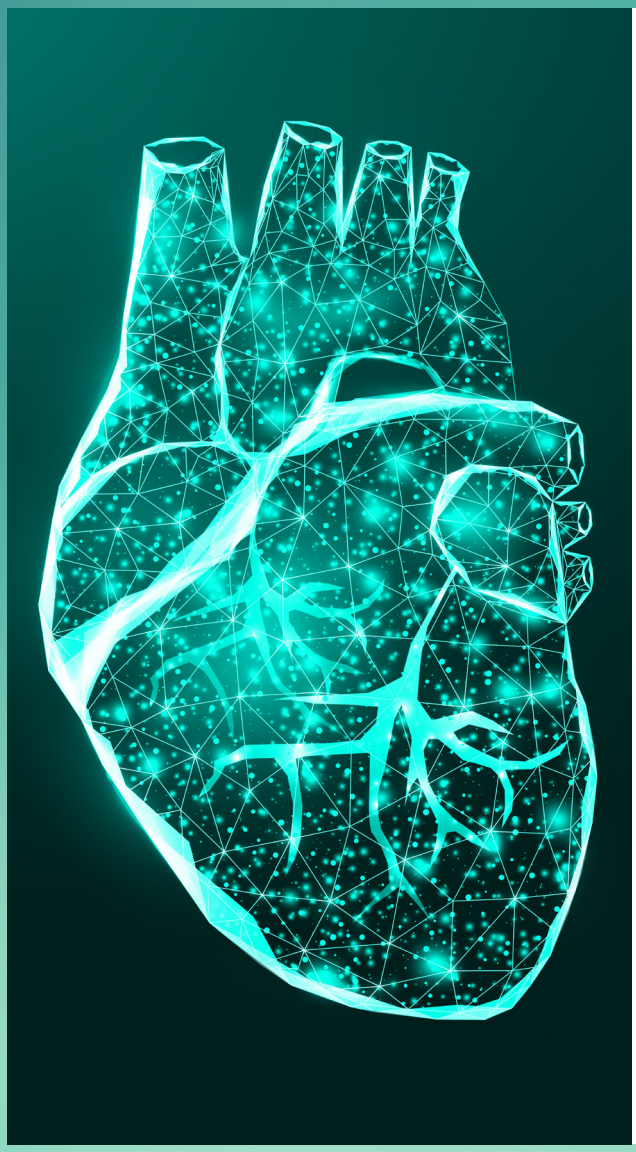
E-ISSN: 2405-819X

CARDIOVASCULAR ACADEMY SOCIETY

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

VOLUME: 12 ISSUE: 1 MARCH 2026



galenos

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

EDITORIAL BOARD

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr
yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: March 2026
ISSN: 2405-8181 **E-ISSN:** 2405-819X
International scientific journal published quarterly.

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

Please refer to the journal's webpage (**https://ijcva.org/**) for "**Journal Policies**" and "**Instructions to Authors**".

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the ICMJE, COPE, WAME, CSE, NISO and EASE.
The **International Journal of the Cardiovascular Academy** (**IJCVA**) is indexed in **Scopus, DOAJ, Embase, CNKI** (**China National Knowledge Infrastructure**), **EBSCO Central & Eastern European Academic Source, Hinari, GOALI, ARDI, AGORA, OARE** and **ProQuest**.

The journal is published online.

Owner: Ömer Kozan on behalf of the Cardiovascular Academy Society

Responsible Manager: Mehdi Zoghi

VOLUME: **12**
ISSUE: **1**
MARCH **2026**

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

CONTENTS

REVIEW

DOI: 10.4274/ijca.2026.53315
Int J Cardiovasc Acad 2026;12(1):1-13

Assessing the Impact of Inclisiran on LDL-C and PCSK9 Reduction in Hypercholesterolemic Patients: A Meta-analysis of Cardiovascular Metabolic Prevention

Agung Cendekia Putra Nusantara[1], Ariella Diandihati Rapsanjani[1], Ikhwan Handirosiyanto[2], Tara Mandiricha[3], Aisyah Silvia Gaffar[1]

[1]University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia
[2]Department of Cardiology and Vascular Medicine, University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia
[3]Department of Pharmacology, University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia

Abstract

Hypercholesterolemia, a major contributor to atherosclerotic cardiovascular disease, remains inadequately controlled despite widespread statin use, particularly in patients with familial hypercholesterolemia or statin intolerance. Inclisiran, a novel small interfering RNA therapeutic, targets hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis to provide sustained low-density lipoprotein cholesterol (LDL-C) reduction. This meta-analysis evaluated the efficacy of inclisiran 300 mg in lowering LDL-C and PCSK9 levels in patients with general hypercholesterolemia or heterozygous familial hypercholesterolemia (HeFH). A systematic search of PubMed, Cochrane, Wiley, and Scopus up to July 2025 identified 11 randomized controlled trials comparing inclisiran 300 mg with placebo. Pooled results showed significant LDL-C reductions of -31.89 mg/dL for general hypercholesterolemia and -61.47 mg/dL for HeFH; PCSK9 decreased by -65.96 ng/mL and -56.41 ng/mL, respectively, with no significant subgroup differences observed. Although the risk of bias was low, heterogeneity (I^2 >50%) and mild funnel plot asymmetry indicated potential variability and small-study effects. Overall, Inclisiran demonstrates consistent and substantial lipid-lowering efficacy across diverse hypercholesterolemic populations, supporting its use as an adjunct or alternative to statins. Its twice-yearly dosing may offer benefits for adherence and long-term lipid control; however, further studies are needed to confirm benefits on cardiovascular outcomes.

Keywords: Inclisiran, hypercholesterolemia, LDL-C, PCSK9

INTRODUCTION

Hypercholesterolemia is a major global health concern and a well-recognized contributor to atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD), stroke, and peripheral arterial disease.[1] Characterized by elevated levels of circulating low-density lipoprotein cholesterol (LDL-C), hypercholesterolemia accelerates the formation of lipid-rich atherosclerotic plaques, leading to vascular inflammation and luminal narrowing.[2,3] The condition may arise from genetic predispositions, such as familial hypercholesterolemia, or be acquired through lifestyle and metabolic factors, including obesity, type 2 diabetes mellitus, and dietary habits.[4,5]

Hypercholesterolemia affects an estimated 45% of the global population, with reported prevalence rates of approximately 30% in Southeast Asia and 35% in Indonesia.[6] Despite the widespread use of statins and other lipid-lowering agents, a significant proportion of hypercholesterolemic patients fail to achieve optimal LDL-C targets, particularly those with familial hypercholesterolemia or statin intolerance.[7,8]

To cite this article: Nusantara ACP, Rapsanjani AD, Handirosiyanto I, Mandiricha T, Gaffar AS. Assessing the impact of inclisiran on LDL-C and PCSK9 reduction in hypercholesterolemic patients: a meta-analysis of cardiovascular metabolic prevention. Int J Cardiovasc Acad. 2026;12(1):1-13

Address for Correspondence: Tara Mandiricha MD, Department of Pharmacology, University of Muhammadiyah Malang Faculty of Medicine, Malang, Indonesia
E-mail: tara@umm.ac.id
ORCID ID: orcid.org/0000-0003-0750-3332

Received: 17.09.2025
Accepted: 01.01.2026
Publication Date: 10.03.2026

LDL-C levels in clinical practice often remain above recommended thresholds, posing a persistent challenge in cardiovascular risk reduction. International data indicate that over 83% of patients with established CAD do not reach the LDL-C goal of <1.4 mmol/L with this proportion rising to approximately 89% in Indonesian populations.[9] In line with these findings, a national multicenter study reported that only 8.5% of patients achieved LDL-C <55 mg/dL and 28.4% reached <70 mg/dL, while 71.6% remained above target and 20.6% had levels ≥ 6 mg/dL.[10,11] As a result, new therapeutic approaches that target distinct molecular pathways have been developed to improve lipid regulation and reduce the risk of cardiovascular disease. This disparity underscores the clinical need for more effective, longer-acting, and better-tolerated lipid-lowering interventions.

Inclisiran, a small interfering RNA (siRNA) agent, represents a novel class of lipid-lowering therapy that targets hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis.[11] By silencing the *PCSK9* gene at the messenger RNA (mRNA) level, inclisiran offers a sustained reduction in circulating PCSK9 and LDL-C with a convenient biannual dosing schedule.[12] Several randomized controlled trials (RCTs), notably the ORION trial program, have evaluated the safety and efficacy of inclisiran in various hypercholesterolemic populations.[13] However, a synthesis of the available evidence is needed to provide a comprehensive, quantitative assessment of inclisiran's lipid-lowering effects, particularly regarding PCSK9 suppression and LDL-C reduction.

This meta-analysis aims to comprehensively assess the impact of inclisiran on LDL-C and PCSK9 levels in patients with hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). This study integrates data from recent RCTs to assess the impact of inclisiran across a broader range of patients, including patients with genetic conditions such as HeFH, in contrast to prior reviews that focused on individual trials or overall cholesterol outcomes.

METHODS

1. Study Methodology

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Eligibility Criteria

The following criteria, presented in Appendix 1, are considered eligible for this study: study population, intervention type, outcomes, study type, and reference standards.

2.1. Populations of the Studies

Individuals diagnosed with elevated blood cholesterol levels, encompassing both general hypercholesterolemia or homozygous familial hypercholesterolemia (HoFH) and specific genetic forms such as HeFH.

2.2. Type of Intervention

The included studies compared the efficacy and safety of inclisiran with those of placebo or other lipid-lowering treatments. However, a limitation of these studies was that inclisiran was administered at a fixed dosage of 300 mg, thereby restricting the evaluation of different dosing strategies or dose-response relationships.

2.3. Outcomes

The primary outcomes assessed in these studies were reductions in LDL-C levels and changes in PCSK9 concentrations.

2.4. Type of Studies

Original research article using human study with RCT only design written in English we included in this study. Narrative review, systematic review, metaanalysis, non-comparative research, in silico studies, *in vivo* studies, technical reports, editor response, scientific poster, study protocol and conference abstracts we excluded. Unavailable full-text article, non-English, irrelevant topics were also excluded.

2.5. Reference Standards

The reference standard was experimental research conducted by qualified professionals to evaluate the effect of inclisiran compared with placebo on reductions in LDL-C and PCSK9 levels.

3. Data Source and Search

The literature search process was carried out using four electronic databases, i.e., PubMed, Cochrane, Wiley, and Scopus. The literature search was conducted through July 2025. The keywords used in electronic databases were combined using Boolean operators. The search strategy employed the following key terms: ("Inclisiran") AND ("siRNA therapy" OR "small interfering RNA") AND ("hypercholesterolemia" OR "high cholesterol"). In addition, the reference lists of the identified studies were reviewed to identify any additional relevant studies. The search strategy and keyword PICOs framework are shown in Appendix 1.

4. Study Selection

After removal of duplicate articles, the retrieved articles were screened by all authors (A.C.P.N., A.D.R., I.H., T.M.) based on

titles and abstracts. Potentially eligible full-text articles were thoroughly assessed using the eligibility criteria described above. Any emerging discrepancies were resolved by consensus among the authors. The entire study selection process was recorded in the PRISMA flow chart.

5. Data Extraction and Analysis

Included studies were extracted using Microsoft Excel 2019 (Microsoft Corporation, USA) and Rayyan.ai. The following data were recorded: author, year, country, study design, experimental intervention, control intervention, intervention duration, and outcome. All statistical tests for the meta-analysis were conducted using Review Manager v5.4 and Stata 19.0.

6. Risk of Bias in Individual Studies (Qualitative Synthesis)

The quality of each included study was assessed by three independent reviewers (A.C.P.N., A.D.R., I.H.); any disagreements were resolved by a fourth independent reviewer (T.M.) according to the Cochrane Risk of Bias (revised tool for risk of bias in randomized trials).

7. Quantitative Data Synthesis (Meta-analysis)

This meta-analysis reported data as mean and standard deviation (SD) with 95% confidence intervals (CIs). We used the heterogeneity level to determine which effect model to use, either a fixed-effect model or random-effect model. Furthermore, the Cochrane chi-squared test and inconsistency (I^2) examine the studies' heterogeneity. A $P < 0.05$ was considered significant; hence, heterogeneity was significant when $I^2 > 50\%$. Random-effects and fixed-effects models were used when heterogeneity was >50% and <50%, respectively. The pooled estimate was presented in our forest plot. Subgroup analysis will be used to assess any heterogeneity among the included studies.

RESULTS

1. Study Selection

The study selection process began with the identification of records from multiple electronic databases shown in Figure 1, including PubMed (n=117), Scopus (n=302), Cochrane (n=32), and Wiley (n=110), yielding a total of 561 records. Prior to screening, 242 duplicate records were removed, leaving 319 records for title and abstract screening. During the screening phase, 51 records were excluded based on titles and abstracts. A total of 268 full-text reports were sought for retrieval; however, 25 could not be retrieved. Subsequently, 243 full-text reports were assessed for eligibility. Of these, reports were excluded for the following reasons: inappropriate study design (n=22), inappropriate comparator (n=20), absence of hypercholesterolemic participants (n=15), and lack of relevant outcomes (n=175). Ultimately, 11 studies met the inclusion criteria and were included in the review.

Many records could not be retrieved due to paywall restrictions, unavailable full texts, duplicate database indexing, or non-English versions without accessible translations. These unretrieved records were documented but excluded from eligibility screening.

Despite the large number of unretrievable reports, none corresponded to RCTs evaluating inclisiran. The final sample of 11 RCTs likely reflects the entire body of currently available trial evidence.

2. Study Characteristics and Result of Individual Studies

A total of eleven RCTs were included in the qualitative synthesis.[14-24] These studies were published up to July 2025, and the majority were conducted at multiple centers. Moreover, there are two studies conducted in the USA and the UK, and one study each in China and Japan. Most studies enrolled patients diagnosed with general hypercholesterolemia or HeFH, in which inclisiran 300 mg was the intervention and placebo the comparator.

Participant ages ranged from 14 to 66 years, with a balanced distribution between male and female subjects. The total sample size across all included studies was approximately 5,365 individuals.

Regarding subject characteristics, a substantial portion of the population had established ASCVD or multiple cardiovascular risk factors. All studies reported outcomes as percentage changes from baseline and absolute mean differences from baseline in LDL-C and PCSK9 levels, which were used as the primary endpoints in the analysis. A detailed breakdown of each study's baseline characteristics and interventions is provided in Table 1.

3. Risk of Bias in Individual Studies (Qualitative Synthesis)

The risk-of-bias assessment of the eleven studies included in the qualitative synthesis indicates that most studies demonstrate a low risk of bias across most assessed domains. The evaluated domains include the randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), and selection of the reported result (D5). Most studies were rated as having low risk (green) in domains D1 through D4. However, several studies presented some concerns (yellow) and even high risk (red), particularly in the domains of D4 and D5. For instance, the study by Koenig et al.[16] showed high risk in D5, which may impact the reliability of its findings.

Table 1. Study characteristics and results of individual studies

No	Author, year	Country	Study design	Age (year)		Sample size		Intervention			Main outcomes
				Inclisiran	Placebo	Inclisiran	Placebo	Drug (dosage)	Control (dosage)	Duration	
1	Yamashita et al.[14]	Japan	RCT double-blind, phase 2	63±10.7	63.8±11.1	96	56	Inclisiran SC 300 mg (single dose)	Placebo	360 days	Reduced LDL-C and PCSK9
2	Luo et al.[15]	China	RCT	59.5±7.45	57.3±9.59	15	10	Inclisiran SC 300 mg (single dose)	Placebo	90 days	Reduced LDL-C and PCSK9
3	Raal et al.[17]	Multicenter	RCT double-blind, phase 3	55.5±2.7	55.5±3.0	242	240	Inclisiran SC 300 mg (single dose)	Placebo	540 days	In adults with HeFH, inclisiran significantly reduced LDL cholesterol compared to placebo.
4	Leiter et al.[18]	USA	RCT	-	-	54	57	Inclisiran 300 mg (single dose)	Placebo	210 days	Reduced LDL-C
5	Fitzgerald et al.[19]	UK	RCT single-blind, phase 1	46±10	48±14	18	6	Inclisiran SC 300 mg (single dose)	Placebo	180 days	Reduced levels of PCSK9 and LDL cholesterol for at least 6 months
6	Ray et al.[20]	UK	RCT double-blind phase 2	63.9±12.8	62±11.4	60	64	Inclisiran SC 300 mg (single dose)	Placebo	360 days	Lower PCSK9 and LDL cholesterol levels among patients at high cardiovascular risk who had elevated LDL cholesterol levels.
7	Wright et al.[21]	USA	RCT double-blind phase 3	64.1±9.98	63.9±9.87	1833	1827	Inclisiran SC 300 mg (single dose)	Placebo	540 days	lowering PCSK9 and lower LDL-C in adults with heterozygous familial hypercholesterolemia
8	Ray et al.[22]	Multicenter	RCT double-blind phase 2	63.3±11.1	61.9±10.6	277	92	Inclisiran SC 300 mg (single dose)	Placebo	1440 days	reductions in LDL cholesterol and PCSK9 concentrations
9	Wiegman et al.[23]	Multicenter	RCT double-blind phase 2	14.6±1.5	15.1±2.7	9	4	Inclisiran SC 300 mg (single dose)	Placebo	330 days	Lowering PCSK9 and lower LDL-C in adolescents with HoFH
10	Ray et al.[24]	Multicenter	RCT double-blind phase 3	62.7±10.6	63.6±9.2	98	105	Inclisiran SC 300 mg (single dose)	Placebo	540 days	LDL-C reductions
11	Koenig et al.[16]	Multicenter	RCT double-blind phase 3	65.1±8.5	64.2±8.6	110	92	Inclisiran SC 300 mg (single dose)	Placebo	510 days	LDL-C reductions

RCT: Randomized controlled trial, LDL-C: Low-density lipoprotein cholesterol, PCSK9: Proprotein convertase subtilisin/kexin type 9, HeFH: Heterozygous familial hypercholesterolemia, HoFH: Homozygous familial hypercholesterolemia

The summary bar chart further illustrates that, while the the majority of data fall into the low-risk category, the presence of some concerns and high-risk ratings in key domains highlights the need for cautious interpretation of the overall evidence shown in Figure 2. The justification and comment for each question are displayed in Appendix 2.

4. Efficacy Outcomes

A total of 11 RCTs were included in the meta-analysis to assess the effect of inclisiran 300 mg compared to placebo on LDL-C levels in patients with hypercholesterolemia.[14-24]

4.1. Change in LDL-C Levels

A subgroup analysis, presented in Figure 3, was conducted to evaluate the efficacy of inclisiran 300 mg in lowering LDL-C and PCSK9 levels across two distinct patient populations: those with general hypercholesterolemia and those with HeFH. In terms of LDL-C reduction, inclisiran showed a statistically significant effect in both subgroups. Among patients with general hypercholesterolemia, the pooled mean difference was -31.89 mg/dL (95% CI: -41.61 to -22.17), while in the HeFH subgroup, the effect was more pronounced, with a mean difference of -61.47 mg/dL (95% CI: -99.10 to -23.85). Despite the larger effect size in the HeFH group, the test for subgroup differences did not reach statistical significance (Chi^2=2.23, P = 0.14), indicating that the difference in LDL-C reduction between the two subgroups may not be statistically significant.

The funnel plot in Figure 4, stratified by subgroup, revealed mild asymmetry, especially among studies involving general hypercholesterolemia, which may indicate publication bias or small-study effects. In contrast, the HeFH subgroup included fewer studies with larger standard errors, limiting the ability to draw firm conclusions about publication bias. Overall, inclisiran consistently reduced LDL-C levels across both populations, with a potentially greater effect in HeFH patients, although the difference between subgroups was not statistically significant.

Visual inspection of the funnel plot suggested mild asymmetry. However, Egger's regression test demonstrated no statistically

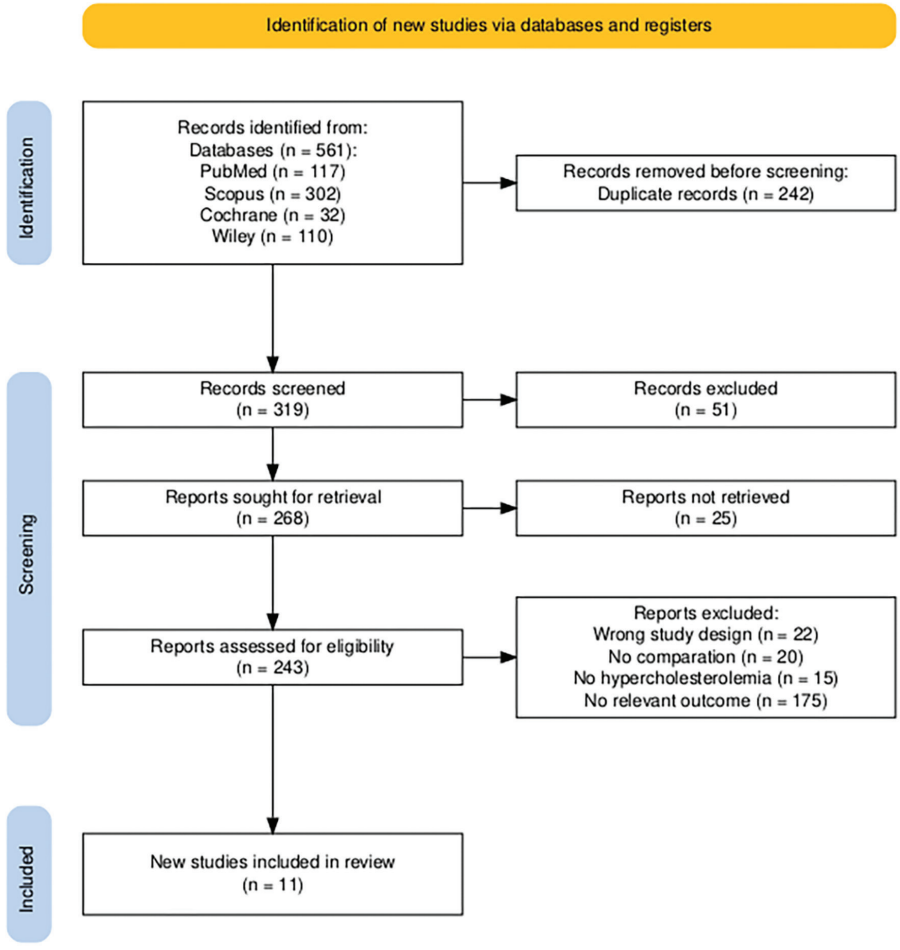


Figure 1. PRISMA flow diagram

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Figure 2. Risk of bias in individual studies (qualitative synthesis). (A) Risk of bias judgement for each included study based on five domains of assessment. (B) Summary bar chart showing the proportion of studies with low risk (green), some concerns (yellow), and high risk (red) for each domain and overall assessment

significant evidence of small-study effects (β=-0.46, standard error=17.60, z=-0.03, $P = 0.979$), as shown in Appendix 3.

An extended random-effects meta-regression was conducted using sample sizes for inclisiran and placebo, and follow-up duration as moderators. Although the overall meta-regression model was statistically significant (Wald χ^2 (3)=21.38, $P = 0.0001$), none of the individual moderators showed a significant association with effect size (all $P > 0.23$), as shown in Appendix 4.

Residual heterogeneity remained extremely high (τ^2=81.29; I^2=99.73%; Q_res $P < 0.0001$), indicating that these variables did not meaningfully explain between-study variance.

4.2. Change in PCSK9 Levels

PCSK9 levels after inclisiran treatment also showed consistent reductions (Figure 5). In the general hypercholesterolemia group, the mean difference was -65.96 ng/mL (95% CI: -85.14 to -46.79), while in the HeFH group, it was -56.41 ng/mL (95% CI: -73.46 to -39.37). Similarly, the test for subgroup differences was not statistically significant (Chi²=0.53, $P = 0.47$), suggesting that inclisiran's effect on PCSK9 reduction is comparable in both populations. Notably, heterogeneity was high in the general hypercholesterolemia group (I^2=100%) and moderate to high in the HeFH group (I^2=68-82%), possibly reflecting differences in study design or patient characteristics.

4.3. Sensitivity Analysis

A sensitivity analysis excluding the Koenig et al.[16] trial—rated as high risk in Domain 5 of the Risk of Bias 2 (RoB 2) assessment—was performed to evaluate its impact on the pooled estimate. Removal of this study resulted in only minimal changes in the effect size, and the CIs overlapped substantially with those of the main analysis. This indicates that the pooled results remain robust despite the presence of one trial at high risk of bias.

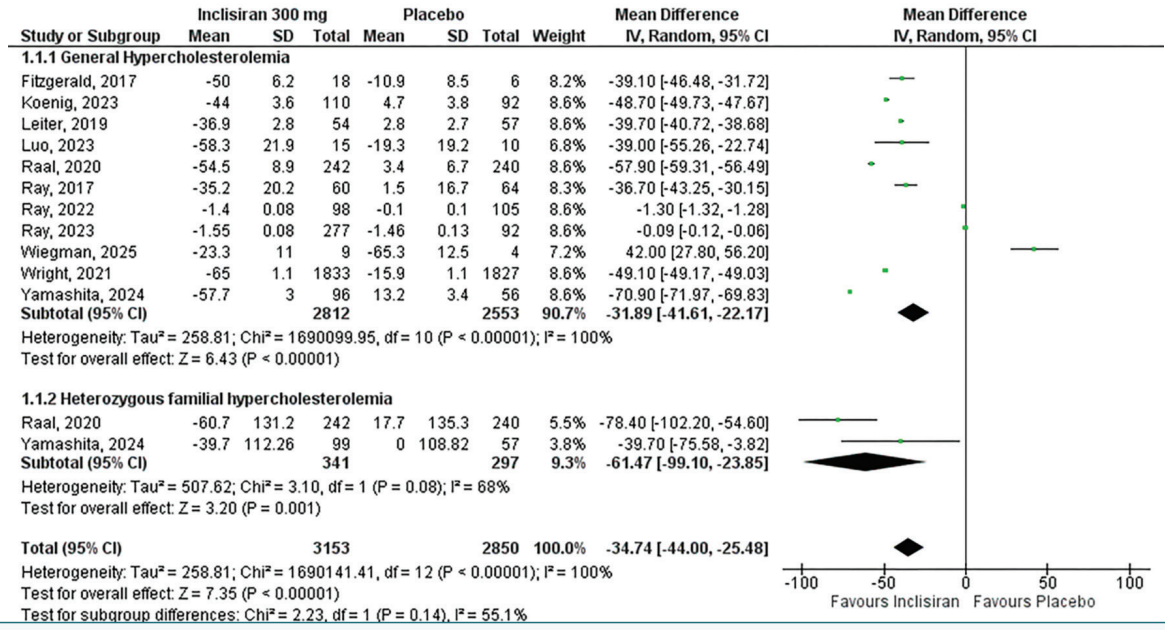


Figure 3. Forest plot of the effect of Inclisiran 300 mg on LDL-C levels in patients with hypercholesterolemia

LDL-C: Low-density lipoprotein cholesterol, CI: Confidence interval, SD: Standard deviation

DISCUSSION

We have systematically investigated 11 RCTs on the clinical efficacy of inclisiran 300 mg in reducing both LDL-C and PCSK9 concentrations in patients with hypercholesterolemia. The pooled results from RCTs demonstrated that inclisiran significantly reduced LDL-C and PCSK9 levels compared to placebo, highlighting its robust lipid-lowering potential. This effect remained statistically significant even when analyzed across different patient subgroups, including those with HeFH, a population known to be at higher cardiovascular risk and often less responsive to conventional therapies. Although the HeFH subgroup appeared to experience a greater reduction in LDL-C, the difference between the HeFH and non-HeFH groups was not statistically significant, suggesting a consistent therapeutic benefit across varying baseline risk profiles. Notably, the meta-analysis revealed a high degree of heterogeneity in both LDL-C and PCSK9 outcomes, which may reflect differences in study design, baseline lipid levels, or population characteristics across the included trials.

One included trial (Koenig et al.[16]) was rated as high risk in Domain 5 of the RoB 2 tool due to concerns related to selective reporting. While the sensitivity analysis demonstrated that excluding this study did not materially alter the findings, its presence may still contribute to uncertainty regarding the strength of the evidence. Therefore, the results should be interpreted with caution, especially regarding consistency across trials.

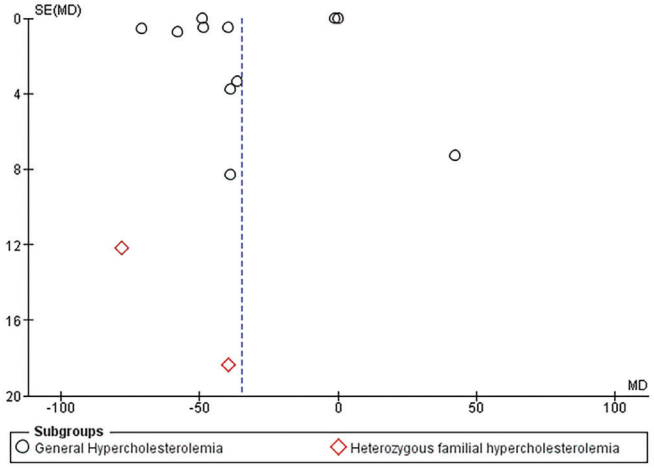


Figure 4. Funnel plot for publication bias by subgroup: LDL-C reduction in general vs. familial hypercholesterolemia

LDL-C: Low-density lipoprotein cholesterol

1. Consistency of Inclisiran Outcomes with Previous Studies and Standard Therapies

Comparable findings concerning the LDL-C-lowering capacity of inclisiran have been consistently observed in a range of RCTs and real-world clinical studies. The most compelling data originate from the ORION clinical trial series (ORION-9, ORION-10, ORION-11), which together confirm the drug's significant and sustained ability to reduce LDL-C levels across diverse patient populations. In particular, the ORION-10 and ORION-11 trials, which investigated individuals with pre-existing ASCVD or

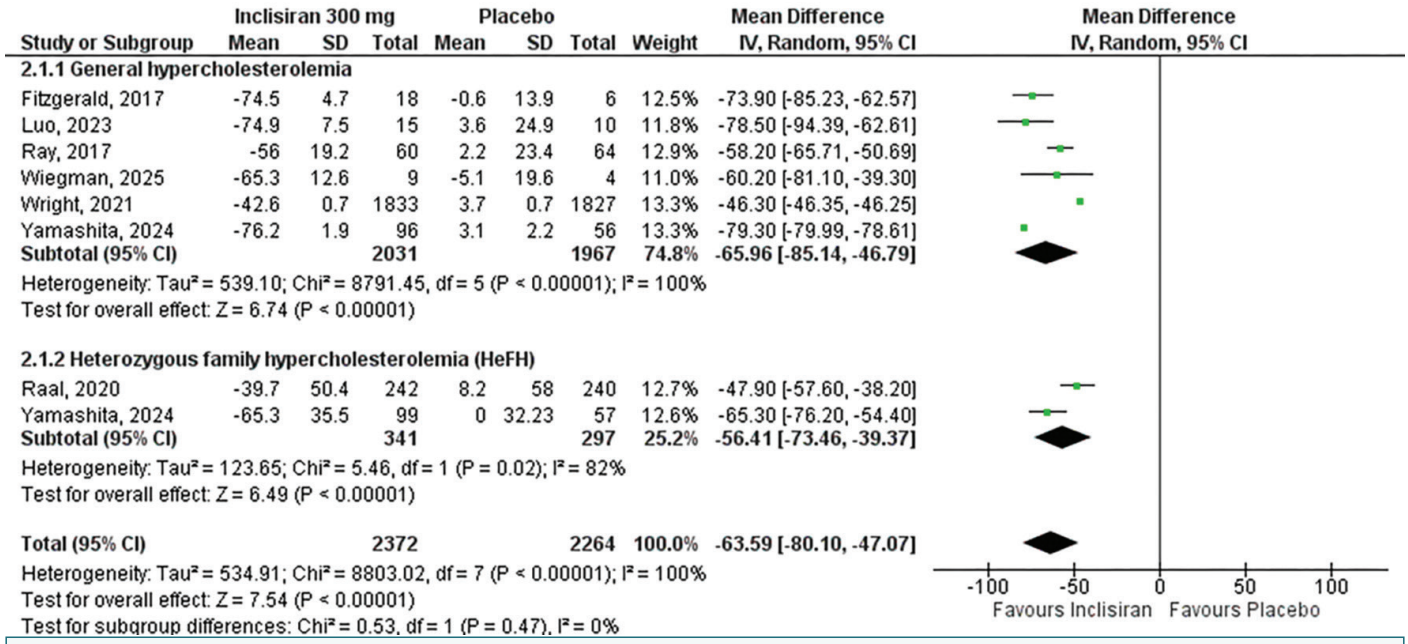


Figure 5. Forest plot of the effect of inclisiran 300 mg on PCSK9 levels in patients with hypercholesterolemia

PCSK9: Proprotein convertase subtilisin/kexin type 9, CI: Confidence interval, SD: Standard deviation

those considered at high cardiovascular risk, reported average reductions in LDL-C of 52.3% and 49.9%, respectively, by day 510.[25] Similarly, ORION-9, which focused on patients diagnosed with HeFH, demonstrated a significant LDL-C reduction of 47.9% compared to placebo.[17] Together, these studies offered the first compelling evidence that inclisiran is an effective long-term lipid-lowering agent, particularly when administered alongside the highest tolerated statin therapy.

Additional support for inclisiran's efficacy has been demonstrated in a retrospective cohort study conducted by Briani et al.[26] which observed a marked decrease in LDL-C concentrations, reaching an average of 58.5±42.8 mg/dL ($P <$ 0.001) as early as 32 days following single administration.[26] Notably, a considerable number of participants achieved the LDL-C thresholds outlined in the 2019 ESC/EAS guidelines, highlighting inclisiran's capacity to facilitate attainment of intensive lipid targets. The study further underscored the central role of statins as first-line therapy for lipid management and proposed inclisiran as a valuable adjunct or alternative, particularly for individuals with inadequate lipid control or statin intolerance.

Despite exploring several moderators, including the sample sizes of both treatment arms and the duration of follow-up, our meta-regression analysis did not identify any statistically significant predictors of effect size. Residual heterogeneity remained extremely high (I^2=99.73%), suggesting that substantial differences among studies persisted even after adjustment.

This indicates that heterogeneity is likely driven by multiple unmeasured clinical or methodological factors, such as variations in baseline LDL-C, background statin therapy, dosing intervals, and trial design across ORION and non-ORION studies.

These findings, together with consistent outcomes observed in both randomized trials and routine clinical use, consolidate the evidence base supporting inclisiran as a potent and dependable lipid-lowering intervention. Its reproducible efficacy across diverse patient profiles, rapid onset of action, and capacity to help patients meet recommended LDL-C goals suggest a meaningful role for inclisiran in comprehensive cardiovascular risk reduction strategies.

2. Implications of Inclisiran as an Adjunct or Alternative to Statin Therapy

Recent evidence drawn from real-world clinical experience increasingly supports the use of inclisiran both as an adjunctive and as an alternative approach in lipid-lowering strategies, particularly for individuals already on statins or for those who cannot tolerate them. The findings of this study support the role of statins as the primary therapy for lowering LDL-C levels. A study by Padam et al.[27] also demonstrated that the reduction in LDL-C was greater in patients who received statins in combinations with inclisiran compared to those who did not (56% vs. 44.9% within 2 months). This effect reflects a synergistic interaction in which statins increase the transcription of LDL receptor mRNA and PCSK9 mRNA, while inclisiran inhibits the translation of PCSK9 mRNA. This ultimately leads to an

increased number of LDL receptors on the cell surface and enhanced clearance of LDL-C from bloodstream.[28]

From safety standpoint, inclisiran classified as a siRNA therapy targeting PCSK9 mRNA-has consistently shown a favorable safety profile in both trial settings and clinical practice.[29] Moreover, inclisiran precise made of action minimizes systematic distribution, which contributes to its enhanced safety characteristics.[30] Inclisiran demonstrates both additive benefits when used alongside statins and independent utility in patients unable to tolerate standard therapies. As such, it fills a crucial therapeutic gap in current cardiovascular prevention strategies, supporting its growing role in long-term atherosclerotic disease management.

3. Benefits of Twice-yearly Dosing in Improving Patient Adherence

Extensive meta-analyses and systematic reviews consistently show that less frequent dosing significantly improves medication adherence in chronic diseases. Studies comparing once-daily regimens to twice-daily or more frequent dosing found adherence rates generally 13-26 % higher for once-daily therapy, with timing adherence (the strictest definition) showing even larger gaps.[31] Another analysis of cardiovascular medications reported regimen adherence lower by ~14 % and timing adherence by ~23% when switching from once- to twice-daily dosing.[32] These findings suggest that by further reducing dosing to every six months, adherence could improve even more, as patients face minimal regimen complexity.[17]

Inclisiran, an siRNA therapy for hypercholesterolemia, is administered only twice yearly after the initial loading doses. Its long-acting mechanism maintains LDL-C suppression for months with minimal follow-up visits. This extended dosing interval reduces cognitive load and "pill fatigue," especially in asymptomatic chronic conditions where motivation wanes over time.[33]

A recent retrospective claims-based study in the USA compared six-month adherence to inclisiran and anti-PCSK9 monoclonal antibodies. Patients on inclisiran achieved a mean proportion of days covered (PDC) of 0.85, which was significantly higher than the 0.70 observed with monoclonal antibodies. Approximately 70% of inclisiran patients achieved PDC ≥80%, compared to 48-51% for alternative injectable agents.[34] These early real-world results align with the expectation that a twice-yearly injectable has superior adherence compared with more frequent injectable or oral regimens.

In the ORION-3 open-label extension study (4-year duration), approximately 79% of patients completed follow-up while receiving inclisiran every six months, indicating strong treatment persistence. LDL-C reductions of 50% were sustained through 4 years, supporting both efficacy and real-world tolerability of infrequent dosing.[35]

4. Inclisiran 300 mg: The Optimal Therapeutic Dose

Phase 2 dose-ranging trials, particularly ORION-1, evaluated inclisiran at various single- and two-dose regimens: 100, 200, 300, and 500 mg. One-year follow-up revealed that the two-dose 300 mg regimen produced the strongest LDL-C reduction (about -52.6%) and had the highest persistence of response through day 360 (83% of participants maintained ≥80% of their baseline LDL-C reduction).[15,36-38] Although the 500 mg dose achieved a similar reduction, it did not materially outperform 300 mg in magnitude or durability, despite being higher in dose.[37]

Comparative meta-analysis further confirmed that 300 mg offered the best balance between efficacy and safety. Network meta-analyses demonstrated that while 100 mg and 200 mg doses produced some LDL-C lowering, the 300 mg dose yielded the greatest reduction, outperforming both lower and higher (500 mg) doses.[38,39] Importantly, adverse event rates remained similar across dose groups, meaning that increasing the dose above 300 mg did not confer meaningful safety advantages or additional therapeutic benefit.[39-41]

Pharmacodynamic data show that a single 300 mg dose suppresses PCSK9 levels by ~75% and LDL-C by ~50% for over 180 days.[37,42] Based on this sustained effect and the enhanced one-year persistence observed in the two-dose regimen, maintenance dosing every six months is feasible without retreatment. This creates a streamlined, efficacious, and convenient dosing schedule that aligns with both patient preference and long-term outcome frameworks.[37,41]

5. Mechanism of Action of Inclisiran siRNA Targeting of PCSK9 to Enhance LDL Receptor Recycling and Reduce LDL-C

Inclisiran is a sophisticated siRNA therapeutic that precisely binds to the mRNA of PCSK9 within hepatocytes. Through asialoglycoprotein receptor-mediated uptake, the GalNAc-conjugated siRNA enters the liver and becomes incorporated into the RNA-induced silencing complex (RISC). The RISC-siRNA complex then rapidly and catalytically cleaves PCSK9 mRNA, preventing its translation into protein.[11,15,43-46] This intracellular targeting contrasts with PCSK9 antibody therapies, which neutralize circulating PCSK9 rather than reduce its production.

By suppressing PCSK9 synthesis, inclisiran effectively halts the PCSK9-mediated lysosomal degradation of LDL receptors. Consequently, more LDLRs are available on the hepatocyte surface to remove circulating LDL-C from the bloodstream.[12,43,45,47,48] Increased receptor density leads to enhanced LDL-C clearance, driving cholesterol reduction.

Clinical pharmacodynamic studies illustrate that inclisiran maintains profound suppression of PCSK9—approximately 75%—and ~50% reduction in LDL-C for at least six months after a single 300 mg dose.[45] This prolonged effect supports its twice-yearly dosing schedule by maintaining plasma LDL-C at reduced levels over extended periods, without requiring frequent administration.

Phase III trials (ORION-10, -11, and -9) consistently showed ~50% LDL-C reduction over 18 months, confirming sustained pharmacodynamic and clinical efficacy.[11,45] These LDL-C reductions were achieved with biannual subcutaneous dosing after initial loading doses, consistent with a durable mechanism.

6. Assessment of Bias, Variability, and Subgroup Differences

Despite the overall low risk of bias across most included studies, a few trials exhibited a high risk of bias, specifically in domain D3 and domain D5. These risks may introduce reporting and attrition biases, which could undermine the internal validity and the reliability of the pooled results. For instance, missing data can distort treatment effects, particularly if loss to follow-up is related to treatment response or adverse events. Similarly, selective outcome reporting may exaggerate the perceived efficacy of inclisiran if only favorable results are disclosed. Although the overall evidence quality is robust, these methodological concerns necessitate cautious interpretation of specific study findings.

The substantial heterogeneity observed across studies (I^2 ranging from 68% to 100%) warrants careful interpretation. Although we performed subgroup analyses comparing general hypercholesterolemia and HeFH, the subgroup interaction was not statistically significant and did not meaningfully reduce heterogeneity. This suggests that the differences between these groups do not account for the variability in effect sizes.

A number of unmeasured or unreported factors likely contribute to the observed heterogeneity. These include substantial differences in baseline LDL-C levels, inconsistent background statin therapy, varying dosing schedules of inclisiran (the standard ORION regimen versus modified regimens), inclusion of both ASCVD and non-ASCVD populations, and heterogeneity in study design features, including follow-up duration, endpoint definitions, and assay methods for LDL-C measurement.

The persistence of high heterogeneity, even after meta-regression, indicates that no single study-level characteristic adequately explains the variability. Therefore, the pooled effect should be interpreted as an average estimate across highly diverse clinical contexts rather than a uniform effect applicable to all populations. Despite this, the directionality of inclisiran's LDL-C-lowering effect remained consistent, supporting the robustness of its pharmacologic action across different settings. Future trials would benefit from more standardized reporting, harmonization of baseline risk profiles, and adequately powered subgroup analyses to clarify which patient groups derive the greatest benefit.

The classification of the HoFH (Wiegman et al.[23]) into the general hypercholesterolemia category was based on the similarity of clinical parameters and treatment context with broader hypercholesterolemia trials.

Although the funnel plot displayed some asymmetry, our formal Egger regression test did not identify statistically significant small-study effects ($P = 0.979$). This suggests that publication bias is unlikely to be the primary explanation for the visual asymmetry. Instead, the extremely high heterogeneity (I^2>99%) across trials may account for the observed asymmetry in the plot. Nonetheless, publication bias cannot be entirely ruled out.

7. Strength and Limitation

This meta-analysis has several strengths. First, it systematically synthesizes evidence from RCTs, which represent the highest level of clinical evidence and minimize the risk of bias. The inclusion of both general hypercholesterolemic populations and a genetically high-risk subgroup—HeFH—allowed for a more nuanced evaluation of inclisiran's efficacy. The consistently significant reduction in both LDL-C and PCSK9 levels across studies highlights the biological plausibility and therapeutic potential of inclisiran, even in the presence of clinical heterogeneity.

Moreover, sensitivity and subgroup analyses were conducted to assess the robustness of the results and identify potential effect modifiers of the treatment, thereby strengthening the credibility of the findings.

Nevertheless, several limitations should be acknowledged in interpreting our results. The number of included studies, particularly those evaluating PCSK9 outcomes, was limited, reducing the statistical power to draw definitive conclusions regarding this biomarker. Additionally, most trials used a fixed dose of inclisiran (300 mg), preventing assessment of dose-response effects or optimization of alternative dosing strategies. The inclusion of studies with small sample sizes and outlier values—such as extreme SDs—may have inflated between-study heterogeneity (I^2=100%). Furthermore, the follow-up periods in most trials were relatively short, limiting our ability to assess long-term cardiovascular outcomes, safety profiles, and patient adherence.

A substantial proportion of records identified in the initial search (200 out of 268, approximately 75%) could not be

retrieved due to restricted access, institutional limitations, or lack of full-text availability. This introduces a potential non-retrieval (accessibility) bias, which may influence the completeness of the evidence base and the assessment of publication bias. Nevertheless, all available full-text RCTs evaluating inclisiran were retrieved, and the final 11 RCTs likely represent the complete set of eligible evidence currently available in English.

The meta-regression results revealed that heterogeneity remained very high (I^2>99%) even after adjusting for sample size and follow-up duration, suggesting that important moderators may be unmeasured or unreported. This limits our ability to fully account for between-study variability.

At least one included study was judged to have a high risk of bias, which may influence the certainty of the pooled estimates. Although sensitivity analyses showed that its exclusion did not significantly change the effect size, residual concerns about selective reporting should be acknowledged.

Future research should aim to address these gaps by conducting large-scale, long-term RCTs with diverse patient populations and endpoints capable of detecting statistically significant differences, such as major cardiovascular events, mortality, and quality of life. Specific attention should be paid to high-risk subgroups—such as elderly individuals, patients with diabetes mellitus, or patients with polyvascular disease—to determine whether therapeutic responses differ across populations. Cost-effectiveness analyses are warranted to inform policy decisions and to support equitable access to inclisiran, a next-generation lipid-lowering agent.

CONCLUSION

This meta-analysis demonstrates that inclisiran 300 mg produces significant and sustained reductions in LDL-C and PCSK9 levels in patients with hypercholesterolemia, including those with HeFH. The lipid-lowering effects were generally consistent across the studied populations; however, these findings should be interpreted within the context of the specific patient groups and trial designs included in the analysis.

The observed biochemical efficacy, together with the biannual dosing regimen, supports inclisiran as a potential adjunctive lipid-lowering therapy, particularly for patients with statin intolerance or inadequate lipid control despite standard treatment. Nevertheless, the current evidence base is largely derived from short-term randomized trials and relies on surrogate lipid endpoints rather than definitive cardiovascular outcomes.

Accordingly, inclisiran should not yet be considered a proven alternative to established lipid-lowering therapies. The impact of inclisiran on major adverse cardiovascular events remains uncertain in the absence of completed large-scale, event-driven outcome trials. Ongoing studies, including ORION-4, are essential for determining its long-term cardiovascular benefit, safety profile, and clinical positioning. Future research should also address cost-effectiveness and real-world adherence to better define the role of inclisiran in routine clinical practice.

Footnotes

Authorship Contributions

Concept: A.C.P.N., A.D.R., I.H., T.M., Design: A.C.P.N., A.D.R., I.H., T.M., Data Collection or Processing: A.C.P.N., A.D.R., I.H., T.M., A.S.G., Analysis or Interpretation: A.C.P.N., A.D.R., I.H., T.M., A.S.G., Literature Search: A.C.P.N., A.D.R., Writing: A.C.P.N., A.D.R., I.H., A.S.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. McCallum RK, Kramer AI, Marchand M, Akioyamen LE, Genest J, Brunham LR. Estimating the prevalence of hypercholesterolemia in indigenous populations: a systematic review and meta-analysis. JACC Adv. 2023;2:100315.
2. Lu Y, Cui X, Zhang L, Wang X, Xu Y, Qin Z, *et al.* The functional role of lipoproteins in atherosclerosis: novel directions for diagnosis and targeting therapy. Aging Dis. 2022;13:491-520.
3. Papafaklis MI, Koros R, Tsigkas G, Karanasos A, Moulias A, Davlouros P. Reversal of atherosclerotic plaque growth and vulnerability: effects of lipid-modifying and anti-inflammatory therapeutic agents. Biomedicines. 2024;12:2435.
4. Berta E, Zsíros N, Bodor M, Balogh I, Lőrincz H, Paragh G, *et al.* Clinical aspects of genetic and non-genetic cardiovascular risk factors in familial hypercholesterolemia. Genes (Basel). 2022;13:1158.
5. Wong SK, Ramli FF, Ali A, Ibrahim N'. Genetics of cholesterol-related genes in metabolic syndrome: a review of current evidence. Biomedicines. 2022;10:3239.
6. Monikasari M, Nugroho KPA, Natawirarindy C, Esperansa PES. The relationship of nutritional status with cholesterol levels in junior high school students in Malang. Indones J Glob Heal Res. 2024;6:179-86.
7. Terentes-Printzios D, Dima I, Benardos P, Mitrou P, Mathioudakis K, Tsolakidis A, *et al.* Real-world data on treatment patterns in at least high cardiovascular risk patients on dual and triple lipid lowering therapy in a Hellenic nationwide e-prescription database. Int J Cardiol Cardiovasc Risk Prev. 2024;21:200261.
8. Lui DTW, Lee ACH, Tan KCB. Management of familial hypercholesterolemia: current status and future perspectives. J Endocr Soc. 2020;5:bvaa122.
9. McEvoy JW, Jennings C, Kotseva K, De Bacquer D, De Backer G, Erlund I, *et al.* Variation in secondary prevention of coronary heart disease: the INTERASPIRE study. Eur Heart J. 2024;45:4184-96.

10. Ambari AM, Hasan H, Dwiputra B, Desandri DR, Hamdani R, Krevani CK, *et al.* Indonesia-INTERASPIRE study: an Indonesian cross-sectional multicenter survey on cardiovascular secondary prevention in coronary heart disease. Med J Indones. 2025;34:158-66.

11. Zhang Y, Chen H, Hong L, Wang H, Li B, Zhang M, *et al.* Inclisiran: a new generation of lipid-lowering siRNA therapeutic. Front Pharmacol. 2023;14:1260921.

12. Wilkinson MJ, Bajaj A, Brousseau ME, Taub PR. Harnessing RNA interference for cholesterol lowering: the bench-to-bedside story of inclisiran. J Am Heart Assoc. 2024;13:e032031.

13. Dutta S, Shah R, Singhal S, Singh S, Piparva K, Katoch CDS. A systematic review and meta-analysis of tolerability, cardiac safety and efficacy of inclisiran for the therapy of hyperlipidemic patients. Expert Opin Drug Saf. 2024;23:187-98.

14. Yamashita S, Kiyosue A, Maheux P, Mena-Madrazo J, Lesogor A, Shao Q, *et al.* Efficacy, safety, and pharmacokinetics of inclisiran in japanese patients: results from ORION-15. J Atheroscler Thromb. 2024;31:876-903.

15. Luo Z, Huang Z, Sun F, Guo F, Wang Y, Kao S, *et al.* The clinical effects of inclisiran, a first-in-class LDL-C lowering siRNA therapy, on the LDL-C levels in Chinese patients with hypercholesterolemia. J Clin Lipidol. 2023;17:392-400.

16. Koenig W, Ray KK, Landmesser U, Leiter LA, Schwartz GG, Wright RS, *et al.* Efficacy and safety of inclisiran in patients with cerebrovascular disease: ORION-9, ORION-10, and ORION-11. Am J Prev Cardiol. 2023;14:100503.

17. Raal FJ, Kallend D, Ray KK, Turner T, Koenig W, Wright RS, *et al.*; ORION-9 Investigators. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382:1520-30.

18. Leiter LA, Teoh H, Kallend D, Wright RS, Landmesser U, Wijngaard PLJ, *et al.* Inclisiran lowers LDL-C and PCSK9 irrespective of diabetes status: the ORION-1 randomized clinical trial. Diabetes Care. 2019;42:173-6.

19. Fitzgerald K, White S, Borodovsky A, Bettencourt BR, Strahs A, Clausen V, *et al.* A highly durable RNAi therapeutic inhibitor of PCSK9. N Engl J Med. 2017;376:41-51.

20. Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, *et al.* Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med. 2017;376:1430-40.

21. Wright RS, Ray KK, Raal FJ, Kallend DG, Jaros M, Koenig W, *et al.*; ORION Phase III Investigators. Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. J Am Coll Cardiol. 2021;77:1182-93.

22. Ray KK, Troquay RPT, Visseren FLJ, Leiter LA, Scott Wright R, Vikarunnessa S, *et al.* Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol. 2023;11:109-19.

23. Wiegman A, Peterson AL, Hegele RA, Bruckert E, Schweizer A, Lesogor A, *et al.* Efficacy and safety of inclisiran in adolescents with genetically confirmed homozygous familial hypercholesterolemia: results from the double-blind, placebo-controlled part of the ORION-13 randomized trial. Circulation. 2025;151:1758-66.

24. Ray KK, Kallend D, Leiter LA, Raal FJ, Koenig W, Jaros MJ, *et al.*; ORION-11 Investigators. Effect of inclisiran on lipids in primary prevention: the ORION-11 trial. Eur Heart J. 2022;43:5047-57.

25. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al; ORION-10 and ORION-11 investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382:1507-19.

26. Briani F, Bagli M, Venturi G, Bacchion F, Mugnolo A. "Inclisiran: Early LDL-C target achievement in a real-life population". Atheroscler Plus. 2025;59:54-8.

27. Padam P, Barton L, Wilson S, David A, Walji S, de Lorenzo F, *et al.* Lipid lowering with inclisiran: a real-world single-centre experience. Open Heart. 2022;9:e002184.

28. Jeong HJ, Lee HS, Kim KS, Kim YK, Yoon D, Park SW. Sterol-dependent regulation of proprotein convertase subtilisin/kexin type 9 expression by sterol-regulatory element binding protein-2. J Lipid Res. 2008;49:399-409.

29. Wołowiec Ł, Osiak J, Wołowiec A, Wijata A, Grześk E, Kozakiewicz M, *et al.* Inclisiran-safety and effectiveness of small interfering RNA in inhibition of PCSK-9. Pharmaceutics. 2023;15:323.

30. Wright RS, Koenig W, Landmesser U, Leiter LA, Raal FJ, Schwartz GG, *et al.* Safety and tolerability of inclisiran for treatment of hypercholesterolemia in 7 clinical trials. J Am Coll Cardiol. 2023;82:2251-61.

31. Coleman CI, Limone B, Sobieraj DM, Lee S, Roberts MS, Kaur R, *et al.* Dosing frequency and medication adherence in chronic disease. J Manag Care Pharm. 2012;18:527-39.

32. Coleman CI, Roberts MS, Sobieraj DM, Lee S, Alam T, Kaur R. Effect of dosing frequency on chronic cardiovascular disease medication adherence. Curr Med Res Opin. 2012;28:669-80.

33. Alaíz ÁR, Gudino LC, de la Isla LP, Pardo HG, Calle DG, Miramontes-González JP. Inclisiran: efficacy in real world-systematic review and meta-analysis. J Clin Med. 2025;14:4163.

34. Niu C, Parlapalli A, Neenan J, Ma X, Osei-Wusu AA, Park J, *et al.* Abstract 12945: six-month adherence among early inclisiran initiators vs. anti-PCSK9 mAbs users: a retrospective analysis of US claims databases. Circulation. 2023;148(Suppl_1):A12945.

35. Wright SR, Ray KK, Troquay RP, Visseren FL, Landmesser U, Koenig W, *et al.* Long-term efficacy and safety of twice-yearly inclisiran in patients with ASCVD and elevated LDL-C: a post-hoc analysis of ORION-3, a 4-year open-label extension study. J Clin Lipidol. 2023;17:e56-7.

36. Ray KK, Bavry AA, Bhatt DL. LDL-C reduction from 6 to 9 months following single or second injection of inclisiran a novel siRNA compound: primary – ORION-1. American College of Cardiology. Published online 17 Mar 2017. Available from: https://www.acc.org/latest-in-cardiology/clinical-trials/2017/03/16/00/58/orion-1

37. Ray KK, Stoekenbroek RM, Kallend D, Nishikido T, Leiter LA, Landmesser U, *et al.* Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. JAMA Cardiol. 2019;4:1067-75.

38. Wang Y, Wang J, Wang S. Comparative effectiveness of inclisiran 100, 300, and 500 mg in a population with hyperlipidemia: a network meta-analysis of randomized controlled trials. Am J Cardiovasc Drugs. 2018;18:271-82.

39. Li J, Lei X, Li Z, Yang X. Effectiveness and safety of inclisiran in hyperlipidemia treatment: an overview of systematic reviews. Medicine (Baltimore). 2023;102:e32728.

40. Katsiki N, Vrablik M, Banach M, Gouni-Berthold I. Inclisiran, low-density lipoprotein cholesterol and lipoprotein (a). Pharmaceuticals (Basel). 2023;16:577.

41. Kosmas CE, Bousvarou MD, Papakonstantinou EJ, Tsamoulis D, Koulopoulos A, Echavarria Uceta R, *et al.* Novel pharmacological therapies for the management of hyperlipoproteinemia(a). Int J Mol Sci. 2023;24:13622.

42. Ferri N, Ruscica M, Fazio S, Corsini A. Low-density lipoprotein cholesterol-lowering drugs: a narrative review. J Clin Med. 2024;13:943.

43. Nishikido T. Clinical potential of inclisiran for patients with a high risk of atherosclerotic cardiovascular disease. Cardiovasc Diabetol. 2023;22:20.

44. Di Giacomo-Barbagallo F, Andreychuk N, Scicali R, Gonzalez-Lleó A, Piro S, Masana L, *et al*. Inclisiran, reasons for a novel agent in a crowded therapeutic field. Curr Atheroscler Rep. 2025;27:25.

45. Sinning D, Landmesser U. Low-density Lipoprotein-cholesterol lowering strategies for prevention of atherosclerotic cardiovascular disease: focus on siRNA treatment targeting PCSK9 (inclisiran). Curr Cardiol Rep. 2020;22:176.

46. Kılıç ME. PCSK9 siRNA inhibitor inclisiran as a treatment option in hypercholesterolemia: a brief review. Turk Med Stud J. 2023;10:105-11

47. Scicchitano P, Milo M, Mallamaci R, De Palo M, Caldarola P, Massari F, *et al*. Inclisiran in lipid management: a literature overview and future perspectives. Biomed Pharmacother. 2021;143:112227.

48. Samuel E, Watford M, Egolum UO, Ombengi DN, Ling H, Cates DW. Inclisiran: a first-in-class siRNA therapy for lowering low-density lipoprotein cholesterol. Ann Pharmacother. 2023;57:317-24.

Appendix Tables: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/47cdcf8e-894a-4357-9d00-86f04f7096a9.pdf

RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.87528
Int J Cardiovasc Acad 2026;12(1):14-22

Assessment of Right Ventricular Function by Echocardiography in Patients with Pulmonary Embolism

Rauf Avcı[1], Nermin Bayar[1], Zehra Erkal[1], Muhammed Rıdvan Ersoysal[1], Batuhan Topcuoğlu[1], Fatih Han Kumtaş[1], Edip Can Özgünoğlu[2], Görkem Kuş[1], Şakir Arslan[1]

[1]Department of Cardiology, University of Health Sciences Türkiye, Antalya Training and Research Hospital, Antalya, Türkiye
[2]Clinic of Cardiology, Antalya Kepez State Hospital, Antalya, Türkiye

Abstract

Background and Aim: Pulmonary embolism (PE) is a cardiovascular disease associated with significant morbidity and mortality. Right ventricular (RV) dysfunction is a major determinant of prognosis in PE, and echocardiography is a key tool for assessing RV function. This study aimed to evaluate RV function by echocardiography in patients with intermediate-high-risk PE, with particular attention to the effect of thrombolytic therapy (TT).

Materials and Methods: This retrospective, observational, comparative cohort study included 36 patients diagnosed with intermediate-high-risk PE between 2017 and 2019. The diagnosis of PE was confirmed by computed tomographic angiography or ventilation-perfusion scintigraphy. Echocardiographic assessment included RV free wall longitudinal strain (RVFWLS), and functional capacity was measured by the 6-minute walk distance (6MWD). Patients were divided into TT and non-TT groups for comparison.

Results: Of 36 patients diagnosed with intermediate-high-risk PE, 58.3% (n=21) received TT, while 41.7% (n=15) did not receive this treatment. The mean RVFWLS was -29.76% in the TT group and -22.8% in the non-TT group ($P = 0.012$). The mean 6MWD was 434 m in the group receiving TT and 357 m in the group not receiving TT. Although 6MWD was higher in the TT group, the difference was not statistically significant ($P = 0.179$).

Conclusion: Echocardiographic evaluation provides valuable insight into RV function in patients with PE. In this cohort of intermediate-high-risk patients, TT was associated with better preservation of RV systolic function, supporting its potential role in selected cases.

Keywords: Embolism, pulmonary, fibrinolytic therapy, right ventricular function speckle tracking echocardiography

INTRODUCTION

Right ventricular (RV) function is a prognostic marker in patients with pulmonary embolism (PE) and plays an instrumental role in guiding treatment decisions. This patient group has been identified as being in the high-risk category for the development of long-term RV dysfunction.[1]

The utilization of thrombolytic therapy (TT) in intermediate-high-risk patients with PE remains a subject of considerable debate. The extant studies have primarily focused on mortality, and there are limited data on the evaluation of the long-term effect of TT on RV function.[2]

The present study investigates the RV function of patients with intermediate-high-risk PE who received TT, aiming to evaluate

To cite this article: Avcı R, Bayar N, Erkal Z, Ersoysal MR, Topcuoğlu B, Kumtaş FH, *et al.* Assessment of right ventricular function by echocardiography in patients with pulmonary embolism. Int J Cardiovasc Acad. 2026;12(1):14-22

Address for Correspondence: Rauf Avcı MD, Department of Cardiology, University of Health Sciences Türkiye, Antalya Training and Research Hospital, Antalya, Türkiye
E-mail: drraufavci07@gmail.com
ORCID ID: orcid.org/0000-0002-8453-205X

Received: 15.09.2025
Accepted: 20.11.2025
Epub: 19.01.2026
Publication Date: 10.03.2026

its long-term impact on RV performance. We hypothesized that TT preserves RV systolic function, as measured by RV free wall longitudinal strain (RVFWLS), in this patient population.

METHODS

Patients who were treated in outpatient clinics or admitted to hospital with a diagnosis of submassive (intermediate-high-risk) PE at University of Health Sciences Türkiye, Antalya Training and Research Hospital between January 2017 and June 2019 were included in this retrospective, observational, comparative cohort study.

The patient data were retrieved from the hospital automation system, archives, outpatient clinic examination records, and patient files. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (decision no: 18/15, date: 08.08.2019).

The study population was selected in accordance with the 2019 European Society of Cardiology (ESC) PE guidelines.[3] A comprehensive analysis was conducted of the clinical presentations, blood parameters, computed tomography (CT) angiography, and echocardiographic (ECHO) findings of patients diagnosed with PE across the entire hospital system. The criteria for RV systolic dysfunction were defined as a RV wall/left ventricular wall ratio >1 on ECHO or CT and a lateral S' velocity of 14 ng/L, according to the 2019 PE guidelines. Patients who met the criteria for intermediate-high-risk PE, as defined by the 2019 ESC PE guidelines, and had received optimal medical treatment for at least three months after the diagnosis of PE were contacted by telephone. RV function was evaluated by ECHO using a Philips EPIQ 7C device. RVFWLS values were expressed as negative percentages; more negative values (i.e., larger absolute values) indicate better RV systolic function. Subsequently, a 6-minute walk test (6MWD) was performed. Patients aged 18 to 80 years who were diagnosed with intermediate-high-risk PE and had follow-up data for a minimum of six months were included in the study. Patients older than 80 years, younger than 18 years, and those with high-risk (massive), intermediate-low-risk, and low-risk PE were excluded from the study.

The term "healed PE" was defined as the absence of occlusive lesions on follow-up CT pulmonary angiography and the absence of perfusion defects on ventilation-perfusion scintigraphy after a minimum of three months of optimal medical therapy. This study is summarized in the central Figure 1.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY). The descriptive statistics were presented as n (%), mean ± standard deviation, and median (min-max). The associations between categorical variables were analyzed using Pearson's chi-square test and Fisher's exact test. The Shapiro-Wilk test was employed to assess the assumption of normality. When measurement values in the

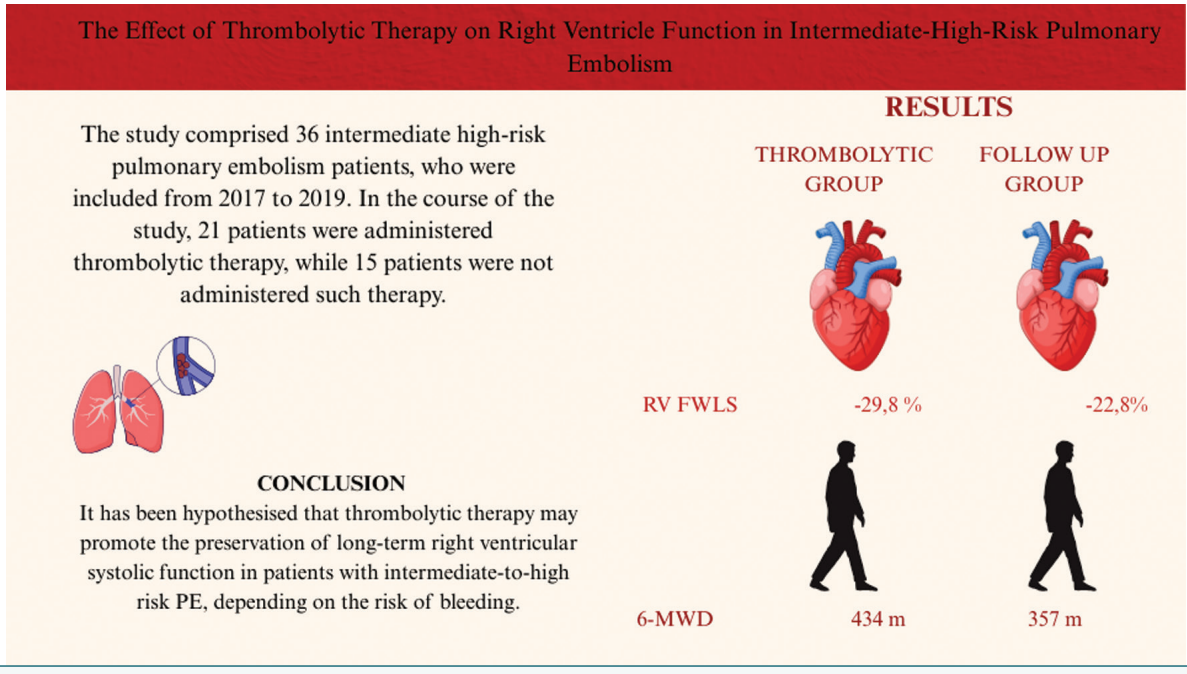


Figure 1. Graphical abstract showing the effect of thrombolytic therapy on right ventricular function in patients with intermediate-high-risk pulmonary embolism

RVFWLS: Right ventricular free wall longitudinal strain, 6MWD: 6-minute walk distance

two groups were not normally distributed, the Mann-Whitney U test was applied. Conversely, when the data followed a normal distribution, the Student's t-test was used. The Kruskal-Wallis test was used to perform non-parametric comparisons among three or more groups, and the Bonferroni-Dunn test was applied as a post-hoc analysis following significant results. Spearman's correlation test was used to analyze ordinal variables or continuous variables that did not follow a normal distribution. Conversely, Pearson's correlation test was used for continuous variables that were normally distributed. Statistically significant results were defined as those with *P*-values less than 0.05.

RESULTS

The study included 36 patients diagnosed with intermediate-high-risk PE. A total of 21 patients (58.3%) received TT, while 15 (41.7%) did not.

Table 1 presents the patients' general characteristics by treatment group. The mean age was 59.62±15.98 years in the TT group and 57.53±12.86 years in the non-TT group. No statistically significant difference in mean age was observed between patient groups across treatment categories (P = 0.679). 38.1% of the patients who received TT were male. An examination of the data revealed no statistically significant differences in gender distribution across the various treatment groups (P = 0.908). No significant differences were observed between groups for other parameters ($P > 0.05$).

Imaging and laboratory findings of patients at the time of diagnosis, stratified by TT groups, are compared in Table 2. The mean RV/left ventricular ratio was 1.12±0.07 in the TT group and 1.10±0.10 in the non-TT group; no significant difference was found (P = 0.674). Troponin T values were significantly higher in the TT group than in the group without TT (P = 0.002). No significant differences were observed between the groups for other ECHO and CT parameters.

The following investigation analyzed the post-treatment RV parameters of the patients according to their TT group (see

Table 1. Baseline demographic and clinical characteristics of patients

Variables	TT (n=21)	No TT (n=15)	*P*-value
Age (years)	59.62±15.98	57.53±12.86	0.679
Gender			
- Female	13 (61.9%)	9 (60%)	0.908
- Male	8 (38.1%)	6 (40%)	
History of CVD	2 (9.5%)	1 (6.7%)	0.999
Clinical presentation at diagnosis of PE			
- Acute	20 (95.2%)	10 (66.7%)	0.063
- Subacute	1 (4.8%)	5 (33.3%)	
Type of anticoagulant used			
- NOAC	8 (38.1%)	3 (20%)	0.295
- OAC	10 (47.6%)	9 (60%)	0.463
- LMWH	3 (14.3%)	3 (20%)	0.463
Temporary risk factors			
- No	14 (66.7%)	9 (60%)	
- Strong	3 (14.3%)	3 (20%)	0.938
- Moderate	1 (4.8%)	1 (6.7%)	
- Weak	3 (14.3%)	2 (13.3%)	
Persistent risk factors			
- No	16 (76.2%)	13 (86.7%)	0.832
- Genetic	3 (14.3%)	1 (6.7%)	
- Cancer	2 (9.5%)	1 (6.7%)	
Idiopathic	11 (52.4%)	9 (60%)	0.650
s-PESI score	1 (1-3)	1 (1-2)	0.825
Duration of dyspnea (days)	2.5 (1-7)	2 (1-28)	0.657

CVD: Cardiovascular disease, PE: Pulmonary thromboembolism, NOAC: New oral anticoagulant, OAC: Oral anticoagulant, LMWH: Low-molecular-weight heparin, s-PESI: Simplified pulmonary embolism severity index, TT: Patients who received thrombolytic therapy, No TT: Patients who did not receive thrombolytic therapy

Table 3). The analysis yielded a statistically significant result: the mean proximal RV outflow tract diameter of the patients who received TT (28.27±3.21) being smaller compared to that of the patient group not receiving TT (32.07±6.43), as indicated by a *P*-value of 0.032. Despite this, the incidence of RV hypertrophy was lower in the patient cohort that underwent TT (5.3%) compared with the cohort that did not receive this therapy (35.7%). However, this difference was not statistically significant ($P = 0.062$). The mean RV wall thickness was lower in patients who received treatment (3.13±0.55) than in those who did not (3.94±1.25) ($P = 0.038$). The mean right atrial (RA) longitudinal diameter of patients who received treatment (45.46±7.38) was smaller than that of patients who did not receive treatment (52.1±9.14) ($P = 0.038$). The analysis revealed no statistically significant differences in the RA area ($P = 0.313$), RV velocity ($P = 0.240$), estimated RV pressure ($P = 0.314$), baseline RVFWLS ($P = 0.114$), and pulmonary artery pressure ($P = 0.157$) between the treatment groups in the study. A subsequent comparison of the inferior vena cava (IVC) diameter between the treatment groups revealed that the IVC diameter in the treated group (11.75±3.89) was significantly smaller than in the untreated group (15.91±5.01) ($P = 0.009$). A greater percentage of patients in the TT group (90%) exhibited a IVC collapse rate exceeding 50% compared with those in the non-therapy group (53.3%) ($P = 0.022$). Mean apical RVFWLS ($P = 0.008$), mean mid RVFWLS ($P = 0.027$), and overall mean RVFWLS ($P = 0.012$) were elevated in the cohort receiving TT. Although the mean 6MWD was higher in the treated group, the difference was not statistically significant ($P = 0.179$).

Table 4 presents the mean values of RVFWLS according to patients' general characteristics and imaging findings at the time of diagnosis. The median RVFWLS values were 27 (20-48) and 17.5 (11-26) in acute and subacute patients, respectively. The mean RVFWLS of acute patients was significantly higher than that of subacute patients ($P = 0.014$). Mean RVFWLS values among patients with thrombus on control CT (21.82±7.08) were lower than among those without it (30.11±7.55) ($P = 0.007$). The mean RVFWLS was lower in patients with chronic thromboembolic pulmonary hypertension than in patients with healed PE ($P = 0.010$). No significant differences were observed between the groups for other parameters.

Table 5 presents the results of the correlation analysis between mean RVFWLS and other variables across all patients and treatment groups. In all patients, a moderate, statistically significant negative correlation was identified between the RA diameter at diagnosis and the mean RVFWLS after treatment (r=-0.557, $P = 0.031$). The patients who received TTwere found to have a statistically significantly strong negative correlation between D-dimer at diagnosis and the mean post-treatment RVFWLS (r=-0.745, $P = 0.008$). In contrast, those patients who did not receive TT had a statistically significantly negative moderate correlation between dyspnea duration at diagnosis and the mean post-treatment RVFWLS (r=-0.580, $P = 0.023$).

Table 2. Comparison of echocardiographic, CT, and laboratory findings between treatment groups

Variables	TT (n=21)	No TT (n=15)	*P*-value
RV/LV ratio	1.12±0.07	1.10±0.10	0.674
Location of thrombus on CT - Main pulmonary artery - Lobar	 19 (95%) 1 (5%)	 12 (100%) 0 (0%)	0.999
D-dimer (ng/mL)	3149.5 (1410-62145)	2478.5 (1032-16447)	0.713
Troponin T (pg/mL)	229 (15-348)	43 (16-197)	**0.002**
Venous Doppler findings	4 (57.1%)	1 (10%)	0.101
LVEF (%)	60 (60-65)	60 (45-65)	0.211
RV diameter (mm)	48 (42-52)	49 (41-51)	0.815
RA diameter (mm)	55 (44-58)	56.5 (48-64)	0.232
TR rating	2.5 (1-3)	3 (2-4)	0.228
SPAP (mmHg)	61 (1-74)	62.5 (37-85)	0.740
Evidence of RV overload	18 (100%)	15 (100%)	-
D-shape	9 (90%)	5 (62.5%)	0.275
Presence of thrombus on control CT	5 (25%)	7 (53.8%)	0.142

RV/LV: Right ventricular to left ventricular diameter, CT: Computed tomography, LVEF: Left ventricular ejection fraction, RV: Right ventricular, RA: Right atrium, TR: Tricuspid regurgitation, SPAP: Systolic pulmonary artery pressure, TT: Patients who received thrombolytic therapy, No TT: Patients who did not receive thrombolytic therapy

Table 3. Comparison of right ventricular echocardiographic parameters and functional measures between treatment groups

Variables	TT (n=21)	No TT (n=15)	*P*-value
Apical A4C RV basal diameter (mm)	34.44±6.73	37.63±8.51	0.224
Apical A4C RV mid diameter (mm)	26.62±5.02	30.84±9.00	0.117
Apical A4C RV long diameter (mm)	47.20±8.98	49.50±8.22	0.442
Proximal RVOT diameter_psla (mm)	28.27±3.21	32.07±6.43	**0.032**
Distal RVOT diameter_pssa (mm)	21.64±4.09	23.99±4.00	0.107
RV/LV diameter A4C baseline	0.84±0.14	0.90±0.20	0.288
RV wall thickness (mm)	3.13±0.55	3.94±1.25	**0.038**
TAPSE (mm) - Normal - Pathological	20.47±4.57 18 (85.7%) 3 (14.3%)	18.15±4.27 11 (73.3%) 4 (26.7%)	0.132 0.418
Tricuspid S velocity (cm/s)	18.83±4.68	16.59±2.94	0.122
RV FAC (%)	50.83±8.71	50.46±12.33	0.924
RA longitudinal diameter (mm)	45.46±7.38	52.10±9.14	**0.031**
IVC diameter (mm)	11.75±3.89	15.91±5.01	**0.009**
IVC collapse ratio - <50% - >50%	 2 (10%) 18 (90%)	 7 (46.7%) 8 (53.3%)	**0.022**
RVFWLS apical (%)	27.76±8.70	19.73±7.16	**0.008**
RVFWLS mid (%)	33.06±8.74	25.27±10.28	**0.027**
RVFWLS basal (%)	27 (17-48)	25 (9-32)	0.114
RVFWLS average (%)	29.76±7.69	22.80±6.96	**0.012**
6MWD (meters)	434.33±137.97	357.27±143.10	0.179
PAP (mmHg)	27 (18-50)	31 (16-90)	0.157

RV: Right ventricular, RA: Right atrium, RVOT: Right ventricular outflow tract, A4C: Apical four-chamber view, TAPSE: Tricuspid annular plane systolic excursion, FAC: Fractional area change, IVC: Inferior vena cava, FWLS: Free wall longitudinal strain, 6MWD: 6-minute walk distance, PAP: Pulmonary artery pressure, TT: Patients who received thrombolytic therapy, No TT: Patients who did not receive thrombolytic therapy

Table 4. Comparison of post-treatment RVFWLS according to patient characteristics

Variables	n	Mean ± SD / median (min-max)	*P*-value
Gender			
- Female	22	28.2±9.27	0.074
- Male	14	23.67±4.52	
Clinical picture at PE diagnosis			**0.014**
- Acute	30	27 (20-48)	
- Subacute	6	17.5 (11-26)	
Anticoagulation therapy			
- NOAC	11	26.9±8.23	0.853
- OAC	19	26.59±6.39	0.949
- LMWH	6	23 (11-48)	0.310
Risk factors			
- Temporary	36	26 (11-48)	0.733
- Persistent	36	25.5 (11-48)	0.278
D-shape during PE			0.611
- Yes	14	25 (11-37)	
- No	4	28 (26-30)	

Table 4. Continued

Variables	n	Mean ± SD / median (min-max)	*P*-value
Development of recurrent VTE			0.952
- Yes	3	25 (21-37)	
- No	33	26 (11-48)	
Presence of thrombus on control CT			**0.007**
- Yes	12	21.82±7.08	
- No	21	30.11±7.55	
Result after treatment			**0.010**
- Improved PE	19	29 (21-48)	
- CTEPH	5	13 (11-23)	
- CTEPD	10	26 (22-32)	

Notes: Data are presented as mean ± standard deviation for normally distributed continuous variables, median (min-max) for non-normally distributed continuous variables, and n (%) for categorical variables

PE: Pulmonary thromboembolism, NOAC: New oral anticoagulant, OAC: Oral anticoagulant, LMWH: Low-molecular-weight heparin, VTE: Venous thromboembolism, CTEPH: Chronic thromboembolic pulmonary hypertension, CTEPD: Chronic thromboembolic pulmonary disease, RVFWLS: RV free wall longitudinal strain, SD: Standard deviation, CT: Computed tomography

Table 5. Post-treatment RVFWLS correlation with patient characteristics and laboratory parameters

	Total		TT		No TT	
Variables	**r**	***P*-value**	**r**	***P*-value**	**r**	***P*-value**
Age	-0.041	0.824[1]	-0.09	0.732[1]	-0.127	0.651[1]
s-PESI	0.066	0.721[2]	0.099	0.705[2]	0.002	0.999[2]
RV/LV ratio at the time of PE diagnosis	0.290	0.179[1]	0.548	0.081[1]	-0.012	0.969[2]
D-dimer during PE	-0.174	0.427[2]	-0.745	**0.008[2]**	0.452	0.141[2]
Troponin T during PE	0.295	0.172[1]	0.044	0.887[1]	0.578	0.080[2]
LVEF during PE	0.17	0.450[2]	-0.344	0.330[2]	0.213	0.506[2]
RV diameter during PE	-0.276	0.284[1]	-0.178	0.673[1]	-0.376	0.319[1]
RA diameter during PE	-0.557	**0.031[1]**	-0.397	0.378[1]	-0.571	0.139[1]
TR degree during PE	-0.112	0.619[2]	0.134	0.711[2]	-0.146	0.651[2]
Estimated SPAP during PE	0.089	0.694[2]	0.025	0.946[2]	0.134	0.678[2]
Dyspnea duration	-0.252	0.171[2]	0.131	0.628[2]	-0.580	**0.023[2]**

Notes: One refers to Pearson correlation test and 2 refers to Spearman correlation test; r: Correlation coefficient

s-PESI: Simplified pulmonary embolism severity index, RV/LV: Right ventricular/left ventricular, PE: Pulmonary thromboembolism, LVEF: Left ventricular ejection fraction, RV: Right ventricular, RA: Right atrium, TR: Tricuspid regurgitation, SPAP: Systolic pulmonary artery pressure, TT: Patients who received thrombolytic therapy, No TT: Patients who did not receive thrombolytic therapy

DISCUSSION

The findings of this study demonstrated that the long-term RVFWLS was superior in the TT group compared with the anticoagulant-only treatment group [-(29.76±7.69%) and -(22.8±6.96%), respectively, $P = 0.012$]. Furthermore, the 6MWD was 434.33±137.97 m in the group receiving TT, and 357.27±143.10 m in the group not receiving TT.

In the correlation analysis, a significant negative correlation was observed between D-dimer levels and RVFWLS in the TT group (r=-0.745, $P = 0.008$). This finding suggests that patients with a higher initial thrombotic burden or higher inflammatory activity demonstrated a more pronounced improvement in RV systolic function following TT. This relationship may reflect the enhanced efficacy of TT in patients with a substantial clot load, in whom the rapid restoration of pulmonary perfusion contributes to improved RV recovery. Therefore, D-dimer may serve not only as a diagnostic and prognostic biomarker but also as a potential indicator of treatment responsiveness in selected PE patients.

In intermediate-high-risk patients with PE, RV dysfunction is associated with increased mortality and morbidity.[4] The development of RV dysfunction may cause organ congestion,

leading to hepatic failure and cardiorenal syndrome. It may also increase hospitalization rates.[5-8] Therefore, RV function is critically important in intermediate-high-risk PE patients.

The intricate geometry of the RV, in conjunction with the predominance of parameters suggesting displacement of the RV basal segment, limits assessment of RV dysfunction. A recently developed ECHO parameter, strain, facilitates the evaluation of the systolic and diastolic function of the RV. Moreover, it enables the early detection of alterations of the ventricular by quantifying changes in myocardial length.[9]

In previous studies, low-dose TT did not increase bleeding complications and concomitantly improved hemodynamic parameters.[10-12] In intermediate-high-risk patients with PE, low-dose TT may help preserve RV function without increasing bleeding events.

The pulmonary embolism thrombolysis (PEITHO) study provided guidance on the efficacy of TT in patients with intermediate-high-risk PE. The PEITHO study focused on early mortality and hemodynamic deterioration.[2] Early hemodynamic deterioration was observed less frequently in the TT group. In contrast, major hemorrhages and strokes occurred more frequently in the TT group. According to the most recent guidelines, TT is not advised for patients with intermediate-high-risk PE because of the increased risk of bleeding complications.[3] A notable feature of the PEITHO study was the use of tenecteplase rather than tissue plasminogen activator, which diverges from standard clinical protocols. This potential difference might have influenced the outcomes observed.

A meta-analysis published in 2023 found similar risks of mortality and major bleeding between systemic TT and anticoagulation therapy in intermediate-risk PE. Intracranial bleeding was found to be more prevalent in the thrombolysis group; however, the results were not conclusive due to the wide confidence interval.[13]

Elderly patients, who represent a particularly vulnerable group with respect to bleeding risk, have recently become the focus of attention for the use of low-dose thrombolytic protocols because of their more favorable safety profile. In the study by Yilmaz and Uzun[14] conducted in submassive PE patients with a mean age of 69 years, the administration of half-dose rt-PA significantly reduced the incidence of death or hemodynamic decompensation without increasing the rates of major or minor bleeding; no intracranial hemorrhage was reported. These findings indicate that, in elderly individuals, low-dose TT may maintain efficacy while keeping the bleeding risk within an acceptable range.[14]

A comprehensive evaluation of the long-term outcomes revealed no statistically significant differences between the study groups in RV function, as determined by conventional evaluation methods. This finding was reported in the PEITHO study published in 2017.[15] In the present study, similar results were obtained for RV function when evaluated by conventional methods. However, the implementation of RVFWLS, a novel parameter of RV function was associated with favorable changes in RV strain values over an extended period in patients undergoing TT.

The RVFWLS enables the evaluation of three segments of the RV. This feature plays a pivotal role in determining whether the contraction of the basal segment of the RV is active or passive. It provides objective data in cases where traditional parameters are inadequate.

In a study by Vitarelli et al.[16] intermediate-risk PE patients (with ECHO evidence of RV dysfunction) were compared with healthy subjects. A comparative analysis revealed that the global RVLS and RVFWLS values were lower in the PE group than in the healthy group. Research findings demonstrate that RVFWLS can predict mortality, the need for cardiopulmonary resuscitation, and recurrent PE.[16]

In the present study, RVFWLS values, which facilitated assessment of subclinical RV dysfunction, differed significantly in patients undergoing TT. Furthermore, the 6MWD, a well-established metric for predicting annual mortality in patients with pulmonary hypertension, was higher in patients receiving thrombolytics. The small number of patients in our study may explain why the 6MWD did not reach statistical significance.

There is no consensus on the standardization of the 6MWD as a prognostic indicator following PE. However, it is a significant prognostic indicator in patients with pulmonary arterial hypertension (PAH).[17] According to the 2022 ESC PAH guideline, the annual mortality rate is reported to be less than 5% for individuals with a 6MWD greater than 440 meters, 5% for those with a 6MWD ranging from 165 to 440 meters, and 10% for individuals with a 6MWD shorter than 165 meters.[18] In the present study, the mean distance was 434 meters in the cohort receiving TT and 357 meters in the cohort not receiving TT. The cohort receiving TT walked a distance close to the 440-meter threshold, which suggests an annual mortality rate of less than 5%, as reported in the ESC PAH guideline. The lack of statistical significance is likely attributable to an inadequate number of patients in the study. However, the observed difference in 6MWD, although not statistically significant, is clinically meaningful and suggests a positive trend toward improved functional capacity with TT.

Study Limitations

This study has several limitations. First, its retrospective, non-randomized design introduces potential selection bias. A significant baseline difference in troponin T levels (higher in the TT group; $P = 0.002$) further reinforces this bias. Although sicker patients received TT and showed better long-term RV function, suggesting a possible therapeutic benefit, this imbalance limits the validity of direct comparisons between the groups. Second, the small sample size (n=36) reduced statistical power and likely explained why the clinically meaningful difference in 6MWD did not reach statistical significance. Third, the multivariate analysis may carry a risk of overfitting, and residual confounding cannot be entirely excluded. Furthermore, the definition of "healed PE" relied on imaging findings (absence of occlusive lesions on CT and absence of perfusion defects on scintigraphy), while ECHO parameters of RV remodeling were not systematically evaluated. Finally, because this was a single-center study, the generalizability of these findings is limited. Larger, multicenter prospective studies are needed to confirm and expand these results.

CONCLUSION

In conclusion, our findings indicate that TT is associated with better long-term RV systolic performance, as reflected by RVFWLS values, in intermediate-high-risk PE patients. The clinically meaningful, though non-significant, improvement observed in 6MWD further supports a potential functional benefit of TT. However, given the small sample size, non-randomized design, and baseline differences between groups, these findings should be interpreted with caution and validated through larger, prospective multicenter studies. Therefore, TT may be considered for intermediate-high-risk PE patients with significant RV dysfunction and a low bleeding risk.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (decision no: 18/15, date: 08.08.2019).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: R.A., N.B., Z.E., M.R.E., B.T., F.H.K., E.C.Ö., G.K., Ş.A., Design: R.A., N.B., Z.E., M.R.E., B.T., F.H.K., E.C.Ö., G.K., Ş.A., Data Collection or Processing: R.A., N.B., M.R.E., E.C.Ö., Analysis or Interpretation: R.A., N.B., Z.E., Ş.A., Literature Search: R.A., N.B., Writing: R.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Matusov Y, Yaqoob M, Karumanchi A, Lipshutz HG, Dohad S, Steinberger J, *et al.* Long term recovery of right ventricular function after treatment of intermediate and high risk pulmonary emboli. Thromb Res. 2023;225:57-62.
2. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, *et al.*; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370:1402-11.
3. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, *et al.*; The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019;54:1901647.
4. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mm Hg or higher. Arch Intern Med. 2005;165:1777-81.
5. Sundaram V, Fang JC. Gastrointestinal and liver issues in heart failure. Circulation. 2016;133:1696-703.
6. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, *et al.* Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589-96.
7. Testani JM, Khera AV, St John Sutton MG, Keane MG, Wiegers SE, Shannon RP, *et al.* Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. Am J Cardiol. 2010;105:511-6.
8. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122:265-72.
9. Wilson R, Eguchi S, Orihara Y, Pfeiffer M, Peterson B, Ruzieh M, *et al.* Association between right ventricular global longitudinal strain and mortality in intermediate-risk pulmonary embolism. Echocardiography. 2024;41:e15815.
10. Goldhaber SZ, Agnelli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis. An international multicenter randomized trial. The Bolus Alteplase Pulmonary Embolism Group. Chest. 1994;106:718-24.
11. Sors H, Pacouret G, Azarian R, Meyer G, Charbonnier B, Simonneau G. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. Chest. 1994;106:712-7.
12. Wang C, Zhai Z, Yang Y, Wu Q, Cheng Z, Liang L, *et al.*; China Venous Thromboembolism (VTE) Study Group. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. Chest. 2010;137:254-62.
13. Mathew D, Seelam S, Bumrah K, Sherif A, Shrestha U. Systemic thrombolysis with newer thrombolytics vs anticoagulation in acute intermediate risk pulmonary embolism: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2023;23:482.

14. Yilmaz ES, Uzun O. Low-dose thrombolysis for submassive pulmonary embolism. J Investig Med. 2021;69:1439-46.

15. Konstantinides SV, Vicaut E, Danays T, Becattini C, Bertoletti L, Beyer-Westendorf J, *et al*. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol. 2017;69:1536-44.

16. Vitarelli A, Barillà F, Capotosto L, D'Angeli I, Truscelli G, De Maio M, *et al*. Right ventricular function in acute pulmonary embolism: a combined assessment by three-dimensional and speckle-tracking echocardiography. J Am Soc Echocardiogr. 2014;27:329-38.

17. Wensel R, Francis DP, Meyer FJ, Opitz CF, Bruch L, Halank M, *et al*. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol. 2013;167:1193-8.

18. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, *et al.*; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43:3618-731. Erratum in: Eur Heart J. 2023;44:1312.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.39306
Int J Cardiovasc Acad 2026;12(1):23-27

The Importance of Role Modeling in Medical Students: A Qualitative Study

Candan Mansuroğlu

Clinic of Cardiology, Ankara Bilkent City Hospital, Ankara, Türkiye

Abstract

Background and Aim: Medical education operates through a master-apprentice model that integrates theoretical knowledge with clinical experience and professional identity formation. This study aimed to explore whom medical students and early-career physicians perceive as role models and which characteristics shape these perceptions.

Materials and Methods: This qualitative study included 6 interns and 7 cardiology residents at Ankara Bilkent City Hospital. The researcher, a cardiology specialist with a master's degree in medical education, conducted an unstructured qualitative study using in-depth, unstructured, face-to-face individual interviews that were video-recorded with consent, transcribed verbatim, and analyzed using Braun and Clarke's thematic analysis. Three independent physicians coded the data, employing regular peer debriefing and member checking. Data saturation was reached.

Results: A total of 40 codes were grouped into nine main themes: definition of a role model, desired characteristics, identified role models, role model deficiency, impact on students, communication skills, professional values, career influences, and systemic factors. Participants identified clinical knowledge, experience, effective communication, and professional behavior as the key components of positive role modeling. Students highlighted that empathy, respectful interactions, and calm crisis management enhanced the impact of role models. Conversely, negative behaviors—such as anger, impatience, and disrespect—reduced role-model effectiveness despite strong clinical skills. Institutional factors, including workload and limited time with educators, also shaped the quality of role-modeling experiences.

Conclusion: Role modeling emerged as a multifaceted process shaped by clinical expertise, humanistic qualities, and institutional context. While students valued strong clinical knowledge, they placed equal emphasis on empathy, respectful communication, and ethical behavior. Negative behaviors often undermined otherwise competent clinicians, creating lasting adverse impressions. Systemic pressures limited opportunities for meaningful engagement, highlighting the need for faculty development that integrates scientific excellence with communication skills and professionalism. This study also draws attention to role modeling as a simple, low-cost, yet highly effective educational strategy that deserves a more prominent place in medical education.

Keywords: Educational models, internship and residency, medical education

INTRODUCTION

The primary responsibility of medical educators is to equip future doctors with theoretical knowledge and practical skills, ensuring they gain professional competence.[1] Esen and Arslantas[2] emphasize that the effective fulfillment of this responsibility is crucial to maintaining the continuity and quality of medicine. However, medical education is not limited to training individuals who can treat diseases; it also aims to develop healthcare professionals who are committed to ethical values and possess empathy and compassion.[3]

To cite this article: Mansuroğlu C. The importance of role modeling in medical students: a qualitative study. Int J Cardiovasc Acad. 2026;12(1):23-27

Address for Correspondence: Candan Mansuroğlu MD, Clinic of Cardiology, Ankara Bilkent City Hospital, Ankara, Türkiye
E-mail: candanmansuroglu@gmail.com
ORCID ID: orcid.org/0000-0002-0311-2046

Received: 07.10.2025
Accepted: 05.12.2025
Epub: 14.01.2026
Publication Date: 10.03.2026

Experienced physicians not only transfer their knowledge and experience to young doctors but also instill the humanistic values of the profession and pass on professional attitudes and behaviors to future generations.[4-8] This study aims to examine medical students' perspectives on role models and the contributions of role models to students' personal and professional development. Additionally, it seeks to identify which characteristics and behaviors of educators are effective in this process and to define the qualities of an ideal role model.

METHODS

Study Design

This study employed a qualitative research design using in-depth, unstructured individual interviews to explore participants' perceptions and lived experiences regarding role modeling. The study adhered to the principles of the Declaration of Helsinki, and ethical approval was obtained from the Ankara Bilkent City Hospital Ethics Committee (decision no: TABED 2/08/2024, date: 15.05.2024).

Research Team and Reflexivity

The study was conducted by a cardiology specialist who holds a master's degree in medical education and whose clinical background aligns with the study context. The researcher was previously acquainted with only one or two participants; the remaining participants were not known to the researcher. This potential source of bias was acknowledged, and reflexive awareness was maintained throughout data collection and analysis. All interviews were conducted solely by the researcher using an open-ended, conversational approach, allowing participants to express their experiences in depth. All study records are securely stored in a locked cabinet located in the researcher's office.

Participants and Sampling

A purposive sampling strategy was used to recruit participants with recent exposure to clinical teaching and role modeling practices. The sample consisted of six sixth-year medical students (interns) from the Faculty of Medicine at Ankara Yıldırım Beyazıt University and seven physicians who graduated from the same institution and were currently working as cardiology residents at Ankara Bilkent City Hospital. Participants were assigned coded identifiers (K1-K13) to ensure confidentiality.

The inclusion criteria were voluntary participation and the ability to engage in an in-depth interview. Data saturation was systematically evaluated and confirmed, with no new codes emerging during the final interviews.

Data Collection

Interviews were conducted face-to-face in the cardiology department physicians' office to ensure comfort and privacy. No structured interview guide was used; instead, participants were guided solely by the overarching topic of role modeling, consistent with unstructured interview methodology. Interviews lasted 26±3 minutes, were video-recorded with participants' consent, and were transcribed verbatim.

The first interview served as a pilot to evaluate the suitability of the questions and the feasibility of the interview technique. Because the pilot interview met methodological standards and contributed relevant data, it was included in the analysis.

Data Analysis

Transcribed data were analyzed using thematic analysis following Braun and Clarke's six-step framework. A detailed description of the analytical process was provided to ensure transparency in coding and theme development.

Three independent physicians coded the data. Multiple coders were included to reduce researcher bias and strengthen analytical credibility. Although no qualitative data-analysis software was used, regular peer debriefing sessions ensured coding accuracy and consensus among coders. No quantitative statistical analysis was performed.

Member checking was performed by sharing interpretations with participants, allowing them to confirm the accuracy of their statements.

A total of 40 codes were generated by systematically identifying recurring meaningful expressions. These codes were then grouped into nine overarching themes:

1. Definition of a role model
2. Desired characteristics
3. Individuals identified as role models
4. Lack of role models and alternative approaches
5. Impact on students
6. Communication skills
7. Professional values and respectability
8. Career choice and its influence
9. Systemic and environmental factors

RESULTS

Participants consistently emphasized clinical knowledge, experience, communication skills, and professional conduct

as central components of role modeling. The analysis yielded four major categories: (1) knowledge and experience, (2) communication with patients, (3) successful clinical performance, and (4) negative behaviors. Illustrative participant quotations and thematic codes are summarized in Table 1.

Positive Role Modeling

Participants frequently identified knowledgeable and experienced clinicians as exemplary role models (K2, K6, K7, K11, K12, K13). Statements such as *"Although our professor is a professor, he greeted us in the clinic…"* highlig ted the perceived importance of humility and respectful professional behavior. Compassionate communication was also emphasized; for example, one participant noted, *"When the doctor entered the patient's room, he spoke kindly."* These accounts indicated that empathy, respect, and clear communication were viewed as essential attributes of effective role models.

Successful clinical performance emerged as another prominent theme. Participants expressed admiration for calm and competent behavior during emergencies, as illustrated by comments such as *"He managed all the crises very calmly…"* (K2, K7). Such composure was interpreted as a sign of professionalism and reinforced students' motivation to emulate these behaviors.

Negative Role Modeling

In contrast, several participants described behaviors that negatively shaped their perceptions of certain educators (K1, K3, K5). One student stated, *"I have never seen someone so angry, he always shouted,"* which suggests that displays of anger, shouting, or disrespect created lasting negative impressions. Materialistic attitudes, lack of empathy, and preoccupation with appearance or wealth were additional factors that participants associated with poor role modeling. These cases were included to reflect the nuanced and multifaceted nature of role-model perception.

Individual Influences

Individual experiences shaped participants' perceptions in diverse ways:

- Observing decisive action during an emergency motivated K2 and strengthened their professional aspirations.
- K8 emphasized compassionate patient communication as the most influential factor.
- K1 felt alienated by an educator who had strong medical knowledge but exhibited "repulsive" interpersonal behavior.
- K3 criticized role models who appeared overly focused on appearance or material wealth rather than on humane qualities.
- K6 initially experienced stress due to a strict educator but later recognized that this environment contributed to both personal and professional growth.

These accounts demonstrate the individualized and sometimes contradictory nature of role-model influence.

Table 1. General frequency analysis of themes and codes
Frequencies are used only to indicate salience in the qualitative dataset

Theme / subtheme	Code / category	Frequency	Illustrative quote
Knowledge and experience	Clinical knowledge & skills	40	*"Although our professor holds an academic title, he greeted us in the clinic and explained, step by step, what we should do"*
Communication with patients	Empathy & compassion	30	*"When the doctor entered the patient's room, he spoke kindly and was compassionate"*
Successful clinical performance	Calmness in emergencies	25	*"He managed all the crises very calmly…"* (K2, K7)
Professional conduct	Respectful & humble behavior	20	*"Although he is a professor, he greeted us in the clinic and listened patiently to our questions"*
Negative role modeling	Anger / shouting	10	*"I had never seen someone so angry; he would always shout"*
	Materialism / appearance focus	8	*"Some educators seemed more concerned with appearance and wealth than with patient care"*
Individual influences	Motivation by example	15	*"Observing decisive action during an emergency motivated me professionally"* (K2)
	Compassionate interaction	12	*"I was most influenced by how kindly the doctor spoke to patients"* (K8)
	Negative perception	5	*"I felt alienated by an educator whose behavior was offensive despite possessing strong medical knowledge"* (K1)
Systemic factors	Workload & time constraints	18	*"A high patient load and limited teaching time reduced meaningful interactions with faculty"*
	Structural limitations	10	*"The system sometimes prevents us from observing educators consistently acting as role models"*

Systemic Factors

Participants also noted several systemic barriers that limited opportunities for meaningful role modeling. High workload, insufficient time for teaching, and structural constraints within the clinical environment reduced faculty-student interaction. These contextual factors shaped students' learning experiences and contributed to variation in their perceptions of role models. Including these elements provided a more comprehensive understanding of the broader educational environment influencing role modeling.

DISCUSSION

The findings of this study show that clinical knowledge and experience remain the primary determinants of positive role modeling, consistent with the global literature, which emphasizes clinical expertise as a fundamental influence on professional identity formation.[9,10] Participants frequently emphasized that knowledgeable and skilled clinicians provided confidence, clarity, and a sense of professional direction, which supports earlier evidence that strong clinical competence is a major factor influencing learners' perceptions.[9]

However, humane qualities—such as empathy, compassion, authenticity, and respectful communication—were equally central to role-model perception. Participants repeatedly described clinicians who displayed kindness, calmness during crises, and ethical behavior as particularly impactful. These findings align with research highlighting that empathetic, patient-centered communication shapes both patient trust and students' internalization of professional standards.[11-13]

Conversely, negative behaviors emerged as a significant area requiring deeper analysis, as they were shown to undermine role-model status even when demonstrated by clinically competent educators. Participants described anger, shouting, impatience, or arrogance as behaviors that elicited strong negative emotional reactions that overshadowed otherwise strong clinical competence. This is consistent with earlier studies demonstrating that negative behaviors can produce long-lasting detrimental effects on learners and their perceptions of professionalism.[14]

A recurring and noteworthy finding was the tension students experienced between admiring clinical mastery and rejecting poor interpersonal traits. Several participants expressed conflict when a technically exceptional clinician demonstrated unprofessional behavior. This contradiction reflects the holistic and multidimensional nature of role modeling, where students evaluate both technical and interpersonal attributes. The literature similarly notes that professional identity is shaped by the integration of clinical skills and humanistic values.[11,13]

Institutional and systemic factors also played an important role in shaping role-modeling experiences. Participants emphasized that heavy workload, limited time, and structural constraints restricted opportunities for meaningful interaction with educators. These results reflect international findings describing how systemic pressures limit role-model availability in clinical environments.[11,15] Nevertheless, even brief positive interactions—such as a moment of compassionate communication—were reported to have a strong formative influence.

Overall, role modeling emerged as a complex, multifaceted process shaped by clinical expertise, interpersonal behavior, ethical conduct, and institutional context. Effective role models were described as individuals who combine professional competence with emotional intelligence, clear communication, and supportive leadership behaviors. Such a profile aligns with established frameworks outlining the multiple roles of medical teachers.[10]

These findings underscore the need for faculty development programs that cultivate both scientific excellence and humanistic professional values, echoing global recommendations for improving role-modeling practices in medical education.[9,10,14]

Study Limitations

This study has several limitations. First, it was conducted at a single-center with a small sample size, which limits the transferability of the findings. Additionally, participants did not answer all questions uniformly, which may have reduced the depth of certain themes. The study lacked quantitative data, and there was no structured pre-interview assessment of participants' characteristics, which could have provided additional context for interpreting the findings. Data analysis was performed manually, and no software-assisted qualitative analysis was used; this limitation was partially mitigated by the involvement of three independent coders. Finally, there is a potential risk of bias due to partial familiarity between the researcher and some participants.

Future studies should adopt multicenter designs, integrate mixed-methods approaches, and include faculty perspectives to provide a more comprehensive understanding of the role-modeling process.

CONCLUSION

This study highlights that role modeling in medical education is a multidimensional process shaped by the interplay of clinical expertise, humanistic qualities, professional behavior, and institutional context. While clinical knowledge and experience remain essential foundations of positive role modeling, students place equal value on empathy, respectful communication, and

ethical conduct. The findings demonstrate that even brief moments of compassionate interactions can have a profound educational impact, whereas negative behaviors—such as anger, impatience, or disrespect—can overshadow strong clinical skills and create lasting adverse impressions.

The tension students experience between admiring technical mastery and rejecting unprofessional attitudes underscores the need to cultivate both competence and character in clinical educators. Moreover, systemic challenges, including heavy workload and limited time for meaningful engagement, continue to constrain effective role modeling across clinical settings.

These results reinforce the urgent need for structured faculty development programs that promote not only scientific excellence but also emotional intelligence, communication skills, professionalism, and reflective practice. Strengthening these areas may enhance the quality of role modeling, support students' professional identity formation, and ultimately contribute to the development of more compassionate, skilled, and ethically grounded physicians.

An additional contribution of this study is its emphasis on bringing the concept of role modeling—an inexpensive, simple, and highly effective educational strategy—more prominently onto the agenda of medical education. By demonstrating its impact through learners' authentic experiences, this study underscores the need to recognize role modeling as a strategic, high-value component of clinical training.

Ethics

Ethics Committee Approval: The study adhered to the principles of the Declaration of Helsinki, and ethical approval was obtained from the Ankara Bilkent City Hospital Ethics Committee (decision no: TABED 2/08/2024, date: 15.05.2024).

Informed Consent: Interviews lasted 26±3 minutes, were video-recorded with participants' consent, and were transcribed verbatim.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

REFERENCES

1. Baykan Z. Being a role model [İyi örnek olma (rol model olma)]. Turkiye Klinikleri J Med Educ-Special Topics. 2017;2:135-9.
2. Esen F, Arslantas D. Milestones of medical education in the historical process [Tarihsel süreç içerisinde tıp eğitiminin dönüm noktaları]. Osmangazi Journal of Medicine. 2023;45:615-28.
3. Tosteson DC. Learning in medicine. N Engl J Med. 1979;301:690-4.
4. Köse C. The self-assessments by the interns studying at a medical school on certain basic professional knowledge and skills [Bir tıp fakültesi intörnlerinin mesleki temel bazı bilgi ve becerileri hakkındaki öz değerlendirmeleri]. STED. 2018;27:176-89.
5. Passi V, Johnson N. The impact of positive doctor role modeling. Med Teach. 2016;38:1139-45.
6. Passi V, Johnson S, Peile E, Wright S, Hafferty F, Johnson N. Doctor role modelling in medical education: BEME guide no. 27. Med Teach. 2013;35:e1422-36.
7. Passi V, Johnson N. The hidden process of positive doctor role modelling. Med Teach. 2016;38:700-7.
8. Paice E, Heard S, Moss F. How important are role models in making good doctors? BMJ. 2002;325:707-10.
9. Levinson W, Lesser CS, Epstein RM. Developing physician communication skills for patient-centered care. Health Aff (Millwood). 2010;29:1310-8.
10. King N. Positive doctor role modeling: is it a two-way street? Med Teach. 2017;39:326.
11. Kutlu M, Çolakoğlu N, Özgüvenç ZP. A study on the importance of empathy in patient-doctor relationship [Hasta hekim ilişkisinde empatinin önemi hakkında bir araştırma]. Sağlıkta Performans ve Kalite Dergisi. 2010;2:127-43.
12. Kılıç F, Hösükler E, Altın İ, Üzün İ. An evaluation of cases with a claim of medical malpractice related to the cardiology department reported by the first forensic medicine expert committee of the forensic medicine institute between 2012 and 2014. Int J Cardiovasc Acad. 2024;10:115-22.
13. Hojat M, Gonnella JS, Nasca TJ, Mangione S, Vergare M, Magee M. Physician empathy: definition, components, measurement, and relationship to gender and specialty. Am J Psychiatry. 2002;159:1563-9.
14. Flin R, O'Connor P, Crichton M. Safety at the sharp end: a guide to non-technical skills. Aldershot (UK): Ashgate Publishing Ltd; 2008.
15. Harden RM, Crosby J. AMEE education guide no 20: the good teacher is more than a lecturer-the twelve roles of the teacher. Med Teach. 2000;22:334-47.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.74429
Int J Cardiovasc Acad 2026;12(1):28-38

Regulating Effect of Weekend Catch-up Sleep on the Relationship between Atrial Fibrillation and Acute Myocardial Infarction

Sefa Erdi Ömür, Çağrı Zorlu, Kayıhan Karaman, Gülşen Genç Tapar, Metin Karayakalı, Ataç Çelik

Department of Cardiology, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Türkiye

Abstract

Background and Aim: Coronary artery disease and atrial fibrillation (AF) are major contributors to cardiovascular morbidity and mortality. Systemic inflammation may link AF to acute myocardial infarction (MI). We investigated whether weekend catch-up sleep (WCS) is associated with acute MI in patients with AF and whether the systemic immune-inflammation (SII) index modifies this association.

Materials and Methods: We conducted a single-center retrospective cohort study including 3,200 patients with AF. Participants were categorized as having no WCS (0 h) or as having WCS present (0<WCS≤1 h). Inflammatory biomarkers and acute MI events during follow-up were evaluated.

Results: Acute MI occurred more frequently in the no WCS group than in the WCS group ($P < 0.001$). In receiver operating characteristic analyses, the SII cut-off values were 352.12 (sensitivity 82%, specificity 83%) for patients without WCS and 212.61 (sensitivity 81%, specificity 81%) for patients with WCS. Kaplan-Meier curves demonstrated a higher risk of acute MI among the no WCS group (log-rank $P < 0.001$).

Conclusion: In this single-center retrospective cohort study, the absence of WCS was associated with a higher risk of acute MI in patients with AF, and the WCS×SII interaction suggested effect modification by inflammatory burden. External validation is warranted.

Keywords: Atrial fibrillation, weekend catch-up sleep, acute myocardial infarction, systemic immune inflammatory index

INTRODUCTION

Cardiovascular diseases, including coronary artery disease (CAD) and atrial fibrillation (AF), remain leading causes of morbidity and mortality worldwide.[1] The prevalence of both CAD and AF increases with age, and these conditions frequently coexist.[2] In patients with non-valvular AF, angiographically documented CAD has been reported in more than half of cases, which is substantially higher than estimates in non-AF populations (~13%).[3,4] Moreover, AF has been associated with incident CAD and acute myocardial infarction (MI), potentially through shared risk factors, a prothrombotic milieu, and hemodynamic alterations.[5]

Inflammation represents a key biological link between AF and ischemic events. Acute MI triggers robust intramyocardial and systemic inflammatory responses, with elevations in circulating biomarkers;[6] inflammatory pathways have long been implicated in AF pathophysiology.[7] Accordingly, practical inflammatory indices that could help identify AF patients at higher risk of MI are of clinical interest. The systemic immune-inflammation (SII) index, derived from routine complete blood

To cite this article: Ömür SE, Zorlu Ç, Karaman K, Genç Tapar G, Karayakalı M, Çelik Ç. Regulating effect of weekend catch-up sleep on the relationship between atrial fibrillation and acute myocardial infarction. Int J Cardiovasc Acad. 2026;12(1):28-38

Address for Correspondence: Asst. Prof. Sefa Erdi Ömür, Department of Cardiology, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Türkiye
E-mail: sefaerdi61@gmail.com
ORCID ID: orcid.org/0000-0002-6209-1732

Received: 20.10.2025
Accepted: 23.12.2025
Epub: 11.02.2026
Publication Date: 10.03.2026

counts (CBC), has been reported to be elevated in both AF and MI;[7] however, its utility for MI risk stratification within AF cohorts remains uncertain.

Sleep is another potentially modifiable determinant of cardiometabolic health. Short sleep duration and poor sleep quality have been linked to adverse cardiovascular profiles, including hypertension (HT), metabolic syndrome, and increased arterial stiffness.[8] Weekend catch-up sleep (WCS)—extending sleep on non-work days to compensate for weekday sleep debt—has been proposed as a mitigating behavior with potential cardiometabolic benefits.[9] However, the impact of WCS on acute MI risk among patients with AF and whether inflammatory burden modifies this association have not been investigated.

Therefore, we investigated the association between WCS and incident acute MI and evaluated the prognostic role of SII in patients with AF.

METHODS

Study Design, Population, and Ethics

This retrospective cohort study included 3,649 consecutive patients admitted to the local university hospital. This cohort comprised consecutive patients with AF who were evaluated at our university hospital, including outpatient clinic visits and inpatient or emergency admissions, between May 2018 and February 2025. Admission status was obtained from the electronic health record. After excluding 449 patients with insufficient data, the final analytic sample comprised 3,200 patients (flowchart). Demographic, clinical, laboratory, procedural, and follow-up information was obtained from the electronic health record and the institutional database using standardized extraction forms. The study complied with the Declaration of Helsinki and received approval from the Local Institutional Ethics Committee of Tokat Gaziosmanpaşa University (decision no: 25-MOBAEK-327, date: 16.10.2025).

AF and acute MI were defined according to the European Society of Cardiology guidelines.[10,11] All patients were followed for 4.23±0.81 years. Two members of the event-adjudication committee independently and blindly adjudicated MI events; discrepancies were resolved by consensus.

Exclusion Criteria

We excluded patients who received thrombolytic therapy before invasive evaluation; patients without invasive assessment within 12 hours of symptom onset (when clinically indicated); patients with any systemic inflammatory or rheumatologic disease, storage disease, anemia, malignancy, hematological disorders (including acute or chronic stroke), advanced renal and/or hepatic failure; patients with active or recent infection; patients who had blood transfusion within the prior 3 months; patients with severe valvular disease or a history of valve surgery; patients aged <18 years; and patients with incomplete core data fields.

Exposure Definition: WCS

Sleep was assessed using National Health and Nutrition Examination Survey (NHANES)[12] items on usual sleep during weekdays (workdays) and weekends (non-workdays). For the present analyses, we focused exclusively on WCS and did not use the weekly mean sleep duration. Given the skewed distribution of WCS, with clustering between 0 and 1 hour, WCS was initially operationalized pragmatically; however, alternative codings were examined in sensitivity analyses (Supplementary Table 1). WCS was computed as weekend sleep minus weekday sleep (in hours) and operationalized as a binary exposure: no WCS (difference=0 h) versus WCS present (0<WCS≤1 h). Participants with WCS>1 h were not excluded; they were retained in the dataset and evaluated in the prespecified sensitivity analyses that used broader WCS definitions (e.g., >0 h, ≥1 h, ≥2 h, and continuous WCS) (Supplementary Table 1). Participants were categorized accordingly. No WCS: 0 hour WCS present: 0<WCS≤1 hour.

Outcomes

The primary outcome was acute MI during follow-up. Secondary descriptors included baseline characteristics and inflammatory indices across WCS categories.

Laboratory Measurements and SII Index

Peripheral venous blood was collected on admission after at least 8 hours' fasting. Routine biochemical tests [lipid panel, fasting plasma glucose, creatinine, liver enzymes, albumin, C-reactive protein (CRP), n-terminal brain natriuretic peptide] and a CBC were measured on an automated analyzer. Clinical definitions: diabetes mellitus was defined as fasting plasma glucose >125 mg/dL, HbA1c >6.5%, or use of antidiabetic therapy; hyperlipidemia was defined as low-density lipoprotein cholesterol >100 mg/dL or use of lipid-lowering medication; and HT was defined as use of antihypertensives or systolic blood pressure/diastolic blood pressure ≥140/90 mmHg. CAD was defined as prior MI, ≥50% epicardial stenosis on angiography, or equivalent evidence on coronary computed tomography angiography. Current smoking was defined as smoking within the past 6 months.

SII was calculated as (platelet count×neutrophil count)/lymphocyte count.

Echocardiography and Coronary Procedures

All patients underwent transthoracic echocardiography in the left lateral decubitus position prior to invasive procedures. Left

ventricular ejection fraction was measured by two experienced cardiologists using the biplane Simpson method. Diagnostic coronary angiography and percutaneous coronary intervention, when indicated, were performed by experienced interventional cardiologists via radial or femoral access using the standard Judkins technique with 6-Fr catheters and a flat-panel digital angiography system.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). Missing data handling: patients with insufficient or incomplete core data fields were excluded from the analysis. For multivariable analyses, we performed complete-case analyses (listwise deletion) within each model, excluding participants with missing values for any covariate included in that specific model. Therefore, the analytic sample sizes could vary across models; model-specific n values are reported in the corresponding tables (e.g., Supplementary Table 2). Continuous variables were assessed for distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests and by visual inspection, and summarized as mean ± standard deviation or median (interquartile range); categorical variables were summarized as n (%). Between-group comparisons used the t-test or Mann-Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate.

The primary analysis used a prespecified Cox proportional hazards model (time-to-event) with time-to-first MI as the outcome; the model included WCS, SII, and the WCS×SII interaction and was adjusted a priori for age, heart rate, CAD, and CRP. Multivariable logistic regression was performed as a secondary and complementary analysis to facilitate visualization of interactions and to report adjusted odds ratios (aOR). The main predictors were WCS category [no WCS vs. WCS present ($0<WCS\leq1$)], SII (continuous; log-transformed if necessary), and the WCS×SII interaction. Covariates were selected a priori based on clinical relevance and the literature: age, heart rate, CAD, and CRP. To assess robustness to exposure coding and to reduce potential misclassification, we conducted pre-specified sensitivity analyses using alternative definitions of WCS: (i) binary (>0 h vs. 0 h), (ii) collapsed categories where necessary because of sparse counts, and (iii) continuous WCS (per 1-hour increase). Alternative thresholds included ≥2 h, where cell counts permitted. These prespecified analyses were performed using multivariable logistic regression and time-to-event Cox models; results are presented in Supplementary Table 1. To address potential residual confounding, we conducted sequential sensitivity analyses with varying covariate adjustment (unadjusted; the primary, prespecified model; and, where available, expanded models adjusted for clinical variables and medications). Results are presented in Supplementary Table 2. Effect modification was evaluated with the interaction term (P-interaction <0.05). When an interaction was present, we fitted stratified, adjusted models across SII tertiles (T1-T3) and reported the results as aORs with 95% confidence intervals (CIs). Stratified/tertile analyses were prespecified as exploratory and used for visualization rather than for threshold determination.

To explore potential non-linearity in the association of SII with MI, we used restricted cubic splines. Model calibration and discrimination for the logistic model were assessed using the Hosmer-Lemeshow test and receiver operating characteristic (ROC) area under the curve (AUC), respectively, and multicollinearity was evaluated using variance inflation factors (VIF) <5. VIF values and tolerances for all covariates are provided in Supplementary Table 3. For interaction models, SII was mean-centered before creating the WCS×SII product term to reduce collinearity. Given the number of secondary and sensitivity analyses, results beyond the prespecified primary model are considered exploratory. Accordingly, we did not apply formal multiplicity adjustment; secondary analyses were interpreted cautiously, with emphasis on effect sizes and 95% CIs. Two-sided $P < 0.05$ was considered statistically significant.

Time-to-event analysis (Cox proportional hazards): to incorporate follow-up time, we fitted a prespecified Cox proportional hazards model with time-to-first MI as the outcome. The model included WCS, SII (log-transformed if needed), and the interaction WCS×SII, and was adjusted for the same covariates. Results from Cox models were expressed as hazard ratios (HR) with 95% CIs. The proportional hazards assumption was evaluated using Schoenfeld residuals (and log-log plots if needed); model discrimination was summarized with Harrell's C-index.

RESULTS

A total of 3,200 patients with AF were included. Baseline demographic, clinical, laboratory, and echocardiographic characteristics, as well as medications, are summarized in Table 1. Age was significantly higher in the WCS-present group, whereas CAD prevalence and heart rate were significantly higher in the group without WCS. Inflammatory indices also differed between groups: CRP, SII, and neutrophil and platelet counts were higher in the no WCS group, whereas lymphocyte counts were higher in the WCS-present group.

Acute MI events and angiographic findings during follow-up are presented in Table 2. The incidence of acute MI was higher in the no WCS group than in the WCS group [515/1977 (26.04%) vs. 249/1223 (20.35%), $P < 0.001$].

Table 1. Basic demographic, clinical and laboratory characteristics, echocardiography results and medications used by the patients included in the study

Variable	0<WCS≤1 (n=1223)	No WCS (n=1977)	*P*
Demographic features			
Age (years)	65±8.3	63.2±9.2	**0.003**
Female gender n (%)	635 (51.92)	1029 (52.04)	0.359
BMI kg/m^2	28.21±2.32	28.41±2.33	0.555
CAD n (%)	392 (32.05)	711 (35.96)	**<0.001**
Diabetes mellitus n (%)	428 (34.99)	691 (34.95)	0.439
Hypertension n (%)	489 (39.98)	790 (39.95)	0.887
Hyperlipidemia n (%)	269 (21.99)	434 (21.95)	0.773
Smoking n (%)	305 (24.93)	474 (23.97)	0.449
HF n (%)	256 (20.93)	415 (20.99)	0.501
Heart rate (bpm)	101.44 (71-142)	120.51 (73-144)	**<0.001**
CHA_2DS_2-VASc score	4.42 (1-7)	4.44 (1-7)	0.864
Laboratory findings			
Glucose (mg/dL)	119.22±12.43	118.98±12.34	0.490
Creatinine (mg/dL)	1.05 (0.82-1.21)	1.08 (0.82-1.23)	0.862
BUN (mg/dL)	22.32 (18-28)	22.02 (17–27.6)	0.443
Sodium (mmol/L)	137.58 (135.9-141.5)	138.13 (135.4-142.3)	0.662
Potassium (mmol/L)	4.38 (3.59-4.66)	4.37 (3.61-4.69)	0.731
Albumin (g/dL)	4.33±1.02	4.24±1.05	0.442
ALT (U/L)	28.63 (22-38)	26.55 (23-40)	0.464
AST (U/L)	23.79 (17-33)	25.15 (18-35)	0.389
TSH (µIU/mL)	1.27±0.53	1.23±0.51	0.742
T4 (µIU/mL)	0.92±0.22	1.01±0.11	0.173
Haemoglobin (g/dL)	11.33±1.56	11.17±1.60	0.438
WBC count (x10^3/µL)	11.99±1.37	12.01±1.29	0.746
Neutrophil (x10^3/µL)	2.27±0.11	2.59±0.13	**<0.001**
Lymphocyte (x10^3/µL)	2.49±0.47	2.17±0.52	**<0.001**
Platelet (x10^3/µL)	301.23±22.45	349.61±21.99	**<0.001**
LDL-cholesterol (mg/dL)	126.44 (100-132)	125.23 (103-130)	0.459
HDL-cholesterol (mg/dL)	27.44 (20-35)	28.61 (22-37)	0.782
Triglycerides (mg/dL)	208.60 (193-258)	210.41 (195-261)	0.567
CRP	15.33 (10-21)	28.90 (15-42)	**<0.001**
SII	274.42±22.10	416.59±21.01	**<0.001**
Echocardiographic parameters			
LVEF (%)	51.13±5.43	51.08±5.37	0.435
LA size (mm)	44.62±3.51	44.32±3.22	0.332
LVDD (mm)	48.59±2.1	48.66±2.4	0.623
LVSD (mm)	36.64±1.9	36.04±2.01	0.951
IVSD (mm)	9.69±1.5	9.34±1.2	0.958
E/e'	13.88±1.8	13.97±1.5	0.329
Mild mitral stenosis n (%)	183 (16.29)	317 (16.03)	0.792
Medications			
Acetylsalicylic acid n (%)	50 (4.08)	80 (4.04)	0.357
ACEi, ARB n (%)	612 (50.04)	989 (50.02)	0.616
Beta blocker n (%)	1100 (89.94)	1781 (90.08)	0.763

Table 1. Continued

Variable	0<WCS≤1 (n=1223)	No WCS (n=1977)	*P*
Statin n (%)	616 (50.36)	990 (50.07)	0.752
Calcium channel blockers n (%)	366 (29.92)	594 (30.04)	0.816
Dihydropyridine	36 (9.83)	60 (10.10)	0.971
Non-dihydropyridine	330 (90.16)	534 (89.89)	0.738
Anticoagulant medication n (%)	1175 (96.07)	1899 (96.05)	0.659
Warfarin	79 (6.72)	115 (6.05)	0.871
Apixaban	329 (28)	532 (28.01)	0.769
Rivaroxaban	352 (29.95)	570 (30.01)	0.873
Edoxaban	317 (26.97)	512 (26.96)	0.795
Dabigatran	98 (8.34)	160 (8.42)	0.734

Continuous variables are presented as mean ± standard deviation or as median (interquartile range) where indicated; categorical variables are presented as n (%)

BMI: Body mass index, CAD: Coronary artery disease, HF: Heart failure, ACEi: Angiotensin-converting enzyme inhibitor ARB: Angiotensin receptor blockers, WBC: White blood cells, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction LVDD: Left ventricular end diastolic diameter, LVSD: Left ventricular end systolic diameter, IVSD: Interventricular septum, LA: Left atrium, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, bpm: Beats per minute, TSH: Thyroid-stimulating hormone, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SII: Systemic immune-inflammatory index, CRP: C-reactive protein, WCS: Weekend catch-up sleep

Table 2. Information on myocardial infarction during follow-up of patients with atrial fibrillation

Variable	0<WCS≤1 (n=1223)	No WCS (n=1977)	*P*
Myocardial infarction	249 (20.35)	515 (26.04)	<0.001
Contrast agent amount (mL)	121.47±18.42	121.23±17.99	0.835
Processing time (min)	42.66±4.71	43.01±4.19	0.597
Number of lesions n (%)			
1	50 (20.08)	103 (20)	0.399
2	174 (69.87)	361 (70.09)	0.467
3	25 (10.04)	51 (9.90)	0.593
Location of the lesion n (%)			
LAD	87 (34.93)	180 (34.95)	0.804
LCX	83 (33.33)	175 (33.98)	0.768
RCA	81 (32.53)	170 (33.00)	0.697

LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, WCS: Weekend catch-up sleep

In the ROC analysis (Figure 1), the optimal SII cut-off for discriminating acute MI among no WCS AF patients was 352.12, with sensitivity of 82% and specificity of 83% (AUC: 0.892, 95% CI 0.873-0.911, $P < 0.01$). Among AF patients with WCS, the SII cut-off was 212.61, with 81% sensitivity and 81% specificity (AUC: 0.792; 95% CI 0.757-0.827; $P < 0.01$).

Kaplan-Meier curves (Figure 2) showed a significantly higher cumulative incidence of acute MI in the no WCS group (log-rank test, $P < 0.001$). In primary time-to-event analyses, the adjusted Cox proportional hazards model showed that WCS present (0<WCS≤1 h) was associated with a lower hazard of incident acute MI compared with no WCS (0 h) (adjusted HR: 0.81, 95% CI 0.69-0.95; $P = 0.010$). In a complementary multivariable logistic regression model (Table 3), heart rate, SII, and absence of WCS were independently associated with acute MI. Using no WCS as the reference, presence of WCS was associated with lower odds of acute MI (aOR: 0.752, 95% CI 0.539-0.889; $P < 0.001$). Results were consistent across alternative WCS codings and sequentially adjusted sensitivity models (Supplementary Tables 1 and 2).

The WCS×SII interaction term suggested effect modification (*P*-interaction: 0.018; Figure 3A). In the multivariable logistic interaction model (Table 4), the presence of WCS remained inversely associated with MI (aOR: 0.752, 95% CI 0.539-0.889; $P < 0.001$) and SII was positively associated with MI (per 100-unit increase: aOR: 1.65, 95% CI 1.22-2.23; $P < 0.001$).

In exploratory stratified analyses across SII tertiles (Figure 3B; Table 5), the association between absence of WCS and acute MI appeared strongest in the highest tertile (T3: aOR: 1.95, 95% CI 1.24-3.06; $P = 0.004$), whereas associations in the lower tertiles were weaker or not statistically significant (T1: aOR: 1.10, $P = 0.460$; T2: aOR: 1.35, $P = 0.058$). These subgroup findings are descriptive and hypothesis-generating.

The association remained consistent in sensitivity analyses using alternative WCS codings (Supplementary Table 1). Findings were also robust in sequential covariate-adjusted models (Supplementary Table 2).

Restricted cubic spline analysis (Supplementary Figure 1) demonstrated that higher SII values were generally associated with increased adjusted odds of acute MI, with a potentially non-linear pattern across the SII range. Accordingly, SII was retained as a continuous variable in the multivariable models.

DISCUSSION

This study is among the first to examine the association between WCS and acute MI in AF, addressing a gap in the literature on compensatory sleep patterns. Our findings reveal that AF patients with no WCS have a significantly higher incidence of acute MI than those with WCS (0<WCS≤1). Beyond this crude association, our primary multivariable model, including an interaction term (WCS×SII), demonstrated that the relationship between WCS and acute MI is modified by the inflammatory burden; the interaction was statistically significant. In stratified, adjusted analyses across SII tertiles, the association between absence of WCS and acute MI was weak and non-significant in the low-SII tertile and borderline in the mid-SII tertile, but was clearly significant and clinically meaningful in the high-SII tertile. These results provide novel insights into the interplay between sleep patterns, systemic inflammation, and cardiovascular risk in AF patients, suggesting that SII may be a candidate marker for risk stratification in this cohort; however, its clinical utility requires external multicenter validation.

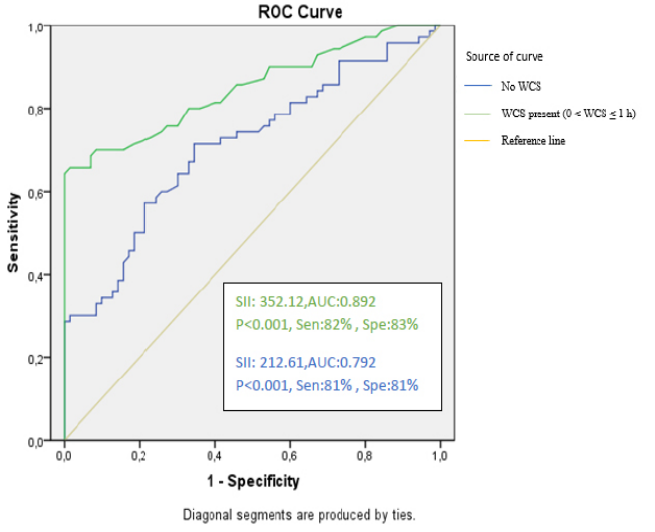


Figure 1. Exploratory ROC curves of SII for discriminating acute MI stratified by WCS status. No WCS: n=1977, events=515; WCS present (0<WCS≤1 h): n=1223, events=249. AUC values are reported with 95% confidence intervals calculated using the DeLong method

ROC: Receiver operating characteristic, SII: Systemic immune-inflammation index, MI: Myocardial infarction, WCS: Weekend catch-up sleep, AUC: Area under curve

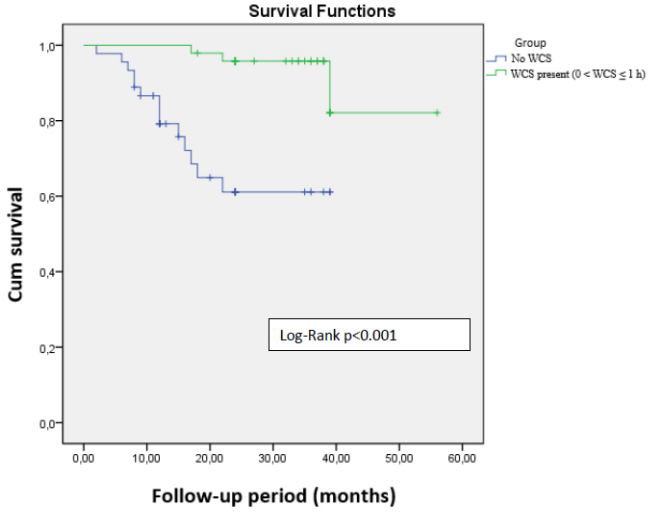


Figure 2. Cumulative incidence of acute MI comparing no WCS vs. WCS present (0<WCS≤1h) (log-rank *P* < 0.001)

MI: Myocardial infarction, WCS: Weekend catch-up sleep

Table 3. Univariate and multivariable regression analyses to identify factors independently associated with acute MI

Variable	Univariate analysis odds ratio (95% CI)	*P*	Multivariate analysis odds ratio (95% CI)	*P*
Age	1.134 (1.02-1.25)	0.018	1.091 (0.95-1.19)	0.274
CAD	1.743 (1.12-2.71)	0.014	1.256 (1.102-1.73)	0.022
Heart rate (per 10 bpm)	1.323 (1.08-1.62)	0.005	1.18 (1.07-1.31)	0.012
CRP	1.392 (1.15-1.67)	<0.001	1.121 (1.02-1.32)	0.008
SII (log or per 100 increase)	1.591 (1.22-1.96)	<0.001	1.65 (1.22-2.23)	<0.001
WCS present (0<WCS≤1 h) vs. no WCS (0 h)	0.741 (0.665-0.825)	<0.001	0.752 (0.539-0.889)	<0.001

Reference category for WCS: no WCS (0 h). Primary adjusted model includes WCS and SII as main predictors, adjusted for age, heart rate, CAD, and CRP (a priori covariates)

MI: Myocardial infarction, CI: Confidence interval, WCS: Weekend catch-up sleep, SII: Systemic immune-inflammatory index, CRP: C-reactive protein, bpm: Beats per minute, CAD: Coronary artery disease

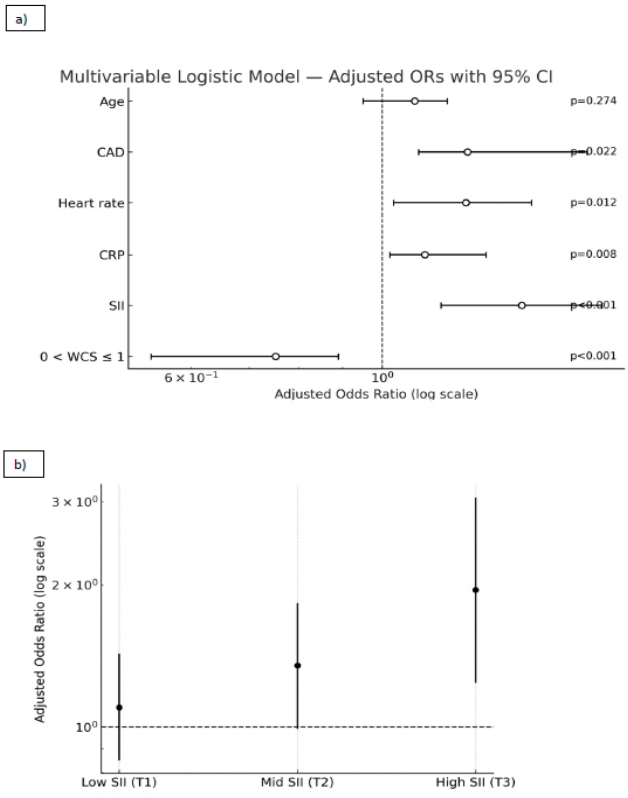


Figure 3. (a) Multivariable logistic model (aOR, 95% CI) forest plot. (b) Effect of no WCS across SII tertiles (aOR, 95% CI)

aOR: Adjusted odds ratio, WCS: Weekend catch-up sleep, CI: Confidence interval, SII: Systemic immune-inflammation index

The relationship between sleep deprivation and cardiovascular outcomes has been well-documented. Chronic sleep insufficiency has been associated with increased risks of HT, CAD, and major adverse cardiovascular events; several pathways have been proposed (e.g., autonomic and inflammatory activation).[8] However, we did not directly measure autonomic tone, endothelial function, or sleep architecture; therefore, mechanistic inferences drawn from our data should be interpreted with caution. Our study builds on this foundation by specifically examining WCS in AF patients, a population at increased risk of thromboembolism and MI owing to prothrombotic states and hemodynamic alterations.[13] Unlike prior studies that broadly assessed total sleep duration or sleep quality,[14] our focus on WCS—a compensatory sleep pattern to offset weekday sleep debt—represents a novel contribution. The significantly higher MI rates in the no-sleep group align with evidence suggesting that irregular sleep patterns exacerbate cardiovascular stress.[15] Importantly, effect modification by SII suggests that sleep-related risk is not uniform; rather, patients with greater systemic immune-inflammatory activation appear to be most susceptible to the adverse consequences of the absence of WCS.

The use of SII as a marker of systemic inflammation is a key innovation of this study. SII integrates multiple inflammatory and immune components, offering a more comprehensive assessment than individual markers such as CRP or neutrophil-to-lymphocyte ratio. Recent studies have validated SII as a predictor of adverse outcomes in CAD and heart failure,[16] but its application in AF patients, particularly in the context of sleep

Table 4. Secondary logistic interaction model with WCS×SII interaction

Variable	aOR (95% CI)	*P*
WCS present (0<WCS≤1 h) [ref: no WCS (0 h)]	0.752 (0.539-0.889)	<0.001
SII (per 100 increase)	1.65 (1.22-2.23)	<0.001
WCS×SII (interaction)	-	0.018
Age (years)	1.02 (1.00-1.04)	0.028
Heart rate (per 10 bpm)	1.18 (1.07-1.31)	0.001
CAD	1.29 (1.03-1.62)	0.015
CRP	1.10 (1.03-1.18)	0.006

Adjusted odds ratios from the primary multivariable model including the WCS×SII interaction. For the interaction term, only *P*-interaction is reported

WCS: Weekend catch-up sleep, SII: Systemic immune-inflammation index, aOR: Adjusted odds ratio, CI: Confidence interval, CAD: Coronary artery disease, CRP: C-reactive protein

Table 5. Stratified associations between WCS and acute MI by SII level

SII group (tertile)	aOR for no WCS vs. WCS present (0<WCS≤1 h) (95% CI)	*P*
Low SII (T1)	1.10 (0.85-1.43)	0.460
Mid SII (T2)	1.35 (0.99-1.83)	0.058
High SII (T3)	1.95 (1.24-3.06)	0.004

Adjusted odds ratios for the association between absence of WCS (no WCS: 0 h) and acute MI within each SII tertile (T1-T3) (reference: WCS present, 0<WCS≤1 h), consistent with the WCS×SII interaction shown in Table 4

WCS: Weekend catch-up sleep, SII: Systemic immune-inflammation index, aOR: Adjusted odds ratio, CI: Confidence interval, MI: Myocardial infarction

patterns, is novel. Consistent with prior reports linking sleep deprivation to elevated inflammatory mediators,[17] our cohort showed higher SII levels in the no WCS group. Because we did not measure cytokines (e.g., interleukin-6) or other mechanistic biomarkers, we cite these pathways only as supportive context rather than direct evidence from our cohort. Moreover, SII demonstrated better discriminatory performance than CRP in acute MI, supported by ROC analysis. Together with the significant WCS×SII interaction, these findings strengthen the biological plausibility that inflammatory activation may amplify the ischemic risk associated with irregular or insufficient recovery sleep.

The finding that, among AF patients without WCS, SII was independently associated with acute MI has several potential clinical implications. Because SII is derived from routine CBC parameters, it is cost-effective, widely accessible, and lends itself to pragmatic risk stratification. Our tertile-based analyses were performed for descriptive presentation and interpretability; tertile cut-points are data-dependent and should not be interpreted as clinical thresholds. Given that the interaction signal is modest (*P*-interaction: 0.018), we interpret effect modification cautiously. These findings should be considered hypothesis-generating and require confirmation in independent, multicenter cohorts before any clinical application. In parallel, the association between the lack of WCS and increased MI risk underscores the importance of addressing sleep patterns in AF management. Sleep hygiene education, cognitive behavioral therapy for insomnia, or structured sleep recovery protocols could be explored as adjunctive strategies warranting evaluation in prospective studies for potential cardiovascular risk reduction.[18] In addition, elevated heart rate in the no WCS group—confirmed as an independent predictor in multivariable analysis—reinforces the need to optimize rate control (e.g., with beta-blockers or non-dihydropyridine calcium channel blockers) in this vulnerable subset.[19] Overall, our findings support the hypothesis that inflammatory burden may modify the association between WCS and MI risk in AF. These observations should be interpreted with caution and confirmed in independent, multicenter cohorts before broader clinical generalization.

This study is among the first to investigate the impact of WCS on acute MI risk in AF patients, addressing a critical gap in the literature regarding compensatory sleep patterns. The large sample size (n=3200) and extended follow-up period (4.23±0.81 years) enhance the reliability of our findings. The use of SII as a prognostic marker in this context is a significant advancement, as prior studies have primarily focused on traditional inflammatory markers.[20] By demonstrating effect-modification and providing stratified, adjusted estimates across SII tertiles, our analysis offers actionable clinical granularity that goes beyond average effects.

Study Limitations

Several limitations should be acknowledged. First, the observational design limits our ability to infer causal relationships among lack of WCS, elevated SII, and acute MI. Reverse causation cannot be excluded; individuals with a higher underlying risk of MI (or subclinical cardiovascular disease) may also experience sleep disturbances or altered sleep patterns, which could influence WCS reporting. Prospective interventional studies are needed to determine whether improving sleep patterns can reduce acute MI risk. WCS was dichotomized (0 hours vs. 0<WCS≤1), which may oversimplify sleep behaviors and result in information loss; future studies should incorporate more granular, device-based metrics (e.g., total sleep duration, sleep efficiency, and regularity indices) obtained using wearable devices, actigraphy, or polysomnography.[21] A major methodological limitation is that WCS was derived from self-reported NHANES items rather than objectively measured sleep. Given the nuanced nature of catch-up sleep, this exposure assessment is prone to recall bias, social desirability bias, and measurement error, which may result in exposure misclassification and could bias effect estimates (most likely toward the null). Although patients with overt systemic inflammatory diseases were excluded, residual confounding from subclinical inflammatory conditions or unmeasured behaviors (e.g., diet, physical activity, and work schedules) cannot be fully ruled out. We attempted to mitigate confounding by presenting expanded, sequential adjustment models (Supplementary Table 2). Nonetheless, important AF- and sleep-related confounders (e.g., AF duration/type, objectively diagnosed sleep apnea, physical activity, socioeconomic factors, shift work, medication adherence, and warfarin time in therapeutic range) were not systematically available; therefore, residual confounding cannot be excluded. Finally, the single-center design may limit generalizability to diverse populations with varying demographic or clinical profiles. Therefore, the findings should be considered hypothesis-generating and require replication in independent datasets with different demographic and clinical profiles.

CONCLUSION

In this retrospective, single-center cohort, absence of WCS was independently associated with increased odds of acute MI among patients with AF. Higher SII and other covariates were also independently associated with MI, and the significant WCS×SII interaction suggested effect modification by inflammatory burden. These findings are associational and require confirmation in external multicenter cohorts that use more granular and, ideally, objective sleep measures before clinical implementation. Future research should focus on validating these findings and exploring targeted sleep and inflammation-modulating interventions to reduce cardiovascular risk in this vulnerable population.

Ethics

Ethics Committee Approval: The study complied with the Declaration of Helsinki and received approval from the Local Institutional Ethics Committee of Tokat Gaziosmanpaşa University (decision no: 25-MOBAEK-327, date: 16.10.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.E.Ö., Concept: S.E.Ö., Design: S.E.Ö., Ç.Z., Data Collection or Processing: S.E.Ö., Ç.Z., K.K., G.G.T., Analysis or Interpretation: S.E.Ö., G.G.T., Literature Search: S.E.Ö., M.K., Writing: S.E.Ö., A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al.*; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76:2982-3021. Erratum in: J Am Coll Cardiol. 2021;77:1958-9.
2. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, *et al.* Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. Circulation. 2018;137:1027-38.
3. Sharma YP, Batta A, Makkar K, Hatwal J, A Gawalkar A, Kaur N, *et al.* Angiographic profile and outcomes in persistent non-valvular atrial fibrillation: a study from tertiary care center in North India. Indian Heart J. 2022;74:7-12.
4. Nucifora G, Schuijf JD, Tops LF, van Werkhoven JM, Kajander S, Jukema JW, *et al.* Prevalence of coronary artery disease assessed by multislice computed tomography coronary angiography in patients with paroxysmal or persistent atrial fibrillation. Circ Cardiovasc Imaging. 2009;2:100-6.
5. Michniewicz E, Mlodawska E, Lopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease - double trouble. Adv Med Sci. 2018;63:30-5.
6. Suleiman M, Khatib R, Agmon Y, Mahamid R, Boulos M, Kapeliovich M, *et al.* Early inflammation and risk of long-term development of heart failure and mortality in survivors of acute myocardial infarction predictive role of C-reactive protein. J Am Coll Cardiol. 2006;47:962-8.
7. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. Circ J. 2015;79:495-502.
8. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32:1484-92.
9. Pizinger TM, Aggarwal B, St-Onge MP. Sleep extension in short sleepers: an evaluation of feasibility and effectiveness for weight management and cardiometabolic disease prevention. Front Endocrinol (Lausanne). 2018;9:392.
10. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, *et al.*; ESC Scientific Document Group. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2024;45:3314-414. Erratum in: Eur Heart J. 2025;46:4349.
11. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al.*; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;44:3720-826. Erratum in: Eur Heart J. 2024;45:1145.
12. Han KM, Lee HJ, Kim L, Yoon HK. Association between weekend catch-up sleep and high-sensitivity C-reactive protein levels in adults: a population-based study. Sleep. 2020;43:zsaa010.
13. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, *et al.* Antithrombotic therapy for atrial fibrillation: CHEST Guideline and expert panel report. Chest. 2018;154:1121-201.
14. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. J Sleep Res. 2012;21:427-33.
15. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. Circulation. 2011;124:2073-81.
16. Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, *et al.* Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50:e13230.
17. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, *et al.* Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol. 2004;43:678-83.
18. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Breen EC, Witarama T, *et al.* Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. Sleep. 2014;37:1543-52.
19. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, *et al.*; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010;362:1363-73.
20. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, *et al.* Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20:6212-22.
21. Ancoli-Israel S, Martin JL, Blackwell T, Buenaver L, Liu L, Meltzer LJ, *et al.* The SBSM Guide to actigraphy monitoring: clinical and research applications. Behav Sleep Med. 2015;13 Suppl 1:S4-38.

Supplementary Table 1. Sensitivity analyses using alternative WCS codings in multivariable models

Sensitivity set	WCS coding	WCS group/ comparison (ref: no WCS: 0 h)	Logistic regression (acute MI) aOR (95% CI)	*P*	Cox model (acute MI) aHR (95% CI)	*P*
S1	Original binary (as in manuscript)	WCS present (0<WCS≤1) vs. 0 h	0.752 (0.539-0.889)	<0.001	0.81 (0.69-0.95)	0.010
S2	Binary (alternative)	>0 h vs. 0 h	0.79 (0.65-0.96)	0.018	0.84 (0.72-0.98)	0.026
S3	3-level (collapsed)*	0-<1 h vs. 0 h	0.77 (0.63-0.95)	0.013	0.83 (0.71-0.98)	0.022
		≥1 h vs. 0 h	0.92 (0.62-1.37)	0.69	0.95 (0.66-1.38)	0.79
S5	Threshold (literature)	≥2 h vs. 0 h	0.756 (0.689-0.891)	0.021	0.85 (0.79-0.91)	0.012
S4	Continuous	Per 1-hour increase in WCS	0.96 (0.90-1.03)	0.24	0.97 (0.91-1.04)	0.33

- WCS was calculated as weekend sleep duration minus weekday sleep duration (in hours), using NHANES items
- Reference category: no WCS (0 h)
- Adjusted covariates (primary model): age, heart rate, coronary artery disease (CAD), and C-reactive protein (CRP)
- *: Higher WCS categories were collapsed where necessary due to sparse counts, to avoid unstable estimates
- Sensitivity analysis additionally evaluated the commonly used threshold of ≥2 h of WCS (where estimable)

WCS: Weekend catch-up sleep, MI: Myocardial infarction, NHANES: National Health and Nutrition Examination Survey, aHR: Adjusted heart failure, CI: Confidence interval, aOR: Adjusted odds ratio

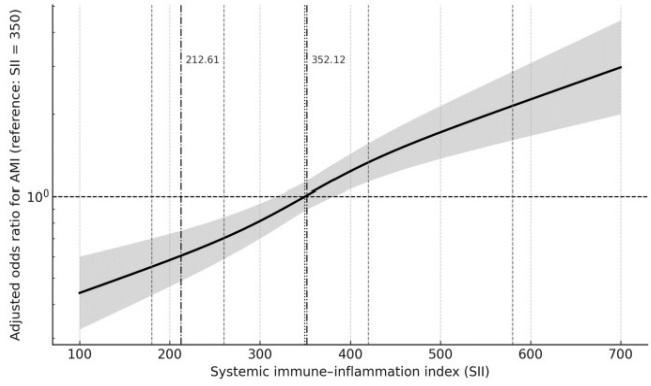
Supplementary Table 2. Sequential covariate-adjustment models for the association between WCS and AMI

Model	WCS coding/ contrast (reference)	Covariate set	Logistic regression (acute MI) OR or aOR (95% CI) for WCS	*P*	Cox model (acute MI) HR or aHR (95% CI) for WCS	*P*	WCS×SII interaction p (if tested)	N
Model 0 (unadjusted)	WCS present (0<WCS≤1 h) vs. no WCS (0 h)	WCS only	0.741 (0.665-0.825)	<0.001	-	-	-	3200
Model 1 (primary adjusted)	WCS present (0<WCS≤1 h) vs. no WCS (0 h)	WCS + SII + age + heart rate + CAD + CRP	0.732 (0.518-0.801)	<0.001	0.81 (0.69-0.95)	0.010	-	3200
Model 1b (primary + interaction)	WCS present (0<WCS≤1 h) vs. no WCS (0 h)	WCS + SII + (WCS×SII) + age + heart rate + CAD + CRP (as in Table 4)	0.752 (0.539-0.889)	<0.001	-	-	0.018	3200
Model 2 (expanded clinical set)	WCS present (0<WCS≤1 h) vs. no WCS (0 h)	Model 1 + eGFR + DM + HT + HL + BMI + current smoking	0.80 (0.62-1.03)	0.08	0.84 (0.72-0.99)	0.034	0.041	3050
Model 3 (expanded + medication proxies)	WCS present (0<WCS≤1 h) vs. no WCS (0 h)	Model 2 + anticoagulant class (warfarin/DOAC) + statin (± ASA/ACEi-ARB/β-blocker/CCB)	0.82 (0.63-1.07)	0.14	0.86 (0.73-1.01)	0.07	0.062	2950

- WCS was computed as weekend sleep duration minus weekday sleep duration (hours) and categorized as no WCS (0 h) vs. WCS present (0<WCS≤1 h)
- Logistic estimates for Models 0 and 1 are taken from Table 3 (univariate and multivariable)
- The Model 1 Cox estimate was obtained from Supplementary Table 1 (time-to-event sensitivity analysis)
- **Model 1b (Interaction model; Table 4):** WCS + SII + (WCS×SII) + **age + heart rate + CAD + CRP** (same a priori covariates as the primary adjusted model)

WCS: Weekend catch-up sleep, MI: Myocardial infarction, OR: Odds ratio, aOR: Adjusted OR, HR: Heart failure, aHR: Adjusted HR, CAD: Coronary artery disease, CRP: C-reactive protein, eGFR: Estimated glomerular filtration rate, SII: Systemic immune-inflammation index, CI: Confidence interval, DM: Diabetus mellitus, HT: Hypertension, HL: Hyperlipidemia, BMI: Body mass index, DOAC: Direct oral anticoagulant, ASA: Acetylsalicylic acid, ACEi: Angiotensin-converting enzyme inhibitör, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker

Supplementary Table 3. Multicollinearity diagnostics (tolerance and VIF) for covariates included in multivariable models			
Model	**Covariate**	**Tolerance**	**VIF**
Primary adjusted model (Table 3)	WCS present (0<WCS≤1 h) vs. no WCS (0 h)	0.92	1.09
Primary adjusted model (Table 3)	SII	0.56	1.79
Primary adjusted model (Table 3)	Age	0.88	1.14
Primary adjusted model (Table 3)	Heart rate	0.84	1.19
Primary adjusted model (Table 3)	CAD	0.90	1.11
Primary adjusted model (Table 3)	CRP	0.52	1.92
Interaction model (Table 4)	WCS present (0<WCS≤1 h) vs. no WCS (0 h)	0.90	1.11
Interaction model (Table 4)	Centered SII (cSII)	0.48	2.08
Interaction model (Table 4)	WCS×cSII	0.41	2.44
Interaction model (Table 4)	Age	0.87	1.15
Interaction model (Table 4)	Heart rate	0.76	1.32
Interaction model (Table 4)	CAD	0.89	1.12
Interaction model (Table 4)	CRP	0.50	2.00
VIF: Variance inflation factors, CAD: Coronary artery disease, CRP: C-reactive protein, SII: Systemic immune-inflammation index, WCS: Weekend catch-up sleep			



Supplementary Figure 1. Restricted cubic spline showing the adjusted association between systemic immune-inflammation index and acute myocardial infarction risk

RESEARCH ARTICLE

DOI: 10.4274/ijca.2026.13008
Int J Cardiovasc Acad 2026;12(1):39-46

Comparative Assessment of High-sensitive CRP and Carotid Stiffness between Patients with and without Coronary Slow Flow

Remon Saleh Adly[1], Sally Magdy Teima[2], Shereen Philip Aziz[3], Ahmed Ibrahim Bedier[2]

[1]Department of Cardiology, Sohag University Faculty of Medicine, Sohag, Egypt
[2]Department of Cardiology, Mansoura University Faculty of Medicine, Dakahlia, Egypt
[3]Department of Clinical Pathology, Sohag University Faculty of Medicine, Sohag, Egypt

Abstract

Background and Aim: Coronary slow flow (CSF) phenomenon represents a distinct clinical entity characterized by delayed coronary opacification despite absence of significant epicardial stenosis. The pathophysiology involves microvascular dysfunction, endothelial impairment, and systemic inflammation. This study evaluated high-sensitivity C-reactive protein (hs-CRP) levels and carotid stiffness parameters in cases with CSF and in controls with normal coronary flow (CF).

Materials and Methods: This case-control study included 60 participants who underwent coronary angiography for chest pain evaluation. Participants (n=30) were divided into two groups: the CSF group, defined by corrected thrombolysis in myocardial infarction frame count >27, and the control group, with normal CF. Bilateral carotid artery ultrasonography and hs-CRP measurement were performed. Carotid stiffness parameters included β-stiffness index, Peterson's elastic modulus, distensibility coefficient, compliance coefficient, and arterial strain.

Results: CSF cases demonstrated significantly higher hs-CRP levels than controls (3.35±1.48 vs. 1.18±0.62 mg/L; $P < 0.001$). Carotid assessment revealed increased carotid intima-media thickness (0.82±0.24 vs. 0.68±0.19 mm, $P = 0.012$), elevated β-stiffness index (7.68±2.71 vs. 6.04±1.62, $P = 0.006$), and Peterson's elastic modulus (637.33±279.7 vs. 379.67±249.81 kPa, $P < 0.001$). Decreased distensibility and compliance coefficients indicated reduced arterial compliance.

Conclusion: CSF is associated with higher hs-CRP and adverse carotid stiffness profiles. These findings support an inflammatory-vascular dysfunction axis in the CSF and justify further studies assessing their prognostic utility.

Keywords: Coronary slow flow, high-sensitivity C-reactive protein, carotid stiffness, arterial compliance, microvascular dysfunction

INTRODUCTION

Coronary slow flow (CSF) is an angiographic phenomenon in which contrast advances slowly to distal coronary landmarks despite the absence of flow-limiting epicardial stenosis. Patients commonly present with angina-like chest pain and ischemic symptoms, yet coronary angiography (CAG) shows no obstructive coronary artery disease, leaving uncertainty about both the mechanism and the prognosis. Contemporary reviews increasingly interpret CSF within the spectrum of ischemia with non-obstructive coronary arteries, where coronary microvascular dysfunction and abnormal coronary vasomotor tone can exist even when the epicardial vessels appear angiographically normal.[1,2]

To cite this article: Adly RS, Teima SM, Aziz SP, Bedier AI. Comparative assessment of high-sensitive CRP and carotid stiffness between patients with and without coronary slow flow. Int J Cardiovasc Acad. 2026;12(1):39-46

Address for Correspondence: Sally Magdy Teima MD, Department of Cardiology, Mansoura University Faculty of Medicine, Dakahlia, Egypt
E-mail: sally88@mans.edu.eg
ORCID ID: orcid.org/0000-0001-7960-4816

Received: 09.09.2025
Accepted: 11.01.2026
Epub: 24.02.2026
Publication Date: 10.03.2026

In daily practice, CSF is identified corrected thrombolysis in myocardial infarction (TIMI) frame count (cTFC), an accessible angiographic surrogate for delayed resting flow, although invasive physiological indices provide a more direct assessment of microvascular function.[2]

Several interrelated pathways may contribute to CSF. Endothelial dysfunction with reduced nitric oxide bioavailability, oxidative stress, and low-grade inflammation can promote microvascular constriction, adverse remodeling, and impaired perfusion, ultimately manifesting as delayed angiographic opacification.[2] High-sensitivity C-reactive protein (hs-CRP) is an accessible marker of low-grade vascular inflammation and residual inflammatory risk in atherosclerotic cardiovascular disease.[3] Prior work has reported higher hs-CRP levels in CSF compared with controls and linked inflammatory activation to endothelial dysfunction and microvascular impairment in this setting.[4,5]

More recently, broader inflammatory indices (e.g., the systemic immune-inflammation index) have also been explored in relation to CSF, reinforcing the concept that CSF may reflect a chronic inflammatory vascular milieu rather than an isolated coronary phenomenon.[6,7]

Large-artery structure and biomechanics offer another window into the systemic vascular milieu in which CSF occurs. Carotid intima-media thickness (CIMT) reflects arterial remodeling, while stiffness indices—including the β-stiffness index, Peterson's elastic modulus, distensibility, compliance, and strain—capture complementary aspects of arterial wall mechanics and have prognostic relevance across cardiovascular conditions.[8,9]

Echo-tracking and ultrasonographic studies have suggested that carotid stiffness is higher in CSF and that stiffness may be related to inflammatory activity.[10] Notably, measured stiffness is strongly influenced by blood pressure, including hypertension, making careful interpretation and appropriate adjustments essential when comparing stiffness parameters between non-randomized groups.[8,9]

Although pooled evidence (e.g., Moawad et al.[11]) supports associations between inflammatory biomarkers and impaired coronary flow patterns, many reports emphasize inflammation alone and do not consistently combine it with detailed carotid biomechanical phenotyping or address blood pressure-related confounding.

Accordingly, the present study, conducted in a rigorously selected cohort that excluded overt inflammatory conditions, was designed to compare hs-CRP levels and a comprehensive panel of carotid stiffness parameters between patients with CSF and controls with normal coronary flow and to contextualize vascular stiffness findings in light of blood pressure, a key determinant of arterial biomechanics.

METHODS

This case-control study included 60 participants (both sexes, aged 18 years or older) who underwent CAG for evaluation of chest pain or suspected myocardial ischemia at Sohag University Hospitals, Egypt, from May to December 2025. The Institutional Review Board/Ethics Committee of Sohag University accepted the study protocol (approval no: Soh-Med-25-5-6PD, date: 12.05.2025). Written informed consent was obtained from all participants prior to enrollment, and the study was conducted in accordance with the Declaration of Helsinki.

Patients referred for diagnostic CAG because of chest discomfort or suspected ischemia were recruited consecutively. The recruitment period was sufficient to achieve the planned sample size.

Based on angiographic findings, participants were divided into two equal groups (n=30): the CSF group, defined by cTFC >27, and the control group, characterized by normal coronary flow (CF) and absence of obstructive coronary artery disease.

Participants were excluded if they presented with any of the following conditions: pregnancy or lactation, a documented history of cardiovascular system (CVS) events, including myocardial infarction or cerebrovascular accident; diagnosed autoimmune disorders; chronic hepatic or renal dysfunction; current or recent infections; a history of malignancy; or concurrent use of medications known to influence inflammatory markers, such as corticosteroids or immunosuppressive agents.

Clinical Assessment and Data Collection

Comprehensive clinical evaluation was performed for all participants, encompassing detailed medical history, including demographic characteristics and smoking habits, anthropometric measurements with calculation of body mass index (BMI), blood pressure measurements, and assessment of comorbid conditions, including diabetes mellitus and hypertension. A complete physical examination was conducted according to standard clinical protocols.

Laboratory Investigations

Venous blood samples were collected after an overnight fast of 8-12 hours for biochemical analysis. hs-CRP concentrations were determined using a high-sensitivity enzyme-linked immunosorbent assay kit, with levels exceeding 2 mg/L were considered elevated according to the American College of Cardiology/American Heart Association guidelines. Additional laboratory parameters included fasting blood glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum creatinine levels, total cholesterol, and triglycerides.

Cardiac Imaging and Angiographic Assessment

Transthoracic echocardiography was performed using standard protocols to evaluate cardiac structure and function. CAG was conducted via the femoral or radial approach, and CF velocity was quantified using the cTFC method to identify cases with the CSF phenomenon.

cTFC was assessed offline by two experienced interventional cardiologists who were blinded to participants' clinical data, laboratory results, and carotid ultrasound measurements. The TIMI frame count was defined as the number of cine frames required for the contrast to reach a predefined distal landmark in each major epicardial artery. For the left anterior descending, the raw frame count was corrected by dividing by 1.7 to yield the cTFC. CSF was defined as cTFC >27 in at least one major coronary artery, in the absence of obstructive epicardial coronary artery disease.

Carotid Artery Evaluation

Bilateral carotid artery ultrasonography was performed using a high-resolution B-mode ultrasound system equipped with a 7.5-MHz linear array transducer. Comprehensive measurements included CIMT assessment, determination of systolic and diastolic arterial diameters, and calculation of multiple arterial stiffness parameters, including the β-stiffness index, Peterson's elastic modulus, the distensibility coefficient, the compliance coefficient, and the arterial strain values.

Carotid systolic diameter (Ds) was measured at peak systole and diastolic diameter (Dd) at end-diastole (electrocardiography-gated when available), and values were averaged over three consecutive cardiac cycles. Stiffness indices were calculated as follows:

- **Arterial strain (%)**: (Ds-Dd)/Dd×100
- **β-stiffness index**: ln [systolic blood pressure (SBP)/diastolic blood pressure (DBP)]/[(Ds-Dd)/Dd]
- **Peterson's elastic modulus**: (SBP-DBP)/[(Ds-Dd)/Dd]
- **Distensibility coefficient**: 2×[(Ds-Dd)/Dd]/(SBP-DBP)
- **Compliance coefficient**: [π (Ds^2-Dd^2)/4]/(SBP-DBP)

where SBP and DBP denote systolic and diastolic blood pressures, respectively.

Sample Size Calculation

G*Power 3.1.9.2 (Universitat Kiel, Germany) was employed to calculate the sample size. We carried out a pilot study (five cases in each group), and we found that the mean [± standard deviation (SD)] of hs-CRP was 3.39±1.66 in the case group and 1.374±0.50 in the control group. The sample size was determined using factors such as an effect size of 0.829, a 95% confidence level, 80% study power, a 1:1 group ratio, and the addition of six cases per group to account for dropout. Therefore, we recruited 30 participants per group.

Statistical Analysis

Data were analyzed using SPSS v29 (IBM©, Armonk, NY, USA). To assess the normality of the data distribution, both the Shapiro-Wilk test and histograms were used. Quantitative data conforming to a parametric distribution were reported as mean and SD and analyzed using an unpaired Student's t-test, whereas non-parametric data were reported as median and interquartile range and analyzed using the Mann-Whitney U test. Conversely, qualitative measures were summarized as frequencies and percentages, and analyzed using the chi-square test or Fisher's exact test, as appropriate for the dataset. Univariate regression was used to estimate the relationship between a dependent variable and one independent variable. Multivariate regression was also used to estimate the relationship between a dependent variable and multiple independent variables. Statistical significance was defined as a two-tailed $P \leq 0.05$.

RESULTS

No significant differences were observed in age, sex, weight, height, BMI, diabetes, and smoking. Hypertension and systolic and DBPs were considerably higher in the CSF group than in the control group ($P < 0.05$) (Table 1 and Figure 1).

Both groups had similar levels of fasting blood glucose, total cholesterol, HDL, LDL, triglycerides, and serum creatinine. hs-CRP was significantly increased in the CSF group compared with the control group ($P < 0.001$) (Table 2 and Figure 2).

Both groups had similar systolic and diastolic diameters. The CSF group had significantly higher CIMT, β-stiffness index, and Peterson's elastic modulus than the control group ($P < 0.05$). Distensibility, compliance, and strain were considerably reduced in CSF group compared to control group ($P < 0.05$) (Table 3 and Figure 3).

In univariate regression analysis, hypertension, systolic and DBP, hs-CRP, CIMT, β-stiffness index, and Peterson's elastic modulus were independent predictors of the occurrence of CSF ($P < 0.05$). In multivariate regression analysis, DBP, hs-CRP, CIMT, β-stiffness index, and Peterson's elastic modulus were independent predictors of the occurrence of CSF ($P < 0.05$), while hypertension and SBP were not independent predictors (Table 4).

Table 1. Demographic data and blood pressure of the studied groups

		CSF group (n=30)	Control group (n=30)	*P*-value	MD/OR (95% CI)
Age (years)		53.73±14.44	55.13±16.54	0.728	-1.4 (-9.43 to 6.63)
Sex	Male	19 (63.33%)	13 (43.33%)	0.121	2.26 (0.8 to 6.36)
	Female	11 (36.67%)	17 (56.67%)		
Weight (kg)		80.03±12.19	82.3±8.73	0.411	-2.27 (-7.75 to 3.21)
Height (cm)		171.07±6.6	168.83±6.49	0.191	2.23 (-1.15 to 5.61)
Body mass index (kg/m^2)		27.36±3.98	29.05±4.26	0.118	-1.69 (-3.82 to 0.44)
Comorbidities	Hypertension	17 (56.67%)	9 (30%)	**0.037***	3.05 (1.05 to 8.84)
	Diabetes mellitus	7 (23.33%)	10 (33.33%)	0.390	0.61 (0.2 to 1.9)
	Smoking	11 (36.67%)	7 (23.33%)	0.260	1.9 (0.62 to 5.86)
Systolic blood pressure (mmHg)		132.07±15	123.5±10.34	**0.013***	8.57 (1.91 to 15.22)
Diastolic blood pressure (mmHg)		88.43±10.32	81.1±8.62	**0.004***	7.33 (2.42 to 12.25)

Data was presented as mean ± standard deviation or frequency (%)

CSF: Coronary slow flow, MD: Mean difference, OR: Odds ratio, CI: Confidence interval, *: Statistically significant $P < 0.05$

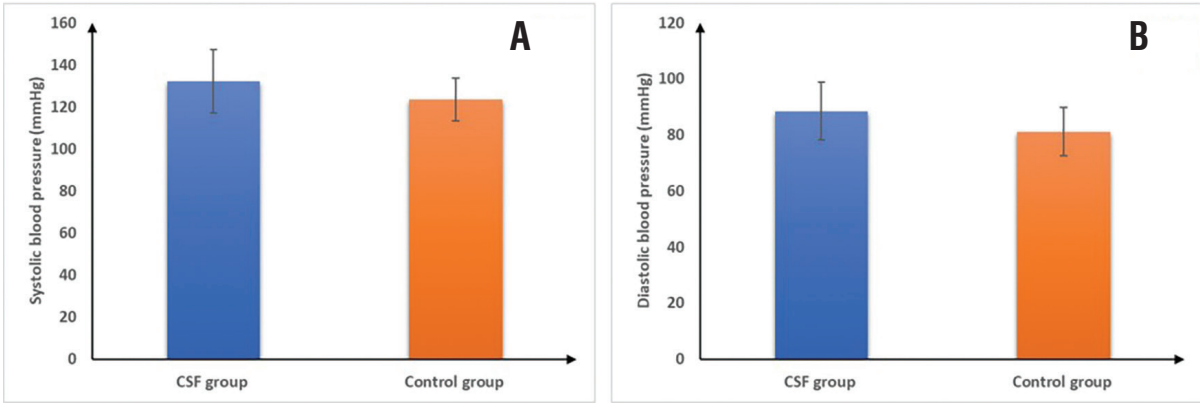


Figure 1. (A) Systolic blood pressure (B) diastolic blood pressure of the studied groups

CSF: Coronary slow flow

Table 2. Laboratory investigation of the studied groups

	CSF group (n=30)	Control group (n=30)	*P*-value	MD (95% CI)
Fasting blood glucose (mg/dL)	108.57±35.62	106.9±27.57	0.840	1.67 (-14.8 to 18.13)
Total cholesterol (mg/dL)	137.57±40.4	127.83±60.83	0.468	9.73 (-16.95 to 36.42)
High density lipoprotein (mg/dL)	40.1±4.87	41.73±6.73	0.286	-1.63 (-4.67 to 1.4)
Low density lipoprotein (mg/dL)	101.17±39.28	120.87±64.44	0.158	-19.7 (-47.28 to 7.88)
Triglycerides (mg/dL)	164.13±31.73	166.43±32.7	0.783	-2.3 (-18.95 to 14.35)
Serum creatinine (mg/dL)	1.04±0.42	0.98±0.31	0.561	0.06 (-0.13 to 0.25)
High-sensitive C-reactive protein (mg/L)	3.655 (2.38-4.28)	1.035(0.78-1.73)	**<0.001***	-2.3 (-2.94 to -1.59)

Data are presented as mean ± standard deviation or median (interquartile range), as appropriate

CSF: Coronary slow flow, MD: Mean or median difference, CI: Confidence interval, *: Statistically significant $P < 0.05$

DISCUSSION

The CSF phenomenon represents a complex clinical entity characterized by delayed opacification of coronary arteries in the absence of significant epicardial stenosis, with emerging evidence suggesting that systemic inflammatory and vascular processes play fundamental roles in its pathogenesis.[12,13]

The present study demonstrates a pronounced elevation of hs-CRP levels in cases with CSF compared with controls, a 2.8-fold increase that underscores the significant inflammatory burden associated with CSF. This finding is consistent with previous investigations: Barutcu et al.[4] reported elevated hs-CRP concentrations in CSF cases and demonstrated positive correlations between inflammatory markers and TFC across all major coronary arteries. Similarly, Ardahanli and Özmen[14] found significantly elevated hs-CRP levels in CSF samples and identified hs-CRP as a sensitive indicator of inflammatory severity with notable diagnostic value.

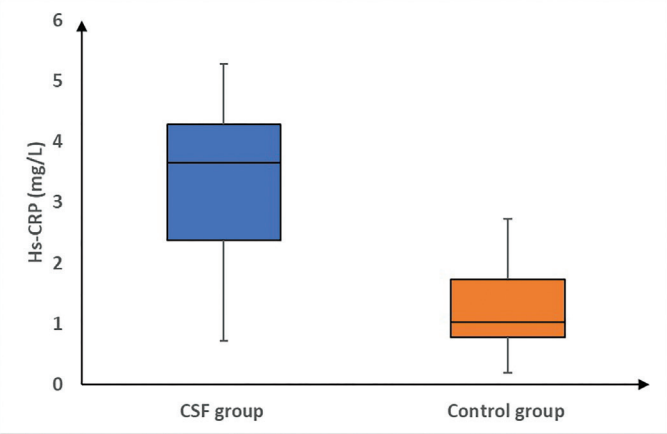


Figure 2. hs-CRP of the studied groups

CSF: Coronary slow flow, hs-CRP: High-sensitive C-reactive protein

Moawad et al.[11] conducted a comprehensive meta-analysis confirming that elevated hs-CRP levels are significant predictors of CSF, no-reflow, and high thrombus burden, thereby supporting inflammation as a fundamental pathophysiological mechanism.

The lack of significant differences in metabolic parameters between CSF cases and controls suggests that traditional risk factors may not be primary contributors, whereas Wen et al.[7] identified the inflammatory burden index as an independent predictor, highlighting the metabolic-inflammatory interface in the condition.

The observed increase in CIMT in CSF cases reflects a broader pattern of systemic vascular pathology that extends beyond the coronary circulation. This finding suggests that CSF may represent a manifestation of generalized arterial disease rather than an isolated coronary microvascular disorder. The increased CIMT observed in our study population indicates structural vascular changes that are characteristic of early atherosclerotic processes, which supports the hypothesis that CSF cases exhibit accelerated vascular aging and an increased CVS risk profile.

Significantly elevated arterial stiffness parameters in CSF cases, as demonstrated by Yang et al.[12] using echo-tracking technology, indicate impaired vascular elasticity and are positively correlated with hs-CRP levels, suggesting that inflammation contributes to vascular structural changes. Similarly, Yang et al.[13] demonstrated elevated carotid artery stiffness parameters in CSF cases and found that these measures independently predicted the condition.

The reduced arterial compliance, as evidenced by decreased distensibility and compliance coefficients in our study population, reflects functional impairment of vascular elastic properties. This pattern is consistent with Wang et al.[14] who reported significantly higher elastic modulus values in CSF cases compared with healthy controls, with differences persisting after adjustment for age and smoking status.

Table 3. Carotid artery ultrasound and stiffness measurement of the studied groups

	CSF group (n=30)	Control group (n=30)	*P*-value	MD (95% CI)
Carotid intima-media thickness (mm)	0.82±0.24	0.68±0.19	**0.012***	0.15 (0.03 to 0.26)
Systolic diameter (mm)	6.12±0.65	5.81±0.83	0.115	0.31 (-0.08 to 0.69)
Diastolic diameter (mm)	5.54±0.69	5.37±0.7	0.368	0.16 (-0.2 to 0.52)
β-stiffness index	7.68±2.71	6.04±1.62	**0.006***	1.64 (0.48 to 2.8)
Peterson's elastic modulus (kPa)	637.33±279.7	379.67±249.81	**<0.001***	257.7 (120.6 to 394.7)
Distensibility coefficient (10^{-3} kPa)	19.8±1.07	23.04±7.35	**0.02***	-3.24 (-5.95 to -0.52)
Compliance coefficient (mm^2 kPa^{-1})	5.24±4.69	7.19±1.82	**0.038***	-1.95 (-3.79 to -0.11)
Strain (%)	7.33±1.86	8.58±2.24	**0.022***	-1.25 (-2.31 to -0.18)

Data are presented as mean ± standard deviation

CSF: Coronary slow flow, MD: Mean difference, CI: Confidence interval, *: Statistically significant $P < 0.05$

This association between hypertension and CSF is supported by the broader understanding of hypertension as a systemic vascular disorder that affects both large and small vessels. Shroff et al.[15] demonstrated relationships between arterial stiffness and CVS biomarkers, including hs-CRP, suggesting that arterial stiffness, inflammation, and cardiac function are interconnected processes.

Low-grade inflammation may facilitate carotid remodeling via endothelial activation, diminished nitric oxide bioavailability, oxidative stress, and upregulated pathways that enhance vascular smooth muscle proliferation and extracellular matrix turnover (e.g., elevated collagen levels and compromised elastin integrity), which collectively result in increased arterial stiffness. Discrepancies among published research may indicate changes in inclusion criteria, comorbidities (notably hypertension), and the exact vascular measures employed.

In our cohort, traditional metabolic parameters were similar between groups. However, because blood pressure/hypertension burden was higher in the CSF group, we performed adjusted analyses to avoid attributing stiffness differences solely to CSF status. The observational design also cannot determine temporality; inflammation and stiffness may precede CSF, arise concurrently from shared vascular pathology, or represent downstream consequences of microvascular dysfunction.

From a clinical standpoint, carotid stiffness indices may complement hs-CRP by reflecting vascular target-organ

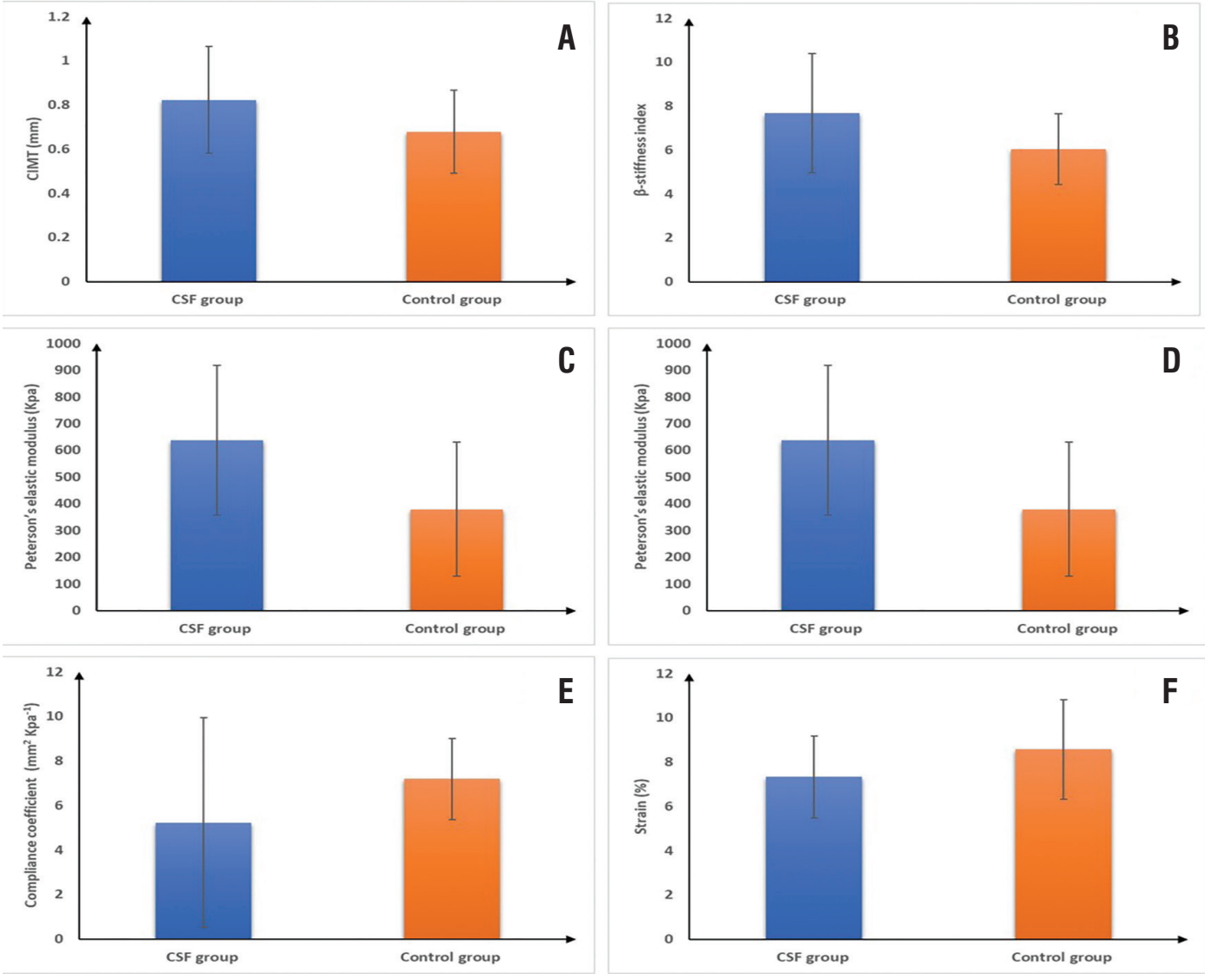


Figure 3. (A) CIMT (B) β-stiffness index (C) Peterson's elastic modulus (D) distensibility coefficient (E) compliance coefficient (F) strain of the studied groups

CIMT: Carotid intima-media thickness, CSF: Coronary slow flow

Table 4. Univariate and multivariate regression of different variables versus occurrence of coronary slow flow

	Univariate			Multivariate		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Body mass index	0.903	0.794 to 1.03	0.121	-	-	-
Hypertension	3.051	1.05 to 8.84	**0.039***	0.014	0 to 2.63	0.109
Systolic blood pressure	1.052	1.01 to 1.09	**0.015***	1.49	0.992 to 2.25	0.055
Diastolic blood pressure	1.081	1.022 to 1.14	**0.006***	1.49	1.04 to 2.11	**0.028***
High-sensitive C-reactive protein	5.65	2.36 to 13.57	**<0.001***	14.90	2.56 to 86.87	**0.003***
Carotid intima-media thickness	22.48	1.77 to 284.79	**0.016***	38.78	1.6637 to 903.96	**0.023***
β-stiffness index	1.39	1.08 to 1.79	**0.010***	1.58	1.11 to 2.23	**0.01***
Peterson's elastic modulus	1.004	1.001 to 1.01	**0.002***	1.01	1.002 to 1.01	**0.001***

*: Statistically significant $P < 0.05$, CI: Confidence interval, OR: Odds ratio

involvement; however, whether stiffness provides incremental prognostic value beyond hs-CRP in CSF patients requires larger prospective studies with hard clinical endpoints.

Study Limitations

First, it was a single-center case-control study with a modest sample size; the pilot-based sample size estimation (n=5 per group) may have inflated the expected effect size, potentially reducing power to detect smaller true differences and widening confidence intervals. Second, CSF was defined using cTFC, an angiographic surrogate that does not directly quantify coronary microvascular function; the absence of invasive physiological assessment (e.g., coronary flow reserve or index of microcirculatory resistance) may have introduced misclassification and diluted associations. Finally, the cross-sectional design precludes causal inference and does not establish whether inflammation, arterial stiffness, or both precede CSF or occur concomitantly.

CONCLUSION

CSF cases showed significantly higher hs-CRP levels, increased carotid stiffness (elevated CIMT, β-stiffness index, and Peterson's modulus), reduced distensibility and compliance, and a higher prevalence of hypertension, highlighting systemic inflammation and vascular dysfunction that may serve as biomarkers of vascular pathology and guide risk stratification and management in CSF.

Ethics

Ethics Committee Approval: The Institutional Review Board/Ethics Committee of Sohag University accepted the study protocol (approval no: Soh-Med-25-5-6PD, date: 12.05.2025).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment, and the study was conducted in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.S.A., S.P.A., Concept: R.S.A., S.P.A., Design: S.M.T., A.I.B., Data Collection or Processing: R.S.A., S.M.T., A.I.B., Analysis or Interpretation: S.M.T., A.I.B., Literature Search: R.S.A., A.I.B., Writing: S.M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Bond RM, Ivy K, Crumbs T, Purewal V, Obang S, Sraow DIS. Coronary microvascular dysfunction and its role in heart failure with preserved ejection fraction for future prevention and treatment. Am J Prev Cardiol. 2025;22:100983.
2. Chalikias G, Tziakas D. Slow coronary flow: pathophysiology, clinical implications, and therapeutic management. Angiology. 2021;72:808-18.
3. Mehta A, Blumenthal RS, Gluckman TJ, Feldman DI, Kohli P. High-sensitivity C-reactive protein in atherosclerotic cardiovascular disease: to measure or not to measure? US Cardiol. 2025;19:e06.
4. Barutcu I, Sezgin AT, Sezgin N, Gullu H, Esen AM, Topal E, *et al*. Increased high sensitive CRP level and its significance in pathogenesis of slow coronary flow. Angiology. 2007;58:401-7.
5. Ardahanli I, Özmen M. C-reactive protein to albumin ratio may be an inflammatory indicator for the coronary slow flow phenomenon. Lokman Hekim Health Sci. 2023;3:32-7.
6. Karauzum K, Karauzum I, Hanci K, Gokcek D, Gunay B, Bakhshian H, *et al*. The systemic immune-inflammation index may predict the coronary slow flow better than high-sensitivity C-reactive protein in patients undergoing elective coronary angiography. Cardiol Res Pract. 2022;2022:7344639.
7. Wen ZG, Long JJ, Wang Y. Association between inflammatory burden index and coronary slow flow phenomenon in patients with chest pain and no obstructive coronary arteries. BMC Cardiovasc Disord. 2024;24:595.
8. Triantafyllias K, Thiele LE, Mandel A, Cavagna L, Baraliakos X, Bertsias G, *et al*. Arterial stiffness as a surrogate marker of cardiovascular disease and atherosclerosis in patients with vasculitides: a literature review. Diagnostics (Basel). 2023;13:3603.

9. Pewowaruk R, Korcarz CE, Bluemke DA, Hamdan MH, Heckbert SR, Lima JAC, *et al*. Carotid artery stiffness mechanisms, heart failure events, and atrial fibrillation in MESA: the Multi-Ethnic Study of Atherosclerosis. Am J Physiol Heart Circ Physiol. 2025;328:H1019-25.

10. Dogan Z, Ileri C, Ozben B, Sunbul M, Tigen MK, Sahin O, *et al*. Evaluation of arterial stiffness and subfoveal choroidal thickness in patients with coronary slow flow. Acta Cardiol Sin. 2023;39:733-41.

11. Moawad MHED, Mektebi A, Tanashat M, Altobaishat O, Abbas A, Ramadan A, *et al*. Use of inflammatory biomarkers as predictors of blood flow and thrombus burden in coronary artery disease patients. JAPAJ. 2023:1-58.

12. Yang S, Wang DZ, Zhang HX, He W, Chen BX. Echo-tracking technology assessment of carotid artery stiffness in patients with coronary slow flow. Ultrasound Med Biol. 2015;41:72-6.

13. Yang S, He W, Li Y, Wang FM, Yin L, Du LJ. Relationship between carotid artery stiffness and total serum homocysteine in coronary slow flow phenomenon: a high-resolution echo-tracking study. Quant Imaging Med Surg. 2022;12:2767-76.

14. Wang YH, Kang YQ, Jin XY, Meng PP, Guan ZY, Jia DL, *et al*. Reference values of the carotid elastic modulus using shear wave elastography and arterial stiffness change in coronary slow flow. Eur J Radiol. 2022;157:110582.

15. Shroff GR, Cen YY, Duprez DA, Bart BA. Relationship between carotid artery stiffness index, BNP and high-sensitivity CRP. J Hum Hypertens. 2009;23:783-7.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2026.58561
Int J Cardiovasc Acad 2026;12(1):47-54

The Clinical Spectrum and Management of Patients with Coronary in-stent Restenosis

Abdelmoamen M. Aboborda[1], Mohamed Abdelghany[1], Ahmed T. Elgengehe[1], Fathy M. Swailem[2], Reham Darweesh[1]

[1]Department of Cardiovascular Medicine, Cairo University Faculty of Medicine, Cairo, Egypt
[2]Department of Cardiovascular Medicine, Benha University Faculty of Medicine, Benha, Egypt

Abstract

Background and Aim: In-stent restenosis (ISR) remains a clinically important limitation of percutaneous coronary intervention (PCI), contributing to recurrent ischemia, repeat revascularization, and adverse outcomes. Despite the widespread use of drug-eluting stents, ISR persists. This study aims to evaluate the prevalence, clinical spectrum, and predictors of ISR in a contemporary tertiary-care setting.

Materials and Methods: A retrospective-prospective observational study was conducted between November 2018 and November 2019. Among 350 angiographic records reviewed, 100 patients with prior PCI were included in the study and underwent clinically driven coronary angiography. ISR was defined as ≥50% luminal narrowing within or adjacent to the stented segment and was classified as focal or non-focal according to the Mehran system. Demographic, clinical, and procedural data were analyzed.

Results: ISR was identified in 50 patients (50%); 38 patients (38%) required target lesion revascularization. Factors associated with ISR included male sex (90% vs. 46%, $P < 0.001$); diabetes mellitus (72% vs. 38%, $P < 0.001$); longer stent length (25.4±9.2 vs. 20.3±4.9 mm, $P < 0.001$); smaller stent diameter (3.02±0.40 vs. 3.41±0.29 mm, $P < 0.001$); and left anterior descending artery (LAD) involvement (52% vs. 10%, $P = 0.002$). Diffuse ISR was present in 46% of patients and was significantly associated with LAD (78.3%) and right coronary artery (56.5%) lesions, smaller vessel size, longer stents, and adverse outcomes, including one death.

Conclusion: ISR affected half of the patients undergoing clinically indicated repeat angiography and was associated primarily with procedural and angiographic characteristics, including smaller vessel caliber, longer stent length, and LAD involvement.

Keywords: In-stent restenosis, drug-eluting stents, coronary arteries, angiography

INTRODUCTION

The advent of percutaneous coronary intervention (PCI) with stenting has fundamentally reshaped strategies for coronary artery disease care, ensuring durable relief from ischemia and diminishing the likelihood of subsequent acute coronary syndromes (ACS).[1] However, despite advances in stent technology, in-stent restenosis (ISR) remains a clinically significant problem. ISR refers to the restenosis of a previously stented coronary segment and, although its incidence has declined with drug-eluting stents (DES) use, continues to account for a considerable proportion of PCI failures worldwide. The clinical burden of ISR is substantial, as it not only necessitates repeat revascularization procedures but also contributes to recurrent angina, myocardial infarction, and increased healthcare costs.[2]

To cite this article: Aboborda AM, Abdelghany M, Elgengehe AT, Swailem FM, Darweesh R. The clinical spectrum and management of patients with coronary in-stent restenosis. Int J Cardiovasc Acad. 2026;12(1):47-54

Address for Correspondence: Abdelmoamen M. Aboborda MD, Department of Cardiovascular Medicine, Cairo University Faculty of Medicine, Cairo, Egypt
E-mail: Drmomen79@gmail.com
ORCID ID: orcid.org/0009-0009-6922-6511

Received: 09.09.2025
Accepted: 16.01.2026
Epub: 17.02.2026
Publication Date: 10.03.2026

The pathophysiology of ISR is multifactorial, involving neointimal hyperplasia, stent underexpansion, vascular remodeling, and, in certain patients, neoatherosclerosis. Various clinical and procedural risk factors such as diabetes mellitus (DM), vessel size, stent length, and lesion location have been consistently associated with ISR. Moreover, the angiographic patterns of ISR—ranging from focal to diffuse proliferative lesions—carry important prognostic implications, as diffuse forms are often more challenging to treat and are associated with higher rates of adverse cardiovascular (CV) events. Thus, understanding the clinical spectrum of ISR and identifying its predictors remain critical for optimizing PCI outcomes in contemporary practice.[3]

The management of ISR poses therapeutic challenges, as the available treatment options—including balloon angioplasty, repeat stenting with DES, drug-coated balloons, and, in selected patients, coronary artery bypass grafting—are influenced by patient characteristics, lesion morphology, and prior procedural details. Contemporary studies suggest that individualized management strategies are essential to improving clinical outcomes and reducing recurrence, yet data remain heterogeneous, especially in resource-limited or real-world tertiary-care settings.[4]

Given these considerations, it is essential to evaluate ISR within different populations and healthcare systems to refine risk stratification and guide management strategies. Because the study population consisted solely of patients undergoing clinically indicated repeat coronary angiography (CAG), the observed ISR prevalence reflects a high-risk, symptom-driven cohort rather than routine post-PCI surveillance.

Therefore, the present study aims to determine the prevalence of ISR among patients with prior PCI who present for clinically indicated CAG at a tertiary referral center and to identify the procedural and clinical predictors associated with its occurrence and angiographic patterns.

METHODS

This study followed a retrospective cohort design with prospective follow-up. Angiographic and procedural data from prior PCI were collected retrospectively, while patients presenting during the study period were prospectively evaluated when undergoing clinically indicated CAG (conducted at Al-Nahda Hospital, Taif, Kingdom of Saudi Arabia, over a 12-month period from November 2018 to November 2019).

Ethical approval was obtained from the Institutional Review Board of Faculty of Medicine Cairo University (approval no: CMDRF132701/2018, date: 16.01.2018) and all patients provided written informed consent prior to enrollment.

Eligibility Criteria

Patients were eligible if they had previously undergone PCI with stent implantation and were subsequently referred for clinically driven CAG during the study period. Because all included patients were referred specifically for clinically indicated CAG due to recurrent symptoms or objective evidence of ischemia, this cohort represents a high-risk diagnostic subset, and the observed ISR prevalence therefore does not reflect that of the general post-PCI population. Patients were excluded if they had chronic total occlusions, stent thrombosis, restenosis in bypass grafts, or incomplete angiographic or procedural data related to their prior PCI.

Clinical and Laboratory Assessment

Clinical evaluation included demographic data, CV risk factors, and presenting symptoms. Laboratory investigations comprised serum creatinine, creatinine clearance, lipid profile, and cardiac biomarkers. All participants underwent a 12-lead electrocardiogram and transthoracic echocardiography to assess left ventricular function and wall motion abnormalities.

Angiographic and Procedural Assessment

Diagnostic CAG followed conventional methodology, and quantitative coronary angiographic assessment was conducted at the stented sites. Parameters analyzed included reference vessel diameter, lesion length, minimal lumen diameter (MLD), and percentage stenosis. ISR was defined as luminal narrowing of at least 50% within the stent or in the adjacent 5 mm segments. ISR severity and stenosis measurements were assessed using quantitative coronary angiography (QCA) when available and visually estimated by experienced operators when QCA was not feasible.

Lesions were further categorized according to the Mehran classification as focal or non-focal (diffuse, proliferative, or occlusive) patterns. ISR patterns were classified independently by two interventional cardiologists, with any discrepancies resolved by consensus. Procedural details of the initial PCI—including stent type, diameter, length, deployment pressure, and use of pre- or post-dilatation balloons—were retrieved from hospital records whenever available.

Management and Follow-up

Management strategies were individualized according to clinical presentation and angiographic findings. Patients with ISR underwent percutaneous interventions, including balloon angioplasty and repeat stenting; surgical referral was considered for selected complex patients. Follow-up data up to six months were collected when available; follow-up data were incomplete for a subset of patients; therefore, time-to-event analyses were interpreted cautiously.

Outcomes

The primary outcome of the study was the prevalence of ISR among patients with prior PCI undergoing clinically indicated CAG. Secondary outcomes included identification of clinical and procedural predictors of ISR, comparison of angiographic patterns between focal and non-focal ISR, and evaluation of 6-month clinical outcomes including recurrent ischemic symptoms, revascularization, and mortality.

Statistical Analysis

Statistical processing was carried out in SPSS version 23.0 (IBM Corp., Chicago, IL, USA). The Shapiro-Wilk test and histograms were used to evaluate the normality of the data distribution. Normally distributed continuous data were presented as mean ± standard deviation, whereas skewed data were summarized as median (range). For between-group comparisons, the independent t-test was applied to parametric variables, while the Mann-Whitney U test was used for non-parametric variables. Categorical outcomes were tabulated as frequencies and percentages and compared using the chi-square test or Fisher's exact test when appropriate. Significance was set at a two-sided threshold of 0.05. Univariate regression was used to estimate the relationship between a dependent variable and one independent variable. Multivariate regression was also used to estimate the relationship between a dependent variable and multiple independent variables. A Kaplan-Meier curve was used to show the time to first postoperative analgesic requirement.

RESULTS

A total of 100 patients with a history of PCI who underwent clinically driven CAG were included in the study. The cohort consisted of 32 females (32%) and 68 males (68%), with a mean age of 53±10 years. Based on angiographic findings, patients were stratified into two groups: 50 patients with documented ISR and 50 patients without ISR. The ISR group was further categorized according to lesion morphology into focal ISR (27 lesions, including 16 at the stent edge and 11 within the stent body) and non-focal ISR (23 lesions, comprising 10 occlusive, 8 diffuse, and 5 proliferative patterns).

With regard to demographic variables, age, sex, family history, smoking, dyslipidemia, hypertension, and DM were not statistically significant. ISR patients had substantially smaller stent diameters, longer stent lengths, more frequent left anterior descending artery (LAD) involvement, and more frequent use of pre- and post-dilatation balloons. Other variables, including residual stenosis, dissection, thrombolysis in myocardial infarction (TIMI) flow, calcification, right coronary artery (RCA) involvement, circumflex artery (CX) involvement, diagonal lesions, obtuse marginal (OM) lesions, ramus lesions, saphenous vein graft (SVG) lesions, and number of stents implanted, were not statistically significant (Table 1).

ISR lesions demonstrated markedly smaller MLDs. Other angiographic parameters, including *de novo* PCI, type B2/C lesions, area stenosis, diameter stenosis, maximum lumen area, maximum lumen diameter, minimum lumen area, lesion length, average reference area, distal reference area, proximal reference area, average reference diameter, distal reference diameter, and proximal reference diameter, were not statistically significant. Regarding outcomes, differences in target lesion revascularization, ACS, and mortality were not statistically significant (Table 2).

Diffuse ISR was associated with notably smaller stent diameters, longer stent lengths, more frequent involvement of the LAD and RCA, and greater use of pre- and post-dilatation balloons. Other variables, including residual stenosis, dissection, TIMI flow, calcification, CX lesions, diagonal lesions, OM lesions, ramus lesions, SVG lesions, and number of stents, were not statistically significant (Table 3).

Diffuse ISR was characterized by significantly smaller distal reference diameters and areas, and a reduced average reference diameter. Other parameters, including proximal reference diameters and average reference areas, were not statistically significant (Table 4).

In univariate regression analysis, stent diameter, stent length, post-dilatation balloon use, and pre-dilatation balloon use were significantly associated with ISR, whereas age and smoking were not. In multivariate regression analysis, stent diameter, stent length, and pre-dilatation balloon were variables independently associated in multivariable analysis of ISR, whereas post-dilatation balloon was not (Table 5).

DISCUSSION

ISR continues to represent a major limitation of PCI, despite advances in stent design and drug-eluting technology. The clinical importance of ISR lies in its contribution to recurrent ischemia, repeat revascularization, and adverse CV outcomes. Numerous studies have attempted to identify predictors of ISR and clarify its angiographic patterns, yet variations in patient characteristics, stent types, and procedural techniques yield conflicting data. In this context, our results merit comparison with prior literature to better delineate the clinical and procedural determinants of ISR and to place our findings in the context of global evidence.[4]

Table 1. Previous procedural data differences between patients with and without ISR

		ISR (n=50)	No ISR (n=50)	*P*	MD/RR (95% CI)
Age (years)		56.58±10.28	56.77±9.03	0.925	-0.19 (-4.03 to 3.65)
Sex	**Male**	44 (88%)	43 (86%)	0.668	1.02 (0.88 to 1.19)
	Female	6 (12%)	7 (14%)		
Family history		4 (8%)	4 (8%)	1	1 (0.26 to 3.78)
Smoking		36 (72%)	33 (66%)	0.668	1.09 (0.84 to 1.42)
Dyslipidemia		34 (68%)	38 (76%)	0.668	0.89 (0.7 to 1.14)
Hypertension		37 (74%)	35 (70%)	0.668	1.06 (0.83 to 1.35)
Diabetes mellitus		36 (72%)	39 (78%)	0.668	0.92 (0.74 to 1.16)
Residual stenosis		3 (6%)	0 (0%)	0.242	2.06 (1.68 to 2.53)
Dissection		2 (4%)	1 (2%)	1	0.97 (0.429 to 2.19)
TIMI					
2		1 (2%)	2 (4%)	1	0.22 (0.034 to 1.41)
3		49 (98%)	48 (96%)		
Calcification		6 (12%)	4 (8%)	0.741	1.22 (0.709 to 2.12)
Post-dilatation balloon		8 (16%)	1 (2%)	**0.031***	1.92 (1.39 to 2.65)
Pre-dilatation balloon		8 (16%)	1 (2%)	**0.031***	1.92 (1.39 to 2.65)
Pressure of deployment (atm)		15.68±1.82	16.31±1.92	0.095	0.63 (-0.10 to 1.36)
Stent diameter (mm)		3.02±0.4	3.41±0.29	**<0.001***	0.39 (0.25 to 0.53)
Stent length (mm)		25.44±9.22	20.31±4.88	**<0.001***	-5.13 (-8.02 to -2.24)
Site					
LAD		26 (52%)	5 (10%)	**0.002***	2.41 (1.68 to 3.45)
RCA		20 (40%)	27 (54%)	0.132	0.751 (0.50 to 1.130)
CX		8 (16%)	16 (32%)	0.787	0.587 (0.322 to 1.07)
Diagonal		2 (4%)	1 (2%)	0.557	1.34 (0.590 to 3.07)
OM		3 (6%)	1 (2%)	0.307	1.53 (0.839 to 2.79)
Ramus		1 (2%)	0 (0%)	1	2.02 (1.65 to 2.46)
SVG		1 (2%)	0 (0%)	1	2.02 (1.65 to 2.46)
Number of stents					
1		28 (56%)	31 (62%)	0.241	-
2		17 (34%)	18 (36%)		
3		5 (10%)	1 (2%)		

*: Significant *P*-value, ISR: In-stent restenosis, MD: Mean difference, RR: Relative risk, CI: Confidence interval, TIMI: Thrombolysis in myocardial infarction, LAD: Left anterior descending artery, RCA: Right coronary artery, CX: Circumflex artery, OM: Obtuse marginal, SVG: Saphenous vein graft, atm: Atmosphere, n: Number

Table 2. Procedural and quantitative CAG characteristics in patients with and without ISR

	ISR (n=50)	No ISR (n=50)	*P*	MD/RR (95% CI)
***De novo* PCI**	9 (18%)	28 (56%)	0.79	3.11 (5.95 to 1.62)
Type B2/C lesions	6 (66.66%)	11 (39%)	0.08	0.58 (1.25 to 0.27)
Area stenosis %	79.11±18.2	74.32±17.9	0.188	-4.79 (-12.11 to 2.53)
Diameter stenosis %	73.18±20.6	71.63±19.7	0.701	-1.55 (-9.52 to 6.42)
Max LA (mm²)	4.93 (0-11.94)	5.12 (0-10.71)	0.617	0.19 (-1.5 to 1.9)
Max LD (mm)	2.365 (0-3.9)	2.381 (0-4.1)	0.336	0.016 (-0.35 to 0.38)
MLA (mm²)	1.47±0.75	2.86±1.21	0.897	1.39 (0.88 to 1.90)
MLD (mm)	0.98±0.44	1.91±0.69	**<0.001***	0.93 (0.59 to 1.27)

Table 2. Continued

	ISR (n=50)	No ISR (n=50)	*P*	MD/RR (95% CI)
Lesion length (mm)	35.9±19.7	38.4±20.8	0.429	2.5 (-5.32 to 10.32)
Average reference area (mm²)	7.04±2.69	7.12±2.77	0.884	0.08 (-0.81 to 0.97)
Distal reference area (mm²)	3.97 (0-16.6)	4.21 (0-15.8)	0.692	0.24 (-2.5 to 3.0)
Proximal reference area (mm²)	9.82±3.11	9.71±3.07	0.859	-0.11 (-0.18 to 0.93)
Average reference diameter (mm)	2.77±0.69	2.82±0.70	0.72	0.05 (-0.18 to 0.28)
Distal reference diameter (mm)	2.06±1.09	2.22±1.21	0.489	0.16 (-0.26 to 0.58)
Proximal reference diameter (mm)	3.48±0.62	3.32±0.59	0.189	-0.16 (-0.4 to 0.12)
Outcomes				
TLR	8 (16%)	2 (4%)	0.092	1.71 (1.17 to 2.51)
ACS	6 (12%)	2 (4%)	0.268	1.56 (0.99 to 2.46)
Mortality	3 (6%)	1 (2%)	0.31	1.532 (0.839 to 2.79)

*: Significant *P*-value, ISR: In-stent restenosis, PCI: Percutaneous coronary intervention, CI: Confidence interval, CAG: Coronary angiography, Max LA: Maximum lumen area, Max LD: Maximum lumen diameter, MLA: Minimum lumen area, MLD: Minimal lumen diameter, n: Number, TLR: Target lesion revascularization, ACS: Acute coronary syndrome, MD: Mean or median difference, RR: Relative risk

Table 3. Procedural differences between focal and diffuse ISR following PCI

	Focal (n=27)	No focal (n=23)	*P*	MD/RR (95% CI)
Residual stenosis	0 (0%)	3 (13.0%)	0.235	0 (0 to 0)
Dissection	0 (0%)	2 (8.7%)	0.490	0 (0 to 0)
TIMI				
2	0	1	0.460	0 (0 to 0)
3	27 (100%)	22 (95.6)		
Calcification	3 (11.1%)	3 (13.0%)	1	0.916 (0.393 to 2.13)
Post-dilatation balloon	1 (3.7%)	7 (30.4%)	**0.01***	0.201 (0.031 to 1.28)
Pre-dilatation balloon	1 (3.7%)	7 (30.4%)	**0.01***	0.201 (0.031 to 1.28)
Deployment pressure (atm)	15.93±2.04	15.39±1.53	0.306	
Diameter (mm)	3.04±0.31	2.62±0.56	**0.002***	-0.42 (-0.63 to -0.21)
Length (mm)	22.11±7.91	29.35±9.26	**0.005***	7.24 (2.95 to 11.53)
Site				
LAD	8 (29.6%)	18 (78.3%)	**<0.001***	0.388 (0.210 to 0.716)
RCA	7 (25.9%)	13 (56.5%)	**0.028***	0.525 (0.274 to 1.004)
CX	4 (14.8%)	4 (17.4%)	1	0.913 (0.433 to 1.92)
Diagonal	2 (7.4%)	0 (0%)	0.183	1.92 (1.46 to 2.51)
OM	3 (11.1%)	0 (0%)	0.239	1.95 (1.48 to 2.59)
Ramus	1 (3.7%)	0 (0%)	1	1.85 (1.44 to 2.45)
SVG	1 (3.7%)	0 (0%)	1	1.85 (1.44 to 2.45)
Number of stents				
≥2	10	12	0.284	
1	17	11		

*: Significant *P*-value, ISR: In-stent restenosis, PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction, LAD: Left anterior descending artery, RCA: Right coronary artery, CX: Circumflex artery, OM: Obtuse marginal, SVG: Saphenous vein graft, atm: Atmosphere, n: Number, MD: Mean difference, RR: Relative risk, CI: Confidence interval

Table 4. Qualitative CAG measurements of area and diameter in focal versus diffuse ISR

	Focal (n=27)	No focal (n=23)	*P*	MD (95% CI)
Average reference diameter (mm)	2.97±0.46	2.54±0.83	***0.024**	-0.43 (-0.77 to -0.09)
Distal reference diameter (mm)	2.51±0.51	1.54±1.37	***0.001**	-0.97 (-1.51 to -0.43)
Proximal reference diameter (mm)	3.44±0.49	3.53±0.75	0.611	0.06 (3.61 to 3.36)
Average reference area (mm²)	7.29±2.09	6.74±3.29	0.468	0.276 (6.47 to 7.56)
Distal reference area (mm²)	5.12±1.98	3.27±4.01	**0.039***	0.316 (3.57 to 4.82)
Proximal reference area (mm²)	9.48±2.55	10.21±3.68	0.409	0.73 (9.22 to 10.47)

*: Significant *P*-value, CAG: Coronary angiography, ISR: In-stent restenosis, n: Number, MD: Mean difference

Table 5. Univariate and multivariate regression of age, stent diameter, stent length, smoking, post-dilatation balloon and pre-dilatation balloon versus ISR

	Univariate			Multivariate		
	Odds ratio	**95% CI**	***P***	**Odds ratio**	**95% CI**	***P***
Age	0.998	0.957 to 1.04	0.923	-	-	-
Stent diameter	0.0813	0.025 to 0.26	**<0.001***	0.0711	0.018 to 0.276	**0.001***
Stent length	1.078	1.02 to 1.134	**0.002***	1.0926	1.027 to 1.16	**0.004***
Smoking	0.754	0.322 to 1.76	0.516	-	-	-
Post-dilatation balloon	0.107	0.012 to 0.89	**0.009***	0.1497	0.0084 to 2.67	0.196
Pre-dilatation balloon	0.107	0.012 to 0.89	**0.009***	0.0798	0.006 to 0.934	**0.044***

*: Significant as *P*-value ≤0.05, ISR: In-stent restenosis, CI: Confidence interval

Differences in ISR prevalence and associated factors compared with earlier cohorts may relate to the high-risk symptomatic population included, variability in DES generations implanted, longer intervals since index PCI, and procedural practices specific to this tertiary-care setting.

In the present study, ISR was documented in 50% of patients with prior PCI. This prevalence reflects the selective nature of our cohort, which included only patients undergoing clinically indicated repeat angiography rather than for routine surveillance, and therefore should not be interpreted as the general prevalence of ISR. All associations identified in this study should be interpreted cautiously, as they are derived from largely unadjusted analyses in a modest sample size.

Several angiographic and procedural factors were associated with ISR, including smaller stent diameter, longer stent length, and LAD involvement. Because baseline clinical follow-up data were incomplete for some patients, six-month outcome analyses could not be reliably performed; consequently, statements implying quantitative follow-up findings were removed to maintain scientific accuracy.

Regarding the prevalence of ISR, our observed prevalence of 50% was higher than the 35% reported by Mercado et al.[5] among 8,000 patients and the 32.5% reported by Reifart et al.[6] among 6,000 patients. Angiographic restenosis rates of 32-40% within 6 months after angioplasty have also been described.[7,8] The higher prevalence in our series may be explained by the strict inclusion criteria that required complete prior PCI data, and by the longer interval between index PCI and repeat angiography in many patients.

Regarding gender differences, we found ISR to be significantly more common among males, a finding that contrasted with Tang et al.[9] who reported a higher risk in females. Conversely, other studies, such as Cassese et al.[10] and Mercado et al.[5] did not find a significant sex-related difference, underscoring ongoing heterogeneity across populations.

Regarding DM, our data confirmed that it was one of the factors associated with ISR, consistent with Cassese et al.[10] Mercado et al.[5] and Lee et al.[11] who reported restenosis rates of 40-60% among DM patients. In contrast, Park and Park[12] reported that DM was not a significant predictor of ISR after DES implantation, suggesting that the prognostic weight of DM may differ between stent eras and patient subsets.

In our series, LAD lesions were significantly associated with ISR, consistent with prior reports. A study of 2,500 patients found an odds ratio (OR) of 1.7 (95% confidence interval 1.5-2.1) for proximal LAD lesions,[13] whereas another, evaluating 1,399 stented lesions, reported an OR of 1.31 for LAD involvement.[14] However, other investigators have shown no association between lesion site and ISR risk,[15] which reflects variability in angiographic contexts.

Regarding stent length and diameter, our findings that longer stent length and smaller stent diameter predicted ISR concur with Kobayashi et al.[16] who reported progressively higher restenosis rates with increasing stent length across 1,090 lesions, and with pooled analyses of four multi-link stent trials that demonstrated an OR of 1.04 per millimeter increase in stent length.[17] Cassese et al.[10] Lee et al.[11] and Mercado et al.[5] similarly documented strong associations between stent morphology and restenosis risk.

Regarding balloon dilatation, the increased ISR risk observed with pre- and post-dilatation balloon inflations in our cohort aligns with prior studies identifying multiple balloon inflations (≥3)[15,18] and higher inflation pressures (>7 atmosphere) as contributors to restenosis. This suggests that greater mechanical trauma may amplify neointimal proliferation and late lumen loss.

A smaller pre-stenting MLD was one of the strongest predictors of ISR in our series, supporting the findings of Park and Park[12] and Kang et al.[19] who similarly identified baseline lumen size as a robust angiographic determinant of restenosis after PCI.

Diffuse-type ISR was found in 46% of ISR patients and was significantly associated with DM, male sex, LAD and RCA lesions, longer stents, and smaller pre-stenting MLD. These findings are consistent with those of Lee et al.[11] Cassese et al.[10] and Mercado et al.[5] who reported DM and smaller vessel size as predictors of diffuse ISR. However, Park and Park[12] observed no significant association between DM and diffuse ISR (19.6% vs. 28.7%, $P = 0.221$), highlighting discrepancies across datasets. Goldberg et al.[20] further demonstrated that diffuse ISR was associated with smaller reference vessel diameter and longer lesion length; these findings are consistent with our results.

Recent evidence (2020-2024) has further emphasized the evolving epidemiology and management of ISR, highlighting variations across DES generations and in contemporary PCI practices.[2,21,22]

All associations identified in this study should be interpreted cautiously, as they are derived from unadjusted analyses.

Study Limitations

This study has several important limitations that should be considered when interpreting the findings. First, the sample size was modest (n=100; ISR events=50), and no a priori sample size or power calculation was performed; therefore, the study may be underpowered for some comparisons, particularly multivariable modeling, with an increased risk of model overfitting, imprecise effect estimates (wide CIs), and a limited ability to adjust for multiple potential confounders. Second, the focal versus non-focal (diffuse, proliferative, or occlusive) subgroup comparisons were primarily exploratory and largely unadjusted; given the small subgroup counts, comprehensive multivariable adjustment was not feasible, and residual confounding cannot be excluded.

Third, the cohort was restricted to patients undergoing clinically indicated repeat angiography at a single tertiary center, introducing selection and referral biases and limiting generalizability to broader post-PCI populations or to routine surveillance cohorts. Fourth, angiographic assessment relied on QCA when available and on visual estimation otherwise; intravascular imaging (intravascular ultrasound/optical coherence tomography) was not used systematically, which may have led to misclassification of lesion morphology and failure to identify certain mechanisms. Finally, follow-up was short and incomplete for a subset of patients, limiting robust time-to-event analyses and inference regarding longer-term outcomes. Accordingly, the present results should be viewed as hypothesis-generating and warrant confirmation in larger, adequately powered, multicenter studies with standardized imaging and complete longitudinal follow-up. Given the number of ISR events (n=50), inclusion of multiple variables in multivariable modeling may increase the risk of overfitting, and effect estimates should therefore be interpreted with caution.

CONCLUSION

ISR affected half of the patients undergoing clinically indicated repeat angiography and was associated primarily with procedural and angiographic characteristics, including smaller vessel caliber, longer stent length, and LAD involvement. Diffuse ISR showed a trend toward more adverse angiographic characteristics; however, outcome differences were not statistically significant. These findings highlight the need for careful procedural planning and closer follow-up in patients with high-risk angiographic features.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Review Board of Faculty of Medicine Cairo University (approval no: CMDRF132701/2018, date: 16.01.2018).

Informed Consent: All patients provided written informed consent prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.A., F.M.S., Concept: M.A., F.M.S., Design: A.T.E., R.D., Data Collection or Processing: M.A., R.D., Analysis or Interpretation: A.M.A., A.T.E., F.M.S. Literature Search: M.A., F.M.S., Writing: A.M.A., R.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Abubakar M, Javed I, Rasool HF, Raza S, Basavaraju D, Abdullah RM, *et al*. Advancements in percutaneous coronary intervention techniques: a comprehensive literature review of mixed studies and practice guidelines. Cureus. 2023;15:e41311.
2. Giustino G, Colombo A, Camaj A, Yasumura K, Mehran R, Stone GW, *et al*. Coronary in-stent restenosis: JACC state-of-the-art review. J Am Coll Cardiol. 2022;80:348-72.
3. Kawai K, Virmani R, Finn AV. In-stent restenosis. Interv Cardiol Clin. 2022;11:429-43.
4. Sartore L, Gitto M, Oliva A, Kakizaki R, Mehran R, Räber L, *et al*. Recent advances in the treatment of coronary in-stent restenosis. Rev Cardiovasc Med. 2024;25:433.
5. Mercado N, Boersma E, Wijns W, Gersh BJ, Morillo CA, de Valk V, *et al*. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. J Am Coll Cardiol. 2001;38:645-52.
6. Reifart N, Schwarz F, Hofmann M, Göhring S, Störger H, Haase J. Ballonangioplastie der stent-restenose: früh- und spätergebnisse der ersten und zweiten PTCA bei fokaler und diffuser stenosierung [Balloon angioplasty of stent restenosis: early and late results of first and second PTCA in focal and diffuse stenosis]. Z Kardiol. 1998;87 Suppl 3:65-71; discussion 79-80. German.
7. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, *et al*. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994;331:489-95.
8. Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, *et al*. Final results of the balloon vs optimal atherectomy trial (BOAT). Circulation. 1998;97:322-31.
9. Tang L, Cui QW, Liu DP, Fu YY. The number of stents was an independent risk of stent restenosis in patients undergoing percutaneous coronary intervention. Medicine (Baltimore). 2019;98:e18312.
10. Cassese S, Byrne RA, Schulz S, Hoppman P, Kreutzer J, Feuchtenberger A, *et al*. Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting. Eur Heart J. 2015;36:94-9.
11. Lee MS, Pessegueiro A, Zimmer R, Jurewitz D, Tobis J. Clinical presentation of patients with in-stent restenosis in the drug-eluting stent era. J Invasive Cardiol. 2008;20:401-3.
12. Park CB, Park HK. Predictors of diffuse-type in-stent restenosis following drug-eluting stent implantation. Exp Ther Med. 2013;5:1486-90.
13. Weintraub WS, Kosinski AS, Brown CL 3rd, King SB 3rd. Can restenosis after coronary angioplasty be predicted from clinical variables? J Am Coll Cardiol. 1993;21:6-14.
14. Kastrati A, Schömig A, Elezi S, Schühlen H, Dirschinger J, Hadamitzky M, *et al*. Predictive factors of restenosis after coronary stent placement. J Am Coll Cardiol. 1997;30:1428-36.
15. Bauters C, Hubert E, Prat A, Bougrimi K, Van Belle E, McFadden EP, *et al*. Predictors of restenosis after coronary stent implantation. J Am Coll Cardiol. 1998;31:1291-8.
16. Kobayashi Y, De Gregorio J, Kobayashi N, Akiyama T, Reimers B, Finci L, *et al*. Stented segment length as an independent predictor of restenosis. J Am Coll Cardiol. 1999;34:651-9.
17. Kereiakes D, Linnemeier TJ, Baim DS, Kuntz R, O'Shaughnessy C, Hermiller J, *et al*. Usefulness of stent length in predicting in-stent restenosis (the MULTI-LINK stent trials). Am J Cardiol. 2000;86:336-41.
18. Glazier JJ, Varricchione TR, Ryan TJ, Ruocco NA, Jacobs AK, Faxon DP. Factors predicting recurrent restenosis after percutaneous transluminal coronary balloon angioplasty. Am J Cardiol. 1989;63:902-5.
19. Kang SJ, Cho YR, Park GM, Ahn JM, Han SB, Lee JY, *et al*. Predictors for functionally significant in-stent restenosis: an integrated analysis using coronary angiography, IVUS, and myocardial perfusion imaging. JACC Cardiovasc Imaging. 2013;6:1183-90.
20. Goldberg SL, Loussararian A, De Gregorio J, Di Mario C, Albiero R, Colombo A. Predictors of diffuse and aggressive intra-stent restenosis. J Am Coll Cardiol. 2001;37:1019-25.
21. Donisan T, Madanat L, Balanescu DV, Mertens A, Dixon S. Drug-eluting stent restenosis: modern approach to a classic challenge. Curr Cardiol Rev. 2023;19:e030123212355.
22. Giacoppo D, Mazzone PM, Capodanno D. Current management of in-stent restenosis. J Clin Med. 2024;13:2377.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2026.44227
Int J Cardiovasc Acad 2026;12(1):55-60

Rate of Blood Pressure Control among Hypertensive Patients with Hemodialysis in Sohag University Hospital

Alaa Ghaleb[1], Hassan Ahmad Hassanien[2], Hager Abdo Mohammad[2], Ahmed Nour Eldin[2]

[1]Department of Cardiology, Sohag University Faculty of Medicine, Sohag, Egypt
[2]Department of Internal Medicine, Sohag University Faculty of Medicine, Sohag, Egypt

Abstract

Background and Aim: Hypertension is a common comorbidity in hemodialysis patients, complicating cardiovascular management. While hemodialysis is known to affect blood pressure, the link between dialysis and hypertension control is not well understood. Our study investigates how hemodialysis affects blood pressure control in hypertensive patients and examines the frequency of cardiovascular events in this population.

Materials and Methods: This cross-sectional observational study included 57 hypertensive hemodialysis patients at Sohag University Hospital. Data collected included demographics, comorbidities, hemodialysis parameters, blood pressure (pre-dialysis, inter-dialysis, and post-dialysis), and incidence of cardiovascular events. Mean arterial pressure (MAP) was also calculated.

Results: The mean age of participants was 48.3 years (±15.18), with 73.68% male. The median hemodialysis duration was 36 months, and the median frequency was 3 sessions per week. A significant reduction in MAP was observed during dialysis on the first day compared to pre-dialysis ($P < 0.001$). Despite these improvements, 64.91% had uncontrolled hypertension, while 35.09% achieved control. Cardiovascular events were infrequent: cerebrovascular stroke (7.02%), myocardial infarction (1.75%), hypertensive urgency (14.04%), and pulmonary edema (1.75%); there were no significant differences between the controlled and uncontrolled hypertension groups.

Conclusion: Hemodialysis was associated with significant short-term, procedure-related blood pressure fluctuations across pre-dialysis, intradialytic, and interdialytic time points; however, sustained blood pressure control remained suboptimal, with most patients classified as uncontrolled. These findings highlight the limitations of relying solely on in-unit blood pressure measurements and support the need for more comprehensive monitoring strategies in hypertensive patients receiving hemodialysis.

Keywords: Hypertension, hemodialysis, cardiovascular events, mean arterial pressure, dialysis, chronic kidney disease, cardiovascular risk

INTRODUCTION

Hypertension is a prevalent comorbidity among patients undergoing hemodialysis and significantly contributes to the cardiovascular burden in this population.[1] Poor blood pressure (BP) control in hemodialysis patients is associated with an increased risk of adverse cardiovascular outcomes, including stroke and myocardial infarction (MI).[2]

The management of hypertension in patients undergoing hemodialysis is complicated by factors such as fluid overload, dialysis-induced hypotension, and the intermittent nature of treatment.[3] These factors contribute to difficulties in maintaining consistent BP control outside the dialysis sessions, leading to frequent fluctuations in BP.[4]

BP control is often suboptimal in hemodialysis patients despite antihypertensive medications. It has been noted that

To cite this article: Ghaleb A, Hassanien HA, Mohammad AH, Eldin AN. Rate of blood pressure control among hypertensive patients with hemodialysis in Sohag University Hospital. Int J Cardiovasc Acad. 2026;12(1):55-60

Address for Correspondence: Hager Abdo Mohammad MD, Department of Internal Medicine, Sohag University Faculty of Medicine, Sohag, Egypt
E-mail: hagerabdo@med.sohag.edu.eg
ORCID ID: orcid.org/0009-0002-8101-5214

Received: 01.09.2025
Accepted: 28.01.2026
Publication Date: 10.03.2026

the effectiveness of these medications can vary significantly, with some patients experiencing inadequate control even with standard treatment regimens.[5]

In addition to BP fluctuations, the presence of other comorbidities, such as diabetes and cardiovascular disease, can complicate the management of hypertension in hemodialysis patients. Studies have shown that the presence of these comorbidities increases the risk of uncontrolled hypertension and poor cardiovascular outcomes.[6]

One of the key challenges in hemodialysis is determining the optimal timing for BP measurements, given the frequent fluctuations during dialysis and interdialytic periods. Previous studies have suggested that BP measurements taken immediately after dialysis may not accurately reflect the patient's typical BP.[7] This study aims to address this gap by evaluating BP control across multiple time points, including pre-dialysis, inter-dialysis, and post-dialysis.

METHODS

A cross-sectional observational study, with repeated BP measurements over a short, predefined period, was conducted among 57 hemodialysis patients at Sohag University Hospital in Egypt from May 2024 to May 2025. The study was approved by the Ethics Committee of Sohag University, and written informed consent was obtained from each participant (registration no: Soh-Med-24-03-08MS, date: 01.03.2024).

Inclusion and Exclusion Criteria

Hypertensive patients aged 18 years or older who were on hemodialysis were included in the study. Hypertension was defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (pre-dialysis BP >140/90 mmHg and/or post-dialysis BP >130/80 mmHg). Exclusion criteria included patients who refused to participate, patients who discontinued hemodialysis, end-stage renal disease patients not receiving hemodialysis, and patients with irregular hemodialysis schedules.

Data Collection

Patient data were collected, including age, sex, duration of hemodialysis, and comorbidities such as diabetes, ischemic heart disease (IHD), liver cirrhosis (LC), lupus nephritis, epilepsy, schizophrenia, rheumatic heart disease, and dilated cardiomyopathy. A full physical exam was conducted, including vital sign measurements (pulse, BP, and temperature).

Blood Pressure Measurement and Control

BP control was assessed according to KDOQI guideline thresholds. Controlled hypertension was defined as BP values consistently below target levels (pre-dialysis <140/90 mmHg and post-dialysis <130/80 mmHg) during the monitoring period, while patients exceeding these thresholds at one or more measurements were classified as having uncontrolled hypertension. BP monitoring frequency, antihypertensive medications, and patients' awareness of their BP target ranges were also recorded. BP measurements were taken over three days.

- Trained nursing staff obtained BP measurements using a calibrated automated sphygmomanometer, with patients seated and at rest for at least 5 minutes. Pre-dialysis and post-dialysis measurements were recorded within 5 minutes before initiation and within 5 minutes after completion of the dialysis session, respectively.
- Day 1 (dialysis day): BP pre-dialysis, inter-dialysis, and post-dialysis.
- Day 2 (interdialytic day): BP was measured twice (AM and PM), in accordance with guidelines recommending increased out-of-clinic BP monitoring, such as home BP monitoring or ambulatory BP monitoring.
- Day 3 (dialysis day): BP measured pre-dialysis, inter-dialysis, and post-dialysis.

Hemodialysis Protocol

Hemodialysis was performed using 1.8-2.2 m^2 high-flux synthetic membranes (Helixon®) and a blood flow rate of 300 mL/min. The bicarbonate-based dialysate had a flow rate of 500 mL/min and contained sodium at 106 mmol/L before bicarbonate addition, adjusted to a final concentration of 140 mmol/L after $NaHCO_3$ supplementation; potassium (2 mmol/L), calcium (1.5 mmol/L), magnesium (0.50 mmol/L), bicarbonate (33 mmol/L), and chloride (111 mmol/L). Sessions were conducted three times weekly for 4 hours.

Complications

Complications, including strokes, MIs, pulmonary edema, and hypertensive urgencies, were documented. Hypertensive urgency was defined by an systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg without end-organ damage.

Statistical Analysis

It was performed using SPSS version 26. Normality was assessed using the Shapiro-Wilk test. Parametric data were analyzed using paired t-tests, while non-parametric data were analyzed using the Wilcoxon test. Comparisons of mean arterial pressure (MAP) across multiple time points were exploratory. Qualitative data were expressed as frequencies and percentages and were analyzed using the chi-square test. A *P*-value of < 0.05 was considered significant.

RESULTS

Fifty-seven hypertensive patients undergoing hemodialysis participated, with ages ranging from 21 to 80 years (mean: 48.3±15.18). Of these, 42 (73.68%) were male and 15 (26.32%) were female. The median hemodialysis duration (interquartile range) was 36 months (18-72), with 3 sessions per week (3-3) and a session length of 4 hours (4-4) (Table 1).

Regarding comorbidities, 9 (15.79%) patients had diabetes mellitus (DM), 6 (10.53%) had IHD, and none had LC. Lupus nephritis was present in 3 patients (5.26%), whereas epilepsy, schizophrenia, rheumatic heart disease, and dilated cardiomyopathy each was found in 1 patient (1.75%) (Table 2).

The MAP was significantly lower during dialysis and post-dialysis on the 1st dialysis day, on the 2nd day (dialysis-free AM), and during dialysis and post-dialysis on the 3rd day, compared to the 1st day pre-dialysis ($P < 0.001$). No significant difference was observed between the 1st day pre-dialysis and either the 2nd day (dialysis-free PM) or the 3rd day pre-dialysis (Table 3).

Out of the 57 patients, 20 (35.09%) had controlled hypertension, while 37 (64.91%) had uncontrolled hypertension. Regarding antihypertensive medications, 30 (52.63%) patients were using calcium channel blockers, 40 (70.18%) patients were on beta blockers, 8 (14.04%) patients were on alpha-2 agonists, 1 (1.75%) patient was on an alpha-1 blocker, 19 (33.33%) patients were using angiotensin blockers, 12 (21.05%) patients were taking diuretics, and 1 (1.75%) patient was on an angiotensin-converting enzyme (ACE) inhibitor.

Four (7.02%) patients experienced cerebrovascular strokes (CVS), 1 (1.75%) patient experienced a MI, 8 (14.04%) patients experienced hypertensive urgency, and 1 (1.75%) patient experienced pulmonary edema. There were no significant differences in age, sex, hemodialysis duration, number of dialysis sessions, or session duration between the controlled and uncontrolled hypertension groups. Comorbidities, including DM, IHD, LC, lupus nephritis, epilepsy, schizophrenia, rheumatic heart disease, dilated cardiomyopathy, and lifestyle factors, were also similar across groups. No LC cases were observed.

The controlled hypertension group had significantly lower MAP than the uncontrolled group at several time points: 1st day during dialysis and post-dialysis; 2nd day (dialysis-free AM and PM); and 3rd day during dialysis and post-dialysis ($P < 0.001$) (Table 4).

Table 1. Demographic data and hemodialysis characteristics of the studied patients

		(n=57)
Age (years)	**Mean ± SD**	48.3±15.18
	Range	21-80
Sex	**Male**	42 (73.68%)
	Female	15 (26.32%)
Hemodialysis duration (months)	**Median**	36
	IQR	18-72
Dialysis sessions (weeks)	**Median**	3
	IQR	3-3
Session duration (hours)	**Median**	4
	IQR	4-4

SD: Standard deviation, IQR: Interquartile range

Table 2. Comorbidities of the studied patients

		(n= 57)
DM	**Yes**	9 (15.79%)
	No	48 (84.21%)
IHD	**Yes**	6 (10.53%)
	No	51 (89.47%)
LC	**Yes**	0 (0%)
	No	57 (100%)
Others	**Lupus nephritis**	3 (5.26%)
	Epilepsy	1 (1.75%)
	Schizophrenia	1 (1.75%)
	Rheumatic heart disease	1 (1.75%)
	Dilated cardiomyopathy	1 (1.75%)
	No	50 (87.72%)

DM: Diabetes mellitus, IHD: Ischemic heart disease, LC: Liver cirrhosis

Table 3. Mean arterial pressure (mmHg) of the studied patients

			(n=57)	*P*-value
1st day (dialysis)	**Pre-dialysis**	**Mean ± SD**	112.92±12.75	
		Range	83.33-133.33	
	During dialysis	**Mean ± SD**	108±12.59	**<0.001***
		Range	83.33-130	
	Post-dialysis	**Mean ± SD**	96.7±13.18	**<0.001***
		Range	80-120	
2nd day (dialysis free)	**AM**	**Mean ± SD**	103.6±11.5	**<0.001***
		Range	83.33-123.33	
	PM	**Mean ± SD**	111.4±10.18	0.086
		Range	93.33-130	
3rd day (dialysis)	**Pre-dialysis**	**Mean ± SD**	113.1±11.05	0.783
		Range	93.33-133.33	
	During dialysis	**Mean ± SD**	105.9±12.34	**<0.001***
		Range	83.33-133.33	
	Post-dialysis	**Mean ± SD**	100±11.94	**<0.001***
		Range	80-123.33	

*: Significant as $P \leq 0.05$. *P*-value compared to pre-dialysis at 1st day, SD: Standard deviation

There were no significant differences in the use of antihypertensive medications (calcium channel blockers, beta blockers, alpha-2 agonists, alpha-1 blockers, angiotensin blockers, diuretics, or ACE inhibitors) between the controlled and uncontrolled hypertension groups (Table 5). Likewise, the incidence of complications such as CVS, MI, hypertensive urgency, and pulmonary edema did not differ significantly between the groups (Table 6).

Table 4. Differences in mean arterial pressure (mmHg) between the studied patients

		Controlled hypertension (n=20)	Uncontrolled hypertension (n=37)	*P*-value
1st day (dialysis free)	**During dialysis**	94.83±7.05	115.05±8.56	**<0.001***
	Post-dialysis	84.67±3.96	103.24±11.72	**<0.001***
2nd day (dialysis free)	**AM**	94.83±8.41	108.38±10.11	**<0.001***
	PM	101.83±8.2	116.58±6.87	**<0.001***
3rd day (dialysis)	**Pre-dialysis**	102.17±8.04	119.01±7.32	**<0.001***
	During dialysis	95.5±10.39	111.53±9.35	**<0.001***
	Post-dialysis	89.67±9.61	105.59±9.03	**<0.001***

*: Significant as $P \leq 0.05$

DISCUSSION

This study examined hypertensive patients undergoing hemodialysis; BP was assessed on three consecutive days (pre-dialysis, inter-dialysis, and post-dialysis), and measurements were also taken in the morning and evening on dialysis-free days. The participants' ages ranged from 21 to 80 years, with a mean age of 48.3±15.18 years. The study population was predominantly male, with 42 (73.68%) males and 15 (26.32%) females, consistent with Skonieczny et al.[8] study, in a retrospective single-center study on 222 hemodialysis patients, reported that 62.4% of their cohort was male, with a mean age of 66.2 years. This difference may be attributed to geographical and environmental factors, as well as the different demographic characteristics of the study populations.

Beyond descriptive comparisons, the observed BP variability may reflect complex interactions between volume status, sympathetic activation, arterial stiffness, and dialysis-related hemodynamic shifts.

Regarding hemodialysis parameters, our study found that the median duration was 36 months, with 3 sessions per week, each session lasting 4 hours. These results align with those of Skonieczny et al.[8], who reported a median dialysis duration of 45.1 months and an average of 720 minutes per week. Tsikliras et al.[9] indicated a dialysis vintage of 35 months, which is close to our findings. In contrast, Nongnuch et al.[10] reported a longer dialysis duration of 42 months in a study of 531 patients undergoing hemodialysis.

Table 5. Differences in anti-hypertensive medications between the studied patients

	Controlled hypertension (n=20)	Uncontrolled hypertension (n=37)	*P*-value
Ca channel blockers	9 (27.27%)	21 (26.92%)	0.872
Beta blocker	14 (41.18%)	26 (32.91%)	
Alpha 2 agonist	1 (2.94%)	6 (7.59%)	
Alpha 1 blocker	0 (0%)	1 (1.27%)	
Angiotensin blocker	5 (14.71%)	15 (18.99%)	
Diuretic	4 (11.76%)	8 (10.13%)	
ACE inhibitor	0 (0%)	1 (1.28%)	

Ca: Calcium, ACE: Angiotensin-converting enzyme

Table 6. Differences in complications between the studied patients

	Controlled hypertension (n=20)	Uncontrolled hypertension (n=37)	*P*-value
CVS	2 (10%)	2 (5.41%)	0.606
MI	0 (0%)	1 (2.7%)	1
HTN urgency	3 (15%)	5 (13.51%)	1
Pulmonary edema	0 (0%)	1 (2.7%)	1

CVS: Cerebrovascular stroke, MI: Myocardial infarction, HTN: Hypertension

Regarding comorbidities, our study identified 9 (15.79%) patients with DM, 6 (10.53%) with IHD, and 3 (5.26%) with lupus nephritis, which is comparable to the results reported by Tsikliras et al.[9], who found that 21.6% of their patients had DM, and 30.2% had coronary artery disease. However, the prevalence of comorbidities varies across studies. For example, Skonieczny et al.[8] found that 34.1% of their patients had DM and 65.9% had cardiovascular disease, while Rootjes et al.[11] reported 27.1% prevalence of diabetes. These variations may be attributed to differences in sample populations, diagnostic criteria, and regional healthcare practices.

Our study found significant differences in MAP between groups with controlled and uncontrolled hypertension. Specifically, MAP was significantly lower on the 1st dialysis day, the 2nd day (dialysis-free AM), and the 3rd day, compared with pre-dialysis MAP on the 1st dialysis day ($P < 0.001$). These findings are consistent with the dialysis-related BP fluctuations described in the literature, where BP decreases post-dialysis due to fluid removal and tends to rise between dialysis sessions as fluid accumulation occurs.[11] Rootjes et al.[11] similarly observed significant post-dialysis reductions in MAP compared to pre-dialysis values, supporting our findings. Furthermore, Skonieczny et al.[8] reported significant reductions in systolic and diastolic BP post-dialysis, aligning with our results.

In our study, 20 patients (35.09%) had controlled hypertension, whereas 37 patients (64.91%) had uncontrolled hypertension. This rate of uncontrolled hypertension aligns with the findings of AL-Ramahi and Amr[12], who highlighted poor BP control in the majority of their cohort. Santos et al.[13] found similar results, with 36 patients achieving controlled BP and 35 having uncontrolled BP.

Regarding antihypertensive medications, our study showed that 30 (52.63%) patients were on calcium channel blockers, 40 (70.18%) were on beta blockers, 8 (14.04%) were on alpha-2 agonists, 1 (1.75%) was on an alpha-1 blocker, 19 (33.33%) were on angiotensin blockers, 12 (21.05%) were on diuretics, and 1 (1.75%) was on an ACE inhibitor. These findings are consistent with Skonieczny et al.[8], who reported the use of beta blockers in 74.1% of patients and calcium channel blockers in 52.9%. Kauric-Klein[14] also found similar usage patterns, with 79.7% of patients on beta blockers and 55% on calcium channel blockers. However, Resmiati et al.[15] reported different patterns, with 74.1% of patients using non-dihydropyridine calcium channel blockers, and only 5.2% using beta blockers. These discrepancies could be due to variations in the availability of medications across regions.

No statistically significant differences in complications were observed between the controlled and uncontrolled hypertension groups; however, the low event rates and modest sample size render the study underpowered to detect meaningful differences in rare cardiovascular outcomes.

Complications in our study were consistent with those reported in the literature. We observed that 4 (7.02%) patients experienced CVS, 1 (1.75%) patient suffered from MI, 8 (14.04%) patients had hypertensive urgencies, and 1 (1.75%) patient had pulmonary edema. These findings are in line with Sánchez-Perales et al.[16], who reported MI in 1.58% of patients, and Agarwal[17], who found an acute MI rate of 3.2/1000 patient years. Sarafidis et al.[18] also noted the high prevalence of hypertension in patients on dialysis, a significant factor contributing to cardiovascular morbidity.

Persistent hypertension despite treatment may be related to inadequate dry-weight assessment, sympathetic overactivity, suboptimal timing of antihypertensive medications, and dialysis adequacy, all of which were not fully captured in the present study.

Study Limitations

This single-center, cross-sectional study with a modest sample size has limited generalizability and does not allow assessment of long-term BP control, antihypertensive effectiveness, or cardiovascular outcomes. BP monitoring was restricted to a three-day period and relied mainly on in-unit measurements rather than ambulatory or home BP monitoring, which limited the accurate estimation of the true BP burden and failed to capture usual interdialytic variability influenced by fluid intake, dietary sodium, and differences in ultrafiltration.

Key determinants of BP in hemodialysis patients—including ultrafiltration volume, interdialytic weight gain, dry-weight adjustments, antihypertensive drug dosing, timing, and adherence—were not systematically assessed, limiting mechanistic and causal interpretation. The exploratory design, absence of a formal power calculation, low event rates, lack of multivariable adjustment, and uncorrected multiple comparisons further restrict statistical inference, while effect sizes and confidence intervals are not routinely reported.

CONCLUSION

This study demonstrates marked short-term BP variability in hypertensive patients undergoing hemodialysis, characterized by transient intradialytic and post-dialytic reductions, yet a high overall prevalence of uncontrolled hypertension. These findings suggest that pre- or post-dialysis BP measurements alone are insufficient to characterize the true BP burden. More comprehensive assessment approaches—ideally incorporating interdialytic, ambulatory, or home BP monitoring—along with individualized volume and antihypertensive management are needed to improve BP evaluation and control in this population.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Sohag University (registration no: Soh-Med-24-03-08MS, date: 01.03.2024).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.G., H.A.H., H.A.M., Concept: H.A.H., A.N.E., Design: A.G., H.A.H., Data Collection or Processing: H.A.M., A.N.E., Analysis or Interpretation: A.G., H.A.H., H.A.M., A.N.E., Literature Search: A.G., A.N.E., Writing: A.G., H.A.M., A.N.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Iatridi F, Theodorakopoulou MP, Karpetas A, Sgouropoulou V, Georgiou A, Karkamani E, *et al.* Association of intradialytic hypertension with future cardiovascular events and mortality in hemodialysis patients: effects of ambulatory blood pressure. Am J Nephrol. 2023;54:299-307.
2. Bansal N, Artinian NT, Bakris G, Chang T, Cohen J, Flythe J, *et al.*; American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular and Stroke Nursing; and Council on Epidemiology and Prevention. Hypertension in patients treated with in-center maintenance hemodialysis: current evidence and future opportunities: a scientific statement from the American Heart Association. Hypertension. 2023;80:e112-22.
3. Hebert SA, Ibrahim HN. Hypertension management in patients with chronic kidney disease. Methodist Debakey Cardiovasc J. 2022;18:41-9.
4. Kim IS, Kim S, Yoo TH, Kim JK. Diagnosis and treatment of hypertension in dialysis patients: a systematic review. Clin Hypertens. 2023;29:24.
5. Lee JY, Han SH. Blood pressure control in patients with chronic kidney disease. Korean J Intern Med. 2021;36:780-94.
6. Hecking M, Madero M, Port FK, Schneditz D, Wabel P, Chazot C. Fluid volume management in hemodialysis: never give up! Kidney Int. 2023;103:2-5.
7. Hamrahian SM, Vilayet S, Herberth J, Fülöp T. Prevention of intradialytic hypotension in hemodialysis patients: current challenges and future prospects. Int J Nephrol Renovasc Dis. 2023;16:173-81.
8. Skonieczny P, Heleniak Z, Karowiec M, Zajączkowski S, Tylicki L, Dębska-Ślizień A, *et al.* Blood pressure control and antihypertensive treatment among hemodialysis patients-retrospective single center experience. Medicina (Kaunas). 2021;57:590.
9. Tsikliras N, Georgianos PI, Vaios V, Minasidis E, Anagnostara A, Chatzidimitriou C, *et al.* Prevalence and control of hypertension among patients on haemodialysis. Eur J Clin Invest. 2020;50:e13292.
10. Nongnuch A, Campbell N, Stern E, El-Kateb S, Fuentes L, Davenport A. Increased postdialysis systolic blood pressure is associated with extracellular overhydration in hemodialysis outpatients. Kidney Int. 2015;87:452-7.
11. Rootjes PA, de Roij van Zuijdewijn CLM, Grooteman MPC, Bots ML, Canaud B, Blankestijn PJ, *et al.*; HDF Pooling Project Investigators. Long-term peridialytic blood pressure patterns in patients treated by hemodialysis and hemodiafiltration. Kidney Int Rep. 2020;5:503-10.
12. AL-Ramahi R, Amr R. Prevalence of uncontrolled hypertension in hemodialysis patients: a cross-sectional study from Palestine. Pal Med Pharm J. 2023;8:123-32.
13. Santos SF, Mendes RB, Santos CA, Dorigo D, Peixoto AJ. Profile of interdialytic blood pressure in hemodialysis patients. Am J Nephrol. 2003;23:96-105.
14. Kauric-Klein Z. Factors affecting blood pressure control in hemodialysis. J hypertens. 2013;2:113.
15. Resmiati M, Sauriasari R, Supardi S. Pharmacist counseling is an important factor in lowering blood pressure of hemodialysis patients with hypertension. Pharm Sci Asia. 2020;47:190-204.
16. Sánchez-Perales C, Vázquez-Ruiz de Castroviejo E, Segura-Torres P, Borrego-Utiel F, García-Cortés MJ, García-García F, *et al.* Incidence of acute myocardial infarction in the evolution of dialysis patients. Nefrologia. 2012;32:597-604.
17. Agarwal R. Hypertension and survival in chronic hemodialysis patients--past lessons and future opportunities. Kidney Int. 2005;67:1-13.
18. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro CJ, *et al.* Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). Nephrol Dial Transplant. 2017;32:620-40.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2026.52523
Int J Cardiovasc Acad 2026;12(1):61-68

Global Longitudinal Strain by Speckle-tracking Echocardiography in Detection of Subclinical Left Ventricular Systolic Dysfunction in Patient with Severe Organic Mitral Regurgitation and Normal Ejection Fraction

Febe Ezzat Shaker Gaballah, Tamer Ragab, Khaled Khashab, Hassan Ebeid, Gomaa Abdelrazek

Department of Cardiology, Fayoum University Faculty of Medicine, Fayoum, Egypt

Abstract

Background and Aim: Primary mitral regurgitation (MR) is a common valvular disorder with significant long-term morbidity if untreated. Conventional echocardiographic indices, such as left ventricular ejection fraction (LVEF) and chamber dimensions, may overestimate ventricular performance and fail to detect early myocardial impairment. Speckle-tracking echocardiography (STE)–derived global longitudinal strain (GLS) has emerged as a highly sensitive parameter for the detection of subclinical systolic dysfunction. To investigate the role of GLS in the early identification of subclinical LV systolic dysfunction in individuals presenting with severe primary MR and preserved LVEF.

Materials and Methods: This study included 100 subjects: 50 with severe MR and normal LVEF, and 50 matched controls. Comprehensive echocardiographic assessment included M-mode, Simpson's biplane, tissue Doppler imaging, and two-dimensional STE (2DSTE). GLS values were derived from 18 myocardial segments and expressed as a bull's-eye map.

Results: Cases with MR had substantially impaired GLS relative to controls (-17.8±3.1 vs. -21.3±2.1; $P < 0.001$). All strain parameters were substantially lower among cases. In contrast, LVEF, measured by both M-mode and Simpson's method, showed no marked variation between groups ($P > 0.05$). Receiver operating characteristic analysis demonstrated that GLS had superior discriminative performance, with sensitivity of 82% and specificity of 66% at a cut-off of -20.35% (area under the curve 0.821, 95% confidence interval 0.737-0.905, $P = 0.001$).

Conclusion: 2DSTE-derived GLS is an effective parameter for the identification of subclinical LV systolic dysfunction in the context of severe primary MR with preserved EF. Its incorporation into clinical practice may optimize the timing of surgical referral before irreversible myocardial damage occurs.

Keywords: Mitral regurgitation, left ventricular dysfunction, echocardiography, global longitudinal strain

INTRODUCTION

Mitral regurgitation (MR) represents one of the most common valvular heart disorders in developed nations. According to European and American guidelines, surgical intervention for primary MR is recommended when patients present with symptoms of severe MR, exhibit left ventricular (LV) systolic dysfunction defined by an ejection fraction (EF) below 60%, demonstrate LV dilatation with an LV end-systolic dimension (LVESD) higher than 45 mm, or develop pulmonary arterial hypertension or new-onset atrial fibrillation (AF).[1]

To cite this article: Gaballah FES, Ragab T, Khashab K, Ebeid H, Abdelrazek G. Global longitudinal strain by speckle-tracking echocardiography in detection of subclinical left ventricular systolic dysfunction in patient with severe organic mitral regurgitation and normal ejection fraction. Int J Cardiovasc Acad. 2026;12(1):61-68

Address for Correspondence: Febe Ezzat Shaker Gaballah MD, Department of Cardiology, Fayoum University Faculty of Medicine, Fayoum, Egypt
E-mail: dr.febeezzat@gmail.com
ORCID ID: orcid.org/0009-0006-9636-4192

Received: 13.10.2025
Accepted: 28.01.2026
Publication Date: 10.03.2026

If only these parameters are considered, subtle myocardial remodeling secondary to increased filling pressures is frequently overlooked, as the LV and left atrium (LA) are initially able to withstand the hemodynamic stress. The recommended thresholds for intervention are relatively high, corresponding to advanced systolic dysfunction, which risks delaying surgical management until irreversible myocardial injury has developed. Therefore, chronic primary MR may be clinically silent for prolonged periods, owing to compensatory changes in LV and LA structure and function, despite substantial regurgitation.[1]

LVEF is widely used in clinical practice as a key parameter for decision-making in patients with MR. Nonetheless, LVEF describes the volumetric change in the LV from diastole to systole, without considering the direction of blood ejection or the intrinsic contractile properties of the myocardium. In MR, a substantial portion of LV output is directed toward the low-pressure LA rather than the systemic circulation, which limits the accuracy of LVEF in assessing true systolic function. Consequently, LV contractility may be overestimated despite the presence of myocardial impairment caused by volume overload.[2]

Echocardiographic assessment of global longitudinal strain (GLS) offers potential value in detecting early myocardial dysfunction in MR, which may be overlooked when relying solely on volume-based indices such as LVEF.[3]

LV-GLS reflects myocardial longitudinal function by quantifying the percentage change in fiber length relative to its original length. Speckle-tracking echocardiography (STE) is the standard method for obtaining GLS, and GLS is increasingly used in routine practice. This parameter provides valuable insight into subclinical LV systolic dysfunction and may aid in optimizing follow-up strategies and determining the appropriate timing for intervention. [4]

Accordingly, this investigation aims to evaluate LV function and detect early subclinical dysfunction in patients with severe primary MR, using GLS derived from STE.

METHODS

Design and Population

This cross-sectional investigation was carried out at Fayoum University Hospital and enrolled 50 patients with severe primary MR and preserved EF, as determined by conventional echocardiography, along with 50 sex- and age-matched healthy volunteers who underwent structured history-taking, physical examination, 12-lead electrocardiogram (ECG), and comprehensive transthoracic echocardiography confirming normal chamber size, valvular structure and function, and preserved EF, with no more than trivial MR. Eligible patients were consecutively enrolled during the study period, February-July 2025.

The study adhered to international ethical standards and local regulatory requirements. Ethical approval for the study was granted by the Faculty of Medicine, Fayoum University Ethics Committee. All participants provided written informed consent (approval code: SCCREIRB-MEDICINFAYOM-GU-001-090225-028, date: 07.09.2015/registration date: 09.02.2025).

Eligibility Criteria

The inclusion criteria included patients aged 25-65 years with severe chronic primary MR, preserved EF, and only insignificant symptoms. Exclusion criteria were as follows: mild or moderate MR; severe MR with EF <55%; significant involvement of other cardiac valves; ischemic heart disease; hypertrophic, dilated, or restrictive cardiomyopathy; hypertension; diabetes mellitus; and AF.

Preserved LVEF for study eligibility was defined as LVEF ≥55% at rest, assessed by the modified biplane Simpson method (with supportive M-mode assessment). Patients with severe MR and LVEF <55% were excluded.

All Cases Were Subjected to the Following

Clinical Assessment

A comprehensive medical history was recorded for every case. This was followed by a thorough general and cardiac examination, including the documentation of vital signs. A standard 12-lead ECG was also performed.

Transthoracic Echocardiography

Echocardiographic studies were conducted using a GE Vivid E95 ultrasound system with advanced cSound image-processing technology and an M5Sc probe. Standard 2D, M-mode, and Doppler imaging included parasternal long- and short-axis views, together with apical four-chamber, two-chamber, and long-axis views. The etiology and severity of MR were assessed. Severity grading was based on color Doppler parameters, including jet area and extent, effective regurgitant orifice area (EROA), and vena contracta width, along with the proximal isovelocity surface area method. In addition, left atrial diameter and volume were measured. To minimize vendor-related variability, all echocardiographic acquisitions and strain analyses were performed using the same vendor platform (GE Vivid E95) throughout the study.

LV Dimensional, Functional, and Tissue Doppler Measurements

LV end-diastolic dimension and LVESD were obtained using 2D M-mode, whereas LV end-diastolic volume, LV end-systolic

volume, EF, fractional shortening (FS), and stroke volume (SV) were evaluated using both M-mode and the modified biplane Simpson method. In addition, pulsed-wave Doppler-based tissue Doppler imaging (TDI) was performed to measure systolic myocardial velocity (Sa) at the lateral and septal mitral annuli.

Two-dimensional Speckle-tracking Echocardiography (2DSTE)

For speckle-tracking analysis, apical four-chamber, two-chamber, and long-axis views were recorded over three consecutive cardiac cycles. GLS was quantified during an end-expiratory breath-hold, with frame rates of 40-80 frames/s obtained by optimizing sector width and image depth, without the use of dual focusing. GLS is reported using the conventional negative sign convention. For categorical interpretation, normal GLS was defined as ≤-18% (more negative), borderline GLS as >-18% to ≤-16%, and impaired GLS as >-16% (less negative). For correlation and receiver operating characteristic (ROC) analyses, GLS was also analyzed as the absolute magnitude (|GLS|), with lower |GLS| indicating worse longitudinal function.

Offline analysis was performed using the vendor-specific software on the same platform, which automatically generated GLS values and a bull's-eye map of all 18 myocardial segments from the three apical views. Offline GLS analysis was performed with partial blinding: observers were blinded to clinical data, but complete blinding to group allocation was not feasible because of obvious MR features on the echocardiographic images.

GLS values were reported using the conventional negative-strain notation (more negative values indicate better longitudinal systolic deformation). Based on prior reference values using the same vendor/platform, preserved GLS was defined as ≤-18% (absolute value ≥18%). Borderline GLS was defined as -18% <GLS≤-16%, and impaired GLS as >-16%.

Statistical Analysis

After coding and double data entry into Microsoft Access, the data were statistically analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) on Windows 7. Frequencies and percentages were used to summarize categorical variables, while continuous variables were described using mean ± standard deviation. The Shapiro-Wilk test was applied to assess normality. Independent-samples t-tests were used to compare two groups, while one-way ANOVA was used when more than two groups were involved. The chi-square test was used to determine associations between categorical variables. Pearson's correlation coefficient was used to measure relationships among quantitative variables. Statistical significance was defined as P <0.05. ROC curve analysis was performed to evaluate the ability of GLS and LVEF to discriminate patients with severe primary MR from healthy controls. The ROC-derived cutoff represents the value that best separates the two groups in this dataset, thereby maximizing sensitivity and specificity, and should not be interpreted as a universal "normal/abnormal" GLS threshold. Multiple linear regressions were used to test the association between quantitative dependent and independent variables and predictive risk factors.

RESULTS

Fifty cases presenting with severe chronic primary MR and preserved EF were recruited, along with 50 age- and sex-matched healthy controls. Age and sex distributions were comparable between the two groups, with no substantial variation detected (P > 0.05) Table 1.

Among cases of severe primary MR, rheumatic etiology was the most frequent (52%), followed by mitral valve (MV) prolapse (22%), degenerative disease (20%), and flail MV leaflets (6%). The mean heart rate (HR) was 77±12 beats/min and mean systolic blood pressure (SBP) was 124.4±11.7 mmHg. EF was 66.7%±5.7 when measured by M-mode and 62.7%±4.6 by Simpson's technique. The mean end-systolic diameter (ESD) was 3.2±0.4 cm. Tissue Doppler parameters included a mean lateral S wave of 8.9±1.5 cm/sec and a mean septal S wave of 7.6±1.3 cm/sec. The mean EROA for MR severity was 0.61±0.28 cm² Table 2.

The study revealed a substantial reduction in all echocardiographic strain parameters among cases (P < 0.001).

Table 1. Baseline demographic and echocardiographic characteristics of the study population

Variable	Cases (n=50)	Controls (n=50)	*P*-value	Significance
Age (years), Mean ± SD	45.7±11.7	45.8±10.8	0.9	NS
Sex, number (%)				
Male	18 (36)	14 (28)	0.52	NS
Female	32 (64)	36 (72)		
EF, Mean ± SD				
EF (M-mode)	66.7±5.7	65.8±3.3	0.33	NS
EF (Simpson)	62.7±4.5	64.1±3.4	0.08	NS

EF: Ejection fraction, NS: Not significant, SD: Standard deviation, n: Number

In the case group, GLS showed no significant correlation with age or vital signs ($P > 0.05$). Notably, 30% of MR cases had impaired GLS, 26% had borderline values, and 44% had non-impaired GLS. GLS was substantially negatively correlated with left atrial volume index (LAVI), right ventricular systolic pressure (RVSP), end-diastolic volume, end-systolic volume, end-diastolic diameter, and ESD ($P < 0.05$), indicating that increases in these measures were associated with a worsening of GLS. Conversely, no marked correlations were observed between GLS and LA diameter, SV, FS, or EF ($P > 0.05$). A substantial positive correlation was identified between GLS and the lateral and septal S waves ($P < 0.05$), suggesting that higher tissue Doppler systolic velocities were associated with improved GLS. While no substantial associations were found between GLS and vena contracta width or jet area, a marked correlation with EROA was detected Table 3, Figure 1 and Figure 2.

Cases exhibited a marked reduction in longitudinal strain in the apical four-chamber, apical two-chamber, and apical long-axis views, all of which reached statistical significance ($P < 0.001$). The average GLS was -17.8±3.1 for cases versus -21.3±2.1 for controls, indicating a significant intergroup difference ($P < 0.001$) Table 4.

The specificity and sensitivity of EF, whether measured by M-mode or Simpson's method, were not statistically significant

Table 2. Etiology, vital signs, and echocardiographic characteristics of cases with severe primary MR

Variable	Mean	SD
Etiology of MR (number and frequency %)		
Mitral valve prolapse	11	22%
Rheumatic heart disease	26	52%
Flail MV leaflets	3	6%
Degenerative	10	20%
Vital signs		
HR (beat/min)	77	12
SBP (mmHg)	124.4	11.7
DBP (mmHg)	73.2	8.8
Echocardiography measures		
SV (mL)	83.6	30.1
FS (%)	39.4	12.4
LA diameter (cm)	4.03	0.72
LAVI (mL/m²)	61	31
EF by M-mode	66.7	5.7
EF by Simpson	62.7	4.6
RVSP (mmHg)	25.3	6.9
EDV (mL)	123.8	43.9
ESV (mL)	41.2	17.4
EDD (cm)	5	0.66
ESD (cm)	3.2	0.47
Tissue Doppler measures		
Lateral S wave (TDI) (cm/sec)	8.9	1.5
Septal S wave (TDI) (cm/sec)	7.6	1.3
MR severity parameters		
Vena contracta (cm)	0.78	0.15
Jet area (cm)	12.1	3.3
EROA (cm²)	0.61	0.28

MR: Mitral regurgitation, SV: Stroke volume, FS: Fractional shortening, LA: Left atrium, LAVI: Left atrial volume index, EF: Ejection fraction, EDD: End-diastolic diameter, RVSP: Right ventricular systolic pressure, DBP: Diastolic blood pressure, SD: Standard deviation, ESV: End-systolic volume, ESD: End-systolic diameter, TDI: Tissue Doppler imaging, EROA: Effective regurgitant orifice area, HR: Heart rate, EDV: End-diastolic volume, SBP: Systolic blood pressure, n: Number, MV: Mitral valve

Table 3. Correlation between GLS and clinical, echocardiographic, and MR severity parameters in case group

Variable	GLS		
	R	*P*-value	Significance
Age and vital signs			
Age (years)	-0.19	0.18	NS
HR (beat /min)	-0.03	0.82	NS
SBP (mmHg)	0.10	0.47	NS
DBP (mmHg)	0.19	0.18	NS
Echocardiography findings			
LA diameter (cm)	-0.21	0.15	NS
LAVI (mL/m²)	-0.48	0.003*	HS
SV (mL)	-0.23	0.10	NS
FS (%)	0.16	0.24	NS
EF (%)	0.11	0.45	NS
RVSP (mmHg)	-0.48	<0.001*	HS
EDV (mL)	-0.41	0.003*	HS
ESV (mL)	-0.45	0.001*	HS
EDD (cm)	-0.42	0.001*	HS
ESD (cm)	-0.48	<0.001*	HS
Tissue Doppler systolic lateral and septal wave			
Lateral S wave (TDI) (cm/sec)	0.35	0.01*	S
Septal S wave (TDI) (cm/sec)	0.45	0.001*	HS
MR severity measures			
Vena contracta	0.16	0.26	NS
Jet area	0.06	0.68	NS
EROA	0.41	0.001*	HS

*: Statistically significant $P < 0.05$, GLS: Global longitudinal strain, NS: Not significant, HS: Highly significant, S: Significant, LA: Left atrium, LAVI: Left atrial volume index, EDV: End-diastolic volume, SV: Stroke volume, FS: Fractional shortening, EF: Ejection fraction, RVSP: Right ventricular systolic pressure, ESV: End-systolic volume, EDD: End-diastolic diameter, SBP: Systolic blood pressure, ESD: End-systolic diameter, TDI: Tissue Doppler imaging, MR: Mitral regurgitation, EROA: Effective regurgitant orifice area, HR: Heart rate, DBP: Diastolic blood pressure

for assessing LV function and contractility in MR cases (P > 0.05). In contrast, LV-GLS demonstrated significant diagnostic value Table 4 and Figure 3.

ROC curve analysis was performed to assess the ability of GLS and LVEF to discriminate between patients with severe primary MR and healthy controls. GLS demonstrated strong discriminative performance, with an area under the curve of 0.821 [95% confidence interval (CI) 0.737-0.905, P = 0.001]. A cut-off value of -20.35% yielded 82% sensitivity and 66% specificity in identifying MR patients (i.e., GLS values that were less negative than -20.35% were more likely to be observed in the MR group). In contrast, LVEF measured by M-mode and Simpson's method showed limited discrimination (P > 0.05) Table 5 and Figure 3.

Multivariate linear regression analysis demonstrated that SBP, LA, EF by M-mode, EF by Simpson, septal S wave (TDI), and RVSP were significant predictors of GLS (P-value <0.05) Table 6.

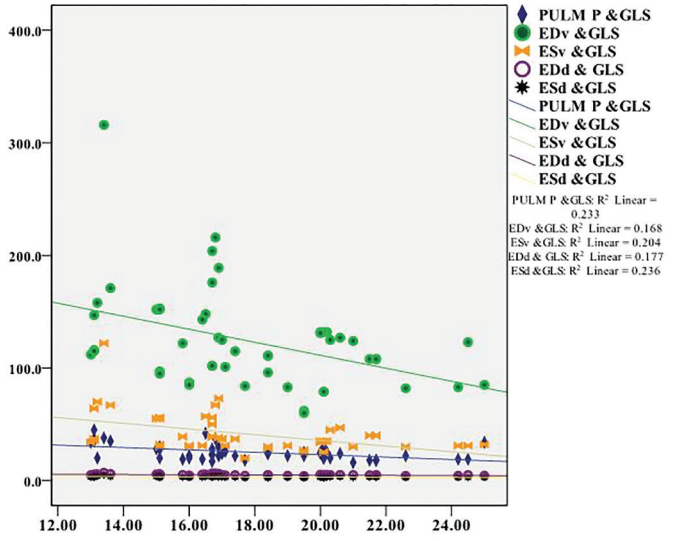


Figure 1. Correlation between GLS and echo-parameters in case group

GLS: Global longitudinal strain, EDV: End-diastolic volume, ESV: End-systolic volume, EDD: End-diastolic dimension/diameter, ESD: End-systolic dimension/diameter

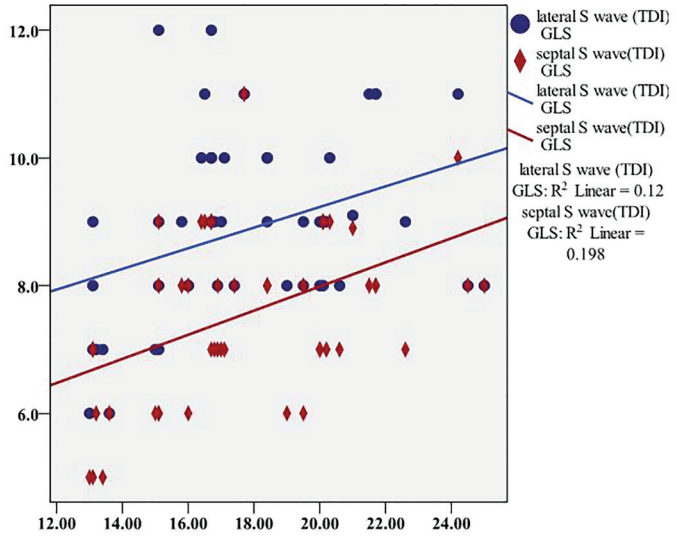


Figure 2. Correlation between GLS and septal and lateral S wave by TDI in case group

GLS: Global longitudinal strain, TDI: Tissue Doppler imaging

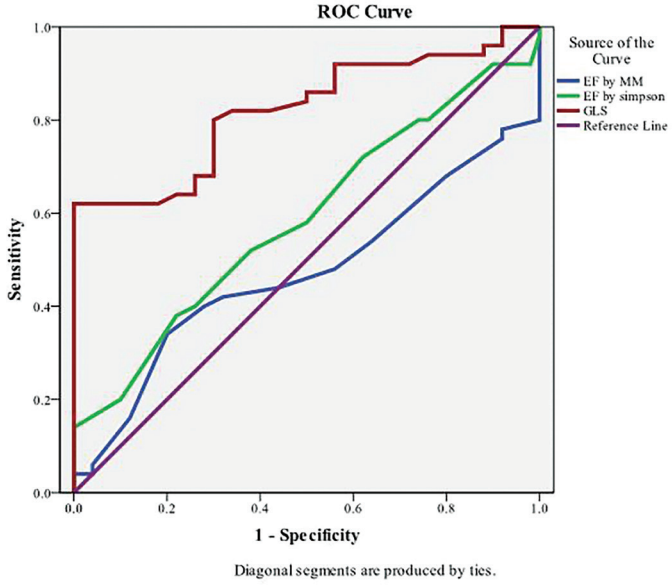


Figure 3: ROC curve for EF level and GLS assessment of LV function in cases of organic MR

ROC: Receiver operating characteristic, MR: Mitral regurgitation, EF: Ejection fraction, GLS: Global longitudinal strain, LV: Left ventricular, MM: M-mode

Table 4. Global and segmental longitudinal strain values in studied groups

Variables	Cases (n=50)		Controls (n=50)		P-value	Significance
	Mean	SD	Mean	SD		
APICAL 4CH LS	-18.1	4.1	-21.3	2.3	**<0.001***	**HS**
APICAL 2CH LS	-19.9	3.2	-21.1	2.4	**<0.001***	**HS**
APICAL LAX LS	-17.7	3.6	-21.1	2.5	**<0.001***	**HS**
GLS	-17.8	3.1	-21.3	2.1	**<0.001***	**HS**

*: Statistically Significant P < 0.05, CH: Chamber, LS: Longitudinal strain, GLS: Global longitudinal strain, LAX: Long axis, SD: Standard deviation, HS: Highly significant, n: Number

DISCUSSION

Primary MR carries an unfavorable long-term prognosis when left untreated, with MV repair or replacement being the only definitive therapy for severe disease. According to European and American guidelines, surgical intervention is recommended for patients with severe MR who present with symptoms, LV dilatation or dysfunction, elevated pulmonary pressures, or new-onset AF. However, conventional echocardiographic parameters frequently fail to identify early structural changes associated with elevated filling pressures, and the guideline thresholds for referral correspond to advanced systolic and structural impairment. As a result, cases are often referred for surgery only in the late stages, when irreversible myocardial damage has already occurred.[1]

A widely accepted hypothesis suggests that in several cardiac disorders, the earliest functional impairment occurs in the longitudinal fibers of the endocardium and epicardium, while the mid-wall circumferential fibers remain relatively preserved or may even compensate by enhanced circumferential shortening. This adaptive mechanism maintains LVEF despite the decline in longitudinal performance. Consequently, speckle-tracking-derived LV-GLS is considered a valuable marker, as it provides a sensitive measure of early myocardial dysfunction.[5]

As this is a cross-sectional case-control study, our findings demonstrate associations between GLS and echocardiographic and MR severity parameters at a single time point, and cannot be used to infer causality or directly evaluate prognosis or postoperative outcomes in our cohort.

Table 5. ROC curve analysis of ejection fraction and global longitudinal strain

Variable	Sensitivity	Specificity	AUC	Cut-off point	*P*-value (CI 95%)
EF (mm)	48%	44%	47.1%	66.5	0.62 (35.5-58.8)
EF by Simpson	58%	50%	58.7%	64.5	0.14 (47.5-69.9)
GLS	82%	66%	82.1%	-20.35	**0.001*** **(73.7-90.5)**

*: Statistically significant $P < 0.05$, EF: Ejection fraction, GLS: Global longitudinal strain, CI: Confidence interval, AUC: Area under the curve

Table 6. Multivariate linear regression analysis to determine the power of different variables in prediction of GLS among study group

Model		Unstandardized coefficients		Standardized coefficients	*P*-value
		B	Standard error	Beta	
1	**(Constant)**	-19.692	9.141		0.038
	Age	-0.061	0.035	-0.231	0.090
	HR	0.027	0.033	0.102	0.429
	SBP	0.095	0.036	0.356	0.014*
	DBP	0.020	0.048	0.055	0.682
	SV	-0.004	0.015	-0.041	0.778
	FS %	0.031	0.032	0.126	0.328
	LA	1.402	0.589	0.325	0.023*
	EF by	-0.298	0.106	-0.542	0.008*
	EF by Simpson	0.610	0.119	0.893	0.001>*
	Lateral S wave (TDI)	-0.224	0.313	-0.104	0.480
	Septal S wave (TDI)	0.890	0.381	0.378	0.026*
	RVSP	-0.192	0.072	-0.423	0.012*
	Vena contracta	4.784	4.399	0.236	0.284
	Jet area	-0.069	0.152	-0.073	0.654
	PISA radius	-2.984	3.062	-0.184	0.337

*: Statistically significant $P < 0.05$, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SV: Stroke volume, FS: Fractional shortening, LA: Left atrium, EF: Ejection fraction, RVSP: Right ventricular systolic pressure, GLS: Global longitudinal strain, PISA: Proximal isovelocity surface area

Our results showed that the mean strain values in the case group were -18.1±4.1 in the apical four-chamber view, -19.7±3.2 in apical two-chamber view, and -17.7±3.6 in the apical long-axis view, with a mean GLS of -17.8±3.1. Among these cases, 30% had impaired GLS, 26% had borderline values, and 44% had preserved GLS. All strain parameters were markedly lower in cases relative to controls ($P < 0.001$).

In contrast, our analysis identified a substantial inverse correlation between GLS and EROA (r=-0.41, $P = 0.001$). This observation corresponds with findings from Nguyen et al.[6], who likewise demonstrated a negative correlation between these parameters, with a coefficient of -0.710.

In the context of the present study, GLS showed a marked inverse correlation with LAVI (r=-0.48, $P = 0.003$). This observation concurs with the work of Santoro et al.[7], who evaluated 504 consecutive cases across varying severities of MR using comprehensive echo-Doppler assessment. Their analysis compared LV and LA sizes, pulmonary artery systolic pressure, and GLS between cases with mild MR (n=392) and those with moderate-to-severe MR (n=112), and also demonstrated a substantial negative correlation between GLS and LAVI ($P < 0.005$).

Our study demonstrated that sensitivity and specificity testing of EF, whether assessed by M-mode or the modified Simpson biplane method, were not statistically significant for evaluating LV function and contractility in MR cases ($P > 0.05$). In our cohort, GLS demonstrated superior discrimination between MR patients and controls compared with that of LVEF; a GLS cut-off of -20.35% provided 82% sensitivity and 66% specificity for distinguishing the groups. This cut-off reflects discrimination within our dataset and should not be interpreted as a universal definition of abnormal GLS.

Our results are in agreement with those of Riebel et al.[8], who performed a prospective cohort study involving 218 cases with varying degrees of MR severity. Baseline and serial six-monthly evaluations of LV-GLS were performed over a median follow-up of 30 months. The study demonstrated significantly lower baseline GLS values in moderate and severe MR compared with mild MR (19.5% and 19.1% vs. 22.3%, $P < 0.01$), despite comparable LVEF. Moreover, GLS decline was detected earlier (at 12 months) and was more substantial in moderate and severe MR (13.6% and 14.5%, respectively) than in mild MR (6.72%). Baseline GLS <18% and a relative GLS reduction exceeding 10% were independent predictors of composite outcomes (HR=1.59, 95% CI 1.17-2.86; HR=1.74, 95% CI 1.2-2.91; $P < 0.01$).

In their systematic review, Krupa and Lall[9] concluded that GLS is a valuable parameter for evaluating LV systolic function and offers prognostic significance for both clinical and echocardiographic outcomes following intervention. They found that GLS thresholds lower than -17.2% to -21% in primary MR and -7% to -9% in secondary MR correlated with poor prognosis. These observations suggest that routine application of GLS in the evaluation of severe MR cases may improve intervention planning and clinical outcome prediction.

Modaragamage Dona et al.[10], through a systematic review, established GLS as an independent prognostic marker for postoperative outcomes, with values reported between -17.9% and -21.7%. Their findings revealed a significant negative association between preoperative GLS and postoperative LVEF. Higher mortality was observed in cases with impaired baseline GLS, whereas early surgical intervention conferred improved long-term survival. Although prior studies suggest prognostic value, our study was cross-sectional and did not evaluate postoperative or long-term outcomes.

In our study, a significant positive relationship was identified between GLS and the lateral and septal S waves ($P < 0.05$), indicating that enhanced tissue Doppler systolic function corresponded to improved GLS. This result concurs with findings from Peverill et al.[11], who investigated 84 subjects (mean age 66±8 years; 29 males) with LVEF of 62±6% and GLS of -17.5±2.3%. They reported, through univariate analysis, that GLS was positively correlated with mitral annular systolic velocity (s') on TDI (r=0.28, $P < 0.01$) and long-axis systolic excursion (r=0.50, $P < 0.001$).

According to the literature, Bijvoet et al.[5] proposed that in asymptomatic cases with severe MR and preserved LVEF, impaired LV-GLS serves as a predictor of postoperative LV dysfunction following MV surgery. Impaired LV-GLS has been shown to correlate not only with a decline in LVEF within 30 days of surgery but also with long-term mortality, as confirmed by several large studies. Therefore, LV-GLS may represent a valuable parameter for clinical decision-making in this patient population.

In their investigation of 506 cases with severe chronic MR, Kim et al.[12] found LV-GLS to be a powerful predictor of clinical outcomes, including HF hospitalization, need for repeat MV intervention, and cardiac death. This prognostic role remained significant in multivariate analysis, independent of LV dysfunction, AF, and surgical approach. The study also established a link between reduced GLS and increased risk of all-cause mortality (HR 1.068, 95% CI 1.003-1.136; $P = 0.040$).

These findings underscore the utility of GLS, assessed by STE, in the early detection of LV dysfunction in patients with severe primary MR. Our results are consistent with prior research that evaluated LV function and structural parameters in this population. The study also reaffirms the superior feasibility and reproducibility of GLS compared with those of LVEF. Thus, incorporating GLS into routine clinical practice may provide valuable adjunctive criteria to guide surgical decision-making.

Study Limitations

This study has several limitations. The relatively small sample size may limit generalizability and may have resulted in underpowered analyses of smaller effects (e.g., LVEF), correlation testing, and ROC-derived cut-offs, as reflected by the CIs. Inclusion of patients >60 years could have influenced GLS, given the age-related decline in strain. Speckle-tracking GLS is inherently image-quality-dependent and vendor-dependent. Although a single platform improves internal consistency, it may limit comparability of absolute GLS thresholds across vendors or software. The etiology of MR was heterogeneous (predominantly rheumatic), and GLS may vary accordingly; therefore, pooling may have attenuated etiology-specific associations. Intra- and interobserver reproducibility was not assessed, and incomplete blinding during GLS analysis may have introduced observer bias. Finally, no a priori sample size/power calculation was performed; however, the observed between-group GLS difference (-17.8±3.1 vs. -21.3±2.1) was large, suggesting adequate power to detect GLS differences despite potential underpowering for more modest associations.

CONCLUSION

GLS by 2DSTE is valuable for identifying subclinical LV systolic dysfunction in patients with severe primary MR and preserved EF. Its incorporation into clinical practice may enhance timing of surgical referral before irreversible myocardial damage occurs. These observations are consistent with prior literature demonstrating the advantage of LV-GLS over EF in detecting subclinical myocardial impairment in MR. However, because this study is cross-sectional and includes a relatively small sample, our ROC and correlation findings should be considered supportive and hypothesis-generating rather than definitive; they warrant validation in larger prospective cohorts.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the Faculty of Medicine, Fayoum University Ethics Committee (approval code: SCCREIRB-MEDICINFAYOM-GU-001-090225-028, date: 07.09.2015/registration date: 09.02.2025).

Informed Consent: All participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.E.S.G., H.E., Concept: T.R., K.K., G.A., Design: F.E.S.G., Data Collection or Processing: G.A., Analysis or Interpretation: F.E.S.G., T.R., Literature Search: K.K., Writing: F.E.S.G., H.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Pastore MC, Mandoli GE, Dokollari A, Bisleri G, D'Ascenzi F, Santoro C, *et al.* Speckle tracking echocardiography in primary mitral regurgitation: should we reconsider the time for intervention? Heart Fail Rev. 2022;27:1247-60.
2. Kamperidis V, Marsan NA, Delgado V, Bax JJ. Left ventricular systolic function assessment in secondary mitral regurgitation: left ventricular ejection fraction vs. speckle tracking global longitudinal strain. Eur Heart J. 2016;37:811-6.
3. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, *et al.* Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the american society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. J Am Soc Echocardiogr. 2017;30:303-71.
4. Robinson S, Rana B, Oxborough D, Steeds R, Monaghan M, Stout M, *et al.* A practical guideline for performing a comprehensive transthoracic echocardiogram in adults: the British Society of Echocardiography minimum dataset. Echo Res Pract. 2020;7:G59-93.
5. Bijvoet GP, Teske AJ, Chamuleau SAJ, Hart EA, Jansen R, Schaap J. Global longitudinal strain to predict left ventricular dysfunction in asymptomatic patients with severe mitral valve regurgitation: literature review. Neth Heart J. 2020;28:63-72.
6. Nguyen VA, Nguyen DT, Ong LTT, Tran AV, Tran BLT, Tran CM. Early detection of reduced left ventricular systolic function by 2D speckle tracking echocardiography in patients with primary mitral regurgitation in a Vietnamese cohort. Glob Cardiol Sci Pract. 2023;2023:e202326.
7. Santoro C, Galderisi M, Esposito R, Buonauro A, Monteagudo JM, Sorrentino R, *et al.* Global longitudinal strain is a hallmark of cardiac damage in mitral regurgitation: the Italian arm of the European Registry of mitral regurgitation (EuMiClip). Cardiovasc Ultrasound. 2019;17:28.
8. Riebel CIB, Ilie Orzan R, Negru A, Agoston-Coldea L. The role of global longitudinal strain in the follow-up of asymptomatic patients with chronic primary mitral regurgitation. J Clin Med. 2024;13:5304.
9. Krupa J, Lall D. Utility of global longitudinal strain in mitral regurgitation: a systematic review. J Indian Acad Echocardiogr Cardiovasc Imaging. 2023;7:93-100.
10. Modaragamage Dona AC, Afoke J, Punjabi PP, Kanaganayagam GS. Global longitudinal strain to determine optimal timing for surgery in primary mitral regurgitation: a systematic review. J Card Surg. 2021;36:2458-66.
11. Peverill RE, Cheng K, Cameron J, Donelan L, Mottram PM. Relationships of global longitudinal strain with s`, long-axis systolic excursion, left ventricular length and heart rate. PLoS One. 2020;15:e0235791.
12. Kim HM, Cho GY, Hwang IC, Choi HM, Park JB, Yoon YE, *et al.* Myocardial strain in prediction of outcomes after surgery for severe mitral regurgitation. JACC Cardiovasc Imaging. 2018;11:1235-44.

CASE REPORT

DOI: 10.4274/ijca.2025.33042
Int J Cardiovasc Acad 2026;12(1):69-72

Ventricular Septal Defect and Complete Atrioventricular Block Following Transcatheter Aortic Valve Implantation: A Case Report

Sefa Erdi Ömür[1], Kayıhan Karaman[1], Elnur Alizade[2]

[1]Department of Cardiology, Tokat Gaziosmanpaşa University, Tokat, Türkiye
[2]University of Health Science Türkiye, Department of Cardiology, Koşuyolu High Specialization Education and Research Hospital, İstanbul, Türkiye

Abstract

Transcatheter aortic valve implantation (TAVI) is an established alternative to surgical aortic valve replacement for severe aortic stenosis (AS) in high-risk patients, yet rare, potentially life-threatening complications still occur. We describe a 75-year-old man with severe symptomatic AS who underwent TAVI using a balloon-expandable Myval prosthesis; the procedure was complicated by complete atrioventricular block requiring permanent pacemaker implantation. At 1-month follow-up, he presented with dyspnea. Transthoracic echocardiography demonstrated a newly developed perimembranous ventricular septal defect (VSD) adjacent to the prosthetic valve, resulting in a significant left-to-right shunt. This case underscores the need for meticulous pre-procedural assessment of the distribution of calcification, careful procedural planning and technique, and post-procedural vigilance for both conduction disturbances and rare structural complications, such as VSD, following TAVI.

Keywords: TAVI, aortic stenosis, ventricular septal defect, atrioventricular block, complication

INTRODUCTION

Aortic stenosis (AS) is the leading valvular disorder in older adults, affecting roughly 2-4% of people over 75 years of age.[1] Surgical aortic valve replacement has traditionally been regarded as the standard therapy. Nevertheless, many candidates are unsuitable because of advanced age, frailty, or significant comorbid conditions. For this cohort, transcatheter aortic valve implantation (TAVI) has emerged as a less invasive and highly effective alternative.

Although TAVI has transformed care for severe AS, procedure-related complications still occur, including vascular trauma, paravalvular regurgitation, coronary obstruction, conduction system disturbances, and, on rare occasions, a ventricular septal defect (VSD). Post-TAVI VSD is a rare complication; large contemporary series report incidences well below 0.5% (e.g., ~0.37%),[2] whereas higher rates (up to ~1.5%) have been described in smaller cohorts with systematic echocardiographic screening that mainly detects small, restrictive defects.[3] We present a rare case of combined complete atrioventricular (AV) block and perimembranous VSD following the implantation of a balloon-expandable valve.

CASE REPORT

A 75-year-old man with New York Heart Association class IV symptoms—dyspnea and angina at rest—was referred for severe AS. His medical history included hypertension, diabetes mellitus, and asthma. Baseline transthoracic echocardiography (TTE) showed preserved left ventricular systolic function (ejection fraction of 55%) and severe calcific AS (Figure 1), with an aortic

To cite this article: Ömür SE, Karaman K, Alizade E. Ventricular septal defect and complete atrioventricular block following transcatheter aortic valve implantation: a case report. Int J Cardiovasc Acad. 2026;12(1):69-72

Address for Correspondence: Asst. Prof. Sefa Erdi Ömür, Department of Cardiology, Tokat Gaziosmanpaşa University, Tokat, Türkiye
E-mail: sefaerdi61@gmail.com
ORCID ID: orcid.org/0000-0002-6209-1732

Received: 28.10.2025
Accepted: 15.12.2025
Epub: 16.01.2026
Publication Date: 10.03.2026

valve area of 0.8 cm², a mean gradient of 45 mmHg, and a peak gradient of 80 mmHg. Coronary angiography demonstrated normal epicardial arteries. With a Society of Thoracic Surgeons score of 5.42%, the Heart Team recommended TAVI.

Multislice cardiac computed tomography (CT) revealed extensive calcification predominantly involving the left coronary cusp. Multislice cardiac CT demonstrated severe asymmetric aortic valve calcification predominantly involving the left coronary cusp, extending toward the left ventricular outflow tract (LVOT) and membranous septum. Calcification severity was reported as an Agatston leaflet calcium score of 3200 or as severe qualitative calcification. CT sizing showed an annular area of 651 mm², a perimeter of 90.4 mm, and coronary heights of 12 mm (left main coronary artery) and 14 mm (right coronary artery), supporting selection of a 29-mm balloon-expandable Myval™ valve. The Myval™ transcatheter heart valve is a balloon-expandable, tri-leaflet bovine pericardial valve mounted on a nickel-cobalt frame with a hexagonal-cell design and a sealing cuff; it is available in conventional, intermediate, and extra-large sizes, facilitating more granular annular sizing. The procedure was performed transfemorally under fluoroscopic guidance using a pre-defined coplanar projection. After pre-dilation with a 25-mm balloon, significant resistance was observed during balloon expansion under rapid pacing; subsequently, a 29-mm balloon-expandable Myval™ (Meril Life Sciences Pvt. Ltd., India) prosthesis was deployed. The final valve position was 2.8 mm ventricular to the annular plane (implantation depth measured on the final angiographic projection), consistent with a neutral/orthotopic implantation strategy. Hemodynamics improved immediately, and the mean transvalvular gradient fell to 10 mmHg. Because of heavy calcification and concern for annular rupture, post-dilation was not undertaken. No resistance or recoil was documented during balloon expansion. No new conduction disturbance was observed during balloon pre-dilation; complete AV block developed immediately after valve deployment and required temporary pacing. Because conduction did not improve, a dual-chamber permanent pacemaker was implanted before discharge (on the second day after TAVI). Pre-discharge TTE with color Doppler interrogation of the interventricular septum (perimembranous region) showed no evidence of a VSD or an interventricular shunt, and no new murmur was noted during the index hospitalization.

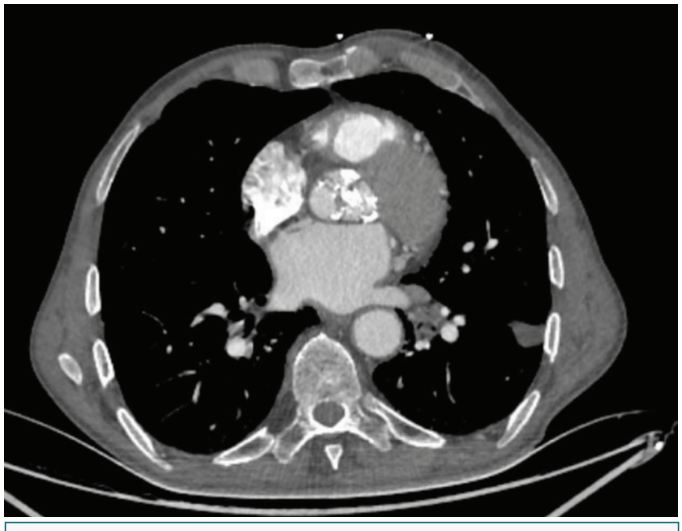


Figure 1. Calcification seen on the aortic valve

At one-month follow-up, he reported worsening dyspnea. Compared with pre-discharge findings (no murmur and no shunt on TTE), a new pansystolic murmur was detected on examination. TTE confirmed normal prosthetic valve function (mean gradient of 10 mmHg), but demonstrated an 8-mm perimembranous VSD adjacent to the prosthetic valve edge (Figure 2A), with color Doppler evidence of a significant left-to-right shunt (Figure 2B) and elevated estimated pulmonary artery (PA) pressures (62/38 mmHg) (Figure 2C). Estimated right ventricular (RV) systolic pressure was 38 mmHg, with mildly abnormal RV size and systolic function (tricuspid annular plane systolic excursion 15 mm, fractional area change 34%). Right-heart catheterization was planned to quantify shunt severity (Qp/Qs: 1.9) and to obtain comprehensive right-sided hemodynamics (right atrium, RV, PA, pulmonary capillary wedge pressure) prior to evaluation for percutaneous versus surgical closure of the VSD.

Written informed consent was obtained from the patient.

DISCUSSION

TAVI may be complicated by a spectrum of adverse events, including vascular and valvular complications, as well as conduction and structural problems. VSD is particularly uncommon but clinically important, with an estimated frequency of 0.37% after TAVI.[2]

Mechanistically, iatrogenic VSD following TAVI is likely multifactorial. Severe asymmetric calcification can predispose the membranous septum to injury during balloon pre-dilation or valve deployment. Excess mechanical stress may shift calcified nodules into the interventricular septum, provoking both conduction block and mechanical disruption. Balloon pre-/post-dilatation in the presence of bulky, asymmetric annular/LVOT calcium may increase focal mechanical stress and can displace/compress calcific nodules toward adjacent structures, including the membranous septum, providing biological plausibility for septal disruption and VSD.[3] In line with this, a review of reported post-TAVR VSD cases found that VSDs were more frequently associated with balloon-expandable valves and with the use of pre- or post-dilatation.[4]

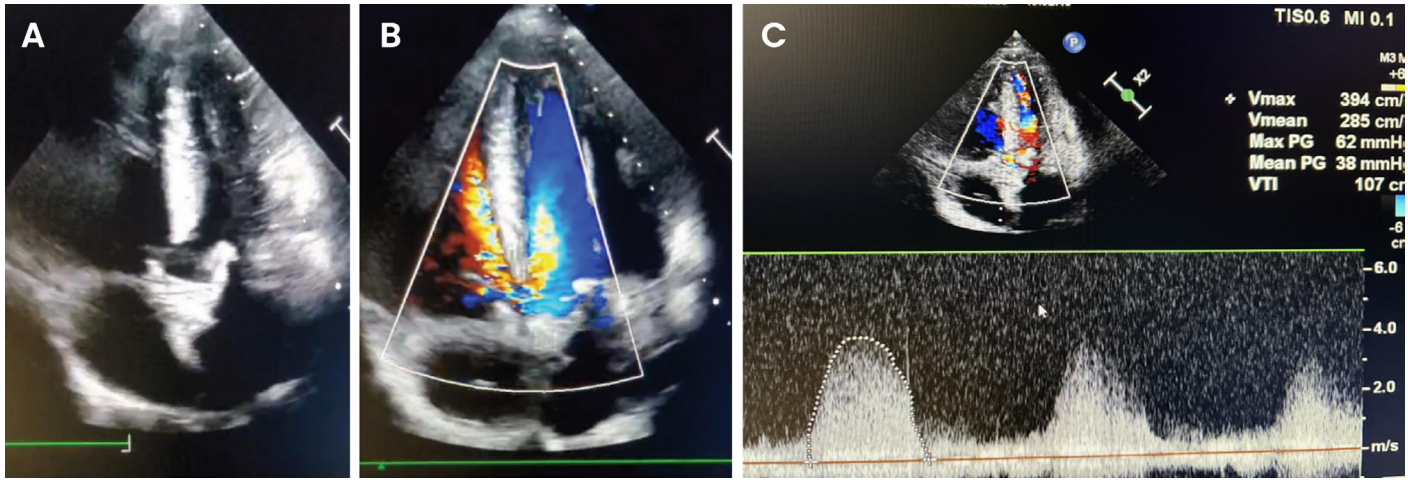


Figure 2. A) 8 mm VSD developing after TAVI, B) VSD shunt from left ventricular to right ventricular, C) 62/38 mmHg gradient formed on the VSD shunt

VSD: Ventricular septal defect, TAVI: Transcatheter aortic valve implantation

Conduction abnormalities are among the most frequent complications of TAVI due to the close anatomical relationship among the aortic annulus, the membranous septum, and the AV node. Situated at the apex of Koch's triangle, adjacent to the membranous septum and subaortic LVOT, the conduction system is vulnerable to compression or trauma during prosthesis expansion, which explains the propensity for AV block in these cases. In the randomized LANDMARK conduction substudy, 30-day new permanent pacemaker implantation rates were similar between Myval and contemporary valves (15% vs. 17%), with complete AV block being the most common indication, supporting the conclusion that clinically relevant conduction injury remains a platform-spanning issue influenced by anatomy, calcification, and deployment mechanics.[5]

Valve design and deployment mechanics may influence the risk of septal injury. Balloon-expandable valves are deployed by acute balloon inflation, which can generate high instantaneous radial stress within the annulus/LVOT and may displace bulky, asymmetric calcification toward the membranous septum—particularly in the presence of moderate-to-severe LVOT calcification—thereby plausibly increasing the risk of adjacent septal trauma.[6] Conversely, self-expanding valves expand more gradually and are often repositionable; however, meta-analyses comparing contemporary platforms have reported higher rates of conduction disturbances and permanent pacemaker implantation with some self-expanding systems than with balloon-expandable devices.[7]

In our patient, severe asymmetric calcification coupled with balloon pre-dilation and prosthesis expansion likely displaced calcium toward the membranous septum, producing immediate AV block and later culminating in a VSD. The absence of a shunt on pre-discharge echocardiography suggests a delayed or progressive septal injury, which became clinically evident at one month. Clinically, the patient developed dyspnea and a new murmur, and echocardiography confirmed a significant left-to-right shunt. Management of post-TAVI VSD depends on size, hemodynamic burden, and symptoms; small, stable defects can be observed, whereas larger or symptomatic defects may require percutaneous or surgical closure.

CONCLUSION

This case illustrates two rare but consequential post-TAVI complications—complete AV block necessitating permanent pacing and a perimembranous VSD with left-to-right shunting—most likely driven by severe asymmetric calcification and balloon manipulation. Thorough pre-procedural imaging, careful valve sizing, and judicious use of balloon dilatation are essential to reduce these risks, and clinicians should maintain vigilance for new murmurs or unexplained dyspnea during follow-up.

Ethics

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.E.Ö., Concept: S.E.Ö., K.K., Design: S.E.Ö., E.A., Data Collection or Processing: S.E.Ö., Literature Search: S.E.Ö., Writing: S.E.Ö., K.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Van Hemelrijck M, Taramasso M, De Carlo C, Kuwata S, Regar E, Nietlispach F, *et al.* Recent advances in understanding and managing aortic stenosis. F1000Res. 2018;7:58.
2. Nona P, Mahmood S, Lemor A, Qintar M, O'Neill B, Lee J, *et al.* Incidence of acquired ventricular septal defect after transcatheter aortic valve replacement: a large single center experience. Catheter Cardiovasc Interv. 2021;98:975-80.
3. Zeniou V, Chen S, Gilon D, Segev A, Finkelstein A, Planer D, *et al.* Ventricular septal defect as a complication of TAVI: mechanism and incidence. Structural Heart. 2018;2:235-9.
4. Ando T, Briasoulis A, Holmes AA, Afonso L, Grines CL, Takagi H. Ventricular septal defect after transcatheter aortic valve replacement: a systematic review. J Cardiol. 2016;67:117-21.
5. Smits P, Rampat R, van Royen N, Amat-Santos I, Hudec M, Bunc M, *et al.* Conduction disturbances and permanent pacemaker implantation after Myval transcatheter heart valve or contemporary standard valves implantation: insights from the LANDMARK trial. J Am Coll Cardiol. 2024;84:B338.
6. Okuno T, Asami M, Heg D, Lanz J, Praz F, Hagemeyer D, *et al.* Impact of left ventricular outflow tract calcification on procedural outcomes after transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2020;13:1789-99.
7. Wang B, Mei Z, Ge X, Li Y, Zhou Q, Meng X, *et al.* Comparison of outcomes of self-expanding versus balloon-expandable valves for transcatheter aortic valve replacement: a meta-analysis of randomized and propensity-matched studies. BMC Cardiovasc Disord. 2023;23:382.