with the left ventricle. Volume-rendering (VR) imaging illustrated the morphology and spatial relationship of the diverticulum (Figure 1 G, H). Coronary angiography revealed 95% stenosis of the left anterior descending artery, and 2 stents were implanted via intervention. Because the diverticulum caused no compression of surrounding structures and the patient declined surgical treatment, follow-up observation was pursued.

To the best of our knowledge, subvalvular diverticula are typically fibrous in origin, and an isolated congenital muscular diverticulum of the LVOT is extremely rare. Multimodality imaging is an effective tool for accurate diagnosis and follow-up, playing a crucial role in guiding treatment.

E-PAGE ORIGINAL IMAGE

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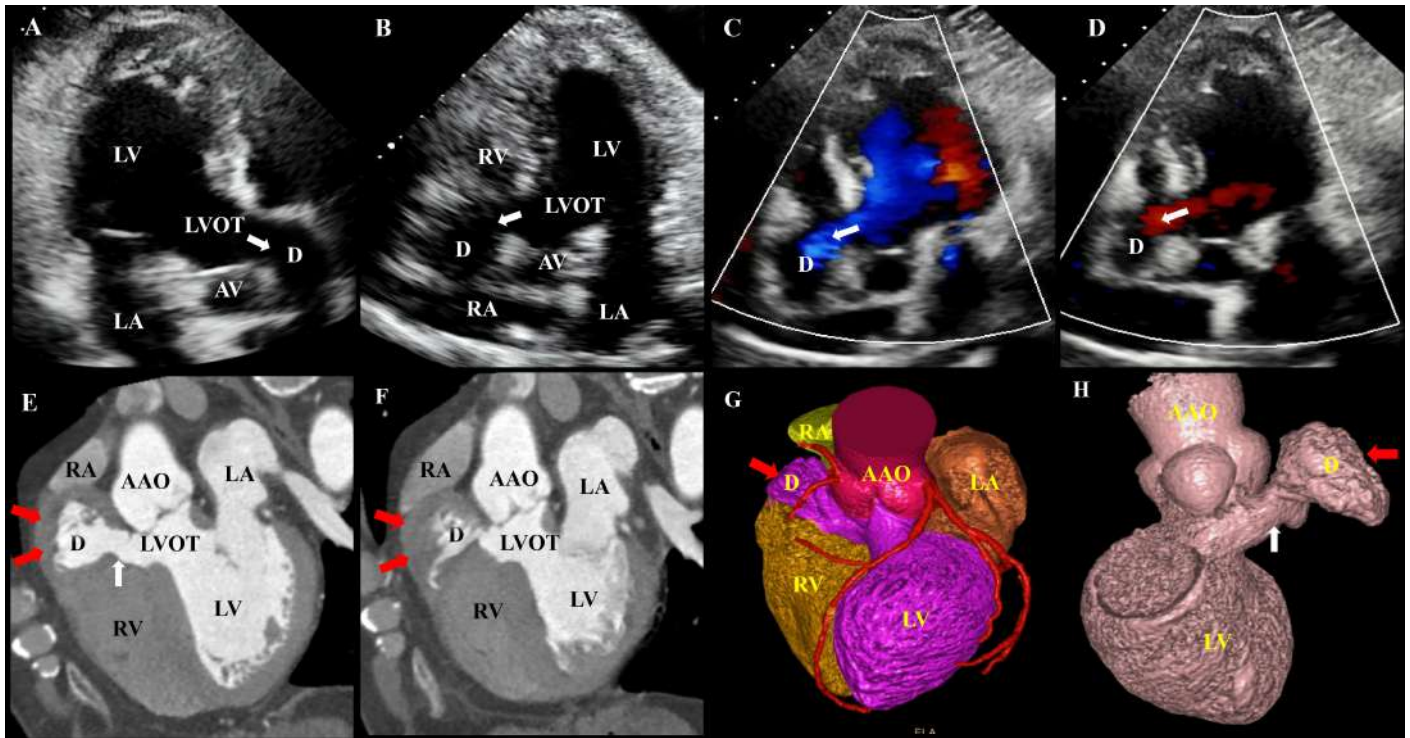


Figure 1. (A-B) Transthoracic echocardiography on apical 3- and 5-chamber views reveal a muscular diverticulum originating from the LVOT and extending toward the right atrioventricular groove. Color Doppler echocardiography reveals blood flowing from the LVOT into the diverticulum during diastole (C) and from the diverticulum into the LVOT during systole (D). (E-F) Cardiac CT angiography reveals the muscular diverticulum (red arrows) is located beneath the right coronary cusp and communicated with the LVOT through a long neck (white arrows). The diverticulum enlarges and its wall thins during diastole, while it decreases in size and its wall thickens during systole. (G) Volume-rendered (VR) imaging clearly showed the anatomical position of the diverticulum relative to the surrounding structures. (H) Volume-rendering (VR) imaging clearly showed the morphology and origination of the diverticulum. AAO, aortic arch; AV, aortic valve; D, diverticulum; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; RA, right atrium; RV, right ventricle.

Artificial Intelligence Usage Statement: Artificial intelligence was not used in this study.

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

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