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List of Contents

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      Nonaka H, Emoto N, Ikeda K, Fukuya H, Rohman MS, Raharjo SB, Yagita K, Okamura H, Yokoyama M. Angiotensin II induces circadian gene expression of clock genes in cultured vascular smooth muscle cells. Circulation. 2001;104:1746-8.
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Editorial

Optimizing Revascularization Outcomes in Chronic Coronary Syndromes

Aninka Saboe[1,2]

Abstract
The value of coronary revascularization in Chronic Coronary Syndromes (CCS) depends on whether it delivers the benefit that justified intervention. Anatomical, physiological, and plaque assessment inform patient selection, but each answers a different clinical question. Applying evolving trial evidence requires attention to the populations studied, outcomes measured, and durability of treatment. Procedural optimization and complete revascularization require the same clinical judgment, with imaging and devices serving defined treatment goals. Medical therapy remains essential regardless of the revascularization strategy. Follow-up connects the procedure to sustained prevention, rehabilitation, and assessment of symptoms and clinical events. Reviewing these outcomes against the original indication, together with the patient's priorities, provides a practical basis for improving care.

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Introduction

Technical success is important, but the value of coronary revascularization lies in its benefit to the patient. In Chronic Coronary Syndromes (CCS), this may mean relief of limiting angina or improved prognosis in an appropriate clinical setting.[1-2] For Percutaneous Coronary Intervention (PCI) and surgery alike, patient selection, procedural quality, and sustained care must remain aligned with that goal (Figure 1). Evolving evidence and patient priorities guide decisions throughout this process.

Patient Selection and Treatment Planning

The first decision is what revascularization is expected to achieve. Extended follow-up of the ISCHEMIA trial found no significant all-cause mortality advantage with an initial invasive strategy over conservative management at a median of 5.7 years.[3] Significant Left Main (LM) disease and Left Ventricular Ejection Fraction (LVEF) <35% were excluded; these findings cannot settle the prognostic question in such patients. Significant LM disease, extensive multivessel disease, and severe ventricular dysfunction require separate consideration.[1-2] Symptom relief is a distinct benefit, supported by placebo-controlled PCI evidence in patients receiving little or no antianginal therapy and the small ORBITA-CTO trial in symptomatic single-vessel chronic total occlusion.[4-5] These are reasons to define the treatment goal, with medical therapy continuing whichever strategy is chosen.[1]

Anatomical assessment establishes stenosis severity, distribution, and complexity. When appropriate, Coronary Computed Tomography Angiography (CCTA) can exclude obstructive disease or define its extent, identifying high-risk anatomy for invasive assessment.[1] Angiographic diameter stenoses ≥70% in non-LM arteries or ≥50% in the LM are conventionally considered significant, although anatomy alone does not establish a PCI indication.[2]

For intermediate stenoses, physiology connects anatomical findings to the decision to intervene. Wire-based hyperemic and nonhyperemic assessment provides established thresholds, including Fractional Flow Reserve (FFR) ≤0.80 and instantaneous wave-free ratio ≤0.89.[1] Angiography-derived approaches offer alternatives, although randomized noninferiority findings remain specific to the platforms tested and their one-year composite endpoints.[6-7] CT-derived FFR can clarify selected stenoses, with interpretation limited by image quality, borderline values, and diffuse disease.[8] The distribution of disease also shapes expectations: observational Pullback Pressure Gradient (PPG) data associate focal disease with less residual angina after PCI.[9] Recognizing diffuse disease helps explain why treating a discrete stenosis may leave symptoms unresolved.

Plaque characterization broadens risk assessment beyond ischemia, without by itself establishing a PCI indication. CCTA identifies low-attenuation plaque and positive remodeling; Intravascular Ultrasound (IVUS), Optical Coherence Tomography

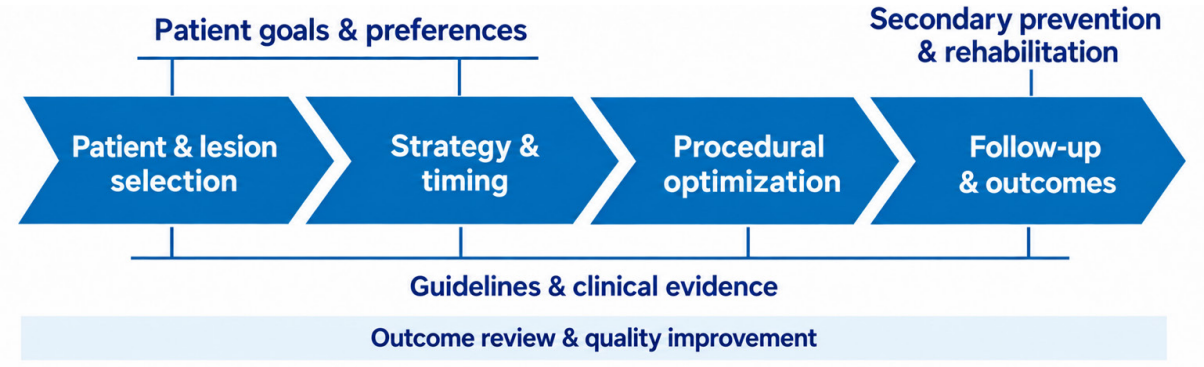

Figure 1. A framework for optimizing revascularization outcomes in chronic coronary syndromes. Planning integrates patient and lesion selection with decisions on strategy and timing. Procedural optimization is followed by assessment of recovery and long-term outcomes. Patient goals and preferences inform treatment decisions, while guidelines and clinical evidence inform all stages. Secondary prevention and rehabilitation support continuing care. Outcome review supports quality improvement across the entire process. The framework applies to PCI and CABG. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

(OCT), and Near-Infrared Spectroscopy (NIRS) add information on plaque burden, Thin-Cap Fibroatheroma (TCFA), and lipid content.[1,10-11] A maximum lipid core burden index within a 4-mm segment (maxLCBI4mm) >400 has been associated with subsequent nonculprit events.[11] Whether treating such plaques prevents clinical events remains unsettled. PREVENT reduced a two-year composite including revascularization and angina hospitalization by adding PCI to medical therapy for selected, imaging-defined non-flow-limiting plaques, without establishing reduced death or Myocardial Infarction (MI).[10] The smaller PROSPECT ABSORB trial improved lumen dimensions but did not demonstrate fewer clinical events and was not powered for clinical efficacy.[12] Plaque findings can strengthen preventive care; routine preventive PCI still requires stronger randomized evidence.

When revascularization is indicated, the choice between PCI and Coronary Artery Bypass Grafting (CABG) depends on anatomical complexity, ventricular function, diabetes, frailty, and the feasibility of complete revascularization. Guidelines favor CABG in suitable surgical candidates with diabetes and multivessel disease involving the Left Anterior Descending (LAD) artery.[2] Longer follow-up helps refine the discussion. In three-vessel disease without LM involvement, FAME 3 found no significant five-year difference in the death, stroke, or MI composite, but more MI and repeat revascularization after PCI.[13] NOBLE found no significant ten-year all-cause mortality difference for unprotected LM disease without additional complex lesions; nonfatal events were not assessed beyond five years.[14] These results do not make the strategies interchangeable. Heart Team discussion needs to place prognosis alongside recovery, procedural risk, and the likelihood of further treatment. Timing in CCS allows for this discussion and medical optimization, while remaining responsive to symptoms and risk.[1-2]

Procedural Quality and Optimization

Once PCI is chosen, imaging is valuable when it changes how the procedure is performed and confirms the result. CCTA can support planning; IVUS or OCT guides lesion preparation, sizing, and assessment of expansion and complications.[1] Intravascular imaging guidance reduced five-year target-vessel failure in complex PCI, whereas separate LM and complex high-risk trials did not demonstrate superiority for their primary endpoints.[15-17] A network meta-analysis combining randomized and observational studies associated intravascular imaging guidance with fewer major adverse cardiovascular events and stent thromboses in calcified lesions.[18] Differences in populations, protocols, and follow-up limit comparisons. The guideline recommendation for intravascular imaging in complex PCI therefore needs to be applied through explicit optimization targets.[1]

The 2026 European LM consensus illustrates how such targets depend on anatomy and technique. Suggested Minimum Stent Area (MSA) ranges are 10–12 mm² in the LM and 7–8 mm² at the LAD ostium for provisional or two-stent PCI. At the circumflex ostium, the benchmark is a Minimum Lumen Area (MLA) ≥4 mm² after provisional crossover, versus an MSA of 6–7 mm² with two stents.[19] These values complement assessment of vessel dimensions, relative expansion, edge injury, malapposition, and stent deformation. Pursuing an absolute area without considering vessel size risks turning an optimization target into a reason for overexpansion.[19]

Contemporary Drug-Eluting Stent (DES) remains the reference treatment for de novo PCI.[20] Drug-Coated Balloons (DCBs) offer an option for selected in-stent restenosis,[1] while their broader use in de novo disease depends on successful lesion preparation and readiness for provisional stenting when needed.[20-21] The trade-off is durability: a sirolimus-balloon strategy met one-year noninferiority for target-vessel failure in the intention-to-treat analysis, not per protocol; both this and a paclitaxel-balloon strategy resulted in more repeat revascularization than DES.[20-21] Indonesian observational studies reported encouraging one-year outcomes in selected patients after DCB-only angioplasty in vessels ≥3.0 mm and completed hybrid DES–DCB procedures for true distal LM bifurcations.[22-23] These experiences merit larger prospective comparative studies. Bioresorbable scaffolds offer temporary support, but their clinical role remains less established: IRONMAN II demonstrated noninferiority for two-year in-segment late lumen loss, not clinical equivalence.[24] Choosing among these approaches requires matching the need for scaffolding and the result of lesion preparation to the strength of evidence for a durable outcome.

Complete revascularization requires a plan for the disease left untreated, whether the procedure is

PCI or CABG. That plan balances residual disease against procedural burden and, for surgery, graft targets and durability.[1] After PCI, residual ischemia helps identify clinically important remaining targets. A prespecified FAME 3 analysis associated a residual functional SYNTAX score >8 after PCI with more five-year death, MI, or stroke than complete CABG, although the subgroup comparisons were not randomized.[25] Physiology-guided target selection is less established for CABG.[2] The practical implication is to document treated lesions, deliberately deferred disease, and targets reserved for staging, rather than equating a successful procedure with completion of treatment.

Follow-up and Long-Term Outcomes

Follow-up begins with completing the agreed plan. For staged PCI in CCS, physiology can guide treatment or deferral of residual intermediate lesions, while symptoms, renal function, and procedural burden inform timing.[1] Remaining targets, the proposed schedule, and responsibility for reassessment need to be clear. The postinfarction evidence addresses a different setting: the European Society of Cardiology (ESC) guidance recommends complete revascularization during index PCI or within 45 days in hemodynamically stable patients with ST-segment elevation MI and multivessel disease undergoing primary PCI.[26] That window cannot be transferred automatically to elective CCS practice. After PCI or CABG, reassessment returns to whether further treatment is justified by residual disease, recovery, and the original goals.[1]

Sustaining benefit also means closing the gap between preventive targets and everyday treatment. After revascularization, Low-Density Lipoprotein Cholesterol (LDL-C) should be <55 mg/dL with a ≥50% reduction from baseline; <40 mg/dL may be considered for recurrent vascular events despite maximally tolerated statin-based therapy or for polyvascular disease.[1,27] In the seven-center Indonesia-INTERASPIRE survey, only 8.5% of 402 participants achieved LDL-C <55 mg/dL.[28] This is not a national estimate, but it brings access, tolerability, and adherence into the same discussion as treatment intensity.

For escalation of lipid-lowering therapy, clinical outcomes and plaque changes provide different kinds of evidence. In a prespecified VESALIUS-CV analysis of stable patients with prior PCI, LDL-C ≥90 mg/dL, and no previous MI or stroke, evolocumab reduced the composite of coronary heart disease death, MI, or ischemic stroke.[29] A recent NIRS meta-analysis found a numerical reduction in maxLCBI4mm with Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitor–based regimens, but neither this subgroup result nor the overall pooled effect was statistically significant.[30] Treatment intensity remains guided by LDL-C and clinical risk.[1,27]

Secondary prevention also requires blood-pressure and diabetes control, smoking cessation, and antithrombotic therapy that balances ischemic protection against bleeding.[1-2] Maintenance treatment deserves periodic reconsideration. In HOST-EXAM, patients event-free during 6–18 months of dual antiplatelet therapy had better net clinical outcomes at ten years with clopidogrel than aspirin, without a significant all-cause mortality difference.[31] This supports considering clopidogrel for maintenance monotherapy after PCI, while reviewing the regimen as bleeding risk and tolerability change.[1-2]

Rehabilitation connects prevention with recovery. The 2026 ESC Guidelines bring exercise, education, psychosocial support, and preventive care together in comprehensive cardiac rehabilitation.[32] Referral is more meaningful when barriers to participation are addressed and the program fits the patient's capabilities. Persistent angina also deserves explanation: residual epicardial disease, microvascular dysfunction, and vasomotor disorders may require different responses.[1] Symptoms, functional capacity, and quality of life therefore belong alongside clinical events and repeat revascularization in the assessment of benefit.

These outcomes provide a basis for service improvement through registries and risk-adjusted review.[2] In Indonesia, regional disparities in catheterization access make coordination between referring clinicians and treating centers particularly important.[33] Recording treatment goals, completion of the agreed plan, preventive therapy, and patient-reported recovery allows services to examine where an appropriate indication failed to translate into benefit. Procedure volume alone cannot answer that question.

Conclusion

In CCS, well-informed revascularization decisions connect an appropriate indication with careful execution and sustained care. New trials refine those decisions by clarifying which patients

benefit, from which strategy, and over what period. The enduring measure of quality is whether patients receive the benefit that justified intervention.

List of Abbreviations

CABG	Coronary Artery Bypass Grafting
CCS	Chronic Coronary Syndromes
CCTA	Coronary Computed Tomography Angiography
DCBs	Drug-Coated Balloons
DES	Drug-Eluting Stent
ESC	European Society of Cardiology
FFR	Fractional Flow Reserve
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending
LDL-C	Low-Density Lipoprotein Cholesterol
LM	Left Main
LVEF	Left Ventricular Ejection Fraction
maxLCBI4mm	maximum lipid core burden index within a 4-mm segment
MI	Myocardial Infarction
MLA	Minimum Lumen Area
MSA	Minimum Stent Area
NIRS	Near-Infrared Spectroscopy
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PPG	Pullback Pressure Gradient
TCFA	Thin-Cap Fibroatheroma

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During the preparation of this work, the author used AI-assisted tools: Grammarly for grammar and language editing and EndNote for reference management. The author remains responsible for the final content.

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Original Article

The Difference Value of Global Pulse Wave Velocity between Type 2 Diabetic and Non-diabetic Patients with Chronic Coronary Syndrome

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Abstract

Background: Coronary Heart Disease (CHD) remains a major health issue in Indonesia. CHD could lead to myocardial infarction and sudden death, highlighting the necessity for cardiovascular examination and appropriate management to prevent increased morbidity and mortality rates. One non-invasive method for assessing CHD was measuring arterial stiffness using Global Pulse Wave Velocity (PWVg). This study aimed to assess the difference in PWVg among patients with Chronic Coronary Syndrome (CCS) with or without Type 2 Diabetes (T2DM).

Methods: This was an analytical cross-sectional study to evaluate the difference in PWVg values among CCS patients with or without T2DM. The study used data from medical records and elective coronary angiography at the Dr. M. Djamil Teaching Hospital's cardiac catheterization laboratory, where PWVg was measured by Doppler echocardiography examination of CCS patients from April 2023 to 2024. Normality testing using the Shapiro-Wilk test was performed before analyzing all numerical data, followed by independent t-tests or Mann-Whitney tests to determine intergroup differences.

Results: The study comprised 36 CCS patients, with 18 samples per group (with and without T2DM). In this study, males were more prevalent in the CCS group without T2DM, smoking risk factors were more commonly found in the CCS group without T2DM, higher Random Blood Glucose (RBG) was found in the CCS group with T2DM, and higher Ankle-Brachial Index (ABI) values were observed in the CCS group without T2DM. Based on statistical analysis, there was a significant difference in PWVg values between the CCS group with T2DM and the group without T2DM (8.3 + 0.7 m/s vs. 7.7 + 0.5 m/s, p=0.009).

Conclusions: T2DM results in higher PWVg values compared to those without T2DM among patients with CCS.

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Introduction

Chronic Coronary Syndrome (CCS) remained a major health concern for communities worldwide.[1-2] Symptomatic CCS and asymptomatic myocardial ischemia both pose risk for myocardial infarction and sudden death, necessitating cardiovascular screening and proper management to prevent increased morbidity and mortality rates.[3-4] Invasive coronary angiography might be performed when clinical evaluation and non-invasive diagnostics indicate a high risk of obstructive coronary lesions. Only a third of patients without a history of CCS undergoing elective cardiac catheterization have obstructive coronary artery lesions. Diagnostic examinations for CCS could be performed non-invasively using arterial stiffness measurements, intima-media thickness, exercise testing, Magnetic Resonance Imaging (MRI), and Multi-Slice Computed Tomography (MSCT). Specifically, arterial stiffness has increasingly been recognized as a functional and structural marker of cumulative exposure to cardiovascular risk factors.[5]

Increased central arterial stiffness was a process of arteriosclerosis and a consequence of many disease conditions, such as Type 2 Diabetes Mellitus (T2DM), atherosclerosis, and chronic kidney disease. Hyperglycaemia and insulin resistance induce mitochondrial dysfunction, oxidative stress, Advanced Glycation End-products (AGEs), disturbances in mitochondrial Ca^{2+} handling, inflammation, activation of the Renin-Angiotensin-Aldosterone System (RAAS), autonomic neuropathy, endoplasmic reticulum stress, cardiomyocyte death, and microvascular dysfunction. These pathophysiological abnormalities led to arterial stiffness.[6-8]

Several studies have shown the association between T2DM, pulse wave velocity, and coronary atherosclerosis. In populations of asymptomatic T2DM patients, increased carotid-femoral Pulse Wave Velocity (cfPWV) or brachial-ankle Pulse Wave Velocity (baPWV) values were associated with the presence and progression of coronary stenosis or visible plaques on Coronary Computed Tomography Angiography (CCTA).[9-10] In a recent study involving 45 T2DM, increased cfPWV values were associated with high-risk coronary plaque types measured by CCTA after a 5-year follow-up.[9] Nam et al. evaluated 615 asymptomatic individuals and demonstrated that increased baPWV was an independent predictor of obstructive Coronary Artery Disease (CAD) detected via CCTA. Similarly, other studies involving healthy individuals consistently showed a positive association between PWV and coronary atherosclerosis assessed through luminal narrowing or Coronary Artery Calcium (CAC) scores on CCTA.[11-15]

Arterial stiffness can cause the early appearance of the cardiac pulsation wave, leading to an increase in central systolic blood pressure, a decrease in diastolic blood pressure, and, consequently, an increase in pulse pressure. Elevated systolic blood pressure increases myocardial oxygen demand, increases ventricular load, thereby inducing left ventricular hypertrophy. Additionally, a decrease in diastolic pressure could jeopardize coronary perfusion, resulting in subendocardial ischemia. Increased pulse pressure and shear stress due to vessel stiffness can lead to arterial remodelling, thickening of arterial wall thickening, and the development of atherosclerotic plaques. Structural and physiological changes in arteries, including vascular tone, thickening of the medial smooth muscle, and modifications in blood viscosity, could alter the rate of arterial pulse wave velocity. After ventricular systole, the pressure generated by the heart was transmitted to the aorta as a wave. Global Pulse Wave Velocity (PWVg) is the time required for a pulse wave to travel from the heart to the peripheral arteries. The velocity of wave transmission will be longer in stiff blood vessels. PWVg could be measured using arterial tonometry or Doppler echocardiography and calculated between the aortic arch and the right common femoral artery by dividing the straight-line distance between them by the transit time.[16-20]

Arterial stiffness assessment was an easy, fast, non-invasive, radiation-free, and affordable examination. PWVg measurement was considered the gold standard for the direct, noninvasive assessment of arterial stiffness and had independent predictive value for primary coronary events. Several analyses indicated that aortic PWVg had better predictive ability for adverse outcomes in subjects with higher early cardiovascular risk (patients with CAD, kidney disease, hypertension, or T2DM) compared to subjects with lower cardiovascular risk (the general population). Therefore, researchers were interested in investigating the difference in PWVg values in CCS patients with or without T2DM patients.[9,21]

Methods

Study Design

This was an analytical cross-sectional study to evaluate the difference in PWVg values among CCS

patients with or without T2DM. The study utilized data from medical records and elective coronary angiography at the Dr. M. Djamil Teaching Hospital's cardiac catheterization laboratory, where PWVg from Doppler echocardiography examination of CCS patients was conducted from April 2023 to 2024.

The Inclusion criteria consisted of patients with CCS, a left ventricular ejection fraction of ≥50%, sinus rhythm, and blood pressure below 140/90 mmHg at the time of examination. Patients presenting with arrhythmia, severe heart failure, significant valvular disease, history of Coronary Artery Bypass Grafting (CABG), acute coronary syndrome, or suboptimal echocardiographic image quality were excluded from participation. Consecutive sampling is used, yielding a sample of 36 respondents.

Before undergoing angiography, all subjects were evaluated for PWVg using Doppler echocardiography equipped with a 3.5-MHz probe. Examinations were performed in a semi-supine position (head of the table elevated at 30°) after at least 10 minutes of rest in a quiet, temperature-controlled room. PWVg was derived from the pulse wave transit time between the aortic arch and the right common femoral artery. The time interval was measured from the onset of the QRS complex on the ECG to the peak of the first systolic upstroke on the Doppler spectral envelope at each sampling site. The distance between the two points was measured using a flexible tape measure, aligned with the transducer positions on the body surface. PWVg was calculated as the ratio between the measured distance and the difference in transit time (PWVg = Δdistance / Δtime).[19]

All Doppler data were digitally stored and analyzed using the echocardiography system's internal caliper software by a trained operator. To minimize inter-observer variability, all echocardiographic measurements, including PWVg determination, were independently validated by two board-certified cardiology consultants with expertise in echocardiography.

Statistical Analysis

A normality test was performed on numerical variables using the Shapiro-Wilk test to assess whether the data were normally distributed. The characteristics of respondents' data on categorical variables were presented in the form of a frequency distribution (frequencies and percentages). Data for numerical variables with a normal distribution were presented in the form of mean and standard deviation. Data for numerical variables with a non-normal distribution were presented in the form of median and minimum-maximum.

Bivariate data analysis was conducted to compare PWVg values in CCS patients with or without Type 2 DM. Data normality was analyzed using the Shapiro-Wilk test. If the data were normally distributed, independent T-tests were performed. If the data distribution was not normal, a non-parametric test, the Mann-Whitney test, was conducted. All analyses were performed using the Statistical Package for Social Sciences (SPSS) program for Windows.

Table 1. Characteristics of study subjects.

Variable	CCS with DM n=18	CCS without DM n=18
Age (years), mean ±SD	59±8.1	59.2±7.9
Sex, n (%)		
Males	10 (55.6%)	16 (88.9%)
Females	8 (44.4%)	2 (11.1%)
Risk Factor, n (%)		
History of Hypertension	11 (61.1%)	13 (72.2%)
Smoker	7 (38.9%)	16 (88.9%)
Family History	3 (16.7%)	3 (16.7%)
BMI (kg/m^2), mean±SD	24.5±2.2	23.8±3
Cholesterol (mg/dl)		
LDL, mean±SD	137.3±38.2	116.5±41.8
HDL, median(min-max)	35.5 (28-62)	41.3 (29-67)
Total cholesterol, mean±SD	209.2±40.4	182.7±48.6
Trygliceride(s), median(min-max)	166.5 (108-428)	141.5 (56-313)

Drugs, n (%)		
ACE-I/ARB	10 (55.6%)	14 (77.8%)
B-blocker	17 (94.4%)	17 (94.4%)
Calcium channel blocker	5 (27.8%)	9 (50%)
Statin	16 (88.9%)	15 (83.3%)
Antiplatelet	18 (100%)	18 (100%)
Nitrate	17 (94.4%)	16 (88.9%)
RBG (mg/dl), mean±SD	202±59.7	110±16.7
Coronary Angiography Result		
CAD 1 VD, n (%)	1 (20%)	4 (80%)
CAD 2 VD, n (%)	3 (37.5%)	5 (62.5%)
CAD 3 VD, n (%)	14 (60.9%)	9 (39.1%)
Echocardiography		
LV EF (%), mean±SD	58.2±5.1	60.6±5
Diastolic dysfunction, n (%)		
Normal	13 (72.2%)	16 (88.9%)
Grade 1	5 (27.8%)	2 (11.1%)
ABI, mean±SD*	1.12±0.09	1.22±0.01
BP Systolic (mmHg), mean±SD	126±9.8	128±7.3
BP Diastolic (mmHg), mean±SD	77.2±7.9	74.7±7.3
Heart Rate (x/min), median (min-max)	66.5 (60-83)	65 (55-87)

CCS, Chronic Coronary Syndrome; DM, Diabetes Mellitus; FH, Familial History; BMI, Body Mass Index; ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; CAD, Coronary Artery Disease; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; RBG, Random Blood Glucose; VD, Vascular Disease; LVEF, Left Ventricular Ejection Fraction; ABI, Ankle Brachial Index; BP, Blood Pressure.

Results

A total of 36 patients who underwent PWVg measurements met the inclusion criteria through consecutive sampling and were taken as research subjects. The basic characteristics of the research subjects are shown in Table 1.

In the patient characteristic data, males were more prevalent in the CCS group without DM; smoking risk factors were more common in the CCS group without DM; higher RBG was observed in the CCS group with DM; and higher ABI values were observed in the CCS group without DM.

Based on the Shapiro-Wilk normality test, the distribution of PWVg group data was found to be normally distributed, allowing the independent-samples t-test to proceed. Table 2 shows the difference in PWVg values in CCS patients with or without Type 2 DM. The mean PWVg values were obtained as 8.3 ± 0.7 m/s in CCS with Type 2 DM and 7.7 ± 0.5 m/s in CCS without Type 2 DM. The P-value of 0.009 indicates that there was a significant difference in the PWVg values between the CCS group with Type 2 DM compared to those without Type 2 DM.

Discussion

Based on the research findings, the basic characteristics of the research subjects indicated that males were more prevalent in the CCS group without DM, and smoking risk factors were more commonly found in the CCS group without DM. Higher RBG was found in the CCS group with DM, and higher ABI values were found in the CCS group without DM. The majority of the subjects were males. This finding was consistent with research by Yao Lu and colleagues in 2023, which found

Table 2. Difference in PWVg values in CCS patients with or without Type 2 DM.

Variable	CCS with DM n=18	CCS without DM n=18	P-Value
PWVg (m/s), mean±SD	8.3±0.7	7.7±0.5	0.009

PWVg, Global Pulse Wave Velocity; CCS, Chronic Coronary Syndrome; DM, Diabetes Mellitus.

that males had higher PWV values than females. Another study by Bo Hyun Kim and colleagues in 2018 found that males had higher PWV values and a higher risk of Coronary Heart Disease (CHD) with more severe lesions than females. This is because women tend to have better endothelial function and vascular reactivity than men, due to the vasodilatory effects of estrogen on blood vessels.[10,22-23]

Smoking was a significant risk factor for arterial stiffness, especially in males who tend to have a higher smoking prevalence than females. There was evidence that compliance of large and medium arteries decreased directly after smoking a cigarette. This result was consistent with previous findings that the annual change ratio in baPWV during the study period was significantly greater in sustained heavy smokers (11.0 ± 1.9 cm/s per year) than in non-smokers (5.5 ± 0.6 cm/s per year). These findings were also consistent with the study by Bo Hyun Kim and colleagues in 2018. Smoking had a negative effect on the hemostatic process that could trigger an imbalance between prothrombotic and antithrombotic factors, which could further initiate and exacerbate arterial and thrombotic diseases.[10, 24-26]

Hirofumi and colleagues found significant differences in PWV between normal subjects and patients with diabetes. Hyperglycemia, insulin resistance, induced metabolic disorders that increase mitochondrial dysfunction, oxidative stress, advanced glycation end products (AGEs), mitochondrial Ca^{2+} handling disorders, inflammation, renin-angiotensin-aldosterone system (RAAS) activation, autonomic neuropathy, endoplasmic reticulum stress, cardiomyocyte death, and microvascular dysfunction. These pathophysiological abnormalities lead to arterial stiffness.[6-8,27]

In 2011, Peter Wohlfahrt found that high PWV values were associated with higher ABI values. Consistent with this study, the researchers found significant differences in ABI values between CCS patients with and without DM, although both remained within the normal range. Increased ABI values were associated with medial arterial calcification, including calcification of the arterial media and the internal elastic lamina. This calcification was a dysregulation of the balance between calcification promotion and inhibition that often occurs in diabetes mellitus, atherosclerosis, and aging. A study by Masoumeh Sadeghi and colleagues in 2011 showed that ABI values were lower in diabetic patients and statistically significant and associated with CAD occurrence.[28-29]

This study showed a difference in PWVg between the CCS group with type 2 DM and the CCS group without type 2 DM, with mean values of 8.3 ± 0.7 m/s and 7.7 ± 0.5 m/s, respectively. These values were higher than the normal value of 7.1 ± 1.1 m/s. The results of this study were supported by other studies, such as the study by M. Cywnar and colleagues in 2006, in which PWV was significantly higher in CAD patients with type 2 DM than in CAD patients without type 2 DM (P=<0.01). Increased arterial stiffness, along with diabetes and other risk factors result in vascular remodeling, increased lumen pressure, and shear stress that accelerate atheroma formation, and stimulate excessive collagen production and deposition in the arterial wall leading to atherosclerosis.[11]

Consistent with this, Kim and colleagues in 2018 examined patients with type 2 DM complaining of chest pain and found that higher baPWV was a significant predictor of coronary artery stenosis detected by coronary MSCT angiography. The study suggested that baPWV values above the cutoff value of 1.650 cm/s might be an acceptable predictor of silent CAD in diabetic patients. In a more recent study involving 45 patients with type 2 DM, an increase in cfPWV was associated with high-risk coronary plaque type, as measured by CCTA, after 5 years of follow-up. PWV reflects arterial stiffness, which was caused by central elastic components and peripheral muscle components. High PWV values have been observed in patients with cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia. Many studies have evaluated the use of PWV to predict cardiovascular risk, and it has been widely measured in various clinical situations. Nakamura et al. suggested that baPWV might be useful for assessing macrovascular damage, and Choi et al. reported a close relationship between baPWV and cardiovascular disease risk factors of metabolic syndrome.[9-10,30-31]

There were differences in basic characteristics across several variables, which could affect PWVg results under these conditions. This study only examines the difference in PWVg between those with DM and those without, without accounting for confounding factors in PWVg values, so further studies are needed.

Conclusion

The patient in this study showed that males were more prevalent in the CCS group without T2DM, smoking risk factors were more commonly found

in the CCS group without T2DM, higher random blood glucose (RBG) was found in the CCS group with T2DM, and higher ABI values were observed in the CCS group without T2DM. Statistical analysis showed a significant difference in PWVg between the CCS group with T2DM and the group without T2DM. Diabetes results in higher PWVg values compared to those without T2DM among patients with CCS.

List of Abbreviations

ABI	Ankle-Brachial Index
ACE-I	Angiotensin-Converting Enzyme Inhibitor
AGEs	Advanced Glycation End Products
ARB	Angiotensin Receptor Blocker
baPWV	Brachial-Ankle Pulse Wave Velocity
BMI	Body Mass Index
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CCS	Chronic Coronary Syndrome
cfPWV	Carotid-Femoral Pulse Wave Velocity
CCTA	Coronary Computed Tomography Angiography
CHD	Coronary Heart Disease
ECG	Electrocardiogram
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
PWVg	Global Pulse Wave Velocity
RAAS	Renin-Angiotensin-Aldosterone System
RBG	Random Blood Glucose
SPSS	Statistical Package for the Social Sciences
T2DM	Type 2 Diabetes Mellitus

Ethical Clearance

This study has received ethical approval from the Ethics Committee of Dr. M. Djamil Hospital / Faculty of Medicine, Universitas Andalas, Padang, Indonesia, and was conducted in accordance with the Declaration of Helsinki.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

FY: Conceptualization, study design, data collection, data analysis, manuscript drafting, and final approval. EFE: Study supervision, methodology validation, echocardiography validation, critical revision of the manuscript, and final approval. YRI: Data interpretation, statistical analysis support, manuscript review, and final approval. HA: Clinical supervision, critical revision of the manuscript, and final approval.

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Conflict of Interest

No conflict of interests.

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The authors declare that no generative AI or AI-assisted technologies were used in the writing, analysis, or preparation of this manuscript. All work represents the original contributions of the authors.

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Original Article

SYNTAX Score 2020 Risk Estimates Between PCI and CABG in Coronary Artery Disease: A Descriptive Study

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Abstract

Background: The SYNTAX Score 2020 is a validated tool that combines anatomical and clinical parameters to estimate long-term outcomes in Coronary Artery Disease (CAD) and guide revascularization decisions between Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG). Although its components are well-defined, further studies are needed to better describe how clinical variables are reflected in risk predictions across diverse populations, including those in Indonesia.

Methods: This descriptive observational, cross-sectional study included 115 patients with angiographically confirmed Three-vessel Disease (3VD) or Left Main Coronary Artery Disease (LMCAD) treated at dr. Doris Sylvanus Regional General Hospital, Palangka Raya, Indonesia, between January and June 2025. The anatomical SYNTAX Score I and SYNTAX Score 2020 were calculated using the official application. Predicted long-term risks for PCI and CABG were summarized descriptively and compared within individual patients.

Results: Predicted risks showed wide inter-individual variability and were generally higher under PCI than CABG. Predicted risks did not always align with anatomical risk assessment alone; differences became apparent when clinical variables were incorporated. Higher predicted risks and larger differences between PCI and CABG were more commonly observed in patients with older age, reduced Left Ventricular Ejection Fraction (LVEF), impaired renal function, greater anatomical complexity, insulin-treated Diabetes Mellitus (DM), and Peripheral Vascular Disease (PVD). Patients without DM or with non–insulin-treated DM were more frequently represented among those with lower predicted risk strata. When comparing PCI and CABG scenarios, most patients remained within the same predicted risk stratum, whereas shifts to higher predicted risk strata occurred more often under PCI.

Conclusions: SYNTAX Score 2020–predicted risks show marked inter-individual variability between PCI and CABG scenarios. Greater clinical and anatomical complexity tended to coincide with higher predicted risks and larger differences between revascularization strategies. Risk stratification based solely on anatomical assessment may be reclassified once patient-specific clinical variables are incorporated. These findings support the use of the SYNTAX Score 2020 to complement clinical judgment and multidisciplinary revascularization decision-making.

Keywords: SYNTAX Score 2020, Coronary Artery Disease, Coronary Revascularization, Interventional Cardiology

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Introduction

Coronary Artery Disease (CAD) is a major global health issue and a leading cause of cardiovascular death. Cardiovascular diseases remain a leading cause of death worldwide, with a substantial burden in Southeast Asia, including Indonesia.[1] Patients with Three-Vessel Disease (3VD) or Left Main Coronary Artery Disease (LMCAD) involvement represent a clinically complex population in which revascularization decisions carry important long-term prognostic implications. In such patients, selecting an optimal revascularization strategy requires careful consideration of both coronary anatomy and individual clinical risk profiles.[2-3]

Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) are established revascularization strategies for complex CAD. Contemporary clinical practice guidelines emphasize that the choice between PCI and CABG should be guided by a multidisciplinary Heart Team approach that integrates anatomical complexity with clinical characteristics rather than relying on anatomical assessment alone.[2-3] This shift reflects the recognition that long-term outcomes following revascularization are influenced by a combination of lesion complexity and patient-specific clinical factors.

The SYNTAX Score was originally developed to quantify coronary anatomical complexity and support revascularization decision-making. Subsequent iterations, including the SYNTAX Score II and the updated SYNTAX Score 2020, expanded this concept by incorporating key clinical variables alongside anatomical features. SYNTAX Score 2020 provides individualized, strategy-specific estimates of 10-year mortality and 5-year major adverse cardiovascular events (MACE) for both PCI and CABG scenarios, offering a framework for contextualized long-term risk assessment at the patient level.[4-5]

Although the components of the SYNTAX Score 2020 are well defined and the model has undergone external validation, information on how clinical characteristics are reflected in its predicted risk estimates across diverse populations remains limited, particularly in Indonesia. In clinical practice, interpretation of revascularization risk often begins with anatomical assessment, as reflected by the SYNTAX Score I; however, incorporation of patient-specific clinical variables may lead to different risk perspectives when estimating long-term outcomes for PCI and CABG. Differences in predicted risks when moving beyond anatomical assessment alone to an integrated clinical framework; comparisons of predicted risks between PCI and CABG scenarios; distributions of absolute risk levels; and their alignment with anatomical complexity and accompanying clinical profiles are less frequently reported. Examining predicted risks across these complementary frameworks may therefore provide additional insights when weighing revascularization strategies within a multidisciplinary clinical context. Accordingly, the present study aimed to provide a descriptive evaluation of SYNTAX Score 2020–predicted risks in this population.

Methods

Study Design and Population

This descriptive observational cross-sectional study was conducted at dr. Doris Sylvanus General Hospital, Palangka Raya, Central Kalimantan, Indonesia. Patients with angiographically 3VD or LMCAD were enrolled between January and June 2025. A non-probability consecutive sampling approach was used, in which all patients who met the inclusion criteria and did not fulfill any exclusion criteria during the study period were included.

The inclusion criteria were the presence of obstructive 3VD or LMCAD on angiography, according to predefined criteria for significant stenosis, and the availability of sufficiently complete clinical and angiographic data to calculate the anatomical SYNTAX Score I and SYNTAX Score 2020. The exclusion criteria included missing key clinical or interview-based variables required for SYNTAX Score 2020 estimation, as well as patients who could not be interviewed.

During the study period, 115 patients fulfilled the eligibility criteria and were included in the descriptive analysis. Most patients presented with Acute Coronary Syndrome (ACS), including ST-segment Elevation Myocardial Infarction (STEMI), Non-ST-segment Elevation Myocardial Infarction (NSTEMI), and unstable angina, whereas a smaller proportion presented with stable angina.

Data Collection and Clinical Assessment

Clinical data were collected from hospital records and patient interviews during hospitalization and follow-up visits. The interviews verified the participants' demographic characteristics, smoking history, and comorbidities using standardized forms.

Diabetes Mellitus (DM) status was categorized as no diabetes; non-insulin-treated diabetes; or insulin-treated diabetes (defined according to standard diagnostic criteria when laboratory data were

available; HbA1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, or random plasma glucose ≥200 mg/dL, and/or a documented physician diagnosis and/or current use of glucose-lowering medication).[6]

Peripheral Vascular Disease (PVD) (recorded primarily based on a history of physician-diagnosed PVD and/or typical symptoms of claudication or critical limb ischemia, and was cross-checked against medical records when available)[7] and Chronic Obstructive Pulmonary Disease (COPD) (defined as a physician-documented diagnosis when available and supplemented by a structured history of prior diagnosis and long-term inhaler use). Objective confirmatory testing (ankle–brachial index or vascular imaging for PVD and spirometry for COPD) was not routinely available for all patients. Therefore, misclassification and underdiagnosis, particularly for COPD and PVD, were considered possible. Renal function was assessed using serum creatinine levels measured with an automated chemistry analyzer (TMS 50i). Creatinine Clearance (CrCl) was calculated using the Cockcroft–Gault equation. Laboratory measurements were obtained primarily from baseline samples collected before coronary angiography as part of the routine clinical evaluation.

Left Ventricular Ejection Fraction (LVEF) was assessed using transthoracic echocardiography performed during index hospitalization. Echocardiographic examinations were conducted using Philips EPIQ CVx 2D and Philips Sparq systems. LVEF measurements were obtained using the Teichholz method by two independent operators blinded to the SYNTAX Score 2020–predicted risk estimates and other study outputs. Echocardiography could be performed either before or after coronary angiography or revascularization, depending on the clinical workflow.

The anatomical SYNTAX Score I was calculated under cardiologist supervision using the official SYNTAX Score 2020 application[8], in accordance with quantitative coronary lesion measurements obtained through Quantitative Coronary Angiography (QCA) (Allura FC system) to ensure accuracy and consistency in evaluating lesion severity and anatomical complexity. Stenosis was classified as significant when there was a luminal narrowing of at least 70% in one angiographic projection, 50% or more in two projections, or 50% or more in the primary coronary arteries.[9] Anatomical coronary complexity was subsequently categorized using the SYNTAX Score I into low (≤22), intermediate (23–32), and high (≥33) anatomical risk groups, in accordance with the original SYNTAX trial classification and current guideline-based frameworks.[3]

The SYNTAX Score 2020 was calculated using the official application-based calculator (SYNTAX Score 2020, Version 1.3.3).[8] The calculator integrates anatomical SYNTAX Score I with predefined clinical variables, including age, smoking status, DM status, PVD, CrCl, COPD, and coronary anatomical category (3VD or LMCAD), to generate model-based predicted risks.

Study Variables

The study variables comprised clinical and anatomical parameters required of calculate the SYNTAX Score 2020, as well as the resulting model-based predicted risks. Clinical variables included age (years), current smoking status (yes/no), DM status (categorized as no diabetes, non–insulin-treated diabetes, and insulin-treated diabetes), PVD (yes/no), COPD (yes/no), CrCl (mL/min), and LVEF (%). Anatomical variables included the anatomical SYNTAX Score I (points), which was analyzed both as a continuous variable and as predefined anatomical risk categories, and the coronary disease category, defined as 3VD or LMCAD.

Outcome Definitions and Statistical Analysis

The primary outcomes were SYNTAX Score 2020–predicted risks, including predicted 10-year all-cause mortality (%) and 5-year MACE (%), generated separately for PCI and CABG scenarios using the SYNTAX Score 2020 calculator. These outcomes represent model-derived predicted risks and do not reflect the observed clinical events or actual patient outcomes.

To explore how the interpretation of revascularization risk may differ when assessment is based on anatomical disease burden alone versus when patient-specific clinical variables are incorporated, predicted risks derived from the SYNTAX Score 2020 were descriptively examined in relation to anatomical risk stratification defined by the SYNTAX Score I. This approach allowed characterization of scenarios in which anatomical assessment alone and integrated clinical assessment would yield different perspectives on the relative PCI and CABG risks.

To facilitate within-patient comparison between revascularization strategies, paired differences in predicted risks were calculated as Δ = PCI − CABG. This direction was intentionally selected to enhance clinical interpretability, whereby positive Δ values indicated a higher predicted risk under PCI than CABG, and negative values indicated a

lower predicted risk under PCI. Using CABG as the reference strategy aligns with contemporary guideline frameworks for complex CAD and with the comparative structure of the SYNTAX Score 2020 model[2-4], without implying the clinical superiority of either revascularization strategy. Based on the direction of Δ, the predicted revascularization profiles were descriptively classified as PCI-favored (Δ < 0), CABG-favored (Δ > 0), or equal (Δ = 0). Paired differences were categorized to indicate the direction and magnitude of predicted risk differences between PCI and CABG. Categories included differences indicating a lower predicted risk with PCI (PCI-favored; Δ < 0), minimal differences indicating similar predicted risks (equipoise; 0–<2%) and progressively larger differences indicating a lower predicted risk with CABG (CABG-favored), categorized as small (2–<5%), moderate (5–<10%), and large (≥10%). These categories were investigator-defined, applied solely for descriptive purposes, and not derived from guideline-recommended thresholds or outcome-based cutoffs.

In addition to paired differences, absolute predicted risks for 10-year mortality and 5-year MACE were further grouped into investigator-defined ordinal strata (<10%, 10–<20%, 20–<40%, and ≥40%), representing increasing levels of predicted risk, to facilitate descriptive visualization and comparison across clinical profiles. These ordinal strata were not provided by the SYNTAX Score 2020 calculator and were used exclusively for descriptive interpretation, including visualization of risk shifting between PCI and CABG scenarios.

Risk shifting was defined descriptively as stability (classification within the same predicted risk stratum under both PCI and CABG), upward shifting (classification into a higher predicted risk stratum under PCI), or downward shifting (classification into a lower predicted risk stratum under PCI). These classifications represent model-based reclassifications.

All analyses were performed on the full study population (n = 115) and were descriptive. Continuous variables were summarized as mean ± standard deviation or range, as appropriate, and categorical variables were presented as absolute frequencies and percentages. No inferential statistical testing, hypothesis testing, correlation analysis, or multivariable modeling was conducted.

Descriptive tables, cross-tabulations, box-and-whisker plots, and heatmap-style visualizations were generated using Microsoft Excel. Pivot tables were used to summarize the distributions of predicted risk differences and risk strata across clinical characteristics, and conditional formatting was applied to create heatmap-style displays for visualization. Statistical summaries were cross-checked using IBM SPSS Statistics version 31.

Table 1. Patient characteristics and SYNTAX Score 2020 input variables.

Parameter	N/Range	Percentage/ Mean ± SD
Gender		
Male	92	80.0
Female	23	20.0
Clinical presentation		
STEMI	51	44.0
NSTEMI	18	16.0
Unstable angina pectoris	43	37.0
Stable angina pectoris	3	3.0
Current smoking		
No	33	28.7
Yes	82	71.3
Peripheral Vascular Disease (PVD)		
No	83	72.2
Yes	32	27.8
Chronic Obstructive Pulmonary Disease (COPD)		
No	115	100.0
Yes	0	0.0

Diabetes mellitus (DM)		
No	77	67.0
Yes, Non-Insulin	14	12.2
Yes, Insulin	24	20.8
SYNTAX Score I		
Low risk (≤ 22)	45	39.1
Intermediate risk (23 – 32)	45	39.1
High risk (≥ 33)	25	21.8
Coronary anatomical category		
Three-vessel disease (3VD)	97	84.3
Left main coronary artery disease (LMCAD)	18	15.7
Age (years)	36 - 83	58.2 ± 9.5
Creatinine clearance (mL/min)	12.0 - 136.0	65.6 ± 23.5
Left ventricular ejection fraction (%)	21.0 - 78.8	47.0 ± 13.1
SYNTAX Score I (points)	8.0 - 47.5	25.3 ± 8.7
SYNTAX Score 2020-predicted risks (%)		
10 year mortality (CABG, %)	3.8 - 97.4	28.6 ± 22.1
10 year mortality (PCI, %)	4.4 - 99.9	34.8 ± 24.4
5 year MACE (CABG, %)	4.0 - 70.3	19.1 ± 13.3
5 year MACE (PCI, %)	4.7 - 92.8	25.5 ± 17.0

Note. Variables presented include clinical and anatomical factors incorporated into the SYNTAX Score 2020 risk prediction model. 3VD: Three-vessel disease ; CABG: Coronary Artery Bypass Grafting; COPD: Chronic Obstructive Pulmonary Disease; LMCAD: Left Main Coronary Artery Disease; NSTEMI: Non–ST-segment Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; PVD: Peripheral Vascular Disease; STEMI: ST-segment Elevation Myocardial Infarction.

Results

Patient Characteristics and SYNTAX Score 2020 Input Profiles

A total of 115 patients who fulfilled the predefined inclusion criteria were included in the study. Patient characteristics and variables incorporated into the SYNTAX Score 2020 calculator are summarized in Table 1. The study population was predominantly male, and ACS constituted the most common clinical presentation, with STEMI being the most frequent subtype.

The SYNTAX Score 2020 model integrates coronary anatomical features, including the presence of 3VD or LMCAD and anatomical complexity quantified by SYNTAX Score I, together with selected clinical variables, namely age, DM status, smoking status, PVD, and CrCl. These input variables demonstrated broad distributions in the present population, reflecting heterogeneity in both anatomical burden and clinical risk profiles.

Accordingly, the SYNTAX Score 2020–derived predicted risks showed substantial inter-individual variability. Predicted 10-year mortality and 5-year MACE varied widely across both CABG and PCI scenarios, with higher mean predicted risks observed under PCI.

Predicted Revascularization Risk Across Anatomical Risk Categories

Predicted revascularization risk derived from SYNTAX Score 2020 was evaluated across anatomical complexity strata defined by SYNTAX Score I (Table 2). Revascularization profiles were determined based on the direction of paired predicted risk differences between PCI and CABG, derived from both SYNTAX Score 2020–predicted risks 10-year mortality and 5-year MACE, with positive Δ values indicating a higher predicted risk under PCI (CABG-favored), negative Δ values indicating a lower predicted risk under PCI (PCI-favored), and Δ = 0 indicating an equal predicted risk.

Among patients categorized as low-risk by the SYNTAX Score I, all were CABG-favored. In the intermediate-risk group, the majority of patients were CABG-favored, and only a small proportion were either PCI-favored of had equal predicted risks for PCI and CABG. Similarly, among patients classified as high-risk by SYNTAX Score I, all demonstrated CABG-favored based on SYNTAX Score 2020–derived predicted risks.

Table 2. Revascularization classification based on SYNTAX Score 2020–predicted risks across anatomical SYNTAX Score I risk categories.

SYNTAX Score I category	SYNTAX Score 2020 revascularization classification		
	Equal	PCI-favored	CABG-favored
	n (%)	n (%)	n (%)
Low risk	0 (0.0)	0 (0.0)	45 (100.0)
Intermediate risk	1 (2.2)	1 (2.2)	43 (95.6)
High risk	0 (0.0)	0 (0.0)	25 (100.0)

Note. Anatomical risk was categorized using SYNTAX Score I as low (≤22), intermediate (23–32), or high (≥33). Classification was based on SYNTAX Score 2020 predicted risks. CABG-favored indicates higher predicted risk under PCI than CABG (Δ = PCI − CABG > 0), PCI-favored indicates lower predicted risk under PCI (Δ < 0), and equal indicates identical predicted risks under PCI and CABG (Δ = 0). Values represent number (percentage) of patients within each anatomical category. CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention.

Table 3. SYNTAX Score 2020–predicted 10-year mortality and 5-year MACE under PCI and CABG scenarios and corresponding paired differences.

Outcome of SYNTAX Score 2020	Range	Mean ± SD
Predicted 10-year mortality (%)		
CABG	3.8 - 97.4	28.6 ± 22.1
PCI	4.4 - 99.9	34.8 ± 24.4
Δ (PCI – CABG)	-0.4 - 20.7	6.2 ± 4.2
Predicted 5-year MACE (%)		
CABG	4.0 - 70.3	19.1 ± 13.3
PCI	4.7 - 92.8	25.5 ± 17.0
Δ (PCI – CABG)	-0.3 - 22.5	6.5 ± 4.8

Note. Predicted risks were generated using the SYNTAX Score 2020 calculator and represent model-based estimates rather than observed clinical outcomes. Δ indicates within-patient paired differences between PCI and CABG predicted risks (Δ = PCI − CABG). CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention.

Distribution of Paired Differences Between PCI and CABG Predicted Risks (Δ)

Within-patient paired differences in predicted risks between PCI and CABG scenarios were calculated as Δ (PCI − CABG), enabling a direct comparison of model-based predicted outcomes for the same individuals under alternative revascularization assumptions.

For the SYNTAX Score 2020–predicted 10-year mortality risk, the mean predicted risk was higher under the PCI scenario than under the CABG scenario, resulting in a positive mean Δ of 6.20%. A similar pattern was observed for the SYNTAX Score 2020–predicted 5-year MACE risk, with a mean Δ of 6.5%, again favoring CABG (Table 3).

Beyond these summary estimates, the Δ values exhibited marked inter-individual variability. As illustrated in Figure 1, most patients demonstrated positive Δ values, indicating higher predicted risks with PCI than CABG; however, the magnitude of this difference varied substantially across individuals. The distribution of Δ values at both endpoints was centered above zero, whereas the spread of values indicated considerable heterogeneity in the magnitude of predicted risk differences between revascularization strategies.

Distribution of Δ Categories and the Equipoise Zone

To enhance clinical interpretability, paired differences in predicted risks were grouped to reflect both the direction and magnitude of the difference between PCI and CABG. Differences indicating a lower predicted risk with PCI were defined as PCI-favored (Δ < 0), minimal differences indicating similar predicted risks were defined as equipoise (0–<2%), and progressively larger differences indicating a lower predicted risk with CABG were categorized as CABG-favored across increasing difference ranges—small (2–<5%), moderate (5–<10%), and large (≥10%).

For the SYNTAX Score 2020–predicted 10-year mortality risk, most patients fell into categories indicating a lower predicted risk with CABG. The largest proportion was observed in the moderate-

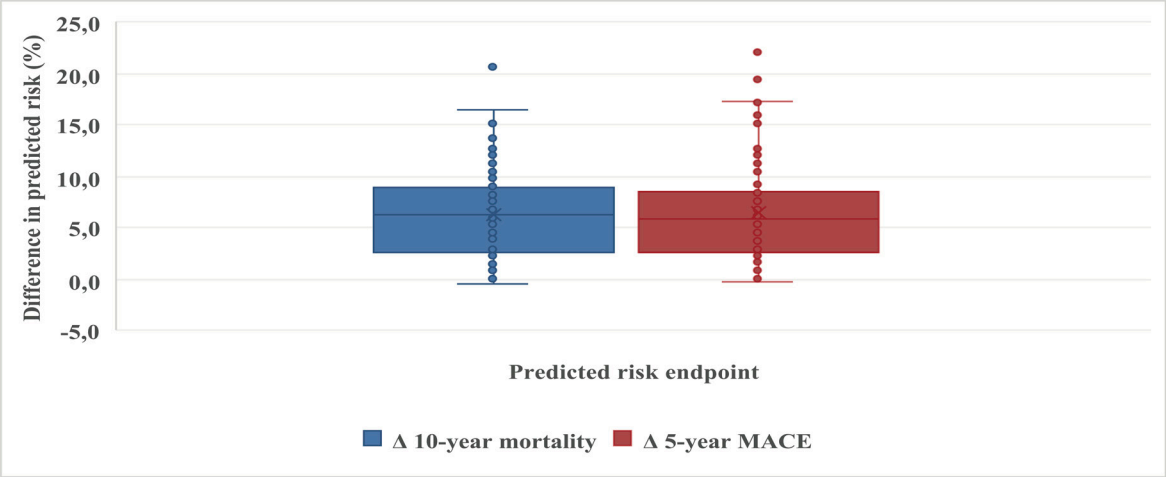

Figure 1. Distribution of within-patient differences in SYNTAX Score 2020-predicted risks between PCI and CABG.

Note. Δ was calculated as PCI minus CABG; positive values indicate higher predicted risk under PCI compared with CABG. The horizontal line within each box represents the median, the box denotes the interquartile range (IQR), whiskers indicate the range of non-outlier values, individual points represent patient-level data, and mean values are shown as × markers. MACE: Major Adverse Cardiovascular Events.

Table 4. Distribution of paired differences (Δ) between PCI and CABG predicted risks according to predefined magnitude categories.

Δ Category	Δ 10-year mortality	Δ 5-year MACE
	n (%)	n (%)
PCI-favored (Δ < 0)	1 (0.9)	1 (0.9)
Equipoise (0–<2%)	21 (18.3)	19 (16.5)
CABG-favored		
Small difference (2–<5%)	28 (24.3)	31 (27.0)
Moderate difference (5–<10%)	46 (40.0)	43 (37.4)
Large difference (≥10%)	19 (16.5)	21 (18.3)

Note. Δ represents within-patient paired differences in SYNTAX Score 2020–predicted risk between PCI and CABG scenarios (Δ = PCI − CABG). Although most patients were classified within CABG-favored categories, approximately 18% for 10-year mortality and 17% for 5-year MACE fell within the equipoise zone (Δ <2%). CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention.

difference range (5–<10%), followed by the smaller (2–<5%) and larger (≥10%) difference categories. A subset of patients showed minimal differences between PCI and CABG, whereas differences indicating a lower predicted risk with PCI were uncommon (Table 4).

A similar pattern was observed for SYNTAX Score 2020–predicted risk 5-year MACE. Most patients were clustered within categories, indicating a lower predicted risk with CABG, while a subset exhibited minimal differences between PCI and CABG. Differences indicating a lower predicted risk with PCI remained infrequent across both endpoints.

Overall, these findings indicate that predicted risk differences favoring CABG predominated in this study. However, the magnitude of Δ varied across patients, with a proportion showing minimal differences consistent with an equipoise range

Risk Shifting Across SYNTAX Score 2020–Predicted Risk Strata

To further characterize how the predicted risk classifications differed between revascularization strategies, the SYNTAX Score 2020–predicted risks were examined across predefined absolute risk strata under both CABG and PCI scenarios. These strata (<10%, 10–<20%, 20–<40%, and ≥40%) were investigator-defined ranges of absolute predicted

(A) SYNTAX Score 2020-predicted 5-year MACE	PCI-predicted risk strata (%)			
CABG-predicted risk strata (%)	<10%	10–<20%	20–<40%	≥40%
<10%	17	11		
10–<20%		24	26	
20–<40%			18	8
≥40%				11
(B) SYNTAX Score 2020-predicted 10-year mortality	**PCI-predicted risk strata (%)**			
CABG-predicted risk strata (%)	<10%	10–<20%	20–<40%	≥40%
<10%	13	5		
10–<20%		20	18	
20–<40%			20	11
≥40%				28

Figure 2. Risk shifting between CABG and PCI scenarios based on SYNTAX Score 2020—predicted risk strata. (A) SYNTAX Score 2020-predicted 5-year MACE. (B) SYNTAX Score 2020-predicted 10-year mortality.

Note. Absolute predicted risks were generated by the SYNTAX Score 2020 calculator and were subsequently grouped into investigator-defined strata (<10%, 10–<20%, 20–<40%, ≥40%) for descriptive visualization. Rows represent CABG-based predictions and columns represent PCI-based predictions. Values indicate absolute numbers of patients. Cells along the main diagonal indicate unchanged predicted risk classification, whereas cells above the diagonal indicate upward shifts to higher predicted risk strata under the PCI scenario. CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention.

risk (%) used to assess shifts in risk classification between PCI and CABG descriptively.

Figure 2 depicts the cross-classification of the predicted risk strata, with rows representing CABG-based predictions and columns representing PCI-based predictions. Cells along the main diagonal indicate patients whose predicted risk strata remained unchanged across revascularization scenarios. In contrast, cells above the diagonal indicate upward shifts to higher predicted risk strata under the PCI scenario.

Across both 10-year mortality and 5-year MACE, a substantial proportion of patients remained in the same predicted risk stratum when moving from a CABG-based to a PCI-based prediction. However, a notable subset of patients experienced upward shifts to higher predicted-risk strata under the PCI scenario, reflecting reclassification to higher predicted-risk categories. Downward shifts to lower-predicted-risk strata were uncommon.

Taken together, these findings indicate that while predicted risk stratification remained stable for many patients across revascularization scenarios, changing the assumed strategy from CABG to PCI frequently resulted in an upward reclassification to higher predicted risk strata for a subset of individuals.

Paired Differences in Predicted Risks According to Clinical Characteristics

To explore how clinical characteristics were distributed across different magnitudes of paired differences, within-patient Δ values for SYNTAX Score 2020–predicted risks 10-year mortality and 5-year MACE were examined according to the predefined Δ categories (Table 5).

Across increasing Δ categories—corresponding to progressively larger CABG-favored predicted risk differences—patients demonstrated less favorable clinical and anatomical profiles. Larger Δ categories were associated with older age, lower LVEF, reduced CrCl, and higher SYNTAX Score I values. In contrast, patients within the equipoise range (Δ <2%) generally showed more preserved LVEF, higher CrCl, and lower anatomical complexity.

Categorical clinical characteristics also varied across Δ categories. Larger Δ categories were characterized by higher proportions of insulin-treated DM, PVD, and 3VD, whereas these features were less prevalent among patients in the equipoise and smaller-difference categories. The distribution of smoking status remained relatively high across all Δ categories without a consistent stepwise pattern.

Table 5. Distribution of paired differences in SYNTAX Score 2020–predicted 10-year mortality and 5-year MACE according to clinical characteristics.

10-year mortality predicted risk													
Δ Category (PCI − CABG)	**Age (mean ±SD)**	**CrCl (mean ±SD)**	**LVEF (mean ±SD)**	**SS I (mean ±SD)**	**DM (n%)**			**Current Smoking (n%)**		**PVD (n%)**		**Coronary Anatomical Category (n%)**	
					No	**Yes, Non-Insulin**	**Yes, Insulin**	**Yes**	**No**	**Yes**	**No**	**3VD**	**LMCAD**
PCI-favored (Δ <0)	63.0 ± NA	65.5 ± NA	65.0 ± NA	23.0 ± NA	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0
Equipoise (0–<2%)	50.4 ± 10.1	81.1 ± 25.1	52.4 ± 12.4	17.6 ± 8.2	81.0	9.5	9.5	71.4	28.6	19.0	81.0	71.4	28.6
CABG-favored													
Small difference (2–<5%)	55.3 ± 9.8	69.8 ± 20.9	48.0 ± 12.9	23.8 ± 8.4	85.7	3.6	10.7	75.0	25.0	14.3	85.7	85.7	14.3
Moderate difference (5–<10%)	61.1 ± 7.1	62.3 ± 23.3	45.5 ± 13.1	26.7 ± 7.0	56.5	15.2	28.3	73.9	26.1	34.8	65.2	87.0	13.0
Large difference (≥10%)	63.6 ± 6.9	50.3 ± 13.8	42.3 ± 12.3	32.7 ± 6.3	47.4	21.1	31.6	57.9	42.1	42.1	57.9	94.7	5.3
5-year MACE predicted risk													
Δ Category (PCI − CABG)	**Age (mean ±SD)**	**CrCl (mean ±SD)**	**LVEF (mean ±SD)**	**SS I (mean ±SD)**	**DM (n%)**			**Current Smoking (n%)**		**PVD (n%)**		**Coronary Anatomical Category (n%)**	
					No	**Yes, Non-Insulin**	**Yes, Insulin**	**Yes**	**No**	**Yes**	**No**	**3VD**	**LMCAD**
PCI-favored (Δ <0)	63.0 ± NA	65.5 ± NA	65.0 ± NA	23.0 ± NA	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	100.0
Equipoise (0–<2%)	50.8 ± 10.0	81.6 ± 26.4	52.3 ± 12.5	16.3 ± 7.3	78.9	10.5	10.5	73.7	26.3	21.1	78.9	73.7	26.3
CABG-favored													
Small difference (2–<5%)	53.5 ± 8.0	71.3 ± 19.4	47.0 ± 12.5	22.8 ± 7.2	90.3	3.2	6.5	71.0	29.0	12.9	87.1	87.1	12.9
Moderate difference (5–<10%)	61.0 ± 7.6	64.9 ± 21.0	47.3 ± 12.2	27.6 ± 6.6	58.1	18.6	23.3	72.1	27.9	27.9	72.1	86.0	14.0
Large difference (≥10%)	65.8 ± 6.2	44.2 ± 15.6	40.5 ± 14.0	32.5 ± 7.7	38.1	14.3	47.6	66.7	33.3	57.1	42.9	90.5	9.5

Note. Δ represents within-patient paired differences in SYNTAX Score 2020–predicted risk between PCI and CABG scenarios (Δ = PCI − CABG). Continuous variables are presented as mean ± standard deviation, and categorical variables as number (percentage). NA denotes not applicable, reflecting categories with a single observation in which standard deviation cannot be calculated. Values summarize model-based predicted risks for the same patients under alternative revascularization assumptions and are presented for descriptive comparison only. Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SS I, SYNTAX Score I; DM, diabetes mellitus; PVD, peripheral vascular disease; 3VD, three-vessel disease; LMCAD, left main coronary artery disease; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events.

Table 6. Distribution of SYNTAX Score 2020–predicted risk strata for 10-year mortality and 5-year MACE according to clinical characteristics under PCI and CABG scenarios.

10-year mortality predicted risk PCI													
Predicted Risk Strata (%)	Age (mean ±SD)	CrCl (mean ±SD)	LVEF (mean ±SD)	SS I (mean ±SD)	DM (n%)			Current Smoking (n%)		PVD (n%)		Coronary Anatomical Category (n%)	
					No	Yes, Non-Insulin	Yes, Insulin	Yes	No	Yes	No	3VD	LMCAD
<10%	42.8 ± 5.5	92.9 ± 19.0	47.6 ± 12.3	19.8 ± 7.0	100.0	0.0	0.0	92.3	7.7	7.7	92.3	92.3	7.7
10–<20%	53.3 ± 6.0	77.3 ± 18.0	51.4 ± 12.8	21.4 ± 8.8	80.0	8.0	12.0	64.0	36.0	12.0	88.0	84.0	16.0
20–<40%	58.2 ± 4.4	63.3 ± 21.9	47.5 ± 12.7	27.1 ± 7.8	60.5	18.4	21.1	63.2	36.8	18.4	81.6	89.5	10.5
≥40%	66.4 ± 7.2	51.3 ± 27.5	43.4 ± 13.4	27.9 ± 8.5	53.8	12.8	33.3	76.9	23.1	53.8	46.2	76.9	23.1
10-year mortality predicted risk CABG													
Predicted Risk Strata (%)	Age (mean ±SD)	CrCl (mean ±SD)	LVEF (mean ±SD)	SS I (mean ±SD)	DM (n%)			Current Smoking (n%)		PVD (n%)		Coronary Anatomical Category (n%)	
					No	Yes, Non-Insulin	Yes, Insulin	Yes	No	Yes	No	3VD	LMCAD
<10%	45.2 ± 7.0	94.2 ± 17.2	49.4 ± 13.9	21.0 ± 8.2	94.4	5.6	0.0	83.3	16.7	5.6	94.4	88.9	11.1
10–<20%	55.5 ± 5.3	67.7 ± 20.0	49.9 ± 11.8	24.4 ± 8.7	71.1	13.2	15.8	63.2	36.8	13.2	86.8	92.1	7.9
20–<40%	60.1 ± 5.5	61.4 ± 18.7	45.4 ± 12.4	26.4 ± 7.5	48.4	19.4	32.3	64.5	35.5	22.6	77.4	83.9	16.1
≥40%	68.0 ± 6.9	49.2 ± 18.7	43.3 ± 14.3	28.0 ± 9.4	64.3	7.1	28.6	82.1	17.9	67.9	32.1	71.4	28.6
5-year MACE predicted risk PCI													
Predicted Risk Strata (%)	Age (mean ±SD)	CrCl (mean ±SD)	LVEF (mean ±SD)	SS I (mean ±SD)	DM (n%)			Current Smoking (n%)		PVD (n%)		Coronary Anatomical Category (n%)	
					No	Yes, Non-Insulin	Yes, Insulin	Yes	No	Yes	No	3VD	LMCAD
<10%	44.7 ± 6.5	94.1 ± 17.4	50.6 ± 13.7	18.7 ± 6.9	88.2	5.9	5.9	82.4	17.6	11.8	88.2	94.1	5.9
10–<20%	55.4 ± 5.7	68.1 ± 18.4	50.2 ± 11.7	23.3 ± 8.1	74.3	8.6	17.1	62.9	37.1	8.6	91.4	85.7	14.3
20–<40%	60.5 ± 6.2	62.6 ± 20.4	44.9 ± 12.5	27.0 ± 8.2	59.1	18.2	22.7	70.5	29.5	34.1	65.9	84.1	15.9
≥40%	70.0 ± 5.5	42.5 ± 14.7	42.7 ± 14.8	30.8 ± 8.1	52.6	10.5	36.8	78.9	21.1	63.2	36.8	73.7	26.3
5-year MACE predicted risk CABG													
Predicted Risk Strata (%)	Age (mean ±SD)	CrCl (mean ±SD)	LVEF (mean ±SD)	SS I (mean ±SD)	DM (n%)			Current Smoking (n%)		PVD (n%)		Coronary Anatomical Category (n%)	
					No	Yes, Non-Insulin	Yes, Insulin	Yes	No	Yes	No	3VD	LMCAD
<10%	48.8 ± 8.4	86.6 ± 20.2	50.9 ± 12.1	20.4 ± 8.3	92.9	3.6	3.6	67.9	32.1	14.3	85.7	92.9	7.1
10–<20%	56.8 ± 4.8	64.3 ± 20.5	46.3 ± 12.5	26.3 ± 8.0	56.0	18.0	26.0	66.0	34.0	16.0	84.0	90.0	10.0
20–<40%	65.8 ± 6.1	56.9 ± 15.0	45.7 ± 12.5	25.8 ± 8.1	73.1	7.7	19.2	80.8	19.2	46.2	53.8	73.1	26.9
≥40%	70.5 ± 6.7	38.8 ± 17.3	43.0 ± 18.1	31.8 ± 8.7	36.4	18.2	45.5	81.8	18.2	72.7	27.3	63.6	36.4

Note. Predicted risk strata are based on SYNTAX Score 2020 estimates under PCI and CABG scenarios. Continuous variables are presented as mean ± standard deviation, and categorical variables as number (percentage). Values represent model-based predicted risks for descriptive comparison across strata. Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SS I, SYNTAX Score I; DM, diabetes mellitus; PVD, peripheral vascular disease; 3VD, three-vessel disease; LMCAD, left main coronary artery disease; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events.

Comparable patterns were observed for both SYNTAX Score 2020–predicted risks 10-year mortality and 5-year MACE, indicating that greater clinical and anatomical complexities clustered among patients with larger CABG-favored predicted risk differences.

Distribution of SYNTAX Score 2020–Predicted Risk Strata According to Clinical Characteristics

The clinical characteristics were further examined across investigator-defined SYNTAX Score 2020–predicted absolute risk strata (<10%, 10–<20%, 20–<40%, and ≥40%), representing increasing levels of predicted risk, under both PCI and CABG scenarios (Table 6).

Across increasing predicted risk strata, patients demonstrated a stepwise gradient of clinical risk. Higher risk strata were characterized by older age, lower LVEF, reduced CrCl, and higher SYNTAX Score I values. These trends were consistently observed under both PCI and CABG scenarios and for both 10-year mortality and 5-year MACE predictions.

The categorical clinical variables also showed stratified distributions. Insulin-treated DM, PVD, and 3VD were more frequent in the higher-predicted-risk strata, whereas the lower strata were enriched for patients without DM, with preserved LVEF, and with lower anatomical complexity. Smoking prevalence tended to be higher in the higher strata, particularly for 5-year MACE. Notably, although the absolute predicted risks differed between PCI and CABG scenarios, the overall clinical profiles within the corresponding risk strata were broadly similar, indicating that SYNTAX Score 2020 stratification captures coherent clinical risk patterns regardless of the assumed revascularization strategy

Discussion

This study provides a descriptive examination of SYNTAX Score 2020–predicted risks for PCI and CABG, highlighting how predicted long-term risk profiles vary across patients when clinical factors are considered alongside anatomical assessment. The findings are interpreted strictly as model-based predictions and are not intended to represent observed clinical outcomes or imply causal treatment effects. Contemporary revascularization guidelines emphasize that decisions should integrate both anatomical complexity and clinical comorbidity within a multidisciplinary Heart Team framework, and the patterns observed in this study are consistent with that principle.[2,10]

Reclassification of Anatomical Risk Profiles Under SYNTAX Score 2020

Risk evaluation frequently begins with anatomical assessment; however, the integration of patient-specific clinical characteristics may prompt a reappraisal of the predicted risk profile and subsequent treatment considerations.

In the present study, comparison between anatomical risk stratification using the SYNTAX Score I and integrated risk assessment using the SYNTAX Score 2020 demonstrated substantial reclassification of revascularization strategy. Among 45 patients categorized as low anatomical risk by the SYNTAX Score I, all (100%) were reclassified to a CABG-favored strategy when clinical variables were incorporated into risk estimation. Similarly, among patients with intermediate anatomical risk, the majority were reclassified to a CABG-favored strategy. These findings provide descriptive evidence that incorporation of clinical factors may meaningfully alter the interpretation of revascularization risk beyond anatomical assessment alone.

These findings are consistent with contemporary guideline recommendations emphasizing that revascularization decisions should integrate both anatomical and clinical characteristics within a multidisciplinary Heart Team framework, rather than relying on anatomical complexity in isolation.[2-3,10] Further discussion of these findings is provided in the subsequent sections

Interpretation of Δ distributions and the equipoise zone

A key observation is the broad inter-individual variability in paired predicted risk differences between PCI and CABG. Because SYNTAX Score 2020 integrates anatomical disease features with clinical variables (age, renal function, ventricular function, diabetes status, PVD, and smoking), heterogeneity in Δ is expected and clinically meaningful: it reflects differences in baseline vulnerability and anatomical complexity, rather than random variation. The redevelopment of SYNTAX Score 2020 was explicitly designed to individualize decision-making between PCI and CABG by predicting 10-year mortality and 5-year MACE using both clinical and anatomical inputs, supporting this interpretive framework.[4-5]

Notably, a clinically relevant proportion of patients fell within the predefined equipoise range (Δ <2%), indicating minimal predicted differences between PCI and CABG for both endpoints (as summarized in Table 4). In practice, this subgroup

is important because guidelines and expert consensus highlight that when predicted risks are similar, and anatomy is suitable for either strategy, final decisions should weigh patient preference, procedural feasibility, local expertise, and additional comorbidities not fully captured by any single tool—again reinforcing the role of multidisciplinary evaluation rather than score-only decisions.[2-3]

Risk shifting and "stability" across predicted strata

The risk shifting analysis (Figure 2) adds an important interpretive layer. The presence of a substantial diagonal (patients remaining in the same stratum under both strategies) can be described as risk classification stability, meaning that for many individuals, their overall risk profile is sufficiently dominated by baseline clinical/anatomical burden such that the predicted stratum does not materially change between PCI and CABG scenarios. Conversely, off-diagonal movement—particularly upward shifting to higher strata under the PCI scenario—identifies a subset in whom predicted risk is more sensitive to the assumed revascularization strategy. Importantly, this should not be interpreted as evidence of observed differences in outcomes, but rather as a descriptive illustration that the model predicts meaningful, strategy-dependent risk changes in a clinically higher-risk subset.

The parallel inclusion of Table 6 (risk strata by clinical characteristics) strengthens interpretability: when upward shifts cluster among older patients, those with worse renal function, lower LVEF, more severe diabetes (insulin-treated), and greater anatomical complexity, the pattern of shifts becomes biologically coherent and clinically readable. This framing also aligns with guideline recommendations that emphasize integrated assessment (clinical and anatomical) and multidisciplinary discussion for decisions regarding complex coronary disease.[2-3,10]

Why larger CABG-favored Δ and higher predicted risk strata clusters in clinically higher-risk phenotypes

Across Tables 5 and 6, patients in categories with greater predicted risk differences favoring CABG and higher predicted risk strata exhibited a more adverse clinical profile. Several pathophysiological mechanisms can plausibly contextualize these descriptive patterns:

1. Ventricular dysfunction (lower LVEF): limited myocardial reserve.

   Lower LVEF implies reduced tolerance to residual ischemia and recurrent ischemic burden. Even modest incomplete revascularization or recurrent ischemia can translate into disproportionate clinical impact in patients with reduced myocardial reserve (e.g., Heart Failure [HF] progression and malignant arrhythmia susceptibility). Thus, it is biologically plausible that patients with lower LVEF cluster in higher predicted risk strata and larger CABG-favored Δ categories, because comprehensive revascularization and durable flow restoration become more consequential as ventricular reserve declines.[2,10]

2. Renal dysfunction (lower CrCl): inflammation, endothelial dysfunction, and prothrombotic milieu.

   Chronic Kidney Disease (CKD) is associated with endothelial dysfunction, chronic inflammation, altered platelet activation, and accelerated atherosclerosis. These processes can increase vulnerability to ischemic events and contribute to poorer long-term outcomes after focal coronary interventions, particularly when the disease is diffuse. Consistent with this, contemporary analyses comparing PCI and CABG in CKD populations highlight that completeness of revascularization and systemic risk burden are important modifiers of long-term prognosis. In Table 6, lower renal function tracking with higher predicted strata supports the interpretation that renal dysfunction acts as a "risk amplifier" within the SYNTAX Score 2020 framework.[11-12]

3. DM severity gradient (no DM → non-insulin → insulin-treated): diffuse disease and microvascular dysfunction.

   The dataset distinguishes diabetes status by treatment (no DM, non-insulin-treated DM, insulin-treated DM), which is clinically important because insulin-treated diabetes often reflects longer duration and more advanced metabolic and vascular disease. Advanced diabetic vasculopathy is characterized by diffuse coronary atherosclerosis, microvascular dysfunction, impaired endothelial nitric oxide signaling, and heightened inflammatory/thrombotic risk factors that may limit the durability of focal lesion treatment and favor strategies that provide more global myocardial perfusion in diffuse disease. Contemporary observational evidence and reviews in

diabetic multivessel disease continue to report better long-term outcomes with CABG compared with PCI in many higher-risk diabetic phenotypes, providing biological plausibility for the clustering of insulin-treated diabetes among higher predicted risk and larger CABG-favored Δ categories observed in Tables 5 and 6.[13-14]

4. Systemic atherosclerosis markers (PVD): diffuse burden beyond the coronaries.

   PVD is a marker of systemic atherosclerotic burden and is associated with diffuse vascular involvement, endothelial dysfunction, and heightened thrombogenicity. Within a descriptive framework, the higher representation of PVD in larger Δ and higher strata groups supports the notion that systemic disease burden meaningfully informs predicted long-term risk—consistent with how SYNTAX Score 2020 weights clinical comorbidity in addition to coronary anatomy.[2,4]

5. Anatomical complexity and completeness of revascularization as a mechanistic bridge

   Anatomical complexity (reflected in SYNTAX Score I and the presence of 3VD or LMCAD) provides a direct mechanistic bridge to larger predicted differences between PCI and CABG. In complex, diffuse, heavily calcified, or bifurcation-rich disease, PCI is more likely to result in incomplete revascularization or higher residual ischemic burden. Over longer time horizons, residual ischemia and incomplete revascularization have been associated with worse cardiovascular outcomes and increased repeat revascularization risk. This is consistent with modern studies and meta-analytic evidence supporting the clinical relevance of achieving complete revascularization, particularly in surgically treated patients and complex disease subsets.[15-16]

   Accordingly, the descriptive association in Tables 5 and 6—higher anatomical complexity tracking with higher predicted strata and more CABG-favored Δ—can be interpreted as the model expressing a clinically intuitive principle: as coronary disease becomes more complex and systemic vulnerability increases, long-term risk predictions diverge more strongly between strategies that treat focal lesions versus those that bypass diseased segments

Smoking Status and COPD in the Context of Predicted Risk

In this study, smoking prevalence remained high across predicted risk strata and across categories of predicted differences between PCI and CABG, although no consistent stepwise pattern was observed with increasing magnitude of predicted differences. This finding suggests that smoking contributes primarily to overall cardiovascular risk captured by SYNTAX Score 2020 rather than clearly differentiating predicted risk between revascularization strategies. Cigarette smoking contributes to cardiovascular risk through mechanisms including endothelial dysfunction, oxidative stress, and vascular inflammation, which accelerate atherosclerosis and increase the likelihood of adverse cardiovascular events. Smoking-induced endothelial impairment alters nitric oxide bioavailability and promotes pro-inflammatory and pro-atherogenic vascular changes, which are reflected in higher absolute predicted cardiac risk.[17-18]

COPD is recognized to be associated with increased cardiovascular morbidity and mortality, largely through shared mechanisms of systemic inflammation, hypoxemia, and overlapping risk factors such as smoking. COPD and cardiovascular disease frequently coexist, and their interaction is linked to elevated risk of ischemic events, HF, and other cardiovascular outcomes in affected populations.[19-20] In the present study, no patients were classified as having COPD. This likely reflects under-recognition or underdocumentation in an acute-care setting, where routine spirometry was not consistently performed, and comorbidity assessment relied on medical records and structured clinical history. As a result, COPD-related patterns in predicted risk could not be examined.

Clinical Implications

Taken together, the results support a practical interpretation of SYNTAX Score 2020 outputs:

1. Predicted risk differences favoring CABG were common, but their magnitude varied widely across patients, underscoring the importance of individualized risk estimation.[4]
2. A distinct subgroup with minimal predicted differences between PCI and CABG was identified, supporting individualized treatment selection in situations where long-term predicted risks are similar and shared decision-making is central.[2-3]
3. Clinical severity gradients (age, LVEF, renal function, diabetes severity, PVD), together

with anatomical complexity, provide a plausible biological explanation for the observed clustering of predicted risks and Δ values.

4. Collectively, these findings indicate that incorporation of clinical factors beyond anatomical assessment can meaningfully influence predicted revascularization risk profiles and treatment selection, reinforcing the importance of integrated evaluation within a multidisciplinary Heart Team framework.[2-3,10]

Study Limitations

This study was descriptive and based on SYNTAX Score 2020–predicted risks rather than observed clinical events or real-world outcomes. The single-center design and predominance of ACS presentations may limit the generalizability of these findings to other populations. The timing of key calculator inputs reflected routine acute care workflows, which may have introduced variability in predicted risk estimates. For conditions in which objective confirmation was not routinely available, including PVD and COPD, structured history-taking and medical record review were used, raising the possibility of under-recognition or misclassification. Notably, the absence of COPD in this study may have led to an underestimation of SYNTAX Score 2020–predicted risks. Evaluation of SYNTAX Score 2020 performance ultimately requires prospective follow-up with observed clinical outcomes, representing an important direction for future studies.

Conclusion

In this study, SYNTAX Score 2020–predicted risks demonstrated marked inter-individual variability between PCI and CABG scenarios. Greater clinical and anatomical complexity—including older age, reduced LVEF, impaired renal function, DM (particularly insulin-treated), PVD, and higher anatomical disease burden—tended to coincide with higher predicted risks and larger differences between revascularization strategies. Risk stratification based on anatomical assessment alone may be reclassified following the incorporation of patient-specific clinical variables. Overall, these descriptive findings support the use of SYNTAX Score 2020 as an integrated decision-support tool to complement clinical judgment within multidisciplinary Heart Team decision-making for complex CAD.

List of Abbreviations

3VD	Three-vessel Disease
ACS	Acute Coronary Syndrome
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CrCl	Creatinine Clearance
DM	Diabetes Mellitus
HF	Heart Failure
IQR	Interquartile Range
LMCAD	Left Main Coronary Artery Disease
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
NSTEMI	Non–ST-segment Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PVD	Peripheral Vascular Disease
QCA	Quantitative Coronary Angiography
STEMI	ST-segment Elevation Myocardial Infarction
SYNTAX	Synergy between percutaneous coronary intervention with taxus and cardiac surge

Ethical Clearance

All methods were carried out according to relevant guidelines and regulations after obtaining approval and recommendations from the Ethics Committee Review Board of dr. Doris Sylvanus General Hospital (reference number 2384/UMPEG/RSUD/03-2025). Patient confidentiality and anonymity were maintained throughout the study.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

Conceptualization: S.I.S. and A.M.M.; methodology: S.I.S. and A.M.M.; sample collection: A.M.M., K. Y., and R.T.A.; formal analysis: A.M.M. and S.I.S.; writing—original draft preparation: A.M.M.; review and editing: A.M.M., S.I.S., and Y.G.; supervision: S.I.S. and Y.G.

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Conflict of Interest

None.

Availability of Data and Materials

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Original Article

One-Year Outcomes of Major Adverse Cardiac Events in Patients with ST-Segment Elevation Myocardial Infarction Who Received Delayed PCI in a Type-B Hospital

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Abstract

Background: Delayed Percutaneous Coronary Intervention (PCI) remains common in resource-limited hospitals due to system-related delays, often resulting in prolonged ischemic time. Although early reperfusion is the standard of care for ST-segment Elevation Myocardial Infarction (STEMI), delayed PCI may still be performed in selected, clinically stable patients. This study aimed to evaluate the one-year incidence of Major Adverse Cardiac Events (MACE) among STEMI patients undergoing PCI in a Type-B hospital, where delayed PCI was the predominant treatment pattern.

Methods: This retrospective cohort study included adult STEMI patients who underwent PCI at PKU Muhammadiyah Gamping Hospital, Yogyakarta, Indonesia, between September 2018 and December 2020. Patients with incomplete medical records or loss to follow-up were excluded. Baseline clinical characteristics, comorbidities, infarct location, and door-to-wire-crossing time were collected. MACE included all-cause mortality, acute pulmonary edema, non-ST-segment elevation myocardial infarction, stroke, and rehospitalization due to reinfarction or acute heart failure within one year after PCI. Kaplan-Meier survival analysis and Mann-Whitney testing were applied.

Results: Among 130 STEMI patients who underwent PCI, 123 (94.6%) received delayed PCI, with a median door-to-wire-crossing time of 10 hours 34 minutes. During one-year follow-up, MACE occurred in 10 patients (7.7%), corresponding to a 92.3% event-free survival rate. No significant association was observed between door-to-wire-crossing time and one-year MACE ($p = 0.927$).

Conclusions: In this single-center study conducted at a Type-B hospital, one-year MACE occurred in 7.7% of STEMI patients undergoing PCI, most of whom received delayed PCI. No significant association was observed between door-to-wire-crossing time and MACE occurrence. Given the observational design and the limited number of events, these findings should be interpreted with caution. Delayed PCI appears feasible in selected patients, but should not be considered equivalent to guideline-recommended early PCI.

Keywords: Delayed PCI, MACE, STEMI, Type-B hospital

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Introduction

Comparative studies between thrombolytic therapy and primary Percutaneous Coronary Intervention (PCI) for ST-segment Elevation Myocardial Infarction (STEMI) have been extensively reported in developed healthcare systems.[1–3] These studies consistently demonstrate that timely primary PCI is associated with improved clinical outcomes and form the basis of contemporary guideline recommendations. However, implementation of these evidence-based standards remains challenging in developing countries, particularly in regional hospitals, where infrastructural limitations and system-level delays frequently hinder timely reperfusion.

STEMI is characterized by acute myocardial ischemia with persistent ST-segment elevation on electrocardiography and elevated myocardial necrosis biomarkers. STEMI accounts for approximately 38% of acute coronary syndrome cases in hospital-based settings.[4] Previous studies have reported that the management of acute coronary syndrome in developing countries, including Indonesia, often deviates from guideline-directed therapy, primarily due to delayed patient presentation and prolonged total ischemic time.[5] Such delays may adversely affect myocardial salvage and long-term clinical outcomes.

Primary PCI remains the preferred reperfusion strategy for STEMI because irreversible myocardial necrosis progresses rapidly following coronary artery occlusion, and the therapeutic benefit of reperfusion is strongly time-dependent.[6] Major Adverse Cardiac Events (MACE), encompassing cardiac death, recurrent myocardial infarction, and repeat revascularization, are widely used as composite clinical endpoints to evaluate the safety and effectiveness of reperfusion strategies.[7] Recent evidence suggests that, in selected and clinically stable patients, delayed PCI combined with Optimal Medical Therapy (OMT) may still be associated with acceptable clinical outcomes; however, data supporting this approach in regional hospitals within developing countries remain limited.[8-9]

In 2018, the cardiac catheterization laboratory at PKU Muhammadiyah Gamping Hospital began providing PCI services for STEMI patients, representing an expansion of cardiovascular care capacity in a regional hospital setting. Given the frequent occurrence of delayed reperfusion in this context, evaluating long-term clinical outcomes after delayed PCI is clinically relevant. This study was therefore conducted to assess one-year MACE among STEMI patients undergoing delayed PCI at PKU Muhammadiyah Gamping Hospital, with the aim of contributing real-world evidence from a resource-limited clinical setting.

Methods

This study employed a retrospective cohort design using observational data. It was conducted at PKU Muhammadiyah Gamping Hospital, Yogyakarta, Indonesia, a Type-B hospital equipped with a cardiac catheterization laboratory capable of performing PCI for STEMI. During the study period, institutional referral protocols required clinically unstable or high-risk STEMI patients to be transferred to tertiary centers. Consequently, PCI at this institution was primarily performed in clinically stable patients who remained hospitalized. The study protocol was reviewed and approved by the Ethics Committee of PKU Muhammadiyah Gamping Hospital. The requirement for informed consent was waived due to the retrospective nature of the study.

All consecutive adult patients (≥18 years) admitted with confirmed STEMI who underwent reperfusion therapy at PKU Muhammadiyah Gamping Hospital between September 2018 and December 2020 were screened. STEMI was diagnosed based on persistent ST-segment elevation on electrocardiography and elevated cardiac biomarkers. A total of 130 patients met the inclusion criteria and were included in the final analysis. Of these, 123 (94.6%) received delayed PCI, whereas the remainder underwent primary PCI. Patients were excluded if they had incomplete medical records, were lost to follow-up, had alternative diagnoses that could confound STEMI (such as myocarditis or Takotsubo cardiomyopathy), or had documented refusal of invasive management. Patients who died before undergoing PCI were not included, as the study population consisted only of individuals who survived to receive PCI.

Total sampling was applied. Data collected from medical records included age, sex, smoking status, STEMI location (anterior or inferior), comorbidities (hypertension, diabetes mellitus, dyslipidemia, obesity, and prior stroke), length of hospitalization, and clinical outcomes during follow-up. Anterior STEMI was defined as myocardial infarction involving the Left Anterior Descending (LAD) artery, whereas inferior STEMI was defined as myocardial infarction involving the Right Coronary Artery (RCA). Delayed PCI was defined as PCI performed more than 12 hours after the onset of chest pain symptoms. In this cohort, delayed PCI

was the predominant treatment pattern. Time to reperfusion was defined as door-to-wire-crossing time, calculated from the patient's arrival at the emergency department to successful guidewire passage across the culprit coronary lesion during PCI.

The primary outcome was the occurrence of MACE within one year following PCI. MACE was defined as a composite of all-cause mortality, acute pulmonary edema, non-STEMI, stroke, and rehospitalization due to reinfarction or acute heart failure within one year after PCI. Follow-up data were obtained from hospital medical records and structured telephone interviews. Mortality was confirmed through hospital documentation or communication with family members when death occurred outside the hospital.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized as absolute numbers and percentages. Continuous variables were presented as mean ± standard deviation or median with minimum and maximum values, as appropriate. The association between door-to-wire-crossing time and one-year MACE was analyzed using the Mann–Whitney U test. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 130 patients with confirmed STEMI who underwent PCI were included in the final analysis. Among them, 123 (94.6%) received delayed PCI. Baseline demographic and clinical characteristics are summarized in Table 1. The majority of patients were male (107 patients, 82.3%), with a mean age of 59.3 ± 11.6 years. Anterior STEMI was the most frequent infarct location (77 patients, 59.2%), while 53 patients (40.8%) presented with inferior STEMI. Common

Table 1. Baseline patient characteristics.

Variables	N	%	Mean ± SD Or Median (min-max)
Age (years ± SD)			59.31 ± 11.63
STEMI Location			
Anterior	77	59.2%	
Inferior	53	40.8%	
Smoking History			
Yes	109	83.8%	
No	21	16.2%	
Sex			
Male	107	82.3%	
Female	23	17.7%	
Comorbidity			
Stroke	11	8.5%	
Hypertension	68	52.3%	
Dyslipidemia	17	13.1%	
Diabetes Mellitus	46	35.4%	
LM disease	18	13.8%	
Weight status			
Underweight	6	4.6%	
Normal	53	40.8	
Overweight	42	32.3%	
Obese 1	25	19.2%	
Obese 2	4	3.1%	
Length of hospital stay, days			3 (0 – 20)
TIMI Flow			3 (1 – 3)
Weight (Kg)			60 (40 – 87)
Height (cm)			165 (145 – 180)
BMI			23.44 (17.58 – 33.20)

Duration of IGD-wire crossing (hours- minutes)	10:34 (1:02 – 23:52)

STEMI: ST-Segment Elevation Myocardial Infarction; TIMI: Thrombolysis in Myocardial Infarction; BMI: Body Mass Index

cardiovascular risk factors included smoking (109 patients, 83.8%), hypertension (68 patients, 52.3%), and diabetes mellitus (46 patients, 35.4%).

During one year of follow-up, 10 patients (7.7%) experienced MACE, whereas 120 patients (92.3%) remained free from MACE. The overall proportion of patients with and without MACE during follow-up is illustrated in Figure 1.

The distribution of individual MACE components is presented in Figure 2. All-cause mortality was the most frequent event, occurring in 4 patients (3.1%). This was followed by acute pulmonary edema in 3 patients (2.3%), non–STEMI in 2 patients (1.5%), and stroke in 1 patient (0.8%). No rehospitalization due to recurrent STEMI was observed during the one-year follow-up period.

Time to reperfusion was assessed using door-to-wire-crossing time, defined as the interval from patient arrival at the emergency department to successful guidewire passage across the culprit coronary lesion during PCI. The median door-to-wire-crossing time was 10 hours 34 minutes (range: 1:02–23:52). Comparison between patients who experienced MACE and those who did not showed no statistically significant difference in door-to-wire-crossing time. Median times were 10:12 hours (3:11–23:30) in the MACE group and 10:47 hours (1:02–23:52) in the non-MACE group (p = 0.927, Mann–Whitney U test). Detailed results of this analysis are presented in Table 2.

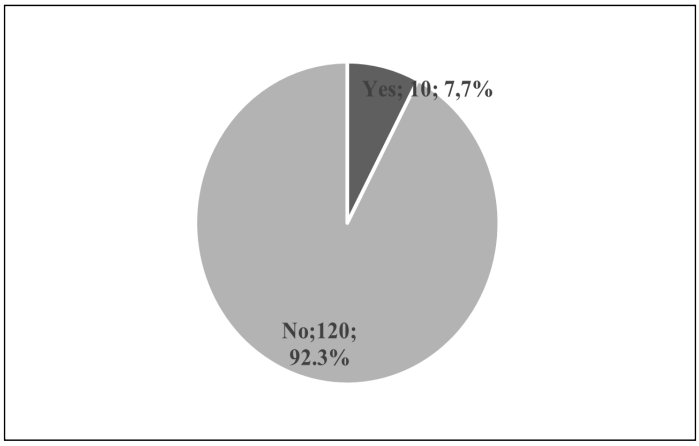

Figure 1. One-year incidence of MACE after delayed PCI.

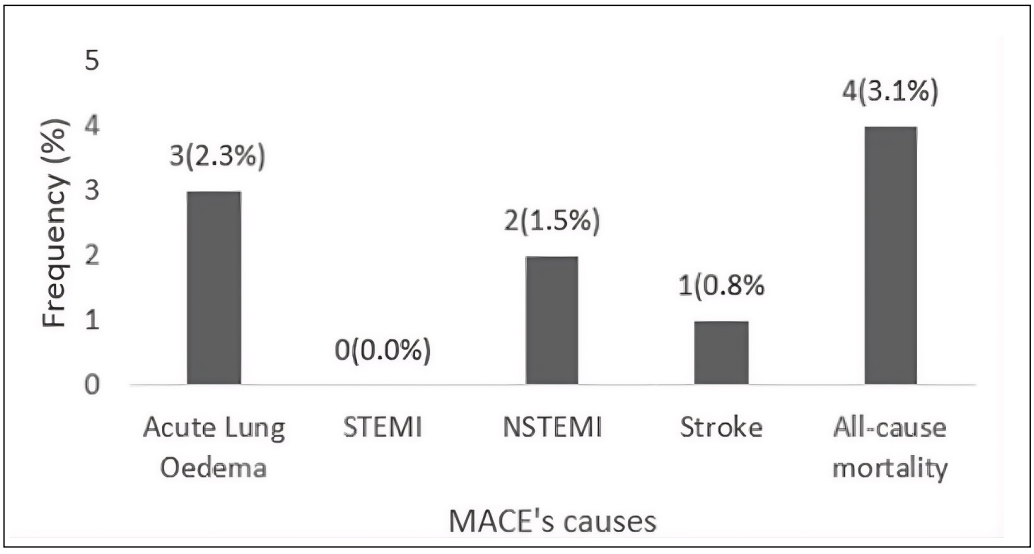

Figure 2. Distribution of MACE components.

Table 2. Association between door-to-wire-crossing time and one-year MACE occurrence.

	MACE at 1 Year		
	Yes	No	p
Door-to-wire-crossing time, (hours:minutes); median (min-max)	10:12 (3:11-23:30)	10:47 (1:02-23:52)	0.927

Chi-Square, Fisher exact, Mean ± SD: Independent T test; Median (min-max): Mann Whitney. MACE: Major Adverse Cardiac Events.

To further characterize the temporal pattern of MACE occurrence, Kaplan–Meier survival analysis was performed. The Kaplan–Meier curve demonstrated a high cumulative event-free survival during the one-year follow-up period, with only a modest decline observed in the early months after PCI. At one year, 92.3% of patients remained free from MACE (Figure 3). Censored observations represent patients without events at the last follow-up.

Discussion

This study evaluated one-year clinical outcomes among patients with STEMI who underwent PCI at PKU Muhammadiyah Gamping Hospital, most of whom received delayed PCI. MACE occurred in 10 patients (7.7%), while 120 patients (92.3%) remained event-free during follow-up. These findings reflect outcomes in a selected population of clinically stable patients who survived to undergo delayed PCI.

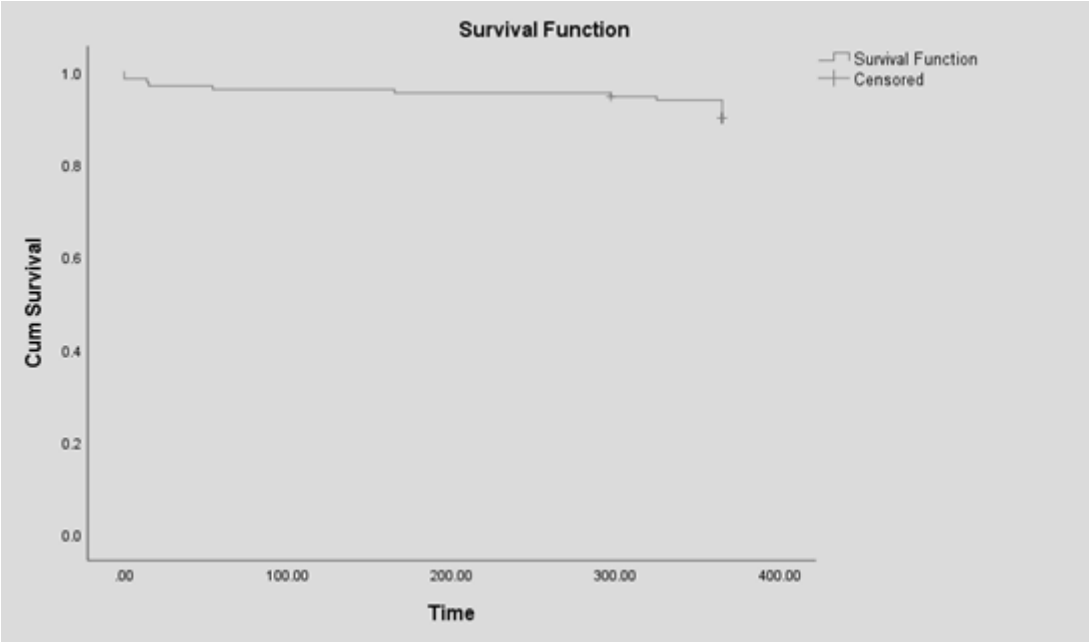

Figure 3. Kaplan-Meier curve of MACE-free survival during one-year follow-up.

The observed MACE rate in this cohort is comparable to previously reported one-year incidences among selected delayed-PCI or late-presenting STEMI populations.[10-11] Similar outcomes have also been reported in low-risk STEMI cohorts, in which delayed and early invasive strategies yielded comparable short-term and mid-term clinical results.[6] The consistent application of guideline-directed medical therapy may have contributed to favorable outcomes, as prior studies demonstrated that high adherence to optimal medical therapy significantly reduces post-PCI MACE risk.[12] In addition, preserved coronary collateral flow has been associated with smaller infarct size and improved ventricular recovery, potentially mitigating adverse outcomes despite delayed reperfusion.[13]

The Mann–Whitney analysis demonstrated no statistically significant association between door-to-wire-crossing time and one-year MACE occurrence ($p = 0.927$; Table 2). However, this finding should be

interpreted cautiously. The small number of MACE events (n = 10) limits statistical power and increases the risk of type II error. Therefore, the absence of statistical significance does not imply equivalence between delayed and guideline-recommended early PCI strategies.[1]

Kaplan–Meier analysis further showed that 92.3% of patients remained free from MACE at one year (Figure 3). This pattern suggests sustained clinical stability among patients who underwent PCI in this cohort, most of whom received delayed PCI. Previous studies have reported that rehospitalization after PCI is often driven by recurrent symptoms and baseline disease severity.[14] Early discharge strategies have also been shown to be safe in carefully selected low-risk STEMI patients, emphasizing the importance of patient selection in determining outcomes.[14] These studies underscore the importance of early and effective intervention in STEMI patients to reduce the incidence of rehospitalization due to MACE.

Several methodological considerations should be taken into account when interpreting these findings. PKU Muhammadiyah Gamping Hospital operates as a Type-B facility with PCI capability, and institutional referral pathways during the study period prioritized early transfer of clinically unstable or high-risk STEMI patients to tertiary centres. Consequently, patients who underwent PCI at this institution predominantly represented a clinically stable cohort, which may partly explain the relatively low observed one-year MACE rate and may limit generalizability to broader STEMI populations or true Type-C hospital settings.

In addition, the retrospective design introduces inherent survivorship bias. The study population was restricted to patients who survived long enough to receive PCI, thereby excluding early mortality occurring during prolonged ischemia. As a result, the present findings primarily reflect outcomes among patients who reached PCI alive and clinically stable, and the overall risk associated with delayed PCI in unselected STEMI populations may be underestimated.

The limited number of MACE events in this study reduces the statistical power to detect potential associations between reperfusion delay and clinical outcomes. Therefore, the absence of a statistically significant association should be interpreted with caution and does not exclude the possibility of a clinically meaningful effect.

Current guidelines consistently emphasize the importance of minimizing total ischemic time in STEMI management.[15–18] Prolonged ischemia has been associated with increased mortality and higher MACE rates in both short- and long-term follow-up.[19–21] Nevertheless, delayed PCI remains common in resource-limited settings due to patient-related and system-level barriers.[5,17] Emerging evidence suggests that delayed PCI may still offer clinical benefit compared with OMT alone in selected late presenter.[11,20] The present study adds context-specific data to this evolving evidence base.

Overall, these findings indicate that delayed PCI, which predominated in this cohort, may be feasible in carefully selected, clinically stable STEMI patients treated in a resource-limited hospital setting when timely reperfusion cannot be achieved. However, the present results do not support non-inferiority or equivalence to guideline-recommended early PCI strategies. Further prospective studies with larger sample sizes and comparative designs are warranted to better define the optimal management of late-presenting STEMI in resource-limited settings.

Conclusion

In this cohort of clinically stable STEMI patients who underwent PCI at a Type-B hospital, most of whom received delayed PCI, the one-year incidence of MACE was 7.7%. No statistically significant association was found between door-to-wire-crossing time and MACE; however, this result should be interpreted cautiously due to the limited number of events. These findings suggest that delayed PCI, which was the predominant treatment pattern in this cohort, may be feasible in selected patients when timely reperfusion is not achievable, but they do not support equivalence to guideline-recommended early PCI. Further studies with larger sample sizes and comparative designs are needed to clarify the long-term outcomes of delayed PCI in resource-limited settings.

List of Abbreviations

MACEs Major Adverse Cardiac Events
PCI Percutaneous Coronary Intervention
OMT Optimal Medical Therapy
STEMI ST-Elevation Myocardial Infarction

Ethical Clearance

The design and conduct of the study were approved by the Local Ethics Committee of PKU Muhammadiyah Gamping Hospital (094/KEP-PKU/III/2022). The requirement for informed

consent was waived due to the retrospective nature of the study.

Publication Approval

All authors have critically reviewed, approved the final version, and agreed the publication of this manuscript.

Authors Contributions

GBP and NM conceived the study and designed the methodology. GBP and NM were responsible for project development and data collection. GBP conducted the statistical analysis and prepared the initial manuscript draft. NM contributed to data interpretation and manuscript preparation. FM and MKA contributed to project development and assisted in manuscript writing and revision. All authors reviewed and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no competing interests.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and institutional data protection restrictions at a single participating center. Data are available from the corresponding author upon reasonable request.

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Generative AI and AI-Assisted Technologies in the Writing Process

Artificial intelligence–based tools, including large language models, were used during the writing and revision process to support language enhancement, proofreading, and structural clarity. All AI-assisted content was carefully reviewed and edited by the authors. The scientific content, data analysis, and conclusions remain entirely the work of the authors, who take full responsibility for the final manuscript.

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Original Article

Serum Endothelin-1 Level >2.0 pg/mL associates with High-Risk Duke Treadmill Score among Chronic Coronary Syndrome Patients

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Abstract

Background: Chronic Coronary Syndrome (CCS) contributes to morbidity and increased risk of acute coronary syndrome within 5 years. Duke Treadmill Score (DTS) is the most robust risk stratification based on cardiac exercise stress test, which predicts 5-year survival. Those with high-risk DTS (DTS <- 11) had the poorest survival. Endothelin-1, a potent vasoconstrictor peptide, affects 5-year survival in CCS. This study sought to investigate whether serum endothelin-1 level and DTS risk stratification were associated among patients with CCS.

Methods: This was a cross-sectional study that recruited consecutive patients with CCS after Coronary Angiography (CAG). The DTS data were collected from the previous Treadmill Test (TMT) and were classified into high-risk DTS (DTS ≤-11) and low-moderate-risk DTS (DTS >-11). A serum sample for measuring endothelin-1 was withdrawn during CAG and used in the ELISA protocol. A high endothelin-1 level was defined as > 2.0 pg/mL. An association between variables was assessed using statistical analysis (significance at $p < 0.05$).

Results: Eighty subjects were enrolled. Median time interval of TMT and endothelin-1 measurement was 30 days. Mean age was 58.48±8.73 years old, with males predominant (82.5%). Hypertension (71.3%) and previous Acute Coronary Syndrome (ACS) (52.5%) were dominant. The proportion of subjects with high-risk DTS was 52.5%. Median endothelin-1 level was 1.8 pg/mL (range: 0.4 - 6.8 pg/mL). Serum endothelin-1 level > 2.0 pg/mL was observed in 34 subjects (42.5%), of whom 23 (67.6%) had high-risk DTS. There was a significantly increased risk of high-risk DTS in subjects with serum endothelin-1 >2.0 pg/mL (OR 2.97; 95% CI 1.18-7.51; p=0.020). Based on bivariate analysis, two variables, namely hypertension (p=0.052) and history of ACS (p=0.036), were also significantly associated with high-risk DTS. In multivariate analysis, endothelin-1 level >2.0 pg/mL had an adjusted OR of 1.75 (95% CI: 0.60-5.13, p=0.305), indicating no statistically significant independent association with high-risk DTS. Hypertension and a history of ACS had an independent and significant association with high-risk DTS.

Conclusions: Among CCS patients, serum endothelin-1 level > 2.0 pg/mL was associated with high-risk DTS from TMT examination. However, this association was not independent, as in hypertension and history of ACS.

Keywords: Chronic Coronary Syndrome; Treadmill Test; Duke Treadmill Score; Endothelin-1; Cardiovascular Disease

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Introduction

Chronic Coronary Syndrome (CCS) is one of Cardiovascular Diseases (CVD), which becomes a substantial contributor to morbidity and reduced quality of life among its patients.[1] A substantial number of patients with CCS ultimately require hospitalization due to Acute Coronary Syndrome (ACS).[1] Major Adverse Cardiovascular Events (MACE) are also significant morbidity and mortality outcomes among patients with CCS, necessitating relevant interventions to prevent the complication.[2]

Non-invasive examination modalities are capable of demonstrating the presence of myocardial ischemia. Cardiac Exercise Stress Test (CEST) with Electrocardiogram (ECG) recording by Treadmill Test (TMT) remains an important and frequently used examination in establishing the diagnosis of CCS by assessing myocardial ischemic response to the application of graded exercise that increases myocardial oxygen demand.[3] In addition to diagnosis, TMT can be utilized to determine risk stratification and assess prognosis in CCS.[3-4] For this purpose, the Duke Treadmill Score (DTS) is one of the robust methods that has been validated by several studies. Risk stratification based on the DTS is divided into low (DTS ≥5), moderate (DTS between 4 and -10), and high risk (DTS ≤-11), which predict 5-year survival in patients with CCS.[4]

Endothelin-1, a potent vasoconstrictor peptide, is proposed as a new prognostic indicator for ACS. Among Indonesians, this vasoactive biomarker is positively associated with poor prognosis in ACS.[5-6] Its role in predicting MACE among CCS patients remains unclear. A previous study in the Asian population showed that endothelin-1 contributes to the development and severity of CCS.[7] This study aimed to examine whether serum endothelin-1 level and DTS risk stratification were associated among Indonesian patients suffering CCS.

Methods

This study used a cross-sectional methodology. The site of this research was Dr. Sardjito Hospital, Yogyakarta, Indonesia. The Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia, granted ethical clearance for this study (Reff. number: KE/FK/1910/EC/2024).

The subjects were patients with CCS who had an elective Coronary Angiography (CAG) examination at the site hospital. The recruitment of subjects was conducted using consecutive sampling. Inclusion criteria were the following: 1) male or female patients with an age of ≥ 30 years old, 2) patients diagnosed with CCS, and 3) patients had biomarker examination. The following were exclusion criteria: (1) patients who had malignancy, (2) patients with chronic kidney disease, (3) patients with proven peripheral artery disease, and (4) patients without adequate TMT interpretation data. Informed consent was signed by all participating subjects. Subjects' enrollment, data collection, and biomarker examination were conducted from 2018 to 2019. For this current study, the analysis was finalized in 2024.

Among all eligible subjects, those who met the inclusion and exclusion criteria were analyzed. Data on demographics, cardiovascular disease risk factors, medications, and TMT results were collected. The TMT results were collected within 1.5 years before biomarker measurement. A CCS is chest pain/discomfort due to a disproportion between myocardial oxygen supply and demand, due to the presence of coronary stenosis, determined by CAG. A TMT is a CEST examination with a conveyor belt whose stress load is regulated by an electric machine and controlled by a programmable protocol by the Treadmill machine. The TMT procedures were Bruce or modified Bruce protocols. The termination criteria for the TMT procedure were in accordance with the national guideline and were determined by the clinicians who supervised the TMT.[4] The exercise time was the duration from the start of exercise until the end of exercise (start recovery). Chest pain was a subjective complaint of chest tightness during TMT and was assessed by clinicians who supervised the TMT as either no angina or angina. Limiting angina was chest pain that prompted subjects to stop the TMT, and non-limiting angina was chest pain present on the TMT but did not prompt subjects to stop the TMT. ST deviation was determined based on the national guideline for CEST.[4]

From the TMT, the DTS is calculated based on the presence of chest pain, time of exercise, and the depth of ST changes from baseline. The formula is: [DTS = exercise time (minutes) – 5 x ST segment deviation (mm) – 4 x index of anginal pain (value 0 = no angina, 1 = non-limiting angina, 2 = limiting angina)].[4] It is a scoring system for risk stratification and is useful for assessing the CVD prognosis in 5 years.[4] In this study, the DTS was classified into high-risk DTS (DTS ≤-11) and low-moderate-risk DTS (DTS >-11).

Endothelin-1 is a peptide measured in serum by ELISA and has normal levels between 0.7 and 2.0 pg/mL.[8] A level of >2.0 pg/mL was defined as a high endothelin-1 level. A blood sample was withdrawn to measure endothelin-1 levels when subjects were admitted to the hospital for a CAG examination. Fasting blood samples from peripheral veins were withdrawn before the CAG procedure, collected in BD Vacutainer tubes (Becton Dickinson, USA), and stored at room temperature for 20–30 min. Subsequently, the Vacutainer tubes were centrifuged at 200 g for 20 min, and the supernatants were stored frozen at −80 °C in the Biobank Unit of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. The process of measuring endothelin-1 was based on the manufacturer's instructions for the Endothelin-1 immunoassay Quantikine® ELISA kit (R&D Systems, Minneapolis, MN, U.S.A.), as previously described.[9]

For statistical analysis, the S.P.S.S. software v.25 (I.B.M., U.S.A.) was used. The categorical data were exhibited as a number (%). The numerical data were presented as the mean and Standard Deviation (SD) when normally distributed, or as the median (range: minimum-maximum values) when skewed. Following the bivariate analysis, a multivariate logistic regression was performed to assess the association between two main variables: serum endothelin-1 level and high-risk DTS. Covariates were included in logistic regression if the p-value was <0.250 in the bivariate analysis. The p-value <0.05 was a statistically significant cut-off.

Results

During patients' eligibility screening, 183 patients underwent CAG and had serum endothelin-1 measurement. Of these patients, 95 lacked adequate TMT data (including DTS), and 8 lacked sufficient variables required for the study. Therefore, 103 patients were excluded from the study. Finally, 80 subjects were enrolled. The median time interval between TMT and endothelin-1 measurement was 30 days (range: 3 – 371 days). The characteristics of the subjects are exhibited in Table 1.

Table 1. Subject characteristics.

Variables	Total (n=80)
Male sex, n (%)	66 (82.5)
Age, years (mean±SD)	58.48±8.73
Diabetes mellitus, n(%)	20 (25.0)
Dyslipidemia, n(%)	41 (51.2)
Hypertension, n(%)	57 (71.3)
Smoking, n (%)	53 (66.3)
History of ACS, n(%)	42 (52.5)
Endothelin-1, pg/mL (median (min-max)	1.8 (0.4-6.8)
Time interval, days (median (min-max))	30 (3-371)
TMT result, n(%)	
High-risk DTS	42 (52.5)
Low-moderate-risk DTS	38 (47.5)
Beta blocker, n(%)	63 (78.8)
ACEi/ARB, n(%)	69 (86.3)
Statin, n(%)	72 (90.0)
Spironolactone, n(%)	3 (3.8)

SD: Standard deviation, ACS: Acute coronary syndrome, TMT: Treadmill test, DTS: Duke treadmill score, ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

Subjects' characteristics show that the mean age was 58.48±8.73 years old. Most of the subjects (82.5%) were males. Cardiovascular risk factors were hypertension (71.3%), diabetes mellitus (25%), active smoker (66.3%), and dyslipidemia (51.2%). Previous ACS occurred in 52.5% of subjects. From the TMT results, the number of subjects with high-risk DTS was 52.5%. Users of Angiotensin-converting Enzyme inhibitor (ACEi)/Angiotensin Receptor Blockers (ARB) drugs were 86.3%, beta blockers 78.8%, statins 90%, and spironolactone 3.8%. For the measurement of endothelin-1 levels,

a median of 1.8 pg/mL was obtained with a value range of 0.4-6.8 pg/mL.

An increased serum endothelin-1 level (>2.0 pg/mL) was observed in 34 subjects (42.5%). Among them, 23 subjects (67.6%) were classified as high-risk DTS, while 32.4% were classified as low-moderate-risk DTS. There was a significantly increased risk of high-risk DTS in subjects with serum endothelin-1 >2.0 pg/mL (OR 2.97; 95% CI 1.18-7.51; p=0.020), as shown in Table 2.

The variables associated with high-risk DTS are shown in Table 3. Based on bivariate analysis, a history of ACS (p=0.036) and endothelin-1 level >2.0 pg/mL (p=0.020) were significantly associated with high-risk DTS. Two covariates (p-value <0.250) were included in the multivariable analysis: hypertension (p=0.052) and a history of ACS. Table 4 shows the results of a logistic regression analysis that included hypertension, a history of ACS, and serum endothelin-1 >2.0 pg/mL. It was found that endothelin-1 level > 2.0 pg/mL had an adjusted OR of 1.75 (95% CI: 0.60-5.13, p=0.305), indicating no statistically significant independent association with high-risk DTR. Nevertheless, hypertension and a history of ACS had statistically independent, significant associations with high-risk DTS, with respective adjusted ORs of 0.31 (95% CI: 0.11-0.90, p=0.032) and 5.97 (95% CI: 1.16-30.65, p=0.032).

Table 2. A bivariate analysis between serum endothelin-1 levels and DTS risk stratification.

Serum endothelin-1 level	DTS Stratification		OR (95% CI)	P value
	High Risk n (%)	Low-moderate Risk n (%)		
Level >2.0 pg/mL	23 (67.6)	11 (32.4)	2.97 (1.18-7.51)	0.020
Level ≤2.0 pg/mL	19 (41.3)	27 (58.7)		

DTS: Duke treadmill score; CI: Confidence interval; OR: Odds ratio.

Table 3. Comparison of variables based on DTS stratification.

Variables	DTS Stratification		P-value
	High Risk n (%)	Low-moderate Risk n (%)	
Age ≥60 years old	11 (57.9%)	8 (42.1%)	0.590
Male sex	34 (51.5%)	32 (48.5%)	0.702
Diabetes Mellitus	10 (50%)	10 (50%)	0.796
Dyslipidemia.	23 (56.1%)	18 (43.9%)	0.509
Hypertension	26 (45.6%)	31 (54.4%)	0.052
Smoke	27 (50.9%)	26 (49.1%)	0.696
History of ACS	18 (42.7%)	24 (57.3%)	0.036
Beta blocker	32 (50.8%)	31 (49.2%)	0.556
ACEi/ARB	35 (50.7%)	34 (49.3%)	0.426
Statin	37 (51%)	35 (49%)	0.292
Spironolactone	2 (66.7%)	1 (33.3%)	1.000
Endothelin-1 level >2.0 pg/mL	23 (67.6)	11 (32.4)	0.020

ACS: Acute coronary syndrome, TMT: Treadmill test, DTS: Duke treadmill score, ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

Table 4. Multivariate analysis for independent association between variables and high-risk DTS.

Variables	Phase I OR (95% CI; p value)	Phase II OR (95% CI; p value)
Serum endothelin-1 level >2.0 pg/mL	1.75 (0.60-5.13); 0.305	-
Hypertension	0.36 (0.12-1.06); 0.063	0.31 (0.11-0.90); 0.032
History of ACS	3.99 (0.66-24.24); 0.132	5.97 (1.16-30.65); 0.032

ACS: Acute coronary syndrome; CI: Confidence interval; OR: Odds ratio.

Discussion

This study showed that in CCS patients who had an increased serum endothelin-1 level > 2.0 pg/mL, there was an increased risk of 5-year mortality, determined by high-risk DTS preponderance. This increased risk was not independently associated due to an interaction with hypertension and a history of ACS. Therefore, a strategy to control hypertension and optimize ACS treatment is necessary to reduce 5-year mortality for patients who have higher serum endothelin-1 levels.

The majority of subjects had hypertension (71.3%), with 45.6% of them in the high-risk DTS. Hypertension was independently associated with high-risk DTS. Studies demonstrated the increased CCS risk among subjects with higher blood pressure, both systolic (>115 mmHg) and diastolic (>75 mmHg), which showed that those with a 20 mmHg increased of systolic blood pressure and a 10 mmHg of diastolic blood pressure had a 2-fold risk to develop CCS.[10]

Previous research determined that a normal serum endothelin-1 level is between 0.7 and 2.0 pg/mL.[8] The level of >2.0 pg/mL indicates high endothelin-1. In this study, 42.5% of subjects had high endothelin-1 levels, and 67.6% were classified as high-risk DTS. This is associated with nearly a threefold increased risk of high-risk DTS stratification. However, this association was not independent of covariates, such as hypertension and a history of ACS. This indicates that elevated endothelin-1 interacts with increased blood pressure and preceding acute CVD event in patients with CCS. Prior studies have shown that elevated endothelin-1 levels in coronary atherosclerosis actively contribute to regional myocardial ischemia.[11]

Endothelin-1, emitted largely by endothelial cells, induces a strong and enduring vasoconstriction response by means of paracrine activity, primarily on its receptors in vascular smooth muscle cells.[12] Endothelin-1 vasoactive response plays a crucial role in CVD, where elevated circulating endothelin-1 or endothelin-1-related peptides frequently occur in CVD. Hypertension, pulmonary hypertension, and atherosclerosis were among the diseases affected by endothelin-1 activity.[12] Endothelin-1 production is triggered by various external stimuli or pathological conditions, such as inflammation, hypoxia, or mechanical stress on the blood vessel wall, which increase endothelin-1 mRNA expression and endothelin-1 release.[13] The inducible pathway is greater and can produce a more significant effect in increasing vasoconstriction or playing a role in pathological conditions such as hypertension or atherosclerosis.[13] In this study, elevated endothelin-1 levels were not independently associated with high-risk DTS stratification. There are possible interactions with variables, namely, history of ACS and hypertension, which showed a significant and independent association with high-risk DTS. These two clinical conditions are associated with elevated endothelin-1 levels.

Exercise stress testing by TMT is an established modality for diagnosis and prognosis of CAD, especially in patients with CCS.[4] For risk stratification of patients having TMT, the DTS is an established scoring system for risk stratification. Patients with high-risk DTS or DTS ≤-11 are considered candidates for CAG because the positivity rates of significant coronary stenosis require revascularisation and increased 5-year mortality.[14] Our study may provide insight into the risk of increased 5-year mortality in patients with CCS who had elevated endothelin-1 levels. These patients may need further strategies for secondary CVD prevention, especially in controlling hypertension and optimizing coronary medication.

Most subjects receive standard medication for CCS, namely beta-blockers (78.8%), ACEi/ARBs (86.3%), and statins (90%). These medications may affect endothelin-1 levels in patients with CCS.[15] In this study, more than half (57.5%) of subjects had an endothelin-1 level below 2.0 pg/mL. However, in this study, the impact of medications was neutral in terms of DTS risk stratification. Further study is needed to investigate the impact of medications on DTS risk stratification.

Several limitations were encountered in this study, namely: (1) small subjects enrolled in this study, which affected the result of multivariates analyis, (2) more than half of the study population was excluded due to incomplete data, (3) several conditions that may affect endothelin-1 levels, such as peripheral artery disease, could not be excluded due to the lack of relevant data, and (4) the study used secondary data, making it impossible to control the interval time of endothelin-1 blood sampling and the TMT examination.

Conclusion

In the conclusion, among patients with CCS, a serum endothelin-1 level > 2.0 pg/mL is associated with high-risk DTS on TMT examination. However, this increased risk was not independently associated due to interaction with hypertension and history of ACS. Hypertension and a history of ACS were

independent predictors for high-risk DTS, which was linked to reduced 5-year survival in CCS patients.

List of Abbreviations

ACEi	Angiotensin-converting Enzyme inhibitor
ACS	Acute Coronary Syndrome
ARB	Angiotensin Receptor Blockers
CAD	Coronary Artery Disease
CAG	Coronary Angiography
CCS	Chronic Coronary Syndrome
CEST	Cardiac Exercise Stress Test
CI	Confidence Interval
CVD	Cardiovascular Disease
DTS	Duke Treadmill Score
ECG	Electrocardiogram
ELISA	Enzyme Link Immunosorbent Assay
mRNA	:messenger Ribonucleid Acid
OR	Odds Ratio
SD	Standard Deviation
TMT	Treadmill Test

Ethical Clearance

Ethical approval was obtained from The Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia (Reff. number: KE/FK/1910/EC/2024).

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

MSP: conception and design, analysis and interpretation of data, drafting the article, and final approval of the version to be published. IAA: conception and design, revising the article critically for important intellectual content, and final approval of the version to be published. IP: conception and design, revising the article critically for important intellectual content, and final approval of the version to be published ABH: conception and design, revising the article critically for important intellectual content, and final approval of the version to be published All authors read and approved the final manuscript

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Conflict of Interest

None.

Availability of Data and Materials

Data and materials generated for this study are available on request to the corresponding author.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

The author declares that no artificial intelligence (AI) tools were used in the writing, analysis, or preparation of this manuscript.

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Original Article

Prevalence and Lipid Profile Associations of Elevated Lipoprotein(a) Among Indonesian Adults: A Cross-Sectional Study

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Abstract

Background: Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein and an independent risk factor for Atherosclerotic Cardiovascular Disease (ASCVD). While 20–30% of adults worldwide have elevated Lp(a), data from Indonesia remain scarce. Given reported differences by sex and metabolic profile, this cross-sectional study aimed to determine the prevalence of elevated Lp(a) and its associations with lipid parameters and Hemoglobin A1c (HbA1c) among adults undergoing routine health screening at a tertiary hospital in Indonesia.

Methods: This cross-sectional study analyzed data from 904 adults who underwent routine health screening at Siloam Hospitals Kebon Jeruk, Jakarta (2021–2024). Data on Lp(a), lipid profile, and HbA1c were extracted from the medical records. The normality of data was assessed using the Shapiro–Wilk test. Group comparisons were performed using the Mann–Whitney U test, and correlations between log-transformed Lp(a) and metabolic parameters were evaluated using Spearman correlation and simple linear regression.

Results: Among 904 participants, 18.8 % had elevated Lp(a) levels (≥ 30 mg/dL). Females showed significantly higher Lp(a) concentrations than males ($p = 0.008$). Low-Density Lipoprotein Cholesterol (LDL-C) levels were slightly higher in participants with elevated Lp(a) but did not differ significantly ($p = 0.14$). On linear regression, LDL-C was positively associated with log-transformed Lp(a) ($B = 0.002$, $p < 0.001$), whereas triglycerides were inversely associated ($B = -0.001$, $p = 0.019$); no robust associations were observed for High-Density Lipoprotein Cholesterol (HDL-C) or HbA1c.

Conclusions: Nearly one in five adults undergoing routine health screening in this Indonesian cohort had elevated Lp(a) levels. Females exhibited significantly higher Lp(a) concentrations than males, and LDL-C showed a modest positive association with Lp(a). These findings reinforce the relevance of Lp(a) as an important, genetically influenced cardiovascular risk marker and support routine Lp(a) screening for improved risk stratification in clinical practice.

Keywords: Lipoprotein (a), Dyslipidemia, Atherosclerosis, Cardiovascular risk factors, Screening.

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Introduction

Lipoprotein(a) [Lp(a)] is a form of Low-Density Lipoprotein (LDL) consisting of an LDL particle covalently bonded to apolipoprotein(a) [apo(a)].[1] This unique composition differentiates Lp(a) from other lipoproteins, providing specific functional characteristics.[2] Lp(a) is recognized as a cardiovascular risk factor that is independent and contributes to the progression of Atherosclerotic Cardiovascular Disease (ASCVD) in several populations.[3-4] Unlike traditional lipid indicators such as LDL Cholesterol (LDL-C), Lp(a) levels are predominantly determined by genetic factors and remain stable throughout an individual's life.[5-6] This genetic stability indicates that Lp(a) is not readily altered by lifestyle modifications, dietary alterations, or pharmacological treatments that influence other lipid metrics.[7-9]

Notwithstanding its therapeutic importance, Lp(a) continues to be inadequately acknowledged and underused in standard cardiovascular risk evaluations.[10] Its impact on ASCVD risk is often overshadowed by more routinely measured lipid indicators, such as LDL-C. Consequently, numerous patients with heightened Lp(a) levels remain unrecognized or insufficiently treated. Moreover, routine screening for Lp(a) is seldom performed in clinical practice, as guidelines frequently omit its inclusion in standard lipid profiles. The issue is exacerbated by the lack of population-specific data on the incidence of elevated Lp(a) levels, particularly in certain communities.[11-12] Comprehending the distribution and prevalence of Lp(a) levels in these groups is essential for enhancing Cardiovascular Disease (CVD) prevention and therapy techniques. Nevertheless, information regarding the epidemiology of Lp(a) in local communities is limited, especially in our town.

Therefore, this cross-sectional study aimed to determine the prevalence of elevated Lp(a) and its associations with lipid parameters (LDL-C, High-Density Lipoprotein Cholesterol [HDL-C], triglycerides) and Hemoglobin A1c (HbA1c) among adults undergoing routine health screening at Siloam Hospitals Kebon Jeruk, Jakarta.

Methods

Materials and Methods

This cross-sectional observational study evaluated the prevalence and distribution of elevated Lp(a) levels in adults undergoing routine health screening. The primary objective was to determine the prevalence of elevated Lp(a) and its associations with lipid parameters and HbA1c.

Data were obtained from the Medical Check-Up (MCU) unit of Siloam Hospitals Kebon Jeruk, Jakarta, for individuals who underwent Lp(a) testing between January 2021 and June 2024. A total of 904 participants were included. Adults aged ≥18 years who underwent routine medical check-up testing with available Lp(a) results were included. Participants with incomplete lipid profiles or HbA1c data were excluded. Because the dataset represented routine health screening, individuals with prior CVD (including ASCVD, coronary stent placement, or cardiac surgery) were not excluded; they were included and analyzed as part of the overall study population. This study received ethical approval from the Faculty of Medicine, Pelita Harapan University (No. 207/K-LKJ/ETIK/V/2025).

Data collection included measurements of Lp(a) levels, with elevated Lp(a) defined as levels of 30 mg/dL or greater, a threshold associated with increased cardiovascular risk.13,14 The medical records were analyzed to extract data on lipid profiles, which included total cholesterol, LDL-C, HDL-C, and triglycerides, in addition to Lp(a) levels. Body Mass Index (BMI) and renal function, evaluated by serum creatinine and estimated Glomerular Filtration Rate (eGFR), were documented. HbA1c levels of participants were included to assess glycemic control, especially among individuals with diabetes risk factors. Furthermore, participants' medical histories were gathered, including the presence of Hypertension (HTN), ASCVD, and Diabetes Mellitus (DM), as well as family histories of HTN, heart disease, and stroke. Demographic variables, including age and sex, were also noted for subgroup analyses.

This observational study used pre-existing data from routine clinical tests, so informed consent was not required for participation. The study adhered to ethical principles of confidentiality and data protection, ensuring that all personal identifiers were removed from the data before analysis.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26. Continuous variables are presented as mean ± Standard Deviation (SD) or median (Interquartile Range [IQR]) depending on data distribution, while categorical variables are summarized as frequencies and percentages. The Shapiro–Wilk test was applied to assess normality. Between-group comparisons were performed using the independent-samples t-test for normally distributed data and the Mann–Whitney U test for

non-normally distributed data. Categorical variables were compared using the chi-square test.

Correlations between Lp(a) and metabolic parameters were examined using Spearman correlation analysis. Simple linear regression was then conducted with $\log_{10}$-transformed Lp(a) as the dependent variable and LDL-C, triglycerides, HDL-C, and HbA1c as independent variables. A two-tailed $p < 0.05$ was considered statistically significant.

Results

The mean age of the participants was 48 ± 13 years, with 58.5% of the participants being male (N = 529). Regarding clinical parameters, the mean systolic blood pressure was 124.5 ± 16.5 mmHg, while the mean diastolic blood pressure was 78.7 ± 10.1 mmHg. The average BMI was 25.9 ± 4.6 kg/m². Regarding comorbidities, HTN was present in 18.7% of the participants (N = 169), diabetes mellitus in 5.1% (N = 46), and established ASCVD in 7.3% (N = 66).

Further baseline data included creatinine levels of 0.9 ± 0.2 mg/dL and an average eGFR of 96.4 ± 17 ml/kg/min. The mean HbA1c was 5.7 ± 1.1%. Lipid profiles showed a mean total cholesterol of 204.2 ± 42.4 mg/dL and a mean LDL-C of 138.7 ± 40.5 mg/dL. The average Lp(a) level was 19.2 ± 28.3 mg/dL. Family history data indicated that 37.8% had a family history of HTN (N = 342), 16.3% had a family history of heart disease (N = 147), and 10% had a family history of stroke (N = 90). Additionally, 15.6% of participants were current smokers (N = 141) (Table 1).

Table 1. Baseline characteristics.

Variables	Value
Age (years)	48 ± 13
Male (%)	58.5
Systolic Blood Pressure (mmHg)	124.5 ± 16.5
Diastolic Blood Pressure (mmHg)	78.7 ± 10.1
Body Height (cm)	165.7 ± 9.0
Body Weight (kg)	71.6 ± 15.6
BMI (kg/m2)	25.9 ± 4.6
Laboratory values	
Creatinine (mg/dL)	0.9 ± 0.2
eGFR (ml/min/1.73m²)	96.4 ± 17
HbA1c (%)	5.7 ± 1.1
Total cholesterol (mg/dL)	204.2 ± 42.4
Triglycerides (mg/dL)	123.6 ± 66.6
High-density lipoprotein (mg/dL)	52.0 ± 13.3
Low-density lipoprotein (mg/dL)	138.57 ± 40.75
Lipoprotein a (mg/dL)	19.2 ± 28.3
Comorbid	
Hypertension (%)	18.7
Diabetes Mellitus (%)	5.1
Established Atherosclerosis CVD (%)	7.3
Family history	
Stroke (%)	10
Heart disease (%)	16.3
Hypertension (%)	37.8
Smoking status (%)	15.6

Abbreviation: BMI, Body Mass Index; CVD, Cardiovascular Disease; eGFR, estimated Glomerular Filtration Rate.

Of the study participants, 81.2% exhibited non-elevated Lp(a) levels (< 30 mg/dL), whereas 18.8% had elevated Lp(a) levels (≥ 30 mg/dL) (Fig 1). Sex differences in Lp(a) levels were observed, with males presenting a mean of 17.3 ± 24.7 mg/dL and females a higher mean of 22.0 ± 32.7 mg/dL. Lp(a) levels were significantly higher in females than in males (Mann–Whitney U = 88 888, p = 0.008; Fig 2).

While the mean LDL-C level in the normal Lp(a) group (Lp(a) < 30 mg/dL) was 137.4 ± 1.46 mg/dL, the elevated Lp(a) group (Lp(a) ≥ 30 mg/dL) had a mean LDL-C level of 144.4 ± 3.41 mg/dL. This suggests that individuals with elevated Lp(a) typically have higher LDL-C levels than those with normal Lp(a) (Fig 3). Median LDL-C levels did not differ significantly between participants with normal and elevated Lp(a) (Mann–Whitney U = 57 865, p = 0.14; Fig 3).

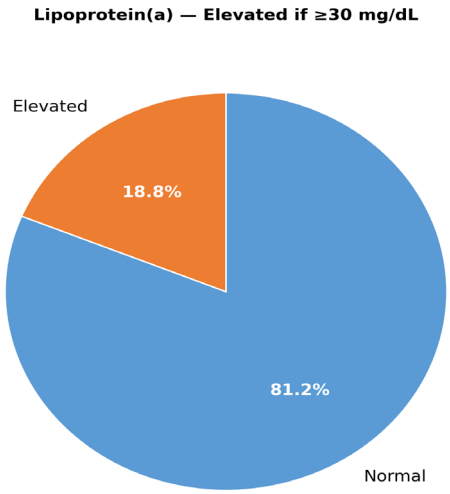

Figure 1. Percentages of elevated Lipoprotein(a).

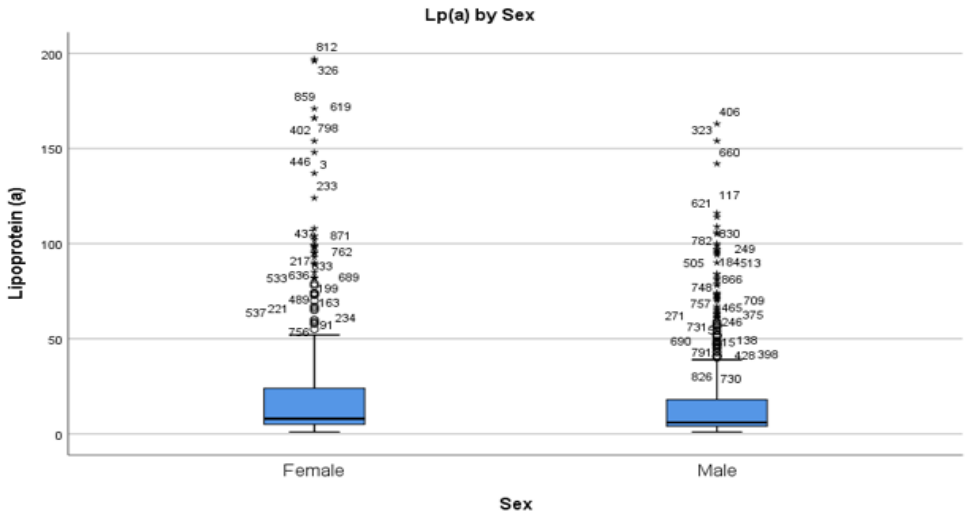

Figure 2. Sex differences in mean Lp(a).

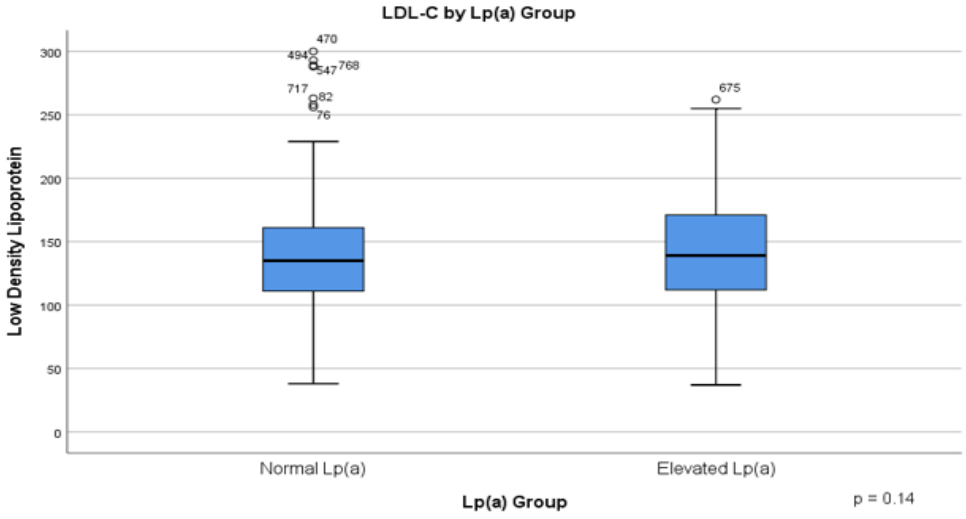

Figure 3. LDL-C differences in elevated vs normal Lp(a).

After comparing LDL-C levels between normal and elevated Lp(a) groups, we further analyzed the relationship between Lp(a) and key metabolic parameters using correlation and regression analyses. Spearman correlation analysis (Table 2) demonstrated a weak positive association between log-transformed Lp(a) and LDL-C ($\varrho = 0.134$, $p < 0.001$). A very weak positive correlation was also observed between log-transformed Lp(a) and HDL-C ($\varrho = 0.088$, $p = 0.008$). No significant correlations were found between log-transformed Lp(a) and triglycerides ($\varrho = –0.056$, $p = 0.094$) or HbA1c ($\varrho = 0.017$, $p = 0.606$).

The linear regression model (Table 3) similarly identified LDL-C as a modest but statistically significant predictor of log-transformed Lp(a) ($B = 0.002$, $p < 0.001$), while triglycerides showed a weak inverse association ($B = –0.001$, $p = 0.019$). HDL-C showed no significant association. HbA1c reached borderline significance in the regression model ($B = 0.027$, $p = 0.043$) but was not significantly correlated with Lp(a) ($\varrho = 0.017$, $p = 0.61$) and was not robust to sensitivity analysis, indicating no meaningful independent association.

Table 2. Spearman correlation between log-transformed Lp(a) and metabolic parameters.

Variable	Spearman's rho (ϱ)	p-value
LDL-C (mg/dL)	0.134	<0.001
Triglycerides (mg/dL)	-0.056	0.094
HDL-C (mg/dL)	0.088	0.008
HbA1c (%)	0.017	0.606

Spearman's rho was used due to non-normal distribution of Lp(a). logLP_A = $\log_{10}$[Lp(a)+1].

Table 3. Linear regression analysis of lipid and metabolic parameters associated with log-transformed Lp(a).

Predictor	B	Std. Error	β (Standardized)	p-value
LDL-C (mg/dL)	0.002	0.000	0.157	< 0.001
Triglycerides (mg/dL)	−0.001	0.000	−0.088	0.019
HDL-C (mg/dL)	0.002	0.001	0.058	0.115
HbA1c (%)	0.027	0.013	0.067	0.043

Dependent variable = $\log_{10}$[Lp(a)+1]; Model $R^2 = 0.037$, $F = 8.67$, $p < 0.001$.

Discussion

In our study, 18.8% of participants had elevated Lp(a) levels, aligning with global prevalence estimates of 20–30% for elevated Lp(a).[1,15-17] This finding supports previous research suggesting that Lp(a) is an under-recognized yet significant cardiovascular risk factor and highlights the potential value of routine screening, especially in populations at risk for ASCVD.

Female participants had higher Lp(a) levels than males, mirroring large cohorts in which women—particularly after menopause—show approximately 15–30% higher concentrations than men.[18] This sex difference is thought to be driven predominantly by genetic variation in the Lipoprotein(a) Gene (*LPA*), which determines apo(a) isoform size and, consequently, Lp(a) secretion rate; individuals carrying smaller apo(a) isoforms (fewer kringle IV type-2 repeats) have higher plasma Lp(a) levels. A greater prevalence of these smaller isoforms or subtle differences in hepatic lipoprotein handling in women may therefore underlie higher Lp(a) independent of hormonal status.[19-21] Estrogen does modulate *LPA* expression. Its decline after menopause is associated with a moderate rise in Lp(a) that can be partly attenuated by hormone therapy. Still, these hormonal influences appear secondary to the strong genetic determination of Lp(a).[18] Consistent with these mechanisms, female sex was significantly associated with elevated Lp(a) in this population.

In our regression model, LDL-C was the only lipid parameter positively associated with Lp(a) ($B = 0.002$, $p < 0.001$), and triglycerides were inversely associated with Lp(a) ($B = -0.001$, $p = 0.019$), whereas HDL-C showed no significant relationship. Although HbA1c reached borderline significance in the multivariable model, this was not corroborated by correlation analysis and was sensitive to extreme values; we therefore did not interpret HbA1c as an independent determinant of Lp(a). Notably, these variables together explained only ~3.7% of the variance in Lp(a) ($R^2 \approx 0.037$), underscoring that Lp(a) is largely independent of traditional metabolic factors. Spearman correlation analysis supported these findings, demonstrating a weak positive association between log-transformed Lp(a) and LDL-C, a very weak but statistically significant correlation with HDL-C, and no significant correlations with triglycerides or HbA1c. Minor differences between Spearman coefficients and regression estimates likely reflect the non-normal distribution of Lp(a) and the differing assumptions of these analytical approaches. The modest Lp(a)–LDL correlation can be explained by shared structure and clearance pathways: each Lp(a) particle contains an LDL-like apolipoprotein B100 core, and both Lp(a) and LDL are cleared via the LDL receptor (which is downregulated by Proprotein Convertase Subtilisin/Kexin type 9 [PCSK9]).[22-23] Consistent with this, therapies that up-regulate LDL receptors, such as PCSK9 inhibitors, substantially reduce Lp(a) levels, supporting an intertwined catabolism of Lp(a) and LDL.[24] In contrast, the inverse Lp(a)–triglyceride relationship observed in our regression analysis may reflect competition for apolipoprotein B (apoB) in the liver. During hypertriglyceridemia, increased Very-Low-Density Lipoprotein (VLDL) output (each VLDL particle requires an apoB) could limit the availability of apoB for Lp(a) assembly.[25] Supporting this hypothesis, insulin-resistant states with high VLDL–triglyceride production tend to show lower Lp(a) levels.[26] Taken together, these findings support Lp(a) as an essentially fixed, heritable cardiovascular risk factor, predominantly genetically determined with only minor modulation by LDL-related and triglyceride pathways.

The results underscore the importance of assessing Lp(a) levels in all adults at least once, in accordance with the American College of Cardiology (ACC)/American Heart Association (AHA) 2018 and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2019 guideline recommendations.[27-28] Routine Lp(a) testing may enhance cardiovascular risk stratification, particularly for individuals with elevated Lp(a) but low ASCVD risk based on traditional lipid measures.[29] Incorporating Lp(a) into standard cardiovascular evaluations could facilitate more targeted prevention strategies and earlier management of at-risk individuals not identified by conventional cholesterol testing.

Although our study provides valuable insights into the prevalence and distribution of elevated Lp(a) in an Indonesian population, several limitations should be acknowledged. This cross-sectional, single-center design precludes causal inference and limits generalizability. Despite adjustment for key lipid and metabolic variables, residual confounding cannot be excluded. Larger, multi-center prospective studies are needed to validate these findings and further explore the clinical implications of elevated Lp(a) as a cardiovascular risk factor. Future studies should also assess the prognostic impact of elevated Lp(a) on long-term cardiovascular outcomes and evaluate potential therapeutic strategies once effective agents become available.

Conclusion

In conclusion, 18.8% of participants in this study had elevated Lp(a) levels, consistent with global prevalence estimates. Females demonstrated significantly higher Lp(a) concentrations than males, and LDL-C showed a modest but statistically significant positive association with log-transformed Lp(a), independent of other lipid parameters. These findings highlight the growing relevance of Lp(a) as a critical cardiovascular risk marker in our community. Routine Lp(a) screening, particularly among individuals with high or borderline cardiovascular risk, may improve risk stratification and enable earlier, more targeted preventive interventions.

List of Abbreviations

ACC American College of Cardiology
AHA American Heart Association
apo(a) Apolipoprotein(a)
apoB Apolipoprotein B
ASCVD Atherosclerotic Cardiovascular Disease
BMI Body Mass Index
CVD Cardiovascular Disease
eGFR Estimated Glomerular Filtration Rate
EAS European Atherosclerosis Society
ESC European Society of Cardiology
HbA1c Hemoglobin A1c
HDL-C High-Density Lipoprotein Cholesterol
HTN Hypertension
LDL-C: Low-Density Lipoprotein Cholesterol
LPA Lipoprotein(a) Gene
Lp(a) Lipoprotein(a)
PCSK9 Proprotein Convertase Subtilisin/Kexin Type 9
VLDL Very-Low-Density Lipoprotein

Ethical Clearance

This study received ethical approval from the Faculty of Medicine, Pelita Harapan University (No. 207/K-LKJ/ETIK/V/2025).

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

Conceptualization and methodology: J.W.H., K.J.S., S.S.I.; Investigation: J.W.H., K.J.S., A.C.R.; Formal analysis: J.W.H., K.J.S., S.S.I.; Visualization and writing – original draft: J.W.H., K.J.S., A.C.R.; Writing – review and editing: S.S.I., L.P.S.; Supervision: L.P.S. All authors have read and approved the final version of the manuscript.

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Conflict of Interest

All authors declare no conflicts of interest.

Availability of Data and Materials

The data that support the study's findings are available in the article.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

No artificial intelligence (AI) tools were used at any stage of this study, including data collection, analysis, visualization, or manuscript preparation. All aspects of the work were performed manually by the authors.

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Original Article

Correlation Between Six-Minute Walk Test and Treadmill Exercise in Post-Coronary Artery Bypass Phase II Rehabilitation Patients: A Cross-Sectional Study

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Abstract

Background: Coronary Artery Bypass Grafting (CABG) improves survival in advanced Coronary Artery Disease (CAD) but is often associated with reduced functional capacity during recovery. Phase II cardiac rehabilitation improves physical performance, yet accessible and reliable tools are needed to monitor progress. Treadmill Cardiopulmonary Exercise Testing (CPET) is the gold standard for assessing aerobic capacity, but it is resource-intensive and not widely available in many settings. The Six-Minute Walk Test (6MWT) is a simple alternative, but its validity compared with treadmill testing in Indonesian post-CABG patients remains underexplored.

Methods: This cross-sectional study was conducted at the National General Hospital Dr. Cipto Mangunkusumo in Jakarta between May 2023 and October 2024. Post-CABG patients who completed an eight-week Phase II cardiac rehabilitation program, were clinically stable, and able to perform both assessments were included. Functional capacity was determined by estimated VO_2Max from the 6MWT and directly measured VO_2Max from a symptom-limited treadmill test using the Modified Bruce protocol. Descriptive statistics summarized baseline characteristics. Spearman correlation coefficient was used to evaluate the relationship between the two tests, with statistical significance set at $p<0.05$.

Results: Fifteen post-CABG patients completed the study. Most were male (73.3%) with a mean age of 59 years. Overweight status was common (46.7%), with hypertension (80.0%), dyslipidemia (66.7%), and diabetes mellitus (53.3%) as frequent comorbidities. Mean 6MWT distance increased from 307.8 ± 85.7 m pre-rehabilitation to 498.5 ± 140.7 m post-rehabilitation. The estimated VO_2Max from the 6MWT followed a normal distribution and is reported as a mean of 18.9 mL/kg/min (SD = 4.2). In contrast, the treadmill-measured VO_2Max was non-normally distributed and is therefore reported as a median of 21.4 mL/kg/min. A significant moderate positive correlation was found between 6MWT and treadmill VO_2Max ($r = 0.689$, $p = 0.005$).

Conclusions: The 6MWT demonstrated a strong, significant correlation with treadmill-based VO_2Max, supporting its use as a practical and cost-effective alternative for functional capacity assessment in post-CABG Phase II rehabilitation. Routine integration of the 6MWT may facilitate individualized exercise prescription and enhance patient monitoring, particularly in resource-limited settings.

Keywords: Coronary Artery Bypass, Cardiac Rehabilitation, Exercise Test, Walking Test, Oxygen Consumption.

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Introduction

Coronary Artery Bypass Grafting (CABG) remains the preferred revascularization strategy for patients with complex multivessel Coronary Artery Disease (CAD). Despite its survival benefits, the procedure is frequently associated with significant postoperative sequelae, including prolonged immobility, sternal instability, and a marked reduction in functional capacity.[1-2] Cardiac rehabilitation plays a pivotal role in mitigating these effects by enhancing physical tolerance and reducing mortality.[3] To prescribe safe and effective exercise intensity, accurate functional assessment is essential. Maximal exercise testing with gas analysis (Cardiopulmonary Exercise Testing [CPET]) or standard treadmill protocols is considered the gold standard for this purpose; however, its implementation in developing regions is often limited by high costs, the need for specialized equipment, and the technical complexity of the procedures.[4]

In resource-limited settings, the Six-Minute Walk Test (6MWT) has emerged as a practical, low-cost alternative that reflects functional capacity for daily living activities. While the 6MWT is widely used, its correlation with maximal treadmill testing has largely been established in Western populations. Applying these findings directly to Indonesian patients is problematic due to well-documented ethnic differences in anthropometry and stride length, which significantly influence walking distance and VO_2Max estimation.[5-6] Recent evidence indicates that the 6MWT is feasible and well-tolerated in adults and older patients immediately following CABG, while other studies have confirmed the reliability of treadmill-based 6MWT protocols across diverse cardiovascular cohorts.[7-8] Despite this reinforcing evidence for the test's general validity, specific validation data regarding its correlation with maximal treadmill testing in Indonesian post-CABG patients is currently lacking.

Consequently, relying on foreign reference standards may lead to inaccurate risk stratification and exercise prescription in the local context. This study aims to explore the correlation between 6MWT and treadmill testing among post-CABG patients in phase II rehabilitation, specifically by: (1) identifying the characteristics of post-CABG patients undergoing phase II cardiac rehabilitation, (2) estimating their functional capacity in terms of VO_2Max using both the 6MWT and treadmill test, and (3) determining the correlation between the 6MWT results and treadmill test outcomes in this patient population. By establishing this relationship, we seek to validate the 6MWT as a reliable surrogate tool for functional assessment in Indonesian cardiac rehabilitation centres where maximal testing is unavailable.

Methods

Study Design

This study used an observational analytic cross-sectional design to assess the correlation between the 6MWT and treadmill exercise testing in post-CABG patients undergoing phase II cardiac rehabilitation at the National General Hospital Dr. Cipto Mangunkusumo, Jakarta. The study was conducted at the Integrated Cardiocerebrovascular Service Unit, Medical Rehabilitation Outpatient Clinic, with data collection taking place from May 2023 to October 2024, following a preparation period from December 2022 to July 2023. Data analysis was scheduled for October to November 2024, with reporting planned for December 2024.

Participants

Participants were included if they were between 18 and 60 years of age and had completed an eight-week Phase II cardiac rehabilitation program following CABG. Patients were excluded if they had musculoskeletal or neurological disorders that impaired their ability to walk, were unable to understand or follow test instructions as indicated by a Montreal Cognitive Assessment Indonesian version (MoCA-INA) score below 26, or had active pulmonary disease, arrhythmia, fever or active infection, a Timed Up and Go (TUG) score greater than 12 seconds, high fear of falling, a frailty score of 3 or more based on the Fried Frailty Scale, or hemoglobin levels below 10 mg/dL. Participants were withdrawn from the study if they experienced test termination criteria during either the 6MWT or treadmill test, such as intolerable chest pain, dyspnea, leg cramps, dizziness, pallor, confusion, cold sweats, cyanosis, or nausea. Subjects who refused to complete the assessment procedures were also considered dropouts.

The sample size used in this study is calculated using a formula for correlational analytic studies. The sample size is determined based on the correlation coefficient (r) with the following formula:

$$n = ((Z\alpha + Z\beta) / (0.5 \times \ln((1 + r)/(1 - r))))^2 + 3$$

Explanation:

α = Type I error, set at 0.05, so $Z\alpha = 1.96$

β = Type II error, set at 0.20 (giving 80%

power), so $Z\beta = 0.842$
r = correlation coefficient
n = required sample size

The correlation coefficient (r) based on the six-minute walk test against Metabolic Equivalents of Task (METs) during treadmill training by Saba et al.[2] is 0.77, resulting in n = 13.38, thus a minimum of 14 subjects.

The study sample consisted of the accessible population who met the inclusion criteria and did not meet any of the exclusion criteria. Sampling was carried out using non-probability sampling, specifically purposive sampling, among individuals from the accessible population who fulfilled both the inclusion and exclusion requirements.

Ethical Considerations

Research ethics approval was issued by the Research Ethics Commission of the Faculty of Medicine, University of Indonesia, with a Letter of Approval from the Research Ethics Committee No. KET- 491 / UN2.F1 / ETIK / PPM.00.02 / 2023 and a Research Permit Letter at National General Hospital Dr. Cipto Mangunkusumo No. YR.02.01 / 2.6.1 / 0915/2023.

Intervention

Each eligible subject was provided with detailed information regarding the study's purpose, procedures, and potential benefits. Written informed consent was obtained prior to participation. Baseline assessments included demographic data (name, age, gender, phone number, religion, and education level), clinical history, and anthropometric measurements (weight, height, and vital signs). Subjects were instructed to wear comfortable clothing and athletic footwear. They then underwent the 6MWT following standardized instructions. The primary outcome from this test was the Six-Minute Walking Distance (6MWD), measured in meters. From this, estimated VO_2Max and METs were calculated along with documentation of any subjective symptoms. Specifically, estimated VO_2Max was calculated using the equation: $VO_2Max = (0.03 \times \text{distance in meters}) + 3.98$, and METs were derived as $VO_2Max/3.5$.

Outcome Measures

The main variables in this study were the predicted VO_2Max and METs derived from the 6MWT as independent variables, and VO_2Max and METs obtained from the treadmill test as dependent variables. Potential confounding variables included age, sex, Body Mass Index (BMI), and height. These factors were considered in both the data collection and analysis phases. The 6MWT standard protocols are described in Supplementary Data 1.

Following the 6MWT, patients received education regarding the treadmill test protocol and were referred to the cardiovascular division of internal medicine for treadmill testing, which was scheduled within 48 hours to 7 days of the initial test. The assessment followed the Modified Bruce Protocol, beginning with a warm-up stage (1.7 mph at 0% grade), followed by progressive 3-minute stages increasing in speed and grade (Stage 1: 1.7 mph, 10% grade; Stage 2: 2.5 mph, 12% grade, etc.), until volitional exhaustion or termination criteria were met. The full procedure is described in Supplementary Data 2.

The test score was defined as the total time (T) in minutes, which was converted into estimated VO_2Max (mL/kg/min) using specific population-based formulas: General: $14.76 - (1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)$; Women: $(2.94 \times T) + 3.74$; Young Women: $(4.38 \times T) - 3.9$; Men: $(2.94 \times T) + 7.65$; and Young Men: $(3.62 \times T) + 3.91$. Final outcomes included measured VO_2Max, METs, and any reported symptoms.

Statistical Analysis

Data processing and statistical analysis were performed using IBM SPSS Statistics version 26 for Macintosh. Descriptive analysis was conducted to evaluate the baseline characteristics and 6MWT outcomes. Categorical data were presented as frequencies and percentages, while continuous data were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed data were reported as means, while non-normally distributed data were presented as medians. The primary analysis assessed the correlation between outcomes of the 6MWT and the treadmill test using the Spearman correlation test, as data were not normally distributed. Correlation strength was classified as weak ($r < 0.40$), moderate ($r = 0.40$-0.69), or strong ($r \geq 0.70$).

Theory/calculation

Low 6MWD and treadmill test performance have been associated with poorer cardiovascular prognosis, and this can be explained by several physiological mechanisms. One key contributor is left ventricular dysfunction. A reduced VO_2Max, determined by both oxygen delivery (including cardiac output and peripheral vascular function) and oxygen utilization (primarily skeletal muscle efficiency), contributes to decreased exercise tolerance. Submaximal functional capacity may be limited either by resting ventricular dysfunction or by dysfunction induced during submaximal exertion.

However, the relationship between exercise capacity and left ventricular function is also influenced by factors such as age, gender, and BMI.[9]

Another important mechanism is myocardial ischemia, indicated by ST-segment depression or elevation during exercise testing.[10] Ischemia occurring at submaximal or maximal workloads may impair myocardial contractility and contribute to lower test outcomes in both VO_2Max and walking distance, as the impaired contractile response may limit cardiac performance under exertion, directly reducing measurable aerobic capacity.[11]

Endothelial dysfunction is also implicated in limiting oxygen delivery. It affects vascular tone, promotes thrombotic events, and alters the vascular wall composition, all of which contribute to a reduced VO_2Max and increased risk of recurrent cardiovascular events.[12] Moreover, poor functional capacity may also reflect an unfavorable cardiovascular risk profile, including dyslipidemia, hypertension, insulin resistance, systemic inflammation, autonomic dysfunction, and prothrombotic states. Together, these factors increase the likelihood of future adverse cardiac events.[13-14]

In this study, functional capacity is assessed using the 6MWT and treadmill exercise testing, both of which provide distance-based outcomes that reflect the integrated physiological responses of multiple organ systems involved in physical exertion, namely the pulmonary, cardiovascular, hematologic, neuromuscular, and muscular-metabolic systems. The 6MWT is chosen for its simplicity, validity, reproducibility, and tolerability, particularly among patients with CAD. Meanwhile, the treadmill test is a maximal-effort assessment and is considered the gold standard for evaluating aerobic capacity. Key indicators such as VO_2Max and METs, derived from these tests, serve as critical parameters for clinical diagnosis and prognostication. The conceptual framework underlying this assessment approach is illustrated in Figure 1.

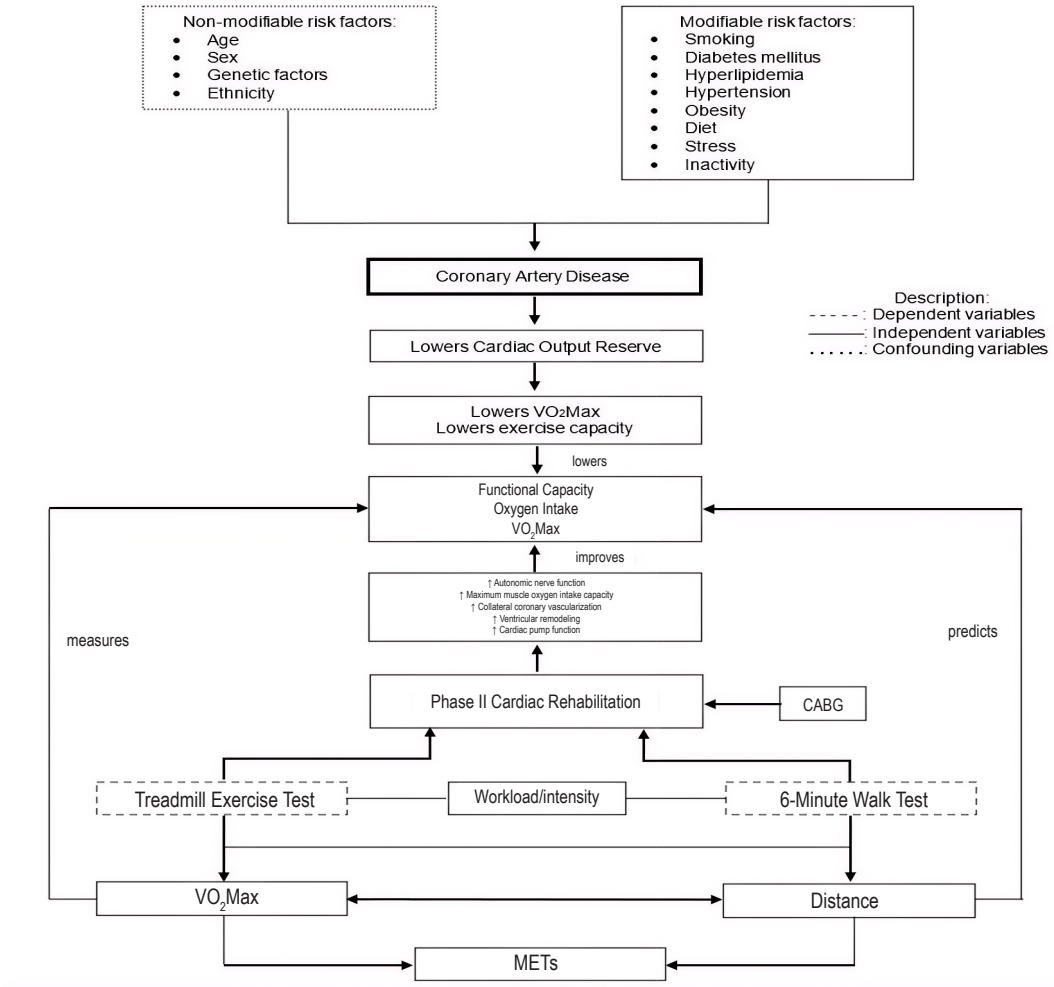

Figure 1. Conceptual Framework of Cardiac Rehabilitation in CAD.
This diagram shows how risk factors lead to coronary heart disease and reduced exercise capacity. Phase II cardiac rehabilitation improves functional capacity, measured by VO_2Max and walking distance, through structured exercise and testing.

Results

Participant Characteristics

The study subjects were post-CABG patients who met the inclusion and exclusion criteria and consented to participate. The recruitment process and outcomes are illustrated in Figure 2. A total of 40 patients were initially screened. Of these, 22 eligible participants (55.0%) failed to attend the baseline assessment. Specifically, ten participants did not attend the first visit for the 6MWT, one had undergone amputation, one experienced urethral rupture, two had strokes, three passed away, and five returned to their hometowns after the procedure.

Eighteen subjects signed the informed consent form. However, three dropped out due to loss to follow-up. Ultimately, 15 subjects completed the post-intervention assessments. This number meets the minimum sample size estimated during the study design phase. Participants underwent Phase II cardiac rehabilitation, consisting of supervised exercise sessions three times per week for eight weeks, totaling 24 sessions.

Several logistical challenges were encountered during the implementation of the study protocol. Initially, data collection was scheduled to be completed by December 2023. However, due to insufficient subject recruitment by the end of that year, the study duration was extended to October 2024. The primary challenge was identifying eligible participants who met the study criteria. No participants experienced adverse events during the exercise sessions, 6MWT, or treadmill exercise testing. Subject characteristics were evaluated to identify potential confounding variables, including age, sex, and BMI. Additional variables assessed were educational attainment and comorbidities. The detailed characteristics are presented in Table 1.

In this study, age was not normally distributed, with a median of 59 years and a range of 39-60 years. The majority of participants were male (73.3%). The mean BMI indicated that 46.7% of participants were overweight. Most participants had completed high school education (46.7%). The most common comorbidities were hypertension, followed by dyslipidemia and diabetes mellitus.

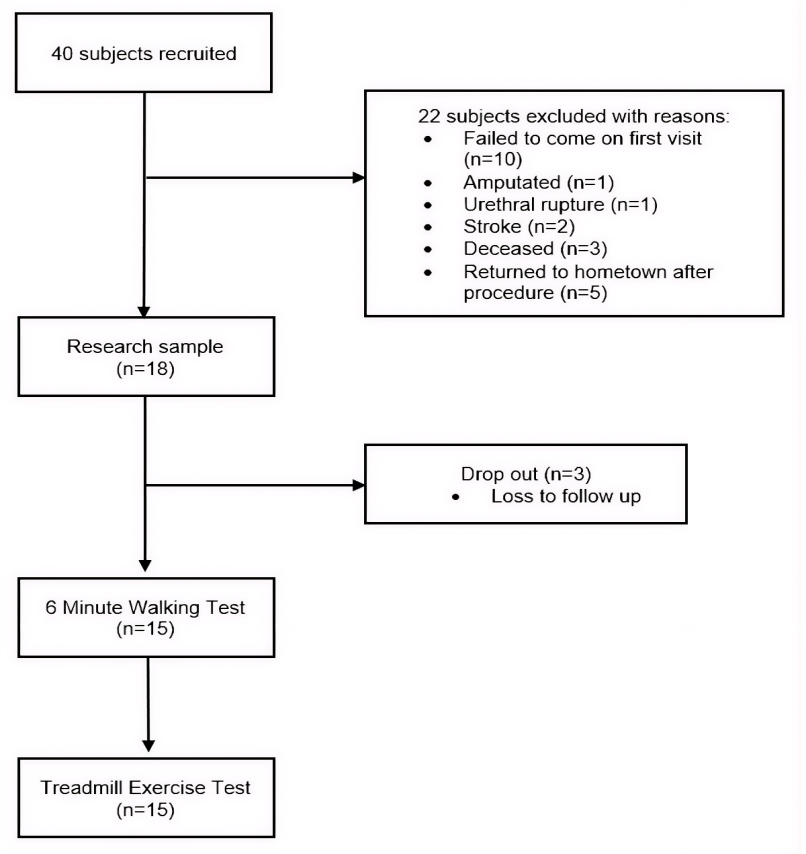

Figure 2. Subject Recruitment Process.
This flowchart outlines the recruitment and retention of study participants.

Table 1. Characteristics of Study Subjects.

Characteristic	n=15
Age (years), median (min-max)	59 (39-60)
Sex, n (%)	
Male	11 (73.3%)
Female	4 (26.7%)
Education Level, n (%)	
Primary School	1 (6.7%)
Middle School	1 (6.7%)
High School	7 (46.7%)
Diploma/Bachelor's Degree	6 (40.0%)
Body Weight (kg), mean (SD)	65.5 (8.8)
Height (cm), mean (SD)	162.5 (6.3)
BMI (kg/m²), n (%)	
Normal	7 (46.7%)
Overweight	7 (46.7%)
Obesity I	1 (6.7%)
Obesity II	–
Medical History, n (%)	
Hypertension	12 (80.0%)
Diabetes Mellitus	8 (53.3%)
Dyslipidemia	10 (66.7%)
Kidney Failure	5 (33.3%)
6-Minute Walk Distance (m), mean (SD)	
Before	307.8 (85.7)
After	498.5 (140.7)

BMI: Body Mass Index; m: meter.

Functional Capacity Based on VO_2Max in the 6MWT and Treadmill Exercise Test

After completing eight weeks of Phase II cardiac rehabilitation, participants demonstrated a substantial improvement in 6MWD, with a mean increase of 190.7 meters from baseline. The estimated VO_2Max from the 6MWT (which was normally distributed) is reported as a mean of 18.9 mL/kg/min (SD = 4.2). In contrast, the treadmill-measured VO_2Max (which was non-normally distributed) is reported as a median of 21.4 mL/kg/min (range: 15.7-35.7). The complete functional capacity data stratified by sex are presented in Supplementary Data 3, and the final summary of results is provided in Table 2.

Correlation Between 6MWD and Treadmill VO_2Max in Post-CABG Patients

A Spearman correlation analysis revealed a statistically significant moderate positive correlation between 6MWD and VO_2Max measured via treadmill testing in post-CABG patients ($r = 0.689$, $p = 0.005$). This finding indicates that a greater 6MWD is associated with higher treadmill VO_2Max, and vice versa. The correlation results are summarized in Table 2.

A scatter plot illustrating the relationship between 6MWD and treadmill VO_2Max is shown in Figure 3. The graph demonstrates that patients with higher VO_2Max values also achieved longer 6MWD walking distances. This reinforces the significant positive association between the two functional capacity indicators.

Discussion

Participants Characteristics

The average age of participants was 59 years (range: 39-60), categorized as late productive age. This finding is comparable to one research in Medan, Indonesia, which reported a mean age of 57.4 years (SD = 5.7) among post-CABG patients.[15] Similarly, another study identified an average age of 66 years (range: 59-72) in male patients post-open-heart surgery.[16] Older age is associated with a gradual decline in cardiorespiratory capacity, which

Table 2. Functional Capacity Outcomes and Correlation Analysis.

Variable	Value	Statistic
6MWT Distance (meters)	498.5 ± 140.7	Mean ± SD
6MWT Estimated VO_2Max (mL/kg/min)	18.9 ± 4.2	Mean ± SD
Treadmill Measured VO_2Max (mL/kg/min)	21.4 (15.7 – 35.7)	Median (Q1-Q3)
Correlation (Spearman's Rho)	0.689	
p-value	0.005	

Data are presented as Mean ± SD for normally distributed variables and Median (Q1-Q3) for non-normally distributed variables.

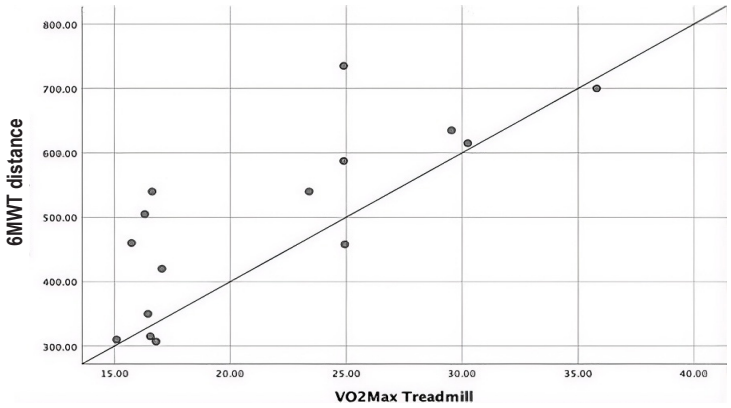

Figure 3. Scatter Plot of 6MWT and Treadmill Exercise Test.
The plot demonstrates that better treadmill exercise performance (higher VO_2Max) is generally associated with better walking endurance, as measured by the 6MWT distance. This supports the use of the 6MWT as a simple, practical indicator of cardiovascular fitness.

may result in slower postoperative improvement. Another significant difference is the proportion of male (11 participants) versus female (4 participants) subjects in this study, which may be considered a study limitation, even though it reflects the general trend in the proportion of CABG patients.[17] The small sample size of female participants may hinder accurate representation of women's responses to rehabilitation and limit the validity of statistical analyses comparing outcomes between the two sexes.

Male participants accounted for 73.3% of the sample, consistent with the literature reporting a higher prevalence of CABG procedures among men.[17-18] Males are associated with greater baseline cardiorespiratory fitness, muscular strength, and skeletal muscle mass, which may influence exercise test outcomes.[19-20]

Nearly half of the participants (46.7%) were classified as overweight, while hypertension was the most prevalent comorbidity (80.0%), followed by dyslipidemia (66.7%) and diabetes mellitus (53.3%). These comorbidities can negatively impact baseline functional capacity and the effectiveness of rehabilitation. This is in line with a multicenter study that found 44% of 7,498 CABG patients were overweight.[21] As was previously studied, overweight status is strongly associated with hypertension, dyslipidemia, and insulin resistance, key risk factors for CAD.[22]

Most participants had a high school education (46.7%), a factor that may influence comprehension of instructions, adherence to rehabilitation protocols, awareness of the benefits of the program, and capacity for independent management.[23]

Impact on 6MWD

Following 8 weeks of cardiac rehabilitation, the mean 6MWD increased significantly from 307.8 meters (SD = 85.7) to 498.5 meters (SD = 140.7), representing a mean improvement of 190.7 meters. The physiological mechanisms underlying these improvements include increased stroke volume and cardiac output, reduced resting heart rate, improved myocardial contractility, and enhanced coronary perfusion through angiogenesis.[24] Peripheral adaptations, such as improved endothelial function, increased nitric oxide production, decreased arterial stiffness, and enhanced skeletal muscle capillarization, also play a critical role in improving peripheral resistance.[25]

At the cellular level, consistent physical training stimulates mitochondrial biogenesis and volume expansion, thereby improving aerobic metabolism and oxidative enzyme activity.[26] These adaptations enhance peripheral oxygen extraction and improve neurohumoral balance by reducing sympathetic activity and enhancing vagal tone.[27] Skeletal muscle adaptations include hypertrophy, increased oxidative capacity, and optimized fiber-type distribution through pathways such as Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (PGC-1α) expression and AMP-activated protein kinase (AMPK) activation.[28] Exercise also reduces systemic inflammation and modulates pro-inflammatory cytokines.[3] Collectively, these mechanisms contribute to the observed improvement in 6MWD.

This phase II cardiac rehabilitation program has been shown to improve functional capacity, as evidenced by a 190.7-meter increase in the 6MWD. This improvement far exceeds the Minimal Clinically Important Difference (MCID) established by the European Respiratory Society/American Thoracic Society, which is 30 meters for minimal change in 6MWD.[29] Contributing factors influencing successful 6MWT outcomes include age, baseline 6MWD, exercise session attendance, supervision and encouragement during the test, and underlying cardiac pathology.[30] While both the 6MWT and treadmill test evaluate aerobic capacity, the 6MWT primarily reflects submaximal functional capacity relevant to daily activities, whereas the treadmill test assesses maximal cardiovascular performance.

Functional Capacity in the form of VO_2Max from the 6MWT and Treadmill Test

The mean VO_2Max derived from the 6MWT was 18.9 mL/kg/min (SD = 4.2), while that from the treadmill test was 21.4 mL/kg/min (range: 15.7-35.7). Saba et al.[2] reported a more significant difference between the two methods, with 6MWT VO_2Max at 11.3 mL/kg/min and treadmill-derived VO_2Max at 23.4 mL/kg/min, a difference of 12.1 mL/kg/min. In contrast, Zanini et al.[31] reported a smaller discrepancy: 18.8 mL/kg/min (SD = 6.1) from the 6MWT versus 19.5 mL/kg/min (SD = 3.6) from treadmill testing, a difference of only 0.7 mL/kg/min. Discrepancies in findings may be attributed to differences in participant demographics, post-operative timelines, and assessment methodologies. Additionally, anthropometric differences between Indonesian and international populations could influence exercise test performance. In general, VO_2Max values derived from treadmill testing tend to be higher than those estimated from the 6MWT. This is expected, given that the 6MWT assesses submaximal endurance, while treadmill testing measures peak aerobic capacity.

The mean METs during the 6MWT was 5.4 (SD = 1.2), while the treadmill test yielded a mean of 6.1 (range: 4.5-10.2). These results indicate a sufficient functional capacity for daily activities such as brisk walking, sweeping, or playing with children. However, activities must be introduced gradually and with proper monitoring.

Correlation Between 6MWD and Treadmill-Derived VO_2Max in Post-CABG Patients

This study demonstrated a statistically significant moderate positive correlation (r = 0.689) between the 6MWD and treadmill-derived VO_2Max in post-CABG patients undergoing Phase II cardiac rehabilitation. These results align with the researcher's expectations, as both tests assess functional capacity, albeit through distinct physiological mechanisms.

The moderate correlation can be attributed to the distinct characteristics of each test: the 6MWT is a submaximal, self-paced assessment, whereas the treadmill test is maximal and standardised. These findings are consistent with more recent evidence. For example, a meta-analysis found a significant correlation between VO_2Max and 6MWD (r = 0.65) in patients with cardiopulmonary conditions.[32]

Previous research demonstrates a strong correlation between 6MWT performance and treadmill test results in cardiac rehabilitation settings. In one updated study, the 6MWT showed a moderate-to-strong correlation (r = 0.70-0.80) with VO_2Max as measured by a treadmill test.[33] These findings reinforce the validity of the 6MWT as a practical tool for evaluating functional capacity. In populations with significant physical limitations, the 6MWT may approximate maximal exertion, further supporting its clinical utility.

While the 6MWT cannot fully replace treadmill testing, it remains an effective tool for screening and monitoring progress in cardiac rehabilitation programmes.[34] This is particularly relevant in clinical settings with limited access to treadmill or CPET facilities, and supports the adoption of the 6MWT as a practical alternative for monitoring functional progress over time. Its simplicity in implementation does not diminish its clinical reliability as a valid assessment tool.

Strengths and Limitations of the Study

Several limitations must be acknowledged. First, the use of purposive sampling may limit the generalizability of findings to the broader

Indonesian post-CABG population. Second, due to the limited sample size (n=15), the estimates may be subject to wide confidence intervals, and multivariate regression analysis to adjust for potential confounders (age, sex, BMI) could not be performed. Future studies with larger, randomized cohorts are needed to statistically isolate the effects of these variables.

Thirdly, this study did not use the gold-standard CPET. Sampling limitations were also present, as many patients at National General Hospital Dr. Cipto Mangunkusumo, reside outside Jakarta, and some were unable to complete the program. Additionally, incomplete data posed a challenge, particularly the lack of post-operative ejection fraction data prior to Phase II cardiac rehabilitation, as this parameter was not included in the standard operating procedures of the hospital.

Despite these limitations, this study presents several strengths. To our knowledge, it is the first to assess the correlation between the 6MWT and treadmill-based testing in post-CABG patients within an Indonesian population. Furthermore, the findings provide evidence that the 6MWT can be reliably administered in healthcare facilities without treadmill infrastructure, thereby broadening access of functional capacity assessments in cardiac rehabilitation programs.

Conclusion

These results indicate that the 6MWT is a practical, accessible, and valid measure of functional capacity in post-CABG patients during Phase II cardiac rehabilitation. Its strong correlation with treadmill-derived VO_2Max underscores its utility as a reliable alternative to more complex exercise testing. Consequently, the 6MWT can effectively guide individualized exercise prescription, monitor patient progress, and facilitate rehabilitation planning in clinical settings where resource constraints may limit access to advanced CPET. Integrating the 6MWT into routine post-CABG rehabilitation protocols may enhance patient outcomes by providing timely, objective assessments of cardiovascular fitness and functional improvement.

List of Abbreviations

6MWT	Six-Minute Walk Test
6MWD	Six-Minute Walking Distance
AMPK	AMP-activated protein kinase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CPET	Cardiopulmonary Exercise Testing
MCID	Minimal Clinically Important Difference
METs	Metabolic Equivalents of Task
MoCA-INA	Montreal Cognitive Assessment – Indonesian Version
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
TUG	Timed Up and Go Test
VO_2Max	Maximal Oxygen Uptake

Ethical Clearance

Research ethics approval was issued by the Research Ethics Commission of the Faculty of Medicine, University of Indonesia, with a Letter of Approval from the Research Ethics Committee No. KET- 491 / UN2.F1 / ETIK / PPM.00.02 / 2023 and a Research Permit Letter at National General Hospital Dr. Cipto Mangunkusumo No. YR.02.01 / 2.6.1 / 0915/2023.

Publication Approval

All authors have approved the publication of this manuscript.

Authors Contributions

AW and TFUT contributed to the conception and design of the study. AW performed data collection, conducted the analysis and interpretation of data, and drafted the initial manuscript. HRPS contributed to the interpretation of data, translated the manuscript into English, and critically revised it for important intellectual content. TFUT supervised the study, contributed to critical revision of the manuscript, and provided final approval of the version to be published. All authors meet the ICMJE authorship criteria and have read and approved the final manuscript.

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Conflict of Interest

None.

Availability of Data and Materials

The study protocols are provided in the Supplementary Materials (Supplementary Data 1 and 2).

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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Original Article

Soluble ST2 as a Marker of Subclinical Right Ventricular Dysfunction in Pulmonary Hypertension Associated With Congenital Heart Disease

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Abstract

Background: Congenital Heart Disease with Pulmonary Hypertension (CHD-PH) increases Right Ventricular (RV) afterload, which may lead to subclinical myocardial impairment before overt systolic dysfunction becomes apparent. Early detection is crucial to prevent progression to right heart failure. Global Longitudinal Strain (GLS) by echocardiography is sensitive for identifying subclinical RV dysfunction despite preserved conventional systolic parameters, but the role of molecular biomarkers remains unclear. Soluble Suppression of Tumorigenicity 2 (sST2) has been proposed as a potential biomarker for subclinical RV dysfunction. This study aims to compare sST2 levels in CHD-PH patients with and without subclinical RV dysfunction as assessed by RV-Global Longitudinal Strain (RV-GLS).

Methods: This cross-sectional study included adult CHD-PH patients (≥18 years) at the Integrated Heart Center, RSUP M. Djamil Padang, from January to June 2025. All participants underwent right heart catheterization and had preserved RV systolic function, as assessed by conventional echocardiography (Three-Dimensional Right Ventricular Ejection Fraction [3D RVEF] ≥45%). RV-GLS was assessed using Speckle-Tracking Echocardiography (STE), and serum sST2 levels were measured. Patients were categorized into subclinical RV dysfunction (GLS > –20%) and without subclinical RV dysfunction (GLS ≤ –20%) groups. Statistical analysis was performed to compare sST2 levels between groups.

Results: Thirty-four patients were included (82% female, mean age 37.8 ± 15.6 years), with secundum Atrial Septal Defect (ASD) as the most common etiology (71%). Median sST2 levels in patients with CHD-PH without subclinical RV dysfunction were 15.65 (6.05–40.90) ng/mL, with a GLS of –20.50 (–27.20 to –20.00)%. In patients with CHD-PH with subclinical RV dysfunction, median sST2 was 15.15 (5.25–47.60) ng/mL, with a GLS of –11.80 (–19.90 to –6.20)%. No statistically significant difference in sST2 levels was observed between groups ($p = 0.89$). In contrast, patients with CHD-PH with subclinical RV dysfunction exhibited significantly higher indexed Pulmonary Arterial Resistance (PAR) and pulmonary-to-Systemic Vascular Resistance ratio (PAR/SVR ratio), indicating increased pulmonary vascular load despite preserved conventional RV systolic function.

Conclusions: sST2 levels did not differ significantly between CHD-PH patients with subclinical RV dysfunction and those without. Subclinical RV dysfunction was associated with higher pulmonary vascular load, as reflected by increased indexed PAR and PAR/SVR ratio, despite preserved conventional RV systolic function. From this may conclude that subclinical RV myocardial impairment in CHD-PH is more closely related to hemodynamic afterload than to molecular stress biomarkers alone. These findings suggest that sST2 alone may have limited utility as a biomarker for detecting subclinical RV myocardial impairment in this population.

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Keywords: Pulmonary Hypertension, Congenital Heart Disease, Subclinical Right Ventricular Dysfunction, Global Longitudinal Strain, Soluble Suppression of Tumorigenicity 2

Introduction

Congenital Heart Disease associated with Pulmonary Hypertension (CHD-PH) represents a complex cardiovascular disorder that imposes significant hemodynamic stress on the Right Ventricle (RV). Chronic elevation of pulmonary arterial pressure leads to progressive RV remodeling and eventually systolic dysfunction, which is a major determinant of morbidity and mortality in this population. Early detection of RV systolic dysfunction is crucial, as timely therapeutic intervention can prevent progression to right heart failure and improve long-term outcomes.[1-2]

Echocardiography remains the most accessible and widely used tool for evaluating RV function in daily clinical practice. Conventional parameters such as Tricuspid Annular Plane Systolic Excursion (TAPSE), Fractional Area Change (FAC), and tissue Doppler-derived S' velocity have been extensively utilized. However, these indices often fail to detect subclinical dysfunction due to their dependence on load conditions and geometric limitations of the RV. Cardiac Magnetic Resonance Imaging (MRI) is currently considered the gold standard for RV assessment, yet its use is constrained by high cost, limited availability, and longer acquisition times, particularly in resource-limited settings.[3-4]

In recent years, Speckle-Tracking Echocardiography (STE) has emerged as a promising modality for quantifying RV-Global Longitudinal Strain (RV-GLS), offering improved sensitivity for detecting early myocardial deformation before conventional parameters become abnormal. In parallel, circulating biomarkers such as soluble Suppression of Tumorigenicity-2 (sST2), a member of the interleukin-1 receptor family, have gained attention for their ability to reflect myocardial stress, fibrosis, and adverse cardiac remodeling.[5-7] Elevated plasma sST2 levels have been reported in various cardiovascular conditions, including heart failure and Pulmonary Hypertension (PH), and may serve as an early indicator of ventricular dysfunction.[8-11]

Despite these advances, there remains a critical gap in the early identification of RV systolic dysfunction among adults with CHD-PH. Current studies have largely focused on imaging or biochemical markers in isolation, with limited evidence integrating both approaches. The relationship between RV-GLS as a sensitive imaging marker and plasma sST2 levels as a biomarker of myocardial stress has not been adequately explored in this population.[12-15] Establishing such a correlation could provide a more comprehensive and practical strategy for early detection of RV systolic dysfunction, especially in settings where advanced imaging modalities are not readily available.[16-20]

Therefore, this study aimed to investigate the correlation between plasma sST2 levels and RV systolic function assessed by echocardiographic parameters, particularly RV-GLS, in adult patients with CHD-PH. The findings are expected to contribute to the development of an integrated, cost-effective diagnostic approach for early detection and monitoring of RV dysfunction in this high-risk population.

Methods

Study Design and Population

This study employed an analytical cross-sectional design conducted at the Integrated Cardiac Service Unit of Dr. M. Djamil General Hospital, Padang, Indonesia, between January and June 2025. The study population consisted of adult patients (aged ≥18 years) with Congenital Heart Disease (CHD) who underwent right heart catheterization at the hospital's Cardiac Catheterization Laboratory.

PH was confirmed when the mean Pulmonary Arterial Pressure (mPAP) measured by right heart catheterization was ≥20 mmHg. A consecutive sampling technique was applied to recruit eligible participants who fulfilled all inclusion criteria, yielding a minimum sample size of 34 subjects.

Importantly, this study focused on CHD-PH patients with preserved RV systolic function as defined by conventional echocardiographic parameters to evaluate the presence of subclinical RV dysfunction using more sensitive myocardial deformation analysis.

Inclusion and Exclusion Criteria

Inclusion criteria were:

- Adult patients (≥18 years) with CHD-PH (mPAP ≥20 mmHg);
- Preserved RV systolic function based on conventional echocardiography, defined as a Three-Dimensional Right Ventricular Ejection Fraction (3D-RVEF) ≥45%;
- Preserved left ventricular systolic function (Left Ventricular Ejection Fraction [LVEF] ≥50%); and
- Willingness to participate, indicated by written informed consent.

Exclusion criteria included:

- Overt right or left ventricular systolic dysfunction (RVEF <45% or LVEF <50%);
- Coronary artery disease, hepatic or renal im-

pairment, or malignancy;
- Systemic inflammation, sepsis, or acute infection;
- Acute pulmonary or neurological disease;
- Active smoking;
- Arrhythmias or the presence of temporary or permanent pacemaker leads in the right ventricle;
- Bundle branch block;
- Poor echocardiographic image quality
- Refusal to participate.

Data Collection and Echocardiographic Assessment

Eligible CHD-PH patients were identified based on right heart catheterization results independently validated by two interventional cardiologists (Ethical Approval No. DP.04.03/D.XVI.XI/505/2024).

All participants underwent comprehensive Transthoracic Echocardiography (TTE) to assess RV structure and function. Conventional RV systolic parameters—including TAPSE, tissue Doppler-derived S' velocity, FAC, and 3D-RVEF- were measured according to current echocardiographic guidelines.

RV-GLS was assessed using two-dimensional STE (2D-STE). Endocardial borders were manually traced, and strain values were automatically calculated by dedicated software.

Based on RV-GLS values, patients with preserved conventional RV systolic function were further categorized into:

- Subclinical RV dysfunction (impaired RV strain): RV-GLS > –20%
- Without subclinical RV dysfunction: RV-GLS ≤ –20%.

This classification reflects myocardial functional impairment detectable by deformation imaging despite normal conventional systolic indices.

Biomarker Measurement

Peripheral venous blood samples (5 mL) were collected from all participants of measure sST2. Plasma samples were processed and analyzed using a commercially available Enzyme-linked Immunosorbent Assay (ELISA) kit at the Biomedical Laboratory, Faculty of Medicine, Andalas University, in accordance with the manufacturer's instructions.

Data Analysis

All data were statistically analyzed using standard software. Univariate analysis was performed to describe the baseline characteristics of the participants. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± Standard Deviation (SD) for normally distributed data or median (minimum–maximum) for non-normally distributed data. Data normality was assessed using the Shapiro–Wilk test. Bivariate analysis was performed to assess the relationship between plasma sST2 levels and RV-GLS values. The independent t-test was used for normally distributed data, and the Mann–Whitney U test was applied for non-normally distributed variables. A p-value <0.05 was considered statistically significant. Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Andalas University, and all participants provided written informed consent prior to enrollment, in accordance with the Declaration of Helsinki (2013 revision).

Results

A total of 82 patients with CHD were evaluated between January and June 2025 at the Integrated Cardiac Service Unit, Dr. M. Djamil General Hospital, Padang. After applying the exclusion criteria, 48 patients were excluded: 32 subjects without PH, 11 subjects with reduced RVEF, 2 subjects with other autoimmune or metabolic diseases, and 3 subjects who declined participation. Thus, 34 patients met the eligibility criteria and were included in the final analysis. Participants were categorized into two groups based on RV-GLS: those with subclinical RV dysfunction (RV-GLS > –20%) and those without (RV-GLS ≤ –20%).

Baseline Characteristics

The baseline characteristics of study subjects are summarized in Table 1. The majority of participants were female (82.2%, n = 28). There were no significant differences in age or Body Mass Index (BMI) between the two groups. The predominant CHD etiology was Atrial Septal Defect (ASD) secundum, accounting for 67.6% (n = 23) of all cases. Most patients were classified as World Health Organization (WHO) functional class II, with no statistically significant difference between groups. All subjects received Phosphodiesterase type 5 Inhibitors (PDE5-i) as first-line therapy for PH, while combination therapy with beraprost was more frequent among patients with subclinical RV systolic dysfunction.

Hemodynamic Parameters

Right heart catheterization findings revealed that Pulmonary Arterial Resistance (PAR), PAR index, and pulmonary-to-Systemic Vascular Resistance ratio (PAR/SVR) were higher in the group CHD-PH

Table 1. Baseline characteristics of study participants.

Variable	CHD-PH without Subclinical RV Dysfunction (n=17)	CHD-PH with Subclinical RV Dysfunction (n=17)	P-value
Demographic characteristics			
Female, n (%)	16 (94.1)	12 (70.6)	0.175[1]
Age (years)	37.76 ± 15.55	35.76 ± 11.51	0.673[2]
Body mass index (kg/m^2)	21.74 ± 4.49	20.03 ± 3.12	0.209[2]
Clinical characteristics			
WHO functional class			0.545[1]
Class I	0 (0)	0 (0)	–
Class II	16 (94.1)	15 (88.2)	–
Class III	1 (5.9)	2 (11.8)	–
Etiology of CHD			0.722[1]
Secundum ASD	11 (64.7)	13 (76.5)	–
Perimembranous VSD	4 (23.5)	3 (17.6)	–
Subaortic double-committed VSD	1 (5.9)	1 (5.9)	–
Patent ductus arteriosus	1 (5.9)	0 (0)	–
Pulmonary hypertension therapy			0.303[3]
PDE5 inhibitor	10 (58.8)	7 (41.2)	–
PDE5 inhibitor + prostacyclin analogue	7 (41.2)	10 (58.8)	–
Right heart catheterization			
Flow ratio (Qp/Qs)	2.91 (0.67–21.27)	2.37 (0.59–19.58)	0.535[4]
PAR (WU)	1.90 (0.19–19.90)	6.19 (0.33–28.16)	0.221[4]
PARi (WU·m^2)	2.70 (0.19–21.40)	10.00 (0.67–42.00)	0.040[4]
PAR/SVR	0.08 (0.01–1.20)	0.33 (0.02–1.26)	0.049[4]
mPAP (mmHg)	40.33 ± 20.09	51.35 ± 20.12	0.115[2]

Notes: [1] Chi-square test, [2] Independent t-test, [3] Fisher's exact test, [4] Mann–Whitney U test.

with subclinical RV systolic dysfunction compared to the group CHD-PH without subclinical RV dysfunction. Among these, the PAR value showed a statistically significant difference between groups, indicating a greater degree of vascular remodeling in patients with impaired RV function.

Echocardiographic Findings

As shown in Table 2, conventional echocardiographic parameters of RV systolic function, including TAPSE, tissue Doppler-derived S' velocity (RVS'), FAC, and 3D-RVEF, were within normal limits in both groups and showed no statistically significant differences. However, advanced assessment using STE showed lower (less negative) median RV-GLS and Free Wall Strain (FWS) in patients with CHD-PH and subclinical RV dysfunction, reflecting subclinical impairment of RV contractility. In contrast, RV dimension parameters did not differ significantly between the two groups.

Plasma sST2 Levels

Table 3 presents serum levels of sST2 in both study groups. The median sST2 concentration in both groups was within the normal range (<35 ng/mL). Statistical analysis revealed no significant difference in sST2 levels between CHD-PH patients with and without subclinical RV dysfunction ($p = 0.89$). This suggests that, in this cohort, sST2 may not reliably differentiate subclinical RV dysfunction in CHD-PH.

Observer Variability

Intraobserver and interobserver variability analyses were performed using the Bland–Altman method, demonstrating excellent agreement in measurements of RV-GLS, FWS, and 3D-RVEF. No significant differences were observed between intra- and interobserver analyses ($p > 0.05$), indicating high reproducibility and reliability of echocardiographic measurements in this study (Table 4).

Table 2. Echocardiographic parameters of right ventricular systolic function and right heart dimensions.

Variable	CHD-PH without Subclinical RV Dysfunction (n=17)	CHD-PH with Subclinical RV Dysfunction (n=17)	P-value
LVEF (%)	67.11 ± 5.90	64.00 ± 7.22	0.184[1]
TAPSE (cm)	2.40 (1.70–3.90)	2.00 (1.70–3.30)	0.579[2]
RV S' (cm/s)	12.00 (10.00–18.00)	12.00 (10.00–19.00)	0.576[2]
FAC (%)	45.00 (35.00–51.00)	40.00 (35.00–49.00)	0.067[2]
3D RVEF (%)	47.80 (45.00–59.40)	49.00 (45.00–58.80)	0.569[2]
RV-GLS (%)	–20.50 (–27.20 to –20.00)	–11.80 (–19.90 to –6.20)	<0.001[2]
RV-FWS (%)	–22.70 (–33.60 to –20.70)	–14.50 (–21.70 to –4.90)	<0.001[2]
TR Vmax (m/s)	3.90 (2.35–6.80)	4.50 (2.20–8.30)	0.692[2]
PVR (Abbas method, WU)	2.86 (1.30–15.00)	4.66 (1.31–10.90)	0.125[2]
RV–PA coupling (mm/mmHg)	0.17 (0.01–0.90)	0.06 (0.01–0.47)	0.167[2]
RA area (mm^2)	23.72 ± 10.73	26.75 ± 11.27	0.428[1]
RA ESV A–L (mL)	97.00 (16.9–166.0)	69.00 (4.84–289.0)	0.770[2]
Basal RV diameter (mm)	50.00 (28.00–58.00)	55.00 (29.0–77.0)	0.214[2]
Mid RV diameter (mm)	42.00 (27.00–60.00)	50.00 (23.00–285.00)	0.088[2]
Longitudinal RV diameter (mm)	83.29 ± 13.35	96.18 ± 25.59	0.075[1]
RV EDV (mL)	161.80 (72.00–270.80)	220.00 (53.00–561.60)	0.179[2]
RV ESV (mL)	81.00 (34.70–127.50)	114.00 (39.20–283.40)	0.031[2]

Notes: [1] Independent t-test, [2] Mann–Whitney U test.

Table 3. Serum sST2 levels.

Variable	CHD-PH without Subclinical RV Dysfunction (n=17)	CHD-PH with Subclinical RV Dysfunction (n=17)	P-value
sST2 (ng/mL)	15.65 (6.05–40.90)	15.15 (5.25–47.60)	0.890[1]

Table 4. Interobserver and intraobserver variability of right ventricular systolic function parameters.

Parameter	Interobserver (Observer 1 vs Observer 2)	P-value	Intraobserver (Measurement 1 vs Measurement 2)	P-value
RV-GLS (%)	–17.95 ± 5.50 vs –19.35 ± 5.20	0.176[1]	–19.35 ± 5.20 vs –19.35 ± 5.67	0.176[1]
RV-FWS (%)	–19.75 ± 5.40 vs –20.70 ± 2.90	0.619[1]	–20.70 ± 2.91 vs –20.73 ± 2.97	0.619[1]
3D RVEF (%)	49.18 ± 4.70 vs 41.35 ± 10.82	0.290[1]	41.35 ± 10.82 vs 40.58 ± 10.48	0.290[1]

Discussion

This study was conducted at RSUP Dr. M. Djamil Padang and included 34 patients diagnosed with CHD-PH. Subjects were categorized into two groups based on RV-GLS: CHD-PH patients with subclinical RV dysfunction (impaired RV strain) and CHD-PH patients without subclinical RV dysfunction, despite preserved conventional RV systolic function.

PH was more prevalent in females in both groups. In the CHD-PH without subclinical RV dysfunction group, 17 patients (94.4%) were female, while in the CHD-PH with subclinical RV dysfunction group, 12 patients (70.6%) were female. These findings are consistent with prior registries and cohort studies, including the PRO-KERALA registry (India, 2021; 62.6% female), the THALES study (Turkey, 2021; 56%), and Ingram et al. (USA; 52.2%). The female predominance in CHD-PH has been attributed to estrogen-mediated pulmonary vascular remodeling, involving upregulation of angiogenic and proliferative factors such as Vascular Endothelial Growth Factor (VEGF), which may accelerate pulmonary vascular disease progression and increase RV afterload, potentially contributing to earlier myocardial strain impairment in women.[3-4,21-24]

The mean age did not differ significantly between groups (CHD-PH without subclinical RV dysfunction: 37.00 ± 15.43 years; CHD-PH with subclinical RV dysfunction: 35.76 ± 13.49 years), consistent with previous studies reporting PH most frequently in patients aged 25–64 years. This aligns with the natural history of uncorrected CHD, in which progression to PH typically manifests symptoms in the 20–30-year age range. Mean BMI was 21.41 ± 4.57 kg/m² in the CHD-PH without subclinical RV dysfunction group and 20.74 ± 3.94 kg/m² in the CHD-PH with subclinical dysfunction group, consistent with the COHARD-PH registry (19.5 ± 6.9 kg/m²). Low BMI may result from malnutrition, growth impairment, tissue hypoxemia, increased cardiac workload, and nutrient malabsorption.[3,25-27]

Most patients were classified as WHO functional class II, reflecting early-stage disease with mild symptoms, consistent with Kucukoglu (Turkey, FC I–II: 46.6%) and contrasting Toma et al., who reported most patients in Functional Class (FC) III (50%). The most common PH etiology was secundum ASD, consistent with COHARD-PH (ASD: 89.3%) and epidemiological estimates (3.89 per 1,000 cases). Combination therapy with PDE5-i and prostacycline analogs was more frequent in the CHD-PH with subclinical RV dysfunction group (58.8%) than in the CHD-PH without subclinical RV dysfunction group (41.2%), consistent with right heart catheterization data showing higher mPAP and PVR, in accordance with 7th World Symposium on Pulmonary Hypertension (WSPH) recommendations.[5,9,24-28]

All subjects met the diagnostic criteria for PH (mPAP ≥ 20 mmHg). Mean PAR and PAR/SVR were higher in the subclinical dysfunction group, supporting Saputra et al.'s (2020) findings. This study demonstrates that subclinical RV dysfunction in CHD-PH is closely associated with increased pulmonary vascular hemodynamic burden, as reflected by PAR and PAR/SVR, rather than differences in circulating sST2 levels. Right atrial and ventricular dimensions and volumes were increased in both groups, larger in the subclinical RV dysfunction group, albeit not significantly, indicating subclinical RV remodeling. Conventional RV systolic function parameters (TAPSE, RVS', FAC, 3D-RVEF) were normal in all patients. RV-GLS and FWS were significantly impaired in the subclinical dysfunction group, indicating subclinical myocardial dysfunction. [22,24,29-32]

Serum sST2 levels, a biomarker of myocardial stress and fibrosis, did not differ significantly between CHD-PH patients with subclinical RV dysfunction and those without in the present study. This finding is consistent with Saputra et al. (2020), a Southeast Asian study involving patients with uncorrected ASD-related PH, which also reported no significant association between sST2 levels and conventional RV systolic parameters. These findings suggest that in CHD-PH, sST2 elevation may not occur during the subclinical phase of RV involvement.[5,24,33,35-36]

In contrast, several previous studies have demonstrated a significant association between elevated sST2 levels and RV dysfunction. Zheng et al. reported that plasma sST2 correlated with disease severity and predicted clinical worsening in patients with PAH, with sST2 showing a sensitivity of 83.3% and specificity of 78.6% for identifying RV dysfunction. Similarly, Geenen et al., in a cohort of 104 adults with PH, found that higher sST2 levels were associated with worse RV dysfunction and higher mean pulmonary arterial and right atrial pressures, and predicted the composite endpoint of death, lung transplantation, or heart failure hospitalization (Heart Rate [HR] 1.45 per 2-fold increase, 95% Confidence Interval [CI] 1.10–1.90), although this association did not remain independent after adjustment for N-terminal pro B-type Natriuretic Peptide (NT-proBNP). However, these studies predominantly included patients with acquired PH and advanced stages of RV dysfunction, often characterized by overt right heart failure and established myocardial remodeling. The discrepancy between these studies and the present findings may therefore be attributed to differences in patient population, disease etiology, and stage of RV involvement.[32,34,37]

In the present cohort, impaired RV-GLS was strongly associated with increased pulmonary vascular load, as reflected by significantly higher PAR and PAR/SVR ratios, despite preserved conventional RV systolic function. This supports the concept that subclinical RV dysfunction in CHD-PH is predominantly driven by hemodynamic afterload rather than molecular stress responses. Similar observations have been reported by Park et al., Crosmann et al., and Hardegree et al., who demonstrated that RV longitudinal strain deteriorates earlier than volumetric indices such as RVEF and closely correlates with invasive pulmonary hemodynamic parameters, reflecting subclinical RV-pulmonary arterial uncoupling.[35-38]

From a regional perspective, data regarding sST2 and subclinical RV dysfunction in Southeast Asian populations remain limited. The consistency between the present findings and prior regional studies underscores the importance of considering ethnic, epidemiological, and disease-specific characteristics when interpreting biomarker utility. This study, therefore, contributes valuable regional data to the growing body of literature on CHD-PH and RV assessment.[24]

RV Global Longitudinal Strain as a Marker of Hemodynamic Afterload

In this study, impaired RV-GLS (RV-GLS) was strongly associated with increased pulmonary vascular hemodynamic burden in patients with CHD-PH, despite preserved conventional RV systolic function and unchanged serum sST2 levels. Patients with CHD-PH with subclinical RV dysfunction exhibited significantly higher PAR and PAR/SVR, indicating that RV-GLS closely reflects RV afterload.[39-40]

These findings highlight the role of RV-GLS as a sensitive marker of subclinical RV–pulmonary arterial uncoupling. Unlike volumetric parameters such as 3D-RVEF, which often remain normal until advanced stages of disease, RV-GLS detects subtle impairment in longitudinal myocardial fibers that are particularly vulnerable to chronic pressure overload. Given that longitudinal shortening is the dominant component of RV contraction, strain abnormalities may emerge earlier than changes in conventional systolic indices.[39-40]

The absence of significant differences in sST2 levels between groups further emphasizes the complementary nature of imaging-based and biomarker-based assessment. sST2 is primarily associated with myocardial inflammation, fibrosis, and adverse remodeling rather than with isolated increases in pressure load. In the subclinical stage of RV involvement observed in this cohort, elevated pulmonary vascular resistance may not yet be sufficient to induce measurable sST2 elevation. This dissociation suggests that RV-GLS may be more sensitive than circulating biomarkers for detecting subclinical hemodynamic stress on the RV.[41-42]

From a clinical perspective, these findings suggest that RV-GLS may serve as a practical, noninvasive tool for identifying CHD-PH patients who are already exposed to significant hemodynamic burden despite preserved 3D-RVEF and normal biomarker profiles. Incorporating RV-GLS into routine echocardiographic evaluation may facilitate earlier risk stratification, closer monitoring, and timely optimization of therapy before overt RV failure develops.[41-42]

Future studies involving larger, multicenter cohorts with longitudinal follow-up are warranted to further elucidate the role of sST2 in CHD-PH. Serial biomarker measurements, integrated with comprehensive hemodynamic and strain-based assessments, may help determine whether sST2 has prognostic value in later disease stages or for monitoring treatment response. Comparative studies between congenital and acquired PH populations may also provide further insight into disease-specific mechanisms of RV adaptation and failure.[41-42]

Limitation of the Study

This study has several limitations. First, variability in PAR among participants may reflect different stages of disease progression, which could influence the severity of RV systolic dysfunction as well as serum sST2 expression. Second, this study did not include patients with Pulmonary Arterial Hypertension (PAH) and PAR > 2 Wood units, or non-CHD control subjects, thereby limiting comparisons of sST2 levels across a broader hemodynamic spectrum and under non-pathological conditions. Third, the potential effects of pulmonary arterial dilator therapy and treatment duration on biomarker levels were not specifically analyzed. Nevertheless, the influence of other potential confounding factors was minimized of applying strict inclusion and exclusion criteria. A comprehensive assessment combining invasive hemodynamic parameters and RV strain analysis may provide complementary information for the early detection of RV dysfunction compared with biomarker evaluation alone. It is important for future research to have larger multicenter cohorts, longitudinal designs, and the combined use of imaging and biomarker approaches to better capture subclinical RV dysfunction.

Conclusion

The majority of CHD-PH patients were adult females, with ASD as the most common underlying etiology. However, subclinical RV dysfunction was associated with significantly higher pulmonary vascular load, as reflected by increased PAR and PAR/SVR ratio. These findings suggest that subclinical RV myocardial impairment in CHD-PH is more closely associated with hemodynamic afterload than with molecular stress biomarkers alone. In contrast, serum sST2 levels did not differ significantly between groups, suggesting that

sST2 may have limited utility for detecting early, strain-defined RV myocardial impairment in this population.

List of Abbreviations

2D-STE	Two-Dimensional Speckle-Tracking Echocardiography
3D-RVEF	Three-Dimensional Right Ventricular Ejection Fraction
ASD	Atrial Septal Defect
BMI	Body Mass Index
CHD	Congenital Heart Disease
CHD-PH	Congenital Heart Disease–Associated Pulmonary Hypertension
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
FAC	Fractional Area Change
FC	Functional Class
FWS	Free Wall Strain
GLS	Global Longitudinal Strain
HR	Heart Rate
LVEF	Left Ventricular Ejection Fraction;
mPAP	Mean Pulmonary Arterial Pressure
MRI	Magnetic Resonance Imaging
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PAR	Pulmonary Arterial Resistance
PDE5-i,	Phosphodiesterase Type 5 Inhibitor
PH	Pulmonary Hypertension
RV	Right Ventricle/Right Ventricular
RV-GLS	Right Ventricular Global Longitudinal Strain
RVEF	Right Ventricular Ejection Fraction
RVS'	Right Ventricular S' Velocity
SD	Standard Deviation
sST2	Soluble Suppression of Tumorigenicity-2
STE	Speckle-Tracking Echocardiography
SVR	Systemic Vascular Resistance
TAPSE	Tricuspid Annular Plane Systolic Excursion
TTE	Transthoracic Echocardiography
VEGF	Vascular Endothelial Growth Factor
VSD	Ventricular Septal Defect
WHO	World Health Organization
WSPH	World Symposium on Pulmonary Hypertension

Ethical Clearance

This study was approved by the Health Research Ethics Committee of RSUP Dr. M. Djamil, with ethical clearance number DP.04.03/D.XVI.XI/505/2024, issued on 14 November 2024.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

All authors have made significant intellectual contributions to this manuscript according to the criteria formulated by the International Committee of Medical Journal Editors (ICMJE), and each has participated sufficiently in the work to take public responsibility for its content. FAA and MY contributed to the conception and design of the study; FAA, MY, K, and HA contributed to the analysis and interpretation of data; FAA drafted the manuscript; FAA, MY, K, and HA were involved in critically revising the manuscript for important intellectual content; and all authors (FAA, MY, K, and HA) gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

The author declares that there is no conflict of interest.

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Original Article

Predischarge Lung Ultrasound B-Lines as a Robust Predictor of 90-Day Rehospitalization in Heart Failure with Reduced Ejection Fraction (HFrEF): Evidence from Clinical and Classification and Regression Tree (CART)-Based Risk Stratification

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Abstract

Background: Heart failure is a major global health burden, with high morbidity, mortality, and substantial rehospitalization rates. Residual pulmonary congestion at discharge is a key determinant of early readmission but is often underestimated using clinical assessment alone. Lung Ultrasound (LUS) offers an objective, bedside tool for detecting pulmonary congestion through B-line quantification. This study aimed to evaluate whether predischarge B-line measurements predict 90-day rehospitalization due to all cardiovascular causes in patients with Heart Failure with reduced Ejection Fraction (HFrEF).

Methods: This retrospective cohort study included 107 adults hospitalized with HFrEF at Wahidin Sudirohusodo Hospital from March to July 2023. LUS was performed prior to discharge using an eight-zone protocol, and total B-line counts were recorded. Clinical, laboratory, and echocardiographic variables were obtained from the Heart Failure Registry and electronic medical records. Patients were followed for 90 days to identify heart failure–related rehospitalization. Statistical analyses included independent t-test, Mann–Whitney U tests, chi-square test, ROC curves, multivariate logistic regression, and a Classification and Regression Tree (CART) model to identify the strongest predictors of rehospitalization.

Results: Among 107 patients (mean age 58.52 ± 12.16 years; 74.77% male), 48 (44.86%) experienced 90-day rehospitalization due to all cardiovascular causes. Rehospitalized patients had significantly higher predischarge B-line counts (25.98 ± 8.23 vs. 17.63 ± 8.03, $p < 0.0001$). A B-line cutoff of ≥20 predicted rehospitalization with 75.7% accuracy, 77.08% sensitivity, 74.58% specificity, and an AUC of 0.754. Renal dysfunction (eGFR 58.72 ± 29.32 vs. 75.43 ± 27.49 mL/min/1.73 m^2, $p = 0.003$; creatinine 1.86 ± 2.01 vs. 1.21 ± 0.76 mg/dL, $p = 0.021$), lower EF (31.6 ± 8.15% vs. 36.64 ± 9.05%, $p = 0.004$), and higher filling pressures (PCWP, E/e') were also significantly associated with rehospitalization. The CART model identified B-line ≥20 as the strongest primary classifier, with additional risk contributed by renal impairment and reduced EF, yielding an accuracy of 90.65% and an AUC of 0.966.

Conclusions: Predischarge B-line quantification is a strong predictor of 90-day rehospitalization in HFrEF. Integration of B-line assessment with renal function and cardiac parameters substantially improves risk stratification. LUS provides a practical, noninvasive tool for optimizing predischarge evaluation and may guide interventions to reduce early rehospitalization.

Keywords: B-Line score, lung ultrasound, heart failure, HFrEF, 90-day rehospitalization

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Introduction

Heart failure remains a major global health problem, with an estimated 64.3 million affected individuals worldwide.[1] In Asia, the burden is substantial, accounting for 31.89 million cases, while Indonesia ranks among the countries with the highest prevalence of heart failure in the region.[2] Despite advances in therapy, heart failure is associated with frequent rehospitalization and significant healthcare costs. Data from the EVEREST trial showed that more than half of patients with systolic heart failure experienced rehospitalization, with a substantial proportion occurring within the first 30 days after discharge.[3-4] Early readmission is also associated with increased medical expenditure.[5]

Residual congestion at discharge is a key contributor to early rehospitalization. Clinical assessment alone is often insufficient to detect persistent pulmonary congestion, particularly in patients without overt symptoms. Lung Ultrasound (LUS) has emerged as a practical bedside tool for evaluating pulmonary edema, with diagnostic performance comparable to computed tomography.[6] B-lines, defined as vertical hyperechoic artifacts arising from the pleural line, reflect increased extravascular lung water and correlate strongly with pulmonary congestion in heart failure. Thresholds such as ≥10 B-lines across eight lung zones or ≥3 B-lines in more than two zones have demonstrated high diagnostic sensitivity.[7]

Despite apparent clinical improvement, many patients are discharged with residual pulmonary congestion, which is associated with adverse outcomes, including rehospitalization and mortality.[6] Objective quantification of congestion before discharge may therefore improve risk stratification and guide treatment optimization. Accordingly, this study aimed to evaluate whether predischarge LUS B-line assessment predicts 90-day rehospitalization in patients with Heart Failure with reduced Ejection Fraction (HFrEF).

Methods

Study Design and Population

This study employed a retrospective cohort design and included patients admitted to the Integrated Heart Center at Wahidin Sudirohusodo Hospital with a confirmed diagnosis of congestive heart failure. All participants were identified through the hospital's Heart Failure Registry and were enrolled between March and July 2023.

Inclusion and Exclusion Criteria

Eligible participants were adults aged 18 years or older who were hospitalized with a primary diagnosis of congestive heart failure and demonstrated a left ventricular Ejection Fraction (EF) of 40% or less on the echocardiographic evaluation performed at admission. Patients were excluded if they had undergone interventional cardiac procedures such as cardiac resynchronization therapy or valve replacement, had underlying pericardial diseases, including effusion or constrictive pericarditis, or exhibited atrioventricular dyssynchrony, such as complete heart block or recent pacemaker implantation. These conditions were excluded because they may independently alter intrathoracic fluid distribution, ventricular filling dynamics, or ventricular synchrony, thereby confounding LUS B-line quantification and limiting the reliability of pulmonary congestion assessment. Patients who declined participation in the study procedures were also excluded. Patients who underwent elective percutaneous coronary intervention (PCI) or planned staged PCI during the follow-up period were not excluded from the study; however, these elective or scheduled procedures were not classified as rehospitalization events unless the admission was primarily driven by worsening heart failure symptoms or cardiovascular decompensation.

Data Collection

Clinical information was obtained from the Heart Failure Registry and supplemented with data from electronic medical records as needed. Variables collected included demographic characteristics, such as age, sex, and body mass index; relevant comorbid conditions and baseline heart failure therapies; laboratory results obtained within the first 24 hours of admission; and echocardiographic findings recorded during initial evaluation. Pre-discharge clinical assessment included the performance of lung ultrasonography to quantify pulmonary B-lines.

Lung Ultrasonography Protocol

Pulmonary congestion was assessed using LUS performed with a portable Philips Lumify device equipped with a linear transducer and preset lung imaging mode. Examinations were conducted across eight thoracic zones, with four regions assessed on each hemithorax. Although the 8-zone protocol is commonly interpreted using a semiquantitative approach (≥3 B-lines per zone), this study employed a total B-line count across all scanned zones to provide a continuous measure of pulmonary congestion. This approach was selected to enhance sensitivity to residual congestion at discharge and

to allow more precise risk stratification, consistent with emerging evidence supporting quantitative B-line assessment beyond traditional zone-based thresholds. The total number of B-lines visualized was used to stratify congestion severity. Mild congestion was defined as 6–15 B-lines, moderate congestion as 16–30 B-lines, and severe congestion as more than 30 B-lines. (Figure 1)

CART Analysis

This analysis is to precisely identify the combination of clinical variables most strongly influencing the incidence of 90-day re-hospitalization, and the Classification and Regression Tree (CART) method was applied. This approach, which relies on a decision-tree structure, was selected for its ability to construct a hierarchical classification model and to effectively capture complex, non-linear relationships among predictor variables that conventional statistical tests might fail to reveal. The variables incorporated into the CART model were those previously identified in bivariate analysis as having a statistically significant relationship with 90-day re-hospitalization status.

The model prominently featured the B-line score as the primary predictor due to its initial high classification power in assessing pulmonary congestion severity. Other variables analyzed included key indicators of renal function (eGFR and creatinine levels), crucial echocardiography parameters describing left ventricular function and filling pressures (EF, PCWP, and the average E/e' ratio), and relevant comorbidities (Ischemic Heart Disease [IHD] and Chronic Kidney Disease [CKD]). Furthermore, the patient's use of aldosterone receptor antagonists was included, given their significant association with re-hospitalization outcomes in preliminary analyses.

B-Line Score Application

The "B-Line Score" was developed as an interactive predictive dashboard utilizing the R Shiny framework to estimate the 90-day re-hospitalization risk in patients with HFrEF. The application integrates key clinical parameters into a clinically actionable risk score derived from CART statistical modeling. The application is hosted online and secured by a mandatory login system that requires registered user authentication. This security feature ensures data confidentiality, prevents unauthorized access, and facilitates the tracking of user activity alongside the storage of individual prediction history.

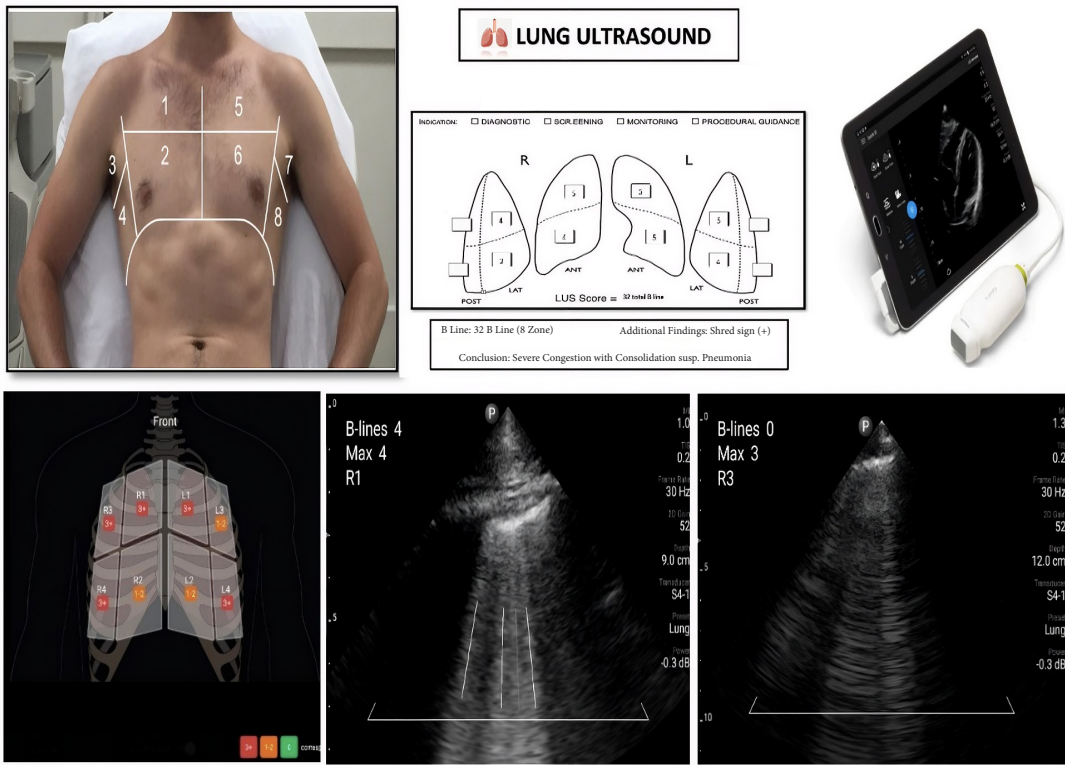

Figure 1. Baseline catient characteristics.

Upon logging in, users enter crucial clinical variables on a dedicated data entry page. These variables include the B-line score obtained from LUS, estimated Glomerular Filtration Rate (eGFR), serum creatinine levels, EF, Pulmonary Capillary Wedge Pressure (PCWP), and the presence of significant comorbidities, namely IHD and CKD. The system processes this data through the pre-trained predictive model and outputs the result as a risk status, either rehospitalization or no rehospitalization, along with the calculated probability percentage. A notable feature is the direct WhatsApp integration, enabling immediate and secure transmission of the prediction results to colleagues or the treating physician via a pre-formatted message link, thereby promoting efficient cross-departmental communication and accelerating evidence-based clinical decision-making. (Figure 2)

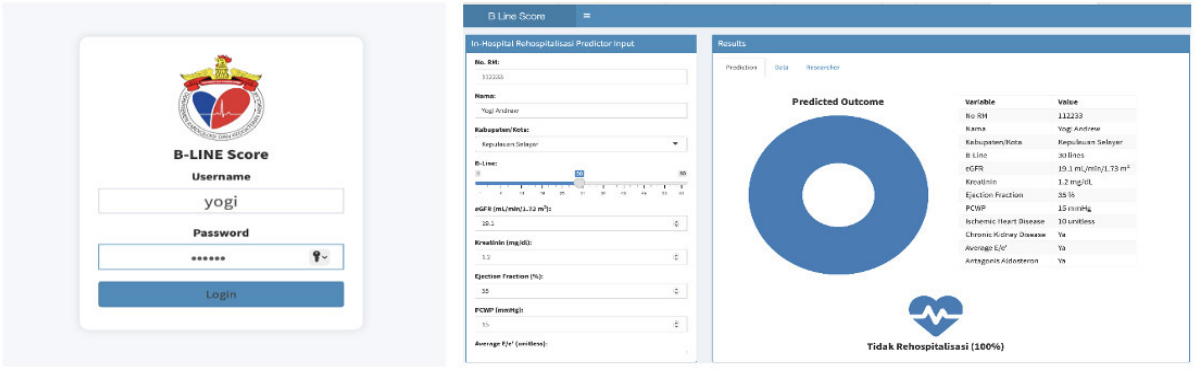

Figure 2. B-Line score application.

interim hospital admissions, admission diagnoses, and dates of hospitalization. When available, supporting medical documentation was requested to corroborate patient-reported events. Hospital admissions solely for elective PCI or planned staged PCI, in the absence of acute heart failure deterioration, were not considered rehospitalization events. The principal outcome of interest was rehospitalization due to cardiovascular causes as a result of worsening congestive heart failure within the 90-day observation period.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were presented as mean±standard deviation. Comparative analyses between rehospitalized and non-rehospitalized patients were performed using the independent t-test, Mann–Whitney U test, and chi-square test. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal B-line cutoff for predicting rehospitalization, with the Youden Index used to determine the point that maximizes sensitivity and specificity. Variables exhibiting significant associations in univariate analysis were included in a multivariate logistic regression to adjust for potential confounders. P values ≤0.05 were considered significant.

Follow-Up and Outcome Measures

All enrolled patients were monitored for 90 days after hospital discharge. Follow-up was conducted by telephone interviews with patients or their caregivers and through review of hospital records. If patients or their caregivers could not be reached after at least three telephone attempts on different days, the patient was classified as lost to follow-up and excluded from the outcome analysis. Rehospitalization events were defined as cardiovascular-related admissions due to worsening congestive heart failure occurring within 90 days after discharge, regardless of whether the admission occurred at Wahidin Sudirohusodo Hospital or at another healthcare facility. Rehospitalizations at other hospitals were identified through structured telephone follow-up, during which patients or their caregivers were specifically asked about

Ethical Considerations

Approval for this study was granted by the Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (Reference No. 1032/UN4.6.4.5.31/PP36/2024). All research procedures adhered to the principles of the Declaration of Helsinki and complied with national and institutional ethical guidelines.

Results

In addition to LUS findings, renal function parameters, natriuretic peptide levels, echocardiographic indices, comorbidities, and medication use were analyzed as complementary markers of congestion severity and heart failure prognosis to contextualize the predictive value of B-lines. A total of 107 patients met the inclusion and exclusion criteria for this study. The descriptive characteristics of the study population are summarized in Table 1. The mean age was 58.52 ± 12.16 years, and the majority were male (74.77%). Rehospitalization due to cardiovascular causes within 90 days occurred in 48 patients (44.86%), while 59 patients (55.14%) did not experience rehospitalization. The mean B-line value was 21.37 ± 9.10, indicating a high burden of interstitial pulmonary congestion. Laboratory assessments showed a mean eGFR of 67.93 ± 29.40 mL/min/1.73 m² and a mean creatinine of 1.50 ± 1.49 mg/dL. NT-proBNP levels averaged 162.87 ± 65.01 pg/mL, with data unavailable in 19 patients (17.75%).

Echocardiographic evaluation demonstrated that all participants had reduced systolic function, with a mean EF of 34.38 ± 8.98%. Diastolic parameters showed elevated filling pressures, reflected by a mean PCWP of 19.86 ± 6.49 mmHg and an average E/e' of 14.48 ± 5.45. Additional comorbidities included IHD in 62 patients (57.94%), hypertensive heart disease in 41 (38.32%), and atrial fibrillation in 17 (15.89%). Hypertension (56.07%) and diabetes mellitus (29.91%) were the most common systemic comorbidities, while CKD was identified in 14 patients (13.08%). Pneumonia was present in 24 patients (22.43%). Regarding medication use, most patients received ACE inhibitors or ARBs (77.57%), beta-blockers (46.73%), diuretics (84.11%), or aldosterone antagonists (56.07%).

Table 1. Baseline patient characteristics.

Variables	Value
Age (years)	58.52±12.16
Gender	
Male	80 (74.77)
Female	27 (25.23)
B-Line	21.37±9.10
90-day rehospitalization	
Yes	59 (55.14)
No	48 (44.86)
Laboratory findings	
eGFR (mL/min/1.73 m²)	67.93±29.4
Creatinine (mg/dL)	1.5±1.49
NT-proBNP (pg/mL)	162.87±65.01
NA	19 (17.75)
Echocardiography	
Ejection Fraction (%)	34.38±8.98
PCWP (mmHg)	19.86±6.49
Average E/e' (unitless)	14.48±5.24
Comorbidity	
Coronary artery disease	30 (28.04)
Ischemic heart disease	62 (57.94)
Hypertensive heart disease	41 (38.32)
Peripheral artery disease	0 (0)
Pulmonary Hypertension	3 (2.8)
Congenital heart disease	1 (0.93)
Atrial Fibrillation	17 (15.89)
Hypertension	60 (56.07)
Diabetes Mellitus	32 (29.91)

Valvular heart disease	27 (25.23)
Rheumatic heart disease	1 (0.93)
Cardiomyopathy	3 (2.8)
Dyslipidemia	23 (21.5)
Cerebrovascular disease	5 (4.67)
Asthma	0 (0)
COPD	0 (0)
Chronic kidney disease	14 (13.08)
Pneumonia	24 (22.43)
Medication	
ACEi/ARB	83 (77.57)
ARNI	5 (4.67)
Calcium channel blocker	3 (2.8)
Beta blocker	50 (46.73)
Diuretics	90 (84.11)
Aldosterone antagonists	60 (56.07)
Tolvaptan	0 (0)
Ivabradin	3 (2.8)
Digoxin	16 (14.95)
SGLT2 inhibitor	1 (0.93)
History of Smoking	
Yes	61 (57.01)
No	46 (42.99)

Values are n (%) or mean ± SD, unless stated otherwise. ACEi: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin Receptor–Neprilysin Inhibitor; B-line: B-line Artifact; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; eGFR: Estimated Glomerular Filtration Rate; E/e': Early Mitral Inflow Velocity to Early Diastolic Mitral Annular Velocity Ratio; NA: Not Available; NT-proBNP: N-terminal Pro-B-type Natriuretic Peptide; PCWP: Pulmonary Capillary Wedge Pressure; SGLT2: Sodium–Glucose Cotransporter-2.

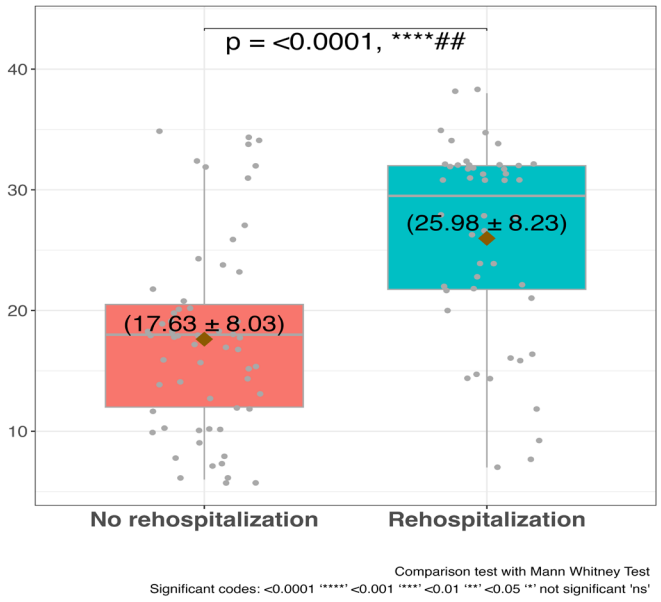

Figure 3. Comparison of B-Line parameters in heart failure patients to 90-day rehospitalization status.

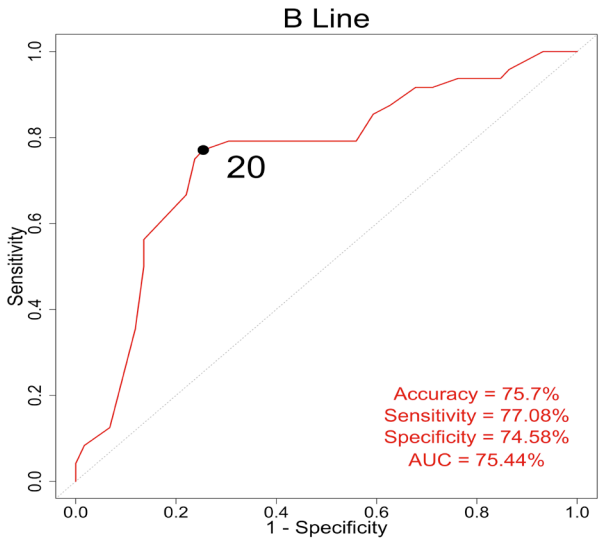

Figure 4. B-line cut-off value ROC curve.

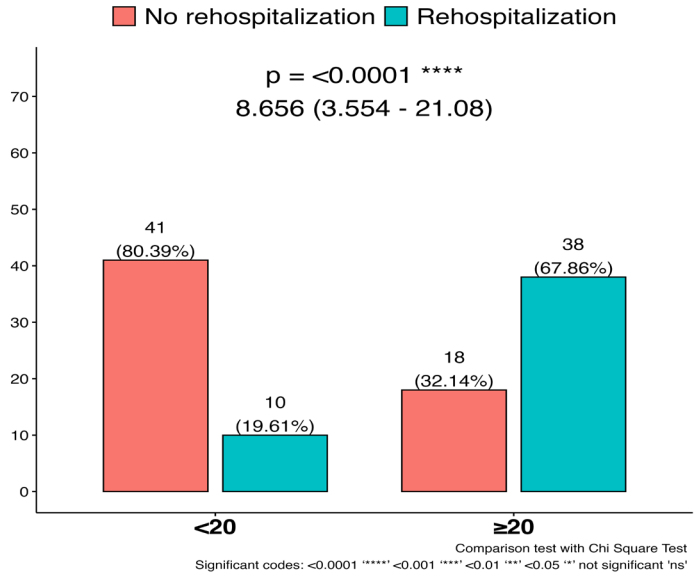

Figure 5. Relationship between B-line cut-off value and 90-day rehospitalization.

As illustrated in Figure 3, the mean B-line value was significantly higher in the rehospitalization group (25.98 ± 8.23) compared with the non-rehospitalization group (17.63 ± 8.03) ($p < 0.0001$). This finding reflects greater pulmonary congestion among patients who experienced rehospitalization. ROC curve analysis (Figure 4) identified a B-line cut-off value of 20, which demonstrated an accuracy of 75.7%, sensitivity of 77.08%, specificity of 74.58%, and an AUC of 75.44% for predicting 90-day rehospitalization. Patients with B-line ≥20 had a significantly higher incidence of rehospitalization ($p <0.0001$), with an odds ratio (OR) of 8.656 (95% CI: 3.554–21.08), as shown in Figure 5.

The association between demographic characteristics and rehospitalization is displayed in Table 2. Neither gender ($p = 0.691$) nor age ($p = 0.085$) was significantly associated with rehospitalization status. These results indicate that demographic factors were not major determinants of early readmission.

Renal and cardiac function were significantly associated with 90-day rehospitalization. Patients without rehospitalization had better renal function, with higher eGFR (75.43 ± 27.49 vs. 58.72 ± 29.32 mL/min/1.73 m², $p = 0.003$) and lower creatinine levels (1.21 ± 0.76 vs. 1.86 ± 2.01 mg/dL, $p = 0.021$). In contrast, NT-proBNP levels did not

differ between groups (p = 0.854). Rehospitalized patients also demonstrated worse cardiac function, characterized by lower EF (31.6 ± 8.15% vs. 36.64 ± 9.05%, p = 0.004) and higher filling pressures, as reflected by elevated PCWP (22.09 ± 7.65 vs. 18.04 ± 4.70 mmHg, p = 0.015) and E/e' (16.28 ± 6.17 vs. 13.02 ± 3.79, p = 0.015). Among comorbidities, CKD was more prevalent in the rehospitalization group (22.92% vs. 5.80%, p = 0.007). In comparison, IHD was more frequent in patients without rehospitalization (74.58% vs. 37.50%, p < 0.001), highlighting the combined impact of renal impairment, cardiac dysfunction, and comorbidity profile on rehospitalization risk.

Table 2. Relationship between variables and 90-days rehospitalization.

Variables	No rehospitalization (n=59)	Rehospitalization (n = 48)	P-value
Age (years)	60.41±10.24	56.21±13.93	0.085[a]
Gender			
Male	45 (76.27)	35 (72.92)	0.691[b]
Female	14 (23.73)	13 (27.08)	
Laboratory findings			
eGFR (mL/min/1.73 m²)	75.43±27.49	58.72±29.32	**0.003**[c]
Creatinine (mg/dL)	1.21±0.76	1.86±2.01	**0.021**[c]
NT-proBNP (pg/mL)	155.38±45.74	170.71±80.25	0.854[c]
NA	14 (23.73)	5 (10.42)	
Echocardiography			
Ejection Fraction (%)	36.64±9.05	31.6±8.15	**0.004**[c]
PCWP (mmHg)	18.04±4.70	22.09±7.65	**0.015**[c]
Average E/e' (unitless)	13.02±3.79	16.28±6.17	**0.015**[c]
Comorbidity			
Coronary artery disease			
Yes	18 (30.51)	12 (25.0)	0.528[b]
No	41 (69.49)	36 (75.0)	
Ischemic heart disease			
Yes	44 (74.58)	18 (37.5)	**<0.001**[b]
No	15 (25.42)	30 (62.5)	
Hypertensive heart disease			
Yes	26 (44.07)	18 (37.5)	0.175[b]
No	33 (55.93)	30 (62.5)	
Peripheral artery disease			
Yes	0 (0)	0 (0)	1.000[b]
No	59 (100)	48 (100)	
Pulmonary Hypertension			
Yes	1 (1.69)	2 (4.17)	0.441[b]
No	58 (98.31)	46 (95.83)	
Congenital heart disease			
Yes	0 (0)	1 (2.08)	0.449[d]
No	59 (100)	47 (97.92)	
Atrial Fibrillation			
Yes	7 (11.86)	10 (20.83)	0.207[b]
No	52 (88.14)	38 (79.17)	
Hypertension			
Yes	36 (61.02)	24 (50.0)	0.253[b]
No	23 (38.98)	24 (50.0)	

Diabetes Mellitus			
Yes	17 (28.81)	15 (31.25)	0.784[b]
No	42 (71.19)	33 (68.75)	
Valvular heart disease			
Yes	12 (20.34)	15 (31.25)	0.196[b]
No	47 (79.66)	33 (68.75)	
Rheumatic heart disease			
Yes	0 (0)	1 (2.08)	0.449[d]
No	59 (100)	47 (97.92)	
Cardiomyopathy			
Yes	2 (3.39)	1 (2.08)	0.999[b]
No	57 (96.61)	47 (97.92)	
Dyslipidemia			
Yes	13 (22.03)	10 (20.83)	0.880[b]
No	46 (77.97)	38 (79.17)	
Cerebrovascular disease			
Yes	4 (6.78)	1 (2.08)	0.377[d]
No	55 (93.22)	47 (97.92)	
Asthma			
Yes	0 (0)	0 (0)	1.000[b]
No	59 (100)	48 (100)	
COPD			
Yes	0 (0)	0 (0)	1.000[b]
No	59 (100)	48 (100)	
Chronic kidney disease			
Yes	3 (5.08)	11 (22.92)	**0.007[b]**
No	56 (94.92)	37 (77.08)	
Pneumonia			
Yes	16 (27.12)	8 (16.67)	0.197[b]
No	43 (72.88)	40 (83.33)	
Medication			
ACEi/ARB			
Yes	47 (79.66)	36 (75.0)	0.565[b]
No	12 (20.34)	12 (25.0)	
ARNI			
Yes	2 (3.39)	3 (6.25)	0.655[d]
No	57 (96.61)	45 (93.75)	
Calcium channel blocker			
Yes	1 (1.69)	2 (4.17)	0.586[d]
No	58 (98.31)	46 (95.83)	
Beta blocker			
Yes	29 (49.15)	21 (43.75)	0.577[b]
No	30 (50.85)	27 (56.25)	
Diuretics			
Yes	46 (77.97)	44 (91.67)	0.054[b]
No	13 (22.03)	4 (8.33)	
Aldosterone antagonists			

Yes	25 (42.37)	35 (72.92)	**0.002**[b]
No	34 (57.63)	13 (27.08)	
Tolvaptan			
Yes	0 (0)	0 (0)	1.000[b]
No	59 (100)	48 (100)	
Ivabradin			
Yes	1 (1.69)	2 (4.17)	0.586[d]
No	58 (98.31)	46 (95.83)	
Digoxin			
Yes	6 (10.17)	10 (20.83)	0.124[b]
No	53 (89.83)	38 (79.17)	
SGLT2 inhibitor			
Yes	1 (1.69)	0 (0)	0.999[d]
No	58 (98.31)	48 (100)	
History of Smoking			
Yes	34 (57.63)	27 (56.25)	0.886[b]
No	25 (42.37)	21 (43.75)	

Values are n (%) or mean ± SD, unless stated otherwise. [a]Independent t-test; [b]Chi square test; [c]Mann-Whitney test; [d]Fisher exact test. ACEi: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin Receptor–Neprilysin Inhibitor; COPD: Chronic Obstructive Pulmonary Disease; eGFR: Estimated Glomerular Filtration Rate; E/e': Early Mitral Inflow Velocity to Early Diastolic Mitral Annular Velocity Ratio; NA: Not Available; NT-proBNP: N-terminal Pro-B-type Natriuretic Peptide; PCWP: Pulmonary Capillary Wedge Pressure; SGLT2: Sodium–Glucose Cotransporter-2.

Most medications, including ACEIs/ARBs, ARNIs, beta-blockers, diuretics, CCBs, ivabradine, digoxin, and SGLT2 inhibitors, were not significantly associated with rehospitalization (all p >0.05). The only medication showing a significant association was aldosterone antagonists (p = 0.002). Their higher use in the rehospitalization group likely reflects more severe underlying disease rather than a causal association.

Cut-off analyses of renal and echocardiographic parameters (Figure 6) demonstrated moderate discriminatory ability for predicting rehospitalization, including eGFR ≤66 mL/min/1.73 m² (accuracy 69.16%, AUC 66.84%), creatinine ≥1.21 mg/dL (AUC 62.96%), EF <32% (AUC 66.12%), E/e' ≥11.54 (AUC 63.75%), and PCWP ≥16.21 mmHg (AUC 63.75), indicating that impaired renal function and elevated filling pressures are associated with increased rehospitalization risk; however, a B-line cut-off ≥20 showed consistently superior predictive performance. Categorical analysis (Figure 7) confirmed significant associations for eGFR <63 mL/min/1.73 m² (p = 0.0002), EF <32% (p = 0.0012), creatinine ≥1.26 mg/dL (p = 0.0045), E/e' ≥11.54 (p = 0.0022), and PCWP ≥16.21 mmHg (p = 0.0021), with odds ratios indicating substantial increases in 90-day rehospitalization risk.

The CART analysis (Figure 8) identified B-line ≥20 as the strongest initial classifier for rehospitalization. Within the B-line ≥20 subgroup, decreased renal function (eGFR <63 mL/min/1.73 m²), elevated creatinine (≥1.26 mg/dL), and reduced EF (<32%) further increased the risk. Among patients with B-line <20, the presence of ischemic heart disease, elevated PCWP, or reduced EF increased the likelihood of rehospitalization. The CART model demonstrated excellent predictive performance, with an accuracy of 90.65%, sensitivity of 98.31%, specificity of 81.25%, and an AUC of 96.66%.

Discussion

This study evaluated the relationship between pulmonary ultrasound findings, specifically B-line quantification, and the risk of 90-day rehospitalization due to cardiovascular causes in patients with heart failure. The findings demonstrate that the number of B-lines at predischarge is strongly associated with rehospitalization and reflects the degree of residual pulmonary congestion. The principal finding is that a higher B-line burden at discharge, particularly a threshold of ≥20 B-lines, is strongly associated with early rehospitalization and reflects clinically meaningful residual pulmonary

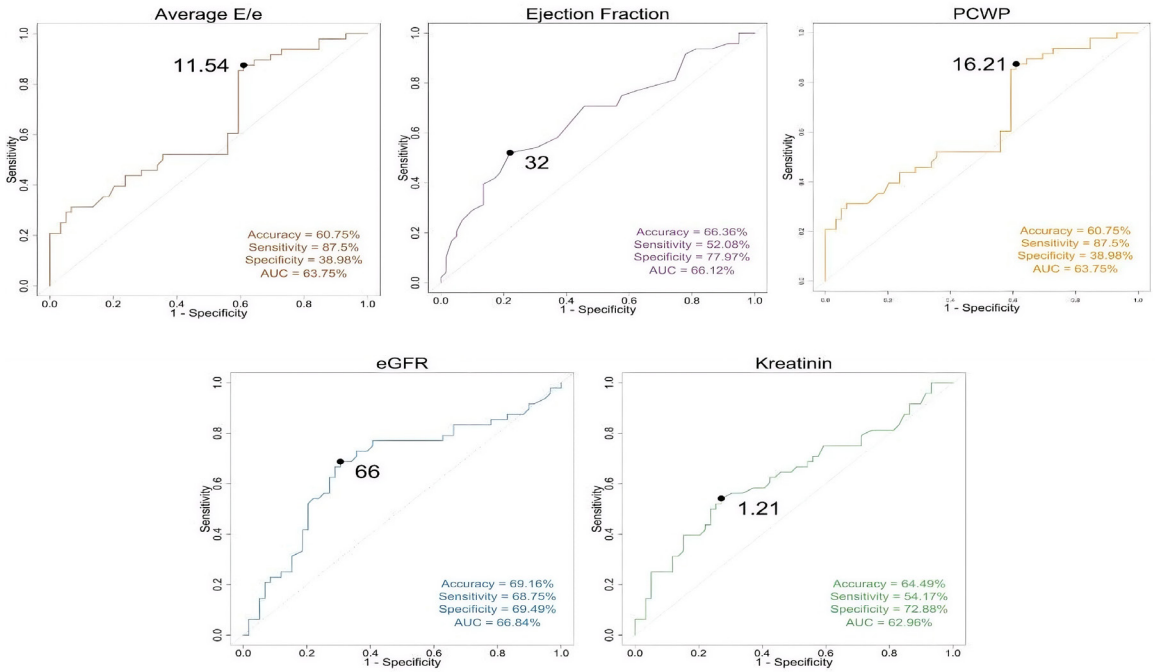

Figure 6. Variables cut-off value ROC curve.

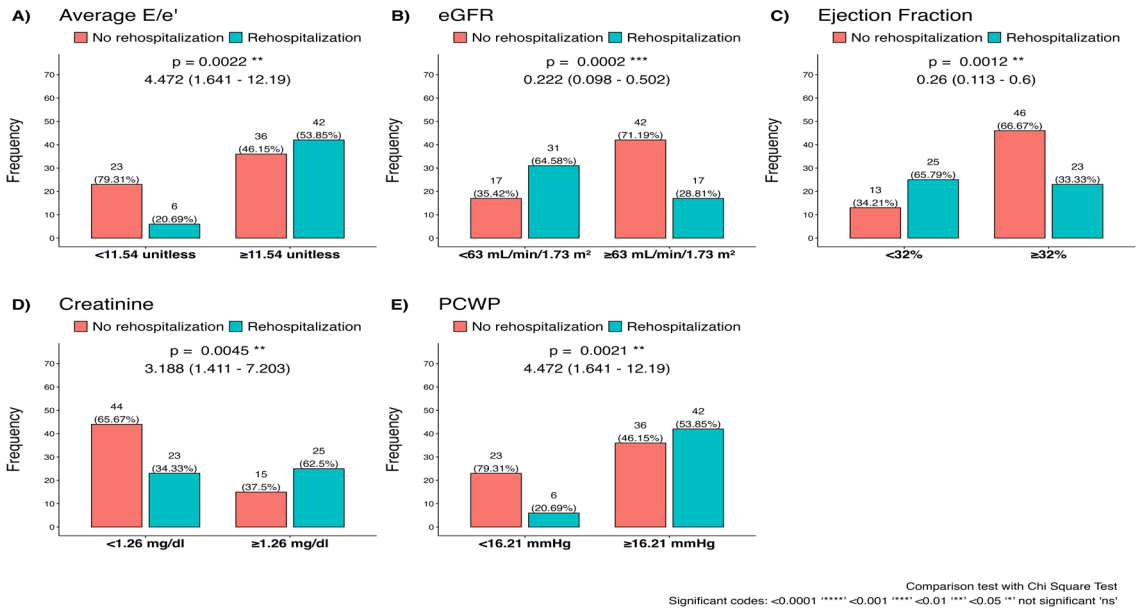

Figure 7. Relationship between the variables, cut-off value, and 90-day rehospitalization.

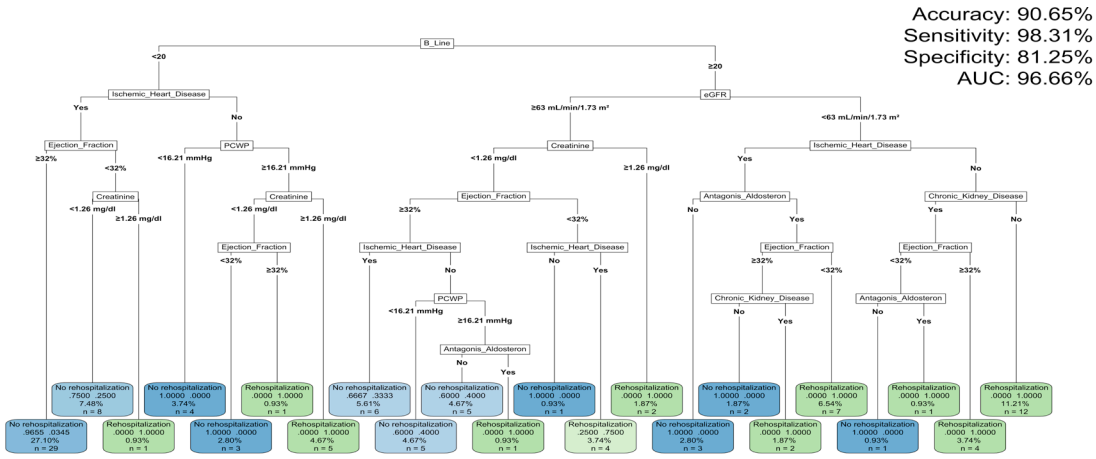

Figure 8. CART model analysis

congestion. These results align with previous studies indicating that clinical congestion at the time of discharge is one of the strongest predictors of adverse outcomes in acute decompensated heart failure. Because clinical signs of congestion do not reliably correlate with filling pressures, the use of additional diagnostic tools is essential to optimize predischarge assessment. Although multiple clinical, laboratory, and echocardiographic variables were associated with rehospitalization, these analyses were performed to contextualize and benchmark the prognostic value of B-lines relative to established markers of congestion and disease severity, rather than to shift the study's primary focus away from LUS. Among all evaluated parameters, B-line quantification demonstrated the most robust and consistent discriminatory performance.[6]

B-lines represent vertical hyperechoic artifacts originating from the pleural line that move synchronously with lung sliding and obscure A-lines, reflecting increased subpleural lung density due to the replacement of air with fluid, collagen, or inflammatory material. Their presence indicates a disturbance in the alveolar-capillary interface and an increase in extravascular lung water.[8] B-lines are considered significant when three or more are visualized between two rib spaces and typically diminish with appropriate management of pulmonary congestion or heart failure.

The present study found a significantly higher number of B-lines in patients rehospitalized within 90 days compared with those not rehospitalized. This supports earlier findings by Rattarasarn et al.,[6] who reported that more than half of hospitalized heart failure patients continued to exhibit residual congestion at predischarge. Their study showed that a B-line count >12 across eight lung zones independently predicted 6-month rehospitalization.[6] Similarly, Gargani et al.,[9] demonstrated that B-line quantification at predischarge is clinically meaningful, with cut-off values >15 and >20 providing optimal accuracy for predicting readmission within 3 and 6 months, respectively.[9] The current study's B-line cut-off of 20 yielded an accuracy of 72.5%, sensitivity of 78.43%, specificity of 68.12%, and an AUC of 72.19%, indicating good discriminatory capability.

Understanding the pulmonary congestion cascade further explains these findings. The process begins with increased left ventricular end-diastolic pressure and elevated PCWP, leading to hemodynamic congestion, which precedes interstitial fluid accumulation and eventually pulmonary edema. The intermediate-stage interstitial pulmonary congestion can be detected by pulmonary ultrasound via B-line visualization before overt symptoms appear.10 In this study, higher PCWP estimates based on E/e' and higher B-line counts were both associated with increased rehospitalization risk, underscoring their role as sensitive markers of congestion.

The EVEREST and ESCAPE trials further support the prognostic significance of congestion markers. The EVEREST trial demonstrated that the presence of significant B-lines was the only independent predictor of heart failure events and 6-month mortality in a multivariate analysis.[3] The ESCAPE trial also emphasized the importance of congestion-related parameters, showing that a substantial proportion of patients developed pulmonary congestion due to elevated left ventricular filling pressures, detectable through B-line assessment.[11]

Renal dysfunction also played a significant role in the risk of rehospitalization in this study. Impaired renal function, reflected by elevated creatinine and reduced eGFR, is a well-established predictor of poor outcomes in heart failure. Rather than acting independently, renal impairment appears to potentiate the prognostic significance of residual pulmonary congestion detected by LUS. A prior study reported increased mortality among patients with eGFR <60 mL/min/1.73 m².[12] Another study also showed that patients with eGFR <45 mL/min/1.73 m² had higher rehospitalization rates.[13] Consistent with these findings, this study identified meaningful cut-off values for creatinine (1.21 mg/dL) and eGFR (66 mL/min/1.73 m²), both of which showed moderate diagnostic accuracy and were significantly associated with rehospitalization. The higher prevalence of CKD in the rehospitalization group reinforces the interplay between renal dysfunction and volume regulation in heart failure.

Importantly, combining multiple significant predictors, including B-line ≥20, reduced EF, impaired renal function, estimated PCWP, and comorbid IHD and CKD, markedly improved the CART model's predictive performance of rehospitalization. This model achieved an accuracy of 90.65%, sensitivity of 98.31%, specificity of 81.25%, and an AUC of 96.66%, demonstrating the advantage of multimodal risk stratification. These results support the growing body of evidence, including the CLUSTER-HF Trial, which showed that LUS-guided management reduces clinical deterioration, rehospitalization, mortality, and NT-proBNP levels, while improving quality of life.[11]

Although the CART analysis demonstrated excellent predictive performance when combining B-lines with renal and echocardiographic parameters, this approach should be interpreted as exploratory. The study was not designed to develop or validate a formal risk stratification model, and such integration is presented to illustrate how LUS may complement conventional assessment in clinical practice. Larger prospective studies are required before such models can be routinely applied. Additionally, B-lines are not specific to heart failure and may be present in other interstitial pulmonary conditions, including fibrosis, pneumonia, and ARDS. However, in patients with established heart failure, especially those with persistent congestion, this limitation becomes less clinically significant.

Conclusion

Predischarge LUS B-line assessment is a strong and clinically relevant predictor of 90-day cardiovascular rehospitalization in patients with HFrEF. A B-line count ≥20 identifies patients with significant residual pulmonary congestion who are at substantially higher risk of early readmission. These findings support the integration of LUS into routine predischarge assessment to improve risk stratification, guide therapy optimization, and potentially reduce rehospitalization rates.

List of Abbreviations

ACEi	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
CART	Classification and Regression Tree
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
E/e'	Early Mitral Inflow Velocity to Early Diastolic Mitral Annular Velocity Ratio
HFrEF	Heart Failure with reduced Ejection Fraction
IHD	Ischemic Heart Disease
LUS	Lung Ultrasound
NA	Not Available
NT-proBNP	N-terminal Pro-B-type Natriuretic Peptide
PCWP	Pulmonary Capillary Wedge Pressure
ROC	Receiver Operating Characteristic
SGLT2	Sodium–Glucose Cotransporter-2

Ethical Clearance

Approval for this study was granted by the Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (Reference No. 1032/UN4.6.4.5.31/PP36/2024). All research procedures adhered to the principles of the Declaration of Helsinki and complied with national and institutional ethical guidelines.

Publication Approval

Institutional approval for publication has been obtained.

Authors Contributions

AFM: Conceptualization, Methodology, Investigation, Writing- Original Draft preparation; YP: Conceptualization, Methodology, Investigation, Resources, Validation, Writing- Original Draft preparation, Writing - Review & Editing, Supervision; PK: Conceptualization, Methodology, Investigation, Resources, Validation, Writing- Original Draft preparation, Writing - Review & Editing, Supervision; AAM: Validation, Writing - Review & Editing, Supervision. All authors read and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Availability of Data and Materials

Data are available from the corresponding author upon reasonable request.

Funding

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Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that no generative AI or AI-assisted technologies were used in writing this manuscript. All content was produced entirely by the authors.

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Review Article

Utilization of Neuromuscular Electrical Stimulation as a Rehabilitation Strategy in Heart Failure with Reduced Ejection Fraction: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Heart Failure with Reduced Ejection Fraction (HFrEF) is associated with substantial functional impairment, and many patients are unable to participate in conventional exercise-based cardiac rehabilitation. Neuromuscular Electrical Stimulation (NMES) has been proposed as an alternative rehabilitation treatment, but its clinical effectiveness remains uncertain. This review aims to evaluate the effectiveness of NMES in improving cardiac function and exercise capacity in patients with HFrEF. A systematic review and meta-analysis of Randomized Controlled Trials (RCTs) was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies comparing NMES with standard medical therapy, exercise training, or no intervention in adult patients with HFrEF were identified through major electronic databases. Risk of bias was assessed using the Cochrane RoB 2.0 tool. Pooled effects were calculated as Mean Differences (MD) with 95% Confidence Intervals (CIs) using Review Manager (RevMan) version 5.4. Twelve RCTs involving 636 participants were included. NMES significantly improved peak oxygen uptake (VO_2 peak) (MD 2.03 mL/kg/min; 95% CI 1.21 to 2.84; $p < 0.00001$), systolic blood pressure (MD −2.02; 95% CI −3.97 to −0.06; $p = 0.04$), Left Ventricular Ejection Fraction (LVEF) (MD −1.38%; 95% CI −2.73 to −0.03; $p = 0.05$), and Heart Rate (HR) (MD 2.19 beats/min; 95% CI 0.44 to 3.95; $p = 0.01$). A borderline significant improvement was observed in the Six-Minute Walk Test (6MWT) distance (MD −11.40 m; 95% CI −23.04 to 0.24; $p = 0.05$). No significant effects were found for diastolic blood pressure (MD −0.12; 95% CI −3.30 to 3.06; $p = 0.94$) or Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores (MD 1.97; 95% CI −9.06 to 13.01; $p = 0.73$). NMES is associated with meaningful improvements in exercise capacity and selected parameters of cardiac function in patients with HFrEF, supporting its role as a potential adjunct rehabilitation treatment.

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Keywords: Neuromuscular Electrical Stimulation, Heart Failure, Reduced Ejection Fraction, Cardiac Rehabilitation

Introduction

Heart Failure with Reduced Ejection Fraction (HFrEF) is a chronic clinical syndrome characterized by impaired left ventricular systolic function, resulting in insufficient cardiac output and markedly reduced exercise tolerance. Beyond central hemodynamic abnormalities, HFrEF is accompanied by significant peripheral skeletal muscle dysfunction, which contributes substantially to functional decline, reduced quality of life, and increased risk of recurrent hospitalization and premature mortality.[1-2]

Heart failure represents a major global health burden, affecting an estimated 64 million individuals worldwide.[3] Approximately 40–50% of these cases are classified as HFrEF, a subgroup associated with particularly high morbidity and mortality.[4] In developed countries, heart failure accounts for millions of hospital admissions annually, with readmission rates approaching one-third within a year.[5] Mortality among patients with heart failure remains substantial, ranging from 10–15% annually, while data from low- and middle-income countries suggest an even higher burden. In addition to its cardiovascular impact, HFrEF imposes profound functional limitations, with many patients experiencing difficulty performing daily activities such as walking, climbing stairs, and carrying loads, thereby reinforcing the need for effective rehabilitation strategies.[6-7]

Exercise-based cardiac rehabilitation is strongly recommended for patients with HFrEF and has consistently demonstrated improvements in exercise capacity, quality of life, and hospital readmission rates.[8] However, real-world participation in conventional rehabilitation programs remains suboptimal.[8] Advanced disease severity, frailty, fatigue, comorbid conditions, and limited exercise tolerance frequently prevent patients from initiating or completing structured exercise training. Consequently, a substantial proportion of patients with HFrEF are unable to access the established benefits of standard cardiac rehabilitation.[9]

Neuromuscular Electrical Stimulation (NMES) has emerged as a clinically relevant alternative rehabilitation strategy. By inducing involuntary skeletal muscle contractions through surface electrical stimulation, NMES enables peripheral muscle activation with minimal cardiovascular stress and without requiring active patient participation.[11] These characteristics make NMES particularly suitable for patients with advanced disease, severe deconditioning, or limited mobility. Despite increasing clinical interest and technological advances that have improved feasibility and safety, evidence regarding the effectiveness of NMES in HFrEF remains heterogeneous.[12] Therefore, this systematic review and meta-analysis aimed to evaluate the effectiveness of NMES in improving cardiac function and exercise capacity in patients with HFrEF.

Methods

Search Strategy

A comprehensive electronic literature search was independently conducted by two reviewers across PubMed, ScienceDirect, Google Scholar, the Cochrane Library, Taylor & Francis, and LILACS to identify Randomized Controlled Trials (RCTs) evaluating NMES as a rehabilitation intervention in patients with HFrEF. Search strategies were constructed using Boolean operators, combining intervention-related terms ("neuromuscular electrical stimulation" OR NMES), condition-related terms ("heart failure with reduced ejection fraction" OR HFrEF), and rehabilitation-related terms ("rehabilitation" OR "cardiac rehabilitation" OR "exercise therapy").

The search was limited to randomized or controlled clinical trials, with additional Boolean filters applied. The literature search covered studies published between January 2014 and May 2025, a period selected to capture evidence generated under contemporary guideline-directed management of HFrEF and clinically relevant NMES protocols. Standardized diagnostic criteria for HFrEF and widely accepted functional outcomes, including peak oxygen uptake and Six-Minute Walk Test (6MWT) distance, were established during this timeframe and remain applicable to current practice. The complete database-specific Boolean search strings are provided in Table 1. Only full-text articles published in English or Indonesian were considered eligible. This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the protocol was prospectively registered with PROSPERO (registration number: CRD420251235578).

Eligibility Criteria

Eligible studies were selected based on predefined criteria encompassing study design, participant characteristics, intervention, and comparator. Only RCTs were included, as they provide the highest level of evidence for evaluating intervention

effectiveness. Eligible articles were required to be published in full text and written in English or Bahasa Indonesia.

The study population consisted of adult participants (≥18 years) of both sexes diagnosed with HFrEF, defined as a Left Ventricular Ejection Fraction (LVEF) <40%, and classified as New York Heart Association (NYHA) functional classes II to IV. Studies were excluded if they enrolled patients with implanted cardiac pacemakers, clinically significant arrhythmias, peripheral arterial disease, uncontrolled diabetes mellitus, unstable angina pectoris, or chronic pulmonary disease, as these conditions could interfere with the safety or interpretation of NMES outcomes.

Table 1. Search string.

Database	Search Field	Search String
PubMed	Title/Abstract + MeSH	("Neuromuscular Electrical Stimulation"[Mesh] OR "neuromuscular electrical stimulation"[Title/Abstract] OR NMES[Title/Abstract]) AND ("Heart Failure with Reduced Ejection Fraction"[Title/Abstract] OR HFrEF[Title/Abstract]) AND ("Rehabilitation"[Mesh] OR rehabilitation[Title/Abstract] OR "exercise therapy"[Mesh]) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract])
ScienceDirect	Title, Abstract, Keywords	("neuromuscular electrical stimulation" OR NMES) AND ("heart failure with reduced ejection fraction" OR HFrEF) AND rehabilitation AND (randomized OR "controlled trial")
Google Scholar	All fields	"neuromuscular electrical stimulation" OR NMES AND "heart failure with reduced ejection fraction" OR HFrEF AND rehabilitation AND "randomized controlled trial"
Cochrane Library	Title, Abstract, Keywords	("neuromuscular electrical stimulation" OR NMES) AND ("heart failure with reduced ejection fraction" OR HFrEF) AND (rehabilitation OR exercise)
Taylor & Francis	All fields	("neuromuscular electrical stimulation" OR NMES) AND ("heart failure with reduced ejection fraction" OR HFrEF) AND rehabilitation AND (randomized OR trial)
LILACS	Title, Abstract	("Neuromuscular Electrical Stimulation" OR NMES) AND ("Heart Failure with Reduced Ejection Fraction" OR HFrEF) AND rehabilitation

Selection Process

The reviewers conducted a duplication check and screened titles and abstracts according to pre-defined criteria in Figure 1.

Risk of Bias Assessment

The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias tool version 2.0 (RoB 2.0). Overall, most studies were judged to have a low risk of bias across the evaluated domains. Some trials exhibited minor concerns, primarily related to deviations from intended interventions and selective outcome reporting. No study was considered to have a high risk of bias in multiple domains. The detailed risk of bias assessment for each study is presented in Figure 2.

Effect Measures

Continuous outcomes, including peak oxygen uptake (VO_2 peak), 6MWT distance, LVEF, systolic blood pressure, and Heart Rate (HR), were summarized as Mean Differences (MDs) with 95% Confidence Intervals (CIs). Dichotomous outcomes, such as all-cause mortality or hospitalization events, were analyzed using Risk Ratios (RR) with corresponding 95% CIs, where applicable. Statistical significance was assessed using two-sided p-values, and pooled estimates were presented graphically using forest plots, with diamond symbols indicating the overall effect across studies.

Synthesis Methods

Quantitative synthesis was planned using Review Manager (RevMan) version 5.4, applying the inverse variance method. A random-effects model was prespecified as the primary analytical approach, with fixed-effects models considered only in cases of low statistical heterogeneity. Heterogeneity was to be assessed using the I^2 statistic. Continuous outcomes were to be pooled as MD, and dichotomous

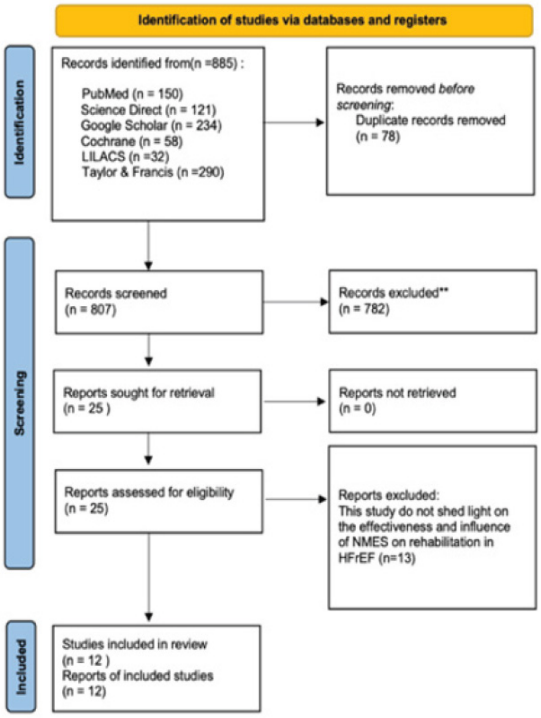

Figure 1. Flow of literature search.

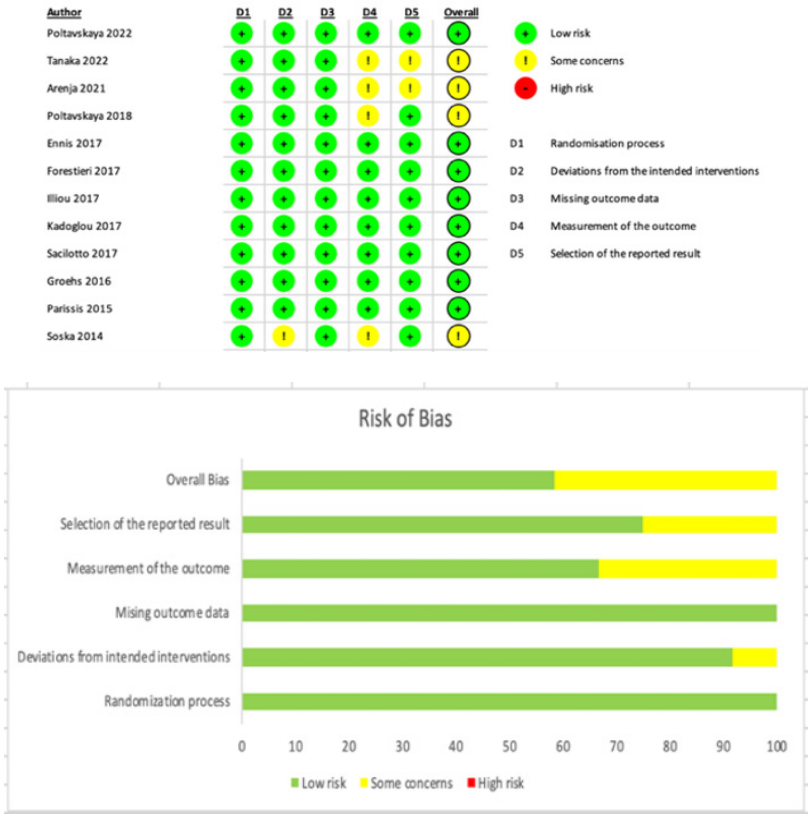

Figure 2. Assessment of the risk of bias score using the Cochrane Risk of Bias Tool 2.0 (RoB 2.0).

outcomes as RR, each with 95% CIs. Statistical significance was evaluated using two-sided p-values, and incomplete data were addressed by contacting study authors where feasible.

NMES interventions were evaluated according to predefined protocol characteristics, including target muscle groups, stimulation parameters, session duration, and intervention length. Control conditions were defined as standard medical therapy, exercise-based rehabilitation, sham stimulation, or no additional intervention. Outcomes of interest included measures of exercise capacity, cardiac function, health-related quality of life, and muscle strength, assessed according to the follow-up periods reported in each study.

Risk of Bias

The RoB 2.0 evaluation indicates that the majority of the included studies exhibited a low risk of bias across the majority of methodological domains. However, a number of studies have highlighted minor concerns in certain areas, particularly about deviations from intended interventions and selective reporting of outcomes, as illustrated in Figure 2.

Results

Study Selection

The systematic literature search identified a total of 885 records across six electronic databases: PubMed (n = 150), ScienceDirect (n = 121), Google Scholar (n = 234), the Cochrane Library (n = 58), LILACS (n = 32), and Taylor & Francis (n = 290). After the removal of 78 duplicate records, 807 articles were screened based on titles and abstracts. Of these, 782 records were excluded for failing to meet the predefined inclusion criteria.

The full texts of 25 articles were subsequently assessed for eligibility. Thirteen studies were excluded following full-text review due to irrelevance to NMES as a rehabilitation intervention in patients with HFrEF or insufficient outcome data. Ultimately, 12 RCTs met the eligibility criteria and were included in the final qualitative and quantitative synthesis. The study selection process is illustrated in the PRISMA flow diagram Figure 1.

Study Characteristics

The final analysis included 12 RCTs conducted between 2014 and 2022 across several countries, including the United Kingdom, Japan, Switzerland, Russia, Brazil, France, Greece, the Czech Republic, and the Netherlands. Sample sizes ranged from 15 to 120 participants per study, with most study populations consisting predominantly of older adults, generally aged over 60 years. Both male and female participants were included, and the severity of heart failure ranged from NYHA functional class II to IV.

Across all included trials, the intervention consisted of NMES applied primarily to lower limb muscle groups, most commonly the quadriceps femoris, hamstrings, tibialis anterior, and gastrocnemius muscles. The included studies evaluated a range of heart failure outcomes, including measures of exercise capacity, cardiac function, HR, and health-related quality of life. Detailed characteristics of the included studies are summarized in Table 2.

Meta-Analysis Results

A total of 12 RCTs were included in the quantitative synthesis. Meta-analysis demonstrated that NMES significantly improved exercise capacity in patients with HFrEF. NMES was associated with a significant increase in VO_2 peak compared with control interventions (MD 2.03 mL/kg/min; 95% CI 1.21 to 2.84; $p < 0.00001$; $I^2 = 47\%$). A borderline but clinically relevant improvement was also observed in the 6MWT distance (MD −11.40 m; 95% CI −23.04 to 0.24; $p = 0.05$; $I^2 = 23\%$).

Regarding cardiovascular parameters, NMES was associated with a modest yet statistically significant improvement in LVEF (MD 1.38%; 95% CI −2.73 to −0.03; $p = 0.05$). A significant reduction in systolic blood pressure was observed in the NMES group compared with controls (MD −2.02 mmHg; 95% CI −3.97 to −0.06; $p = 0.04$; $I^2 = 50\%$), whereas no significant difference was found in diastolic blood pressure (MD −0.12 mmHg; 95% CI −3.30 to 3.06; $p = 0.94$; $I^2 = 80\%$). HR was also significantly different between groups following NMES intervention (MD 2.19 beats/min; 95% CI 0.44 to 3.95; $p = 0.01$; $I^2 = 0\%$).

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Table 2. Characteristics study inclusion.

No.	Source	Country	Total Sample	Age	Gender	Treatment History	Frequency	Stimulation	Time	Frequency	Duration
1.	Poltavskaya, 2022.[12]	United Kingdom	n= 30 (intervention), n= 30 (control)	≥18 years old	M = 42, F = 18	Loop diuretics, ACE-I or ARBs, B-blockers, and MRA	25 Hz	The anterior and posterior muscles of the femur and tibialis in both legs were stimulated.	1 second of contraction, 2 seconds of relaxation	5 days a week	30-60 minutes per day
2.	Tanaka, 2022.[13]	Japan	n= 15 (intervention), n= 16 (control)	≥ 75 years	M = 14, F = 17	NR	20 Hz	Quadriceps femoris, hamstring, tibialis anterior, and triceps muscles	A 5-second contraction phase was followed by a 2-second relaxation period.	5 times a week	30-40 minutes per day
3.	Arenja, 2021.[14]	Switzerland	n= 9 (intervention), n= 8 (control)	≥ 60 years	M = 13, F = 14	Aspirin, anticoagulants, statins, ACE-I or ARBs, β-blockers, and MRA	25 Hz	The upper and lower portions of the anterior and posterior femoral and tibial muscles in both legs.	A 2-second contraction phase was followed by a 5-second relaxation period.	5 days a week for 6 weeks	30 minutes per day
4.	Poltavskaya, 2018.[15]	Russia	n=10 (intervention), n=16 (control)	> 18 years	M = 22, F = 4	ACE inhibitors/ ARBs, MCRAs, loop diuretics, beta-blockers	4 Hz	Anterior and posterior thigh and shin muscles	NR	for 3-7 weeks	30-240 minutes per day
5.	Ennis, 2017.[16]	United Kingdom	n= 30 (intervention), n= 30 (control)	59-80 years old	M = 42, F = 18	NR	4-5 Hz	Quadriceps and hamstring muscles	NR	5 times a week	60 minutes per day
6.	Forestieri, 2017.[17]	Brazil	n=24 (intervention), n=25 (control)	> 40 years	M = 8, F = 41	ACE-I, Diuretics	40 Hz	Quadriceps and gastrocnemius (calf) muscles	A contraction phase lasting 10 seconds was followed by a relaxation phase of equal duration.	2 times in 1 day for 2 weeks	60 minutes per day
7.	Iliou, 2017.[18]	Francis	n= 50 (intervention), n= 41 (control)	18-80 years old	M = 70, F = 21	NR	10 Hz	Bilateral Quadriceps femoral muscle	NR	for 4-8 weeks	30-60 minutes per day

8.	Kadoglou, 2017.[19]	Netherlands	n= 60 (intervention), n= 60 (control)	> 60 years	M = 68, F = 52	ACE-I, B-Blockers, Diuretics, MRAs	25 Hz	Quadriceps and gastrocnemius (calf) muscles	A contraction period of five seconds was succeeded by a relaxation period lasting two seconds.	5 days per week for 6 weeks	30 minutes per day
9.	Sacilotto, 2017.[20]	Brazil	n= 18 (intervention), n= 10 (control)	38-64 years	M= 24; F = 4	Diuretics, spironolactone, digoxin, beta-blockers, antiarrhythmics, antiplatelets, statins, CCBs, nitrates, ACE inhibitors	50 Hz	Bilateral femoral quadriceps	A contraction phase lasting three seconds was followed by a relaxation phase of nine seconds.	2 times a week for 7 weeks.	50 minutes per day
10.	Groehs, 2016.[21]	Brazil	n= 15 (intervention), n= 15 (control)	18-70 years old	M = 27, F = 3	B-blockers, ACE-I or ARBs, diuretics, anticoagulants, digitalis, statins, vasodilators, and antiplatelet agents.	10 Hz	Quadriceps and gastrocnemius (calf) muscles	A contraction period of twenty seconds was followed by an equal duration of relaxation.	8-10 consecutive days	60 minutes per day
11.	Parissis, 2015.[22]	Greece	n= 15 (intervention), n= 15 (control)	≥ 70 years old	M = 20, F = 10	ACE-I, B-Blockers, and Diuretics	25 Hz	Quadriceps and gastrocnemius (calf) muscles	A contraction phase of five seconds was followed by a relaxation phase lasting two seconds	5 days per week for 6 weeks	30 minutes per day
12.	Soska, 2014.[23]	Czech	n= 23 (intervention), n= 26 (control)	> 60 years	M = 29, F = 20	ACE-I, B-Blocker, Diuretic, Digoxin, Statin	10 Hz	Bilateral Quadriceps femoral muscle	A contraction phase lasting twenty seconds was followed by an equal twenty-second relaxation phase	2 times in 1 day for 12 weeks	60 minutes per day

Info : NR (Not Reported), M (Male), F (Female).

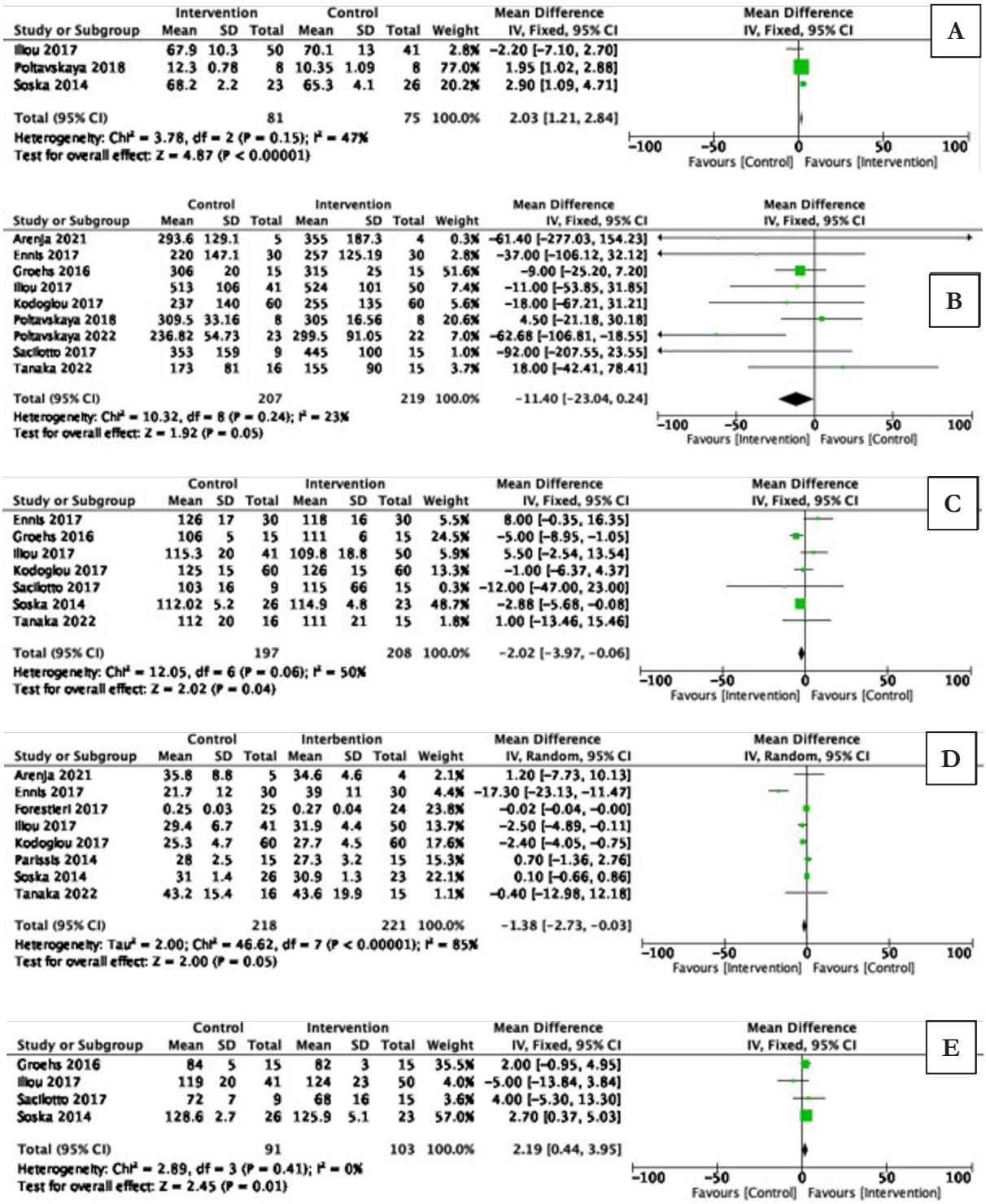

Figure 3. Results that have a significant effect of NMES on HFrEF rehabilitation. (A) VO_2 Peak, (B) 6 Minute Walking Test (6MWT), (C) Systolic Blood Pressure (SBP), (D) Left Ventricular Ejection Fraction (LVEF%), (E) Heart Rate (HR).

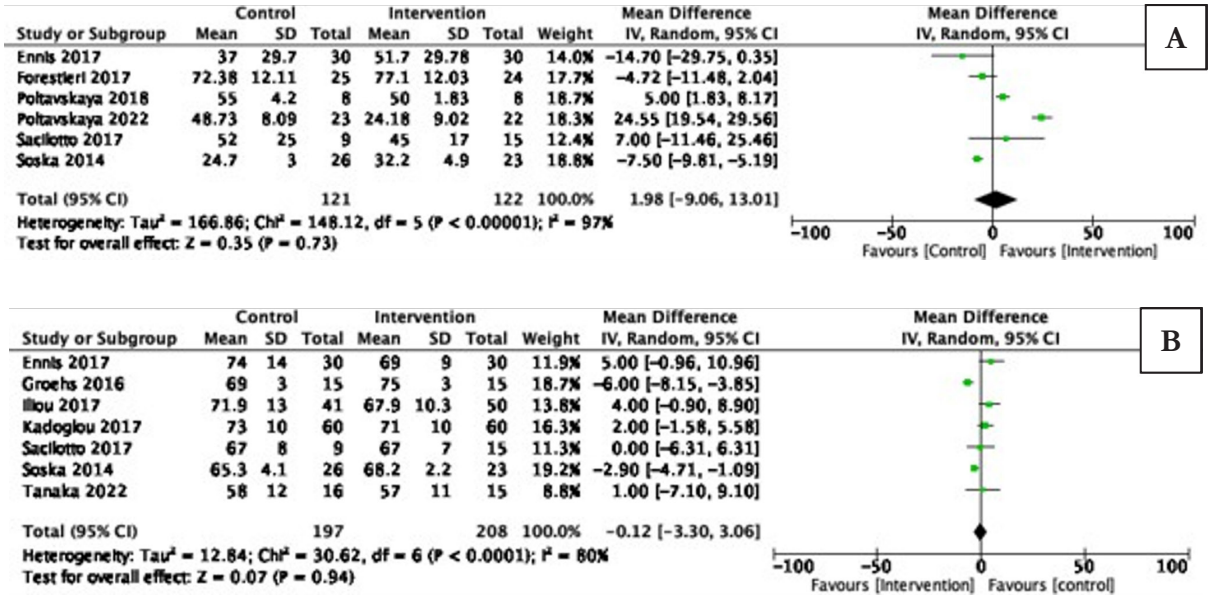

Figure 4. Results that have no significant effect of NMES on HFrEF rehabilitation (A) Minnesota Living with Heart Failure Questionnaire (MLHFQ) Score, (B) Diastolic Blood Pressure (DBP).

Discussion

NMES confers significant benefits on exercise capacity and selected cardiovascular parameters in patients with HFrEF. Pooled analyses showed a robust improvement in peak oxygen uptake and a borderline improvement in 6MWT distance, alongside modest but significant improvements in LVEF, systolic blood pressure, and HR. In contrast, no significant effects were observed on diastolic blood pressure or on health-related quality of life, as assessed by the MLHFQ. These findings indicate that NMES primarily improves objective physiological and functional outcomes rather than subjective patient-reported measures.[12-23]

The improvement in exercise capacity observed with NMES highlights its key advantage in addressing peripheral limitations that substantially contribute to exercise intolerance in HFrEF. Beyond impaired cardiac output, patients with HFrEF commonly exhibit skeletal muscle atrophy, reduced oxidative enzyme activity, and impaired peripheral perfusion, all of which limit functional performance.[24] NMES induces involuntary muscle contractions that enhance muscle fiber recruitment, increase local blood flow, and improve mitochondrial oxidative capacity, thereby improving aerobic efficiency without imposing excessive cardiovascular stress.[10] This peripheral mechanism provides a plausible explanation for the observed increases in VO_2 peak and walking capacity. It supports previous evidence suggesting that NMES can partially replicate the physiological benefits of exercise in patients unable to tolerate conventional training.[24-25]

In addition to its peripheral effects, NMES may exert favorable systemic and hemodynamic influences. The observed reduction in systolic blood pressure and modulation of HR suggest an improvement in autonomic balance, particularly through attenuation of heightened sympathetic nervous system activity, which is a hallmark of advanced heart failure.[25] Reduced sympathetic tone may lower systemic vascular resistance and cardiac workload, thereby indirectly supporting ventricular performance.[26] The modest improvement in LVEF observed in this analysis likely reflects these indirect neurohumoral and hemodynamic effects rather than a direct inotropic action on the myocardium. The absence of a significant effect on diastolic blood pressure is consistent with the primary action of NMES on muscle contraction and vascular tone rather than ventricular relaxation dynamics.[27]

From a clinical standpoint, the findings of this meta-analysis underscore the practical advantages of NMES as an adjunct rehabilitation strategy in HFrEF. NMES can be delivered with minimal physical effort, low cardiovascular strain, and high feasibility across inpatient, outpatient, and home-based settings. These characteristics make NMES particularly valuable for patients with advanced disease, frailty, or severe exercise intolerance populations that are frequently excluded from

conventional exercise-based cardiac rehabilitation despite strong guideline recommendations.[25,27] While NMES should not be viewed as a substitute for comprehensive cardiac rehabilitation, its ability to improve objective functional and hemodynamic parameters supports its selective integration into individualized rehabilitation programs.[28]

Overall, this meta-analysis suggests that NMES offers meaningful physiological and functional benefits in patients with HFrEF, particularly in improving exercise capacity and selected cardiovascular measures. At the same time, its effects on quality-of-life outcomes remain inconsistent. These findings reinforce the role of NMES as a supportive and accessible rehabilitation modality that may help bridge the gap between guideline-based recommendations and the real-world limitations of rehabilitation in heart failure care.

Conclusion

NMES provides measurable benefits in patients with HFrEF. Based solely on pooled analyses, NMES was associated with significant improvements in peak oxygen uptake and a borderline improvement in 6MWT distance. In addition, modest but statistically significant improvements were observed in LVEF, systolic blood pressure, and HR. No significant effects were identified for diastolic blood pressure or health-related quality of life.

Taken together, these findings support the role of NMES as a beneficial adjunct rehabilitation intervention for patients with HFrEF, particularly for those who are unable to engage in conventional exercise-based rehabilitation.

List of Abbreviations

6MWT	Six-Minute Walk Test
CI	Confidence Interval
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Heart Rate
LVEF	Left Ventricular Ejection Fraction
MD	Mean Differences
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NMES	Neuromuscular Electrical Stimulation
NYHA	New York Heart Association
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized Controlled Trials
RR	Risk Ratio
VO_2	Oxygen uptake

Ethical Clearance

Not applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

All authors contributed substantially to the conception, design, and intellectual development of this systematic review and meta-analysis. BDA led the study conceptualization, literature search strategy, data extraction, statistical interpretation, and manuscript drafting. SA and DH contributed to data screening, risk-of-bias assessment, and verification of extracted datasets. R and I supported methodological validation and assisted in the synthesis and interpretation of pooled outcomes. H provided critical intellectual input, supervised the overall research process, and revised the manuscript for important scientific content and methodological rigor. All authors critically reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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Review Article

Coronary Vulnerable and High-Risk Plaque: Current Concepts, Selective Preventive PCI, and an ISIC Position Statement

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Abstract

The concept of coronary vulnerable plaque has evolved from a histopathological concept into a potential therapeutic target for precision cardiovascular prevention. Recent evidence has expanded this paradigm beyond the traditional vulnerable-plaque construct towards the broader concept of high-risk plaque, encompassing rupture-prone plaques, erosion-prone plaques, calcified nodules, plaque burden, inflammatory activity, healing capacity, and patient-level susceptibility to thrombosis. Advances in Coronary Computed Tomography Angiography (CCTA), Intravascular Ultrasound (IVUS), Optical Coherence Tomography (OCT), Near-Infrared Spectroscopy (NIRS), molecular imaging, and Artificial Intelligence (AI) have substantially improved the detection and characterization of high-risk plaque. Circulating lipid, inflammatory, metabolic, and renal biomarkers provide complementary information regarding patient vulnerability. Concurrently, contemporary pharmacological therapy has substantially improved the natural history of coronary atherosclerosis by promoting plaque stabilization, fibrous cap thickening, lipid core regression, and attenuation of vascular inflammation.

The emergence of preventive Percutaneous Coronary Intervention (PCI) for non-flow-limiting vulnerable plaques, particularly following the PREVENT trial, has reignited interest in focal treatment before clinical destabilization. Nevertheless, important uncertainties remain regarding patient selection, diagnostic thresholds, imaging strategies, device selection, long-term durability, cost-effectiveness, and applicability in resource-limited healthcare systems. Drug-Eluting Stents (DES) remain the most established device platform, whereas next-generation bioresorbable scaffolds and Drug-Coated Balloons (DCB) may offer future approaches to local plaque treatment without permanent metallic implantation. Although Coronary Artery Bypass Grafting (CABG) does not directly treat vulnerable plaques, it may indirectly protect selected patients with diffuse multivessel disease by bypassing plaque-bearing coronary segments.

For Indonesia and other resource-constrained healthcare systems, future implementation should emphasize pragmatic implementation rather than widespread adoption of advanced technologies. Emphasis should remain on aggressive Optimal Medical Therapy (OMT), selective use of advanced imaging, careful identification of patients at the highest absolute cardiovascular risk, structured operator training, national registries, and rigorous evaluation of cost-effectiveness. The ultimate objective is not simply to detect more vulnerable plaques but to prevent more myocardial infarctions and cardiovascular deaths through efficient use of healthcare resources.

The Indonesian Society of Interventional Cardiology (ISIC) recommends that aggressive systemic prevention, centered on OMT, should remain the foundation of care. Advanced plaque imaging and preventive PCI should be reserved for carefully selected patients with converging high-risk plaque characteristics, high patient-level risk, and a favorable benefit–risk profile.

Keywords: High-risk plaque; vulnerable plaque; preventive PCI; precision prevention; coronary computed tomography angiography; intravascular ultrasound; optical coherence tomography; biomarkers; bioresorbable scaffold; drug-coated balloon

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Introduction

Despite remarkable advances in cardiovascular prevention, lipid-lowering therapy, antithrombotic treatment, and coronary revascularisation, Coronary Artery Disease (CAD) remains one of the leading causes of morbidity and mortality worldwide. Acute Coronary Syndromes (ACS) continue to impose a substantial clinical and socioeconomic burden because many events arise unexpectedly from angiographically non-obstructive lesions rather than from severely flow-limiting stenoses. This long-standing paradox has driven the development of the vulnerable-plaque concept, traditionally defined as an atherosclerotic lesion with a high propensity for rupture, erosion, thrombosis, and the subsequent occurrence of myocardial infarction or sudden cardiac death.[1–3]

The traditional concept of vulnerable plaque has been largely based on plaque morphology. Plaque rupture has traditionally been regarded as arising from Thin-Cap Fibroatheroma (TCFA), which contains a large lipid-rich necrotic core covered by a thin fibrous cap infiltrated by macrophages. Other features such as positive remodeling, large plaque burden, spotty calcification, intraplaque hemorrhage, inflammation, and adverse endothelial shear stress have also been associated with plaque destabilization.[4–7] However, later clinical studies have shown that plaque morphology alone is not enough to predict future events with high positive predictive value. Many plaques with high-risk features remain clinically silent. Plaque vulnerability itself is dynamic and may evolve under the influence of systemic inflammation, lipid metabolism, thrombogenicity, hemodynamic forces, and pharmacological therapy.[8-9]

More recently, accumulating evidence has substantially refined this traditional paradigm. The 2025 JACC Cardiovascular Imaging Position Statement proposed the broader concept of the high-risk plaque, acknowledging that coronary thrombosis may arise not only from rupture-prone TCFA but also from erosion-prone plaques and eruptive calcified nodules. In addition, plaque-related risk is determined by plaque burden, inflammatory activity, endothelial injury, local hemodynamic conditions, healing capacity, and the amount of myocardium subtended by the lesion.[10] This contemporary framework shifts the focus from a single vulnerable lesion toward a more integrated assessment of high-risk plaque, high-risk patient, and high-risk coronary phenotype. Because plaque morphology alone has limited positive predictive value, this evidence has prompted a major conceptual shift. Today's thinking has come to recognize that plaques do not act alone. Future prevention should focus not only on vulnerable plaque but also on high-risk plaque, vulnerable patients, and high-risk coronary phenotypes. This phenotype encompasses plaque morphology, plaque biology, systemic inflammatory milieu, metabolic risk, hemodynamic stress, genetic susceptibility, and treatment responsiveness.[8,10] In this context, imaging is not only a tool to label a plaque as "vulnerable", but part of a wider risk-stratification ecosystem intended to guide precision prevention. This framework proposed by Vergallo and colleagues represents one of the most comprehensive contemporary models of coronary vulnerability and serves as an important conceptual foundation for the present Indonesian Society of Interventional Cardiology (ISIC) position statement. The conceptual evolution from the traditional vulnerable-plaque paradigm towards the integrated high-risk coronary phenotype proposed in this Position Statement is summarised in Figure 1.

The advent of preventive Percutaneous Coronary Intervention (PCI) has further fuelled this debate. The PREVENT trial showed that in selected patients with non-flow-limiting vulnerable plaques, preventive PCI plus Optimal Medical Therapy (OMT) reduced the risk of target vessel failure compared with OMT alone.[11] This trial is an important milestone because it provides randomized evidence in support of focal treatment of selected high-risk plaques. Nonetheless, PREVENT should be viewed as the start of a new clinical hypothesis rather than the final justification for widespread plaque stenting. The trial leaves some questions unanswered. Who should we screen? Which imaging modality to use? What plaque features should prompt intervention? What device platform fits best? Is the benefit driven by hard endpoint prevention or by reduction in softer events like unstable angina and revascularisation? Is the approach cost-effective across various healthcare systems?

These are particularly relevant questions for Indonesia. Indonesia has a substantial and increasing burden of cardiovascular disease, marked geographic variation in access to catheterization laboratories, limited availability of advanced intracoronary imaging in many regions, and constrained healthcare resources and budgetary capacity.[12–14] Future adoption of high-risk plaque assessment and preventive PCI must be clinically meaningful, economically defensible, and operationally feasible. A strategy developed in high-income healthcare

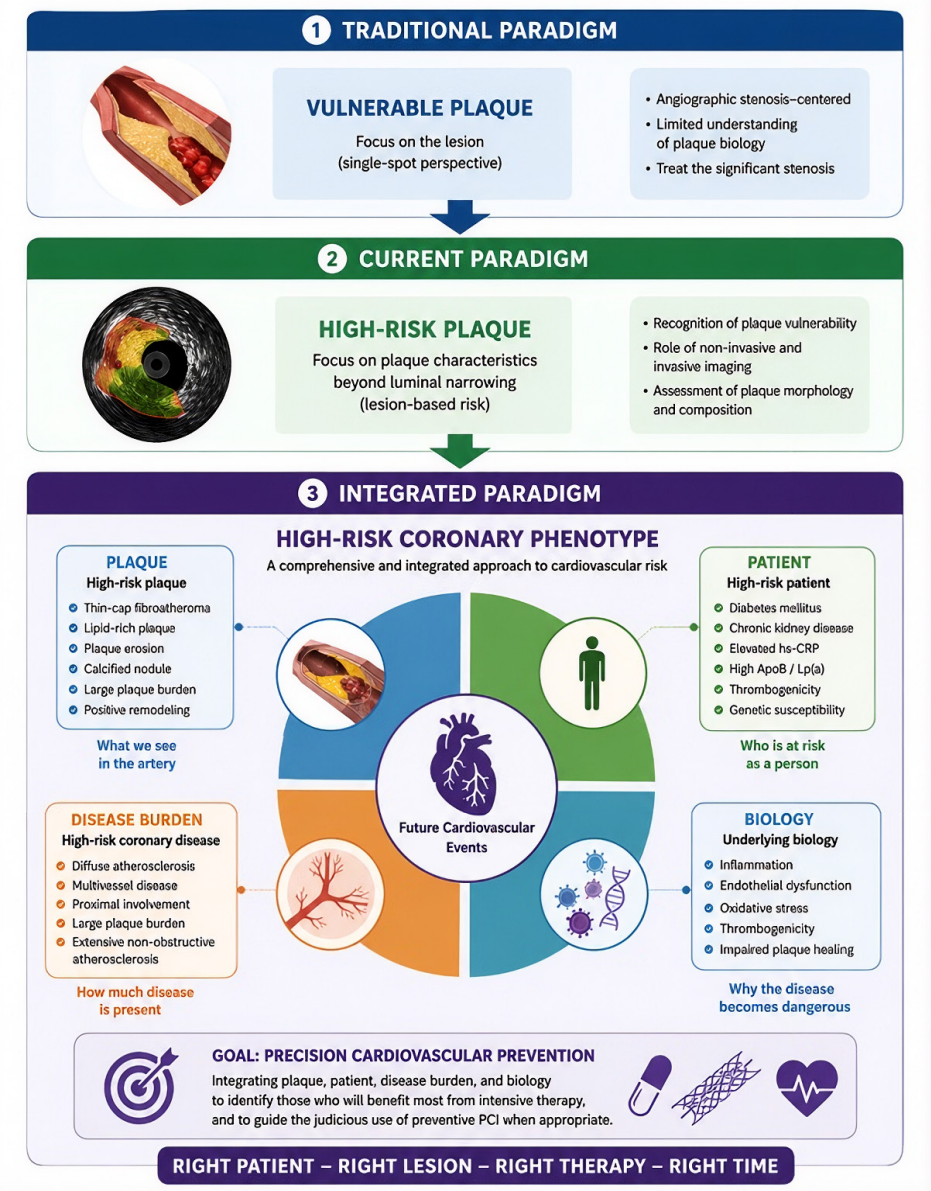

Figure 1. Evolution of the Coronary Risk Paradigm.
This figure illustrates the evolution from the traditional vulnerable-plaque paradigm to the contemporary high-risk plaque concept and, ultimately, to an integrated high-risk coronary phenotype. The traditional paradigm focused primarily on angiographic stenosis and individual rupture-prone lesions, whereas the current paradigm incorporates plaque characteristics beyond luminal narrowing. The integrated paradigm combines plaque morphology, patient-level vulnerability, overall disease burden, and biological activity to support precision cardiovascular prevention. The overarching goal is to identify the right patient, the right lesion, and the right therapy at the right time.

systems cannot be directly implemented in Indonesia without contextual adaptation. The aim should be to achieve the largest reduction in cardiovascular events for every unit of healthcare resources invested. Accordingly, the primary objective is not to detect a greater number of high-risk plaques, but to identify those patients in whom additional diagnostic or therapeutic intervention is most likely to improve clinical outcomes.

This position statement reviews future directions in the management of coronary vulnerable plaque, including invasive and non-invasive diagnosis; pharmacological stabilization; preventive PCI; Coronary Artery Bypass Grafting (CABG); emerging device platforms, such as Drug-Eluting Stents (DES), bioresorbable scaffolds, and Drug-Coated Balloons (DCB); and implementation challenges relevant to Indonesia and other resource-

limited settings. In addition, this position statement reflects the perspective of the ISIC, which recognizes the growing importance of imaging-defined plaque vulnerability and the emerging role of preventive PCI, while emphasizing that OMT remains the cornerstone of management. ISIC supports a cautious, evidence-based, imaging-guided, and highly selective approach to preventive plaque intervention, recognizing that patient-level risk, healthcare resource considerations, procedural safety, and cost-effectiveness must remain central to clinical decision-making, particularly in Indonesia and similar resource-constrained healthcare systems.

Against this background, ISIC believes that the contemporary management of coronary vulnerability should move beyond a purely lesion-centered paradigm. Although advances in coronary imaging have improved the identification of high-risk plaque features and recent evidence has reinvigorated the debate on preventive PCI, current evidence does not support indiscriminate intervention on all imaging-defined vulnerable plaques. Rather, OMT should remain the foundation of care, while advanced imaging and preventive PCI should be reserved for carefully selected patients in whom the anticipated clinical benefit outweighs procedural risks, costs, and resource implications.

From Vulnerable Plaque to High-Risk Plaque and High-Risk Coronary Phenotype

The historical concept of the vulnerable plaque originated from pathological studies of culprit lesions responsible for fatal coronary thrombosis. These landmark investigations established plaque rupture, plaque erosion, and calcified nodules as the principal pathological substrates underlying ACS. Plaque rupture is typically associated with TCFA, characterized by a large lipid-rich necrotic core covered by a thin fibrous cap infiltrated with inflammatory cells, particularly macrophages. Plaque erosion, in contrast, is characterized by endothelial denudation, a proteoglycan-rich extracellular matrix, and a predominance of smooth muscle cells with relatively less lipid accumulation. Calcified nodules, although less common, may also precipitate coronary thrombosis through disruption of the luminal surface.[4-5]

For more than two decades, TCFA has been regarded as the archetypal vulnerable plaque. Nevertheless, advances in pathology, intracoronary imaging, and clinical investigation have demonstrated that coronary thrombosis cannot be explained by a single morphological substrate alone. Coronary events arise from multiple biological pathways, including plaque composition, vascular inflammation, endothelial integrity, thrombogenicity, hemodynamic forces, vascular healing, and systemic patient-related factors. Consequently, the traditional lesion-centered paradigm has gradually evolved into a broader, more biologically comprehensive framework.

Contemporary evidence therefore favors the concept of the high-risk plaque, which extends beyond rupture-prone TCFA to encompass erosion-prone plaques, eruptive calcified nodules, extensive plaque burden, inflammatory activity, endothelial dysfunction, impaired healing capacity, and adverse local hemodynamics. Importantly, the probability that an individual plaque will result in an acute coronary event is determined not only by its intrinsic morphology but also by the biological vulnerability of the patient in whom it resides. This conceptual evolution recognizes that plaque-related risk is dynamic rather than static and reflects the complex interaction between local plaque characteristics and systemic disease processes.[10]

The 2025 JACC: Cardiovascular Imaging Position Statement by Vergallo and colleagues represents the most comprehensive contemporary synthesis of this evolving concept. Rather than defining vulnerability solely according to plaque morphology, the document proposes an integrated framework that incorporates lesion characteristics, plaque biology, inflammatory activity, endothelial injury, vascular healing, hemodynamic stress, the amount of subtended myocardium, and patient-level susceptibility to thrombosis.[10] This framework acknowledges that clinically relevant coronary events occur when multiple determinants of vulnerability converge, rather than as the consequence of a single morphological abnormality.

Accordingly, contemporary coronary risk assessment has shifted from identifying isolated vulnerable plaques towards recognizing the broader high-risk coronary phenotype. This phenotype integrates three complementary domains: high-risk plaque, high-risk patient, and high-risk coronary disease. High-risk plaque describes adverse morphological and biological plaque characteristics; high-risk patient reflects systemic factors such as persistent dyslipidemia, residual inflammatory risk, diabetes mellitus, Chronic Kidney Disease (CKD), thrombogenicity, and genetic susceptibility;

whereas high-risk coronary disease encompasses diffuse atherosclerotic burden, extensive plaque distribution, proximal lesion location, and the volume of myocardium at risk. Considered together, these domains provide a more accurate representation of future cardiovascular risk than plaque morphology alone.

This paradigm shift also explains why the predictive value of imaging-defined vulnerable plaque has historically been modest. Several prospective studies, including PROSPECT, have consistently demonstrated that lesions exhibiting large plaque burden, positive remodeling, TCFA, or small minimal lumen area are associated with a significantly higher probability of subsequent cardiovascular events.[15] However, the absolute event rate attributable to any individual lesion remains relatively low. Similar observations have subsequently been confirmed using Optical Coherence Tomography (OCT), Near-Infrared Spectroscopy (NIRS), and Coronary Computed Tomography Angiography (CCTA), each demonstrating that although high-risk plaque features are prognostically important, the majority of imaging-defined high-risk plaques never progress to clinically manifest ACS.[16–19]

Several biological mechanisms explain this apparent paradox. First, plaque vulnerability is inherently dynamic. Lesions that appear biologically active at one time point may subsequently stabilize or regress under intensive lipid-lowering and anti-inflammatory therapy. Second, plaque disruption frequently occurs without clinical manifestation because thrombosis remains limited or is effectively counterbalanced by endogenous fibrinolytic mechanisms. Third, systemic determinants—including inflammation, diabetes mellitus, renal dysfunction, smoking, coagulation status, and residual lipid burden—substantially influence whether plaque disruption ultimately culminates in myocardial infarction. Finally, patients rarely harbor a single vulnerable lesion; rather, they often exhibit diffuse coronary atherosclerosis containing multiple plaques at different stages of biological evolution. Consequently, focal treatment of one lesion cannot eliminate the systemic processes responsible for continued disease progression.

The recognition of these limitations has profound implications for future preventive strategies. The central clinical question is no longer whether an individual plaque fulfills the criteria for vulnerability, but whether the overall coronary phenotype places the patient at sufficiently high absolute risk to justify escalation beyond OMT. This broader perspective aligns with the principles of precision cardiovascular prevention, whereby diagnostic imaging, circulating biomarkers, clinical characteristics, and therapeutic responsiveness are integrated to guide personalized management.

An additional dimension of this evolving paradigm is the concept of plaque healing. Increasing pathological and intracoronary imaging evidence suggests that repeated episodes of clinically silent plaque disruption may be followed by reparative healing, characterized by increased fibrous tissue deposition and progressive plaque stabilization. Conversely, the absence of healed plaque may identify lesions with persistent biological activity despite similar anatomical appearance.[10] Recognition of plaque healing further emphasizes that plaque morphology represents only a single component of vulnerability and reinforces the importance of considering biological activity alongside structural characteristics.

Taken together, these observations establish an important conceptual transition. Accordingly, the central challenge is no longer plaque detection itself, but appropriate patient selection. The value of advanced plaque imaging ultimately lies in identifying patients whose overall coronary phenotype justifies intensification of therapy beyond optimal medical treatment. This integrated framework provides the scientific foundation for precision prevention and underpins the recommendations presented throughout this ISIC Position Statement.

Future Directions in Non-invasive Diagnostics

Coronary CT Angiography: A Scalable Platform

Coronary CT angiography is expected to play an increasingly important role as a scalable non-invasive platform for future assessment of high-risk coronary plaque. Compared with invasive imaging, CCTA is non-invasive and more scalable for broader risk stratification. Several high-risk plaque features can be identified by modern CCTA, including low-attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign. These features have been associated with increased risk of myocardial infarction and coronary death in observational studies.[20–22]

The future role of CCTA may extend beyond the assessment of anatomical stenosis. Quantitative plaque analysis provides measures of total plaque volume, non-calcified plaque volume, low-

attenuation plaque burden, calcified plaque burden, and progression over time. Serial CCTA may be useful for assessing the response to intensive lipid-lowering therapy or anti-inflammatory treatment. This is particularly relevant because plaque stabilization, not just luminal improvement, may represent the desired therapeutic endpoint in vulnerable plaque management.

In resource-limited settings, CCTA may provide a practical gatekeeper role. Instead of routine intracoronary imaging in all patients undergoing angiography, CCTA may help identify patients with extensive non-obstructive plaque burden or high-risk plaque features who might benefit from intensification of medical therapy and, in selected cases, invasive plaque assessment. The strengths, limitations, and potential future roles of currently available and emerging diagnostic modalities are summarised in Table 1.

Imaging of Perivascular Fat and Radiomics, Artificial Intelligence

Artificial Intelligence (AI) and radiomics may further enhance the value of CCTA. Traditional visual interpretation can only extract a small fraction of the information present in CT datasets. Radiomics can extract high-dimensional quantitative features related to plaque texture, attenuation heterogeneity, vessel geometry, and perivascular tissue characteristics. These features may be combined with clinical variables, laboratory markers, and longitudinal data by machine-learning algorithms to create individualized risk prediction.

Another promising marker is the perivascular fat attenuation index. Perivascular adipose tissue is a surrogate for local vascular inflammation because inflammatory signals from the coronary wall affect adipocyte lipid content and CT attenuation. Perivascular fat assessment could thus offer indirect information on coronary inflammation, complementing anatomical plaque assessment.[23] In the future, CCTA may serve as a comprehensive non-invasive coronary vulnerability platform integrating plaque morphology, perivascular inflammation, coronary flow modeling, and clinical risk.

By enabling automated plaque characterization, quantitative assessment of plaque burden, and individualized risk prediction, AI-enhanced CCTA may help narrow the traditional gap between non-invasive and invasive plaque assessment, although prospective outcome validation remains essential.

However, AI-CCTA for Indonesia should be treated pragmatically. Its promise is contingent on scanner quality, standardized acquisition protocols, computational infrastructure, validation in local populations, and reimbursement policy. As an expert position, ISIC considers that broad adoption of proprietary AI-CCTA platforms should be preceded by local validation, demonstration of incremental clinical value, and evaluation of cost-effectiveness.[13-14] Local validation studies and registries should therefore be prioritized.

Table 1. Complementary roles of contemporary imaging modalities in high-risk coronary plaque assessment.

Imaging modality	Principal information provided	Major strengths	Main limitations	Clinical implication
CCTA	Plaque burden, phenotype, low-attenuation plaque, positive remodeling	Non-invasive, scalable, AI-assisted quantitative analysis	Limited fibrous-cap resolution; affected by calcification/ motion	First-line risk stratification and selection for further evaluation
IVUS	Plaque burden, remodeling, lumen dimensions	Excellent penetration; PCI optimization	Limited fibrous-cap resolution	Structural plaque assessment and PCI optimization
OCT	Fibrous cap, rupture, erosion, macrophages, thrombus	Highest spatial resolution	Limited penetration; contrast required	Assessment of plaque vulnerability and procedural guidance
NIRS-IVUS	Lipid-core burden (maxLCBI4mm)	Direct lipid assessment	Limited availability	Refines lesion-level risk in specialized centers

Notes: No single imaging modality captures all dimensions of coronary plaque vulnerability. CCTA provides a scalable non-invasive assessment of plaque burden and phenotype, whereas IVUS, OCT, and NIRS offer complementary information on plaque structure, microarchitecture, and composition. Integrated interpretation of these modalities,

together with clinical characteristics, circulating biomarkers, and OMT, may improve patient selection for advanced imaging or selective preventive PCI. Routine use of invasive imaging should remain individualized and guided by clinical context, expected impact on management, and resource availability.

Molecular Imaging

Molecular imaging offers a biologically attractive approach, as plaque destabilization is driven not only by morphology but also by inflammation, microcalcification, apoptosis, protease activity, and thrombosis. Positron Emission Tomography (PET) using tracers such as 18F-fluorodeoxyglucose and 18F-sodium fluoride has been investigated for the detection of vascular inflammation and active microcalcification.[24-25] Experimental tracers that target macrophages, integrins, somatostatin receptors, fibrin, and matrix metalloproteinases may further refine biological characterization.

Although it has scientific interest, molecular imaging may not be a routine tool for vulnerable plaque screening in Indonesia in the near future. Its scalability is limited by cost, limited availability, radiation exposure, tracer logistics, and uncertain treatment implications. Its most appropriate role may be in research, drug development, and selected tertiary center evaluation of inflammatory plaque biology. Molecular imaging may identify which systemic therapies alter plaque inflammation and which biological phenotypes remain high-risk despite optimal conventional therapy.

Future Directions in Invasive Diagnosis

Intravascular Ultrasound (IVUS)

IVUS remains one of the cornerstones of intracoronary imaging modalities. It allows deep tissue penetration and quantification of vessel size, plaque burden, remodeling, and minimum lumen area. IVUS-derived plaque burden has been consistently associated with future events, and plaque burden ≥70% has been one of the most reproducible high-risk features in prospective studies.[15]

Future IVUS platforms may increasingly be combined with radiofrequency analysis, automated plaque quantification, co-registration with angiography, and AI-assisted interpretation. IVUS may be especially useful in large vessels, left main disease, diffuse atherosclerosis, and situations where contrast load must be minimized. In many centers in Indonesia, IVUS is more available than OCT and may therefore represent the most practical invasive platform for early adoption of plaque-guided strategies.

IVUS does have limitations, however. Its axial resolution is insufficient to directly measure thin fibrous caps or to identify microstructural features of plaque erosion. Virtual histology and other tissue characterization algorithms have improved plaque classification, but are not equivalent to histology. Thus, IVUS should be used to detect plaque burden and remodeling rather than as an independent tool for all dimensions of vulnerability.

Optical Coherence Tomography

Among the intracoronary imaging modalities available for clinical use, OCT offers the highest resolution. It can directly assess fibrous cap thickness, lipid arc, macrophage accumulation, microchannels, calcification, plaque rupture, plaque erosion, and thrombus. OCT is thus uniquely suited to characterize TCFA and mechanisms of ACS.[16-17]

Within the high-risk plaque framework, OCT occupies a particularly important position because it is the only clinically available intracoronary imaging modality that can directly measure fibrous cap thickness in vivo. In addition to identifying TCFA, OCT may help characterize plaque rupture, plaque erosion, thrombus, macrophage accumulation, microchannels, calcific nodules, and healed plaque. Therefore, OCT may be especially useful when preventive PCI is being considered, provided that the result will meaningfully alter management.

OCT could play two major roles in the future management of vulnerable plaque. First, it can improve risk stratification in non-flow-limiting lesions when preventive PCI is considered. Second, it can optimize PCI by providing adequate lesion preparation, stent expansion, apposition, and edge assessment.[26] Preventive PCI is performed in lesions that may not yet be ischemia-producing, raising ethical and clinical issues regarding procedural safety and optimization.

Cost, the need for contrast injection, limited penetration depth, and the requirement for expertise are the main barriers to OCT. OCT should not be used as a general screening tool indiscriminately in Indonesia. Instead, it should be concentrated in centers with proper training and applied to carefully selected cases, including ambiguous culprit lesions, high-risk non-culprit lesions in patients with recurrent events, and research registries. In research settings, serial OCT or IVUS may also provide valuable surrogate markers of plaque stabilization

or regression during intensive lipid-lowering or anti-inflammatory therapy, although their routine use for treatment monitoring cannot currently be recommended.

Near-Infrared Spectroscopy and Multimodal Imaging

NIRS detects lipid-rich plaques by their chemical signature and quantifies lipid burden using parameters such as the maximum lipid-core burden index within any 4-mm segment (maxLCBI4mm). NIRS is often combined with IVUS, allowing simultaneous evaluation of lipid content and plaque structure. Studies have demonstrated that lipid-rich plaques detected by NIRS-IVUS are associated with future coronary events.[18-19]

Multimodality imaging is an important future direction, because no single modality captures all dimensions of vulnerability. OCT provides microstructural detail, IVUS provides plaque burden and vessel remodeling, NIRS provides lipid content, and angiography provides procedural orientation. Future hybrid catheters or integrated software platforms might combine structural, compositional, biological, and hemodynamic information into a single vulnerability score. A next step in hybrid intravascular imaging is the integration of Optical Coherence Tomography with Near-Infrared Spectroscopy (OCT–NIRS) in a single catheter. By combining the very high axial resolution of OCT for assessment of fibrous cap thickness and microstructure with the compositional information of NIRS on lipid burden, OCT–NIRS has the theoretical potential to identify TCFA with large lipid cores and macrophage-related optical signals within one pullback, thereby improving selection of lesions for preventive PCI compared with single-modality imaging. First-in-human experience with a next-generation combined DeepOCT–NIRS system suggests that such multimodality catheters can provide enhanced plaque characterization and procedural guidance, although their clinical impact on outcomes and cost-effectiveness still needs to be established in larger studies.[27]

However, hybrid imaging may remain expensive and restricted to specialized centers. Its future role in Indonesia should be assessed through specific clinical research, not by immediate routine implementation.

Future patient selection will likely evolve beyond plaque morphology alone by integrating complementary physiological and biological information, although the precise role of coronary physiology, endothelial function, and microvascular assessment in selecting candidates for preventive PCI remains to be established.

Pharmacological Treatment: The Mainstay of Plaque Stabilization

Any discussion of vulnerable plaque management must start with pharmacological therapy. Systemic therapy is directed at the entire coronary tree, not just a single imaged lesion. The advantage of this is crucial, as vulnerable plaques are often multiple, dynamic, and located within diffuse atherosclerosis.

Biomarkers, Residual Risk, and the High-Risk Patient

Plaque imaging describes local lesion-level vulnerability, whereas circulating biomarkers reflect the systemic milieu that determines whether plaque disruption becomes clinically manifest. Lipid-related markers such as LDL cholesterol, non-HDL cholesterol, apolipoprotein B (Apo B), triglyceride-rich lipoproteins or remnant cholesterol, and Lipoprotein(a) [Lp(a)] may identify residual atherogenic risk not fully captured by angiographic stenosis or a single plaque phenotype. ApoB is particularly useful when LDL cholesterol and atherogenic particle number are discordant, whereas Lp(a) represents a largely genetically determined risk modifier that remains relevant even when LDL cholesterol is well controlled.[28-29]

Inflammatory biomarkers provide complementary information on patient-level vulnerability. High-sensitivity C-reactive protein (hs-CRP) is the most practical marker of residual inflammatory risk, while the interleukin-1β, interleukin-6, and NLRP3 inflammasome pathways provide mechanistic links between systemic inflammation, endothelial injury, plaque destabilization, and thrombosis.[30–32] The clinical implications remain context-dependent because benefits from anti-inflammatory treatment have varied across patient populations.[33]

Metabolic and renal factors, including diabetes, glycaemic control, CKD, smoking, obesity, thrombogenicity, and bleeding risk, further modify the probability that an imaging-defined high-risk plaque will produce a clinical event. In Indonesia, readily available measurements—including a standard lipid profile, glycated hemoglobin (HbA1c), and renal function, with hs-CRP, ApoB, and at least one lifetime Lp(a) measurement in selected patients where feasible—may help prioritize intensive systemic prevention before costly invasive plaque

assessment. Biomarkers should complement, not replace, plaque imaging.

The concept of plaque healing further reinforces the central role of systemic therapy. Plaque stabilization is not limited to lipid-core regression or fibrous cap thickening; it also includes favorable biological healing following subclinical plaque disruption. In this context, OMT may reduce risk not only by modifying plaque morphology but also by improving the systemic milieu that determines whether plaque disruption becomes clinically manifest as thrombosis.

Aggressive Lipid-Lowering Therapy

Statins remain the mainstay of plaque stabilization. High-intensity statin therapy reduces cardiovascular events, induces plaque regression, increases fibrous cap thickness, reduces lipid content, and exerts anti-inflammatory effects.[34-35] Ezetimibe adds benefit for LDL cholesterol lowering and outcomes when added to statins, especially after ACS.[36] PCSK9 inhibitors further lower LDL cholesterol and reduce cardiovascular events in high-risk patients.[37-38] Multimodality imaging in PACMAN-AMI showed favorable changes in plaque burden, lipid content, and fibrous cap thickness when alirocumab was added to high-intensity statin therapy.[39]

Future lipid management may increasingly focus on earlier, deeper, and more durable reductions in LDL cholesterol. Inclisiran, a small interfering RNA therapy targeting PCSK9 synthesis, is administered twice yearly and may enhance adherence, although outcome data remain an important consideration.40 Inhibition of ANGPTL3 and other emerging lipid pathways may become relevant for select patients with refractory dyslipidemia.

Another major future target is Lp(a). High Lp(a) levels are genetically determined and associated with atherosclerotic cardiovascular disease. Antisense oligonucleotides and small interfering RNA therapies targeting Lp(a) are being investigated, including pelacarsen and olpasiran. If outcome trials are positive, Lp(a)-lowering therapy might become an important component of precision prevention in patients with residual risk despite optimal LDL cholesterol control.[29]

For Indonesia, the biggest near-term opportunity remains improving access and adherence to proven, affordable lipid-lowering therapy. From a public-health perspective, improving access and adherence to proven, affordable therapies such as high-intensity statins and ezetimibe may provide broader population-level benefit before widespread deployment of costly advanced imaging or intervention.[12,14] PCSK9 inhibitors, inclisiran and future Lp(a) therapies should be initially reserved for very-high-risk patients within evidence-based and economically sustainable frameworks.

Anti-inflammatory treatment

Inflammation is central to plaque initiation, progression, destabilization, and thrombosis. The CANTOS trial showed that targeting interleukin-1β reduced recurrent cardiovascular events regardless of lipid lowering, providing proof of concept for inflammatory risk reduction.[30] Colchicine has since become a more practical anti-inflammatory therapy. Low-dose colchicine has been shown to reduce cardiovascular events in trials in post-myocardial infarction and chronic coronary disease populations.[31-32] Plaque-specific imaging data from COLOCT suggested favorable OCT changes in fibrous cap thickness and lipid or inflammatory features, whereas CLEAR SYNERGY did not reduce major cardiovascular events in a broad acute myocardial infarction population, highlighting the importance of clinical context and patient selection.[33,41]

Future anti-inflammatory strategies could focus on the NLRP3 inflammasome, the interleukin-6 pathway, residual inflammatory risk measured by hs-CRP, or imaging-defined coronary inflammation. However, anti-inflammatory therapy has to be balanced against cardiovascular benefit, infection risk, tolerability, drug interactions, and cost.

In Indonesia, a cheap and widely available drug such as colchicine is attractive. However, implementation should be guided by guideline-based indications, careful patient selection, assessment of renal function, and attention to gastrointestinal intolerance and drug interactions. In the absence of compelling cost-effectiveness data, broader implementation of expensive biologic anti-inflammatory agents may be difficult in Indonesia.

Antiplatelet therapy

Plaque disruption causes clinical events through thrombosis. Antiplatelet therapy is still crucial after ACS and PCI, whereas some high-risk patients with chronic coronary disease could benefit from intensified antithrombotic strategies. However, antithrombotic intensification increases bleeding risk and does not directly stabilize plaque architecture. Future precision prevention will combine plaque burden, thrombotic risk, inflammatory markers, and bleeding risk to personalize antithrombotic therapy. A summary of current and emerging pharmacological strategies for plaque stabilization is presented in Table 2.

Table 2. Future pharmacological strategies for high-risk plaque stabilization.

Therapeutic strategy	Primary mechanism	Current evidence	Main limitations	Clinical implication
High-intensity statins	LDL-C reduction	Established	Residual risk persists	Foundation therapy
Ezetimibe	Additional LDL-C reduction	Established	Moderate incremental efficacy	Early combination
PCSK9 inhibitors	Profound LDL-C lowering	Established in very-high-risk patients	Cost/access	Residual lipid risk
Inclisiran	PCSK9 synthesis inhibition	Outcome evidence evolving	Long-term data evolving	Adherence-enhancing option
Lp(a)-lowering therapy	Lp(a) reduction	Investigational	Outcome trials ongoing	Future precision therapy
Colchicine	Anti-inflammatory	Selected CAD evidence	Variable tolerability	Residual inflammatory risk
IL-1β/IL-6/NLRP3	Targeted inflammation	Emerging	Cost/availability	Future therapy
Antithrombotic intensification	Reduce thrombosis	Established in selected patients	Bleeding risk	Individualised therapy

This table summarises current and emerging pharmacological strategies aimed at reducing plaque vulnerability through modification of lipid burden, vascular inflammation, thrombosis, and other residual cardiovascular risk pathways. Contemporary management should prioritize aggressive systemic prevention, with intensive lipid-lowering therapy remaining the foundation of treatment. Novel therapies targeting Lp(a), inflammatory pathways, and thrombosis may further individualize treatment in selected patients, although several approaches remain investigational and should be implemented according to evolving clinical evidence, cost-effectiveness, and local healthcare resources.

Antiplatelet requirements are particularly important for preventive PCI. Treating non-flow-limiting plaques with a device exposes patients to Dual Antiplatelet Therapy (DAPT) and potential bleeding. Thus, device platforms that enable shorter DAPT without compromising safety may become attractive, particularly in patients at high bleeding risk.

Preventive PCI: Promise, Limitations and Future Indications

Preventive PCI aims to seal or passivate vulnerable plaques before they rupture or erode, leading to ACS. The biological rationale is plausible. Stenting or scaffolding of a high-risk plaque may lead to the formation of a neointimal layer, sequestration of thrombogenic lipid core material from contact with the bloodstream, normalization of local wall stress, and enlargement of the lumen. The clinical question is whether this focal approach adds any meaningful benefit beyond OMT. Importantly, preventive PCI should be viewed as a focal mechanical strategy directed at carefully selected lesions, whereas high-risk coronary disease is often diffuse, dynamic, and biologically heterogeneous. Therefore, preventive PCI cannot substitute for systemic prevention and should be considered only when local plaque risk, patient-level vulnerability, and procedural feasibility converge. Moreover, because coronary atherosclerosis is fundamentally a diffuse systemic disease, coronary events frequently arise from multiple biologically active plaques distributed throughout the coronary tree. Consequently, successful treatment of a single high-risk plaque does not eliminate the patient's ongoing residual cardiovascular risk, underscoring why aggressive OMT and comprehensive risk-factor control must remain the cornerstone of management.

Early randomized evidence came from the PROSPECT ABSORB trial, which demonstrated that PCI of angiographically mild lesions with large plaque burden was feasible and could increase minimum lumen area, but was not powered to assess clinical events.[42] The PREVENT trial subsequently randomized patients with non-flow-limiting vulnerable plaques to preventive PCI plus OMT versus OMT alone. The trial showed a significant reduction in target vessel failure at 2 years and sustained benefit at longer follow-up.[11]

These results are important, but there are several issues which demand careful interpretation. PREVENT included selected patients, used intravascular imaging-defined criteria and was performed in experienced centers. The primary

composite endpoint included ischemia-driven revascularisation and hospitalization for unstable or progressive angina. The absolute rate of events was rather low, and the size of benefit for hard endpoints such as cardiovascular death or myocardial infarction needs further confirmation.

Importantly, the relative benefit demonstrated in PREVENT should not obscure the fact that the absolute risk of future events arising from any individual imaging-defined high-risk plaque remains relatively low. Consequently, the clinical value of preventive PCI depends less on plaque detection itself than on identifying patients with a sufficiently high absolute cardiovascular risk in whom the expected reduction in myocardial infarction or other clinically meaningful events outweighs procedural risk, prolonged DAPT, and healthcare resource utilization. This distinction reinforces the concept that preventive PCI should be regarded as a strategy for carefully selected high-risk patients rather than for imaging-positive plaques in general.

The future role of preventive PCI, therefore, should be selective rather than universal. Potential candidates may include patients with documented CAD and focal non-flow-limiting lesions with multiple high-risk imaging features, large plaque burden, recurrent events despite optimal therapy, diabetes, multivessel disease, or high-risk proximal coronary segments. Preventive PCI should not be performed solely because plaque appears lipid-rich or because advanced imaging is available.

In Indonesia, preventive PCI should initially be restricted to centers with expertise in intracoronary imaging, high procedural volume, established PCI quality metrics, and the capacity to participate in national registries. This cautious approach would protect patients, preserve resources, and generate local evidence.

Choice of Device for Preventive PCI

Drug-Eluting Stents

Current DES represent the most established device platform for PCI. They deliver well, have low restenosis rates, better polymer biocompatibility, thin struts, and a wealth of outcome data. If preventive PCI is performed today, the new-generation DES will likely remain the default device.

Conceptually, preventive PCI differs fundamentally from conventional PCI. In obstructive coronary lesions, permanent metallic stenting is justified because it relieves myocardial ischemia and prevents acute vessel closure. In contrast, in non-flow-limiting high-risk plaques, the anticipated benefit is preventive and probabilistic rather than immediate. Consequently, concerns have been raised regarding overtreatment, late stent failure, neoatherosclerosis, prolonged DAPT, and cumulative device burden, particularly in patients with diffuse CAD, where a permanent metallic implant may be placed in a lesion that might never have progressed to a clinical event. Therefore, despite stronger evidence for DES at present, it might not be the ideal long-term platform for preventive plaque sealing.

Bioresorbable vascular scaffold

Bioresorbable Vascular Scaffolds (BVS) are conceptually attractive for the treatment of vulnerable plaque, as they can potentially provide temporary plaque sealing and mechanical support without the implantation of a permanent metallic device. However, the first-generation Absorb scaffold was limited by thick struts, a challenging implantation technique, increased scaffold thrombosis, and unfavorable safety signals compared with contemporary DES.[43] This experience appropriately tempered enthusiasm.

But the failure of first-generation devices does not invalidate the larger idea. Development of new-generation bioresorbable scaffolds should focus on thinner struts, improved radial strength, enhanced deliverability, optimized degradation kinetics, and alternative materials such as magnesium alloys or improved polymer platforms. Magnesium-based scaffolds and newer polymeric scaffolds with reduced risk of thrombosis and preservation of temporary plaque passivation are potential future candidates.

From an expert-consensus perspective, an optimal scaffold for preventive PCI would ideally seal the plaque, promote neocap formation, minimize inflammation, preserve vessel physiology, resorb predictably, and preserve future surgical or percutaneous options. Whether new-generation BVS can achieve this balance remains an open question. Their role should be investigational until large randomized data show safety and clinical benefit in vulnerable plaque populations.

Drug-Coated Balloons

Another interesting future direction is DCB. The theoretical appeal is significant: deliver antiproliferative therapy without permanent implantation. In the management of vulnerable plaque, DCB could potentially modify the plaque surface, reduce neointimal proliferation after lesion

preparation, and avoid the need for a permanent metal or scaffold. Shorter DAPT requirements may also be appealing.

However, the present evidence base for DCB in de novo vulnerable plaques is minimal. Adequate lesion preparation is generally required for DCB therapy and is best established in in-stent restenosis and selected small-vessel de novo disease. Without a scaffold, treatment of lipid-rich vulnerable plaques may not reliably seal the fibrous cap or the lipid core. Aggressive lesion preparation can also theoretically injure a non-flow-limiting plaque and increase procedural risk.

Thus, DCB should be regarded as a hypothesis-generating future technology, rather than a current strategy for preventive plaque treatment. Research should elucidate whether DCB alone, DCB after mild plaque modification, or hybrid DCB-bioresorbable strategies can safely stabilize vulnerable plaques.

Is there a role for CABG?

CABG does not directly treat vulnerable plaques. It does not seal thin fibrous caps, reduce local inflammation, or modify plaque composition. Thus, CABG should not be considered a vulnerable plaque therapy at the lesion level.

However, CABG may have an indirect protective role in certain patients with diffuse multivessel disease. CABG may protect the myocardium from future events in proximal segments by bypassing long segments of plaque-bearing coronary arteries, especially when durable arterial grafts, such as the left internal mammary artery to the left anterior descending artery, are used. This may, in part, explain the prognostic advantage of CABG in selected patients with diabetes, complex multivessel disease, or left main CAD.

Table 3. Future revascularisation and device strategies for high-risk plaque management.

Strategy	Principal concept	Current evidence	Main limitations	Clinical implication
DES preventive PCI	Permanent plaque sealing	Supported by PREVENT	Permanent implant; overtreatment	Current default
1st-generation BVS	Temporary scaffold	Unfavourable vs DES	Thrombosis risk	Historical lesson
New-generation BVS	Temporary plaque passivation	Emerging	Need RCTs	Potential future platform
Drug-coated balloon	Drug delivery without implant	Limited for plaque	No mechanical sealing	Investigational
CABG	Bypass plaque-bearing segments	Established	Not lesion-specific	Diffuse disease strategy

This table summarises the current evidence and future perspectives regarding revascularisation strategies and device platforms for imaging-defined high-risk coronary plaque. Contemporary DES represent the most established platform when preventive PCI is considered, whereas new-generation BVS and DCB remain investigational approaches requiring further clinical validation. CABG should be regarded as a patient-level revascularisation strategy for diffuse or complex CAD rather than as a lesion-level therapy for vulnerable plaque.

Within the vulnerable plaque framework, CABG should be considered at the patient-phenotype level, not the plaque level, in the future. Patients with diffuse high-risk atherosclerosis, diabetes, complex anatomy, impaired ventricular function, or high SYNTAX score may benefit more from surgical revascularisation than from repeated focal PCI of multiple non-flow-limiting plaques. This underscores the importance of multidisciplinary Heart Team decision-making. The potential roles, advantages, limitations, and future directions of preventive revascularisation strategies are summarised in Table 3.

Resource-Aware Implementation in Indonesia

A different strategy is required for the Indonesian context. Advanced plaque imaging and preventive PCI may benefit selected patients, but indiscriminate use may increase costs without commensurate population-level benefit. A national approach should rest on five principles: optimization of systemic prevention, clinical selectivity, economic responsibility, local data generation, and workforce readiness. In Indonesia, adoption of the high-risk plaque concept should not imply indiscriminate expansion of advanced imaging or preventive PCI.

Rather, the Vergallo framework should be adapted as a risk-stratification concept to identify which patients may benefit most from intensified medical therapy, selective imaging, registry enrolment, or highly selected focal intervention.

First, OMT needs improvement. Indonesia should focus on improving access to high-intensity statins, adherence programs, smoking cessation, hypertension control, management of diabetes, cardiac rehabilitation, and secondary prevention post-ACS. These are scalable interventions and are likely to have the greatest benefit to society.

Second, advanced imaging should be used judiciously. CCTA may be the most scalable non-invasive platform for risk stratification, whereas IVUS and OCT should be concentrated in tertiary centers and reserved for patients in whom imaging results will alter management. Given current infrastructure and resource constraints, routine intracoronary imaging of all angiographic lesions may be difficult to justify outside selected clinical scenarios, registries, or research programs.[13-14]

Third, preventive PCI should be introduced as part of structured programs rather than through unregulated expansion. Candidate lesions should ideally meet the rigorous criteria used in randomized trials: non-flow-limiting physiology, significant plaque burden, multiple imaging-defined high-risk features, and a patient-level high-risk phenotype. Procedures should be performed by trained operators using optimized, imaging-guided PCI techniques.

Fourth, Indonesia needs country data. A national high-risk plaque registry should capture patient characteristics, imaging findings, treatments, devices, procedural details, medications, costs, and long-term clinical outcomes. Without local data, policy decisions will be based entirely on extrapolation from elsewhere.

Finally, human-resource development is essential. Technology without adequate expertise may expose patients to avoidable harm. Standardized training in OCT, IVUS, CCTA plaque interpretation, physiological assessment, and preventive PCI decision-making should be implemented. Imaging core laboratories and competency-based certification may help to reduce variability and improve quality. From a health-system perspective, indiscriminate plaque detection may increase procedural volume without proportionate clinical benefit. Therefore, the principal objective of advanced imaging should be to improve patient selection rather than to maximize plaque detection.

Proposed Algorithm for the Future

An Indonesian algorithm may pragmatically start with patient-level risk assessment, not plaque hunting. All patients with established CAD should be treated with optimized medical therapy. Further risk stratification may be considered in patients with recurrent events, diabetes, multivessel disease, premature coronary disease, or extensive plaque burden on non-invasive imaging. CCTA can detect the diffuse high-risk plaque phenotype. Invasive imaging may then be considered if the result will influence the choice of treatment. Preventive PCI may be considered for focal lesions with non-flow-limiting physiology but multiple high-risk features in patients at high absolute risk. Diffuse multivessel high-risk anatomy may warrant consideration of CABG, as surgical revascularisation may provide wider myocardial protection.

This stepwise approach is intended to align technological innovation with healthcare sustainability. The proposed diagnostic pathway for high-risk coronary plaque assessment in Indonesia is illustrated in Figure 2. The proposed algorithm deliberately begins with patient-level risk assessment rather than plaque identification, reflecting the principle that patient selection is more important than plaque detection alone.

ISIC Position Statement

The ISIC recognizes and adopts the contemporary transition from the traditional vulnerable plaque paradigm to the broader concept of high-risk plaque, as emphasized in the 2025 JACC Cardiovascular Imaging Position Statement by Vergallo and colleagues. Coronary thrombosis may arise from rupture-prone plaques, erosion-prone plaques, or eruptive calcified nodules. Therefore, risk assessment should integrate plaque morphology, plaque burden, inflammatory activity, endothelial injury, healing capacity, local hemodynamic conditions, myocardial territory at risk, and patient-level vulnerability. The proposed ISIC adaptation of major and minor high-risk plaque features is presented in Table 4. The ISIC also recognizes that advances in intracoronary imaging have substantially improved contemporary understanding of coronary plaque biology and vulnerability. Imaging-defined high-risk plaque characteristics are associated with increased future cardiovascular risk and provide prognostic information beyond angiographic stenosis severity alone.

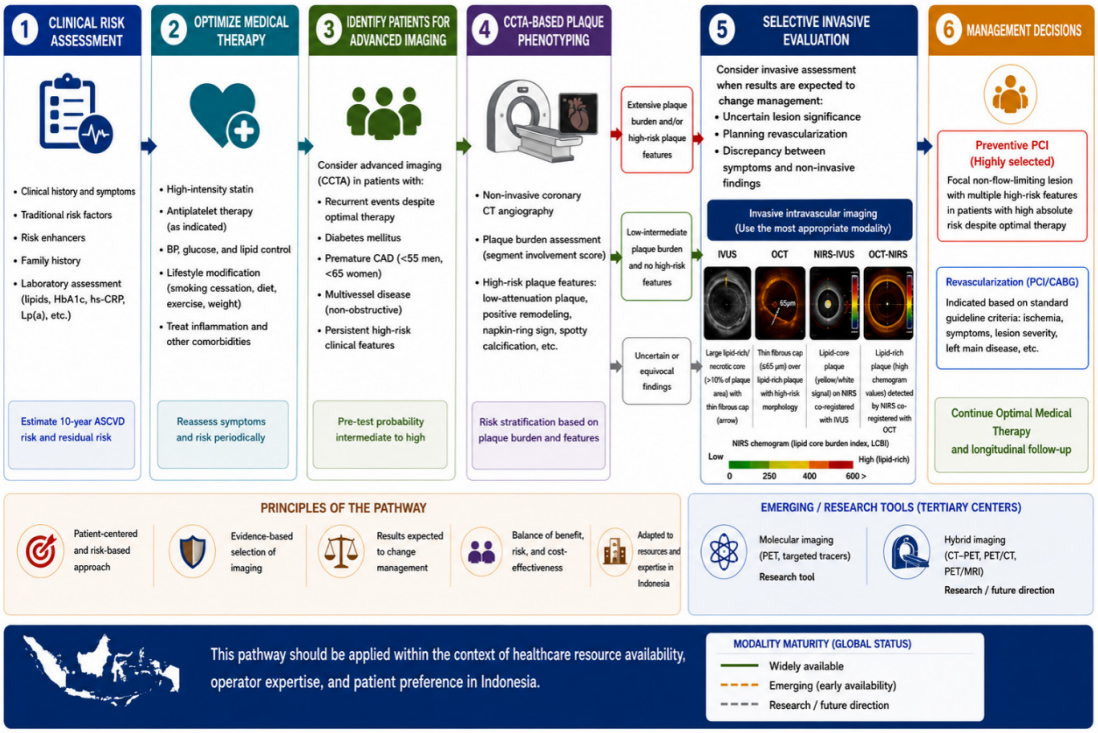

Figure 2. Proposed diagnostic pathway for high-risk coronary plaque assessment in Indonesia. This figure presents a stepwise diagnostic pathway beginning with clinical risk assessment and optimization of medical therapy. Patients with recurrent events, diabetes, premature CAD, multivessel disease, or persistent high-risk clinical features may undergo CCTA-based plaque phenotyping, followed by selective invasive evaluation with IVUS, OCT, or NIRS-IVUS when the findings are expected to change management. Preventive PCI is considered only for focal non-flow-limiting lesions with multiple high-risk plaque features in patients with high absolute clinical risk. The pathway should be interpreted as a resource-aware clinical framework rather than a mandate for routine plaque screening.

Table 4. Proposed ISIC adaptation of high-risk plaque features.

Domain	Representative features	Clinical implication	Role in patient selection
Plaque morphology	Thin cap, lipid core, plaque burden	Higher lesion vulnerability	Lesion-level risk
Plaque biology	Inflammation, endothelial injury	Active disease	Biological risk
Biomarkers	LDL-C, ApoB, Lp(a), hsCRP	Residual risk	Patient-level risk
Clinical modifiers	Diabetes, CKD, recurrent ACS	Higher absolute risk	Patient selection
ISIC interpretation	Integrated assessment	No single feature sufficient	Individualised decisions

This table presents the proposed ISIC framework for integrating plaque morphology, biological activity, systemic biomarkers, and clinical characteristics of assessing high-risk coronary plaque. The proposed classification is intended to facilitate comprehensive risk stratification rather than provide automatic indications for preventive PCI. Decisions regarding treatment escalation should integrate plaque characteristics with patient-level vulnerability, expected absolute cardiovascular risk, procedural feasibility, anticipated clinical benefit, and healthcare resource considerations.

The ISIC supports the use of major and minor high-risk plaque features as a conceptual framework for risk stratification. However, in the Indonesian context, these features should not be interpreted as automatic indications for preventive PCI. Instead, they should be used to guide the intensification of OMT, the selective use of advanced imaging, structured follow-up, and carefully selected interventions in experienced centers.

However, current evidence remains insufficient to support routine preventive PCI for all non-flow-limiting imaging-defined vulnerable plaques. Most vulnerable plaques do not subsequently rupture or produce clinical events, and coronary atherosclerosis fundamentally represents a diffuse systemic disease process requiring comprehensive systemic preventive therapy.

Aggressive OMT, therefore, remains the foundation of management for patients with high-risk coronary plaque. Intensive lipid lowering, anti-inflammatory therapy, smoking cessation, glycaemic control, blood pressure optimization, and lifestyle modification should remain central therapeutic priorities. Assessment of residual lipid, inflammatory, metabolic, and renal risk should complement plaque imaging and guide the intensity of systemic prevention.

Advanced intracoronary imaging using OCT, IVUS, NIRS, or hybrid imaging approaches may be considered in selected patients to further characterize plaque morphology, plaque burden, and biological plaque activity, particularly in complex coronary disease or in patients with high residual cardiovascular risk.

Preventive PCI may be considered selectively in carefully selected patients with multiple converging high-risk plaque features, particularly when supported by advanced intracoronary imaging and performed at experienced centers with expertise in imaging-guided PCI. Key ISIC considerations regarding the use of preventive PCI are summarised in Table 5.

Routine preventive PCI for all imaging-positive plaques is not currently recommended. Decisions regarding preventive PCI should integrate plaque morphology, patient-level vulnerability, ischaemic burden, procedural feasibility, bleeding risk, anticipated exposure to DAPT, and healthcare resource considerations.

The ISIC additionally recognizes the importance of ongoing clinical trials and future technological advances, including OCT-NIRS integration, AI-assisted plaque analysis, computational hemodynamic modeling, and biological imaging approaches, which may further refine future preventive strategies.

Accordingly, the ISIC supports a cautious, evidence-based, imaging-guided, and highly selective approach to preventive PCI, pending further evidence on hard clinical outcomes, long-term safety, cost-effectiveness, and optimal patient selection. For clarity, the key ISIC position statements are summarised in Table 6.

Table 5. Proposed ISIC considerations for preventive PCI.

Clinical scenario	Recommendation	Principal rationale	Clinical implication
Optimal medical therapy	Mandatory	Foundation of care	All patients
TCFA alone	Not sufficient	Low absolute event rate	Do not PCI on morphology alone
Multiple high-risk features	Consider	Higher event probability	Individualised selection
Diabetes/residual risk	Consider	Higher absolute risk	Integrate imaging
Diffuse disease	Prioritise systemic therapy	Competing plaques	Avoid focal-only strategy
Routine PCI for all imaging-positive plaques	Not recommended	Insufficient evidence	Avoid overtreatment

This table summarises the practical considerations proposed by the Indonesian Society of Interventional Cardiology (ISIC) regarding preventive PCI. The recommendations emphasize that aggressive OMT remains mandatory first-line treatment and that preventive PCI should be reserved for carefully selected patients in whom multiple plaque-related and patient-level risk factors converge. These considerations are intended to support clinical judgment rather than replace individualized multidisciplinary decision-making.

Table 6. Key ISIC position statements on high-risk coronary plaque and selective preventive PCI.

Key recommendation	Supporting concept	Strength	Clinical implication
Integrated high-risk coronary phenotype	Beyond vulnerable plaque	Core	Precision prevention
Integrate plaque + patient biology	Multidimensional risk	Core	Comprehensive assessment
OMT cornerstone	Systemic disease	Strong	Mandatory first-line
Selective CCTA	Gatekeeper	Conditional	Patient selection
Selective IVUS/OCT/NIRS	Change management	Conditional	Complementary imaging
Selective preventive PCI	High absolute risk	Conditional	Carefully selected patients
No routine PCI for all imaging-positive plaques	Avoid overtreatment	Not recommended	Evidence insufficient
DES current standard	Technology evolving	Current evidence	Individualised device
Resource-aware implementation	Indonesian context	Priority	Sustainable adoption

This table summarises the principal recommendations of the Indonesian Society of Interventional Cardiology (ISIC) regarding the contemporary management of high-risk coronary plaque. These position statements reflect the current balance of available evidence and emphasize that OMT remains the cornerstone of management, whereas advanced coronary imaging and preventive PCI should be applied selectively in carefully chosen patients. The recommendations are expected to evolve as further evidence emerges from ongoing clinical trials, technological innovation, and future studies evaluating long-term clinical outcomes and cost-effectiveness.

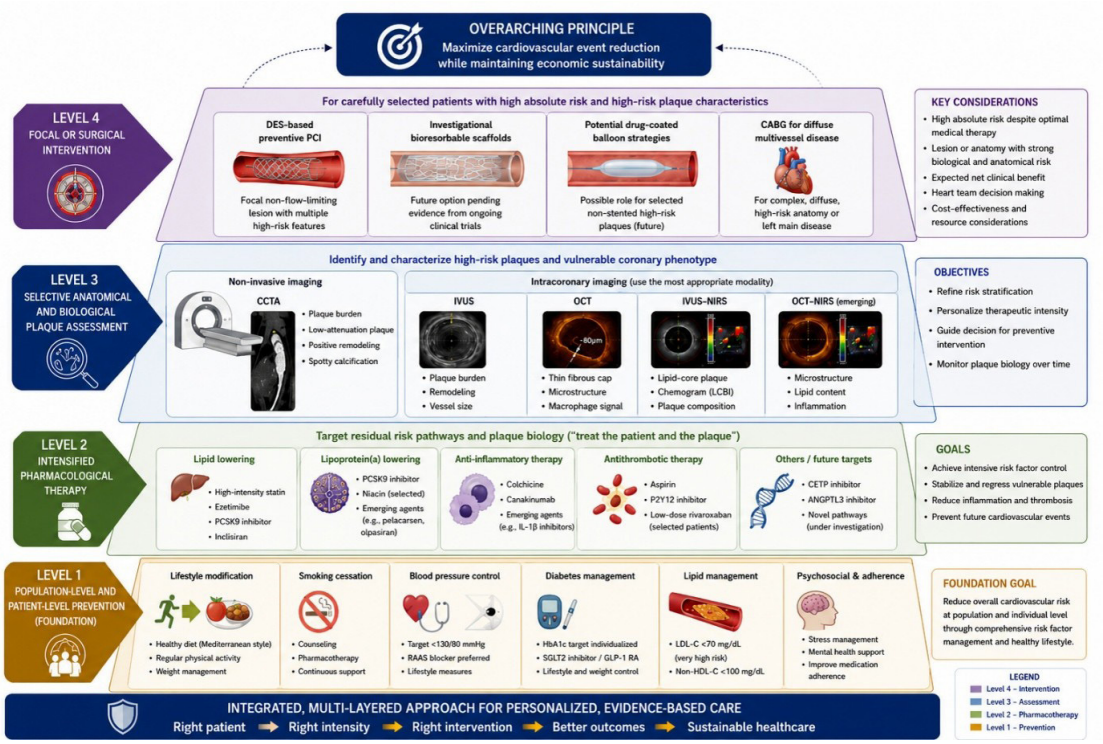

Figure 3. Future therapeutic framework for high-risk coronary plaque management.
This figure illustrates a layered therapeutic framework for high-risk coronary plaque management. The foundation is population-level and patient-level prevention, including lifestyle intervention, smoking cessation, blood pressure control, diabetes management, lipid lowering, and psychosocial risk reduction. Subsequent layers include intensified pharmacological therapy, selective anatomical and biological plaque assessment, and focal or surgical intervention in carefully selected patients. The framework emphasises that OMT remains the foundation of care, while preventive PCI and other revascularisation strategies should complement, not replace, systemic prevention.

Conclusion

The future of coronary vulnerable and high-risk plaque management should focus not merely on detecting vulnerable lesions, but on identifying high-risk plaques, high-risk patients, and high-risk coronary phenotypes in whom additional diagnostic or therapeutic escalation is likely to improve clinical outcomes.

Consistent with the ISIC position statement, OMT remains the foundation of management for patients with high-risk coronary plaque. Advanced imaging modalities, including CCTA, IVUS, OCT, NIRS, and emerging hybrid technologies, may improve risk stratification and guide individualized treatment in selected patients. Preventive PCI remains a promising but highly selective strategy and should not be routinely applied to all imaging-defined vulnerable plaques pending further evidence. The overall future therapeutic framework integrating prevention, imaging, pharmacological therapy, and selective intervention is illustrated in Figure 3.

The ISIC recognizes that the framework proposed by Vergallo and colleagues provides an important conceptual advance. Nevertheless, in Indonesia and other resource-limited healthcare systems, this framework must be implemented pragmatically. The priority should remain aggressive, affordable, and scalable systemic prevention, while advanced imaging and preventive PCI should be reserved for patients in whom the expected absolute benefit justifies procedural risk and resource use.

For Indonesia, future implementation should be pragmatic, evidence-based, and resource-conscious, balancing technological innovation with healthcare sustainability while maximizing cardiovascular risk reduction at both the patient and population levels.

In the view of ISIC, the future value of precision prevention will depend less on detecting an increasing number of high-risk plaques and more on identifying patients in whom additional intervention meaningfully reduces myocardial infarction and cardiovascular death. Patient selection therefore remains more important than plaque detection alone.

List of Abbreviations

ACS	Acute Coronary Syndrome
AI	Artificial Intelligence
Apo B	Apolipoprotein B
BVS	Bioresorbable Vascular Scaffold
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCTA	Coronary Computed Tomography Angiography
CKD	Chronic Kidney Disease
DAPT	Dual Antiplatelet Therapy
DCB	Drug-Coated Balloon
DES	Drug-Eluting Stent
HbA1c	glycated hemoglobin
hs-CRP	high-sensitivity C-Reactive Protein
ISIC	Indonesian Society of Interventional Cardiology
IVUS	Intravascular Ultrasound
LDL-C,	Low-Density Lipoprotein Cholesterol
Lp(a)	Lipoprotein(a)
maxLCBI4mm,	maximum lipid-core burden index within any 4-mm segment
NIRS	Near-Infrared Spectroscopy
OCT	Optical Coherence Tomography
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
RCT	Randomized Controlled Trials
TCFA	Thin-Cap Fibroatheroma.

Ethical Clearance

Not applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

All authors contributed to the conception, drafting, and revision of the article, provided final approval for publication, agreed on the journal, and took accountability for all aspects of work.

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Review Article

Aerobic Exercise Only or in Combination with Resistance Exercise Provides a Significant Reduction in Blood Pressure: A Narrative Review

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Abstract

Hypertension is a major global health concern and a leading risk factor for cardiovascular disease. While pharmacological therapy remains central, lifestyle interventions, particularly Aerobic Exercise (AE), offer a cost-effective, safe, and sustainable strategy for reducing Blood Pressure (BP) and improving cardiovascular health. Evidence indicates AE consistently lowers Systolic Blood Pressure (SBP) more than Diastolic Blood Pressure (DBP), with clinically meaningful reductions in both. This review aimed to synthesize current evidence on the effects of AE, alone or combined with Resistance Training (RT) or dietary interventions, on BP in individuals with hypertension, elucidate underlying mechanisms, identify moderating factors, and evaluate safety considerations. A narrative review of English-language articles published from 2015 to 2025 was conducted via PubMed, including original and review studies, as well as selected textbooks. Keywords included "aerobic exercise", "exercise", "hypertension", "blood pressure", "coronary artery disease", and "cardiovascular disease". Eligible studies were synthesized into themes reflecting acute and chronic exercise responses, combination interventions, mechanistic pathways, influencing factors, and safety. Thirty-four publications (26 original articles, 6 reviews, 2 textbooks) were included. AE alone or combined with RT consistently reduced SBP, with smaller reductions in DBP, whereas the combination with a hypocaloric diet primarily enhanced cardiorespiratory fitness and body composition. Mechanisms include improved endothelial function, autonomic regulation, metabolic efficiency, and anti-inflammatory effects. Effect size was influenced by age, sex, Body Mass Index (BMI), medication use, exercise timing, and vascular stiffness. Safety data indicated high tolerability, minimal adverse events, and strong adherence. AE is a safe and effective non-pharmacological intervention for hypertension, producing clinically significant BP reductions, particularly in SBP. Combining AE with RT or dietary modification offers additional cardiometabolic benefits. These findings reinforce AE as a cornerstone of hypertension management and support its integration into routine clinical practice.

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Introduction

Hypertension is a leading global health problem and a major risk factor for Cardiovascular Diseases (CVD), affecting more than one billion adults worldwide.[1] Its high prevalence, combined with the associated risk of stroke, myocardial infarction, heart failure, and chronic kidney disease, makes hypertension a central focus of preventive and therapeutic strategies in modern medicine. While pharmacological therapy remains a cornerstone of hypertension management, it is often accompanied by side effects and long-term adherence challenges. Therefore, current international guidelines strongly emphasize the integration of non-pharmacological interventions, particularly lifestyle modifications, alongside pharmacological treatment.[2-4]

Among lifestyle interventions, regular physical exercise has been widely recognized as a cost-effective and sustainable strategy for reducing Blood Pressure (BP) and improving cardiovascular health. Aerobic Exercise (AE), in particular, has been identified as one of the most effective modalities in the prevention and treatment of CVD, including Coronary Artery Disease (CAD), hypertension, and type 2 Diabetes Mellitus (DM).[5-7] Substantial evidence indicates that AE contributes to significant reductions in both Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), with consistent improvements observed across diverse populations and age groups.[8] Epidemiological studies have indicated that a reduction of just 2 mmHg in SBP is associated with a 6% decrease in stroke mortality and a 4% decrease in CAD mortality. In contrast, a 5 mmHg reduction corresponds to approximately 14% and 9% lower risks of these conditions, respectively.[9]

Professional organizations have published exercise guidelines recommending AE at moderate intensity for at least 30 minutes per day, five days per week, or at higher intensity for at least 20 minutes per day, three times per week.[10] However, the magnitude of the antihypertensive response may vary depending on exercise intensity, frequency, and duration.[11] Moreover, factors such as baseline BP levels, comorbidities, and adherence also play important roles in determining the effectiveness of exercise.[10,12]

Given the clinical importance of AE, further discussion is warranted to clarify its role in the comprehensive management of hypertension. This narrative review aimed to provide an overview of AE in hypertensive patients, focusing on the acute and chronic responses of AE, evidence on the effects of AE alone or in combination with other exercises or interventions on BP, the mechanistic links between AE and BP reduction, and safety issues in the implementation of AE in hypertension management. Such an overview is essential to support clinicians in optimizing exercise prescriptions as part of an integrated strategy to combat hypertension and reduce the global burden of CVD.

Methods

This narrative review synthesized current evidence on the effects of AE, either alone or in combination with Resistance Training (RT), on BP in individuals with hypertension and CVD. A comprehensive literature search was conducted in PubMed, chosen for its wide biomedical coverage, using the following keywords: *"aerobic exercise"* or *"aerobic training"*, *"exercise"* or *"training"*, *"hypertension"* or *"hypertensive"*, and *"blood pressure"*. The search was limited to English-language articles published between 2015 and 2025. Both original and review articles were eligible, provided the full text was available to ensure data quality. In addition, textbooks and earlier seminal references were considered when particularly relevant to the topic. All retrieved publications were screened for relevance, and those meeting the inclusion criteria were synthesized narratively, with emerging themes identified.

Results

A total of 34 references were included in this review, consisting of 26 original articles, 6 review articles, and 2 standard textbooks. The evidence was synthesized into six main themes. First, studies addressing acute and chronic responses to AE demonstrated consistent distinctions between transient hemodynamic changes and long-term adaptations in cardiovascular and metabolic function. Second, evidence on the effects of AE alone and in combination with RT, derived from 11 original studies across diverse populations, showed a robust reduction in SBP, with smaller effects on DBP. Variability in outcomes was linked to exercise timing and training modality. Third, in examining AE combined with a hypocaloric diet, one original and one review article indicated that diet was the dominant factor in lowering blood pressure. At the same time, AE contributed mainly to improvements in Cardiorespiratory Fitness (CRF) and body composition. Fourth, mechanistic studies consistently highlighted improved endothelial

function, autonomic regulation, metabolic efficiency, and anti-inflammatory effects as key pathways underlying the antihypertensive benefits of AE. Fifth, factors influencing the magnitude of BP reduction included age, sex, Body Mass Index (BMI), antihypertensive medication use, and vascular stiffness. These moderators were reported across both original and review articles. Finally, six trials demonstrated that AE, alone or in combination with RT, is safe and well-tolerated, with no serious cardiovascular events and high adherence rates. Overall, the evidence supports AE as an effective and safe intervention for lowering BP, with additional benefits when combined with RT or dietary modification.

Discussion

Acute and Chronic Responses to AE in Hypertension

AE, also known as cardiorespiratory endurance training, involves repetitive movements of large muscle groups, accompanied by cardiovascular and respiratory adaptations that support sustained physical activity without premature fatigue. This type of exercise is specifically designed to enhance CRF and highlight the essential role of oxygen in energy metabolism.[10,13]

AE acutely increases cardiac workload by elevating Stroke Volume (SV) and Heart Rate (HR), thereby augmenting Cardiac Output (CO). This is accompanied by a transient rise in Systemic Vascular Resistance (SVR), which increases Mean Arterial Pressure (MAP). In contrast, chronic regular exercise leads to reductions in resting BP.[13-14]

Regular AE induces a range of physiological adaptations across multiple systems. In terms of BP, resting BP generally remains unchanged in normotensive individuals, but a slight reduction is often observed in hypertensive individuals. Regarding blood volume and blood lipids, total blood volume increases following regular training. Muscle glycogen storage is enhanced on a biochemical level, supporting improved energy availability during exercise. However, the relative proportion of fast-twitch and slow-twitch fibers does not significantly change, although the cross-sectional area occupied by these fibers may be altered depending on training stimuli. From the energy system perspective, exercise training promotes several key adaptations. Anaerobic glycolysis capacity increases, along with muscle glycogen storage and enzyme activity. Maximal oxygen uptake (VO_2max) improves, reflecting enhanced aerobic capacity. In addition, the use of triglycerides as an energy source increases, along with an increased metabolic rate of both fats and carbohydrates.[13]

Exercise is recognized as a cornerstone in the prevention and management of hypertension. In general, regular physical activity has been shown to prevent the development of hypertension in a clear dose-response manner. Each additional 10 Metabolic Equivalent (MET)-hours per week of physical activity is associated with a 6% reduction in the risk of developing hypertension. In individuals with established hypertension, exercise programs produce an average BP reduction of 5–8 mmHg; in those with prehypertension, 2–4 mmHg; and in normotensive individuals, 1–2 mmHg. Thus, the higher the baseline BP, the greater the magnitude of BP reduction achieved through physical activity.[15]

Aerobic, Resistance, and Combined Exercises Prescription

The studies analyzed used a variety of AE methods, but most employed structured, measured moderate-intensity activities. Methods used included treadmill walking, cycling on a cycle ergometer, brisk walking outdoors, jogging, swimming, and video-based aerobic dance. Exercise intensity was generally defined using a percentage of heart rate, either maximum Heart Rate (HRmax) or Heart Rate Reserve (HRR), or aerobic capacity such as VO_2max/VO_2peak, with the most common intensity ranges being 50–75% HRR, 60–75% HRmax, or Rating of Perceived Exertion (RPE) 12–14 (Table 1). One study employed specific-intensity methods, such as adjusting stride frequency with a metronome or using VO_2-peak-based intervals in High-Intensity Interval Training (HIIT) protocols.[16-17] The majority of protocols were continuous moderate-intensity training, while a small number employed HIIT or variations such as dance aerobics. Exercise supervision varies from fully structured and supervised to independent practice without formal supervision.[18]

The exercise duration in these studies ranged from 8 to 16 weeks, with most programs lasting 12 weeks. The typical training frequency was 2–3 times/week, but some studies recommended up to 3–5 times/week. Each session lasted 20-60 minutes, and most studies employed a training structure consisting of a 5–10-minute warm-up, a 20–45-minute core exercise phase, and a 5–10-minute cool-down (Table 1). Some studies employed a measured progression in both duration and intensity, such as increasing duration from 20 to 40 minutes and increasing intensity from 50% to

70% of VO_2max or gradually increasing HRR from 40% to 70%.[19-20] However, some other protocols maintained moderate intensity without systematic progression. Overall, the AE protocols used show considerable variation but remain consistent with the basic principles of AE: moderate-intensity exercise, gradual duration, and regular frequency to achieve optimal cardiovascular adaptation.

In addition to AE, several studies provided detailed descriptions of the RT and their integration within combined aerobic–resistance exercise programs. The types of RT varied across trials but were generally structured, machine-based, and targeted major muscle groups. One study implemented one of the most comprehensive RT protocols, consisting of 12 multi-joint and single-joint machine exercises (e.g., chest press, seated row, leg press, quadriceps extension), performed initially as 2 sets of 18–20 maximal repetitions and progressed to 3 sets of 10–14 repetitions taken to volitional exhaustion, with all loads automatically monitored through the TechnoGym digital system.[20] Another study also employed machine-based RT involving 6 core movements (leg press, bench press, knee extension, biceps direct threading, knee flexion, and low row) using 4 sets of 8–12 repetitions at 60–80% 1-Repetition Maximum (RM).[21] Meanwhile, one study used 6 resistance exercises performed for 2 sets of 10 repetitions at 60% 1-RM, with 1-RM directly assessed via integrated machine ergometers, ensuring precision in load prescription.[22] Isometric RT represented a distinct modality, as demonstrated by a previous study that prescribed handgrip training at 30% Maximal Voluntary Contraction (MVC) for 2-minute bouts with 1-minute rest, performed 5 days per week using a calibrated digital device. Collectively, these findings demonstrate that RT interventions across studies used structured, measurable, and reproducible methods targeting strength adaptations relevant to cardiovascular health.[18]

Table 1. Summary of exercise protocols given in previous studies.

Author (Year)	Exercise Protocol

Ammar (2015).[23]	• Frequency: 3x/week for 12 weeks
	• Intensity:
	  ○ Warm-up or cool-down: 40% MHR (220-age)
	  ○ Main phase: Moderate intensity (60-75% of predicted MHR)
	  ○ MHR Formula: 210 – Age
	• Time: 30 minutes/session (5 minutes warm-up or cool-down, 20 minutes main aerobic phase)
	• Type: Treadmill walking
	• Progression: No progression applied.

Belozo et al. (2018).[25]	• Frequency: 3x/week (non-consecutive days, 48h rest) for 8 weeks • Intensity: Moderate intensity (70-80% of predicted MHR) • Time: 30 minutes per session • Type: Continuous treadmill walking • Progression: No progression applied.
Brito et al. (2019).[31]	Morning Training (MT) • Frequency: 3x/week • Intensity: Moderate intensity (50-70% of predicted maximal heart rate, or RPE 12-14) • Time: 45 minutes per session (including 5 minutes warm-up and 5 minutes cool-down) • Type: continuous aerobic walking/jogging • Training time of day: Morning sessions: 07.00-09.00 AM • Progression: Intensity maintained within moderate HR/RPE range. No progression applied. Evening Training (ET) • Frequency: 3x/week • Intensity: Moderate intensity (50-70% MHR or RPE 12-14) • Time: 45 minutes per session • Type: Continuous aerobic walking/ jogging • Training time of day: Evening sessions: 06.00-08.00 PM • Progression: HR monitored to keep moderate intensity. No progression applied.

Caminiti et al. (2021).[22]	• Frequency: 3x/week • Intensity: Moderate intensity (RPE 13-14) • Time: 10 min warm-up or cool-down, 60 min aerobic treadmill walkin • Type: Treadmill walking • Progression: Intensity maintained at RPE 13-14. No structured progression applied.

Feairheller et al. (2014).[53]	• Frequency: 3x/week for 6 months
	• Intensity: Started at 50% Vo_2max
	• Time: Started at 20 min
	• Type: Supervised aerobic exercise
	• Progression:
	  ○ Duration progressed from 20 to 40 min
	  ○ Intensity progressed from 50% to 65% VO_2max

Gorostegi-Anduaga et al. (2018).[17]	MICT
	• Frequency: 2x/week for 16 weeks
	• Intensity: Moderate (65% VO_2peak)
	• Time: 45 min/session
	• Type: Treadmill or cycle ergometer
	• Progression: Intensity maintained
	High-Volume HIIT
	• Frequency: 2x/week
	• Intensity:
	  ○ Intervals at 90% VO_2peak
	  ○ Recovery at 65% VO_2peak
	• Time: 45min/session
	• Type: Treadmill + cycling
	• Progression: Progressive workload via HR-based adjustments, fixed interval structure
	Low-Volume HIIT
	• Frequency: 2x/week
	• Intensity:
	  ○ Intervals at 90% VO_2peak
	  ○ Recovery at 65% VO_2peak
	• Time: 20 min/session
	• Type: Treadmill + cycling
	• Progression: Progressive workload via HR-based adjustments, fixed interval structure

He et al. (2018).[16]	• Frequency: 3x/week for 12 weeks • Intensity: 45-50% VO_2max, controlled using step frequency (Metronome) • Time: 60 minutes/session • Type: Outdoor brisk walking • Progression: Step frequency adjusted based on predicted VO2max. Intensity remained moderate.

Li et al. (2024).[32]	• Frequency: 4x/week for 12 months (At least 1 supervised group session per week; 3 sessions using uploaded videos at home)
	• Intensity:
	  ○ Moderate intensity based on MHR (The target intensity was not specified as a percentage of MHR)
	  ○ MHR formula: 208 − (0.7 × age in years)
	• Time: 60 minutes (10 minutes warm-up or cool-down, 40 minutes core aerobic exercise)
	• Type: Stair climbing, jogging, brisk walking, or cycling
	• Progression: Intensity was adjusted using heart rate monitoring (maintained at moderate intensity)

Lopes et al. (2021).[19]	• Frequency: 3x/week for 12 weeks • Intensity: started at 50% of VO_2 max, RPE 11-14 • Time: initial duration 20 minutes/session (10 minutes warm-up or cool-down, 40 minutes core aerobic exercise) • Type: Outdoor brisk walking • Progression: Weekly progression based on tolerance. Alternating between +5 minutes added to exercise duration and +5% of VO_2 max added to exercise intensity. Progression continued until reaching 40 minutes at 70% VO_2 max.
Maruf et al. (2013).[24]	• Frequency: 3x/week for 12 weeks • Intensity: 50–70% of HRR • Time: 45 minutes/session (5 minutes warm-up or cool-down, 35 minutes core aerobic exercise) • Type: Aerobic dance exercise using a 45-minute exercise video • Progression: Both intensity and duration of the aerobic dance segments were progressively increased. Progression continued until reaching 45 minutes at 50–70% HRR.
Pedralli et al. (2020).[21]	• Frequency: 2x/week for 12 weeks • Intensity: 50–75% of HRR, RPE 11-14 • Time: 40 minutes/session • Type: Aerobic exercise using a cycle ergometer • Progression: Progressive intensity increased within the 50–75% HRR range.
Pagonas et al. (2017).[18]	• Frequency: 3-5x/week for 12 weeks • Intensity: Started at 40% of HRR • Time: 60 minutes/session • Type: Aerobic exercise (Walking, jogging, cycling, or swimming) • Progression: No progression applied.
Schroeder et al. (2019).[20]	• Frequency: 3x/week for 8 weeks • Intensity: RPE 12-13 • Time: 30 minutes/session • Type: Aerobic exercise using a treadmill or ergocycle • Progression: ○ Intensity progressively increased from 40% to 70% HRR ○ Allowed self-selected increases as long as HRR remained ≤80%.

ET, evening training; HIIT, high-intensity interval training; HR, heart rate; HRR, heart rate reserve; MHR, maximum heart rate; MICT, moderate-intensity continuous training; MT, morning training; RPE, rating of perceived exertion; VO2max, maximal oxygen uptake; VO2peak, peak oxygen uptake.

Combined AE and RT (CT) was also clearly described in several trials, with most studies integrating AE and RT within a single session. CT sessions consisted of 30 minutes of AE (treadmill or cycle ergometer) followed by 30 minutes of RT, using the same RT exercises and intensities as the RT-only group but with reduced volume (2 sets and only 8 exercises).[20] One previous study used a protocol in which participants performed 40 minutes of treadmill-based AE at an RPE of 13–14 before 20 minutes of RT, following the priority principle to perform AE first.[22] Another study applied a balanced CT approach, prescribing 20 minutes each of AE and RT per session, with RT performed at 60–80% 1-RM.[21] Across these studies, the RT component of CT programs was consistently machine-based, moderate-to-high intensity, and matched to the independent RT protocols. In contrast, aerobic components were performed at moderate intensities defined via HRR or RPE. This demonstrates that the combined interventions were systematically structured, with clearly delineated durations, intensities, and exercise sequences that adhered to established exercise prescription principles.

Evidence of The Effects of AE Alone and in Combination with RT

AE, whether performed alone or in combination with RT or other interventions such as a hypocaloric diet, has been consistently shown to reduce BP in individuals with hypertension (Table 1). The magnitude of the effect varies depending on population characteristics and clinical conditions. For instance, Ammar (2015, 2016) reported

that in overweight postmenopausal women with hypertension, AE combined with antihypertensive medication significantly reduced both SBP and DBP, with the greatest reductions observed in afternoon sessions (SBP −27 mmHg, DBP −15.4 mmHg), highlighting the potential influence of exercise timing on hemodynamic responses.[23]

Similar findings were observed in patients with resistant hypertension, where a 12-week AE program significantly lowered both SBP and DBP, particularly during daytime measurements, while improving CRF without altering body composition or metabolic profile.[19] Conversely, in patients with uncontrolled essential hypertension, AE did not significantly change mean SBP or DBP compared to controls; however, a greater proportion of participants in the exercise group achieved BP control.[24] In specific populations, such as obese individuals with type 2 DM, continuous AE did not produce statistically significant reductions in BP. However, effect-size analysis suggested a stronger trend toward improvement in SBP.[25] Brisk walking interventions similarly demonstrated significant reductions in SBP across various intensities, whereas DBP remained largely unchanged, confirming that AE preferentially lowers SBP.[16] Collectively, these studies confirm that SBP reductions are more consistent and clinically relevant, as SBP contributes more substantially to cardiovascular risk in middle-aged and older adults.[25-26]

Exercise timing also plays a crucial role in BP outcomes. AE performed in the afternoon or evening tends to induce greater reductions than morning sessions, possibly due to modulation of circadian rhythms and autonomic regulation.[23,27-28] Findings from the included studies also provide insights into morning–evening BP variability, which is clinically relevant given its association with cardiovascular events in hypertensive patients. One study reported that afternoon exercise produced significantly greater improvements in SBP and DBP than morning exercise, aligning with earlier evidence suggesting that morning sessions may attenuate or negate post-exercise hypotension. These studies suggest that physiological responses to exercise differ across the circadian cycle, where morning training may not produce optimal reductions in peripheral vascular resistance, thereby contributing to variability in BP responses.[23]

Mechanistically, exercise interacts with neuroendocrine factors such as cortisol and melatonin, thereby enhancing the effects of Post-Exercise Hypotension (PEH) and modulating SVR, with afternoon exercise particularly effective in reducing SBP by decreasing vascular resistance.[29-30] More detailed evidence further demonstrates that only evening exercise elicited significant reductions in both clinic and ambulatory BP, accompanied by reductions in systemic vascular resistance, decreases in total variability of systolic BP, and increases in cardiac baroreflex sensitivity. In contrast, morning exercise produced minimal SBP reductions, comparable to those in the control group, likely due to interference from peak antihypertensive medication activity during the morning hours.[31] These findings collectively indicate that variations in BP across the morning and evening are not only present but also mechanistically relevant, reinforcing the notion that afternoon or evening AE may provide superior benefits in lowering BP and modulating autonomic control in hypertensive individuals.

Across the included studies, RT alone demonstrated heterogeneous effects on BP, with outcomes varying according to modality, intensity, and training duration. Dynamic RT in Schroeder et al. did not reduce either SBP or DBP despite increasing muscular strength, likely due to the short 8-week duration and relatively normal baseline BP of participants.[20] Isometric Handgrip (IHG) protocols, proposed as a time-efficient antihypertensive strategy, also failed to reduce office or ambulatory BP in the largest sham-controlled trial to date, highlighting that previous positive IHG findings in small samples may have been influenced by placebo effects or baseline normotension.[18] In contrast, another study reported modest but clinically relevant SBP reductions (≈4 mmHg) from dynamic RT performed at 60–80% 1RM, together with improvements in endothelial function, suggesting that sufficiently intense and properly dosed RT can improve vascular health in hypertensive adults.[21] Meanwhile, one study did not isolate RT-only effects. Still, it reinforced that the BP-lowering response of RT alone is typically smaller than that of AE, and that combining RT with AE confers broader benefits on BP variability and vascular regulation.[22] None of the four studies specifically evaluated the role of breathing regulation during RT, and no evidence emerged that breathing control contributed meaningfully to hemodynamic responses. Overall, the evidence suggests that RT alone can provide selected vasculoprotective benefits. Still, its antihypertensive effects, particularly for IHG, are inconsistent and generally inferior to those of AE or CT exercise modalities.

The combination of AE and RT demonstrates variable effects, depending on the population and the measured outcomes. In older adults, combined AE-RT reduced 24-hour and nighttime BP variability more than AE alone. However, mean BP reductions were similar, except for greater nighttime DBP reduction in the AE group.[22] In prehypertensive and hypertensive adults, Combined Training (CT) improved endothelial function, with absolute SBP reductions observed in AE and RT alone, whereas the combination more influenced DBP.[21] Schroeder et al. (2019) reported that only AE-RT effectively lowered both peripheral and central DBP, whereas AE or RT alone had a limited impact, and that both AE-RT and AE or RT alone also enhanced functional capacity and cardiovascular risk profiles.[20] Pagonas et al. (2017) further confirmed that AE exerts broader antihypertensive effects than RT alone, particularly IHG, which did not significantly modulate SVR or arterial elasticity. Collectively, these findings indicate that the antihypertensive benefits primarily derive from the aerobic component, while RT serves a complementary role by improving vascular function, functional capacity, and body composition.[18,20-22]

Alternative modalities such as Tai Chi may offer comparable or even superior BP reductions in prehypertensive populations. In a 12-month intervention, Tai Chi reduced office SBP by −2.40 mmHg more than AE, with greater improvements in 24-hour SBP, nighttime SBP, heart rate, and SBP load, highlighting its potential as an effective non-pharmacological strategy.[32]

AE remains the cornerstone of non-pharmacological hypertension management, consistently lowering SBP and offering additional benefits for CRF and vascular health. Exercise timing, population characteristics, and combination with RT or dietary interventions can modulate the magnitude of BP reductions, supporting individualized prescription in clinical practice.[16,18-26,28,31-32]

Table 2. Evidence of implementation of aerobic exercise in hypertension management.

Author (Year)	Objective	Subjects	Results
Ammar (2015).[23]	To investigate the effect of AE timing (morning vs evening) on BP and lipid profile in postmenopausal overweight women with hypertension	• N = 45 postmenopausal overweight women with hypertension • Age: 49–60 years • Group allocation: ○ Group A (medication control): ACE inhibitor only, once daily for 3 months ○ Group B (morning AE + medication): morning exercise (09:00–11:00) + ACE inhibitor ○ Group C (evening AE + medication): evening exercise (16:00–18:00) + ACE inhibitor.	• SBP decreased significantly in all groups, largest reduction in evening AE (−27 mmHg, 9.6% improvement) • DBP decreased significantly in all groups, largest reduction in evening AE (−15.4 mmHg, 16.3% improvement) • HDL increased significantly, highest in evening AE (+14.2 mg/dL) • LDL decreased significantly, greatest in evening AE (−36 mg/dL) • Triglycerides decreased significantly, greatest in morning AE (−47 mg/dL, 19.5% improvement) • Total cholesterol decreased in all groups, largest reduction in evening AE (−34.8 mg/dL).
Belozo et al. (2018).[25]	To examine whether continuous AE (3x/week, total 90 min/week, 70–80% HRmax) improves BP and HR in obese hypertensive individuals	• N = 8 adults (3 men, 5 women • Age: 45.3 ± 3.9 years • Characteristics: obese (BMI 33.44 ± 8.6 kg/m²), hypertension, type 2 DM • Weight: 89.09 ± 22.0 kg; height: 1.63 ± 0.1 m	• No significant changes in BP pre- and post-15-min exercise within each session • Area under the curve analysis for SBP/DBP not significant, but effect size: systolic large (ES = 0.85), diastolic small (ES = 0.33)

Brito et al. (2019).[31]	To compare 10-week morning AE (7–9 am) vs evening AE (6–8 pm) on BP (clinic & ambulatory) and cardiovascular hemodynamic/autonomic mechanisms	• Men, 30–65 years, mild–moderate hypertension, controlled with antihypertensive medication for≥4 months • RCT, 3 groups: morning AE (n=15), evening AE (n=15), CON (stretching, n=20, divided morning/evening)	Clinic BP • Morning SBP decreased in morning AE and evening AE; only evening AE was significantly lower than control and > morning AE • Evening SBP decreased only after evening AE, significant vs morning AE and CON • DBP decreased after evening AE, not significant vs CON ABP • 24h SBP: unchanged • 24h DBP & asleep DBP decreased only after evening AE, significant vs morning AE and CON Hypotensive effect • Evening AE: Clinic SBP −5/−8 mmHg (morning/evening), DBP −3/−4 mmHg; 24h DBP & asleep DBP −3 mmHg • Morning AE: minimal SBP reduction, very small effect
Caminiti et al. (2021).[22]	To compare the 12-week AE vs AE-RT combination on 24-h BP variability and 24-h BP	• N = 55 completed protocol (AE=27, CT=28) • All on antihypertensive medication, mean age ± 68 years • Groups: AE only and AE-RT combination (CT)	• CT is more effective than AE in reducing systolic BP variability, especially 24-h and nighttime SBP variability • No significant difference for daytime systolic BP variability • Both modalities reduced SBP & DBP, except nighttime DBP decreased more with AE
Feairheller et al. (2014).[53]	To test whether 6-month AE improves vascular health in previously sedentary African-American adults, focusing on NMD, plasma NO, carotid IMT, office BP, ABP	• N = 26 • Characteristics: African-American, 40–75 y, 21 women (10 pre-, 11 postmenopause), 5 men • Mean age 53.4 ± 6.2 y, VO_2max 27 mL/kg/min, BMI 31.4 ± 5.9 kg/m²	• 6-month AE improved vascular health: ○ ↓ carotid IMT ○ ↑ FMD ○ ↓ endothelial microparticles ○ ↑ plasma NO • No significant changes in BP (office, ABP) or NMD
Gorostegi-Anduaga et al. (2018).[17]	To investigate the effects of different AE intensities/volumes (High-volume-MICT, high-volume-HIIT, low-volume-HIIT) combined with a hypocaloric diet on BP, body composition, CRF, and antihyper tensive medication use in sedentary overweight/obese adults with hypertension	• N = 175 (120 men, 55 women) • 4 intervention groups: Diet only (DO), high-volume-MICT, high-volume-HIIT, low-volume-HIIT	• All groups, including DO, had significant reductions in SBP, DBP, and MAP; no between-group differences • SBP −7–9 mmHg, DBP −3–5 mmHg; effects driven mainly by DASH diet, independent of exercise intensity/volume
He et al. (2018).[16]	To evaluate whether 12-week brisk walking reduces BP in essential hypertensive (EP) patients and attenuates the BP increase during heavy physical activity	• N = 69 postmenopausal women (55–60 y): 46 EP, 23 NBP control • Groups: EP-AE (brisk walking), EP-CON (no exercise), and NBP control	• Before intervention: EP > NBP in SBP and DBP • After intervention: ○ EP-AE: resting SBP ↓8.3 mmHg, low-intensity SBP ↓15.6 mmHg, high-intensity SBP ↓22.6 mmHg ○ DBP unchanged ○ NBP stable ○ CON showed a trend of increased BP

Li et al. (2024).[32]	To assess the effectiveness of Tai Chi vs AE in lowering BP in prehypertensive patients	• N = 342 (173 Tai Chi, 169 AE) • Age 18–65 y, prehypertension (SBP 120–139 or DBP 80–89 mmHg)	• 12-month Tai Chi decreased office SBP more than AE (−2.40 mmHg) • ABP: Tai Chi better for 24h SBP (−2.16 mmHg) and nighttime SBP (−4.08 mmHg) • Tai Chi also reduced nighttime pulse rate and SBP load compared to AE
Lopes et al. (2021).[19]	To determine whether 12-week AE is more effective than UC in lowering 24-h ambulatory BP in resistant hypertension patients	• N = 53 completed follow-up, 24 women (45%), mean age 60.1 ± 8.7 y • Groups: Exercise (AE + UC, n=26), CON (UC only, n=27)	• AE 12-week significantly reduced 24h ABP and office SBP compared with UC • Effect most pronounced on daytime BP • Increased CRF without changes in body composition/metabolic parameters • Program feasible, safe, and highly adherent
Maruf et al. (2013).[24]	To evaluate the additional effect of AE on BP reduction and antihypertensive medication use in uncontrolled essential hypertension patients already on ≥2 medications	• N = 63 (AE: 32, CON: 31), mean age AE 50.3 ± 8.4 y, CON 52.3 ± 8.1 y • Overweight (BMI 28.4 vs 26.0 kg/m²)	• No significant differences in SBP and DBP between AE + medication vs medication only • BP control rate higher in AE group (56.7% vs 35.5%) • Both groups showed SBP and DBP reduction, more pronounced in the AE group
Pedralli et al. (2020).[21]	To evaluate the effects of AE, RT, and CT on endothelial function (FMD), 24h ABP, cardiac structure/function, VO_2max, and maximal muscle strength	• Adults with prehypertension or hypertension (SBP ≥130 or DBP ≥80 mmHg), N = 37 (21F,16M) • Groups: AT (n=14), RT (n=14), CT (n=14)	• FMD increased significantly in all groups: AE +3.2%, RT +4.0%, CT +6.8% (Cohen's d 0.6–0.9), no between-group differences • 24h ABP: SBP ↓ in AE (−5.1 mmHg) and RT (−4.0 mmHg), not in CT; DBP ↓ in CT (−3.2 mmHg) • Daytime BP reduction more pronounced; night unchanged • VO_2max ↑ in AE and RT; EF ↑ in AE; muscle strength ↑ in RT; waist circumference ↓ in AE and CT; triglycerides ↓ in all groups
Pagonas et al. (2017).[18]	To compare the effects of AE and IHG training on office BP, 24h ABP, systemic vascular resistance, and arterial elasticity	• N = 75 hypertensive patients, groups: AE (n=25), IHG (n=25), sham training (n=25) • 9 dropouts, per-protocol analysis N = 66	• Only AE significantly reduced office BP and 24h ABP • IHG and sham training had no antihypertensive effect
Schroeder et al. (2019).[20]	To compare the effects of AE, RT, and CT on peripheral & central BP and CVD risk factors	• N = 69 (45–74 y, 61% female), mild–moderate hypertension or high BP (SBP 120–149 / DBP 80–99 mmHg, no antihypertensives), overweight/obese (BMI 25–40), sedentary • Baseline: age 58 ± 7 y, BMI 32.4 ± 5.2, SBP 131 ± 13, DBP 81 ± 9	• BP: CT: DBP ↓4 mmHg (peripheral & central, significant) • AT and RT: no significant SBP/DBP change • AT + CT: HR ↓2 bpm vs control ($p<0.02$) • Body composition & CVD risk: AT best for BMI, weight, fat mass ↓; RT: waist −1.7 cm, TG −26 mg/dL; CT: lean body mass +0.8 kg, ↑ CRF & strength; composite CVD risk score ↓ more than control

ABP, ambulatory blood pressure; ACE, angiotensin-converting enzyme; AE, aerobic exercise; BMI, body mass index; BP, blood pressure; CON, control; CRF, cardiorespiratory fitness; CT, combined training; CVD, cardiovascular disease; DASH, dietary ap-

proaches to stop hypertension; DBP, diastolic blood pressure; EF, ejection fraction; EP, essential hypertension; EP-AE, essential hypertension-aerobic exercise; EP-CON, essential hypertension-control; ES, effect size; FMD, flow-mediated dilatation; HDL, high-density lipoprotein; HIIT, high-intensity interval training; HR, heart rate; HRmax, maximum heart rate; IHG, isometric hand grip; IMT, intima-media thickness; LDL, low-density lipoprotein; MICT, moderate-intensity continuous training; NBP, normal blood pressure; NMD, nitroglycerin-mediated dilation; NO, nitric oxide; RCT, randomized controlled trial; SBP, systolic blood pressure; SHT, UC, usual care; VO2max, maximum oxygen uptake.

Evidence of The Effects of AE in Combination with a Hypocaloric Diet

The study by Gorostegi-Anduaga et al. (2018) provides valuable insights into the interaction between AE and dietary interventions in the management of hypertension. In this trial, all intervention groups, including those receiving only a hypocaloric diet and those combining the diet with various forms of AE (high-volume Moderate Intensity Continuous Training [MICT], high-volume HIIT, and low-volume HIIT), demonstrated significant reductions in SBP and DBP as well as MAP. The magnitude of SBP reduction (approximately −7 to −9 mmHg) and DBP reduction (approximately −3 to −5 mmHg) was similar across groups, indicating that dietary factors played a dominant role in lowering BP, regardless of exercise intensity or volume.[17]

These findings align with previous evidence showing that dietary interventions, particularly hypocaloric approaches based on the Dietary Approaches to Stop Hypertension (DASH) pattern, exert strong antihypertensive effects and can serve as a primary non-pharmacological strategy. In this context, AE offers additional benefits, notably improvements in CRF, body composition, and potential reductions in antihypertensive medication requirements. However, when combined with diet, the relative contribution of exercise to BP reduction may appear less pronounced, given the predominant effect of nutritional intervention.[17]

This evidence highlights the value of a multimodal approach to hypertension management, where a healthy diet serves as the core component, and AE provides complementary benefits beyond BP control, including improvements in functional capacity, metabolism, and overall cardiovascular health.[17,33]

Mechanistic Links Between AE and BP Reduction

AE has been shown to reduce BP through a complex network of central and peripheral adaptations. A key pathway involves improvements in endothelial function: repeated increases in limb blood flow during rhythmic, large-muscle activity elevate shear stress along the arterial intima, thereby upregulating endothelial Nitric Oxide Synthase (eNOS) and enhancing Nitric Oxide (NO) bioavailability. This adaptation augments vasodilatory capacity and progressively lowers systemic vascular resistance both at rest and during submaximal effort.[34-36] Regular AE also improves arterial compliance and reduces vascular stiffness, effects that are strongly linked to enhanced baroreflex sensitivity and greater hemodynamic stability.[37] Moreover, exercise training downregulates sympathetic vasomotor tone while shifting autonomic balance toward parasympathetic dominance, thereby dampening excessive sympathetic drive, a mechanism supported by both experimental and clinical studies.[38] Collectively, these vascular and autonomic adaptations explain the sustained reductions in BP observed following long-term AE.

Beyond vascular adaptations, metabolic changes play a crucial role in mediating the BP-lowering effects of AE. Regular AE promotes skeletal muscle capillarization and mitochondrial biogenesis, enhancing oxidative capacity, increasing VO2max, and improving insulin sensitivity.[39-41] Improved glycemic control attenuates hyperinsulinemia-driven sympathetic activation and renal sodium retention, mechanisms closely linked to the pathophysiology of hypertension.[42] In parallel, AE induces favorable shifts in adipokine secretion, reduces systemic inflammation, and mitigates oxidative stress, all of which contribute to vascular protection.[43] Exercise also exerts beneficial effects on lipid metabolism, typically characterized by higher HDL cholesterol, lower triglycerides, modest reductions in LDL cholesterol, and preferential loss of visceral adiposity, thereby lowering hemodynamic load.[44] Although weight reduction independently reduces BP, consistent evidence shows that the antihypertensive benefits of AE often occur even in the absence of significant weight loss, highlighting the importance of weight-independent hemodynamic and autonomic adaptations.[45-46]

The BP response is also exercise-dose dependent. Higher volumes of moderate-to-vigorous AE generally produce greater reductions, up to a ceiling beyond which additional time yields diminishing returns. Interval formats can create strong shear stimuli in shorter sessions, whereas continuous moderate-intensity work may be

preferable for adherence in some patients. Program personalization, such as balancing intensity, volume, enjoyment, and orthopedic tolerance, is central to sustained benefit.[47]

Factors Influencing the BP Response to AE

The hypotensive effects of AE are multifactorial and are shaped by individual characteristics, clinical conditions, vascular properties, and exercise parameters. Key individual determinants include age, sex, BMI, and baseline physical activity, while clinical factors encompass hypertension severity, pharmacological status, and the presence of resistant hypertension. Vascular factors, such as arterial stiffness, also modulate the response, whereas exercise type, duration, and intensity dictate the magnitude of BP reduction.[9,48-51]

Acute and chronic AE consistently demonstrate significant reductions in BP. Carpio-Rivera et al. (2016) reported that a single AE session lowers SBP by approximately −4.8 mmHg and DBP by −3.2 mmHg, independent of intensity, duration, or participant characteristics. This PEH has clinically meaningful implications, as a 2 mmHg decrease in SBP can reduce stroke mortality by 6% and coronary heart disease mortality by 4%.[9]

Individual responses are modulated by physiological and demographic factors. Men typically exhibit greater reductions in SBP than women, potentially due to differences in autonomic tone and baroreflex sensitivity, with menstrual cycle phases also influencing outcomes. Age and BMI further modify the hypotensive response; aging increases arterial stiffness and microvascular remodeling, attenuating BP reductions, whereas lower BMI is associated with greater SBP decreases, consistent with obesity-related sympathetic overactivity, endothelial dysfunction, and chronic inflammation.[9,48]

Arterial stiffness is a critical determinant of exercise-induced modulation of BP. Elevated pulse wave velocity and augmentation index, common in aging and hypertensive populations, precede isolated systolic hypertension. AE that enhances arterial elasticity can therefore slow vascular stiffening and the progression of age-related hypertension.[48]

Exercise program characteristics further influence PEH. Carpio-Rivera et al. (2016) found that jogging is more effective than walking in lowering both SBP and DBP, while longer duration and progressive-intensity protocols yield larger reductions. This underscores that total exercise load, rather than intensity alone, primarily determines hemodynamic response.[9]

Genetic factors appear to have minimal impact. A meta-analysis by Bruneau Jr et al. (2016) indicated that sample characteristics, such as age, sex, BMI, and baseline BP, accounted for more than half of the variability in BP response. In contrast, gene polymorphisms contributed less than 1%. Only one genetic factor variant showed a modest association with DBP, highlighting the dominant role of non-genetic factors.[49]

Clinical characteristics also shape exercise outcomes. Nascimento et al. (2017) noted that patients with resistant hypertension may display variable responses, including potential adverse effects.[50] Similarly, Saco-Ledo et al. (2021) demonstrated that a single AE session can lower 24-hour ambulatory BP in both medicated and unmedicated hypertensive patients by reducing sympathetic activity, increasing local vasodilator release, and eliciting vascular adaptations. Larger reductions are generally observed in non-medicated individuals, likely due to interactions between pharmacotherapy and exercise effects.[50-51] Overall, these findings reinforce the need for individualized exercise prescriptions in hypertension management, accounting for personal, clinical, vascular, and program-specific factors to optimize the BP-lowering effects of AE.

Safety Issues in the Implementation of AE in Hypertension Management

AE is generally safe for individuals with hypertension when introduced progressively and tailored to their comorbid status. Clinical guidelines recommend halting exercise if abnormal physiological responses occur, such as inappropriate heart rate response to intensity, a drop in SBP ≥20 mmHg with increasing workload, a rise in DBP ≥15 mmHg, new or worsening angina, severe dyspnea, pallor or cyanosis, dizziness, confusion, or leg ischemia consistent with claudication. In such cases, training should be paused until medical evaluation and program adjustment are completed.[10,52]

Musculoskeletal injuries are the most common exercise-related complications. These are usually linked to sudden increases in intensity or volume, insufficient recovery, biomechanical issues, or prior injuries. Gradual progression, cross-training, appropriate footwear, and inclusion of resistance exercises to strengthen key kinetic chains effectively reduce injury risk and support sustained AE participation. Serious cardiovascular events during moderate-intensity AE are rare under supervision, and pre-participation screening further minimizes risk.[10]

Evidence from clinical trials confirms the safety of structured AE programs. In a 16-week randomized controlled trial, no major complications or cardiac events occurred, indicating that both MICT and HIIT can be safely implemented with appropriate supervision in patients receiving pharmacological therapy.[17] Similarly, a 12-month study comparing AE and Tai Chi reported excellent tolerability with no serious adverse events, demonstrating that structured exercise is feasible even in individuals with cardiovascular risk factors.[32]

Other studies reinforce these findings. In a trial by Lopes et al. (2021), adherence to the exercise program was high (98.8% of sessions attended), with only minor events such as transient dizziness or mild musculoskeletal discomfort reported. No participants withdrew due to adverse events, highlighting that careful monitoring and individualized adjustments can ensure safety.[19] Maruf et al. (2013) reported similar outcomes in middle-aged, overweight hypertensive adults, with no adverse events during the intervention and adherence rates of approximately 77%.[24] Pedralli et al. (2020) confirmed that both AE and CT protocols were feasible and safe for individuals with elevated BP and low baseline physical activity levels over 8 weeks.[21]

Even in studies involving different exercise modalities, safety remained consistent. Pagonas et al. (2017) showed that AE and IHG training were well tolerated, with no serious complications, although some participants discontinued due to changes in medication or adherence challenges.[18] Schroeder et al. (2019) observed excellent compliance and tolerability across all training types, with participants consistently achieving prescribed intensity and volume, and no adverse events reported over 8 weeks.[20]

Overall, these findings demonstrate that AE, whether delivered as MICT, HIIT, or in combination with RT or alternative exercises like Tai Chi, is safe and well-tolerated for individuals with hypertension when programs are supervised, progressively implemented, and adapted to participant capacity. High adherence rates and minimal minor events further support the feasibility and clinical relevance of AE as a cornerstone of non-pharmacological hypertension management.[32]

Conclusion

AE is an effective and safe non-pharmacological strategy for the prevention and management of hypertension. Consistently, it produces greater reductions in SBP than in DBP through mechanisms that enhance endothelial function, improve autonomic regulation, and reduce SVR, with benefits that are independent of weight loss. The effectiveness of the intervention is influenced by factors such as age, sex, BMI, medication status, and timing of exercise sessions. Combining AE with RT or a hypocaloric diet further enhances cardiometabolic benefits, although BP reduction is primarily driven by the aerobic component. Moreover, AE exhibits a favorable safety profile, with minimal risk of adverse effects and high adherence rates. These findings underscore that AE is a key component in hypertension management and can be readily integrated into routine clinical practice.

List of Abbreviations

ABP	Ambulatory Blood Pressure
AE	Aerobic Exercise
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CO	Cardiac Output
CRF	Cardiorespiratory Fitness
CT	Combined Training
CVD	Cardiovascular Disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
eNOS	Endothelial Nitric Oxide Synthase
FMD	Flow-Mediated Dilatation
HDL	High-Density Lipoprotein
HIIT	High-Intensity Interval Training
HR	Heart Rate
HRmax	Maximum Heart Rate
HRR	Heart Rate Reserve
IHG	Isometric Handgrip
IMT	Intima-Media Thickness
LDL	Low-Density Lipoprotein
MAP	Mean Arterial Pressure
MICT	Moderate-Intensity Continuous Training
MVC	Maximal Voluntary Contraction
NO	Nitric Oxide
PEH	Post-Exercise Hypotension
RCT	Randomized Controlled Trial
RPE	Rating of Perceived Exertion
RT	Resistance Training
SBP	Systolic Blood Pressure
SV	Stroke Volume

SVR	Systemic Vascular Resistance
VO_2max	Maximal Oxygen Uptake
VO_2peak	Peak Oxygen Uptake

Ethical Clearance

Not applicable.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

(a) Conception and design, or analysis and interpretation of data; WN and AN (b) Drafting the article or revising it critically for important intellectual content; WN, AN, and TP (c) Final approval of the version to be published; WN, AN, and TP.

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Case Report

Cardiac Tamponade due to Purulent Pericarditis

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Abstract

Background: Purulent pericarditis, though uncommon in the antibiotic era, remains highly fatal when diagnosis or drainage is delayed. Its presentation often mimics viral hepatitis, sepsis, or parasitic infections—particularly in endemic, low-resource regions—leading to underrecognition. This case reported the development of purulent pericarditis with initial equivocal signs and symptoms, followed by progressive hemodynamic deterioration.

Case Illustration: A 40-year-old previously healthy man presented with fever, dyspnea, stabbing chest and abdominal pain, and dark urine. Examination revealed jaundice, pericardial friction rub, and hepatosplenomegaly. Laboratory tests showed leukocytosis, hyperbilirubinemia, and elevated liver enzymes. Initial echocardiography demonstrated a 2-cm circumferential effusion without signs of tamponade. Two days later, despite stable symptoms, he developed hypotension with new fibrinous effusion and right atrium collapse. Emergency pericardiocentesis drained 1.7 L of thick, purulent fluid. Hemodynamics improved rapidly after drainage. Prednisone and colchicine were initiated once infection control was achieved to limit fibro-inflammatory response and reduce the risk of constriction. Liver function normalized, and follow-up echocardiography showed minimal residual effusion. At follow-up, the patient remained asymptomatic.

Conclusions: This case highlights that purulent pericarditis can occur in immunocompetent individuals without typical risk factors, possibly from overlooked infection in low-resource settings. Hemodynamic collapse may occur even with small increases in pericardial effusion volume, owing to fibrin-induced pericardial stiffness and reduced compliance. Serial echocardiography is therefore critical when symptoms appear stable. Early pericardiocentesis is both diagnostic and therapeutic, reducing bacterial and inflammatory load, while carefully selected adjunctive anti-inflammatory therapy may prevent chronic constrictive sequelae.

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Keywords: Purulent pericarditis, Cardiac tamponade, Constrictive pericarditis.

Introduction

Purulent pericarditis remains a highly lethal form of pericardial disease if not promptly diagnosed and managed. It is characterized by the accumulation of purulent exudate in the pericardial space, typically resulting from direct extension from adjacent infections, hematogenous spread, or iatrogenic causes such as cardiac surgery or previous pericardiocentesis.[1] Despite being an uncommon entity, the nonspecific and often insidious presentation of purulent pericarditis poses a significant diagnostic challenge.

Common risk factors include immunosuppression, diabetes mellitus, previous thoracic interventions, malignancy, and uremia, and common causative microorganisms include streptococci, staphylococci, Haemophilus spp., and M. tuberculosis.[2-3] In low-resource settings, poor access to healthcare, delayed treatment of primary infections, and high burden of Tuberculosis (TB) and parasitic diseases may contribute to underreported cases.

Before the time of antibiotics, purulent pericarditis had a mortality rate exceeding 90%.[4] Although this number has declined, outcomes remain poor when diagnosis and intervention are delayed. The clinical presentations may mimic viral or tuberculous pericarditis, sepsis, or systemic inflammatory conditions, and echocardiographic findings can initially appear benign. However, the disease may progress rapidly, culminating in cardiac tamponade, constrictive pericarditis, or death.[3] Diagnosis, immediate drainage, and tailored antimicrobial therapy are essential.

Here, we presented a case notable for the development of purulent pericarditis with initial equivocal signs and symptoms, followed by progressive hemodynamic deterioration. It highlights critical management principles: the value of serial echocardiographic assessments, the need for intervention despite seemingly unchanging clinical symptoms, and the role of adjunctive therapies in preventing complications such as constrictive pericarditis.

Case Illustration

A 40-year-old male presented with a 14-day history of fever (38.5°C), chills, dyspnea, stabbing chest and abdominal pain, and dark-colored urine. He had just returned from working as a chef in another border town and denied any recent travel abroad, any animal contact, flood exposure, or known infectious contacts. There was no prior history of significant illness. On physical examination, he was icteric. A pericardial friction rub was heard on auscultation. Hepatosplenomegaly and right upper quadrant tenderness were noted on palpation. Electrocardiogram (ECG) revealed atrial fibrillation with rapid ventricular response (Figure 1).

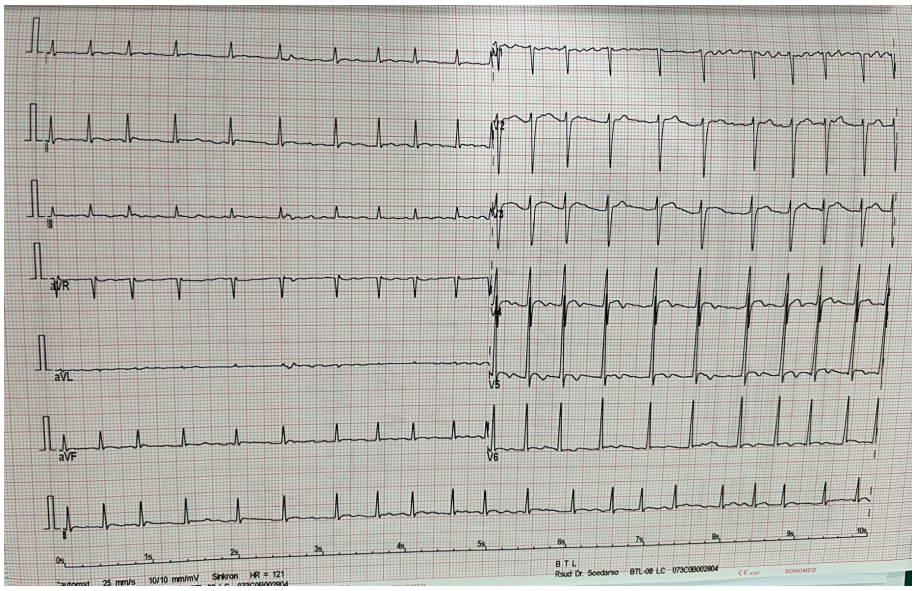

Figure 1. ECG during admission showed atrial fibrillation with rapid ventricular response.

Laboratory findings showed leukocytosis (20,000/mm³) with neutrophilia, hyperbilirubinemia (total 8.7 mg/dL, direct 7.1 mg/dL), and markedly elevated liver enzymes (aspartate transferase [AST] 684 U/L; alanine transferase [ALT] 438 U/L). Renal function and coagulation parameters were within normal limits. Abdominal ultrasonography revealed mild hepatosplenomegaly, minimal ascites, and bilateral pleural effusions. Initial Transthoracic Echocardiography (TTE) demonstrated a 2 cm circumferential pericardial effusion without signs of tamponade (Figure 2). He initially refused pericardiocentesis due to fear. Intravenous (IV) ceftriaxone, furosemide, and hepatoprotector were started.

Two days after admission, the patient became hypotensive (Blood Pressure [BP] 70/50 mmHg), and his rhythm was still atrial fibrillation with a rate ranging from 110 to 130 bpm. His extremities were a little cold to the touch, pulses were still adequate on palpation, and no delay of capillary refill time. He denied worsening chest discomfort and exhibited no overt respiratory distress; he reported feeling slightly better. Repeat echocardiography showed a mildly increased effusion, now fibrinous in appearance, with the right atrium starting to collapse, and exaggerated respiratory variation in mitral and tricuspid inflow (Figure 3). Dobutamine was initiated, and further counseling regarding the urgency and risks of intervention was provided, after which the patient consented.

Emergency pericardiocentesis was performed, draining approximately 500 mL of thick, greenish, purulent fluid initially, followed by production of 1,200 mL of purulent fluid over the next 24 hours (Figure 4). Fluid analysis revealed an extremely high leukocyte count (29,240 cells/mm³), Polymorphonuclear (PMN) predominance (>90%), and a high protein level (5 g/dL). The culture of the pericardial fluid remained sterile, likely due to prior antibiotic exposure in this patient. Tests for TB using GeneXpert (Cepheid, U.S.), malaria, and leptospirosis were negative. The patient showed immediate hemodynamic improvement and resolution of symptoms following pericardial drainage, with BP rising to 100/70 mmHg while

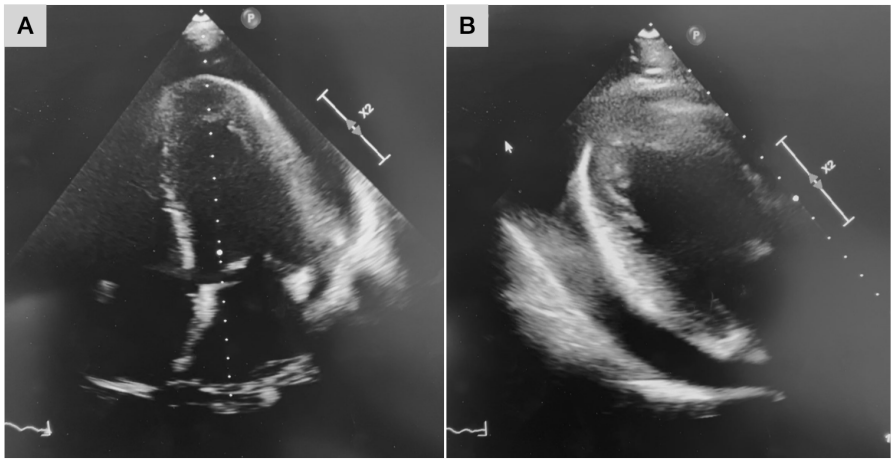

Figure 2. (a) Apical 4-chamber view and (b) parasternal long axis view showing circumferential tamponade.

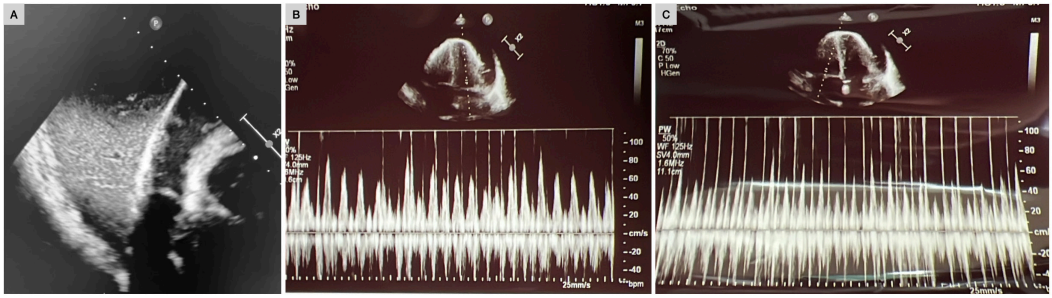

Figure 3. (a) Fibrinous appearance of effusion with exaggerated respiratory inflow variations in (b) mitral and (c) tricuspid.

Figure 4. Pericardial drain production within 24 hours showing greenish purulent fluid.

remaining tachycardic at a heart rate of 100 bpm. Dobutamine was gradually tapered with close hemodynamic monitoring.

By day five, liver enzymes and leukocyte counts had returned to normal, and bilirubin levels had decreased (total 2.8 mg/dL, direct 2.4 mg/dL). Prednisone (1 mg/kg/day), colchicine, and bisoprolol were added to his regimen. By day nine, drain output had decreased significantly, and TTE revealed minimal residual effusion (Figure 5). A respiratory variation >25% in mitral and tricuspid inflow velocities with subtle diastolic interventricular septal shuddering raised early suspicion of constrictive physiology, though medial e' velocity was not greater than lateral e' velocity, and no hepatic vein flow reversal was observed. Patient remained asymptomatic and hemodynamically stable. The pericardial drain was removed, and the patient was discharged on tapering doses of corticosteroids, together with bisoprolol and colchicine. At the 1-month follow-up, he remained asymptomatic, and echocardiography no longer demonstrated diastolic septal bounce, although mitral and tricuspid respiratory variations remained >25%. His rhythm remained atrial fibrillation with a controlled ventricular rate of 80-90 bpm. Bisoprolol was continued for rate control. With a CHADS-VA score of 0, no oral anticoagulant was initiated.

Discussion

This case emphasizes the ambiguous presentation of purulent pericarditis, which masquerades as what was initially thought to be viral hepatitis, sepsis, or parasitic infection like malaria and leptospirosis, which are considered endemic in the region, due to overlapping systemic signs such as jaundice, fever, leukocytosis, and acute liver injury. The absence of classical risk factors does not exclude

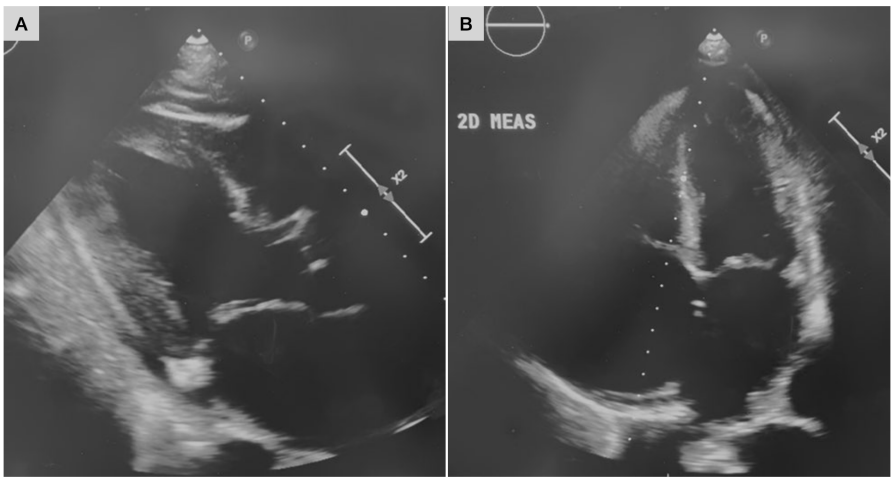

Figure 5. Evaluation of post-drainage TTE showed minimal residual effusion.

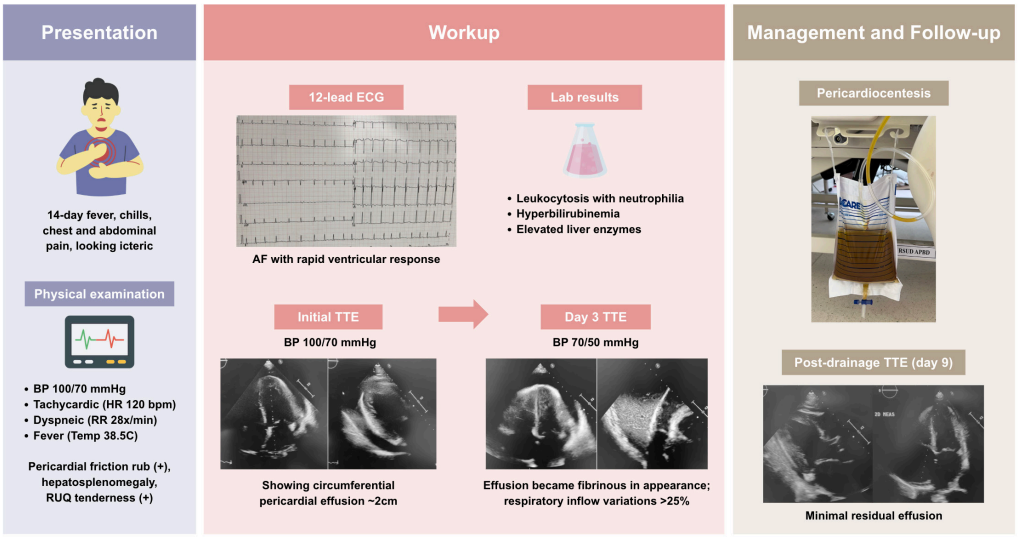

Figure 6. Overall illustration of the case.

the possibility of a preceding infection, given his prior residence in a low-resource border area with limited access to healthcare facilities, which may have increased the likelihood that a minor localized or systemic infection was overlooked or managed symptomatically without professional evaluation.

While TTE remains the cornerstone of diagnosis, its sensitivity for tamponade signs may be limited early in the disease. Thus, serial echocardiographic evaluations are essential, particularly when hemodynamic instability develops in the absence of worsening symptoms. The hemodynamic deterioration despite no symptom progression and a mildly increased effusion illustrates a phenomenon of symptomatically equivocal tamponade, where the inflammation and fibrinous composition might have contributed to the constrictive pericardial physiology, creating a scenario where reduced pericardial compliance amplifies ventricular interdependence that even modest negative intrathoracic pressure during inspiration can precipitate right-sided chamber collapse and a fall in left-sided stroke volume, explaining why decompensation can occur with only slight increases in effusion volume.[5] This shows that imaging can guide decisions when clinical monitoring is insufficient.

Drainage is both diagnostic and therapeutic in purulent pericarditis. Guidelines from ESC and AHA endorse immediate pericardiocentesis for any hemodynamically significant effusion, particularly when a specific or purulent cause is suspected.[6-7] Aside from relieving pressure, drainage is also therapeutic by decreasing bacterial load and removing pro-inflammatory mediators, thereby limiting ongoing pericardial injury, highlighting the importance of early and clear communication about risks and benefits of intervention.

Empirical antibiotic therapy should target common causative agents like Staphylococcus aureus and Streptococcus spp. Third-generation cephalosporins, such as ceftriaxone, are appropriate for community-acquired infections, whereas nosocomial infections or infections in immunocompromised patients may require vancomycin or broader-spectrum agents.[8] The lack of growth in fluid culture is not uncommon and does not exclude bacterial etiology, or suspicion can be raised for other fastidious organisms.[9] Adjunctive corticosteroids remain controversial, especially in infectious pericarditis. However, if inflammatory features are present, such as elevated CRP or pericardial fibrin in our case, they may reduce the risk of constriction by modulating fibroinflammatory responses.[10] Colchicine, proven in idiopathic and recurrent pericarditis, may also benefit post-purulent effusions once infection is controlled.[11] In our case, we favored corticosteroids over Non-Steroidal Anti-Inflammatory Drug (NSAIDs) once infection control was reasonably established (sterile cultures with clinical improvements), to avoid NSAID-related hepatotoxicity in the setting of acute liver injury, to minimize potential renal or platelet effects during recovery, and to achieve a quicker anti-inflammatory effect; colchicine was added as a steroid-sparing adjunct.

One of the dreaded complications of purulent pericarditis is constrictive pericarditis, occurring in 20-30% of cases,[6] which may evolve weeks

to months post-resolution. Signs of constrictive pericarditis include persistent respiratory variation in inflow velocities, abnormal septal motion, medial e' velocity exceeding lateral e' velocity, strain reversus, and diastolic hepatic vein flow reversals.[12] In our case, TTE suggested some constrictive signs, but conservative monitoring was chosen given the absence of clinical signs. Advanced imaging, such as cardiac MRI or CT, may help confirm constrictive physiology in cases of ambiguity. Pericardiectomy remains the definitive treatment for persistent symptomatic constriction.[13] From this case, we learned that:

- Clinical deterioration in purulent pericardial effusion may occur silently and should be suspected. In patients with sepsis and pericardial effusions, serial imaging is vital
- Pericardiocentesis should be promptly considered in suspected purulent pericarditis when there is considerable and accessible fluid accumulation despite the absence of definitive tamponade signs, due to the high risk of rapid decompensation.
- Sterile cultures do not rule out bacterial pericarditis; negative results should not delay or alter treatment in an appropriate clinical context.
- Adjunctive anti-inflammatory agents (e.g., colchicine, steroids, or NSAIDs) play an important role in sequelae prevention when infection is controlled but inflammation persists. Agent selection should consider hepatic and renal profiles, bleeding risk, and the need for rapid control of inflammation.

Conclusion

This case illustrates the deteriorative course purulent pericarditis may take, evolving from sepsis-like symptoms to tamponade within a couple of days. Symptom stability can be misleading, and echocardiographic surveillance plays an essential role in the detection of decompensation. Immediate drainage, empiric antibiotics, and targeted adjunct therapies are key components in management and can significantly improve outcomes. Ongoing monitoring is required to detect complications such as constrictive pericarditis.

List of Abbreviations

AHA	American Heart Association
ALT	Alanine Transferase
AST	Aspartate Transferase
BP	Blood Pressure
BPM	Beats per Minute
CRP	C-Reactive Protein
ECG	Electrocardiogram
ESC	European Society of Cardiology
IV	Intravenous
NSAID	Non-Steroidal Anti-Inflammatory Drug
PMN	Polymorphonuclear
TB	Tuberculosis
TTE	Transthoracic Echocardiography
TV	Tricuspid Valve

Ethical Clearance

Not Applicable.

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All authors consent to the publishing of this manuscript.

Authors Contributions

JAS: conception, case management, data collecting, writing and revision of manuscript; DSP: supervision, case management, revision, approval of final manuscript.

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Case Report

Multifocal Atrial Tachycardia in a 9-Month-Old Infant: A Case Report with Therapeutic Insights

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Abstract

Background: Supraventricular tachycardia is the most common arrhythmia in infants, with an estimated prevalence between 1/250 and 1/1000. Multifocal Atrial tTachycardia (MAT), a rare subtype accounting for less than 1% of supraventricular tachycardia in infants and children, is characterized by multiple atrial foci, variable P-wave morphologies, and irregular ventricular response. When incessant, MAT may lead to tachycardia-induced cardiomyopathy and congestive heart failure. This report describes a 9-month-old infant with MAT and left ventricular dysfunction, emphasizing diagnostic challenges and therapeutic strategies.

Case Illustration: A previously healthy 9-month-old female infant presented for urgent evaluation due to progressive dyspnea and tiredness during breastfeeding, which had begun approximately two months earlier and worsened in the last two weeks. Her mother noted perioral cyanosis during crying and feeding. On examination, she was tachypneic (60 breaths/min), tachycardic (180 bpm), and mildly dehydrated. Transthoracic echocardiography revealed a dilated left ventricle with moderate systolic dysfunction (ejection fraction 35%). A 12-lead electrocardiogram demonstrated multifocal atrial tachycardia with at least three distinct P-wave morphologies and irregular R-R intervals, and Holter monitoring confirmed an incessant pattern (>30% of the day). Three synchronized direct current cardioversion attempts (0.5, 1.0, and 1.23 J/kg) failed to restore sinus rhythm. Intravenous amiodarone was initiated (loading dose 5 mg/kg over 1 hour, followed by 10 mcg/kg/min), later transitioned to oral therapy (5 mg/kg/day). Within 48 hours, sinus rhythm was restored, heart failure symptoms resolved, and follow-up echocardiography showed improved ejection fraction (55%). Propranolol (1 mg/kg/day) and digoxin (5 mcg/kg/day) were added for rate control. The patient was discharged asymptomatic after one week, with no relapse at 6-month follow-up.

Conclusions: MAT is a rare cause of supraventricular tachycardia in infants and may present with congestive heart failure due to tachycardia-induced cardiomyopathy. Incessant forms are typically defined by an arrhythmia burden greater than 30% of the day on Holter monitoring. Failure of direct current cardioversion is a hallmark of MAT, reinforcing the role of pharmacologic management. Early recognition and rate and rhythm control with agents such as amiodarone, propranolol, and digoxin can lead to rapid recovery of left ventricular function and an excellent prognosis in infants without structural heart disease.

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Keywords: Multifocal atrial tachycardia, infant, supraventricular tachycardia, rate control

Introduction

Supraventricular Tachycardia (SVT) is the most common arrhythmia encountered in infants, with an estimated prevalence between 1/250 and 1/1000.[1] Multifocal Atrial Tachycardia (MAT), a subtype of SVT, is characterized by multiple atrial foci firing irregularly, leading to variable P-wave morphologies and irregular ventricular rates.[1] While rare in pediatrics, MAT can lead to tachycardia-induced cardiomyopathy if incessant. This report describes a case of MAT in a 9-month-old infant, highlighting diagnostic challenges and effective medical management.

Case Illustration

A 9-month-old female infant presented for urgent medical evaluation due to shortness of breath (dyspnea) and tiredness during breastfeeding, which began approximately two months prior. Over the last two weeks, the symptoms worsened. Her mother also noticed some cyanosis around the lips during simple activities, such as crying or drinking.

On physical examination, the infant was tachypneic (respiratory rate 60 breaths/min), tachycardic (heart rate 180 bpm), and showed signs of mild dehydration. Echocardiography revealed a dilated left ventricle with moderate systolic dysfunction (ejection fraction 35%). Electrocardiography (ECG) demonstrated multifocal atrial tachycardia with varying P-wave morphologies and irregular R-R intervals. Holter monitoring confirmed that MAT was incessant, occupying >30% of the day.

A series of synchronized cardioversions (three consecutive shocks at 0.5, 1.0, and 1.23 Joules/kg) failed to revert the arrhythmia. Intravenous amiodarone was initiated (loading dose 5 mg/kg over 1 hour, followed by 10 mcg/kg/min infusion). After 24 hours of intravenous amiodarone infusion, the oral formulation was initiated (maintenance 5 mg/kg/day). Within 48 hours, sinus rhythm was restored, with resolution of symptoms and improved ejection fraction (55%) on follow-up echo. Propranolol (1 mg/kg/day) and digoxin (5 mcg/kg/day) were added for rate control. The patient was discharged asymptomatic after one week, with no relapse at 6-month follow-up.

Discussion

The MAT, also known as chaotic atrial tachycardia, is defined as a tachycardia with at least three morphologically distinct P-waves.[2] It is also characterized by irregular P-P, R-R, and P-R intervals, as well as an isoelectric baseline between the P-waves.[2] This arrhythmia usually lasts for minutes to hours, with a normal sinus rhythm between episodes. Incessant arrhythmias are typically those that persist for >30% of the day on Holter monitoring.[2] Children older than 1 year rarely have documented MAT.[3] It accounts for <1% of supraventricular tachycardia in infants and children, with most series showing a clear predominance in infants.[3] Another interesting aspect of MAT refers to its coexistence with atrial fibrillation or Atrial Flutter (AFL).[4] This was observed in the present case (Figure 2B).[4]

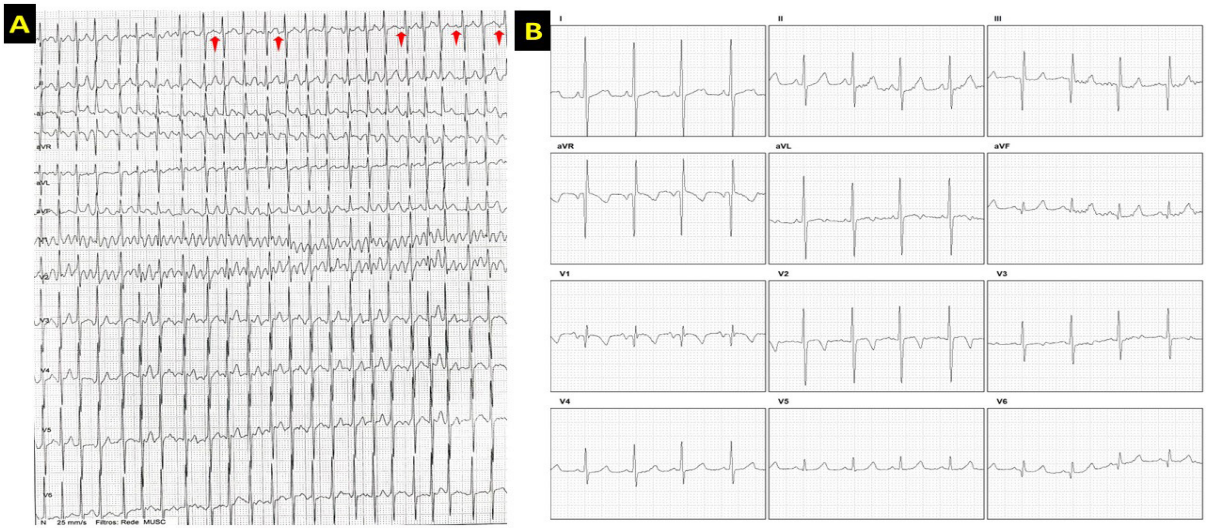

Figure 1. (A) The 12-lead electrocardiogram obtained at admission shows multifocal atrial tachycardia (MAT) with at least three distinct P-wave morphologies (A, red arrows, Lead I). (B) The 12-lead electrocardiogram obtained during follow-up showed a normal sinus rhythm.

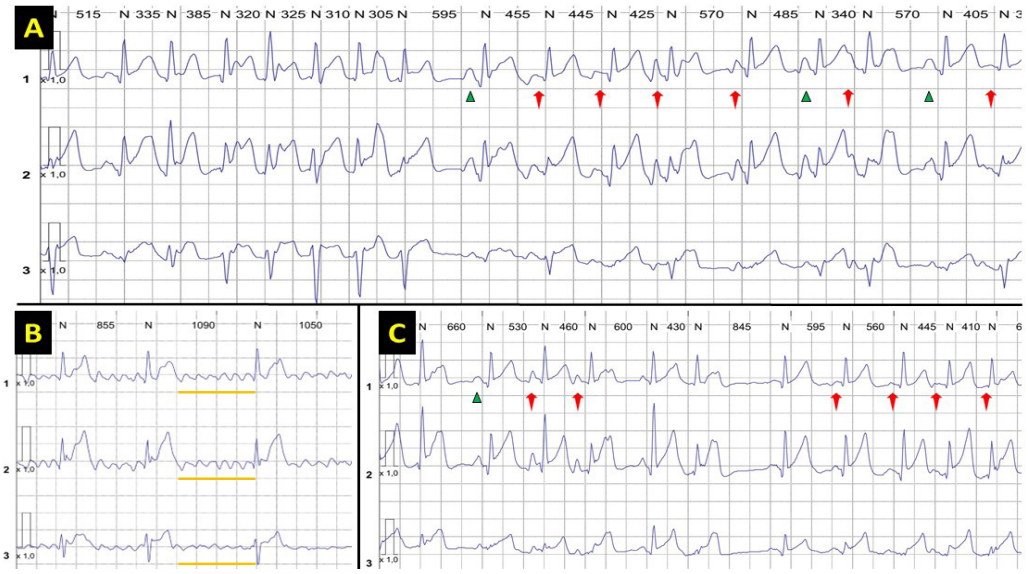

Figure 2. (A and C) The 24-hour Holter monitoring shows MAT (red arrows) with sinus beats (green arrowheads) and periods of atrial flutter (B).

In infants under 1 year of age, MAT is infrequently documented and is often associated with precipitating factors such as respiratory infections (e.g., bronchiolitis or pneumonia), electrolyte imbalances (particularly hypokalemia or hypomagnesemia), and underlying conditions such as prematurity or perinatal hypoxia.[5-6] These triggers may promote atrial irritability through autonomic nervous system dysregulation or inflammatory responses affecting atrial foci.[5-6] Studies have shown that several patients with MAT have been diagnosed in the context of a respiratory infection.[6] This also occurred in the present case. Although this association was proposed decades ago, little evidence supports a causal relationship.[2]

Atrial flutter involves a macroreentrant circuit typically around the cavotricuspid isthmus in the right atrium, resulting in rapid atrial rates (250-350 bpm) with organized, sawtooth-like flutter waves on ECG, often leading to 2:1 Atrioventricular (AV) conduction and ventricular rates of 150 bpm in infants.[13] In the context of incessant tachycardias like MAT, AFL episodes can precipitate hemodynamic instability, exacerbate congestive heart failure through sustained tachycardia-induced cardiomyopathy, and increase the risk of thromboembolic events due to atrial stasis, particularly if prolonged beyond 48 hours.[14] Subsequent events may include progression to atrial fibrillation, recurrent heart failure, or, rarely in pediatrics, the need for anticoagulation if structural heart disease coexists.[14] In this case, the transient AFL resolved with rate control therapy, underscoring the importance of early diagnosis via Holter monitoring.[4]

In adults, on the other hand, this arrhythmia is more prevalent, particularly in elderly patients with comorbidities, like chronic obstructive pulmonary disease, coronary artery disease, or diabetes mellitus.[7] The prognosis in children without structural heart disease is usually excellent.[7] In patients with left ventricular dysfunction, rate control usually provides rapid and complete resolution, without relapse.[7]

Regarding treatment, there are no randomized trials to support pharmacological treatment in MAT.[2] Direct Current (DC) cardioversion is generally ineffective in MAT due to its multifocal ectopic origin, involving multiple automatic atrial foci rather than a single reentrant circuit amenable to electrical disruption.[8-9] Literature suggests that the immature atrial myocardium in infants may further reduce the efficacy of cardioversion, as the shock fails to suppress all ectopic sites simultaneously, potentially exacerbating atrial stunning or proarrhythmic effects.[8-9] In contrast, medical therapy targeting rate control—such as beta-blockers (e.g., propranolol, which antagonizes beta-adrenergic receptors to decrease sympathetic stimulation, suppress automaticity in ectopic atrial foci, and slow atrioventricular nodal conduction) and digoxin (which enhances vagal tone via Na+/K+-ATPase inhibition, increasing intracellular calcium and prolonging AV nodal refractoriness)—addresses the underlying enhanced automaticity and AV nodal conduction, achieving sustained sinus

rhythm restoration in most pediatric cases without structural heart disease.[10-11] Amiodarone is reported to be effective and superior to other agents for achieving rhythm control in MAT, as it prolongs the action potential duration and refractory period via multiple ion channel blockade (class III effect), while also exhibiting beta-blocking and calcium channel antagonism properties.[12] DC cardioversion failure is a hallmark of this arrhythmia and should not be considered if a correct diagnosis is made.[2,4] In most series, digoxin is the most commonly used medication to slow the ventricular response.[2] Beta-blockers are also excellent options.[11]

Conclusion

MAT accounts for <1% of SVT in infants and often coexists with AFL.[4] While DC cardioversion is ineffective[8-9], rate control with agents such as digoxin, propranolol, and amiodarone yields an excellent prognosis in cases with left ventricular dysfunction, as demonstrated here.[7,10-12]. Early recognition and medical management are crucial to prevent cardiomyopathy.

List of Abbreviations

SVT	Supraventricular Tachycardia
MAT	Multifocal Atrial Tachycardia
ECG	Electrocardiography/ Electrocardiogram
AFL	Atrial Flutter
AV	Atrioventricular
DC	Direct Current
Na^+/K^+-ATPase	Sodium–Potassium Adenosine Triphosphatase

Ethical Clearance

This article was approved by the local ethics committee (Universidade Federal de Santa Maria Ethics Committee, email: cep.ufsm@ufsm.br) – number 7.135.118. Patient Consent Statement: Patient´s responsible provided full written consent.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

All authors made substantial contributions according to the ICMJE criteria. Diego Chemello contributed to the conception and design of the work, drafted the manuscript, critically revised it for important intellectual content, and approved the final version to be published. Leticia Hadlich Correa de Barros and Patricia Rodrigues Lemos Cardoso contributed to the conception and design of the work, participated in drafting the manuscript, and approved the final version to be published. Camila Sales Fagundes and Patricia Chagas participated in drafting the manuscript and approved the final version to be published.

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Case Report

Myocarditis Mimicking STEMI Complicated by Complete Atrioventricular Block: Diagnostic and Therapeutic Insights

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Abstract

Background: Myocarditis, or myocardial inflammation, may share similar characteristics to Acute Coronary Syndrome (ACS), particularly ST-Elevation Myocardial Infarction (STEMI). This condition is further augmented when a Complete Atrioventricular Block (CAVB) is present. Despite being rare, this condition may pose additional diagnostic and therapeutic challenges.

Case Illustration: We report a 54-year-old woman with fatigue, dyspnea, fever, nausea, and watery diarrhea for three days. Upon admission, she experienced hypotension, pulmonary congestion, and a complete Atrioventricular (AV) block, with ST-segment elevation seen on the lateral leads. Initial laboratory results revealed markedly elevated high-sensitivity troponin T and C-reactive Protein (CRP). Bedside echocardiography showed a prominently reduced Ejection Fraction (EF) (40%) alongside the presence of regional wall motion abnormalities. Urgent coronary angiography revealed only non-obstructive coronary disease and no obstructive coronary disease. A temporary pacemaker and inotropic support were initiated. Given the presence of systemic prodromal symptoms and the absence of coronary obstruction, myocarditis was strongly suspected. High-dose intravenous methylprednisolone was given as an anti-inflammatory treatment in suspected fulminant myocarditis with cardiogenic shock and complete AV block. Recognizing that immunosuppressive therapy is not routinely recommended for all myocarditis cases, especially without biopsy confirmation. Cardiac magnetic resonance imaging subsequently confirmed myocarditis, demonstrating myocardial edema and subepicardial late gadolinium enhancement. The patient was discharged after receiving guideline-directed medical therapy and tapering corticosteroids, with preserved ventricular function on follow-up 1 month after discharge.

Conclusions: This report illustrates the importance of a stepwise diagnostic approach to differentiate myocarditis from STEMI, particularly when complicated by conduction disturbances such as CAVB. Early recognition and timely initiation of immunosuppressive therapy can lead to favorable outcomes.

Keywords: Myocarditis, STEMI mimic, atrioventricular block, cardiac magnetic resonance, case report.

Introduction

Myocarditis is a myocardial inflammatory disease that can closely mimic Acute Coronary Syndromes (ACS), particularly ST-Elevation Myocardial Infarction (STEMI). Both may present with chest discomfort, ST-segment elevation, and markedly elevated troponin.[1-2] Diagnostic uncertainty is further increased when myocarditis is complicated by Complete Atrioventricular Block (CAVB), a rare but high-risk manifestation that can resemble infarction with conduction system involvement and may precipitate cardiogenic shock. In such scenarios, rapidly distinguishing myocarditis from STEMI is critical, as management strategies diverge substantially, especially regarding the role of urgent revascularization versus advanced imaging and, in selected cases, immunosuppressive therapy.[1,3]

Distinguishing myocarditis from ACS in such circumstances is crucial, as therapeutic strategies differ markedly. We report a case of acute myocarditis presenting as a STEMI mimic complicated by CAVB, initially managed as ACS, before subsequent multimodal evaluation established the correct diagnosis. This case demonstrates that a systematic diagnostic approach is key to identifying myocarditis, particularly in ACS-like presentations with conduction abnormalities.

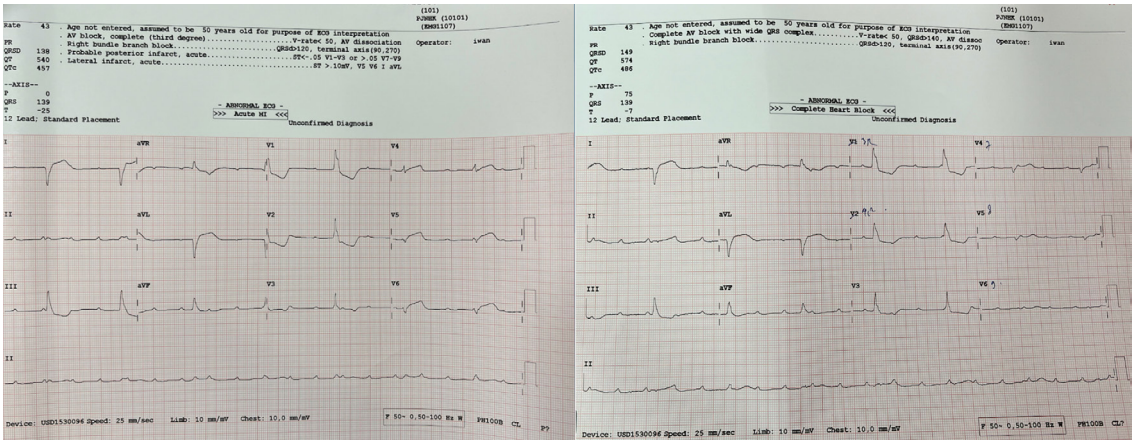

Figure 1. Initial 12-lead electrocardiograms (ECG) on presentation. The tracings demonstrate complete (third-degree) atrioventricular block with a ventricular escape rhythm at 40 bpm, wide QRS complexes with right bundle branch block morphology, and ST-segment elevation in leads I, aVL, V5–V6, with reciprocal ST depression in the inferior leads and right precordial leads. These findings were initially suggestive of acute myocardial infarction with high-grade conduction disturbance.

Case Illustration

A 54-year-old woman was brought into the emergency department with progressive fatigue, dyspnea, fever, nausea, and watery diarrhea for three days. She denied chest pain or palpitations. No history of hypertension, diabetes mellitus, dyslipidemia, or significant family history of cardiovascular disease was recognized. Upon admission, her blood pressure was 90/60 mmHg, heart rate 44 bpm, respiratory rate 28/min, and oxygen saturation 95% on room air. Physical examination revealed bilateral pulmonary rales and signs of dehydration, but no peripheral edema.

Electrocardiography (ECG) demonstrated a CAVB with a ventricular rate of 40 bpm, ST-segment elevation in leads I, aVL, V5–V6, and reciprocal depression in inferior and right precordial leads (Fig 1). Initial laboratory results showed markedly elevated high-sensitivity troponin T (6212 ng/L) and C-reactive Protein (CRP) levels (62 mg/L). Bedside echocardiography showed a prominently reduced Ejection Fraction (EF) (40%) alongside the presence of regional wall motion abnormalities, particularly in the anterolateral and inferolateral segments.

The initial working diagnosis was late-onset STEMI high lateral, complicated by CAVB with ventricular escape rhythm. The patient was initially planned to undergo primary percutaneous coronary intervention; however, the patient's coronary angiography revealed a non-significant coronary artery disease (30% proximal Left Anterior Descending [LAD] stenosis) (Fig 2). To tackle the CAVB, a temporary pacemaker was placed. Myocarditis was strongly suspected afterwards, given the lack of plausible evidence in the patient's

coronary angiography and the presence of systemic prodromal symptoms.

The patient developed cardiogenic shock with Society for Cardiovascular Angiography and Interventions (SCAI) stage C and was started on inotropic therapy. A high-dose intravenous methylprednisolone (500 mg/day for three days, followed by tapering) was initiated alongside antibiotics for concomitant pneumonia. Dobutamine infusion and supportive care were continued. The patient demonstrated gradual clinical improvement, with a reduction of CRP and hs troponin T level (Table 1), EF recovery to 56%, and restoration of sinus rhythm. Blood culture was performed to search for the aetiology of myocarditis, but it showed no bacterial growth.

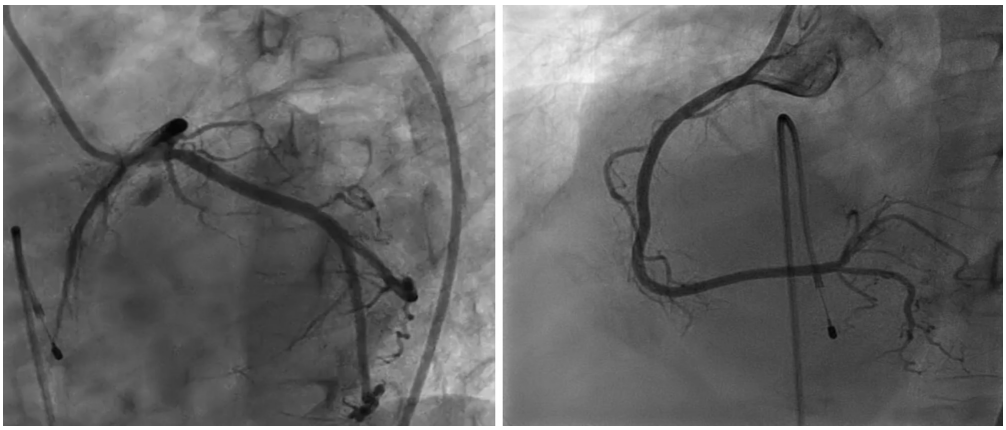

Figure 2. Coronary angiography images. (Left) Left coronary system demonstrating normal left main (LM), left anterior descending (LAD) artery with only non-obstructive coronary disease, and normal left circumflex (LCX). (Right) Right coronary artery (RCA) without significant stenosis. Overall, no evident obstructed coronary artery was seen, supporting the diagnosis of myocarditis.

Table 1. Laboratory investigations from day of admission to discharge.

Blood investigations	Day 0	Day 1	Day 2	Day 3	Day 4	Day 6	Day 8	Day 9	Day 10
Haemoglobin (g/dL)	12.5	-	-	-	10.6 ↓	13.3	14.5	-	-
Haematocrit (%)	37.7	-	-	-	31.5 ↓	39.2	43.3	-	-
Leukocyte (/µL)	7720	-	-	-	14640 ↑	15810 ↑	21700 ↑	-	-
Segment (%)	70	-	-	-	94.6 ↑	94.3 ↑	-	-	-
Lymphocytes (%)	19.9	-	-	-	2.3	1.5	-	-	-
Thrombocyte (/µL)	227000	-	-	-	213000	257000	384000	-	-
Albumin (g/dL)	-	3.6	-	-	-	-	-	-	-
Total bilirubin (mg/dL)	0.5	-	-	-	-	-	-	-	-
SGPT (U/L)	-	142 ↑	-	-	191 ↑	-	-	-	-
SGOT (U/L)	-	263 ↑	-	-	96 ↑	-	-	-	-
AFP (U/L)	-	-	73	-	-	-	-	-	-
hs Troponin T (ng/L)	6212 ↑	-	-	-	-	-	-	-	191 ↑
NT-pro BNP (pg/mL)	-	-	61273 ↑	-	-	-	-	-	5373 ↑
Ureum (mg/dL)	60	101	-	-	78	-	-	-	-
Creatinine (mg/dL)	1.63 ↑	1.34 ↑	-	-	0.95	-	-	-	-

eGFR (mL/ min/1,73 m²)	37 ↓	47 ↓	-	-	71	-	-	-	-
Natrium (mmol/L)	132	-	136	136	135	-	-	-	-
Potassium (mmol/L)	4.0	-	3.7	3.9	4.0	-	-	-	-
Chloride (mmol/L)	95	-	98	96	91	-	-	-	-
Calcium (mmol/L)	2.16	-	2.0	2.03	2.16	-	-	-	-
Magnesium (mg/dL)	2.5	-	2.7	2.7	2.6	-	-	-	-
CRP (mg/L)	62 ↑	-	-	-	23 ↑	27 ↑	-	-	-
Urinalysis	-	Leuko-cytes +3, leukocyte esterase +2	-	-	-	-	-	Negative leukocyte, negative leukocyte esterase	-

AFP = alpha-fetoprotein; SGPT = alanine aminotransferase; SGOT = aspartate aminotransferase; hs-Troponin T = high-sensitivity troponin T; NT-proBNP = N-terminal pro–B-type natriuretic peptide; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate.

At a 1-month outpatient follow-up, the 12-lead ECG demonstrates sinus rhythm at 84 bpm, right axis deviation, a PR interval of 150 ms, a QRS duration of 80 ms, poor R-wave progression, and low-voltage QRS complexes. No pathological Q waves, no ST-segment elevation or depression, and no T-wave inversion were observed. (Figure 2). These findings were consistent with the initial emergency room presentation, supporting recovery from acute myocarditis.

Cardiac Magnetic Resonance imaging (CMR) was performed during follow-up. This examination revealed myocardial edema and subepicardial Late Gadolinium Enhancement (LGE) in the lateral wall (Fig 4), two features consistent with acute myocarditis. The patient was discharged and was given heart failure Guideline-Directed Medical Therapy (GDMT) and tapering corticosteroids. At one-month follow-up, she remained asymptomatic with preserved ventricular function.

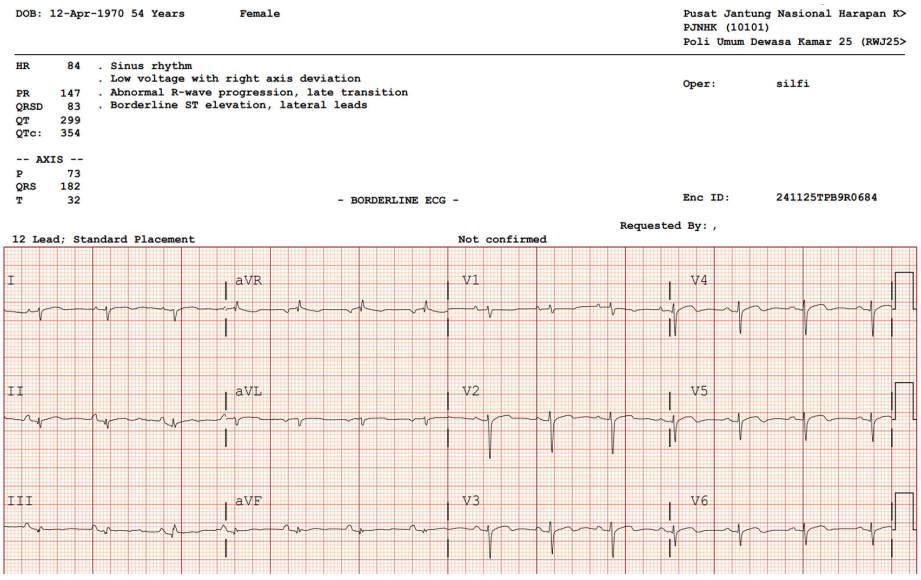

Figure 3. The follow-up ECG demonstrates sinus rhythm at 84 bpm with low QRS voltage, right axis deviation, delayed R-wave progression, and borderline ST-segment elevation in the lateral leads. Complete atrioventricular block has resolved.

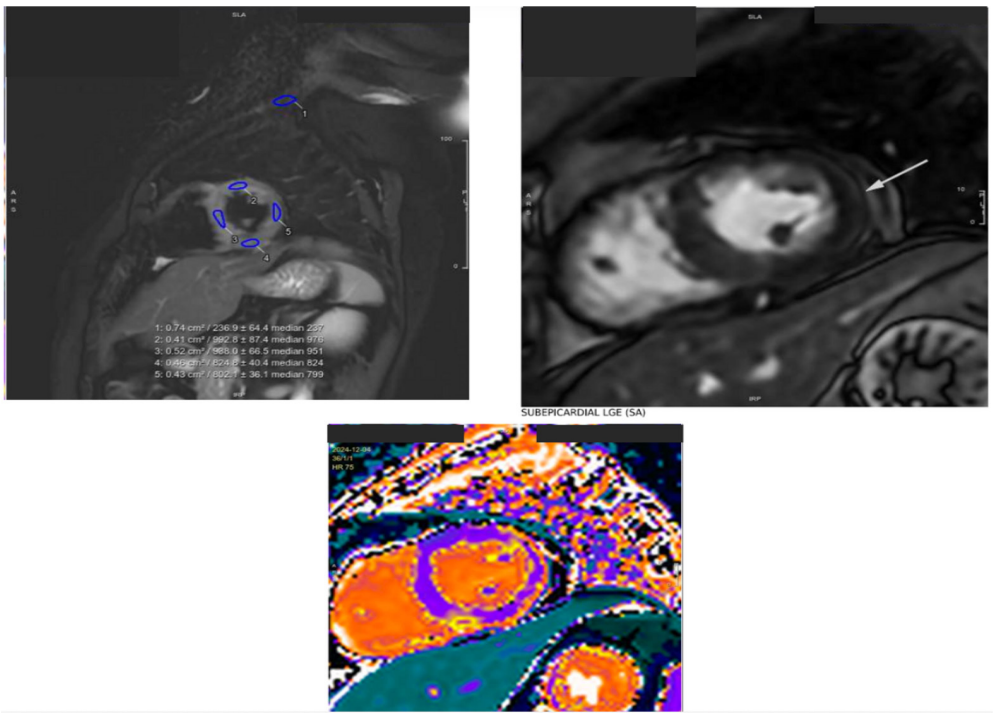

Figure 4. Cardiac magnetic resonance (CMR) images demonstrating myocardial inflammation. (Top left) T2-weighted imaging in all mid-segments of the left ventricle (LV) shows increased signal intensity consistent with myocardial edema (blue regions of interest). (Top right) Late gadolinium enhancement (LGE) was identified in the subepicardial region of the lateral wall (arrow), indicating myocardial injury and fibrosis. (Bottom) Native T1 mapping with elevated value in mid lateral segment, further supporting presence of myocardial edema. These findings fulfill the updated Lake Louise criteria and confirm the presence of acute myocarditis.

Discussion

The case provided addresses the diagnostic complexity of acute myocarditis presenting with simultaneous ST-segment elevation and CAVB. Such coexistence is particularly rare.[1-3] The complete AV block in this case is most likely due to direct inflammatory involvement of the AV node and the His (Purkinje) system. In myocarditis, immune-mediated cell injury and edema within the specialized conduction tissue can acutely interrupt impulse propagation from atria to ventricles, producing a high-grade or complete block that may improve as inflammation resolves, as observed in our patient.[4] While ST-segment elevation is frequently reported in myocarditis, which has been found to occur in up to 85% of cases, high-grade AV block remains distinctly uncommon and is generally associated with more fulminant phenotypes or specific etiologies such as giant cell myocarditis, sarcoidosis, or Lyme carditis.[1-3] The presence of both findings initially justified an emergent diagnosis of ACS, emphasizing the real-world challenge of differentiating myocarditis from STEMI.

In our patient, several features ultimately favored a diagnosis of acute myocarditis over true STEMI.[2] Clinically, the presentation was dominated by systemic prodromal symptoms (fever, diarrhea, malaise) and absence of typical ischemic chest pain, which is more consistent with viral or immune-mediated myocardial inflammation than with plaque rupture. On ECG, the initial tracing showed complete AV block with lateral ST-segment elevation and reciprocal changes, but follow-up ECG demonstrated restoration of sinus rhythm with low-voltage QRS complexes, poor R-wave progression, and only borderline lateral ST elevation without the development of pathological Q waves, suggesting transient inflammatory injury rather than fixed transmural necrosis. Coronary angiography revealed only discrete proximal LAD stenosis and no culprit obstructive lesion, while subsequent CMR demonstrated diffuse myocardial edema and subepicardial LGE in the lateral wall. This constellation of clinical, electrocardiographic, angiographic, and tissue-characterization findings supported myocarditis as the unifying diagnosis.[2-3]

In this patient, by performing an urgent coronary angiography, we managed to quickly exclude the presence of obstructive coronary artery disease, thereby redirecting the diagnostic approach toward non-ischemic causes. This stepwise process is consistent with guideline-based recommendations that mandate invasive evaluation when ACS cannot be confidently excluded.[2-3] The systemic prodromal features fever, diarrhea, and malaise added further clinical weight to the suspicion of viral or immune-mediated myocarditis.[5-7]

The subsequent use of CMR was decisive. CMR, incorporating T2-weighted imaging, native T1 mapping, and LGE, is now established as the primary non-invasive reference standard for diagnosing myocarditis.[1,5]

In this case, the combination of myocardial edema and subepicardial LGE fulfilled the updated Lake Louise criteria, hence, providing reliable confirmation. Cardiac magnetic resonance in this patient met the updated 2018 Lake Louise criteria for acute myocarditis, showing myocardial edema and non-ischemic subepicardial late gadolinium enhancement in the lateral wall. These findings confirmed the diagnosis and, given the limited extent of LGE together with the patient's functional recovery, suggest a relatively favorable prognosis. Beyond diagnostic accuracy, LGE and tissue mapping carry prognostic significance; extensive LGE (>20% of left ventricular mass) and increased extracellular volume have been linked to a higher risk of sudden cardiac death and adverse remodelling.[1] Our patient demonstrated localized subepicardial LGE with functional recovery, underscoring the heterogeneity of outcomes in myocarditis.

Therapeutically, the patient's favourable response to high-dose corticosteroids raises important considerations. In this case, the decision to initiate high-dose intravenous methylprednisolone was guided by the fulminant presentation with cardiogenic shock, severe LV dysfunction, and high-grade AV block.[8] All of these are strongly suggestive of an intense inflammatory process involving both the myocardium and the conduction system. Contemporary consensus documents and guidelines acknowledge that, although routine immunosuppression is not recommended for uncomplicated lymphocytic myocarditis, empirical intravenous corticosteroids may be considered in fulminant or complicated acute myocarditis to stabilize hemodynamics while awaiting or in the absence of definitive etiologic clarification.[8] High-dose glucocorticoids are intended to attenuate immune-mediated myocardial injury, reduce myocardial edema, and mitigate inflammatory infiltration, which may lead to faster recovery of ventricular function and resolution of high-grade block (as observed in our patient). Although the role of immunosuppression in myocarditis remains debated, emerging evidence suggests that in selected infection-negative or immune-mediated myocarditis, corticosteroids may expedite recovery and reduce arrhythmic risk.[3] The clinical improvement in this case, resolution of CRP as an inflammatory parameter with restoration of sinus rhythm and normalization of EF, aligns with such findings. This case highlights the unique coexistence of STEMI-like ST-segment elevation, complete AV block, and non-obstructive coronary arteries, a combination that strongly points toward acute myocarditis rather than true infarction and underscores the diagnostic challenge for clinicians.

Finally, this case reiterates how the integration of clinical suspicion, invasive and non-invasive imaging, and individualized therapy plays such an important role in managing patients. For clinicians, the key learning point is that myocarditis should always be one of the main differential diagnoses of patients with STEMI-like presentations complicated by conduction abnormalities, particularly when coronary angiography reveals non-obstructive disease. Early recognition and tailored management may significantly alter the trajectory of these patients, converting a potentially fatal presentation into a favorable recovery.

Conclusion

The provided case demonstrates how diagnosing myocarditis mimicking STEMI that is further complicated by complete AV block may be a challenge among physicians. A structured approach integrating coronary angiography and advanced CMR is essential to establish a reliable diagnosis. Early recognition and timely initiation of corticosteroid therapy were temporally associated with the patient's clinical and functional improvement. However, the favorable course was likely multifactorial and may also reflect supportive heart failure management and the self-limited nature of the underlying inflammatory process. Clinicians should remain vigilant for myocarditis in ACS-like presentations with conduction abnormalities, as prompt differentiation has major therapeutic and prognostic implications.

Learning Points

- Acute myocarditis can closely mimic STEMI when presenting with ST-segment elevation and markedly elevated troponin, particularly when accompanied by complete atrioventricular block.
- The coexistence of STEMI-like ECG changes, complete AV block, and non-obstructive coronary arteries should prompt consideration of myocarditis and trigger advanced tissue-characterization imaging with CMR.
- CMR fulfilling the updated 2018 Lake Louise criteria (myocardial edema and non-ischaemic subepicardial LGE) is pivotal for confirming myocarditis and provides prognostic information based on the extent and distribution of LGE.
- In conclusion, biopsy-unproven myocarditis with cardiogenic shock and complete AV block, high-dose corticosteroid therapy may be considered on an individualized basis, recognizing that improvement is likely multifactorial and that routine immunosuppression is not recommended for all myocarditis phenotypes.

List of Abbreviations

ACS	Acute Coronary Syndrome
AFP	Alpha-fetoprotein
AV	Atrioventricular
bpm	Beats per minute
CAVB	Complete Atrioventricular Block
CMR	Cardiac Magnetic Resonance
CRP	C-reactive protein
ECG	Electrocardiogram
EF	Ejection Fraction
eGFR	Estimated glomerular filtration rate
GDMT	Guideline-Directed Medical Therapy
hs-Troponin T	High-sensitivity troponin T
LAD	Left Anterior Descending
LGE	Late Gadolinium Enhancement
LM	Left Main
LCX	Left Circumflex
LV	Left Ventricle
NT-proBNP	N-terminal pro–B-type natriuretic peptide
RCA	Right Coronary Artery
SCAI	Society for Cardiovascular Angiography and Interventions
SGOT	Aspartate aminotransferase
SGPT	Alanine aminotransferase
STEMI	ST-Elevation Myocardial Infarction

Ethical Clearance

Not applicable.

Publication Approval

All authors are consent to the publication of this manuscript. Written informed consent was obtained from the patient.

Authors Contributions

RM and HA collected clinical data, prepared the figures, and drafted the manuscript. RS, CA, DYH, BW supervised clinical management, provided critical revisions, and contributed to the final interpretation. All authors read and approved the final version of the manuscript.

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Conflict of Interest

None.

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Available upon request.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

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