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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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      Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.
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    - Book
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Editorial

A Model of Cardiac Preparticipation Screening for Sports Competition in Indonesia: Challenges and Future Perspectives

Dwita Rian Desandri[1,2], Averina Octaxena Aslani[2]

Abstract

Sudden Cardiac Death (SCD) among athletes remains a preventable tragedy. Yet, Indonesia lacks a national registry, standardized protocols, and systematic data amid rising coronary artery disease prevalence and regional cardiovascular risks unique to the Asia-Pacific. While countries like Italy have reduced SCD by 89% through mandatory electrocardiogram-based screening, Indonesia's Law No. 11 of 2022 mandates athlete health services without specifying details of Cardiac Preparticipation Screening (CPS), resulting in inconsistent implementation across events such as the quadrennial *Pekan Olahraga Nasional* (PON, National Sports Week).

This editorial proposes a feasible and cost-effective CPS model for PON athletes, comprising personal and family history, physical examination, and 12-lead electrocardiography based on the 2017 International Criteria, delivered through collaboration among the Indonesian Heart Association (IHA), the National Sports Committee (KONI), and relevant ministries. Piloted with trained general practitioners and cardiologists at designated training centres, the model aligns with World Health Organization (WHO) screening recommendations, minimizes cost per athlete, and reserves echocardiography for high-risk cases.

By generating Indonesia's first athlete SCD data, enhancing provider training, and enabling a scalable nationwide rollout, this framework promises to quantify cardiovascular risks, avert fatalities, and position Indonesia as a leader in equitable sports cardiology for resource-constrained settings. Thereby, transforming competitive sport from potential peril into an unalloyed benefit.

(Indonesian J Cardiol, 2026;47;1-7)

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Introduction

Cardiac Preparticipation Screening (CPS) for athletes represents a vital intersection of sport, science, and public health. The need to identify conditions that could predispose to sudden cardiac events in young, ostensibly healthy individuals has driven a long-standing debate about what screening should include, how it should be implemented, and what benefits we can realistically expect. Several countries have adopted CPS as a routine protocol, underscoring its life-saving benefits for athletes despite the challenges of balancing sensitivity, specificity, accessibility, and cost.[1] However, CPS remains a significant clinical challenge for Indonesian athletes owing to inconsistent infrastructure, the high prevalence of undetected cardiac conditions, and limited standardized protocols.

Recently, the Philippine Heart Association (PHA) urged the adoption of a national framework for cardiac screening in athletes. While no standardized national recommendations currently exist for cardiovascular screening among Filipino athletes, as Indonesia is facing now, the PHA has been calling for such a framework.[2]

In this editorial, we discuss the current status of Sudden Cadiac Death (SCD) and cardiac risk among Indonesian athletes, the state of CPS, the challenges shaping policy and practice, and future perspectives on more effective, equitable screening that protects Indonesian athletes without overburdening programs or families. In the long term, Indonesia could avert preventable tragedies while safeguarding the joys and benefits of competitive sport.

Current Status of SCD and Cardiac Risk in Indonesian Athletes

Indonesia has no unified national registry for sports-related cardiac deaths, and no formal systematic investigation has been conducted after any reported SCD event. Consequently, any published incidence remains speculative. The five documented SCD cases in 2024 that happened during sports are fragments of a much larger, unseen picture rather than a complete dataset. These events, however, align with global concerns: that intense physical exertion can unmask structural or electrical heart disease in otherwise superficially "healthy" individuals.

Underlying this vulnerability is an evolving cardiovascular disease profile. Data from the Indonesian Ministry of Health indicate that Coronary Artery Disease (CAD) prevalence increased from 0.3% in 2013 to 1.5% in 2018, making CAD the most common cardiovascular disease in the national burden of disease landscape.[3] As lifestyle factors shift toward more sedentary behavior outside sport, yet more people pursue vigorous training or competition, the collision between underlying cardiovascular pathology and high-intensity exercise can become a lethal combination. A young runner collapsing during a race serves as a reminder that even recreational athletes can carry undetected risk.

The Asia–Pacific region further complicates the epidemiological picture. Compared with Europe, this region features higher rates of certain inherited arrhythmia syndromes (e.g., Brugada syndrome) and cardiomyopathies, as well as a greater prevalence of rheumatic valvular disease and Kawasaki-related sequelae. Combat sports such as martial arts are also widely popular, which increases the risk of commotio cordis, a form of impact-induced ventricular fibrillation. Socioeconomic and health system heterogeneity further amplifies risk variability: Indonesia ranks 16th in world Gross Domestic Product (GDP), yet national health coverage remains uneven, and medical service costs, although lower than in many Western countries, are not uniformly affordable or accessible.[4-5] These factors conspire to make SCD in Indonesian athletes a preventable, rather than inevitable, tragedy.

Current State of Cardiac Preparticipation Screening

Developed countries such as the United States and several European nations have long implemented systematic CPS programs for athletes, often mandated by law or national sports federations, thereby enabling precise tracking of sports-related cardiac mortality and morbidity. Italy's Veneto region, for example, introduced mandatory CPS in 1982 (including history, physical exam, and 12-lead Electrocardiogram [ECG]) which reduced SCD rates in screened athletes by 89% over 26 years (from 3.6 to 0.4 per 100,000 athlete-years), while non-athlete rates remained stable; this program has since documented over 42,000 at-risk conditions identified nationwide through prospective

registries.[6] In the US, the American Heart Association (AHA) recommends annual history and physical exams for over 8 million young competitive athletes, supplemented by ECG in high-risk states like Texas, with the National Center for Catastrophic Sport Injury Research logging ~100 SCD cases yearly (incidence ~1:50,000–200,000), mostly hypertrophic cardiomyopathy or coronary anomalies.[7] These systems not only quantify low baseline risks but also refine protocols via data-driven refinements, such as the 2017 International ECG criteria that cut false positives by 50% while preserving sensitivity.

In stark contrast, Indonesia lacks a national SCD registry, relying instead on fragmented reports that underscore preventable gaps amid rising coronary artery disease prevalence, for example, the 2025 deaths of athletes Bejo Sugiantoro and Agil Tri Nugroho, and the iconic 2000 case of footballer Eri Irianto. Moreover, although Indonesia's Law No. 11 of 2022 on the National Sports System mandates health services, facilities, and personnel to ensure athlete safety in competitive events, it omits requirements for CPS and detailed protocols, creating opportunities for structured cardiac screening models.[8]

The Controversies that Shape Policy and Practice

Preparticipation screening is conducted by the relevant governing body, such as national federations, regional National Sports Committee of Indonesia (KONI) committees, or sports clubs, depending on the level of competition. For instance, ahead of the Liga 1 season (Indonesia's premier football league, akin to the English Premier League), all clubs must complete Federation Internationale de Football Association (FIFA)'s Pre-Competition Medical Assessment (PCMA). This protocol encompasses medical history, physical examination, cardiovascular and musculoskeletal examinations, ECG, laboratory tests, and echocardiography.[9] The results will form the basis for team registration.

To our knowledge, no cases of SCD have been reported in major national sports competitions in Indonesia, such as the *Pekan Olahraga Nasional* (National Sports Week, PON). Nevertheless, given the large number of participating athletes and the lack of comprehensive SCD data, systematic cardiac preparticipation screening is essential for the upcoming PON.

However, realizing this goal in Indonesia requires overcoming key logistical and infrastructural barriers. First, rural and remote provinces in Indonesia often have difficulty accessing public hospitals, ECG machines, or even advanced cardiac diagnostic tools like echocardiography and exercise stress testing, leading to inconsistent screening protocols across regions.[8] Second, local or regional tournaments rarely enforce formal preparticipation screening, leaving athletes at higher risk of undetected cardiac conditions. Third, many venues lack on-site Automated External Defibrillators (AEDs) and trained personnel, while delayed emergency medical services worsen outcomes following sudden cardiac events.

Additionally, another key consideration for establishing CPS in Indonesia is economic feasibility at scale. The strength of this screening model lies not in elaborate spreadsheets but in its inherent affordability and the substantial returns it generates from a modest upfront investment, which reflects the pragmatic strategies adopted by other nations that have successfully scaled athlete cardiac screening. Italy, for example, has sustained mandatory nationwide preparticipation screening since 1982 through public funding and partnerships with sports federations, evaluating millions of athletes annually at per-person costs far below those of advanced treatments, and achieving an 89% reduction in SCD without fiscal strain.[1] Similarly, FIFA mandates cardiac screening (including ECG) for all World Cup participants across diverse economies, enforced via shared governance with member associations, demonstrating that targeted protocols, backed by international standards, remain viable even in resource-constrained settings.

As a foundational examination, medical history, physical examination, and ECG form the bedrock of comprehensive CPS. Under Indonesia's National Law No. 8 of 2015 on Ministry of Sports regulations, cardiac screening at the National Sports Hospital in Jakarta costs IDR 375,000.[10] This may break down to IDR 50,000–200,000 for medical history and physical examination, and IDR 100,000–200,000 for ECG.

Referrals to provincial hospitals or the National Cardiovascular Centre in Jakarta (for echocardiography, Holter monitoring, or advanced imaging) share queues with the general population, unlike professional football clubs with private insurance.[8] To address this, we propose collaborations with referral centres to expedite diagnostics. Costs at the National Cardiac

Centre Jakarta include: Echocardiography IDR 1,000,000; Holter ECG IDR 1,000,000; CPET IDR 2,500,000; CT angiography IDR 4,900,000; Cardiac Magnetic Resonance Imaging (MRI) IDR 7,000,000.

Ultimately, implementing CPS yields substantial societal returns: averting even a single SCD spares immense social, emotional, and systemic costs that far exceed program expenses.

The Future Perspective toward Indonesia's Equitable Preparticipation Screening

Any screening programme must meet the World Health Organization (WHO) criteria (established in 1968, revised since): the target condition must pose a major health burden; exhibit a recognisable latent and early symptomatic stage; have available, acceptable diagnostic tools; treatments must exist; and the process must be economically justified.[11] SCD in athletes fulfils these criteria: it is a high-impact, low-prevalence event with often subclinical pathologies (e.g., cardiomyopathies, arrhythmias, valvular disease, coronary artery disease), amenable to interventions like implantable cardioverter-defibrillators, ablation, and pharmacotherapy. The quadrennial PON, with its large cohorts of athletes, offers an ideal platform to pilot a WHO-aligned cardiac screening framework.

Implementation

Screening occurs at training centres or provincial residences. Athletes provide informed consent (parental for ages 14–18); players who refuse consent are excluded.

Screening Team

The Indonesian Heart Association (IHA) proposes collaboration with KONI and the Ministry of Youth and Sports for provincial teams comprising:

- 2–3 trained General Practitioners (GPs) for history and examination;
- 2–3 trained GPs for ECG interpretation and data entry;
- 3–4 nurses for ECG and vitals;
- 2–3 IHA-assigned cardiologists to oversee and perform echocardiography as needed;
- 1 KONI staff liaison.

With only one sports cardiologist nationwide (at Jakarta's National Cardiac Centre), IHA will train participating GPs/cardiologists via a short course. GPs/nurses will be sourced from referral hospitals or local residents. Ambiguous cases will be referred centrally for teleconsultation with the sports cardiologist at Jakarta's National Cardiac Centre, in collaboration with the doctor in charge at designated training centres. If further examination is required that cannot be performed locally, athletes will be referred to the National Cardiac Centre in Jakarta.

History and Physical Examination

Standardized via the 14-item American Heart Association (AHA) checklist, recommended by the Asian Pacific Society of Cardiology (APSC) consensus.[4,7,12-13] The Pre-Participation Examination Monograph (PPE-4) supplements this.[14-16] However, both yield high false-positive rates and inferior sensitivity/specificity versus ECG.

Electrocardiography

ESC and AHA endorse pre-participation screening, though components differ.[12,17] ECG addition reduces SCD incidence and outperforms history/physical exam.[18-19] APSC deems a 12-lead ECG appropriate if capacity exists, the standards are met, and it is interpreted in accordance with the 2017 International Criteria.[4,20] Southeast Asian data (e.g., Singapore) show athlete-specific variants, such as anterior T-wave inversions, necessitating regional norms.[21] Borderline/red-flag ECGs will be reviewed onsite by cardiologists.

Echocardiography

Transthoracic Echocardiography (TTE) clarifies morphology, function, and coronary artery origins, but is not routinely performed here due to resource limitations (2 cardiologists/site).[4,22] Available onsite via referral hospital; detects ~10% more abnormalities post-normal screening.[23]

Further Investigations and Limitations

Advanced tests occur at referral hospitals, pending mitigation of the queue via committee-hospital coordination. Additional limitations:

- Securing KONI approval, potentially overlapping general checks (to be addressed with international cost-effectiveness data);
- Exclusion of athletes >35 years, a target for future expansion.

Conclusion

In summary, Indonesia stands at a pivotal moment to transform cardiac preparticipation screening from fragmented practice to a unified, data-driven safeguard for its athletes. By piloting an affordable, ECG-led model at events like PON, supported by the safety

mandates of Law No. 11/2022 and partnerships across IHA, KONI, and the Ministry of Youth and Sports, this framework addresses critical gaps in SCD surveillance, regional disparities, and access to diagnosis while meeting WHO criteria for feasibility and equity.

Successful rollout promises not only to quantify Indonesia's athletes' cardiac risks for the first time but also to avert tragedies amid rising CAD burdens, mirroring Italy's 89% reduction in SCD through sustained, scalable protocols. In the long term, ministerial enforcement, provider training on international ECG and other advanced examination standards, as well as phased nationwide expansion, will ensure that the benefits of competitive sport endure without fatal costs, positioning Indonesia as a model for resource-smart screening within the diverse epidemiological landscape of the Asia Pacific.

List of Abbreviations

AED	Automated External Defibrillators
AHA	American Heart Association
APSC	Asian Pasific Society of Cardiology
CAD	Coronary Artery Disease
CPET	Cardiopulmonary Exercise Testing
CPS	Cardiac Preparticipation Screening
CT	Computed Tomography
ECG	Electrocardiogram
ESC	European Society of Cardiology
FIFA	Fédération Internationale de Football Association
GDP	Gross Domestic Product
GP	General Practicioners
IDR	Indonesian Rupiah
IHA	Indonesian Heart Association
KONI	National Sports Committee of Indonesia
MRI	Magnetic Resonance Imaging
PCMA	Pre-Competition Medical Assessment
PON	National Sports Week
PHA	Philippine Heart Association
PPE	Preparticipation Examination
SCD	Sudden Cardiac Death
TTE	Transthoracic Echocardiography
WHO	World Health Organization

Conflict of Interest Statement

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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, analysis, or conclusions presented in this manuscript.

Reference

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Original Article

Utilization of Red Blood Cell Distribution Width in Predicting Length of Stay in Patients Treated in Cardiovascular Intensive Care Unit: A Cohort Study

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Abstract

Background: The risk stratification of mortality in critically ill patients with heart disease has long been available and validated. Red Blood Cell Distribution Width (RDW) has traditionally been used in the differential diagnosis of anemias. High RDW is associated with worse outcomes in diverse scenarios, including in critical illness. This study aimed to investigate the correlation of RDW value with the length of Cardiovascular Intensive Care Unit (CICU) stay.

Methods: This cohort study was conducted at Prof. Dr. R. D. Kandou Hospital in Manado from February to May 2021. The study subjects were patients treated in the CICU. Statistical analysis was performed using Spearman's correlation and linear regression.

Results: Among 97 patients studied, the median Red Cell Distribution Width – Coefficient of Variation (RDW-CV) was 13.6% (Interquartile Range [IQR] 12.7-15.3), and the median CICU length of stay was 2.0 days (IQR 2.0-4.5). RDW demonstrated a significant positive correlation with CICU length of stay (Spearman's $\rho = 0.317$, $p = 0.002$). Linear regression analysis revealed that each 1% increase in RDW was associated with a 0.213-day rise in length of stay ($B = 0.213$, $\beta = 0.244$, $R^2 = 0.059$, $p = 0.016$).

Conclusions: Higher RDW values are significantly associated with longer CICU stay. As an easily accessible parameter, RDW shows promise as a useful prognostic marker for risk stratification in cardiac critical care.

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Keywords: Red Blood Cell Distribution Width, Cardiovascular Intensive Care Unit, Length of Stay, Prognostic Marker, Cardiac Critical Care

Introduction

Cardiovascular Disease (CVD) remains the leading cause of disease burden worldwide and was responsible for 6.2 million deaths between the ages of 30 and 70 in 2019.[1] The incidence of CVD is increasing globally and includes several specific conditions, including Heart Failure (HF), Ischemic Heart Disease (IHD), hypertensive heart disease, peripheral vascular disease, and Atrial Fibrillation (AF).[2]

The Red Cell Distribution Width (RDW) is a simple, rapid, and readily available hematological parameter that measures the heterogeneity of red blood cell size and is now automatically generated by all commercially available hematological analyzers along with a Complete Blood Cell Count (CBC).[3] Clinical studies in CVD patients have reported that RDW is a novel independent predictor of all-cause mortality and Major Adverse Cardiac Events (MACE).[4-6] The association between RDW and CVD may involve several mechanisms, including inflammation, nutritional disturbances, and alteration in erythropoiesis.[7]

This study aimed to investigate the correlation between RDW value and Length of Stay (LOS) in the Cardiovascular Intensive Care Unit (CICU).

Methods

This was an analytical observational study with a cohort design. The study was conducted at Prof. Dr. R. D. Kandou Hospital in Manado from February to May 2021. Subjects included all patients treated in the CICU during this period. Patient data were obtained from medical records. Statistical analyses were performed using Spearman's rank correlation and linear regression.

Results

This study analyzed 97 CICU patients with distinct clinical profiles. As detailed in Table 1, the cohort had a mean age of 55.7 years and was predominantly male (71.1%). Acute coronary syndrome was the most common primary diagnosis (60.8%), while hypertension was the most prevalent preexisting condition (58.8%).

RDW demonstrated a significant positive correlation with CICU LOS (Spearman's $\rho = 0.317$, $p = 0.002$), as shown in both Figure 1 and Table 2. Linear regression analysis further indicated that each 1% increase in RDW was associated with a 0.213-day rise in LOS ($B = 0.213$, $\beta = 0.244$, $R^2 = 0.059$, $p = 0.016$).

Table 1. The demographic and clinical characteristics of study subjects (n=97).

Variables	Value (n=97)
Sex	
Men, n (%)	69 (71)
Women, n (%)	28 (29)
Age (years)	55.7 ± 14.1
BMI (kg/m2)	24.2 (22.2 – 26.1)
Smoking, n (%)	43 (44)
Primary Diagnosis at Presentation	
Acute Coronary Syndrome, n (%)	59 (60.8)
Acute Heart Failure, n (%)	16 (16.5)
Shock and Cardiac Arrest, n (%)	1 (1.0)
Arrhythmia and other, n (%)	17 (17.5)
Controlled Comorbidities, n (%)	4 (4.1)
Preexisting Conditions	
Hypertension, n (%)	57 (58.8)
Diabetes mellitus, n (%)	25 (25.8)
Chronic kidney disease, n (%)	21 (21.6)
Dyslipidemia, n (%)	15 (15.5)
Laboratory Parameters	
RDW-CV (%)	13.6 (12.7 – 15.3)
Outcome	
CICU length of stay (days)	2.0 (2.0 – 4.5)

Note: Data are presented as n(%), mean ± standard deviation, or median (IQR); BMI: Body Mass Index; RDW-CV: Red Blood Cell Distribution Width – Coefficient of Variation; CICU: Cardiovascular Intensive Care Unit.

Table 2. Spearman Correlation between RDW value (%) and length of CIC stay (days).

Variable	Correlation Coefficient (r)	n	p-Value
RDW value vs CICU length of stay	0.317	97	0.002*

*Significant (p<0.00); RDW: Red Cell Dsitribution Width, CICU: Cardiovascular Intensive Care Unit.

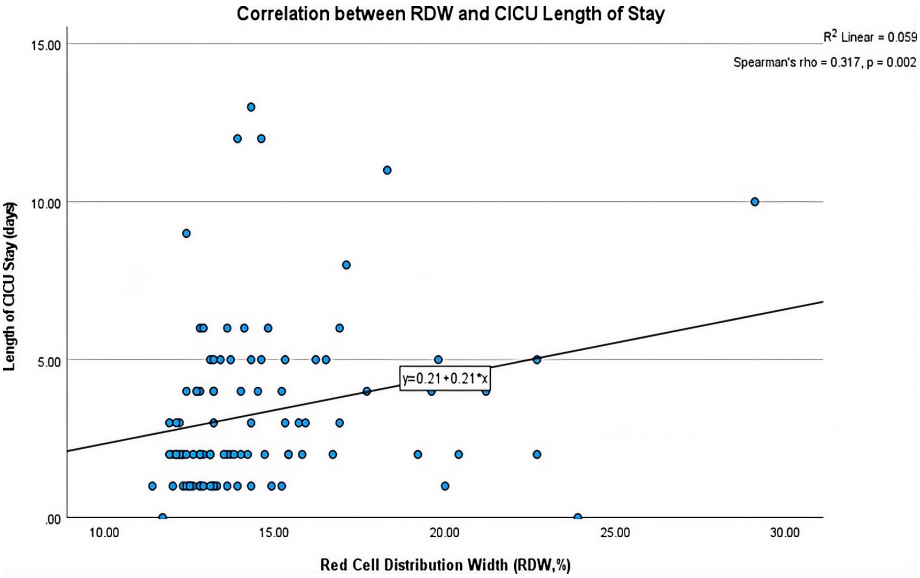

Figure 1. Scatter plot demonstrating the correlation between Red Cell Distribution Width (RDW) and the length of stay in the Cardiovascular Intensive Care Unit (CICU). The solid line represents the line of best fit from linear regression analysis ($R^2 = 0.059$). The correlation was statistically significant (Spearman's ρ (rho) = 0.317, p = 0.002).

As presented in Table 3, significant variations in LOS were observed across diagnostic categories (Kruskal-Wallis, p = 0.011). Acute Heart Failure (AHF) patients had the longest stays (5.06 ± 2.69 days), followed by acute coronary syndrome (3.02 ± 2.71 days), arrhythmia (2.76 ± 1.64 days), and controlled comorbidities (2.50 ± 2.63 days). Among preexisting conditions, non-hypertensive patients had significantly longer stays than hypertensive patients (4.05 ± 2.70 vs. 2.79 ± 2.48 days, p = 0.019). No other comorbidities were significantly associated with LOS.

Subgroup analysis based on primary diagnosis revealed that the correlation between RDW and CICU LOS was strongest in patients with acute coronary syndrome (ρ = 0.275, p = 0.035), as shown in Table 4. A similar but non-significant trend was observed in patients with AHF (ρ = 0.295, p = 0.268), likely due to the limited sample size. No meaningful correlation was found in arrhythmia patients (ρ = 0.006, p = 0.983).

Discussion

This study demonstrates a significant positive correlation between RDW and CICU LOS (Spearman's ρ = 0.317, p = 0.002), with each 1% increase in RDW associated with a 0.213-day increase in hospitalization duration. This finding aligns with Havens *et al.*[6] who demonstrated that RDW predicts outcomes in critically ill emergency patients. General surgery patients and Meynaar *et al.*[7] who established RDW as a mortality predictor in critically ill populations.

The significant variation in LOS across diagnostic categories underscores the importance of initial clinical presentation in determining healthcare resource utilization.[8] AHF patients had the longest stays (5.06 days), consistent with the

Table 3. Association between diagnosis categories, preexisting conditions, and CICU length of stay.

Variable	n	Mean LOS ± SD (days)	P-value
Primary Diagnosis Category			0.011
Acute Coronary Syndrome	59	3.02±2.71	
Acute Heart Failure	16	5.06±2.69	
Shock and Cardiac Arrest	1	5.00	
Arrhythmia and other	17	2.76±1.64	
Controlled Comorbidities	4	2.50±2.63	
Preexisting Conditions			
Hypertension			0.019
No	40	4.05±2.70	
Yes	57	2.79±2.48	
Diabetes Mellitus			0.981
No	72	3.31±2.41	
Yes	25	3.32±3.24	
Chronic Kidney Disease			0.675
No	76	3.25±2.64	
Yes	21	3.52±2.64	
Dyslipidemia			0.644
No	82	3.26±2,45	
Yes	15	3.60±3.54	

Note: SD, standard deviation; LOS, Length of stay.

Table 4. Correlation between RDW and CICU length of stay by primary diagnosis.

Primary Diagnosis	n	Spearman's ρ	P-value
Acute Coronary Syndrome	59	0.275	0.035
Acute Heart Failure	16	0.295	0.268
Arrhythmia and other	17	0.006	0.983

complex management challenges described in HF populations by Jung *et al.* and Felker et *al.*[8-9]

The pathophysiological basis for RDW's association with prolonged hospitalization involves several interconnected mechanisms. Elevated RDW reflects impaired erythropoiesis due to chronic inflammation and nutritional deficiencies, as explained by Weiss and Goodnough in anemia of chronic disease.[10] Our findings corroborate Allen *et al.*, who validated RDW's prognostic mechanisms in HF.[11] In acute coronary syndrome, the inflammatory cascade promotes endothelial dysfunction while suppressing erythrocyte maturation, consistent with chronic inflammation pathways in CVD described by Zyga and Kolovos.[5] This link between elevated RDW and worse outcomes in IHD is supported by Li *et al.* in coronary artery disease patients and Sahin *et al.* in non-ST elevation myocardial infarction.[12-13]

In HF, the relationship is more complex due to neurohormonal activation influencing the clinical course. Van Kimmenade *et al.* demonstrated RDW's association with 1-year mortality in AHF, further supporting our findings.[14]

The paradoxical finding that non-hypertensive patients had longer CICU stays than hypertensive patients (4.05 vs. 2.79 days, p = 0.019) may reflect more established treatment protocols in hypertensive patients or more acute decompensations in non-hypertensive patients requiring prolonged workup, consistent with patterns of risk adjustment in cardiovascular outcomes described by Krumholz *et al.*[15]

From a clinical perspective, RDW's accessibility and low cost make it valuable in resource-limited settings as a routinely available parameter.[3] The association between RDW and prolonged CICU stay suggests potential utility in triaging and risk stratification in cardiac critical care.

Study Limitations

This study has several limitations. First, the analysis focused on LOS without examining other clinical outcomes such as mortality or MACE. Second, the single-center design and sample size limit generalizability and statistical power for subgroup analyses. For instance, the small sample size in the AHF subgroup (n=16) likely contributed to the non-significant result despite a suggestive correlation. Finally, RDW was measured only at admission, preventing assessment of its dynamic changes during hospitalization. Despite these limitations, our findings provide valuable insights into RDW's prognostic utility in cardiac critical care.

Conclusion

This study establishes a significant positive correlation between RDW and the LOS in the CICU. Furthermore, our findings highlight significant variations in LOS across diagnostic categories, with AHF associated with the longest hospitalizations. The paradoxical association between hypertension and shorter stays suggests complex interactions between chronic conditions and acute care outcomes. Therefore, RDW represents a valuable prognostic tool, particularly when considered alongside diagnostic category and comorbidity profile.

List of Abbreviations

AF	Atrial Fibrillation
AHF	Acute Heart Failure
BMI	Body Mass Index
CBC	Complete Blood Cell Count
CICU	Cardiovascular Intensive Care Unit
CVD	Cardiovascular Disease
HF	Heart Failure
IHD	Ischemic Heart Disease
LOS	Length of Stay
MACE	Major Adverse Cardiac Events
RDW	Red Cell Distribution Width
RDW-CV	Red Cell Distribution Width – Coefficient of Variation
SD	Standard Deviation

Ethical Clearance

This study is a sub-analysis of a larger research project entitled "The Use of M-CARS and Bagaswoto Score in Predicting Mortality Rate and Hospitalization Length of Stay in Patient with Cardiovascular Intensive Care Unit" which received ethical approval from the Health Research Ethics Committee of RSUP Prof. Dr. R. D. Kandou Manado (Approval No. 061/EC/KEPK-KANDOU/V/2021, dated May 3, 2021). The data used in this sub-study were obtained from the same patient cohort as the parent study. As a member of the research team, the author was authorized to use the data for this specific analysis. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

KSKS: Conceptualization, methodology, formal analysis, investigation, data curation, writing – original draft, writing – review & editing, visualization, project administration; ML: Supervision, writing – review & editing; DU: Supervision, writing – review & editing; FMY: Formal analysis, data curation, writing – review & editing; BO: Resources, supervision, writing – review & editing; RD: Investigation, data curation, writing – review & editing; CS: Investigation, data curation, writing – review & editing; J: Investigation, data curation, writing – review & editing.

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Conflict of Interest

None.

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Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author(s) used ChatGPT solely for language polishing and grammar correction. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the final content of the publication. No AI tools were used for data analysis, interpretation, or generation of scientific ideas.

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Original Article

Association Between Cardiovascular Risk Factors and IVUS-Derived Coronary Calcium Score in the Indonesian Population

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Abstract

Background: Coronary artery calcification reflects the chronic burden of atherosclerosis and contributes to procedural complexity during Percutaneous Coronary Intervention (PCI). While coronary calcium has been extensively studied using Computed Tomography (CT), data on Intravascular Ultrasound (IVUS)-derived calcium characteristics in Southeast Asian populations remain limited. The Southeast Asian population, particularly Indonesians, may exhibit distinct patterns of atherosclerosis influenced by genetic, lifestyle, and metabolic factors. Therefore, we sought to investigate the association between cardiovascular risk factors and IVUS-derived total coronary calcium score in an Indonesian population.

Methods: This single-center, retrospective observational study included consecutive patients who underwent IVUS-guided PCI between January 2020 and December 2021. Data on patient demographics and cardiovascular risk factors were obtained from medical records. The IVUS calcium scores recorded in the database were independently reanalyzed and validated by an experienced interventional cardiologist to ensure consistency and accuracy. Associations between cardiovascular risk factors and total IVUS calcium score were assessed using Spearman's rank correlation and the Kruskal–Wallis test.

Results: A total of 111 patients were included in this study with a mean age of 61.3 ± 10.2 years; 72.1% were male. Hypertension, was present in 60.4%, type 2 Diabetes Mellitus (DM) in 45.0%, dyslipidemia in 38.7%, and active smoking in 40.5%. The mean IVUS total calcium score was 1.93 ± 1.41. Among individual risk factors, dyslipidemia ($\rho = 0.22$, $p = 0.021$) and smoking ($\rho = -0.24$, $p = 0.009$) were significantly associated with calcium score. Patients with ≥2 risk factors had higher mean calcium scores (2.15 ± 1.35) compared with those with ≤1 risk factor (1.15 ± 1.33; $p = 0.028$).

Conclusions: The total IVUS calcium score correlated significantly with the presence of dyslipidemia in this Indonesian population. A cumulative increase in cardiovascular risk factors was associated with greater coronary calcium burden, suggesting that multifactorial risk exposure plays an important role in coronary calcification in this population.

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Keywords: IVUS, coronary calcification, Indonesia, intravascular imaging.

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Introduction

Coronary artery calcification is a hallmark of advanced atherosclerosis and a key determinant of procedural complexity during Percutaneous Coronary Intervention (PCI). Intravascular Ultrasound (IVUS) allows direct in vivo quantification of coronary calcium distribution and burden. Greater coronary calcification has been shown to correlate with poorer procedural and long-term clinical outcomes, including reduced stent expansion, higher restenosis rates, and increased adverse cardiovascular events.[1-3]

While global studies have identified age, hypertension, diabetes, and dyslipidemia as major contributors to coronary calcification, ethnic and regional variations exist.[4] The Southeast Asian population, particularly Indonesians, may exhibit distinct patterns of atherosclerosis influenced by genetic, lifestyle, and metabolic factors.[5] However, studies using IVUS-derived calcium scoring in this population are scarce. Therefore, this study aims to explore the association between cardiovascular risk factors and IVUS-derived coronary calcium score among Indonesian patients undergoing PCI.

Methods

This retrospective, cross-sectional study included consecutive patients who underwent IVUS-guided PCI between January 2020 and December 2021. Eligible patients were aged ≥18 years and had adequate IVUS image quality for calcium quantification. Cardiovascular risk factors, including Hypertension, type 2 Diabetes Mellitus (DM), dyslipidemia, and current smoking, were recorded from medical records. The definition of risk factors was available in Supplementary Table 1.

Table 1. IVUS Calcium score.

Parameter	Definition	Score
Calcium arc >270° in ≥5 mm length	Presence of a superficial calcium arc exceeding 270° over a continuous segment of at least 5 mm in length.	Yes = 1, No = 0
360° circumferential calcium	Presence of complete 360° circular calcification involving the vessel wall.	Yes = 1, No = 0
Calcified nodule	Presence of a protruding, irregular surface composed of aggregated small calcium deposits on a calcified plate.	Yes = 1, No = 0
Vessel diameter <3.5 mm	Measured at the site of maximum calcium; defined as small vessel if <3.5 mm.	Yes = 1, No = 0

The IVUS Calcium Score is a composite index derived from four morphological parameters assessed on Intravascular Ultrasound (IVUS) imaging. Each criterion is scored as 1 if present and 0 if absent, giving a total score ranging from 0 to 4.

IVUS Acquisition and Analysis

All procedures were performed using 40-MHz or 60-MHz IVUS catheters (Boston Scientific, USA). The IVUS calcium scores recorded in the institutional database were independently re-analyzed and validated by an experienced interventional cardiologist to ensure consistency and accuracy. Re-evaluation of IVUS images was conducted using the Image Viewer application by an expert interventional cardiologist who was blinded to the pre-existing IVUS calcium score recorded in the database. In cases of discrepancy, a second independent reviewer provided adjudication.

Calcium was defined as a bright echo with posterior acoustic shadowing. If two separate calcium deposits were present in the same cross-section, only the largest was included; the total continuous length of superficial calcium was measured. The following parameters were assessed: maximum continuous superficial calcium angle, total continuous superficial calcium length, length of superficial calcium >270°, presence of calcified nodules (protruding irregular surface of aggregated small calcium deposits on a calcified plate), and vessel diameter at the site of maximum superficial calcium. The nearest frame with a visible vessel wall was used to determine

vessel diameter when shadowing prevented direct measurement at the maximum calcium site. Calcium burden was quantified using a composite Total IVUS Calcium Score (range 0–4), based on the presence of (1) calcium arc >270°, (2) calcium length ≥5 mm, (3) nodular calcification, and (4) full 360° circumferential calcium.

Statistical Analysis

All statistical analyses were performed using Python version 3.11 (Python Software Foundation, Wilmington, DE, USA) with the SciPy and Pandas libraries, which implement standard statistical algorithms equivalent to those used in SPSS and R. Continuous variables were summarized as mean ± Standard Deviation (SD) or median (Interquartile Range [IQR]) depending on data distribution, and categorical variables as frequencies and percentages.

Data normality was assessed visually and confirmed using the Shapiro–Wilk test, demonstrating a non-normal distribution for calcium scores. Therefore, nonparametric tests were applied. Associations between individual cardiovascular risk factors—hypertension, DM, dyslipidemia, and smoking—and the total IVUS calcium score were analyzed using Spearman's rank correlation coefficient (ρ). Comparisons of total IVUS calcium scores among groups defined by the number of risk factors (0–4) were evaluated using the Kruskal–Wallis test. A two-tailed p-value < 0.05 was considered statistically significant. A graphical visualization of the calcium score distribution and mean trend by risk factor count was created using the Matplotlib and seaborn packages in Python.

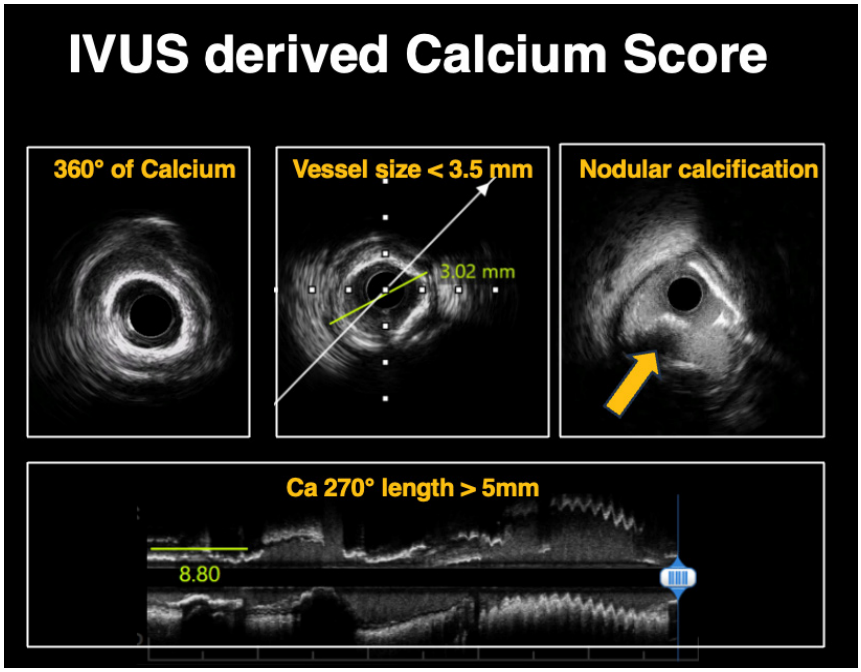

Figure 1. IVUS-derived calcium score components.
Representative intravascular ultrasound (IVUS) images illustrating the four parameters used to calculate the IVUS-derived calcium score. The score is based on the presence of: 360° of calcium indicating circumferential calcification (top left panel), vessel size <3.5 mm measured at the site of maximum calcium (top middle panel), nodular calcification characterized by a protruding, irregular calcium surface (yellow arrow, top right panel), and calcium arc >270° extending ≥5 mm in length (bottom panel). Each component is assigned a value of 1 if present and 0 if absent, yielding a total score ranging from 0 to 4.

Results

A total of 111 patients who underwent IVUS-guided PCI were included in this analysis (Table 2). The mean age was 61.3 ± 10.2 years, and the majority were male (72.1%). The mean Body Mass Index (BMI) was 25.4 ± 3.8 kg/m², reflecting a predominantly overweight cohort. Hypertension was present in 60.4%, DM in 45.0%, dyslipidemia in 38.7%, and current smoking in 40.5% of patients. Clinical presentation consisted of Acute Coronary Syndrome (ACS) in 32.4% and Chronic Coronary Syndrome (CCS) in 67.6% of the study population. The left anterior descending artery was the most frequently treated vessel (49.5%), followed by the right coronary artery (34.2%) and left circumflex artery (16.2%). The median IVUS total calcium score was 2 (IQR, 1–3), with a range of 0-4, indicating that moderate calcification was commonly observed

The correlation between cardiovascular risk fac-

Table 2. Baseline demographic and clinical characteristics (n = 111).

Variable	Mean ± SD or / Median (IQR)
Age (years)	61.3 ± 10.2
Male (sex), n (%)	80 (72.1)
Body Mass Index (kg/m²), n (%)	25.4 ± 3.8
Hypertension, n (%)	67 (60.4)
Diabetes mellitus, n (%)	50 (45.0)
Dyslipidemia, n (%)	43 (38.7)
Current smoker, n (%)	45 (40.5)
Clinical presentation, n (%)	
ACS (*)	36 (32.4)
CCS	75 (67.6)
Vessel Location, n (%)	
LM	4 (3.6)
LAD	60 (54.1)
LCx	10 (9)
RCA	37 (33.3)
IVUS total calcium score, median (IQR)	2 (1–3)

Abbreviations: SD = Standard Deviation, IQR = Interquartile Range, ACS = Acute Coronary Syndrome, CCS: Chronic Coronary Syndrome, LM: Left Main, LAD: Left Anterior Descending, LCx: Left Circumflex, RCA: Right Coronary Artery, IVUS = Intravascular Ultrasound. *ACS include Unstable angina pectoris, Non ST – Elevation Myocardial Infarction, and ST Elevation Myocardial Infarction.

Table 3. Correlation between cardiovascular risk factors and IVUS total calcium score.

Risk Factor	Spearman ρ	P-value
Hypertension	0.15	0.107
Diabetes Mellitus	0.15	0.104
Smoking	−0.24	0.0098
Dyslipidemia	+0.22	0.0214

Table 4. IVUS total calcium score by number of risk factors.

Number of Risk Factors	n	Mean ± SD	Median	Range
0	5	2.20 ± 1.30	2.0	1–4
1	33	1.15 ± 1.33	1.0	0–4
2	46	2.15 ± 1.35	2.5	0–4
3	24	1.79 ± 1.47	1.5	0–4
4	3	2.33 ± 1.53	2.0	1–4

SD: Standard Deviation; Kruskal–Wallis H = 10.85, p = 0.028.

tors and the IVUS total calcium score is shown in Table 3. Spearman correlation analysis revealed that dyslipidemia was significantly positively associated with total IVUS calcium score ($\rho = 0.22$, $p = 0.021$), whereas current smoking was significantly negatively associated ($\rho = -0.24$, $p = 0.009$). Hypertension and DM were not significantly correlated with calcium score ($p > 0.05$).

When categorized by the total number of risk factors, patients with two or more risk factors had markedly higher calcium scores than those with one or no risk factors (Kruskal–Wallis H = 10.85, p = 0.028) (Table 4). Patients with a greater number of cardiovascular risk factors demonstrated higher total calcium scores. The overall distribution pattern showed that calcium burden increased progressively with the number of risk factors (Figure 2).

Discussion

In this study, we found that the total IVUS-derived calcium score correlated significantly with dyslipidemia and the cumulative number of cardiovascular risk factors. In contrast, hypertension and DM were not independently associated with calcium burden. These findings suggest that lipid-related metabolic disturbances may play a more prominent role in coronary calcification than blood pressure or glycemic control. The graded increase in IVUS calcium score with increasing numbers of risk factors further supports the hypothesis that cumulative metabolic stress accelerates vascular calcification.

The positive association between dyslipidemia and coronary calcium score is consistent with prior studies showing that lipid deposition and oxidation trigger osteogenic transformation of vascular smooth muscle cells, leading to microcalcification within the intima and media.[6] Elevated Low-Density Lipoprotein Cholesterol (LDL-C) and oxidized lipids stimulate inflammation and apoptosis, promoting calcium deposition as a late manifestation of chronic atherosclerotic activity.[7] These mechanisms have been supported by both histopathologic and imaging studies using IVUS and Optical Coherence Tomography (OCT), demonstrating that lipid-rich plaques often evolve into heavily calcified lesions over time.[7-8]

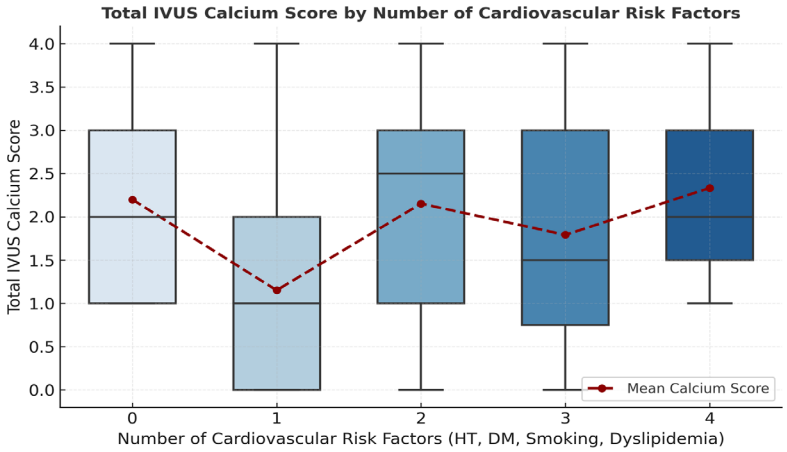

Figure 2. IVUS calcium score by number of risk factors.
The red dashed line represents the trend of mean values.

Another potential explanation for the observed association between dyslipidemia and higher calcium burden lies in the effect of statin therapy. Statins, while effectively reducing lipid content and stabilizing plaques, have been shown to increase calcified plaque volume through mechanisms of plaque healing and stabilization. This "paradoxical" increase in calcification represents plaque stabilization rather than disease progression, as statins promote the transformation of vulnerable, lipid-rich plaques into more stable, fibrotic, and calcified forms.[9]

Interestingly, our data showed an inverse correlation between current smoking and calcium score. This apparent paradox has also been reported in several imaging studies, which have revealed that smokers tend to have lipid-rich, necrotic plaques that are less calcified. Smoking is associated with increased inflammation and plaque instability, promoting rupture rather than stable calcification. Therefore, the lower calcium score in smokers does not indicate a reduced atherosclerotic burden, but rather a predominance of softer, non-calcified lesions that carry a higher short-term risk of acute coronary events.[10]

The overall calcium burden in our cohort (median IVUS calcium score 2 [IQR 1–3]) appears comparable to that reported in other Asian populations, but generally lower than values observed in Western cohorts. This difference may reflect ethnic, dietary, or lifestyle factors that influence atherogenesis and plaque maturation. Studies such as MESA (Multi-Ethnic Study of Atherosclerosis) have shown that Asian individuals often exhibit lower coronary calcium scores at similar risk factor levels compared with Western populations. Genetic factors affecting lipid metabolism and calcium regulation, as well as lower average dietary intake of saturated fat, may contribute to these findings.[11-12]

Our findings emphasize the importance of comprehensive lipid control and multifactorial risk management in preventing the progression

of coronary calcification. The stepwise increase in calcium burden with the accumulation of multiple risk factors highlights the cumulative effect of metabolic and inflammatory stress on atherosclerosis progression. Clinically, these results suggest that patients presenting for coronary intervention who harbor several risk factors should be approached with heightened awareness, as they are more likely to have heavily calcified and technically demanding lesions.

Limitations

This study has several limitations. The retrospective design may introduce selection bias, and the sample size was modest. All patients were treated at a single center, limiting generalizability. Quantitative calcium scoring by IVUS, while reproducible, remains semi-quantitative and may differ slightly between operators. Finally, the study did not evaluate longitudinal outcomes, so the prognostic impact of the IVUS calcium score could not be assessed.

Conclusion

In summary, this study demonstrates that dyslipidemia and cumulative cardiovascular risk factors are significantly associated with increased coronary calcification as quantified by the IVUS-derived calcium score in an Indonesian population. These results reinforce the central role of lipid metabolism and multifactorial risk exposure in driving coronary atherosclerosis and calcification.

List of Abbreviations

ACS	Acute Coronary Syndrome
BMI	Body Mass Index
CAD	Coronary Artery Disease
CCS	Chronic Coronary Syndrome
CT	Computed Tomography
DM	type 2 Diabetes Mellitus
IQR	Interquartile Range
IVUS	Intravascular Ultrasound
LAD	Left Anterior Coronary
LCx	Left Circumflex
LDL-C	Low-Density Lipoprotein Cholesterol
LM	Left Main
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
MESA	Multi-Ethnic Study of Atherosclerosis
RCA	Right Coronary Artery
SD	Standard Deviation

Ethical Clearance

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki. Ethical approval was obtained from the Dr. Hasan Sadikin General Hospital ethics committee.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

All authors have made a significant intellectual contribution to the manuscript according to the criteria formulated by the International Committee of Medical Journal Editors.

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None.

Conflict of Interest

The authors declare that no conflict of interest occurs for this work.

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Original Article

Evaluation of Serum Uric Acid as a Potential Predictive Biomarker in Pulmonary Arterial Hypertension Evaluation

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a relatively rare fatal disease, confounding many cardiopulmonary diseases. Systolic pulmonary artery pressure (sPAP), measured by Transthoracic Echocardiography (TTE), can be taken as a surrogate marker for diagnosing this disease. Uric Acid (UA), a marker of oxidative stress, has been investigated as a potential predictive biomarker for risk stratification. Our study was conducted to ascertain the incidence and severity of sPAP, to evaluate the level of UA levels, and to establish a correlation.

Methods: This is an observational case-control study that included 51 cases of PAH diagnosed by sPAP ≥36 mm Hg, along with 51 controls. Serum UA was assayed using a spectrophotometric method. Statistical analysis was performed using Microsoft Excel and SPSS version 20.0.

Results: Cases were observed in the range of 24 to 87 years (average 48 years) with female predominance. UA levels were significantly higher in cases than in controls. Females showed slightly lower levels of UA as compared to males. Correlation analysis indicated a significant positive correlation between sPAP and uric acid levels. Receiver Operating Characteristic (ROC) analysis demonstrated that serum UA had 68% predictive accuracy for sPAP severity at a cutoff of 5.45 mg/dL.

Conclusions: The level of UA, a routine biomarker analysed in laboratories, is found to be increased in PAH patients and closely correlates with the severity of sPAP. This suggests a potential role of UA as a predictive biomarker in PAH management.

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Keywords: Oxidative Stress, Pulmonary Arterial Hypertension, Risk Assessment, ROC Curve, Uric Acid.

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Introduction

Pulmonary Arterial Hypertension (PAH) is a multifaceted pathophysiological life-threatening disorder associated with various cardiovascular and respiratory diseases. It is characterized by chronic elevation of Pulmonary Arterial Pressure (PAP) and Pulmonary Vascular Resistance (PVR) due to progressive occlusive pulmonary vasculature remodelling, ultimately leading to Right Ventricular Hypertrophy (RVH), causing cardiac failure and death. PAH is a comparatively rare disease with variable prevalence globally, ranging from 0.4 to 1.4 per 100,000 persons.[1] The disease was defined arbitrarily in First World Symposium on Pulmonary Hypertension convened in Geneva in 1973 as a mean Pulmonary Artery Pressure (mPAP) of >25mm Hg at rest by cardiac catheterization which is the gold standard having both diagnostic and prognostic utility.[2] In the Sixth World Symposium in 2018, PAH was estimated to be mPAP> 20 mm Hg and the severity was classified as mild (20- 40 mm Hg), moderate (41-55 mmHg) and severe (> 55 mmHg).[3]

The incidence and prevalence of PAH are increasing due to heightened awareness and suspicion among clinicians, increased access to echocardiograms, an ageing population, and improved quality of treatment. In a study by Malligreddy AR et al. on the current status and barriers of PAH in India, diagnostic evaluations for PAH were found to be limited. Patients and physicians were hesitant about the invasive right heart catheterization.[4] The correct and final diagnosis of PAH is delayed from the time of presentation of non-specific symptoms of right ventricular dysfunction due to the initial exclusion of common clinical conditions. Non-invasive Transthoracic Echocardiography (TTE) plays a pivotal role as an initial screening test, detecting preclinical conditions, assessing outcomes, and monitoring the efficacy of therapeutic interventions.[5] PAH diagnosis is suggested initially by a tricuspid regurgitant jet velocity >2.8 m/s corresponding to a systolic Pulmonary Artery Pressure (sPAP) of ≈35mmHg.[6]

The etio-pathogenesis of PH is a complex myriad of genetics and metabolonomics generating a lot of circulating biomarkers like BNP, N-Terminal pro–B-type Natriuretic Peptide (NT-proBNP), Troponins (T, I), Inflammatory markers (C-Reactive Protein [CRP]), cytokines (Interleukin [IL]-6, IL-8, IL-10) etc.[7] In a meta-analysis by Smits AJ et al, IL-6 and Uric Acid (UA) were found to have significant predictive value with low risk of bias.[8] Thus, there is increased interest in the exploration of the potential utility of non-invasive serum biomarkers for faster diagnosis and initiation of treatment before the development of right heart failure that might help in improving the overall survival and quality of life.

Significant positive correlation between UA and the severity of idiopathic PAH was first elaborated as an independent risk factor for poor prognosis of survival by Nageya et al in 1999.[9] Zhou Y et al observed that dynamic UA concentration can help in assessing the severity and predict prognosis in connective tissue disease associated PAH.[10] In a study done by Yan L et al for the prognostic impact of hyperuricemia on long term mortality of PAH, it was found that elevated levels of circulating UA at baseline significantly correlated with increased severity and increased risk of 5-year mortality.[11] These findings were also corroborated by Luo J et al which established that UA can be used as a practical and economic biomarker for risk stratification and therapeutic response in PAH.[12] Thus hyperuricemia closely correlates with symptom severity and high mortality in PAH. Further research is required to establish UA as an independent risk factor of prognosis in PAH.

This study was conducted to identify serum UA as a potential predictive marker of sPAP, which can be clinically utilised in patients with PAH.

Methods

The present study was an observational case–control study conducted at the Post Graduate Department of Biochemistry in collaboration with the Department of Cardiology for a period of 9 months from August 2023 to April 2024.

Inclusion Criteria

51 cases of pulmonary artery hypertension diagnosed by sPAP ≥ 36 mm Hg attending the Outpatient Department (OPD) of the Department of Cardiology of the tertiary care centre were included for the study. Sampling was done by simple random sampling. The sample size was calculated using a 95% confidence level, a 5% margin of error, and a Prevalence of PAH of 1.4%, as provided by calculator.net. An equal number of age-, sex-, and socioeconomic status-matched healthy volunteers served as controls.

Exclusion Criteria

Patients having renal function disorders, being obese, and on medications that can affect UA were excluded from this study. Patients with metabolic disorders, diabetes mellitus, and hypertension, critically ill patients, or those with other co-morbidities were excluded from the study. Patients unwilling to provide consent for the study were also excluded.

Biochemical Analysis

After obtaining written informed consent from patients, 3 mL of fasting venous blood was collected and centrifuged to separate serum. Samples were kept at -20°C until analysis. Serum UA was assayed by the spectrophotometric method using reagent kits in an auto analyzer (BS-390 MISPA Clinia auto analyzer by AGAPPE / TBA 1200FR).

Statistical Analysis

For quantitative data, statistical analysis was performed using Microsoft Excel and SPSS version 20.0 (IBM Inc., Chicago, Illinois). Results were expressed as Mean and Standard Deviation for continuous variables and as percentages for categorical variables. Data were compared using an independent-samples t-test. The correlation was assessed using Pearson's correlation coefficient. Bar graphs and scatter plots were done. A p-value of < 0.05 was considered statistically significant.

Ethics Statement

The study was approved by the Institutional Ethics Committee, SCB Medical College and Hospital, Cuttack, Odisha. (1525/ 16.08.2023)

Results

The present study of 51 PAH patients observed ages ranging from 24 to 87 years (48.07 ± 16.75), whereas controls were 50.35 ± 17.20 years; the difference was not statistically significant. (p = 0.5) PAH patients had a female predominance of 55% (28 cases) as compared to males, 45% (23 cases).

sPAP in PAH patients was found to be significantly higher at 53.27 ± 11.42 mm Hg compared to controls (sPAP of 28.6 ± 3.6 mm Hg), which was found to be statistically significant(p-value = 0.0001). The levels of UA in patients with PAH (6.11 ± 2.17 mg/dL) were significantly higher than in controls (3.9 ± 1.36 mg/dL; p < 0.0001). Male PAH patients 6.4 ± 2.3 mg/dL; females 5.9 ± 2.1 mg/dL. [Table 1, Figure 1]

Table 1. Socio-demographic and Investigative characteristics of pulmonary arterial hypertension patients and controls

Parameter	PAH Patients (n = 51)	Controls (n = 51)	P-value
Age, years	48.07± 16.75	50.35 ± 17.20	0.5
Gender, n (%)			
Male	23 (45%)		1.00
Female	28 (55%)		
sPAP, mmHg	53.27 ± 11.42	28.6 ± 3.6	0.0001
Serum uric acid, mg/dL	6.11 ± 2.14	3.9 ± 1.36	0.0001
Male	6.4 ± 2.3	-	
Female	5.9 ± 2.1	-	

sPAP: systolic Pulmonary Arterial Pressure.

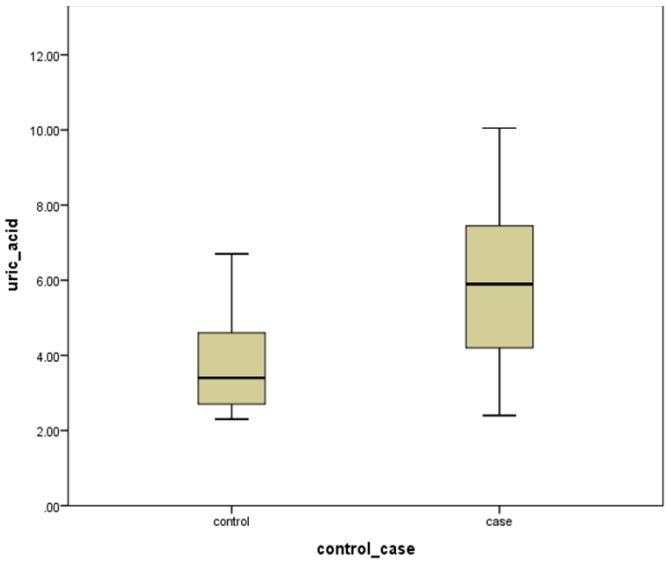

Figure 1. Box-plot diagram showing the levels of uric acid in controls and cases.

Serum UA levels were analyzed according to the severity of PAH, categorized by the levels of peak sPAP. In patients with mild PAH (sPAP: 36-50 mmHg) the serum UA levels was 6.23 ± 2.35 mg/dL, in cases of moderate PAH (sPAP: 50-70 mmHg), UA levels slightly decreased to 6.23 ± 1.76 mg/dL and in severe PH cases (sPAP> 70 mmHg) showed a decrease in UA levels to 5.34 ± 2.16 mg/dL. Analysis of the correlation between serum UA levels and peak systolic sPAP in patients with PAH yielded correlation coefficients (r) and associated p-values, indicating the strength and significance of these associations. Notably, there is a significant positive correlation between sPAP and UA levels (r = 0.470, p = 0.001), suggesting an association with PAH severity. [Table 2, Figure 2]

Table 2. Comparison of Serum Uric Acid level as per severity in pulmonary arterial hypertension patients.

Severity (level of sPAP)	No of cases (n)	Uric acid (in mg/dL)
Mild(36-50 mmHg)	28	6.23 ± 2.35
Moderate (50- 70 mmHg)	16	6.23 ±1.76
Severe (> 70 mmHg)	7	5.34 ± 2.16

sPAP: systolic Pulmonary artery pressure

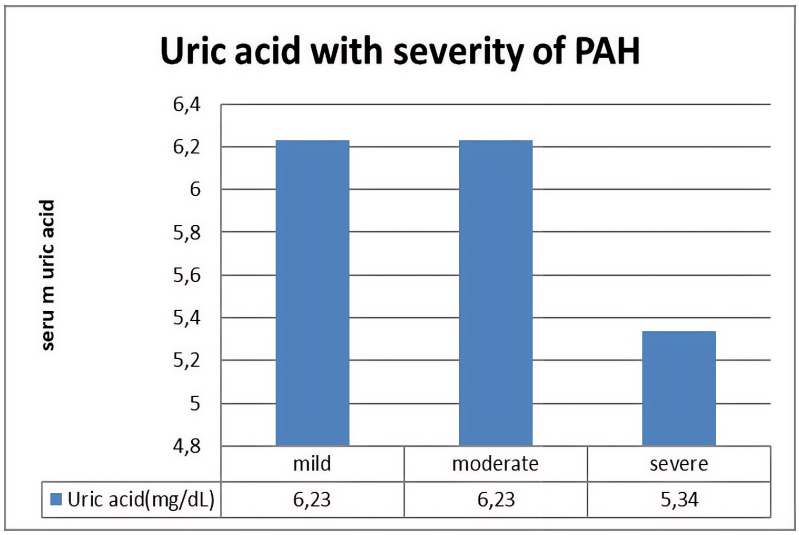

Figure 2. Comparision of uric acid as per the severity of pulmonary hypertension patients.

On analysis of the Receiver Operating Characteristic curve (ROC) for serum UA by plotting false positives (1-specificity) in X-axis and true positives (sensitivity) in Y-axis to ascertain the predictive accuracy of our parameters for Severe Pulmonary Arterial Hypertension, the Area Under the Curve (AUC) for UA was 0.680 with a 95 % confidence interval 0.563- 0.796. The cutoff value for serum UA was 5.45 mg/dL, with 77.8% sensitivity and 65.6% specificity. [Table 3, Figure 3]

Discussion

PAH is a chronic progressive fatal disease characterized by increased precapillary pulmonary hypertension and elevated pulmonary vascular resistance, presenting with non-specific symptoms like dyspnea and ultimately leading to right heart failure and death.[13] The global incidence and prevalence of PAH vary widely worldwide as a rare complication of various heterogeneous disorders, with an approximate incidence of 1 %. [14]

Table 3. Diagnostic accuracy of uric acid with pulmonary hypertension.

AUC (Area Under Curve)	(95 % CI)	Cut-off	Sensitivity	Specificity
0.680	(0.563- 0.796)	5.45	77.8%	65.6%

In our study, cases of PAH were observed across a range of ages from 24 to 87 years, with a mean age of 49 years. There is a female discrepancy (55%) reported, similar to other studies, with a greater incidence of PAH in females but better outcomes labelled as 'estrogen paradox'.[1]

Serum UA, the final product of purine metabolism, has been implicated as a surrogate marker and an indicator of impaired oxidative stress and redox balance, which are involved in the pathobiochemistry of various cardiovascular disorders, and has also been a significant predictor of PAH.[15] In our study, the levels of serum UA in PAH cases (6.11 ± 2.14 mg/dL) were higher than those of controls (3.9 ± 1.36 mg/dL), which was statistically significant (p value < 0.0001) and showed a significant positive correlation with sPAP(r = 0.470, p = 0.001). Females had slightly lower levels of UA (5.9 ± 2.1 mg/dL) than males (6.4 ± 2.3 mg/dL). On comparing the severity of PAH, the level of UA showed a decreasing trend of 6.23 ± 2.35 mg/dL in mild PAH, 6.23 ± 1.76 mg/dL in moderate PAH, and 5.34 ± 2.16 mg/dL in severe PAH.

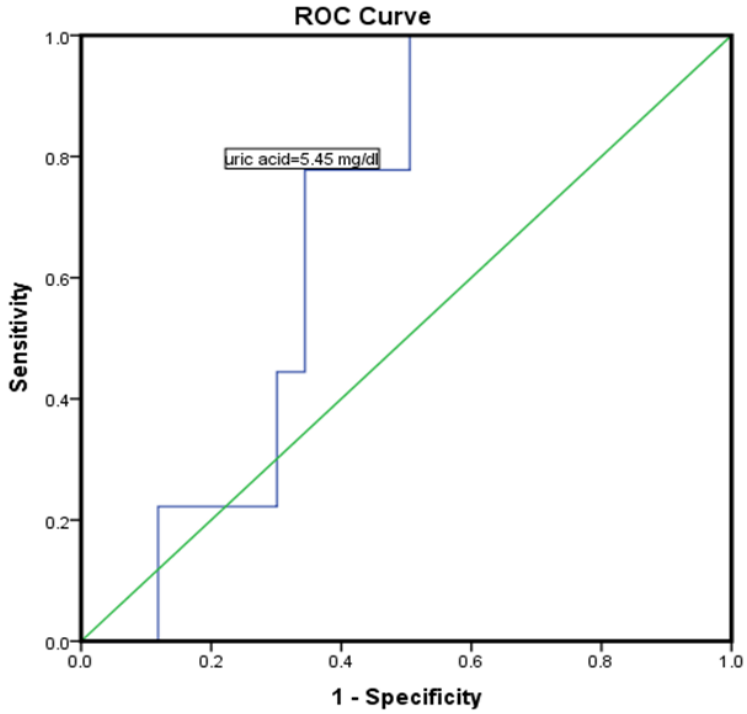

Figure 3. Comparision of uric acid as per the severity of pulmonary hypertension patients.

However, the correlation and variation of serum UA with severity could not be ascertained in our study due to the limited study period and the smaller sample size. The significant positive correlation of UA with PAH irrespective of the causative etiology in concurrence with our study has been demonstrated by various studies like Wang J et al in PAH associated connective tissue disorder[16], Nagaya N et al in primary PAH patients[11], Luo J in PAH associated with congenital heart disease[14], Simpson CE et al in systemic sclerosis related PAH [17], Aghdashi M et al demonstrated increased levels of UA in PAH patients with systemic lupus erythromatosis.[18] Experimental studies such as Watanabe T[19], Li Q[20], and Savale L[21] have also demonstrated disturbed UA metabolism in PAH model rats. Clinical studies, such as Du P et al., have shown that higher levels of UA are independently associated with adverse outcomes in PAH[22], and Li Wt et al. have shown that serum UA levels can be used as a non-invasive marker to evaluate the efficacy of PAH-targeted medications.[23]

The findings of our study indicate that UA should be routinely assessed in patients with PAH to diagnose disease progression of severe PAH, monitor the course of treatment, and assess the efficacy of therapeutic interventions. This study corroborates that serum UA can be used as an independent biomarker for the diagnosis and risk stratification of PAH.

There are several limitations to our study. First, the sample size of this study was small, and studies with multicentre large sample sizes are required to confirm the association of UA in PAH. Furthermore, the diagnosis of PAH was made based only on systolic pulmonary arterial pressure without right heart catheterization due to the unavailability of the diagnostic procedure. Hence, further research is essential for the clinical implementation of UA as a prognostic marker in PAH.

Conclusion

In this study, we analyzed 51 cases of pulmonary hypertension and 51 age-, sex-, and socioeconomic status-matched healthy controls over a 9-month study period of using systolic pulmonary artery pressure obtained from echocardiography. We have observed that the level of UA is higher in patients with pulmonary hypertension than in controls. A significant positive correlation was found between UA and the severity of systolic pulmonary arterial hypertension. The ROC curve analysis showed a sensitivity of 68% for serum UA, indicating that it is a strong predictor of this study and supporting our findings. Hence, multicentre studies with larger sample sizes are necessary to objectively define the role of UA in pulmonary hypertension, thereby enhancing the validity of the observation.

List of Abbreviations

AUC	Area Under the Curve
BNP	Brain Natriuretic Peptide
CRP	C-Reactive Protein
IL	Interleukin
mPAP	Mean Pulmonary Arterial Pressure
NT-proBNP	N-Terminal pro–B-type Natriuretic Peptide
OPD	Outpatient Department
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PVR	Pulmonary Vascular Resistance
ROC	Receiver Operating Characteristic
RVH	Right Ventricular Hypertrophy
sPAP	Systolic Pulmonary Arterial Pressure
TTE	Transthoracic Echocardiography
UA	Uric Acid

Ethical Clearance

The study was approved by the Institutional Ethics Committee, SCB Medical College and Hospital, Cuttack, Odisha. (1525/ 16.08.2023).

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

MM was in charge of methodology, design of the study, analysis and interpretation of data, drafting the article, revising and editing it, correspondence and making the final published version; SNR was responsible for conceptualization, data collection supervision, interpretation of clinical data, revision of article critically for important intellectual content; BP was responsible for statistical analysis and interpretation of data analysis, drafting the article; PKS was responsible for supervision of data collection, revision of analysis and revising the article; SJ was responsible for data collection and compilation of data, conducting the experiment analysis, drafting the article. All authors were responsible for the final approval of the version to be published.

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Conflict of Interest

None.

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Original Article

Gulf of Tomini Cardiac Arrhythmia Research and Exploration (G-CARE): A Multicenter Hospital-Based Outpatient ECG Study

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Abstract

Background: Cardiac arrhythmias pose a significant burden on global health, especially in underserved regions with limited access to diagnostics. In Indonesia, particularly in the Gulf of Tomini, epidemiologic data on arrhythmia prevalence are scarce.

Methods: The G-CARE (Gulf of Tomini Cardiac Arrhythmia Research and Exploration) study was a hospital-based, multicenter, cross-sectional study conducted from 2023–2025 across four referral centers in Gorontalo Province. Adults aged ≥18 years who underwent 12-lead ECG examination were included through purposive sampling. ECGs were interpreted by board-certified cardiologists and classified by arrhythmia type.

Results: A total of 3,177 patients were included (mean age: 53.9±14.9 years; 54.6% female). Normal ECGs were found in 43.4%. The most common abnormalities were ischemic ST-T changes (18.9%, 95% CI: 17.5–20.3), QTc prolongation (15.5%, 95% CI: 14.2–16.8), and left ventricular hypertrophy (10.1%, 95% CI: 9.1–11.2). Atrial fibrillation/flutter occurred in 3.5% (95% CI: 2.8–4.3), AV block in 3.7% (95% CI: 3.0–4.5), and Brugada Pattern in 0.4% (95% CI: 0.2–0.8). Age-related increases were observed for AF, AV block, and QT prolongation. PVC morphology showed high-risk features (QRS >160 ms, coupling interval <300 ms) in young adults.

Conclusions: The G-CARE study identifies a high prevalence of electrocardiographic abnormalities among adults undergoing ECG in outpatient settings within the Gulf of Tomini region. Because the study used hospital-based purposive sampling of patients who had an ECG ordered as part of routine clinical care, these estimates may be biased by selection and do not directly represent the general population. Rather than serving as definitive evidence to support mass, population-level ECG screening, our findings should be considered hypothesis-generating and supportive of conducting a properly designed population-based study (with probability sampling) to determine the actual community burden and to inform screening policy.

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Keywords: Cardiac arrhythmia, epidemiology, atrial fibrillation, Brugada syndrome, premature ventricular complex

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Introduction

Cardiac arrhythmias represent a diverse group of electrical disturbances ranging from benign, asymptomatic findings to severe, life-threatening conditions such as ventricular fibrillation and complete heart block.[1] Globally, arrhythmias are estimated to affect approximately 1.5% to 5% of the general population, with Atrial Fibrillation (AF) being the most frequently encountered subtype.[2–4] This burden is expected to increase significantly in tandem with global population aging and the rising prevalence of cardiovascular risk factors, including hypertension, diabetes mellitus, and coronary artery disease. In Indonesia, epidemiological data on arrhythmias remain limited, especially in non-urban and resource-limited settings. Most prior studies have been concentrated in major urban centres, where access to health services and diagnostic tools is more readily available.[5-6] In contrast, there is a critical lack of population-based data from remote or underserved regions such as the Gulf of Tomini—an expansive coastal area in Eastern Indonesia with unique sociodemographic and environmental characteristics.[7-8]

The Gulf of Tomini region, located in the northern-central part of Sulawesi Island, is characterised by a predominant indigenous Gorontaloan community. In neighbouring regencies across the gulf, small but growing proportions of Bugis-Makassar (migrants) and Mongondow descent also reside, owing to historical migration and interregional mobility. Given that the Gorontaloan ethnic group represents the vast majority of the local population (in Gorontalo Province, >90% identify as Gorontaloan), the local electrophysiological and arrhythmic profile may reflect genetic and sociocultural factors distinct from those widely reported in Java or other major islands. We therefore posit that ethnic/genetic heterogeneity could be a relevant modifier of arrhythmia prevalence and Electrocardiography (ECG) characteristics in our cohort. This region is home to diverse ethnic communities and is characterized by varying dietary habits, physical activity patterns, and limited availability of cardiologic services. According to the 2023 Indonesian Health Survey, the provinces surrounding the Gulf of Tomini report disproportionately high rates of non-communicable diseases—including hypertension, diabetes, stroke, and chronic kidney disease—compared to the national average.[4,9] These conditions are known contributors to arrhythmogenesis and suggest a potentially high but undocumented burden of electrical cardiac disorders in this population.

Despite these risk factors, there has been no comprehensive investigation into the prevalence and patterns of arrhythmias in the Gulf of Tomini. This significant knowledge gap hampers both preventive strategies and early detection efforts. Moreover, the region's limited access to advanced diagnostics, such as echocardiography, Holter monitoring, and electrophysiological studies, further complicates the identification and management of high-risk arrhythmias.

To address this, the Gulf of Tomini Cardiac Arrhythmia Research and Exploration (G-CARE) study was initiated. This multicentre, hospital-based, epidemiologic investigation employs standardized 12-lead ECG interpretation to determine the prevalence of arrhythmia subtypes and to characterize demographic patterns among affected patients. The findings are expected to inform local and national health authorities in planning region-specific screening strategies, early referral systems, and investment in arrhythmia care infrastructure for underserved Eastern Indonesian populations.

Methods

Study Design

G-CARE is a cross-sectional, hospital-based, multicentre study conducted in Gorontalo Province, Indonesia. The study involved four referral hospitals representing the Gulf of Tomini region (Aloei Saboe General Hospital, Toto Kabila General Hospital, Ainun Habibie General Hospital, Tani dan Nelayan General Hospital). The study period spanned from February to July 2025, utilizing retrospective ECG records from January 2023 to January 2025. The study exclusively included ECG records from outpatient visits, reflecting arrhythmia patterns encountered in community-based clinical practice.

For this study, "outpatient visits" refers to non-admitted encounters occurring in the hospital's outpatient departments. These included: (1) general outpatient clinics (including internal medicine/general practice consultations), (2) specialized cardiology outpatient clinics (cardiology clinics where patients are referred for cardiac symptoms or follow-up), and (3) other ambulatory outpatient services where an ECG may be ordered (for example, pre-operative assessment clinics or chronic-disease follow-up visits). ECGs included in the study were obtained as part of routine clinical care and were recorded in the hospital's ECG archives. Because ECGs were included only when clinicians ordered them for clinical evaluation or risk assessment, the

dataset is c for individuals with symptoms or known cardiovascular risk factors rather than representing a randomly sampled community population.

Population and Sampling

The accessible population consisted of patients who had undergone ECG examinations at the outpatient clinic during the data collection period. Purposive sampling was used to select ECGs that met predefined quality and completeness criteria. These inclusion criteria were intended to ensure reliable ECG interpretation; however, this approach is a non-probability sample and introduces selection bias. Inclusion criteria were: (1) age ≥18 years, and (2) complete, interpretable 12-lead ECG recordings. Exclusion criteria included: (1) incomplete or technically unreadable ECG records, and (2) presence of acute or unrelated medical conditions not relevant to the study's objectives (e.g., trauma or post-surgical evaluations not related to cardiology).

Data Collection

All selected ECG records were accompanied by demographic data, including patient age and sex. Each ECG was independently interpreted by two board-certified cardiologists at each participating center. In cases of disagreement, a third senior cardiologist reviewed the tracing to achieve consensus. Detected arrhythmias were categorized into subtypes using standard diagnostic criteria, including AF/flutter, Atrioventricular (AV) blocks (first to third degree), Premature Ventricular Contractions (PVC), Brugada pattern, Wolff–Parkinson–White (WPW) pattern, QTc interval abnormalities, and conduction disturbances such as bundle branch blocks. PVCs were identified when at least one premature ventricular beat was present on a standard 12-lead ECG. Because a 10-second ECG does not provide sufficient duration to assess ectopic burden, the term 'frequent PVC' was not applied. PVC morphology was defined according to standard electrocardiographic criteria: (1) Right Bundle Branch Block (RBBB)-type PVCs, representing left ventricular origin (QRS ≥120 ms with rsR' or qR in V1); and (2) Left Bundle Branch Block (LBBB)-type PVCs, representing right ventricular origin (broad notched/slurred R wave in V5–V6 with absent Q waves in I and V6). These definitions were applied consistently across all ECGs, including AV block definitions and classification. AV block was defined and categorized using standard electrocardiographic criteria. First-degree AV block was defined as a PR interval > 200 ms with 1:1 AV conduction. Second-degree AV block (Mobitz I/Wenckebach) was defined by progressive PR prolongation culminating in a dropped QRS. Second-degree AV block (Mobitz II) was defined by intermittent non-conducted P waves with constant PR intervals in the conducted beats. High-grade AV block referred to ≥2 consecutive non-conducted P waves with some preserved AV conduction (e.g., 3:1, 4:1). Third-degree (complete) AV block was defined by AV dissociation with independent atrial and ventricular rhythms. PVC coupling intervals and QRS durations were measured manually by visual estimation ("by eye") using the standard ECG paper calibration (25 mm/s, 10 mm/mV). Early repolarization was defined as J-point elevation ≥0.1 mV in at least two contiguous inferior or lateral leads, following established consensus criteria. Cardiologists applied consistent measurement across tracings to ensure reproducibility. To illustrate this approach, a supplementary figure has been added, demonstrating how the coupling interval was identified between the preceding sinus beat and the premature ventricular complex. Standard diagnostic criteria were applied consistent with international recommendations including guidelines from the American Heart Association (AHA), American College of Cardiology (ACC), and the Heart Rhythm Society (HRS). Although the Minnesota Code is widely used in population-based epidemiologic studies, our hospital-based study relied on clinical diagnostic criteria appropriate for outpatient evaluation.

Variables and Outcomes

The primary outcome was the presence of any arrhythmia on ECG. Subtypes were defined per conventional ECG criteria. Secondary variables included age (<55, 55-64, and >64) and sex (male or female).

Statistical Analysis

Descriptive statistics were used to calculate prevalence estimates and characterize the study sample. The distribution of arrhythmia subtypes was stratified by age and sex. Chi-square or Fisher's exact tests were used to assess associations between arrhythmia prevalence and demographic variables, with 95% confidence intervals provided for key estimates. Statistical analyses were performed using STATA version 18.0. Results were displayed using summary tables and graphs.

Results

A total of 3177 eligible adult subjects were included in the final analysis of the G-CARE study. Data analysis was performed using STATA

18.0 to assess the distribution and characteristics of electrocardiographic abnormalities. The dataset comprised categorical and continuous variables, including age, sex, and multiple ECG parameters classified into arrhythmia types and conduction disorders. Descriptive statistics were used to estimate prevalence. At the same time, chi-square tests and Fisher's exact tests were used in bivariate analyses to evaluate associations between arrhythmia types and demographic factors.

The study involved 3,77 adult subjects, with a mean age of 53.92 years (SD ±14.95), ranging from 18 to 96 years. The majority were female (54.6%), while males comprised 45.4% of the cohort. Normal ECG findings were observed in 43.4% of participants. AV block (116 cases; 3.7%, 95% CI: 3.0–4.5) and atrial fibrillation/flutter (111 cases; 3.5%, 95% CI: 2.8–4.3) were also prevalent. Although less common, other clinically significant conduction and rhythm disorders of clinical significance were identified, including right bundle branch block (5.0%) and premature ventricular complexes (2.9%). Although rare (0.4%), the Brugada ECG pattern was present in both type 1 and type 2/3 variants, underscoring the need for greater awareness of this arrhythmogenic condition. Other structural and conduction abnormalities, such as left anterior hemiblock (0.7%), left posterior hemiblock (0.2%), and WPW syndrome (0.5%), were also documented (see Table 1).

Among male participants, age was significantly associated with increased prevalence of several arrhythmic conditions. AF was notably more common in older age groups, rising from 1.4% in those <55 years to 6.8% in those aged 65 and above ($p<0.001$). Similarly, AV block prevalence rose from 1.3% in the youngest group to 9.4% in the elderly ($p<0.001$), indicating progressive conduction system

Table 1. Study sample characteristic.

Baseline Characteristic (N=3177)	N or Distribution	Percentage
Age	53.9 ± 14.95 (18–96)	
Male Sex	1441	45.4
Initial ECG Diagnosis		
No ECG Abnormality	1378	43.4
Atrial Fibrillation/Flutter	111	3.5
Premature Ventricular Complex	93	2.9
AV Block (1st degree, 2nd degree, and 3rd degree)	116	3.7
Right Bundle Branch Block (RBBB)	158	5.0
Left Bundle Branch Block (LBBB)	23	0.7
Left Anterior Hemi Block (LAHB)	21	0.7
Left Posterior Hemi Block (LPHB)	6	0.2
ST and/or T wave changes suggestive for myocardial ischemia	599	18.9
Left Ventricular Hyperthrophy	322	10.1
Right Ventricular Hyperthrophy	19	0.6
Left Atrial enlargement	69	2.2
Right Atrial Enlargement	8	0.3
Brugada Pattern	12	0.4
Type 1	8	0.3
Type 2 or 3	4	0.1
Long QT Interval	492	15.5
Early Repolarization Pattern	25	0.8
Wolff Parkinson White Syndrome	15	0.5
Type A	5	0.2
Type B	10	0.3

ECG: Electrocardiography; AV: Atrioventricular; RBBB: Right Bundle Branch Block LBBB: Left Bundle Branch Block LAHB: Left Anterior Hemi Block LPHB: Left Posterior Hemi Block.

degeneration with aging. These findings highlight the impact of age-related electrical remodelling in males.

QTc prolongation was also significantly more frequent in older males, affecting 16.1% of those under 55 and nearly one-fourth (24.8%) of those aged ≥65 (p<0.001). The first detection of the Brugada ECG pattern was most frequent in the 55–64 age group (2.2%), then decreased again in the oldest age group. The overall prevalence of conduction abnormalities increased with age (from 6.4% in <55 to 12.6% in ≥65; p<0.001), supporting the notion that advanced age is associated with progressive conduction disturbances. PVC prevalence showed no significant age trend in men (p=0.40) (See Table 2).

In contrast to male patients, the distribution of atrial fibrillation across age groups in female participants did not show a statistically significant trend (p = 0.81). However, the absolute frequency still increased slightly with age. However, AV block prevalence was significantly higher in older women, increasing from 4.1% in those under 55 years to 8.8% in those 65 years and above. Conduction abnormalities were also more prevalent in older females, rising from 6.0% in <55 to 10.1% in ≥65 (p=0.02), consistent with trends observed in males. QTc prolongation was common but did not differ significantly by age group (p = 0.47), although the overall rate remained high in women (17.6%). Other arrhythmias, such as PVCs, WPW, and Brugada patterns, did not demonstrate meaningful variation with age (See Table 3).

Analysis of PVC morphology based on QRS duration revealed notable differences by age but not by sex. Among male patients, the majority of PVCs had a QRS duration ≥160 ms (34 cases), whereas females showed a more even distribution across QRS durations <140 ms, 140–159 ms, and ≥160 ms (p = 0.09). Age-related trends were highly significant (p<0.001). The youngest group (<55 years) accounted for the most considerable number of PVCs with QRS ≥160 ms (31 cases), suggesting early onset of potentially malignant ventricular

Table 2. Distribution of arrhythmia and conduction disorders by age group in male patients.

Variable	<55 (n/%)	55–64 (n/%)	65+ (n/%)	Total (n/%)	P-value
Atrial Fibrillation					
No	752 (98.6)	353 (95.9)	289 (93.2)	1394 (96.7)	0.00
Yes	11 (1.4)	15 (4.1)	21 (6.8)	47 (3.3)	
AV Block					
No	753 (98.7)	354 (96.2)	281 (90.6)	1388 (96.3)	0.00
Yes	10 (1.3)	14 (3.8)	29 (9.4)	53 (3.7)	
Premature Ventricular Contraction					
No	743 (97.4)	356 (96.7)	297 (95.8)	1396 (96.9)	0.40
Yes	20 (2.6)	12 (3.3)	13 (4.2)	45 (3.1)	
Brugada Pattern					
No	761 (99.7)	360 (97.8)	309 (99.7)	1430 (99.2)	0.00
Yes	2 (0.3)	8 (2.2)	1 (0.3)	11 (0.8)	
WPW Pattern					
No	757 (99.2)	368 (100.0)	308 (99.4)	1433 (99.4)	0.24
Yes	6 (0.8)	0 (0.0)	2 (0.6)	8 (0.6)	
QTc Interval					
Normal	640 (83.9)	287 (78.0)	233 (75.2)	1160 (80.5)	0.00
Prolonged	123 (16.1)	81 (22.0)	77 (24.8)	281 (19.5)	
Conduction Disorder					
No	714 (93.6)	336 (91.3)	271 (87.4)	1321 (91.7)	0.00
With Conduction Abnormality	49 (6.4)	32 (8.7)	39 (12.6)	120 (8.3)	

AV: Atrioventricular; WPW: Wolff–Parkinson–White.

Table 3. Distribution of arrhythmia and conduction disorders by age group in female patients.

Variable	<55 (n/%)	55–64 (n/%)	65+ (n/%)	Total (n/%)	P-value
Atrial Fibrillation					
No	658 (96.3)	522 (96.7)	492 (95.9)	1672 (96.3)	0.81
Yes	25 (3.7)	18 (3.3)	21 (4.1)	64 (3.7)	
AV Block					
No	655 (95.9)	516 (95.6)	468 (91.2)	1639 (94.4)	0.00
Yes	28 (4.1)	24 (4.4)	45 (8.8)	97 (5.6)	
Premature Ventricular Contraction					
No	651 (95.3)	514 (95.2)	482 (94.0)	1647 (94.9)	0.56
Yes	32 (4.7)	26 (4.8)	31 (6.0)	89 (5.1)	
Brugada Pattern					
No	680 (99.6)	538 (99.6)	511 (99.6)	1729 (99.6)	1.00
Yes	3 (0.4)	2 (0.4)	2 (0.4)	7 (0.4)	
WPW Pattern					
No	678 (99.3)	535 (99.1)	507 (98.8)	1720 (99.1)	0.58
Yes	5 (0.7)	5 (0.9)	6 (1.2)	16 (0.9)	
QTc Interval					
Normal	574 (84.0)	439 (81.3)	417 (81.3)	1430 (82.4)	0.47
Prolonged	109 (16.0)	101 (18.7)	96 (18.7)	306 (17.6)	
Conduction Disorder					
No	642 (94.0)	497 (92.0)	461 (89.9)	1600 (92.2)	0.02
With Conduction Abnormality	41 (6.0)	43 (8.0)	52 (10.1)	136 (7.8)	

AV: Atrioventricular; WPW: Wolff–Parkinson–White.

conduction abnormalities in this population.

PVC coupling interval analysis revealed that the majority of PVCs in both males and females had a coupling interval <300 ms, suggesting a pattern of early ectopic activity. There were no statistically significant differences between male and female patients in the distribution of coupling intervals (p=0.348). However, a slightly higher proportion of long-coupled PVCs (≥600 ms) was observed in females. When stratified by age, no significant associations were found (p = 0.190). However, a pattern emerged in which the youngest group (<55 years) had the highest number of short-coupled PVCs, while longer coupling intervals were more frequently seen in older patients (See Table 4).

Table 5 presents the distribution of PVC morphologies, classified as LBBB or RBBB, by gender. PVCs with RBBB morphology were significantly more frequent in males (6.2%) than in females (3.9%) (p = 0.00). In contrast, PVCs with LBBB morphology—which typically indicate a right ventricular origin, especially from the Right Ventricular Outflow Tract (RVOT)—were uncommon in both sexes and showed no statistically significant difference between males (0.8%) and females (0.7%) (p = 0.81). This finding appears inconsistent with previous epidemiologic studies that report LBBB-type PVCs as the most common morphology in the general population, particularly in cases of idiopathic or outflow-tract PVCs.

Age-wise analysis showed that LBBB-type PVCs became slightly more prevalent with age, increasing from 0.3% in those <55 years to 1.2% in those ≥65 (p = 0.02). Although the absolute numbers were small, this trend supports the hypothesis of progressive left-sided conduction slowing or structural ventricular remodelling with aging. RBBB-type PVCs, while more common overall, did not exhibit a significant association with age (p = 0.51) (See Table 5).

Among the 12 patients identified with Brugada Pattern in the G-CARE study, the majority (n = 8) were classified as having type 1 Brugada ECG pattern, which is considered diagnostically definitive. The remaining four cases were classified as type 2 or 3 patterns, which are less specific and often require pharmacologic provocation for confirmation. Type 1 cases were predominantly observed in males (87.5%), consistent with the established global epidemiology of Brugada syndrome, which shows

Table 4. PVC characteristic (QRS duration and coupling interval) by sex and age.

Variable	QRS <140 ms	QRS 140–159 ms	QRS ≥160 ms	P-value (QRS)	CI <300 ms	CI 300–599 ms	CI ≥600 ms	P-value (CI)
Sex								
Male	4	8	34	0.09	38	8	0	0.348
Female	12	9	27		42	5	0	
Age Group								
<55	3	3	31	0.000	28	8	0	0.190
55–64	7	3	23		30	3	0	
≥65	6	11	7		22	2	0	

Table 5. PVC morphology (LBBB and RBBB) by sex and age group.

Variable	LBBB - No	LBBB - Yes	P-value (LBBB)	RBBB - No	RBBB - Yes	P-value (RBBB)
Sex						
Male	1430	11	0.81	1351	90	0.00
Female	1724	12		1668	68	
Total	3154	23		3019	158	
Age Group						
<55	1442	4	0.02	1373	73	0.51
55–64	899	9		858	50	
≥65	813	10		788	35	
Total	3154	23		3019	158	

LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block.

Table 6. Characteristic Brugada ECG pattern.

Variable	Type 1 (n=8)	Type 2 or 3 (n=4)
Age	59.25	52
Male	7	4
Sinus Rhythm	5	4
Sinus Bradycardia	0	0
Sinus Tachycardia	3	0
Atrial Fibrillation	0	0
PR Interval	171.75	193.25
QT Interval Correction	415	410.5

a strong male predominance. The mean age of type 1 patients was 59.25 years, indicating that the phenotype may emerge or be more easily detected in later adulthood, even in populations without widespread access to advanced cardiac diagnostics (See Table 6).

Electrocardiographic characteristics of patients with Brugada syndrome revealed that most were in normal sinus rhythm at the time of recording. Five of the eight patients with type 1 exhibited baseline sinus rhythm, whereas the remaining three demonstrated sinus tachycardia. Several type 1 Brugada ECG recordings demonstrated sinus tachycardia, likely reflecting physiologic variation during outpatient recording rather than autonomic imbalance. Interestingly, none of the patients exhibited sinus bradycardia or atrial fibrillation, which are frequently reported in symptomatic Brugada cohorts. This may suggest that the individuals identified in this study were in early or asymptomatic stages, or that the ECGs were obtained in non-provocative conditions.

Discussion

The G-CARE study represents the first large-scale, multicentre epidemiologic investigation of electrocardiographic abnormalities in the coastal provinces of Eastern Indonesia. This study identified a considerable prevalence of arrhythmias

and conduction abnormalities among adults who underwent outpatient ECG examinations in the Gulf of Tomini region. Because the dataset consists of ECGs obtained during outpatient encounters at referral hospitals, it is important to recognize several mechanisms by which prevalence estimates may be inflated relative to the general population. First, clinicians are more likely to order ECGs for symptomatic patients (palpitations, syncope, chest pain) or for those with known cardiovascular risk factors (hypertension, diabetes, prior cardiac disease), thereby enriching the sampled population for arrhythmias and conduction abnormalities. Second, specialized cardiology outpatient clinics and referral centers often see patients with more complex or persistent problems, creating a referral bias. Third, certain high-risk conditions (e.g., symptomatic Brugada syndrome or malignant ventricular arrhythmias) may be overrepresented among hospital attenders. In contrast, other conditions—particularly asymptomatic or transient abnormalities in the community—may be undersampled. Collectively, these biases tend to push prevalence estimates upward relative to an age- and sex-matched, community-derived sample. For this reason, the prevalence figures reported here should be interpreted as the frequency of ECG-detected abnormalities in the outpatient hospital setting rather than as community prevalence. Future work employing probability-based sampling (community door-to-door surveys, primary-care registry sampling, or population cohorts) and statistical weighting will be required to infer population-level prevalence.

QTc Prolongation and Public Health Implications

A notable and alarming finding in this study is the high prevalence of prolonged QTc intervals, identified in 15.5% of participants. This figure, while falling within the broad prevalence range reported in previous studies (3% to 44.1%), aligns closely with studies reporting rates of approximately 34.1%.[10-11] The detection of QTc prolongation in both genders and across age categories—particularly concentrated among older males—highlights a potentially underrecognized public health risk. Several established determinants of QTc prolongation, such as increasing age, male sex, hypertension, and diabetes mellitus, were also prevalent in our study population[10,12–14], potentially compounding the observed burden. Clinically, prolonged QTc is a harbinger of malignant ventricular arrhythmias, including torsades de pointes and ventricular fibrillation, both of which are associated with increased risk of sudden cardiac death. This risk is further magnified in low-resource settings, where timely access to defibrillation or ICD therapy remains limited.[15] Long QTc values were identified based on standard cut-offs (QTc ≥ 460 ms in females, ≥ 440 ms in males, Bazett's correction). However, we were unable to systematically exclude acquired causes (e.g., medication use, electrolyte disturbances) due to the retrospective design and incomplete clinical data. Future studies should stratify congenital versus acquired prolonged QT and separate cardiac versus non-cardiac cohorts to obtain accurate prevalence estimates.

Age-Related Trends in Atrial Fibrillation and AV Block

Another critical observation concerns AF and AV block, which both showed marked age-related increases, particularly among males aged ≥65 years. These patterns reflect the well-documented phenomena of age-related atrial remodelling, sinus node dysfunction, and fibrotic degeneration of the His-Purkinje system.[16-17] However, what makes our findings unique is the identification of these conduction abnormalities in a population that is generally underrepresented in cardiovascular literature—semi-rural, outpatient adults from coastal Indonesia. Our findings on the prevalence of atrial fibrillation among outpatients (3.5%) are broadly comparable to national data from the InaHRS multicentre registry, which included 13 tertiary centres across Indonesia. However, the demographic profile of the G-CARE cohort—comprising semi-rural, mixed general-outpatient participants—differs substantially from that of the urban, referral-based population represented in InaHRS. This contextual difference may explain minor variations in prevalence and supports the need for regional ECG registries to capture arrhythmia characteristics beyond major urban centers.

High-Risk PVC Morphology in Young Adults and Unexpected Patterns in PVC Morphology

The predominance of PVCs with RBBB morphology in our cohort contrasts with several population-based studies reporting that LBBB-type PVCs (commonly originating in the RVOT) are more frequent in idiopathic PVC series. Several non-mutually exclusive explanations are plausible. One possibility is that left-ventricular structural disease or focal left ventricular scarring—possibly related to ischemic heart disease, prior myocarditis, or regional cardiomyopathy—could generate PVCs manifesting with RBBB morphology. Another is that

referral and selection patterns concentrate patients with concerning symptoms or prior structural heart disease into the hospital outpatient sample, inflating the relative proportion of left-ventricular ectopy. Finally, regional or genetic differences in arrhythmogenic substrate cannot be excluded. We note, however, that the absolute number of LBBB-type PVCs in our sample was small; therefore, formal subgroup comparisons are limited by sample size and power. To further explore this finding, we recommend: (1) a descriptive comparison of demographic and clinical characteristics between patients with RBBB- vs LBBB-type PVCs (age, sex, clinical history, ECG features), (2) echocardiographic or cardiac MRI assessment to identify underlying structural disease among RBBB-PVC patients, and (3) prospective registry or ambulatory monitoring to determine the burden and prognostic significance of these morphologies in the region. In the absence of a larger dataset, the present manuscript presents this observation as an essential hypothesis for follow-up rather than as definitive evidence of a region-specific arrhythmogenic phenotype.[20-22]

Detection of Brugada Syndrome and in a Non-Provoked Setting and Wolff–Parkinson–White (WPW) syndrome

Perhaps the most clinically provocative finding of the G-CARE study is the identification of Brugada patterns, including spontaneous type 1 ECG patterns in 8 subjects (0.3%). Brugada syndrome is an inherited arrhythmogenic disorder associated with a high risk of sudden cardiac death, particularly in younger males. Its detection in a non-provoked setting—outside of pharmacologic challenge or febrile states—suggests that a subset of individuals in the Gulf of Tomini region may carry pathogenic SCN5A variants or other channelopathies that remain undiagnosed due to the absence of electrophysiology labs and genetic services. QTc interval was analysed separately in the general dataset as part of conduction abnormalities and was not used as a diagnostic parameter for Brugada syndrome.

Interestingly, we observed a mean age of ~59 years for type 1 Brugada-pattern ECGs, which at first glance appears older than typical descriptions emphasizing risk in younger males. Several considerations may explain this discrepancy. In hospital-based cross-sectional datasets, older age at detection can reflect delayed diagnosis (limited prior ECG screening), survivorship or ascertainment bias (younger individuals with malignant phenotypes may have experienced events before presenting to outpatient clinics), or age-dependent phenotypic expression influenced by comorbidities or extrinsic triggers (fever, drugs, electrolyte disturbances). It is also possible that the individuals identified in this study represent asymptomatic carriers whose ECG phenotype becomes manifest later in life or in the presence of coexisting conditions.[23-25]

In addition to Brugada syndrome, we identified 15 cases (0.5%) of WPW syndrome, a pre-excitation disorder that may predispose patients to paroxysmal supraventricular tachycardias or even sudden cardiac arrest. While the absolute prevalence may appear modest, the identification of WPW on outpatient ECGs underscores the value of routine screening in identifying asymptomatic yet potentially high-risk individuals—particularly when more advanced modalities, such as Holter monitors or event recorders, are unavailable.[26]

Sex-Based Differences in Arrhythmogenesis

The observed sex-based differences in arrhythmia expression are also noteworthy. Men exhibited higher rates of AF and Brugada patterns, whereas AV block was more prevalent among older women. The absence of a significant age-related increase in atrial fibrillation among females may relate to oestrogen's cardioprotective effect on atrial structural remodelling, lower prevalence of hypertension and coronary artery disease, and differences in autonomic tone. These trends are consistent with known sex-specific electrophysiological responses—such as oestrogen's protective effect on atrial remodelling—but the biological underpinnings remain complex. They are likely influenced by a combination of hormonal, structural, and autonomic factors.[27-28]

Early-Onset Electrical Abnormalities and Subclinical Risk

Our data also suggest that early arrhythmogenic risk is under-recognized. A substantial number of patients under 55 years displayed QT prolongation, PVCs, or even early repolarization patterns. These findings may serve as early electrophysiologic markers of subclinical cardiovascular disease or inherited channelopathies, particularly in a region where comorbid conditions such as diabetes, hypertension, and CKD are highly prevalent. These patterns support the hypothesis that arrhythmogenic substrates may develop earlier in populations with high burdens of noncommunicable diseases.

From a public health standpoint, the study provides a strong justification for ECG-based screening in outpatient settings, particularly in remote or coastal regions. The detection of clinically

actionable arrhythmias in nearly 60% of ECGs reviewed—despite no pre-screening for cardiac symptoms—suggests that the cost-effectiveness of ECG screening may be far higher than previously assumed in low- and middle-income countries (LMICs), especially when interpreted by trained cardiologists.[29-30]

The implications for health system planning are significant. Given that ECG is a low-cost, non-invasive modality, its use could be expanded as part of primary cardiovascular screening programs, particularly for populations at risk of sudden cardiac death, including those with strong family histories, prior syncope, or unexplained seizures. Training primary care physicians to recognize high-risk ECG features could facilitate earlier referrals and potentially life-saving interventions.

Importantly, our study highlights the utility of hospital-based retrospective ECG analysis as a surrogate for population-based surveillance in resource-limited environments. While accurate community-based screening would offer broader generalizability, our data nevertheless capture real-world outpatient practice patterns and serve as a foundational step toward scalable arrhythmia registries in Indonesia and comparable settings.

In terms of novelty, this is the first published study to stratify arrhythmia burden in the Gulf of Tomini—an underserved region with distinctive sociodemographic and environmental characteristics. The study not only contributes original epidemiologic data but also provides a framework for future research on arrhythmia genetics, electrophysiologic mapping, and implementation of preventive cardiology strategies in rural Southeast Asia.

Conclusion

In this multicenter hospital-based outpatient ECG study from the Gulf of Tomini region, a high prevalence of ECG abnormalities was identified among adults who underwent clinically indicated ECG testing. These findings generate essential hypotheses about potential regional patterns of arrhythmia and conduction disease, but cannot be extrapolated to the community without confirmatory population-based research. We therefore recommend that policymakers and researchers consider (1) designing probability-based community studies to quantify true population prevalence, (2) performing prospective clinical and imaging follow-up for patients with high-risk ECG features, and (3) prioritizing targeted screening or referral pathways for high-risk subgroups rather than immediate mass ECG screening across the general population.

Study Limitations

This study should be interpreted in light of several limitations. First, it was conducted in a hospital-based outpatient setting rather than through population-based sampling. As a result, individuals who underwent ECG examination were more likely to present with symptoms, cardiovascular risk factors, or established cardiac disease, which introduces selection bias and may lead to overestimation of arrhythmia prevalence compared with the general community.

Second, although the dataset included both cardiac and non-cardiac patients, the absence of stratification between these groups limits the ability to determine the actual community burden of arrhythmias. Similarly, while QTc prolongation was prevalent, our retrospective design did not allow us to systematically exclude acquired causes (e.g., medications, electrolyte disturbances), which could have influenced the reported prevalence.

Third, ECG interpretation was based on clinical diagnostic guidelines (AHA/ACC/HRS) rather than the Minnesota Code, which is traditionally employed in epidemiologic surveys. While this approach reflects real-world outpatient practice, it may limit comparability with prior population-based studies.

Fourth, PVC coupling intervals and QRS durations were measured manually by visual inspection ("by eye") on standardized ECG paper. Although this method is widely accepted in clinical practice and is consistently applied by cardiologists, it exhibits greater interobserver variability than digital calliper techniques.

Taken together, these limitations highlight that the findings should be regarded as hypothesis-generating rather than definitive prevalence estimates. Future research employing probability-based community sampling, prospective clinical follow-up, and integration of advanced diagnostic tools will be necessary to confirm and extend these observations in the general population.

List of Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
AHA	American Heart Association
AV	Atrioventricular

ECG	Electrocardiogram
G-CARE	Gulf of Tomini Cardiac Arrhythmia Research and Exploration
HRS	Heart Rhythm Society
LAHB	Left Anterior Hemi Block
LBBB	Left Bundle Branch Block
LMICs	Low- and Middle-Income Countries
LPHB	Left Posterior Hemi Block
PVC	Premature Ventricular Contraction
RBBB	Right Bundle Branch Block
RVOT	Right Ventricular Outflow Tract
WPW	Wolff–Parkinson–White

Ethical Clearance

This study was conducted in accordance with the Declaration of Helsinki. It was approved by the Health Research Ethics Committee of the State University of Gorontalo, with ethics committee reference number 116/UN47.B7/KE/2025. Written informed consent was obtained from all participants before the study commenced.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

MNIS: Writing – review & editing, Writing – original draft, Validation, Methodology, Data accuracy, Investigation, Conceptualization. ZKY: Writing – review & editing, Writing – original draft, Validation, Project administration. DPI: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition. MYID: Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization.

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None.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Availability of Data and Materials

De-identified data and analytic code are available from the corresponding author upon reasonable request and subject to institutional policies.

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Generative AI and AI-Assisted Technologies in the Writing Process

No AI tools were used to generate, analyse, or interpret data, figures, or scientific content. All text was reviewed, verified, and edited by the authors, who take full responsibility for the content.

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Original Article

Non - Fluoroscopic Transesophageal Echocardiography Guided Transcatheter Closure of Atrial Septal Defects: Single Centre Experience in The North of Sumatra Island, Indonesia

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Abstract

Background: Non-fluoroscopic, transesophageal-guided percutaneous closure of Atrial Septal Defect (ASD) can be a first-line strategy to reduce radiation exposure and its cumulative effec. We report our experience as the first center located far from the capital city of Indonesia that routinely performs transcatheter closure of ASD under the guidance of Transesophageal Echocardiography (TEE) without fluoroscopy.

Methods: We collected data of patients whose ASD was successfully closed percutaneously from May 2020 to August 2024. For a total of 116 patients of secundum ASD that are suitable for device closure, we routinely intend to do non-fluoroscopy transcatheter ASD closure guided by TEE.

Results: The zero-fluoroscopy technique was successfully performed in 111 patients. The ASD diameter is 10-40 mm, and the mean size of the occluding device is 9-42 mm. The mean procedural times are 55.81 ± 22.7 minutes. The success rate is 95% with only one case of pericardial effusion. Five cases were excluded as they were finally assisted by fluoroscopy due to the limitation of the echocardiographic view.

Conclusions: A thorough transcatheter ASD closure technique guided by TEE can routinely be performed without fluoroscopy.

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Keywords: Atrial septal defect, GUCH, Echocardiography, Transcatheter closure, non-fluoroscopic.

Introduction

The non-fluoroscopic technique of transcatheter closure of Atrial Septal Defect (ASD) was developed by Ewert in 2000 in order to avoid radiation exposure in children.[1] Transcatheter ASD device closure with Transesophageal Echocardiography (TEE) guidance alone was proved to be as effective and safe as ASD closure with fluoroscopy guidance in children.[2] In Indonesia, this technique was first successfully performed in pregnant woman by team of National Heart Centre Harapan Kita Jakarta in 2018.[3] Being located quite far from Jakarta, capital city of Indonesia, in a separated island, Heart Centre of Adam Malik General Hospital Medan has been routinely performing this non-fluoroscopic technique since May 2020. As an established heart centre located on the island of Sumatra, Indonesia, we report our experience with this technique.

Methods

This study is a descriptive observational study that cross-sectionally analyses registry data of our centre. Our registry is an updated, institution-based, and confidential registry maintained by the Paediatric Cardiology and Congenital Heart Disease Division of the Cardiology Department at Adam Malik General Hospital. This registry has been running since 2020. All ASD patients who are recorded for ASD device closure will be included in this study as the target population. We intend to apply non-fluoroscopic ASD device closure initially; therefore, we exclude patients for whom this approach can't be performed. Registry data collection and statistical analysis are being performed by two distinct individuals, each of whom is independent and blind to the operator of the procedure. TEE was performed to ensure the suitability of all rims that are adequate for transcatheter closure.[4]

Indication and Contraindication

Initially, patients were clinically diagnosed with secundum ASD and confirmed by TTE. Pediatric ASD patients who are interested in having contraindications complicating Pulmonary Hypertension (PH) will proceed to Right Heart Catheterization (RHC) to calculate the flow ratio and pulmonary resistance. For the majority of our patients are Grown Up with Congenital Heart Disease (GUCH) we practiced most of the recommendations from European Society of Cardiology (ESC) Guidelines 2020 for the Management of Adult Congenital Heart Disease of as well as Indonesian Heart Association Guidelines for Adult with Congenital Heart Disease 2020.[5-6] Patient diagnosed with secundum ASD with clinically significant left to right shunt with signs of Right Ventricle (RV) volume overload will be admitted to the hospital to have RHC as a method to confirm Pulmonary Arterial Hypertension (PAH) (Pulmonary Vascular Resistance [PVR]>3WU). ASD with an increased flow ratio (Qp/Qs > 1.5) will be closed, with the option to perform balloon testing to weigh the benefit versus the risk of closure in a patient with PVR < 3 WU and Left Ventricle (LV) disease. In a patient with low PVR and without LV disease, ASD should be closed with a Class I Recommendation. In a patient with PVR 3-5 WU, ASD can be closed with Class IIa Recommendation. Meanwhile, patients with PVR>5WU will be recommended to have months of PAH treatment before closure with a fenestrated device, only when PVR falls below 5 WU after PAH treatment and the flow ratio >1.5.[5-6]

Minimal invasive ASD with device closure will be conducted when ASD rims are categorized as suitable for transcatheter closure. At our centre, when rims are identified, we adopt a non-fluoroscopic approach as our first-line method.

Preparations and Pre-Medications

We intended to conduct this technique over all secundum ASD with sufficient rims (≥5 mm from the defect to the superior or inferior vena cava, right upper or lower Pulmonary Vein (PV), coronary sinus, mitral or tricuspid valve), ASD without any other heart conditions requiring surgical correction, ASD>40mm, or the diameter of the left side of occluder not larger than the overall length of the atrial septum. All patients gave informed consent to be sedated and intubated, and then underwent this procedure without fluoroscopy.

We applied this technique to patients with deficient rims only when the other rims were adequate. Although it would be challenging, for example, on even posterior rims that are deficient, as long as the opposite rims are supporting and the other rims are well enough, we still proceed with this technique. For aortic rim deficiency or even no aortic rim at all, this technique was also planned in the first place, only if the surrounding rims were adequate. If two or more sides of the rims were not deemed sufficient, or if the patient's safety was at risk, even when only one rim was insufficient, we excluded them and proceeded directly to surgical closure. Another challenging condition was malalignment of ASDs and oval form of ASDs (ratio of the shortest diameter to the longest diameter = 0.75) or floppy

rims.[7-8] We still proceed with the procedure for those challenging cases. Regarding the possibility of erosions, we follow patients with these challenging conditions by performing TTE hours after closure. Some preparations are also needed within the protocols. To minimize the risk of infection, we administered a single intravenous loading dose of antibiotics, followed by two subsequent doses, for prophylaxis. After ASD was totally occluded, we then gave furosemide 40 mg iv (1 mg/kg) to reduce the chances of surging of the left atrial pressure. Unfractionated heparin (100 IU/kg) was given shortly after the guiding stiff wire reached the PV.

Technical Aspects and Bail-put Considerations

Procedural success depends on accurate measurement of working length, defined as the distance from the third intercostal space at the right mid-clavicular line to the right femoral venous puncture site (or the left if right femoral vein puncture fails). This measurement serves as a critical safety parameter, preventing excessive catheter advancement and cardiac perforation.[8]

The procedure was performed in a routine operating room under TEE guidance without fluoroscopy. All patients underwent general anaesthesia with intubation. TEE was used to perform a comprehensive post-intubation study, assessing all aspects of ASD anatomy (location, size, presence of additional defects, and adequacy of the various rims).[4] The procedure is stepwise described in Figure 1.

If any difficulty was encountered with the echo field of view, we switched to fluoroscopy. Of the 116 patients, five patients were helped by fluoroscopy. We infrequently perform balloon sizing; among 116 patients, only 1 was helped by this procedure, performed under fluoroscopy.

Device embolism is the most frequent complication of percutaneous transcatheter closure of ASD, which could be lethal. Snaring will be the first move to manage the embolism while the device is dislodged during the procedure. If possible and safe, we will attempt to resolve the defect by restarting the procedure and, if needed, adding techniques (e.g., balloon sizing) or repeating the examination of all rims to obtain the precise device size. If the embolism occurs at a high-risk site and cannot be snared, or if it is snared but fails to be captured, the patient will be referred for surgery. All procedures were performed in a catheterization laboratory, with a cardiopulmonary bypass unit on standby in the operating room adjacent to the catheterization laboratory. Thus, a patient could be converted to open heart surgery immediately in order to retrieve the device and repair the ASD.[4]

Other possible complications include thromboembolic events, progression of PH, and new valvular abnormalities such as mitral or tricuspid regurgitation, aortic regurgitation, or erosion that causes pericardial effusion and arrhythmia. If complications are mild, we will observe for several hours to determine whether they improve or worsen. Worsening into more severe complications will lead to open heart surgery to manage the complication and take the device out, following defect closure.[17]

Devices

As previously described, the defect was sized based on the maximum defect diameter. The diameter for each patient was selected in accordance with the TEE result, with a diameter 2 to 4 mm in excess of the maximum defect diameter.4 Another option for sizing, the occluding device size was determined by 20% of the defect size. If the oval size were the same, we could use the same device size as the defect size. The Left Atrium (LA) septal diameter was measured precisely. What to avoid is so that the disk wouldn't close the PV, touch the tricuspid, or erode the aorta. We consider placing the disk slightly over the aorta in cases with a zero to minimal aortic rim. The largest device size successfully done in our centre is 42mm.

Device selection at our center was the MemoPart™ ASD occluder. The MemoPart ASD occluder was a self-expanding double-disc device made of nitinol mesh, stainless steel bushing(s), suture line, and polyester fabric membrane. The other device, Occlutech ASD, was made of Titanium oxide-covered nitinol with a spunbonded PET patch for faster endothelialisation, and there is a unique ball connection between the pusher and occluder. This made the Occlutech ASD more rigid. We had two cases using this device that were complicated by Cobra deformity (Table 1). The other device was Amplatzer™ Septal Occluders (ASO). This retrievable device became the device of choice for most interventional cardiologists for decades. In one case, we performed the procedure using a fenestrated device because there was a simultaneously high mean LA pressure on the RHC.

Education, Follow-up, and Long-term Medication

If the high flow condition was accompanied by PH (mean PAP >20 mmHg), we also treat the patient with a pulmonary vasodilator agent (PDE5 inhibitors) alongside the afterload reducing agent,

such as Angiotensin-Converting Enzyme (ACE) inhibitors or beta-blockers, and a diuretic if there were still signs of pulmonary congestion due to lung overflow. Aspirin (3-5mg/kg) was given for a period of six months of period.[4]

After a successful procedure, appropriate patient education and follow-up are also essential parts of the treatment. We gave instructions on how to care of the oral hygiene and prevent the development of caries. PH treatments needed to be continued as the physical fitness improved, as long as the PH signs and symptoms were also diminished.

Results

From May 2020 to August 2024, 111 secundum ASDs were closed under the guidance of TEE. Five were excluded due to the need of fluoroscopy to help complete the procedure. There were 21 (19%) male patients and 90 (81%) female patients (Table 1). Our first case was a 64-year-old lady with a 24 mm defect. The patients' mean age was 37 ± 14.3 years, and their mean body weight was 53 ± 26.3 kg. The sizes of the secundum ASDs ranged from 10 to 40 mm, and there were descriptions of rim size in Table 1. Five patients had complex ASD with posterior rim deficiency. Four of them had minimal, thin, and floppy, and one of them had no posterior rim at all. From all five cases, anterior rims are long enough to support the device, ranging from 12-20mm. The mean size of the device was 28 ± 7.5 mm (ranging from 6–36 mm). The mean procedural time IS 55.8 ± 22.7 minutes.

Discussion

It has been reported that radiation exposure during percutaneous coronary interventions decreased significantly (by 36%) between 2008 and 2018 in Germany. However, physicians and patients remain exposed to low-dose fluoroscopy, further stimulating substantial interest in radiation-free cardiac interventions. At a high-volume medical centre in Italy, the proportion of zero-fluoroscopy procedures increased from 8.5% in 2017 to 22.9% in 2021, fully demonstrating this developmental trend.[9]

To contribute academically, our study findings consistently recommend a non-fluoroscopic technique as the first option for transcatheter ASD

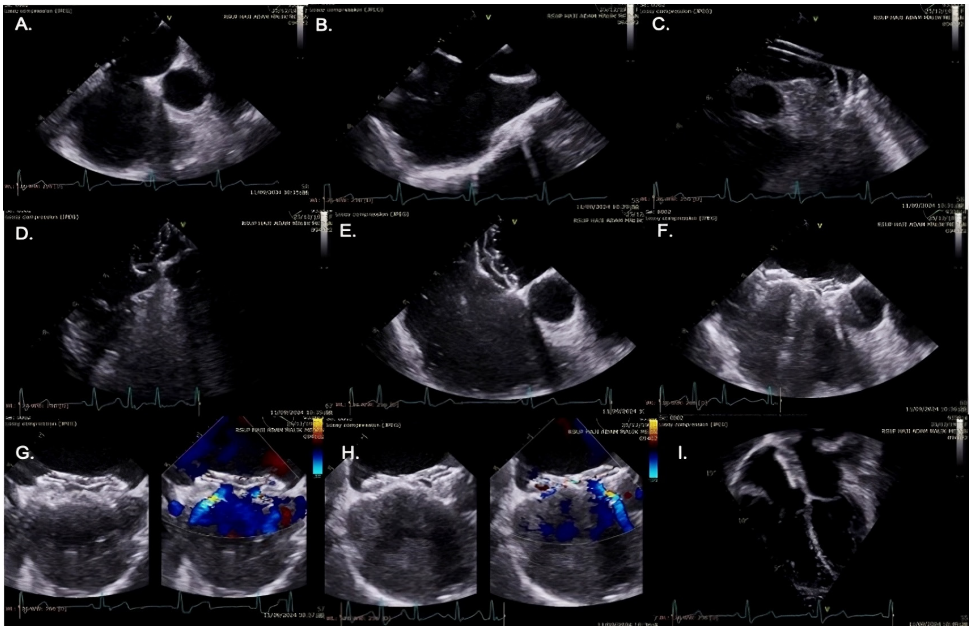

Figure 1. A-B: After ASD size and rim measurement by TEE, the procedure is started by advancing a Multipurpose Catheter (MP) across the defect to reach the left PV. C: A stiff wire is inserted following the MP to guide the delivery sheath to the left PV. D: After the device is inserted through the introducer into the delivery sheath, we push the LA disk out mostly into the PV. E: Then we dragged the delivery sheath and tried to position the LA disk align with the rims. This approach was very well done by viewing the aorta and posterior rim (30°-40°). F-G: The RA disk was deployed and captured all of the appropriate rims. H: Only a central and minimal shunt was seen. I: Device is seen on TTE 4 chamber view.

Table 1. Baseline demographic data of secundum ASD patients.

Parameter	N
Female (n)	90 (81.1)
Age (yrs)	37 ± 14.3
Weight (kg)	53 ± 26.3
Body Surface Area (m^2)	1.71 ± 2.09
Defect Size (mm)	28 ± 7.55
Procedural Time (mins)	55.8 ± 22.7

Table 2. Measurements of ASD rims .

Rims	Mean (SD)
Aortic (mm)	6 (4.025)
Mitral (mm)	12.69 (5.587)
Posterior (mm)	12.14 (6.012)
Superior (mm)	7.72 (4.349)
Inferior Vena Cava (mm)	13.35 (6.746)
Superior Vena Cava (mm)	12.20 (5.927)

The successful rate was 95%, and only one successful closure was complicated by a manageable pericardial effusion. From two cases of embolization, one case had no aortic rim and a floppy Inferior Vena Cava (IVC) rim. Another case had malalignment, and the aortic rim was floppy and thin.

Table 3. Rate of performance of non-fluoroscopy transcatheter ASD closure technique in Heart Centre of Adam Malik General Hospital.

Parameter	n = 111 (%)
Succeed	105 (94.6%)
Succeed with self-limited complication	1 (0.9%)
*pericardial effusion, erosion of RA and RV	
Not successful	5 (4.5%)
Device emboli (2)	
Deformity of the device, not recoil (2)	
Inadequate device size (1)	

device closure. The main issue in this technique was the operator's performance in tracking the guidewire and sheath in the 2D view of TEE. Visualization of the tip of the catheter, wires, and deployment of the device is critical for the safety and efficacy of device closure of ASD. Thus, an operator skilled in transcatheter intervention and an experienced echocardiographer were mandatory.[3]

Radiation exposure was the second issue that would benefit from this procedure compared with conservative fluoroscopy. This made an advantage for some populations who were at risk of some conditions (ASD with pregnancy) and other comorbidities (worsening of heart failure or PH).[3,10] Most of the studies underwent this procedure on children. Our centre would gave an unique perspective of how 98% of ASD patients were adults.

The 'cobra-like' configuration of the ASO device is a rare but known complication of percutaneous treatment of atrial septal defects that occurs in 0-3% of published series.[15] It is, in fact, the extreme variant of a series of distortions deriving from a change in position of the device's nitinol wires. This deformity can happen in either the RA or the LA disc.[16] These distortions range from a slight bulge to the 'cobra-like' formation. Some reasons are implied by a manufacturing defect, the excessively distal release of the device, which can push the LA disc into the free wall of the left atrium, the left atrial appendage, or the PV orifice, and by deformation of these structures or difficulties in positioning the device within the sheath. Difficulty loading the device, twisting the device while advancing it through a smaller sheath, or kinking the delivery catheter can also be reasons. In two of our cases (Figure 2), deformities were

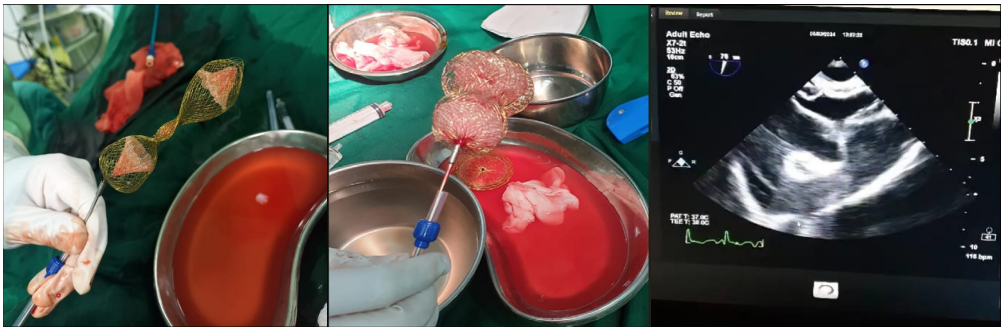

Figure 2. Device deformities causing unsuccessful procedure, from left to right: Cobra deformity, LA disc bulging, and fixed deformity as seen through TEE.

happening with the same brand. The greater length of wire between the disc margin and the centre of the device compromises its memory of shape.[16] We have tried to do clockwise or the back-and-forward movement within the sheath, which may have favoured relocation of the wires, leading to recovery of the usual configuration, but still couldn't fix the deformities. For the patient's safety, we postponed the procedure.

Our study consists mostly of adults. We have only eight patients under 17 years old, with a 6-year-old as the youngest. We consider this a special circumstance arising from the limitation of working in a general hospital, where admission to the Paediatric Department for patients under 18 years is obligatory. The authors of this study are cardiologists working at the Heart Centre within the general hospital, where most of the paediatric patients under 18 are referred to the Paediatric Department to ensure that children are managed by a paediatrician as their primary physician. A paediatrician can possibly consult a cardiologist at Heart Centre, but usually they will have the procedures under a paediatrician (cardiology consultant). Although we, as Cardiologists (interventional paediatric consultants), are technically permitted and legally authorized to perform transcatheter ASD device closure, practical regulations for this shared competency across age groups and subsets are still being developed for general hospitals in Indonesia. Additionally, at Adam Malik General Hospital, the Paediatric Department is located in a separate building and under a different managerial unit from our Heart Centre. This situation is similar to that in other hospitals in Indonesia, except at the National Heart Centre in Jakarta, where all patients with congenital heart disease of any age are managed by Cardiologists because it is a specialized hospital.

Different from the child population, we should consider the ASD size, device size, occurrence of PH, and diastolic dysfunction that can lead to higher left atrial pressure, which can worsen after ASD closure. When we compare our study to findings from the application of this technique on the child population, there are obvious differences in children, such as shorter procedural times, smaller ASD device closure, and lower rates of complications (embolization and erosion or pericardial effusion).[13] The device deformities, e.g., cobra head deformity itself, are often reported in adult patients who are related to larger device size and delivery sheath variances, and multiple attempts of placing the device on some deficient rims of ASD. Both children and adults undergoing non-fluoroscopic ASD device closure are guided by TEE, which is superior in image resolution because the probe is positioned adjacent to the left atrial posterior wall, placing the interatrial septum within the optimal imaging range.[9]

Another major concern in ASD closure is the risk of post-procedural elevation in LA pressure, particularly in older adults with diastolic dysfunction. Holzer et al. suggest performing a test occlusion; if the mean LA pressure increases by more than 3 mmHg, the use of a fenestrated occluder may be warranted.[17] We don't apply these approaches; otherwise, we follow the Indonesian and ESC guidelines on GUCH. We also continue heart failure medications that can control LA pressure, as well as PH medications.

Considering the advantages of this technique, Percutaneous and Non-Fluoroscopic (PAN) procedures use echocardiographic guidance as an alternative to conventional fluoroscopy. This eliminates radiation exposure while maintaining procedural efficacy. Implementation of the PAN

procedure follows a comprehensive, systematic framework designed to ensure procedural safety and efficacy across varying levels of complexity. The overall approach can be structured into four sequential phases: patient selection, preoperative assessment, intraoperative team coordination, and postoperative evaluation.[9]

TEE can be used to monitor the occlusion device's release, particularly to confirm correct placement, verify complete release, confirm the absence of residual shunt, and assess the condition of the atrial valve. In our procedures, once the occlusion device was confirmed to be correctly placed, we released the device in full to assess its effect of the device.[13]

Some disadvantages are evident compared with conventional (fluoroscopic) ASD device closure. This non-fluoroscopic technique may be controversial in terms of procedural time. The main factors associated with procedure time include: the process to reach the PVs, because there may be some difficulty in tracking the tip of the catheter and/ or guidewire with TEE, and the course of device deployment, as the angle between the sheath and atrial septum may not be good enough, so that redeployment may be needed. Although longer procedural times were required in certain cases, especially in the early stages of the study, procedural time decreased markedly as operators gained experience.[4] Another possible disadvantage of this technique is that it is performed under general anaesthesia, necessitating a period of strict observation after the procedure.[9] These disadvantages related to longer procedural time can be mitigated over time as the operator and teammate are already in line with one another through their learning curve. This study provides insight into the safety of this technique. Another issue is that we should widen our possibilities to use another choice of ASD closure device to help the success rate for each device, which should have its own superiority and infirmity.[15]

This is a registry-based study. To address our study limitation, we plan to continue monitoring and to complete follow-up of patients' clinical conditions to provide further analysis of factors associated with symptom improvement. As a heart center located relatively far from the capital city of Indonesia, this established registry is useful of describing the application of this technique in the early era of non-fluoroscopic approaches to structural heart disease management (Figure 3).

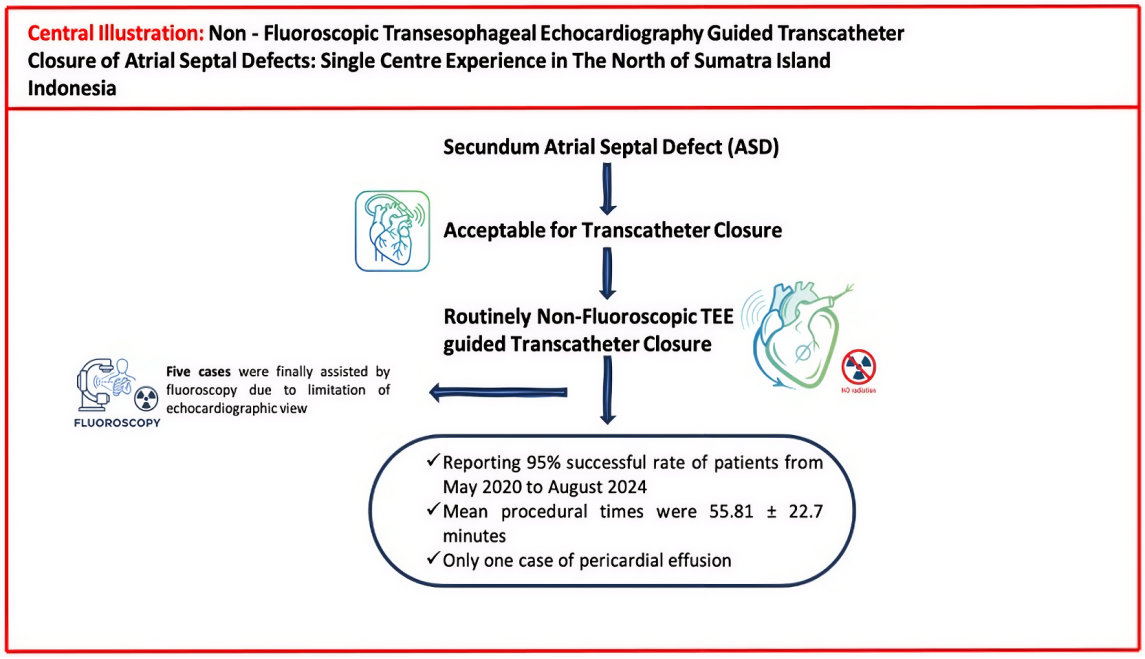

Figure 3. Central illustration of the study.

Conclusion

Non-fluoroscopy transcatheter closure of secundum ASD can routinely be performed. With some adjustments, operators who are already accustomed to the TEE view and this thorough procedure can be protected from the harm of radiation.

List of Abbreviations

ACE	Angiotensin-Converting Enzyme
ASD	Atrial Septal Defect
ASO	Amplatzer Septal Occluders
ESC	European Society of Cardiology
GUCH	Grown Up with Congenital Heart Disease
IRB	Institutional Review Board
IU	International Units
IVC	Inferior Vena Cava
LA	Left Atrium / Left Atrial
LV	Left Ventricle
MP	Multipurpose Catheter
PAH	Pulmonary Arterial Hypertension
PAN	Percutaneous and Non-Fluoroscopic
PAP	Pulmonary Arterial Pressure
PDE5	Phosphodiesterase type 5
PH	Pulmonary Hypertension
PV	Pulmonary Vein
PVR	Pulmonary Vascular Resistance
Qp/Qs	Flow ratio (Pulmonary-to-Systemic Flow Ratio)
RHC	Right Heart Catheterization
RV	Right Ventricle
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
WU	Wood Units

Ethical Clearance

The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013, where applicable. Institutional Review Board (IRB) approval was obtained from Adam Malik Hospital. All patients have given informed consent for their inclusion in the study, where applicable.

Publication Approval

All patients have given informed consent for their inclusion in the study, where applicable.

Authors Contributions

Ali Nafiah Nasution & Bertha Gabriela Napitupulu (Pediatric Cardiology and Congenital Heart Disease Division) and Tengku Winda Ardini & Joy Wulansari Purba (Echocardiography and Cardiovascular Imaging (Non Invasive Cardiology) Division) accomplished for substantial contribution to the conception and design of the study and the analysis of clinical data, drafting the manuscript and final approval of the version to be published. All of those four people together with Cut Aryfa Andra (The Head Faculty of Cardiology and Vascular Medicine Study Program), Anggia Chairuddin Lubis as (The Head of Cardiology and Vascular Medicine Department) and Abdullah Afif Siregar (Professor on Pediatric Cardiology and Congenital Heart Disease Division) contributed to give final approval of the version to be published.

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Conflict of Interest

All authors have disclosed any conflicts of interest relevant to this work.

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Original Article

Relationship Between Preoperative Risk Factor Profiles and Clinical Outcomes In Patients Undergoing Isolated CABG Treated In the ICU: A Retrospective Observational Study

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Abstract

Background: Atherosclerotic Cardiovascular Disease (ASCVD) causes around 31% death all over the world. This disease can be managed with Coronary Artery Bypass Graft (CABG). Although its success ratio continues to increase, patients tend to have more complex conditions, which complicate the results.

Methods: This retrospective cohort study was conducted with samples consisting of ≥ 18 years old patients who underwent isolated CABG between January 2017 and June 2022 and were admitted to the Intensive Care Unit (ICU) afterward. Clinical outcomes measured were prolonged ICU and intrahospital mortality. A 77-hour post-procedural ICU treatment period is considered the standard of care.

Results: A total of 2611 patients were included. The mean age was 59 years. Geriatric, overweight, obesity, kidney failure, Heart Failure with reduced Ejection Fraction (HFrEF), Cardiogenic Shock, Left Main Disease (LMD), and Pre Incision Intra-Aortic Balloon Pump (IABP) are associated with prolonged ICU care; while female gender, Family history of ASCVD, Diabetes, Hypertension, Acute Coronary Syndrome (ACS), Stroke, and history of cardiac surgery are associated with higher mortality. The lengthening of ICU care is also associated with higher mortality (OR 4.02; p<0.00). According to multivariate analysis, the factors associated with prolonged ICU are geriatric, obesity, kidney failure, stroke, HFrEF, Cardiogenic shock, very poor Ejection Fraction (EF), urgent procedure and pre incision IABP, meanwhile factors associated with mortality are female, diabetes, stroke, history of ACS<24H, poor and very poor EF, History of Cardiac Surgery, and prolonged ICU itself.

Conclusions: In Indonesian isolated CABG patients, prolonged ICU stay and increased mortality are independently driven by specific demographic, comorbid, and clinical factors, necessitating targeted preoperative risk assessment to optimize outcomes.

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Keywords: Mortality, Prolonged ICU, Isolated-CABG, Risk Factor, Indonesia.

Introduction

Atherosclerotic Cardiovascular Disease (ASCVD) is a major global health problem and accounts for approximately 31% of deaths worldwide. In Indonesia, ASCVD is one of the leading causes of mortality, alongside cancer and stroke.[1] Coronary Artery Bypass Grafting (CABG) is a well-established treatment option for this condition. The procedure is generally performed in patients with high-risk coronary occlusion or multivessel disease. Patients with failed Percutaneous Coronary Intervention (PCI) are also candidates for CABG, in accordance with the American College of Cardiology and American Heart Association (ACC/AHA) guidelines.[2]

Although the success rate of CABG continues to improve, patients undergoing this procedure tend to be older and have more complex clinical conditions. As a result, many of these patients require a prolonged stay in the intensive care unit.[3] Several predictive scoring systems are currently available to assess prognosis in patients undergoing major cardiac surgery, including CABG. However, the validation of these systems remains limited in Asian populations.[2] The length of stay in the intensive care unit also needs to be revisited, considering that prolonged Intensive Care Unit (ICU) stay has been associated with increased mortality during hospitalization as well as after hospital discharge.[4-5]

Studies examining the relationship between clinical profiles of patients undergoing isolated CABG and postoperative outcomes, especially length of stay in the intensive care unit, remain limited in Indonesia. A study conducted in Taiwan found that sex, smoking history, hypertension, procedural status, and renal function were independent risk factors for prolonged intensive care stay. Another study from Canada identified similar factors and further demonstrated that a prior history of CABG, diabetes, cerebrovascular disease, and ventricular function were associated with readmission mortality among CABG patients.[5-6] This study aims to describe the clinical profiles of patients undergoing isolated CABG who are treated in the intensive care unit and to evaluate their association with prolonged ICU stay and in-hospital mortality in Indonesia.

Methods

This retrospective cohort study was conducted in Harapan Kita National Heart Center. The study included patients aged 18 years or older who underwent an isolated CABG procedure between January 2017 and June 2022 and were admitted to the ICU after the procedure. Data were collected from the registry of the Adult Surgery Division, Research and Development Installation of Harapan Kita National Heart Center using a total sampling method.

Several variable groups were analyzed in this study, including classical ASCVD risk factors, comorbid factors, and cardiology-specific risk factors. Smoking status was defined as patients who were former smokers or current active smokers. Diagnosis of diabetes (E.11), dyslipidemia (E.78), and hypertension (I.10) in the sample were established by the physician during hospitalization. Information on family history of ASCVD and comorbid conditions, other than renal failure, was obtained from the patient's medical history as recorded by the resident physician at the time of initial admission to the emergency department. A patient's history of Acute Coronary Syndrome (ACS) was defined as prior hospitalization due to cardiac arrest or the presence of clinical evidence based on electrocardiography or echocardiography.

The diagnosis of atrial fibrillation used in this study was made based on electrocardiographic findings obtained either at the time of admission to the emergency department or during hospitalization before the procedure. Ejection Fraction (EF), Left Main Disease (LMD) and the number of arteries involved were determined by echocardiography. Urgent procedures were defined as those performed in patients with hemodynamic instability or persistent chest pain. Emergency procedures were defined as those performed in patients with unsuccessful PCI. The use of pre-incision Intra-Aortic Balloon Pump (IABP) was defined as the insertion of the IABP performed in the operating room prior to the skin incision. Pre-incision IABP was generally performed in patients with an EF below 30%, accompanied by impaired cardiac performance based on echocardiography by eye-balling method, or with hemodynamic instability requiring inotropic support.

A duration of 77 hours or ±3 days of post-procedure care in the intensive care unit was set as a benchmark for the length of normal care according to several previous studies and the 90th percentile of the current dataset.[4-6] The period of re-entry to the intensive care unit after transfer from a regular ward was not accounted for in this study. The clinical outcomes measured in this study were prolonged ICU stay and in-hospital mortality.

Table 1. Patient risk factor profile and their relationship with length of care and mortality.

Variable	Total		Prolonged		P-value	OR	95% CI	Mortality		P-value	OR	95% CI
	n	%	n	%				n	%			
Age Group Category												
Young Adult	134	5.09	9	6.77	0.26	0.66	0.32-1.28	4	3.01	0.65	0.68	0.25-1.88
Elderly	1913	73.27	183	9.57	0.23	0.84	0.64-1.11	81	4.23	0.94	0.98	0.64-1.51
Geriatric	564	21.60	69	12.23	0.05	1.35	1.01-1.80	26	4.61	0.63	1.12	0.71-1.75
Nutritional Status												
Underweight	55	2.11	6	10.91	0.82	1.11	0.47-2.61	2	3.64	0.82	0.85	0.20-3.52
Normal	467	17.89	40	8.57	0.26	0.82	0.57-1.16	22	4.71	0.59	1.14	0.71-1.84
Overweight	521	19.95	35	6.72	0.01	0.59	0.41-0.86	21	4.03	0.78	0.93	0.58-1.52
Obese	1548	59.29	179	11.56	0.01	1.56	1.19-2.06	65	4.20	0.87	0.97	0.66-1.43
Sex												
Male	2219	84.99	222	10.00	0.90	0.98	0.69-1.40	84	3.79	0.01	0.53	0.34-0.83
Female	392	15.01	40	10.20	0.90	1.02	0.72-1.47	27	6.89	0.01	1.88	1.20-2.94
Classic ASCVD Risk Factor												
Smoker	1384	53.01	131	9.47	0.30	0.87	0.68-1.13	53	3.83	0.26	0.80	0.54-1.17
Family History of ASCVD	398	15.24	40	10.05	0.99	1.00	0.70-1.43	25	6.28	0.03	1.66	1.05-2.62
Diabetes	1089	41.71	106	9.73	0.67	0.94	0.73-1.23	64	5.88	0.00	1.89	1.29-2.77
Dyslipidemia	940	36.00	93	9.89	0.89	0.98	0.77-1.28	40	4.26	1.00	1.00	0.67-1.49
Hypertension	1727	66.14	184	10.65	0.14	1.23	0.93-1.63	85	4.92	0.02	1.71	1.09-2.67
Comorbid Factor												
Kidney Failure	186	7.12	42	22.58	0.00	2.92	2.02-4.24	10	5.38	0.43	1.31	0.67-2.55
Cr Clearance 50-85	1208	46.27	125	10.35	0.72	1.05	0.81-1.35	50	4.14	0.76	0.94	0.64-1.38
Cr Clearance <50	419	16.05	68	16.23	0.00	1.86	1.38-2.51	22	5.25	0.28	1.30	0.81-2.11
Dialysis	34	1.30	10	29.41	0.00	3.84	1.82-8.13	1	2.94	0.74	0.71	0.10-5.34
Stroke	201	7.70	26	12.94	0.15	1.37	0.89-2.11	17	8.46	0.00	2.28	1.33-3.90
COPD	35	1.34	5	14.29	0.40	1.50	0.58-3.91	1	2.86	0.68	0.66	0.9-4.86
Immunosuppressant Therapy	14	0.54	0	0.00	-	-	-	1	7.14	0.59	1.74	0.23-13.41
Cerebrovascular Disease	109	4.17	11	10.09	0.98	1.01	0.53-1.90	6	5.50	0.51	1.33	0.57-3.10
Vascular Disorder	17	0.65	3	17.65	0.30	1.93	0.55-6.80	1	5.88	0.74	1.41	0.19-10.74

Cardiology Specific Factor												
History of ACS	1047	40.10	106	10.12	0.90	1.02	0.78-1.32	53	5.06	0.09	1.38	0.95-2.03
<24 Hours	48	1.84	8	16.67	0.12	1.82	0.84-3.93	6	12.50	0.00	3.34	1.39-8.04
1-7 Days	68	2.60	11	16.18	0.09	1.76	0.91-3.40	7	10.29	0.01	2.69	1.20-6.03
8-21 Days	68	2.60	11	16.18	0.09	1.76	0.91-3.40	3	4.41	0.95	1.04	0.32-3.36
>21 Days	724	27.73	63	8.70	0.16	0.81	0.60-1.09	31	4.28	0.96	1.01	0.66-1.54
Missing	139	5.32										
HFrEF (EF<41%)	544	20.83	113	20.77	0.00	3.40	2.60-4.44	31	5.70	0.06	1.50	0.98-2.30
Cardiogenic Shock	13	0.50	10	76.92	0.00	31.03	8.55-113.49	2	15.38	0.05	4.15	0.90-18.96
Atrial Fibrillation	26	1.00	3	11.54	0.79	1.18	0.35-3.95	2	7.69	0.38	1.89	0.44-8.11
Left Main Disease	895	34.28	108	12.07	0.01	1.39	1.07-1.80	43	4.80	0.32	1.22	0.83-1.81
Blood Vessel Abnormalities												
One	48	1.84	5	10.42	0.81	1.12	0.44-2.87	2	4.17	0.95	1.05	0.25-4.38
Two	243	9.31	25	10.29	0.89	1.03	0.67-1.59	8	3.29	0.44	0.75	0.36-1.56
Three	2320	88.85	232	10.00	0.87	0.97	0.65-1.44	101	4.35	0.47	1.28	0.66-2.48
Ejection Fraction	54.00 (±13.910)											
Good (>50%)	1616	61.89	105	6.50	0.00	0.46	0.34-0.59	53	3.28	0.00	0.51	0.35-0.74
Moderate (31-50%)	789	30.22	104	13.18	0.00	1.60	1.23-2.08	37	4.69	0.47	1.16	0.78-1.74
Poor (21-30%)	139	5.32	26	18.71	0.00	2.18	1.39-3.41	16	11.51	0.00	3.26	1.86-5.69
Very Poor (<=20%)	22	0.84	10	45.45	0.00	7.73	3.31-18.07	5	22.73	0.00	6.89	2.50-19.03
Procedural Status												
Elective	2431	93.11	219	9.01	0.00	0.32	0.22-0.46	95	3.91	0.00	0.42	0.24-0.73
Urgent	175	6.70	41	23.43	0.00	3.07	2.11-4.47	15	8.57	0.00	2.29	1.30-4.03
Emergency	5	0.19	2	40.00	0.03	6.02	1.00-36.17	1	20.00	0.08	5.67	0.63-51.18
Pre-Incision IABP	60	2.30	32	53.33	0.00	11.59	6.86-19.59	3	5.00	0.77	1.19	0.37-3.86
History of Cardiac Surgery	32	1.23	3	9.38	0.90	0.93	0.28-3.06	4	12.50	0.02	3.30	1.13-9.57

ASCVD: Atherosclerotic Cardiovascular Disease; COPD: Chronic Obstructive Pulmonary Disease; ACS: Acute Coronary Syndrome; HFrEF: Heart Failure with Reduced Ejection Fraction; IABP: Intra-Aortic Balloon Pump.

Data analysis was conducted using SPSS 17, which was manufactured in the USA in 2009. Continuous variables were presented as mean and standard deviation, while categorical variables were presented as frequency and proportion. All of the categorical variables were then compared with the clinical outcomes using bivariate logistic regression analysis with the chi-square test. Variables with a P-value of < 0.25 in bivariate analysis were then reanalyzed using the multivariate logistic regression analysis, and variables with a P-value of <0.05 were considered as independent risk factors.

Results

A total of 2611 patients met the inclusion and exclusion criteria. The median age of the patients was 59 years, with the majority being elderly and having obesity. Geriatric status, Body Mass Index (BMI)>23, renal failure with creatinine clearance <50 or requiring dialysis, and history of stroke were significant factors associated with prolonged ICU stay. Female sex, history of ASCVD, diabetes, hypertension, and stroke were significantly associated with mortality. Although a history of ACS was not associated with clinical outcomes, an onset of ACS <7 days prior to the procedure was significantly associated with mortality. LMD, Heart Failure with reduced Ejection Fraction (HFrEF), and cardiogenic shock were also significantly associated with prolonged ICU stay (Table 1).

Approximately 10% (n=262) of the patients required prolonged intensive care, of whom 15 required readmission to the ICU after transfer to a regular ward. Prolonged ICU stay was significantly associated with mortality, with an odds ratio of 4.017 for patient death. This warrants a separate focus to improve future patient clinical outcomes (Table 2).

Table 2. Relationship between length of stay and patient mortality.

Variable	Mortality		P-value	OR	95%
	n	%			
Normal Intensive Care Period	79	3.4	0.000	4.017	2.61-6.19
Prolonged Intensive Care Period	32	12.3			

After reanalysis using the logistic regression method, it was found that geriatric status, obesity, severe decline in renal function and dialysis, cardiogenic shock, HFrEF, especially with EF <20%, urgent procedure, and pre-incision IABP were independently associated with prolonged ICU stay. Female sex, history of ASCVD, diabetes, stroke, ACS <24 hours, EF <30%, prior cardiac surgery, and prolonged ICU stay were identified as independent risk factors for mortality (Table 3).

Discussion

This study was conducted at a national referral center for cardiovascular disease. Therefore, the study population can be considered representative of patients undergoing isolated CABG in Indonesia. The majority of patients in this study were elderly patients and had obesity as their nutritional status. The geriatrics age group (p=0.02; OR 2.54; 95% CI 1.15-5.60) and obesity (p=0.00; OR 1.82; 95% CI 1.35-2.45) were independently associated with prolonged ICU stay. According to Kao et al. (2022), age was significantly associated with the length of the treatment duration, particularly at older ages (70.9 ± 12.2; p = 0.002). An interesting finding in this study was that patients requiring prolonged ICU care had a lower BMI compared to those with shorter ICU stays (23.6±3.9 vs 25.4±3.2). As the referenced study was conducted in Taiwan, the BMI parameter used was consistent with the Asian population standards, which are also applicable to Indonesia.[6] Mortality among patients undergoing isolated CABG in this study was relatively low and comparable with previous studies. Suwatri et.al. (2022) reported mortality rates of 5.7% in patients undergoing off-pump coronary artery bypass and 16.2% in those undergoing coronary artery bypass grafting. The difference between these two bypass methods was not significantly associated with mortality.[7]

Gender was not associated with length of ICU stay in this study; however, it was associated with a higher risk of mortality, with an odds ratio of 1.88 (p=0.009; 95% CI 1.17-3.00). In contrast, a research by Hassan, et al. (2012) found slightly different results where female sex among patients undergoing major cardiac surgery was significantly associated with prolonged ICU stay (p<0.0001). Although the study included various types of cardiac surgery, CABG was the most frequently performed procedure in their cohort.[8]

Table 3. Multinomial logistic regression for the clinical outcome.

A. Prolong ICU

Variable	P-value	OR	95% CI
Age Group			
Elderly	0.10	1.89	0.89-4.01
Geriatric	0.02	2.54	1.15-5.60
Nutritional Status			
Obesity	0.00	1.82	1.35-2.45
Risk Factor			
Hypertension	0.42	1.13	0.83-1.50
Comorbid Factors			
Kidney Failure			
Cr Clearance <50	0.02	1.51	1.08-2.12
Dialysis	0.00	4.75	2.13-10.58
Stroke	0.04	1.59	1.02-2.47
Cardiology Specific Factor			
History of ACS			
<24 Hours	0.84	1.10	0.43-2.79
1-7 Days	0.53	0.77	0.35-1.71
8-21 Days	0.69	0.85	0.37-1.92
>3 Weeks	0.66	0.93	0.68-1.28
HFrEF	0.00	0.07	0.16-3.13
Cardiogenic Shock	0.00	20.46	4.20-99.65
Left Main Disease	0.83	1.03	0.77-1.38
Ejection Fraction			
Moderate	0.08	1.32	0.97-1.80
Poor	0.17	1.46	0.85-2.51
Very Poor	0.00	5.05	1.88-13.59
Procedural Status			
Urgent	0.00	2.78	1.76-4.41
Emergency	0.42	2.78	0.23-33.64
Pre Incision IABP	0.00	5.47	2.96-10.09

B. Mortality

Variable	P-value	OR	95% CI
Female	0.04	1.76	1.04-2.97
Risk Factor			
Smoker	0.70	0.91	0.58-1.43
Family History of ASCVD	0.02	1.80	1.10-2.92
Diabetes	0.01	1.75	1.17-2.61
Hypertension	0.14	1.42	0.89-2.25
Stroke	0.04	1.83	1.02-3.26
Cardiology Specific Factor			
History of ACS			
<24 Hours	0.01	3.37	1.27-8.91
1-7 Days	0.08	2.26	0.90-5.69

HFrEF	0.68	0.90	0.54-1.49
Cardiogenic Shock	0.60	1.58	0.28-8.93
Ejection Fraction			
Poor	0.00	3.30	1.76-6.19
Very Poor	0.00	8.72	2.86-26.61
Procedural Status			
Urgent	0.24	1.48	0.77-2.85
Emergency	0.50	2.40	0.18-31.23
Pre Incision IABP	0.08	0.30	0.08-1.13
History of Cardiac Surgery	0.04	3.53	1.07-11.67
Prolong ICU Period	0.00	3.53	2.18-5.70

ACS: Acute Coronary Syndrome; HFrEF: Heart Failure with reduced Ejection Fraction; IABP: Intra-Aortic Balloon Pump; ASCVD: Atherosclerotic Cardiovascular Disease; ICU: Intensive Care Unit.

Smoking, which is a well-established risk factor for cardiovascular diseases, was not associated with clinical outcomes in this study. Similarly, Saxena et al. (2022) found that smoking was not significantly associated with mortality within 30 days after surgery. However, smoking was associated with late mortality after 37 months in both active smokers (OR 1.41, 95% CI 1.26-1.59; p<0.001) or former smokers (OR 1.73, 95% CI 1.47-2.05; p<0.001).[9] Only severe renal failure, dialysis, and stroke were found as independent risk factors for prolonged ICU stay in this study. Previous studies obtained different results, where other comorbidities such as diabetes, hypertension, history of ASCVD, dyslipidemia, cerebrovascular disease, vascular disease, and COPD all had a significant association with prolonged ICU stay among patients undergoing isolated CABG.[5] History of ASCVD, diabetes, hypertension, and stroke was all associated with mortality in this study. However, after multivariate analysis, hypertension was no longer a significant predictor. According to the EuroSCORE II model for predicting mortality in major cardiac surgery, a history of ASCVD and insulin-treated diabetes are included as predictive parameters, whereas hypertension and stroke are not.[10] In the present study, most patients with a history of stroke had limited mobility, which may have contributed to an increased risk of mortality. In contrast, another study conducted by Herlitz et al. (1996) found that patients with hypertension tended to have increased mortality during the first 30 days after CABG and that late mortality (between days 30 and 2 years) was significantly higher than in non-hypertensive patients.[11]

LMD, HFrEF, cardiogenic shock, and EF<50% were identified as cardiology-specific factors associated with prolonged ICU stay in the bivariate analysis. However, after multivariate analysis, only HFrEF, cardiogenic shock, and EF <20% remained independently associated with prolonged ICU stay. Previous studies conducted by Heimrath et al. (2007) obtained slightly different results, where ventricular function <50% was found to be 1.3 times (95%CI 1.1-1.5), causing intensive care readmission or death.[5] In contrast, Gonasdotir et al. (2020) reported that only a history of ASCVD was independently associated with prolonged ICU stay.[12] Oliveira et al. (2013) also found that EF<50% was not associated with prolonged ICU stay, although it was an independent factor for longer length of stay in the general ward.[13] Although in this study the involvement of the left main artery was not an independent risk factor for prolonged ICU period, the previous study conducted by Heimrath et al. (2007) reported opposite findings. That study also reported that the number of blood vessels beyond the main vessels was significantly associated; these associations were not observed in the present study.[5] Regarding mortality, Rinaldi et al. (2022) reported that left ventricular function <30% increased by 3.23 times (p=0.017; 95%CI = 1.23-8.45) the risk of death within 30 days after the procedure. That study also found that Myocardial Infarction (MI) occurring within 3 months before the procedure had no significant relationship with 30-day mortality. In contrast, the present study found that the incidence of MI occurring <24 hours prior to the procedure was associated with a 3.14-fold increase in in-hospital mortality.[2]

The use of pre-incision IABP was independently associated with prolonged ICU stay in this study. Previous studies have reported similar results where

the use of preoperative IABP had a significant relationship with longer ICU stay; those associations did not remain significant after multivariate analysis.[5-6] On the other hand, the use of preoperative IABP has been reported as a potential protective factor for mortality. A meta-analysis by Zangrillo et al. (2015) demonstrated that preoperative IABP use was associated with a reduced risk of in-hospital mortality as well as mortality within 30 days after the procedure.[14] Prolonged ICU stay itself was significantly associated with mortality, increasing the risk of death by 4.01 times (p = 0.000; 95% CI 2.61-6.19). Although this finding is consistent with the results of previous studies, the OR found in this study was relatively higher when compared to the study of Heimrath et.al. (2007), which obtained a HR of 2.47 (p = 0.001; 95%CI 1.89-3.22).[5]

Limitation of Study

Several limitations must be considered when interpreting the findings of this research. First, the retrospective observational design is inherently subject to bias, including information bias, and does not allow for the establishment of a causal relationship between risk factors and outcomes. Second, as this study was conducted at a single tertiary referral center (Harapan Kita National Heart Center), the patient population may include patients with more complex clinical conditions than those treated at general hospitals. This may limit the external validity and generalizability of the results to other healthcare settings in Indonesia.

Furthermore, data on family history and certain comorbidities were obtained through patient interviews at the time of admission, which may have introduced recall bias. Finally, the analysis did not account for the total duration of intensive care for patients who required ICU readmission after transfer to a general ward, which may have led to an underestimation of the overall intensive care burden in those cases.

Conclusion

Among patients undergoing isolated CABG in Indonesia, independent risk factors for prolonged ICU stay include geriatric age, obesity, severe renal impairment, cardiogenic shock, EF <20%, urgent procedure status, and pre-incision IABP use. In-hospital mortality was independently associated with female sex, history of ASCVD, diabetes, stroke, ACS within 24 hours prior to the procedure, EF <30%, and previous cardiac surgery. Furthermore, prolonged ICU stay was significantly associated with increased mortality, with an odds ratio of 4.017. These findings underscore the importance of comprehensive preoperative risk assessment to optimize clinical outcomes and improve intensive care utilization in patients undergoing isolated CABG.

List of Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
EF	Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
IABP	Intra-Aortic Balloon Pump
ICU	Intensive Care Unit
LMD	Left Main Disease
MI	Myocardial Infarction
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention

Ethical Clearance

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki. Ethical approval was obtained from the National Cardiovascular Center Harapan Kita ethics committee.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

RZ: Contributed to conceptualizing the research topic and title, establishing the research outline, and coordinating the entire study process—encompassing sampling, data processing, and manuscript preparation; DFS: Responsible for direct field sampling and the analysis of medical records as the primary study data. They also performed data analysis, drafted the results, and completed the comprehensive preparation of the manuscript; BW: Contributed to providing critical insights for defining the research concept and its expansion, establishing the framework for data analysis, and

providing strategic guidance on the direction of the discussion; S: Contributed to providing critical insights for defining the research concept and its expansion and providing strategic guidance on the direction of the discussion; BH: Contributed to providing critical insights for defining the research concept and its expansion and providing strategic guidance on the direction of the discussion.

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Conflict of Interest

The authors declare no conflict of interest.

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The author(s) did not use generative AI or AI-assisted technologies in the writing of this manuscript. All content, data analysis, and interpretations are the original work of the authors.

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Review Article

Unveiling the Burden of Prevalence of Congenital Heart Defects in Down Syndrome Patients in Indonesia: A Systematic Review and Meta-analysis

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Abstract

Down syndrome or trisomy 21 is frequently accompanied by Congenital Heart Disease (CHD), which is a major cause of mortality and morbidity within the first two years of life in children with Down Syndrome (DS). This systematic review and meta-analysis aimed to analyze the literature to assess the pooled prevalence of overall CHDs among children with DS in Indonesia. The search was conducted across major databases, including PubMed, Google Scholar, ScienceDirect, Cochrane, and Garuda (an Indonesian database), using Boolean operators and a range of keywords. Citation management was performed using the Rayyan Intelligent Systematic Reviews website (https://www.rayyan.ai/). Quantitative data synthesis was conducted using Comprehensive Meta-Analysis version 4.0 (Biostat, Englewood, NJ, USA). Initially, 1,915 citations were retrieved from the primary search; after screening titles and assessing full texts, a total of 11 articles were included in this study. A total of 1,078 subjects from 11 different studies were analyzed. The overall pooled prevalence of CHDs among children with DS was 44.6% (95% CI: 34.9% to 54.8%). We also found a high degree of heterogeneity between the studies (I^2 = 88.8%), and inspection of the forest plot revealed that the distribution of the plotted data was asymmetrical. Approximately one in two children with DS in Indonesia has at least one type of CHD. These findings highlight the need for early routine cardiac screening to reduce morbidity and mortality. We recommend further research to provide more data to assess the prevalence of CHD

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Introduction

Down Syndrome (DS), also known as trisomy 21, is a genetic condition characterized by an extra copy of chromosome 21. Affected individuals usually have developmental variations and characteristic morphological traits, and one of the most common associated conditions is Congenital Heart Disease (CHD). Indonesia is believed to have around 300,000 individuals with DS, representing around 3.75% of the global population, which is roughly one case per 1,000 live births. This underscores the importance to identify the pattern and prevalence of congenital heart disease in the DS population.[1-2]

CHD is one of the major causes of morbidity and mortality among individuals with DS, particularly during the first two years of life. Therefore, understanding the prevalence of CHD among individuals with DS is crucial. Between 40% and 63.5% of individuals with DS are affected by CHD. Several common types of CHD in DS populations include Atrioventricular Septal Defects (AVSDs), Ventricular Septal Defects (VSDs), and Patent Ductus Arteriosus (PDA).[3]

Thus, the prevalence of CHD needs to be well known in this population for proper early diagnosis and intervention, especially in rural areas. Early diagnosis can significantly improve outcomes and quality of life through appropriate medical and surgical management.[4] Understanding the prevalence will help raise awareness, guide stakeholders, and inform healthcare policy, resource allocation, and the development of rules and protocols uniquely adapted to the needs of individuals with CHD and DS in Indonesia. Recognition of the high prevalence of congenital heart defects among individuals with DS serves as a cornerstone for further improvements in both clinical care and research in Indonesia.

Methods

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 recommendations.[5] This review is registered under CRD42024596794 PROSPERO, the international prospective register of systematic reviews (URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024596794).

Literature Search

This study was conducted from October 1, 2024, to October 25, 2024. The databases used in this review were PubMed, ScienceDirect, Google Scholar, Cochrane, and Garuda (an Indonesian journal database). Our search strategy involved the use of keywords, MeSH terms, and the Boolean operators AND and OR. The search keywords used were as follows: Down syndrome; trisomy 21; Down's Syndrome; congenital heart defect; congenital heart disease; CHD; Indonesia; prevalence; incidence; epidemiology. No language or year of publication restrictions were applied. The inclusion criteria were as follows: (1) patients with a confirmed diagnosis of DS, (2) studies conducted in Indonesia, and (3) pediatric populations. The exclusion criteria were (1) studies not reporting CHD prevalence, (2) studies outside of Indonesia. A detailed search strategy is provided in Supplementary Table 1 to ensure reproducibility of the systematic review.

Study Selection

The search and selection process was performed by the first two authors. Both authors evaluated the titles, abstracts, and full texts of the search results to determine if they met the inclusion criteria in this systematic review. Conflicts between the two authors were settled by discussion or agreement with a third author. When additional research information was needed, the two authors contacted the study's corresponding author of the study via the listed email address. Subsequently, all data required for this study were extracted from the included articles and recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA).

Data Management

The initial search results from all databases were organized, and all duplicates were removed using the Rayyan platform for Intelligent Systematic Reviews (https://www.rayyan.ai/).[6] After screening the titles, abstracts, and full texts, all relevant data were documented and extracted into a Microsoft Excel spreadsheet.

Quality Assessment

The quality of the studies was assessed by two authors; any disagreements among the reviewers were resolved through discussion with the third author. Study quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists according to study design: prevalence/cross-sectional, cohort, or case-control. Each study was scored based on the proportion of applicable criteria met. Studies with >75% of criteria met were classified as high quality, those meeting 50–75% as medium quality, and those meeting <50% as low quality.[7]

Statistical Analysis

The meta-analysis in this study was conducted using Comprehensive Meta-Analysis (CMA) software, version 4.0 (Biostat, Englewood, NJ, USA).[8] Given the expected high heterogeneity among studies, a random-effects model was used. To explore the sources of heterogeneity, we conducted subgroup analysis stratifying studies by JBI score, publication year, study setting, and study location. Heterogeneity was assessed using Higgins' I^2 statistic; higher values indicate greater heterogeneity. Publication bias was assessed using Egger's regression test, Begg's test, and visual inspection of funnel plots. The symmetry of the plot indicates whether there is publication bias. A trim-and-fill method was applied to estimate the potential impact of missing studies.

Results

Search Results

The initial search across all the databases yielded a total of 1,915 studies, 46 duplicates were identified and removed; 1,869 studies remained eligible for title and abstract screening. During abstract screening, 1,839 studies were excluded for having unrelated objectives. Following full-text review of 25 studies, 11 articles were ultimately included in this study. The search and selection process is illustrated in Figure 1.

Characteristics of the Included Studies

A total of 11 studies met the inclusion criteria and were included in this study[9-19], originating from six different cities: Semarang (n=3), Yogyakarta (n=3), Bandung (n=2), Denpasar (n=1), Surabaya (n=1), and Surakarta (n=1). All studies were published between 2015 and 2024, with sample sizes ranging

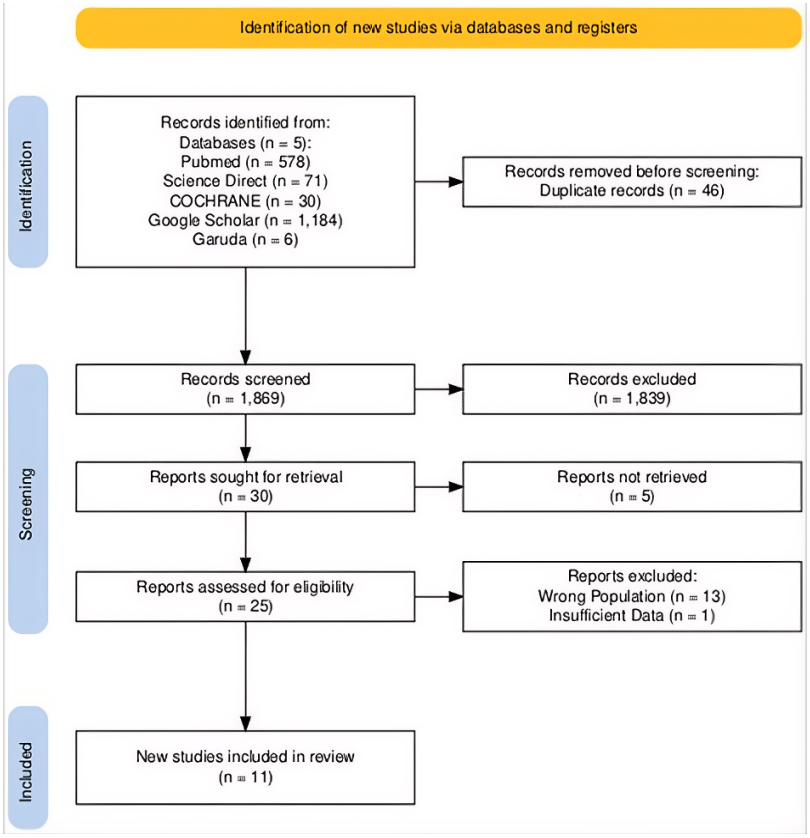

Figure 1. PRISMA flow chart for the summary of the search and screening processes.

from 30 to 355 individuals with DS. All studies employed observational designs, including cross-sectional, cohort, and case-control studies. Table 1 presents the main characteristics of the included studies, including study location, sample size, study design, and primary findings.

Overall Prevalence of CHDs

A random-effects meta-analysis was performed (Figure 2) to estimate the pooled prevalence of CHDs among individuals with DS in Indonesia, revealing a prevalence of 44.6% (95% CI: 34.9%–54.8%). The prevalence rates across studies ranged

Table 1. Basic characteristics of selected studies.

Study	City	Study Design	Sample Size	Age, range	Males	Prevalence (%)
Arifiyah *et al.*, 2017[9]	Semarang	Cross Sectional	41	6 months-6 years	58.5%	53.7
Azzahra *et al.*, 2022[16]	Semarang	Retrospective	66	4 months-6 years	NR	66.7
Gartika *et al.*, 2018[12]	Bandung	Cross Sectional	70	NR	NR	27.1
Hariyanti *et al.*, 2022[19]	Surakarta	Cross Sectional	36	2 months–5 years	58,33%	50.0
Hisbiyah *et al*, 2022[18]	Surabaya	Cross Sectional	80	1 month-18 years	61,25%	25.0
Patria *et al*, 2024[11]	Yogyakarta	Cross Sectional	355	NR	55.2%	64.8
Rajamany *et al*, 2018[17]	Bandung	Retrospective	95	0-14 years	NR	29.5
Santoso *et al.*, 2015[10]	Semarang	Cross Sectional	30	0-6 years	66,67%	33.3
Simamora *et al.*, 2022[14]	Yogyakarta	Cohort	236	0-3 years	50%	53.8
Windiani *et al.*, 2021[13]	Denpasar	Cross-sectional	32	1-12 years	28,1%	50.0
Zevanya *et al*, 2024[15]	Yogyakarta	Case Control	37	NR	51.4%	37.8

DS: Down Syndrome; JBI: Joanna Briggs Institute, NR: not reported

from 25.0% to 66.7%. Significant heterogeneity was observed (I^2 = 88.8%); Egger's test indicated a p-value of 0.045 as shown in Table 2, and the funnel plot (Figure 3) demonstrated an asymmetrical distribution of the data.

The Prevalence of CHD Subtypes

A random-effects meta-analysis was conducted, as shown in Table 3, to estimate the pooled prevalence of CHD subtypes in individuals with DS in Indonesia. The analysis revealed that the most common subtype was PDA, followed by Atrial Septal Defect (ASD) and AVSD.

The Subgroup and Sensitivity Analysis

To explore potential sources of heterogeneity, we performed subgroup analyses using different criteria. When stratified by the JBI score (quality of the study), eight studies rated as high quality had a pooled prevalence of 45.8% (95% CI: 34.3–57.7%), while medium-quality studies revealed a prevalence of 41.2% (95% CI: 25.9–58.3%), with no significant difference between subgroups (p = 0.66). Stratification by publication year revealed that studies published before 2022 reported a lower prevalence (37.5% [95% CI: 27.5–48.8%]) than

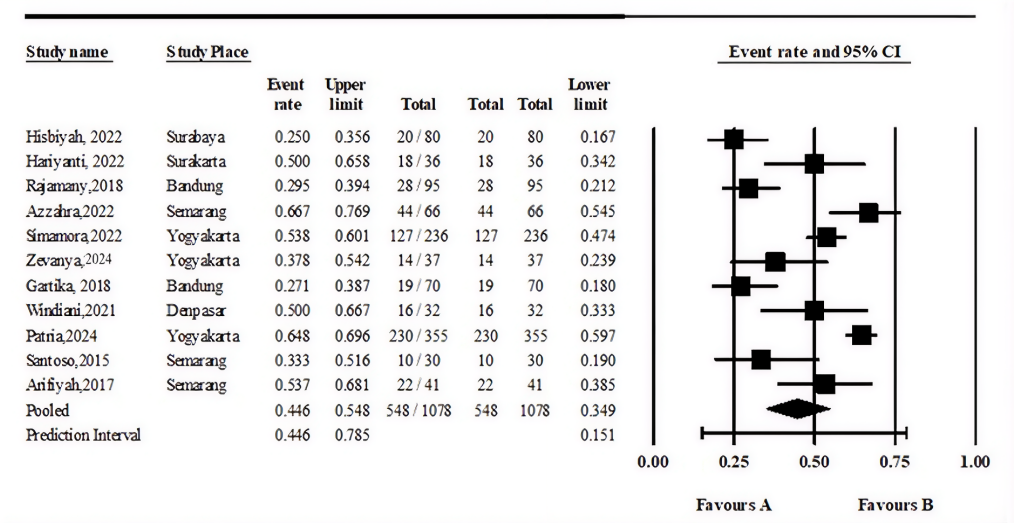

Figure 2. A forest plot illustrating the combined prevalence of Congenital Heart Disease (CHD) in individuals with Down syndrome (DS).

Table 2. Test for heterogeneity and publication bias.

Test for heterogeneity	
Q	89.964
DF	10
Significance level	P < 0.0001
I2 (inconsistency)	88.884%
Publication bias	
Egger's test	
Significance level	P = 0.045
Begg's test	
Kendall's Tau	-0,18182
Significance level	P = 0.43627

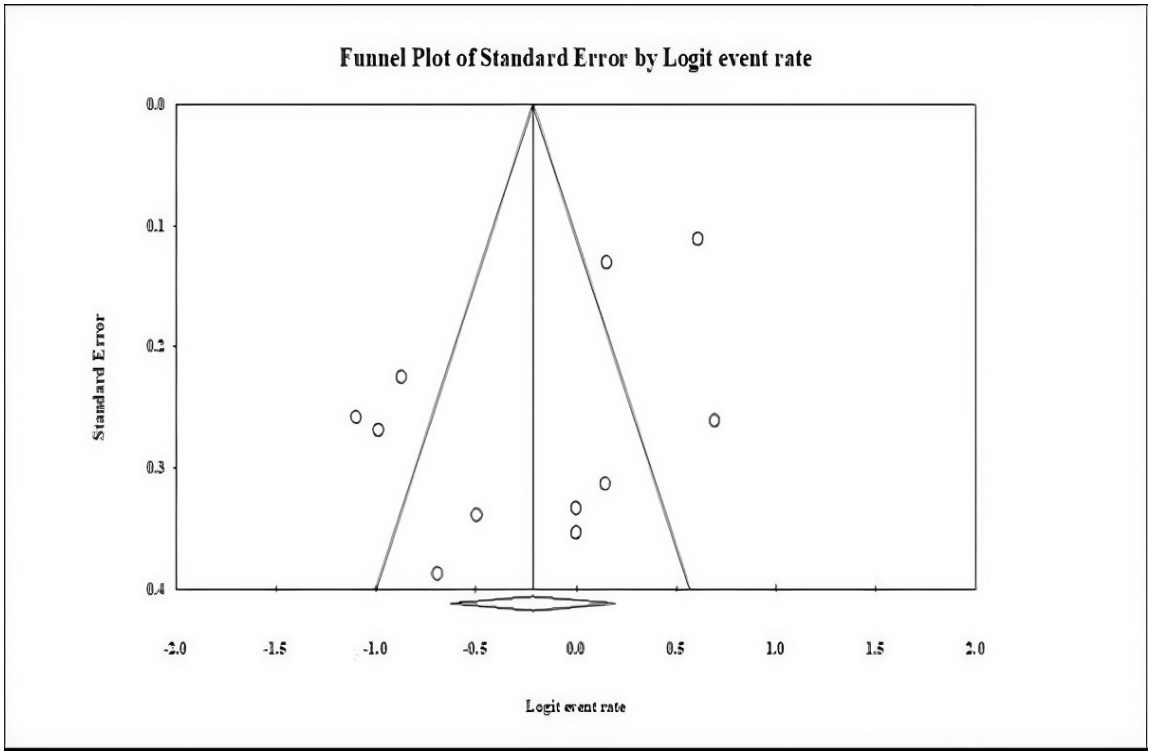

Figure 3. A funnel plot displaying the asymmetrical distribution of prevalence data points.

studies published after 2022 (50.1% [95% CI: 38.0–62.2%]), although the difference was not statistically significant (p = 0.13). Subgroup analysis by study setting showed that hospital-based studies had a higher pooled prevalence (47.5%; 95% CI: 37.0–58.2%) than community-based studies (31.3%; 95% CI: 22.1–42.3%; p = 0.036), suggesting a possible effect of diagnostic accessibility. Finally, subgroup analysis based on study location showed that Yogyakarta reported the highest prevalence with 54.4%, followed closely by Semarang with 52.3%. The complete results of the subgroup analyses are presented in Table 4

.

Quality and Risk of Bias

The quality of each study was assessed using the JBI critical appraisal checklist based on its type of study. Most studies showed low risk of bias, especially in the domains of sampling method, measurement of the outcome, and data analysis. We used a cutoff of 75% to define a good quality study, where 8 out of 11 studies met these criteria, where 3 studies were considered to be medium quality because the JBI score was between 50-75%, where the most common type of bias among these medium quality studies was confounding bias. Figure 4 illustrates the overall quality assessment results. Although the

Table 3. Test prevalence of CHD subtypes.

Subtype of CHD	Events Rate of CHD subtypes (95% CIs)
Patent ductus arteriosus	0.297 (0.205–0.409)
Atrial septal defect	0.278 (0.187–0.393)
Atrial-Ventricular septal defect	0.159 (0.116–0.215)
Ventricular septal defect	0.153 (0.115–0.201)
Tetralogy of fallot	0.038 (0.020–0.072)
Others	0.099 (0.043–0.215)

CHD : Congenital Heart Disease.

Table 4. Subgroup analysis of CHD prevalence in Indonesian down syndrome patients.

Subgroup	No. Studies	Pooled Prevalence (95% CI)	p (between)	I^2 (%)
JBI Score				
High	8	0.458 (0.343–0.577)	0.663	90.5
Medium	3	0.412 (0.259–0.583)		73.1
Year of Publication				
<2022	5	0.375 (0.275–0.488)	0.135	67.1
≥2022	6	0.501 (0.381–0.622)		89.3
Study Setting				
Community-Based	2	0.313 (0.221–0.423)	0.036	22.4
Hospital-Based	9	0.475 (0.370–0.582)		88.7
City				
Bandung	2	0.285 (0.221–0.359)	0.000	0
Semarang	3	0.523 (0.339–0.700)		77.5
Yogyakarta	3	0.544 (0.422–0.660)		85.7
Surakarta	1	0.500 (0.342–0.658)		0
Surabaya	1	0.250 (0.167–0.356)		0
Denpasar	1	0.500 (0.333–0.667)		0

JBI : Joanna Briggs Institute

funnel plot demonstrated asymmetry, suggesting possible publication bias, the trim-and-fill sensitivity analysis indicated that such bias did not materially affect the pooled estimate (Table 5).

Discussion

This systematic review and meta-analysis includes 1,078 individuals with DS from 11 studies conducted in Indonesia. Our pooled analysis revealed that the prevalence of CHD among DS patients in Indonesia was 44.6%, with reported rates across included studies ranging from 25.0% to 66.7%. This wide variation reflects substantial heterogeneity (I^2 = 88.88%). Such heterogeneity is likely attributable to differences in the geographic regions of the studies, variations in the methods and criteria used for CHD diagnosis, patient demographics, and study settings. Several reports have indicated that echocardiography, as an advanced tool for CHD diagnosis, and the availability of specialized centers for CHD may affect the reported prevalence of CHD among DS patients.[20-22]

The reported prevalence of CHD in DS patients in Indonesia is 44.6%, this number is relatively similar to previously mentioned international studies, but slightly lower compared to other studies from Saudi Arabia, which was 66.1%, Sweden, 54%, Turkey, 52.1%, and Brazil, with a prevalence rate of 50% 23–25, while slightly higher than reports from Sudan (43%) and Egypt (36%) 24,26. These variations could be due to disparities in health infrastructure, early diagnosis, and prevention. Previous studies have stated that in countries with higher incomes, where diagnostic tools are readily available, CHD in DS individuals is higher due to early detection and greater accuracy compared to lower income countries.[27-28]

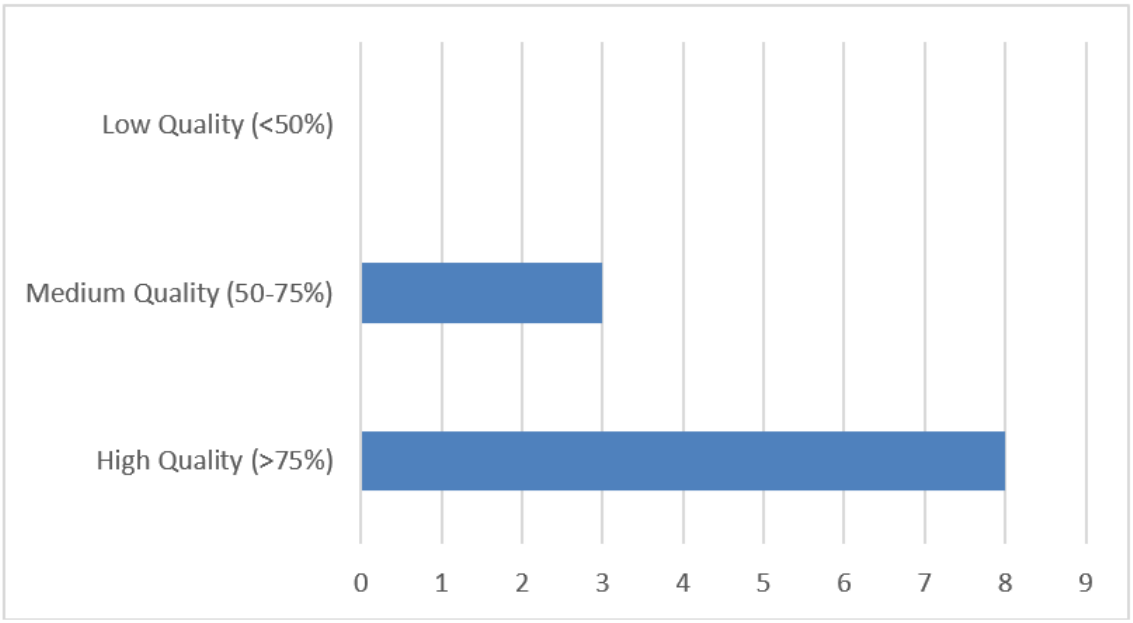

Figure 4. JBI quality assessment of included studies.

Table 5. JBI quality assessment of included studies.

Parameter	Original Meta-Analysis	Trim-and-Fill Adjusted
Number of studies	15	15
Number of imputed studies	-	0
Pooled prevalence (%)	44.6 95% CI (34.9 – 54.8)	44.6 95% CI (34.9 – 54.8)

To explore heterogeneity, we conducted a subgroup analysis, which revealed that hospital-based studies had a higher prevalence (47.5%) than community-based studies (31.3%; p = 0.036). These results indicate that diagnostic accessibility plays a key role in case detection. Similar results were observed in a subgroup analysis by location, with Yogyakarta and Semarang showing higher prevalence than other cities. These findings imply that geographic differences in healthcare access and referral pathways may influence CHD detection rates. In contrast, JBI Score (study quality) and publication year did not significantly explain heterogeneity. Unfortunately, we could not fully explore other potential sources of heterogeneity, such as diagnostic methods, genetic, ethnic, and age, due to limited data. These unmeasured factors may partially explain the variability in reported CHD prevalence across the 11 included studies.

The potential for publication bias was indicated by an asymmetrical funnel plot and a significant result of Egger's test (P = 0.045). This type of bias can occur when smaller studies with lower or non-significant prevalence estimates are unpublished, potentially raising the pooled prevalence. To examine this, we conducted a trim-and-fill analysis and found that no adjustments were necessary, no studies were added or removed. The pooled prevalence remained 44.6% (95% CI: 34.9–54.8%), suggesting minimal effect from bias. Nevertheless, underreporting of smaller, low-prevalence studies may still subtly elevate the estimate and contribute to the high heterogeneity observed across studies (I^2 = 88.8%).[29-31] Given these results, it is essential to approach the data with caution, particularly from smaller studies, and underscore the need for comprehensive reporting of all study outcomes. Developing centralized national databases and unified CHD assessment procedures could help minimize bias and improve the reliability of prevalence estimates in DS populations. Overall, despite evidence of possible publication bias, the stability of the pooled prevalence supports the validity of our main findings.

We also analyzed different types of CHD, previous studies have found that the type of CHD varies significantly between the different geographical regions. According to western studies, the most reported CHD in DS patients from Western countries is AVSD, followed by VSD and ASD[24,32].

However, a different pattern is observed in Asian countries such as Korea and Pakistan where the most common type of CHD is ASD and followed by VSD and PDA.[24,33] In our analysis in Indonesia, the most common types of CHDs are PDA and ASD, while AVSD was less common. These findings may thus reflect ethnic and genetic variation, together with differences in diagnostic tools and health practices across the regions.[21,34] The high number of PDA suggests that clinicians should prioritize early neonatal echocardiography, especially in regions with limited access to pediatric cardiology, to ensure timely detection and management of PDA, thereby reducing preventable complications.[35]

Our pooled estimate remained consistent across sensitivity and subgroup analyses, indicating strong reliability. Despite this, the high level of heterogeneity highlights the importance of implementing nationwide, uniform screening and reporting frameworks. As CHD remains the leading cause of morbidity and mortality in the DS population, strengthening early detection pathways and ensuring access to cardiology services, especially in rural areas, is important.

Limitations

The strengths of our study include a comprehensive search strategy; multiple databases were used with no language or date restrictions imposed. However, there are some limitations. First, most of the included studies were conducted in urban areas of Indonesia, which may not fully represent the national prevalence of CHD in DS patients. The absence of data from rural areas could give a biased view of the situation since healthcare access is poorer in those areas. Patients in urban tertiary centers are more likely to be diagnosed due to better access to echocardiography and specialized cardiology services.[36] Second, high heterogeneity was observed across all studies, although subgroup analysis and trim-and-fill test were performed, some heterogeneity may still persist. Finally, the small sample size in some included studies does not allow for drawing a conclusion representative of the broader population of DS patients in Indonesia. Therefore, large-scale epidemiological studies are needed to better characterize the true national burden of CHD among individuals with DS in Indonesia.

Conclusion

To our knowledge, this is the first meta-analysis reporting on the overall prevalence of CHD among DS patients in Indonesia. The pooled prevalence was 44.6%. This high prevalence underscores the urgent need for action by the government, healthcare workers, and community members. Therefore, integrated strategies and policies should be developed to promote early detection, prevention, and management of CHDs in the Indonesian DS population. However, the reliability of our findings is limited by significant inter-study heterogeneity and the risk of publication bias. We recommend further studies to provide higher-quality evidence regarding the prevalence of CHD.

List of Abbreviations

ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
CHD	Congenital Heart Disease / Defect
CMA	Comprehensive Meta-Analysis
CI	Confidence Interval
DS	Down Syndrome
JBI	Joanna Briggs Institute
PDA	Patent Ductus Arteriosus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
VSD	Ventricular Septal Defect

Ethical Clearance

Not applicable.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

The authors confirm their contributions to the paper as follows: study concept and formulated the methodology: PPPAS, SAF and LY; literature search, study selection, data collection, bias risk assessment and data analysis: PPPAS and SAF; prepared, reviewed and finalized the manuscript: PPPAS, SAF and LY; project supervision: LY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of Interest

None.

Availability of Data and Materials

Not applicable.

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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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Review Article

The Role of Inspiratory Muscle Training for Enhancing Functional Capacity in Post-Heart Valve Surgery Patients: A Scoping Review

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Abstract

Valvular Heart Disease (VHD), particularly Rheumatic Heart Disease (RHD), is a major health burden in Indonesia, often requiring heart valve surgery. Post-operative respiratory muscle dysfunction and reduced functional capacity hinder recovery. Inspiratory Muscle Training (IMT) is a non-invasive intervention that improves respiratory muscle strength and functional outcomes. This scoping review evaluates the role of IMT in enhancing functional capacity among patients after heart valve surgery. A systematic search of PubMed and Scopus identified Randomized Controlled Trials (RCTs) and cohort studies involving adult patients who underwent IMT interventions after heart valve surgery. The search strategy combined controlled vocabulary (Medical Subject Headings [MeSH]) Key terms included: ("heart valve surgery" OR "valve replacement" OR "valvular heart disease") AND ("inspiratory muscle training" OR "respiratory muscle training") AND ("functional capacity" OR "exercise capacity" OR "respiratory muscle strength" OR "pulmonary function"). Outcomes included functional capacity, respiratory muscle strength, pulmonary function, Post-operative Pulmonary Complications (PPCs), and hospital Length of Stay (LOS). Data were synthesized narratively. Four RCTs (273 patients) showed IMT significantly improved Maximal Inspiratory Pressure (MIP), Six-Minute Walk Distance (6MWD), and pulmonary function [Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1)]. Interventions of 4–12 weeks reduced PPCs and LOS. Optimal benefits were observed with 8–12-week protocols. IMT enhances functional capacity, respiratory muscle strength, and pulmonary function post-heart valve surgery, with the potential to reduce complications and costs. Its integration into rehabilitation programs is recommended, particularly in regions with high RHD prevalence, such as Indonesia. Further studies should standardize protocols and assess long-term outcomes.

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Keywords: Cardiac Rehabilitation, Functional Capacity, Heart Valve Surgery, Inspiratory Muscle Training, Pulmonary Function.

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Introduction

Valvular Heart Disease (VHD) poses a substantial global health challenge, impacting over 40 million individuals, with a particularly high prevalence in Low and Middle-Income Countries (LMICs) like Indonesia, where Rheumatic Heart Disease (RHD) accounts for approximately 94% of mitral valve pathologies.[1-2] RHD, resulting from untreated streptococcal infections, causes progressive valve damage, often necessitating surgical interventions such as valve repair or replacement to restore cardiac function and alleviate symptoms like dyspnea, fatigue, and heart failure.[3] In Indonesia, RHD remains a leading cause of VHD, particularly among younger populations, highlighting the critical need for effective post-operative rehabilitation strategies to optimize recovery and reduce long-term morbidity.[2]

Heart valve surgery, while essential, introduces significant physiological challenges. The median sternotomy approach disrupts chest wall mechanics, leading to reduced Functional Residual Capacity (FRC) and inspiratory muscle weakness.[4-5] Prolonged mechanical ventilation and post-operative immobilization further exacerbate respiratory muscle dysfunction, increasing the risk of Post-operative Pulmonary Complications (PPCs) such as atelectasis, pneumonia, and pleural effusion.[6-7] These complications impair functional capacity, defined as the ability to perform daily physical activities, and negatively affect Quality of Life (QoL).[8] Patients with comorbidities like heart failure or Chronic Obstructive Pulmonary Disease (COPD), common in VHD populations, face amplified risks, as these conditions exacerbate respiratory and cardiovascular limitations.[9] Inspiratory Muscle Training (IMT) is a non-invasive rehabilitation technique that employs resistive load devices to strengthen the diaphragm and intercostal muscles, enhancing ventilatory efficiency and reducing dyspnea.[10] By targeting inspiratory muscle weakness, IMT improves Maximal Inspiratory Pressure (MIP), exercise capacity (e.g., Six-Minute Walk Distance [6MWD]), and pulmonary function parameters (e.g., Forced Vital Capacity [FVC], Forced Expiratory Volume in 1 second [FEV_1]).[11-12] Although IMT has shown promise in populations undergoing Coronary Artery Bypass Grafting (CABG) and managing chronic heart failure, its specific application in post-heart valve surgery patients remains underexplored.[13-14] This gap is particularly significant in RHD-prevalent settings like Indonesia, where cost-effective, scalable interventions are essential to address resource constraints.[2]

This scoping review aims to synthesize evidence on IMT's role in enhancing functional capacity in post-heart-valve-surgery patients, focusing on outcomes such as respiratory muscle strength, exercise capacity, pulmonary function, PPCs, and hospital Length of Stay (LOS). By addressing the novelty of IMT as a targeted intervention for this population, the study seeks to inform clinical practice and guide future research in cardiopulmonary rehabilitation, with particular relevance for LMICs facing high RHD burdens.

Methods

This scoping review adhered to the Joanna Briggs Institute (JBI) methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines to ensure methodological rigor and transparency.[15] A systematic literature search was conducted on May 2, 2025. PubMed and Scopus were selected for their comprehensive coverage of biomedical and rehabilitation literature, and to maintain feasibility, given the scope of this scoping review. We acknowledge that supplementing the search with other databases, such as Embase or Cochrane Library, could have identified additional records. However, the selected databases were deemed sufficient to capture the core relevant literature. The restriction to English-language publications may have introduced language and publication bias, particularly by omitting relevant studies from LMICs in non-English-speaking regions. The search strategy combined controlled vocabulary (Medical Subject Headings [MeSH]) and free-text terms to enhance sensitivity and specificity. Key terms included: ("heart valve surgery" OR "valve replacement" OR "valvular heart disease") AND ("inspiratory muscle training" OR "IMT" OR "respiratory muscle training") AND ("functional capacity" OR "exercise capacity" OR "respiratory muscle strength" OR "pulmonary function"). Boolean operators (AND, OR) were used to structure queries, and filters were applied to restrict results to human studies and English-language publications. Manual screening of the reference lists of included studies and relevant reviews was conducted to identify additional articles. The detailed search strategy, including database-specific queries, is provided in Table 1 to support reproducibility.

Table 1. Search strategy.

Database	Search Query	Results (n)
PubMed	(Heart valve [MeSH] OR "Heart Surgical Procedure" [MeSH] OR "Surgical Procedure" [Title/Abstract] OR "Cardiac Surgical Procedure" [Title/Abstract] OR "Heart Valve" [Title/Abstract] OR "Cardiac Valves" [Title/Abstract]) AND ("Inspiratory Muscle Training" [Title/Abstract]) AND ("Respiratory function test" [MeSH] OR "Respiratory Function Test" [Title/Abstract] OR "Lung Function Test" [Title/Abstract] OR "Pulmonary Function Test" [Title/Abstract])	33
Scopus	(heart valve [Title/Abstract] OR "Heart Surgical Procedure" [Title/Abstract] OR "Surgical Procedure" [Title/Abstract] OR "Cardiac Surgical Procedure" [Title/Abstract] OR "Heart Valve" [Title/Abstract] OR "Cardiac Valves" [Title/Abstract]) AND ("Inspiratory Muscle Training" [Title/Abstract]) AND ("Respiratory function test" [Title/Abstract] OR "Respiratory Function Tests" [Title/Abstract] OR "Lung Function Test" [Title/Abstract] OR "Pulmonary Function Test" [Title/Abstract])	62

Search Date: May 2, 2025
Filters Applied: English language, Human studies, No publication years restriction.

Eligibility Criteria

Stringent inclusion and exclusion criteria were established to ensure alignment with the review's objectives. Studies were included if they: (1) were randomized controlled trials (RCTs) or cohort studies involving adult post heart valve surgery patients (e.g., aortic or mitral valve repair/replacement); (2) evaluated IMT interventions using resistive load devices (e.g., POWERbreathe®, Threshold IMT); (3) reported outcomes related to functional capacity (e.g., 6MWD), respiratory muscle strength (e.g., MIP), pulmonary function (e.g., FVC, FEV_1), PPCs, or LOS; and (4) were published in English with full-text availability. A comprehensive list of eligibility criteria is available in Table 2.

Study Selection and Data Extraction

The search retrieved 95 records (PubMed: 33, Scopus: 62), which were imported into EndNote for deduplication, yielding 86 unique records. Two reviewers (HW, DMS) independently screened titles and abstracts using Rayyan.ai, a systematic review platform, to identify eligible studies. Discrepancies were resolved through discussion, with a third reviewer (MLD) and a fourth reviewer (FA) consulted for unresolved conflicts. Twelve articles underwent full-text review. Although cohort studies were eligible for inclusion, none met all eligibility criteria upon full-text assessment. Consequently, only four RCTs were included in this review. The selection process is illustrated in a PRISMA flow diagram (Figure1). Data were extracted using a standardized

Table 2. Eligibility criteria.

Criteria	Inclusion	Exclusion
Study Design	Randomized Controlled Trials (RCTs), cohort studies	Systematic reviews
Population	Adult Patient with post heart valve surgery (e.g., aortic or mitral valve repair/replacement)	Patients who did not undergo heart valve surgery, no specific comorbidities were excluded
Intervention	Inspiratory Muscle Training (IMT) using resistive load devices (e.g., POWERbreathe®, Threshold IMT)	
Outcomes	Functional capacity (e.g., 6MWD), respiratory muscle strength (e.g., MIP), pulmonary function (e.g., FVC, FEV1), PPCs, LOS	
Language		Non-English publications
Access		Full-text not available

RCTs: Randomized Controlled Trials, IMT: Inspiratory Muscle Training, 6MWD: Six-Minute Walk Distanc, MIP: Maximal Inspiratory Pressure, FVC: Forced Vital Capacity, FEV_1: Forced Expiratory Volume in 1 Second, PPCs: Post-Operative Pulmonary Complications, LOS: Length of Stay.

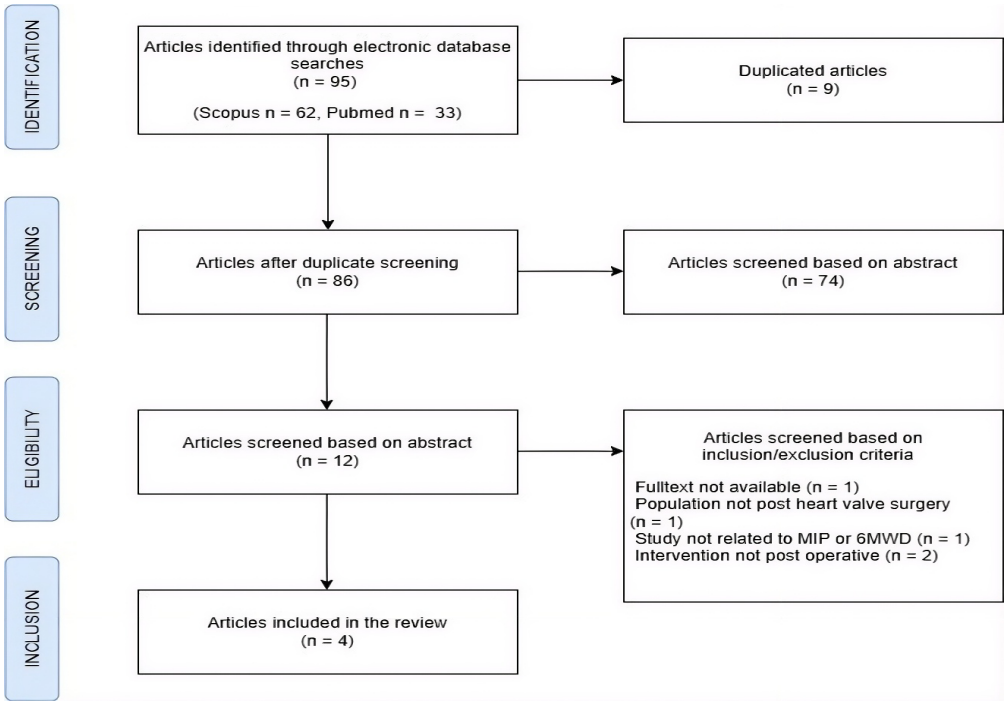

Figure 1. PRISMA flow diagram.

Table 3. Study characteristics.

Study	Country	Design	Sample Size	Mean age (years)	Male (%)	Population
Cargnin *et al.* (2019)	Brazil	Double-blind RCT	25 (IMT: 13, Control: 12)	61.3	56.5	Post-elective heart valve replacement, no complications
Kodric *et al.* (2013)	Slovenia	Double-blind RCT	52 (IMT: 36, Control: 16)	68	75	Post-major cardiac surgery with diaphragmatic paralysis
Xu *et al.* (2023)	China	Double-blind RCT	96 (IMT+CR: 48, CR: 48)	78.8	50	Post-transcatheter aortic valve replacement (TAVR)
Hegazy *et al.* (2021)	Egypt	Double-blind RCT	100 (IMT: 50, Control: 50)	45.7	41	Post-mitral valve replacement

RCT: Randomized Controlled Trial, IMT: Inspiratory Muscle Training, CR: Cardiac Rehabilitation, COPD: Chronic Obstructive Pulmonary Disease.

template that captured study characteristics (e.g., author, year, country), participant demographics (e.g., age, sex, comorbidities), intervention details (e.g., IMT device, intensity, duration), and outcomes. Extraction was performed by HW and verified by DMS, MLD, and FA to ensure accuracy. The extracted data are summarized in Table 3, and the intervention protocols are detailed in Table 4. The authors screened the search results by first reviewing article titles and then abstracts. Articles with titles and abstracts aligned with the study objectives underwent full-text review; included articles were further explored to meet and enrich the review's purpose.

Results

Study and Participant Characteristics

Four RCTs involving 273 post-heart-valve-surgery patients were included and were conducted in Brazil, Slovenia, China, and Egypt. Sample sizes ranged from 25 to 100 participants, reflecting variability in study scope. Participants had a mean age of 63,4 years, with 60–80% male, consistent with the global epidemiology of VHD.[1] Surgical procedures primarily involved aortic or mitral valve replacement, though one study included CABG patients due to similar post-operative respiratory challenges.[16] Comorbidities such as heart

Table 4. Intervention details.

Study	IMT Device	Intensity	Duration	Frequency	Control Group
Cargnin *et al.* (2019)	POWERbreathe® Kinetic KH1	30–40% MIP, adjusted weekly	4 weeks	2 sessions/day, 7 days/week	Sham IMT (minimal resistance)
Kodric *et al.* (2013)	Threshold IMT	Adjusted based on % MIP, progressive	12 months	1–2 sessions/ day, 5–7 days/ week	Standard care (deep breathing exercises)
Xu *et al.* (2023)	Threshold IMT	30–50% MIP, increased 5–10% weekly	During LOS	1–2 sessions/ day, 5–7 days/ week	Cardiac rehabilitation (CR) alone
Hegazy *et al.* (2021)	Threshold IMT	40–80% MIP, increased progressively	8 weeks	1–2 sessions/ day, 5–7 days/ week	Standard care (early mobilization)

MIP: Maximal Inspiratory Pressure, LOS: Length of Stay. Intensity was typically set as a percentage of baseline MIP, with progressive increases based on patient tolerance. Control groups varied, with sham IMT or standard care (e.g., deep breathing, mobilization) used to ensure valid comparisons. Xu et al. integrated IMT with cardiac rehabilitation, including aerobic and resistance exercises.

failure, COPD, and hypertension were prevalent, influencing baseline functional capacity and recovery.[17-18] The geographic diversity of the studies underscores IMT's global applicability, while the male predominance highlights a need for research on female patients. Study characteristics, including participant demographics and surgical details, are provided in Table 3.

Study and Participant Characteristics

IMT interventions used threshold-based resistive devices (e.g., POWERbreathe®, Threshold IMT) that provide precise control of inspiratory resistance.[16-18] Initial intensities were set at 30–40% of baseline MIP, with progressive increases of 5–10% weekly based on patient tolerance. Intervention durations ranged from 4 to 12 weeks, with sessions lasting 20–30 minutes, conducted 1–2 times daily, 2–7 days per week. Two studies integrated IMT into Cardiac Rehabilitation (CR) programs, incorporating endurance or resistance exercises to enhance overall recovery.[18-19] Control groups received sham IMT (minimal resistance) or standard care, such as deep-breathing exercises and early mobilization, thereby ensuring valid comparisons. The heterogeneity in protocols reflects the absence of standardized IMT guidelines for this population, a critical area for future research. Intervention details are summarized in Table 4.

Outcomes

Exercises Capacity

All studies reported significant improvements in 6MWD, a reliable measure of exercise capacity, in IMT groups compared to controls. Cargnin et al. observed a 6MWD of 447.2 ± 96.6 m in the IMT group versus 314.7 ± 94.1 m in controls after 4 weeks ($p = 0.019$), indicating rapid functional gains. Xu et al. reported a 41.51 m increase in 6MWD at 1 month in the IMT plus CR group versus CR alone ($p=0.041$), highlighting synergistic effects.[18] Hegazy et al. reported a 6MWD of 509.5 ± 16.6 m in the IMT group versus 410.9 ± 10.3 m in controls after 8 weeks ($p < 0.001$), suggesting greater benefits with longer interventions.[19] These improvements likely stem from enhanced ventilatory efficiency and delayed respiratory metaboreflex, reducing peripheral muscle fatigue.[20]

Respiratory Muscle Strength

Significant increases in MIP were reported across all studies.[16–19] Kodric et al. reported a 77.78% improvement in diaphragmatic mobility and significant gains in MIP ($p<0.001$) after 12 months, indicating sustained benefits.[17] Hegazy et al. reported an MIP of 89.78 ± 5.1 cmH_2O in the IMT group versus 72.16 ± 5.5 cmH_2O in controls after 8 weeks ($p<0.001$), reflecting rapid strength gains.[19] These findings suggest IMT promotes inspiratory muscle hypertrophy and oxidative capacity, critical for post-operative recovery.[21]

Pulmonary Function

Three studies reported improved FVC and FEV_1 with IMT.[16,18-19] Hegazy et al. observed significant increases in FVC, FEV_1, and FEV_1/FVC ratio ($p<0.001$) after 8 weeks, indicating enhanced lung expansion.[19] Xu et al. reported a 0.21 L FEV_1 increase at 1 month in the IMT plus CR group ($p=0.034$), suggesting early benefits.[18] These improvements likely result from stronger inspiratory muscles facilitating greater lung volumes and reducing atelectasis.[22]

Post-Operative Pulmonary Complications (PPCs)

Xu et al. reported a lower PPC rate in the IMT plus CR group (6.9% vs. 20%, p=0.028), likely due to enhanced cough effectiveness and alveolar recruitment.[18] This highlights IMT's preventive potential in high-risk patients.

Length of Stay (LOS)

Xu et al. found a shorter LOS in the IMT plus CR group (11 vs. 12.5 days; p=0.016), attributable to fewer PPCs and faster recovery.[18] This underscores IMT's economic benefits.

Quality of Life (QoL)

Limited QoL data showed improved dyspnea scores with IMT, but intergroup differences were inconsistent, possibly due to variable measurement tools and short follow-ups.[17,19] Outcome details are summarized in Table 5.

Discussion

This scoping review confirms that IMT significantly enhances functional capacity, respiratory muscle strength, and pulmonary function in patients post-heart valve surgery. The findings demonstrate 15–30% increases in the 6MWD and 15–33% improvements in Maximal Inspiratory Pressure (MIP), indicating substantial gains in physical endurance and respiratory efficiency.[16-17,19] These improvements are particularly crucial in addressing common post-operative complications, such as respiratory muscle weakness, reduced lung volumes, and impaired gas exchange, which are frequently exacerbated by median sternotomy and prolonged mechanical ventilation.[4-5] Furthermore, the observed reductions in PPCs and LOS underscore the clinical and economic value of IMT, particularly in LMICs like Indonesia. RHD contributes to a high burden of VHD. [2,19]

Table 5. Outcome measures and results.

Study	Outcome Measures	Result
Cargnin et al. (2019)	6MWD, MIP, FVC, FEV_1, PEF	IMT group: Restored MIP and pulmonary function to pre-operative levels after 4 weeks; 6MWD = 447.2 ± 96.6 m vs. 314.7 ± 94.1 m (control, p = 0.019); MIP correlated with 6MWD (r = 0.45, p = 0.025) and spirometry (r = 0.40–0.51, p<0.05).
Kodric et al. (2013)	MIP, diaphragmatic mobility, VC, MRC dyspnea score, MRADL	IMT group: 77.78% improved diaphragmatic mobility (p<0.001); MIP increased (p<0.001); VC increased from 70.8% ± 16.5% to 86.0% ± 17.1% (p<0.001); improved MRC and MRADL scores (p<0.001). Control: 87.5% no improvement.
Xu et al. (2023)	6MWD, MIP, FVC, FEV1, PPCs, LOS	IMT+CR group: 6MWD increased by 41.51 m at 1 month (p = 0.041); MIP increased by 7.76 cmH_2O at 1 month (p = 0.017); FEV_1 increased by 0.21 L (p = 0.034); PPCs 6.9% vs. 20% (p = 0.016); LOS 11 vs. 12.5 days (p = 0.016).
Hegazy et al. (2021)	6MWD, MIP, FVC, FEV1, FEV1/FVC	IMT group: Significant increases in FVC, FEV_1, FEV^1/FVC (p<0.001); MIP = 89.78 ± 5.1 cmH_2O vs. 72.16 ± 5.5 cmH2O (p<0.001); 6MWD = 509.5 ± 16.6 m vs. 410.9 ± 10.3 m (p<0.001); benefits sustained at 6 months.

6MWD: Six-Minute Walk Distance, MIP: Maximal Inspiratory Pressure, FVC: Forced Vital Capacity, FEV_1 = Forced Expiratory Volume in 1 Second, PEF: Peak Expiratory Flow, VC: Vital Capacity, PPCs: Post-Operative Pulmonary Complications, LOS: Length of Stay, MRC: Medical Research Council, MRADL: Manchester Respiratory Activities of Daily Living.

IMT works by strengthening the diaphragm and intercostal muscles, thereby improving ventilatory efficiency and reducing the work of breathing[10] This physiological adaptation helps delay the onset of the respiratory metaboreflex, a phenomenon in which respiratory fatigue limits oxygen delivery to peripheral muscles during exertion.[20] By enhancing respiratory endurance, IMT allows patients to sustain physical activity for longer durations, directly contributing to improved functional capacity. Additionally, the observed increases in FVC and FEV_1 suggest that IMT promotes lung expansion and reduces atelectasis, both of which are critical to preventing PPCs such as pneumonia and pleural

effusions.[22] Collectively, these benefits enhance patients' ability to perform Activities of Daily Living (ADLs), ultimately leading to better QoL, a particularly important outcome in RHD-affected populations, where chronic disability is a major concern.[2,8]

In Indonesia, where healthcare resources are often constrained, IMT presents a cost-effective and scalable intervention. Its low cost, portability, and ease of use make it highly suitable for home-based rehabilitation, reducing dependence on specialized facilities.[23] Given that shorter hospital stays directly translate to lower healthcare costs, IMT could play a pivotal role in optimizing post-surgical recovery in LMICs.[18] Moreover, integrating IMT with CR programs, as demonstrated in two included studies, may amplify its benefits, suggesting that a multimodal rehabilitation approach could further enhance recovery outcomes.[18-19]

Despite these promising findings, several limitations must be acknowledged. First, the small number of included studies (n=4) and their modest sample sizes (25–100 participants) limit the generalizability of the results. Furthermore, the male predominance (60–80%) across the included studies limits the generalizability of our findings to female patients. Women exhibit distinct cardiopulmonary physiology, including generally smaller lung volumes and a more curved diaphragm, which may influence their baseline respiratory muscle strength and their response to IMT. While research on sex-specific responses to IMT in cardiac populations is limited, studies in other fields suggest that training adaptations can differ between sexes. Therefore, the efficacy and optimal protocol of IMT for women post-heart valve surgery remain unclear and warrant dedicated investigation in future trials with adequate female representation to ensure equitable and effective rehabilitation. Additional limitations include clinical and methodological heterogeneity in the included trials. The IMT protocols varied in duration (4–12 weeks) and intensity (30–60% MIP), hindering the establishment of a standardized regimen. The short follow-up periods (up to 3 months) in these studies restrict insights into the long-term sustainability of IMT benefits. Furthermore, one study included patients undergoing Transcatheter Aortic Valve Replacement (TAVR), a less invasive procedure than conventional open-heart surgery, which may influence postoperative recovery trajectories. The concomitant interventions also differed: two studies integrated IMT into comprehensive cardiac rehabilitation programs, whereas others did not, potentially confounding the assessment of IMT's isolated effects.[16,18-19] To address these gaps, future research should prioritize larger multicenter Randomized Controlled Trials (RCTs) with diverse patient populations, including more women, older adults, and individuals undergoing various surgical approaches, particularly conventional open-heart surgery. Studies should directly compare the effects of IMT alone versus IMT combined with comprehensive CR to determine the optimal rehabilitative strategy. Standardizing IMT protocols, such as adopting an 8–12 week training period at 30–60% of maximal inspiratory pressure (MIP), would enhance comparability across studies and facilitate the development of evidence-based clinical guidelines. Additionally, exploring telerehabilitation models could improve accessibility for patients in rural and remote areas, where healthcare infrastructure is limited.[24] Another promising avenue is the combination of IMT with Expiratory Muscle Training (EMT), which may further optimize respiratory and functional outcomes by addressing both inspiratory and expiratory muscle weakness.[25]

Conclusion

IMT has emerged as a highly effective, evidence-based intervention for significantly improving functional capacity, respiratory muscle strength, and pulmonary function in patients recovering from heart valve surgery. This scoping review synthesizes preliminary but compelling evidence indicating that IMT is a promising, low-cost therapeutic adjunct for enhancing functional capacity, respiratory muscle strength, and pulmonary function in patients following heart valve surgery. Its demonstrated potential to mitigate postoperative pulmonary complications and reduce hospitalization duration underscores its significant clinical utility and economic value, particularly in resource-constrained healthcare systems endemic for RHD.

To consolidate these findings and facilitate their integration into standard clinical practice, subsequent research must be directed toward the development and validation of standardized IMT protocols. There is a critical need for larger, methodologically rigorous trials with extended follow-up periods to assess long-term sustainability. Such studies must prioritize inclusive recruitment strategies to ensure adequate representation of female patients and should specifically target under-researched geographical regions, notably Southeast Asia. Addressing these evidence gaps will be

instrumental in establishing IMT as a fundamental component of post-operative cardiopulmonary rehabilitation, ultimately aiming to improve patient-centered outcomes and alleviate global healthcare burdens.

List of Abbreviations

6MWD	Six-Minute Walk Distance
ADLs	Activities of Daily Living
CABG	Coronary Artery Bypass Grafting
COPD	Chronic Obstructive Pulmonary Disease
CR	Cardiac Rehabilitation
EMT	Expiratory Muscle Training
FEV	Forced Expiratory Volume
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
IMT	Inspiratory Muscle Training
JBI	Joanna Briggs Institute
LMICs	Low and Middle-Income Countries
LOS	Length of Stay
MeSH	Medical Subject Headings
MIP	Maximal Inspiratory Pressure
MRC	Medical Research Council
MRADL	Manchester Respiratory Activities of Daily Living
PEF	Peak Expiratory Flow
PPCs	Post-operative Pulmonary Complications
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RCTs	Randomized Controlled Trials
RHD	Rheumatic Heart Disease
TAVR	Transcatheter Aortic Valve Replacement
VHD	Valvular Heart Disease

Ethical Clearance

Not Applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

All authors contributed substantially to this manuscript. They were involved in the conception and design of the study, drafting the article, critical revision for important intellectual content, and final approval of the version to be published. All authors agree 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

None.

Availability of Data and Materials

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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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Case Reports

Myocardial Remission in High Burden Outflow Tract Premature Ventricular Complex-Induced Cardiomyopathy after Radiofrequency Catheter Ablation: Case Report

Mochamad Rizky Hendiperdana[1], Erika Maharani[2]

Abstract

Background: Premature Ventricular Complex (PVC)-induced Cardiomyopathy (PVC-CMP) is a spectrum of dilated cardiomyopathy.

Case Illustration: A 51-year-old female patient who was diagnosed with high suspicion of PVC-CMP underwent successful 3D mapping radiofrequency catheter ablation with a good result. Post-ablation 24-hour ECG-Holter evaluation showed a significant reduction of PVC burden. Echocardiographic evaluation 5 months post-ablation showed improvement in left ventricular systolic function parameters. The presence of high-burden PVC with a typical outflow tract origin could raise suspicion of a specific PVC-CMP aetiology. PVC burden emerged as a major predictor of the development of CMP. Several criteria can be used to identify PVC-CMP. Our case met those descriptive criteria, increasing the likelihood of PVC-CMP.

Conclusions: PVC-CMP should be considered in patients with dilated cardiomyopathy who are accompanied by frequent outflow tract origin PVC (> 10 % burden). Early recognition of PVC-CMP is essential, as removal of the primary aetiology improves ventricular structure and function.

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Keywords: PVC-induced cardiomyopathy, Premature Ventricular Complex, Catheter Ablation, Myocardial Remission, Heart Failure

Introduction

Premature Ventricular Complex (PVC)-induced Cardiomyopathy (PVC-CMP) is a dilated cardiomyopathy spectrum that has greater reversibility.[1-2] Early recognition of PVC-CMP is essential, since the removal of its primary aetiology will lead to improvement in ventricular structure and function.[1,3] Longitudinal strain echocardiography evaluation is a reliable method to detect initial changes in ventricular systolic function and to track therapeutic response in this patient population.[4-5]

Case Illustration

A 51-year-old female patient with a chronic palpitation history presented to the emergency ward with shortness of breath for 1 week before admission. The symptom worsened over 4 days, accompanied by chest tightness. The patient has no history of routine medication use. The patient denied any history of recent pregnancy, no history of recent fever or flu-like syndrome, and no history of alcohol consumption or other drugs. The patient's previous history was a hospital admission caused by palpitation 17 years ago, without knowing the cause. No familial history of cardiac disease was noted.

On-admission vitals sign: blood pressure 140/90 mmHg, pulse 85 beats/min, regular, and SpO_2 97 % in room air. Electrocardiogram (ECG) showed sinus rhythm with bigeminy and trigeminy PVC with Left Bundle Branch (LBBB) and inferior axis morphology, which suggests Outflow Tract (OT) origin. Echocardiography findings showed Left Ventricle (LV) dilation with Left Ventricular End-Diastolic Volume (LVEDV) of 185 mL, reduced LV systolic function with Left Ventricular Ejection Fraction (LVEF) of 37% (Simpson's Biplane) and reduced LV Global Longitudinal Strain (GLS) of -9.2%, as well as LV global hypokinesia and severe functional Mitral Regurgitation (MR) as shown in Figure 1 and Video 1.

Blood test examination showed normal renal function, serum troponin I, and thyroid function. At hospital admission, the patient was diagnosed with Dilated Cardiomyopathy (DCM) with high

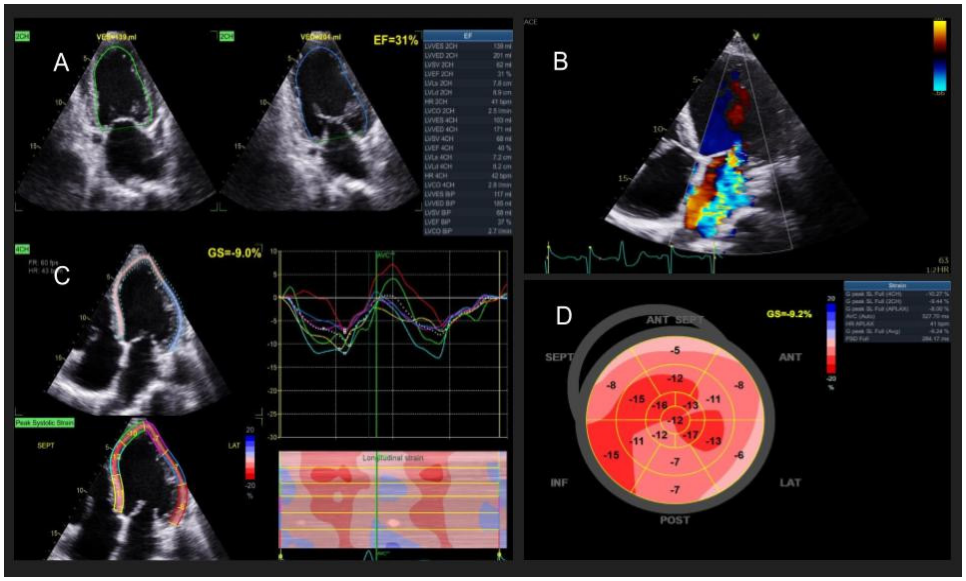

Figure 1. Baseline echocardiography examination: A. LVEF assessment by Simpson biplane method; B. Apical 4-chambers view showed dilated LV with severe MR; C. 4 chamber LV GLS tracing showed reduced 4ch GLS value; D. Average GLS showed reduced value (-9.2 %) (LVEF: Left ventricle ejection fraction; LV: Left ventricle; MR: Mitral regurgitation; GLS: Global longitudinal strain).

suspicion of PVC-CMP. A 24-hour Holter monitor showed very frequent LBBB with inferior-axis morphology, and OT-origin PVC with a 35% PVC burden. (Figure 2). Coronary Computed Tomography Angiography (CCTA) was noted for non-significant stenosis (50 % stenosis at proximal left anterior descending (LAD) artery, 30 % stenosis at mid LAD, mixed plaque with 50 % stenosis at proximal right coronary artery, and left circumflex artery was normal).

Standard guideline-directed medical therapy (GDMT) for Heart Failure with reduced Ejection Fraction (HFrEF) was administered and up-titrated during hospital admission, including a loop diuretic,

bisoprolol 5 mg o.d., spironolactone 25 mg o.d., and sacubitril/valsartan 100 mg b.d. The patient's definitive management for the high clinically suspicious PVC-CMP was made. The patient was referred for further management, including radiofrequency catheter ablation.

The patient underwent successful radiofrequency catheter ablation with a favorable outcome using the 3D EnSite$_{TM}$ electroanatomical mapping system. Multifocal PVCs from the Left Coronary Cusp (LCC) were detected. The mapping revealed the highest LAT of -34 ms, with a QS pattern, in the unipolar lead at the anterior LCC. Multiple radiofrequency ablations were delivered at those areas (30 W, 45°C, 17 ml/sec), and PVCs were terminated.

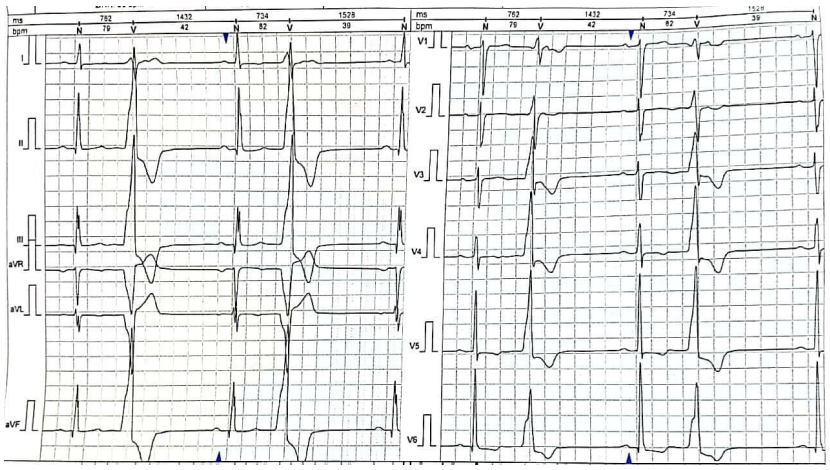

Figure 2. Baseline Holter electrocardiography showed sinus rhythm with bigemini outflow tract premature ventricular complex.

Post-ablation 24-hour ECG-Holter monitoring showed sinus rhythm with a minimal PVC burden of 3%. There was no symptom persistence. Echocardiographic evaluation 5 months post-ablation showed LV volume reduction (LVEDV 163 mL) with LVEF improvement to 43%, an increase in LV GLS value to -14%, and a decrease in mitral regurgitation severity as shown in Figure 4 and Video 2. This echocardiographic finding depicts reverse remodelling following removal of the primary insult in cardiomyopathy.

Discussion

We reported a 51-year-old female patient clinically suspected of PVC-CMP in our local community hospital settings. Tachycardia-induced cardiomyopathy is a known reversible cause of LV systolic dysfunction. Hence, the aetiology of HFrEF, in the absence of any apparent reason, with frequent PVCs, must be carefully investigated.[1,6] In our case, the presence of a high PVC burden of typical OT origin from ECG could raise a high suspicion index of specific PVC-CMP etiology.[3]

Among patients with PVC burden > 10%, it was reported that the prevalence of PVC-CMP is about 7%.[7] Furthermore, PVC burden > 10% is considered significant enough to trigger CMP.[1-2] Several studies revealed the correlation between PVC burden and the degree of LV dysfunction. A patient with low LVEF at initial presentation was found to have a higher mean of PVC burden.[7] Therefore, PVC burden was reported to become a major predictor of PVC that can develop into CMP (OR 1.25 for each percent increase in PVC burden).[1] In our case, the patient showed a PVC burden of 35 % from a 24-hour ECG-Holter monitor, which obviously increases the chance for the patient to develop PVC-CMP.

The most common PVC-CMP is idiopathic Ventricular Arrhythmia (VA), which commonly originates from the OT.[2,6] Our patient also showed a typical OT origin of PVC, which increased the possibility of PVC-CMP diagnosis, though 3D electroanatomical mapping showed the PVC location origin was from LCC.

There is no specific test or marker to confirm PVC-CMP. The underlying tachyarrhythmia is not always documented at initial presentation, particularly in cases of paroxysmal AF or flutter.[6] Therefore, a 24-hour Holter monitoring may be helpful as a first-line tool for diagnosing PVC-CMP

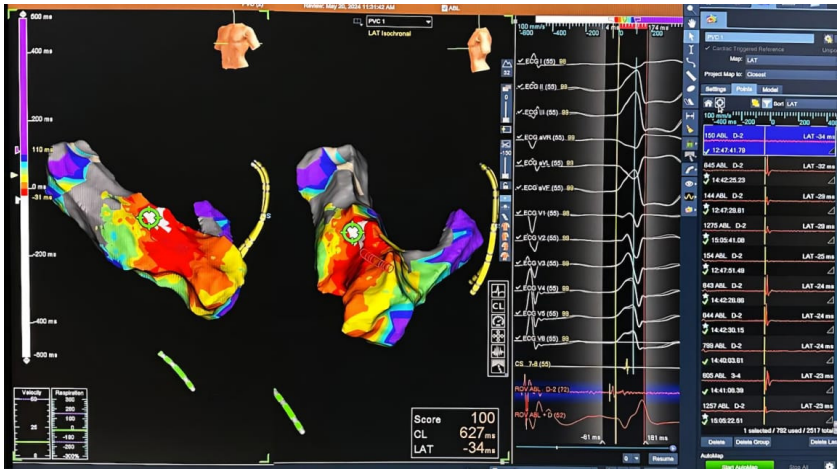

Figure 3. 3D Electroanatomical mapping of premature ventricular complex ablation.

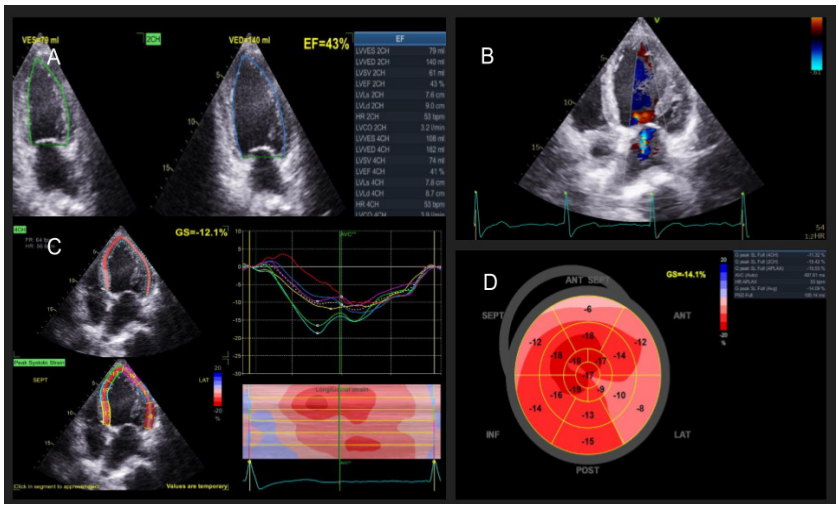

Figure 4. Post-catheter ablation echocardiography examination: A. LVEF assessment by Simpson biplane method showed LVEF improvement; B. Apical 4-chambers view showed LV volume reduction with MR severity reduction; C. 4-chamber LV GLS tracing showed reduced 4-ch GLS value; D. Average GLS showed improved value (-14.1 %) (LVEF: Left ventricle ejection fraction; LV: Left ventricle; MR: Mitral regurgitation; GLS: Global longitudinal strain).

in patients with frequent PVC and ventricular systolic dysfunction. In our case, we meticulously obtained the patient's clinical history of exclude other DCM aetiologies. Routine blood tests, including renal function, thyroid function, serum troponin I, and an infection marker, exclude potential aetiologies of LV dysfunction, such as myocarditis, thyrotoxicosis, diabetic cardiomyopathy, and end-stage kidney disease.

The role of non-invasive diagnostics for the evaluation of systolic function, for instance, the longitudinal strain imaging echocardiography, is of paramount importance to recognize even the subclinical LV systolic dysfunction in PVC-CMP cases,[4-5] especially in limited hospital settings, to exclude any underlying coronary artery disease that underlies systolic dysfunction. Fortunately, the patient's CCTA result was typical, thus we can exclude significant epicardial coronary stenosis as an aetiology of the patient's DCM. However, the final diagnosis of PVC-CMP can only be made if there is an improvement of myocardial systolic function after precipitating PVC has been eliminated, as observed in our case.[1-3,6]

There are challenges in daily clinical practice to differentiate among PVCs that induce cardiomyopathy or VA manifestation in primary cardiomyopathy. In this concern, echocardiography and PVC characteristics could help to define the primary cause. Bozkurt et al describe several criteria for PVC-CMP. Those criteria are global hypokinesis with 'not too low' LVEF of 37 ± 10%,

monomorphic PVC pattern, PVC burden > 10%, and outflow tract or epicardial QRS morphology on ECG. Unfortunately, CMR criteria cannot be evaluated because CMR is of available in our setting.[9] However, Ailoaei et al showed that higher PVC burden and LBBB with inferior axis morphology are predictors of LGE presence by CMR in PVC with a structurally normal heart.[10]

On the other hand, different yet similar criteria for PVC-CMP were recently proposed by Bhushan and Asirvatham. These criteria apply to otherwise young, healthy individuals with no evidence of abnormal cardiovascular substrate who have more than 20,000 PVCs per day, with no more than two PVC morphologies, OT-origin PVCs, or fascicular origin, and preserved myocardial wall thickness, and are the best candidates for a PVC-CMP.[2,11] Our case met all the criteria mentioned above.

Hence, echocardiographic and PVC characteristics could help determine whether PVC is the primary cause of CMP. These criteria could be helpful in clinical practice for defining PVC-CMP for referral to radiofrequency catheter ablation, given its reversibility. PVC-CMP should always be considered in patients with idiopathic DCM who are accompanied by frequent OT origin PVC (more than 10% burden).[6,12]

A catheter ablation management strategy of high-burden OT PVC is superior to pharmacological anti-arrhythmic therapy in suppressing arrhythmic events without differences in complications. It is recommended as first-line therapy for OT PVC. Catheter ablation is also recommended as a first-line management strategy for PVC-CMP, with a reported success rate of approximately 90%.[12] In our case, we performed a 3D electroanatomical mapping system that revealed LCC as the origin of the patient's PVCs. After successful catheter ablation, as confirmed by 24-hour ECG-Holter monitoring, we observed improvement in LV systolic function and echocardiographic parameters. Despite improvements of LV GLS parameters, they did not fully recover to the standard GLS value (-14%), and the follow-up period was limited to a short-term evaluation. The short-term follow-up in our case reflects a limitation in this report. However, this finding indicated a glimpse of myocardial recovery that may be complete with extended follow-up.

El Kadri et al reported a study in 30 patients with PVC-CMP who underwent catheter ablation. The study population had a mean age of 59.1 ± 12.1 years, a mean baseline LVEF of 38 ± 15%, and a mean PVC burden of 22.7 ± 11.6%. Improvement of LVEF was observed in the successfully ablated patient (33.9% ± 14% to 45.7% ± 17%; $p < 0.0001$), with a corresponding significant reduction in PVC burden (23.1% ± 8.8% to 1% ± 0.9%; $p < 0.0001$). This study found that PVC-CMP cardiomyopathy is a reversible pathological entity after PVC ablation, even though the improvement is not fully recovered.[13] The other previous individual case reports of PVC-CMP with their baseline clinical characteristics and follow-up are summarized in Table 1.

Although the exact mechanism of PVC-induced cardiomyopathy remains unclear, the best-described cellular mechanism, extrapolated from animal studies, involves beat-to-beat variation in action potential duration that reduces the inward and outward movement of L-type calcium current in cardiac myocytes and ultimately results in repolarization heterogeneity. Other cellular pathophysiology of PVC-CMP is related to impaired cardiomyocyte calcium handling from increased levels of phosphorylated ryanodine

Table 1. Summary table of the previous case report of premature ventricular complex-cardiomyopathy with its baseline and follow-up LVEF and PVC burden.

Author (year)	Sex/Age	Baseline LVEF (%)	Baseline PVC burden (%)	Follow-up LVEF (%)	Follow-up PVC burden (%)	Management
Chung *et al* (2021)[14]	M/65	43	32	53	<1	RFCA (no recurrency)
Senapati *et al* (2020)[15]	M/74	43	40	57	2	RFCA (no recurrency)
Sun *et al* (2022)[16]	M/53	34	80	46	1	RFCA (no recurrency)
Bekke *et al* (2025)[17]	M/28	45	30	60	Absent	RFCA (no recurrency)

Abbreviation note: LVEF: Left Ventricular Ejection Fraction; PVC: Premature Ventricular Complex; M: Male; RFCA: Radiofrequency Catheter Ablation.

receptor 2, Na/Ca exchanger 1, Ca^{2+}/calmodulin-dependent protein kinase II-alpha, with the result of downregulation of Sarcoplasmic Reticulum (SR) and decrease of SR $[Ca]^{2+}$ store.[18-19]

In addition, LV dyssynchrony is described as a necessary feature of that may be associated with PVC-CMP.[19] The long-term and frequent LV dyssynchrony can contribute to the development of LV dysfunction because of asymmetrically increased wall thickness in the late-activated LV segment and myocardial perfusion alteration.[18] Myocardial remission and recovery will be developed because of the reversal of the aforementioned process. The PVC-CMP pathological process is a reversible condition after primary PVCs are terminated.[18-19]

Conclusion

We reported a PVC-CMP patient who showed signs of a significant recovery process after successful catheter ablation. The non-significant coronary lesion which was shown by CCTA describes the high burden of PVC in this case, which was established as a primary insult for cardiomyopathy development. Causal factor management in PVC-CMP led to myocardial remission.

List of Abbreviations

CCTA	Coronary Computed Tomography Angiography
CMP	Cardiomyopathy
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
GDMT	Guideline-Directed Medical Therapy
GLS	Global Longitudinal Strain
HFrEF	Heart Failure with reduced Ejection Fraction
LBBB	Left Bundle Branch Block
LCC	Left Coronary Cusp
LGE	Late-Gadolinium Enhancement
LV	Left Ventricle
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
MR	Mitral Regurgitation
OT	Outflow Tract
PVC	Premature Ventricular Complex
PVC-CMP	Premature Ventricular Complex-induced Cardiomyopathy
SR	Sarcoplasmic Reticulum
VA	Ventricular Arrhythmia

Ethical Clearance

Not Applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

All authors have made a significant intellectual contribution to the manuscript according to the criteria formulated by the International Committee of Medical Journal Editors.

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Generative AI and AI-Assisted Technologies in the Writing Process

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Case Reports

Double-Chambered Right Ventricle in Adults: Characteristic Echocardiographic Features from an Incidental Case

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Abstract

Background: A Double Chambered Right Ventricle (DCRV) is an uncommon congenital heart defect in which an abnormal muscular bundle divides the Right Ventricle (RV) into two chambers with different pressure levels. Diagnosing DCRV in adults is challenging because it is often asymptomatic and may be misdiagnosed.

Case Illustration: We present a 37-year-old male with a history of an uncorrected Ventricular Septal Defect (VSD), who was incidentally found to have type 2 DCRV on echocardiography during evaluation for abdominal pain. No residual VSD was detected, possibly due to spontaneous closure. Electrocardiography (ECG) revealed first-degree Atrioventricular (AV) block. Chest radiography showed cardiomegaly with a Cardiothoracic Ratio (CTR) of 0.56. Transthoracic Echocardiography (TTE) demonstrated an anomalous muscular bundle that divided the RV into a high-pressure proximal chamber and a low-pressure distal chamber, accompanied by left atrial and ventricular enlargement.

Conclusions: DCRV in adults is often misdiagnosed as pulmonary stenosis, especially in patients with mild or no symptoms. TTE and Doppler imaging are key diagnostic modalities for accurate diagnosis; however, advanced imaging techniques such as Transesophageal Echocardiography (TEE) may be required in complex cases. Management includes symptom control, such as beta-blockers, and further evaluation to determine the need for surgical intervention.

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Keywords: Adult congenital heart disease, double-chambered right ventricle, echocardiography, ventricular septal defect

Introduction

Double Chambered Right Ventricle (DCRV) is an uncommon congenital heart defect, representing only about 0.5-2.0% of all congenital cardiac anomalies.[1] It is defined by hypertrophy of muscular bundles within the Right Ventricle (RV) that partition the chamber into two cavities, a high-pressure proximal chamber and a low-pressure distal chamber.[2] Most patients are diagnosed during childhood or adolescence, commonly before the age of 20. Nevertheless, some individuals may remain asymptomatic until adulthood, which can result in a delayed diagnosis.[3]

Reports of DCRV in adult patients are rare, especially in Indonesia. Furthermore, diagnosis in adults is challenging, and DCRV is often misdiagnosed as pulmonary stenosis.[4] We present a case of DCRV in a 37-year-old male in Indonesia who was detected incidentally during evaluation of a non-cardiac complaint. Several adult cases of DCRV have been reported, most commonly presenting with exertional dyspnea, chest pain, or during evaluation of a Ventricular Septal Defect (VSD) after a cardiac murmur was incidentally detected on routine examination. In contrast, our patient, who had a history of congenital heart disease during childhood, was diagnosed incidentally while being evaluated for a non-cardiac complaint. This report aims to emphasize the importance of considering DCRV as a differential diagnosis in adult individuals with prior congenital heart disease presenting with a systolic murmur, even in the absence of typical symptoms. Additionally, this case highlights the crucial role of echocardiography as an essential tool for accurate diagnosis of DCRV.

Case Illustration

A 37-year-old male was admitted to the cardiology department for further assessment of a prominent systolic heart murmur. He initially came with complaints of intermittent sharp pain in the epigastrium extending to the lower abdomen for one week, accompanied by nausea, vomiting, weakness, and sudden episodes of palpitations without clear triggers. On physical examination, a prominent ejection systolic murmur graded 5/6 with a palpable thrill was detected, most prominent along the left sternal border. The patient was diagnosed with a VSD in early life, which had been managed conservatively with daily medication and without corrective surgery. Twelve years earlier, the patient had been hospitalized for 40 days due to infective endocarditis. After a treadmill test showed good tolerance, he discontinued follow-up and cardiac medications. He had no complaints of chest pain, breathlessness, excessive sweating, or loss of consciousness. However, he occasionally experienced dizziness and blurred vision, which he attributed to a long-standing history of hypotension. There was no history of drug allergies, chronic or infectious diseases, or growth and developmental issues during childhood. Family history revealed that his mother and first brother had died of heart disease, though not related to congenital heart defects.

On physical examination, the patient was comfortable at rest with a New York Heart Association (NYHA) functional class II status. Vital signs demonstrated normotension with Blood Pressure (BP) of 107/66 mmHg, a regular Heart Rate (HR) of 74 beats/min, afebrile temperature of

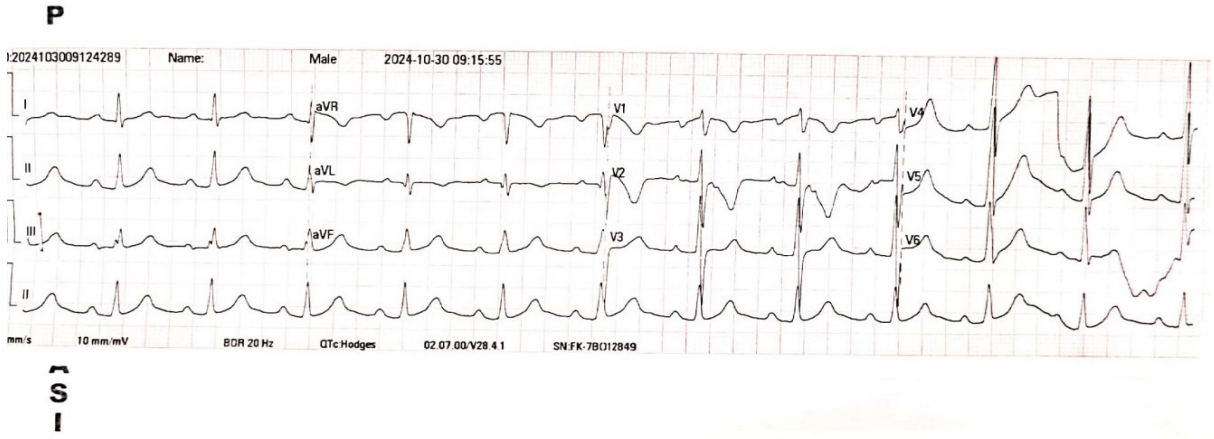

Figure 1. The electrocardiogram shows a prolonged PR interval and T-wave inversion in leads V1-V2.

36.5°C, respiratory rate 20 times/min, and oxygen saturation on room air was 92%, which increased to 94% with supplemental oxygen at 3 L/min via nasal cannula. Exercise tolerance was mildly reduced; the patient experienced shortness of breath after climbing one flight of stairs or walking approximately 100–200 meters at a normal pace. The patient's Body Mass Index (BMI) was 21.6 kg/m^2, which falls within the normal range according to the Asia-Pacific classification for Asian populations. Thoracic examination revealed pectus excavatum, symmetrical chest movements, and no visible ictus cordis. Chest palpation showed good fremitus conduction bilaterally and a palpable thrill on the left sternal border. On percussion, the upper left cardiac margin was identified at the second intercostal space along the left parasternal line. At the same time, the lower border was found at the sixth intercostal space at the left midclavicular line, and the right margin at the fifth intercostal space near the right parasternal line. Cardiac auscultation demonstrated a harsh grade 5/6 systolic ejection murmur that was audible across the precordium, with maximal intensity at the left parasternal area, particularly at the second to fourth intercostal spaces. The murmur could also be heard along the right sternal border. Lung auscultation revealed normal vesicular breath sounds bilaterally. Examination of the mucous membranes revealed no central cyanosis, and all four extremities were warm with good perfusion.

On Electrocardiography (ECG), a prolonged PR interval with a duration of 0.22 – 0.24 seconds, together with T-wave inversion, was noted in leads V1-V2. Additionally, QRS complex spikes were observed in lead III (Figure 1). Chest radiography demonstrated an enlarged cardiac silhouette, with a Cardiothoracic Ratio (CTR) of 0.56 (Figure 2). Laboratory evaluation was generally unremarkable. Nonetheless, a reduced Mean Platelet Volume (MPV) (8.2 fL, reference 9.0-13.0) and a mildly decreased serum creatinine (0.7 mg/dL, reference 0.9-1.3) were observed.

Two-dimensional transthoracic echocardiography was performed using a 3.0-MHz phased-array transducer on a LOGIQ P7 ultrasound system (GE Healthcare). Parasternal long-axis and short-axis views revealed an abnormal muscular bundle that separated the RV into two cavities. Both the left atrium and left ventricular appeared dilated, while the interventricular septum and posterior left ventricular wall were non-thickened. The interatrial septum and interventricular septum were intact, with a normal Ejection Fraction (EF) of 69%, a Tricuspid Annular Plane Systolic Excursion (TAPSE) value of 20 mm, and normokinetic wall motion. No valvular abnormalities or VSD were observed. Continuous wave Doppler across the muscular septation demonstrated a holosystolic antegrade jet with a peak velocity of approximately 2.0 m/s, corresponding to an estimated pressure gradient of 16 mmHg, consistent

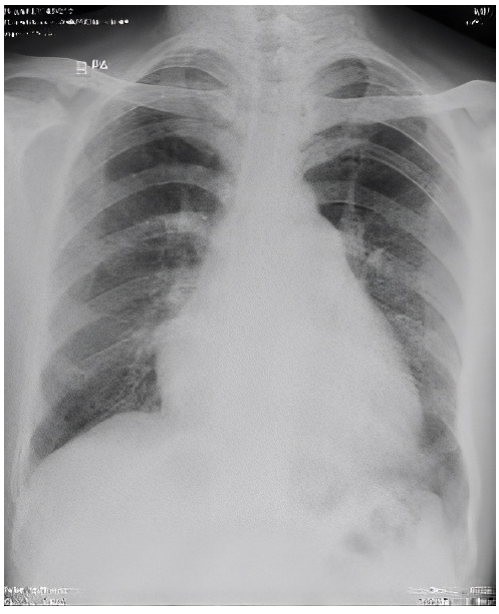

Figure 2. Chest X-ray (posteroanterior view) showing cardiomegaly.

with mild right-ventricular outflow tract obstruction (Figures 3 and 4). Overall, Transthoracic Echocardiography (TTE) indicated preserved left-ventricular diastolic function and normal right-ventricular systolic performance. Based on these results, a diagnosis of DCRV was made. He was referred to Dr. Sardjito General Hospital for further evaluation and was started on beta-blocker therapy to help reduce cardiac workload. However, he declined further evaluation or routine follow-up and surgical consultation, choosing instead to continue with medical management. Consequently, no advanced imaging or surgical intervention was performed.

On follow-up echocardiography performed one year later, TTE demonstrated preserved left-ventricular systolic function (Left Ventricular Ejection Fraction [LVEF] 72%) and normal right-ventricular performance (TAPSE 20 mm). The right atrium appeared dilated with a diameter of 54 mm, while the RV measured 40 mm in true dimension and 26 mm in the mid-cavity region. No new valvular abnormality or residual ventricular septal defect was identified (Figures 5). Continuous-wave Doppler aligned to the mid–right-ventricular jet recorded a peak velocity of 3.29 m/s and an estimated pressure gradient of 43 mmHg (calculated by $4v^2$; sweep speed 50 mm/s), indicating moderate right-ventricular outflow tract obstruction (Figure 6).

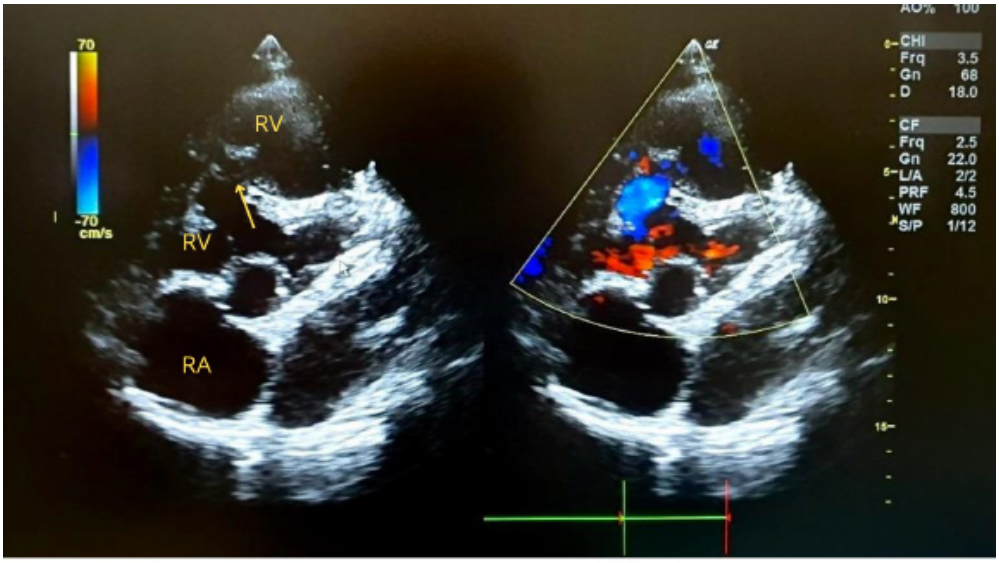

Figure 3. Two-dimensional transthoracic echocardiography (parasternal short-axis view at the level of the mitral valve leaflets) without (left) and with (right) color-flow Doppler demonstrates an abnormal muscular bundle that separates the RV into two cavities.

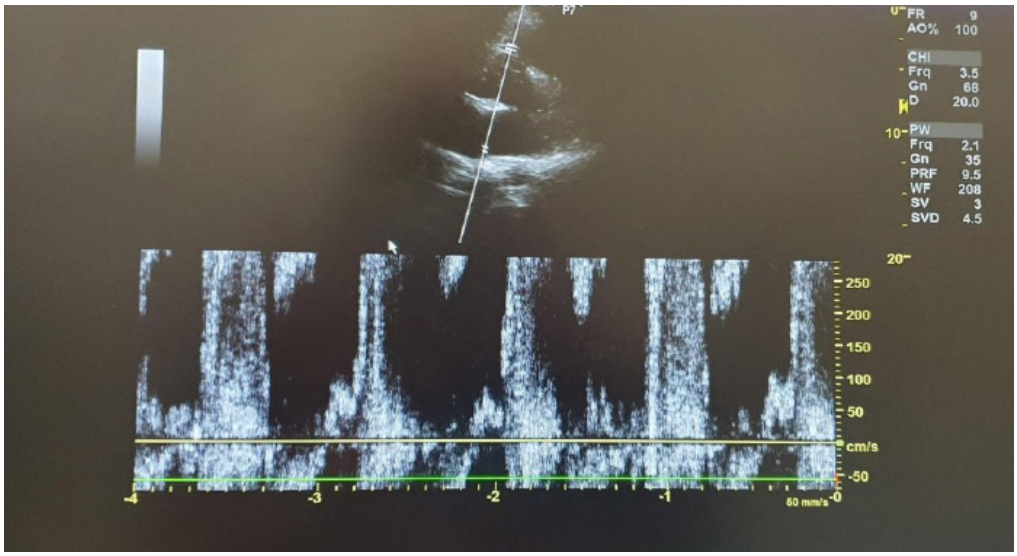

Figure 4. Continuous-wave spectral Doppler across the muscular septation demonstrates a peak holodiastolic antegrade continuous flow gradient, indicative of RV outflow obstruction.

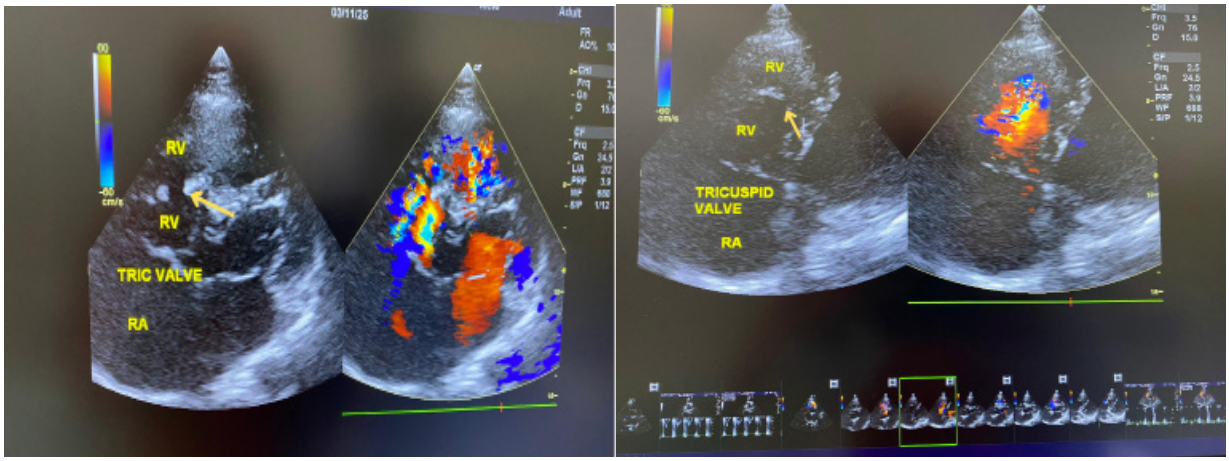

Figure 5. Follow-up TEE shows RV-focused four-chamber and RV-inflow views demonstrate a hypertrophied mid-RV muscular bundle with color-Doppler aliasing across the obstruction. Continuous-wave Doppler aligned through the jet (parasternal short-axis at the great vessels) recorded Vmax 3.29 m/s (peak ≈43 mmHg, $4v^2$), indicating moderate intracavitary obstruction consistent with DCRV.

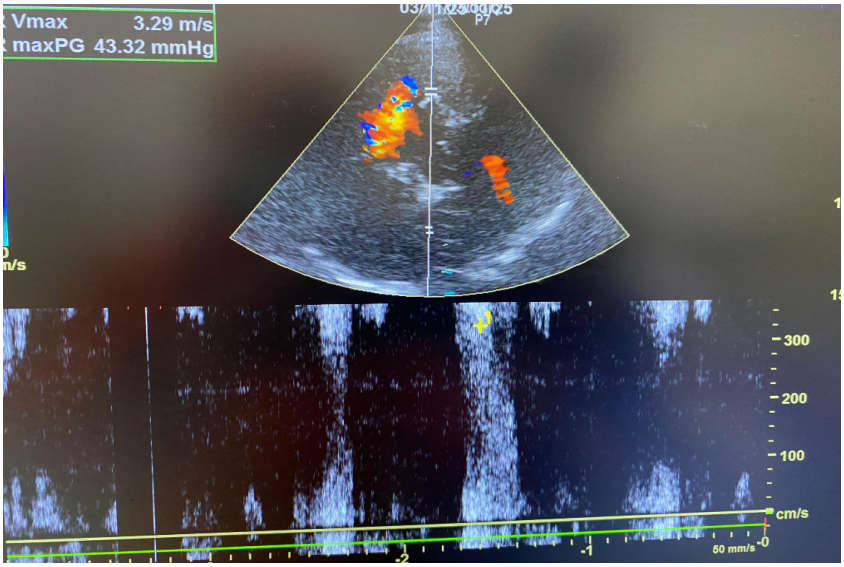

Figure 6. CW-Doppler through the mid-RV obstruction showing Vmax 3.29 m/s and peak gradient 43.3 mmHg (sweep 50 mm/s), consistent with moderate mid-RV obstruction in DCRV.

Discussion

DCRV is a congenital heart defect in which the RV is partitioned into two cavities: a proximal chamber with elevated pressure and a distal chamber with lower pressure.[5] Ventricular muscle fibers generally extend from the Atrioventricular (AV) junction to the ventriculo-arterial junction. The RV has three components: the inlet, apical trabecular, and outlet regions. The inlet segment accommodates the tricuspid valve and its supporting apparatus, which regulate appropriate valve opening and closure. The trabecular region extends to the ventricular apex and is typified by thin myocardial walls and prominent trabeculations. In contrast, the outlet region, also termed the infundibulum, arises from the ventricular base as a uniform muscular layer that supports the pulmonary valve leaflets. This region is smoother than the other regions because it lacks trabecular muscles.[4]

Based on these anatomical features, several hypotheses have been proposed to explain the development of DCRV. In DCRV, abnormal hypertrophy of muscle bundles occurs in certain parts of the RV, particularly in the trabecular or outlet regions. One of the main causes is the adaptation of the RV to increased flow through a VSD, leading

to hypertrophy of the supraventricular crest and the formation of an obstruction. In addition, displacement of the septomarginal trabeculation or moderator band to a higher position also contributes to hypertrophy. This displacement results in abnormal thickening of the muscle, which forms a new muscular layer connecting the septoparietal trabeculation with the apical trabecular region of the RV. The thickened muscle forms a muscular bundle that obstructs blood flow, separating the RV into proximal and distal chambers with different pressures. As a result, obstruction occurs and disrupts normal blood flow within the RV.[5]

Garg et al. (2020) reported that DCRV can be classified into two patterns of intracavitary obstruction. Type 1 is defined by the presence of an anomalous muscular bundle crossing the RV cavity, considered the main cause of intraventricular obstruction. In contrast, type 2 is primarily related to marked hypertrophy of the parietal and septal walls. The pressure gradient within the ventricle tends to be greater in type 1 compared with type 2. An underlying VSD is most often linked with type 2 DCRV.[6] This case is classified as type 2 DCRV based on the patient's history of VSD during childhood. The absence of valvular abnormalities or VSD on TTE can be explained by the fact that VSDs are known to undergo spontaneous closure as children grow, especially in small defects, through various mechanisms. One possible mechanism is the proliferation of fibrous tissue surrounding the defect margins, which gradually results in septal closure. In membranous VSD, closure can occur through attachment of the septal leaflet of the tricuspid valve to the defect margin, a mechanism known as endocardial adhesion. Turbulent blood flow through the VSD may also damage the endocardium, producing a jet lesion that contributes to defect closure. In muscular VSDs, myocardial growth around the defect may contribute to defect closure.[7]

DCRV can develop progressively postnatally. Hypertrophy of the muscular bundles driven by high velocity jet flow may lead to mid-cavitary obstruction that becomes clinically apparent only in adulthood. Even when the VSD later closes, the established muscular remodeling can sustain or further the progression of the obstruction.[3] In our patient, the persistent anomalous right-ventricular muscular bundle and the absence of a VSD are consistent with this trajectory. Several studies have reported that asymptomatic adults with an anomalous muscular bundle and an intact ventricular septum might have previously had a VSD that spontaneously closed.[8] DCRV has been reported to occur many years after the closure of a VSD. It is speculated that the persistent effect of high-velocity VSD jets on the RV wall may, over time, activate genetic factors that promote the release of growth signals and cause thickening of the heart muscle, even after the VSD has already closed.[9] Accordingly, a prior VSD that closed spontaneously remains plausible, and the absence of a current shunt is consistent with this. Nevertheless, in this patient, the mid-ventricular obstruction may still progress because jet-driven muscular hypertrophy can develop postnatally and

Table 1. Comparison with previously published adult DCRV cases.

Study (Author, Year)	Age/Sex	Mode of Detection & Symptoms	Obstruction Site	Imaging	Hemodynamics	ECG	Management
Garg et al., 2020	18-year-old male	Progressive shortness of breath for the past 2 months	A muscle band protruding from the RV free wall to the interventricular septum	Two-dimensional TTE using a 3.0 MHz transducer and a Vivid S5 cardiac ultrasound system (GE Healthcare, Milwaukee, WI, USA)	Continuous-wave Doppler across this turbulent jet revealed flow acceleration of 6.0 m/s, corresponding to a pressure gradient of approximately 144 mmHg	Increased amplitude of the R wave on V1, inverted T waves on V1–V6, and right-axis deviation	Refused for operative correction.
Malone et al., 2023	40-year-old patient	Routine evaluation of VSD, asymptomatic	RV septation by muscular bundles and flow acceleration. The pulmonic valve is normal, with no evidence of VSD	TTE, Cardiac catheterization, and ventriculogram	TTE on the parasternal short-axis view was suggestive of DCRV, with the highest intracavity gradient measured at 39 mm Hg	Not available	Surgical resection for DCRV

Malone et al., 2023	20-year-old patient	Severe pulmonary stenosis and RVH with concerns for tetralogy of Fallot	RVH with hypertrabeculation	TTE, CMR	A severe gradient across the RVOT. Peak and mean gradients 96 and 41 mmHg	RVH & RV strain pattern	Surgical closure of the VSD and resection of the RV muscle bundles and outflow tract obstruction.
Romano et al., 2007	29-year-old man	Mild exertional dyspnea, dizziness, and chest pain during the last 3 years	A 17 mm perimembranous VSD. Slow velocity flow from left to RV; the aortic root was slightly deviated to the right. RV hypertrophy and a muscular septation inside this cavity	TTE	A peak gradient of 80 mmHg.	Sinus rhythm, RAD, right ventricular overload and a minor degree of Right Bundle Branch Block (RBBB)	Surgical resection
Satria et al., 2021	36-year-old woman	Pulmonary stenosis	Perimembranous outlet (PMO) VSD with left-toright shunts	TEE & TTE	Left-to-right shunts of 0.7-0.8 cm in diameter, pressure gradient of 100 mmHg, visible bulkhead at 1/3 distal RV, turbulence (+) with a pressure gradient of 130 mmHg between the two walls	Not available	Surgery with VSD closure and resection of the septum.

ECG: Electrocardiogram; RV: Right Ventricle; VSD: Ventricular Septal Defect; DCRV: Double-Chambered Right Ventricle; RVH: Right Ventricular Hypertrophy; CMR: Cardiac Magnetic Resonance; RVOT: Right Ventricular Outflow Tract; TTE: Transthoracic Echocardiography; RAD: Right Axis Deviation; TEE: Transesophageal Echocardiography.

persist after the defect has closed. Management should therefore be guided by the severity and progression of right-ventricular obstruction and patient symptoms, rather than shunt status alone.

The history of infective endocarditis in this patient may be related to the hemodynamic disturbances and pressure gradients within the cardiac chambers. Vegetations on the endocardium usually form in areas with pressure gradients that cause turbulent blood flow. Congenital heart disease with high-velocity blood flow, with or without prosthetic material, increases the risk of infective endocarditis. Any lesion that causes turbulent blood flow, regardless of the presence of a shunt, can predispose to infective endocarditis. Individuals with congenital heart disease are at particularly high risk for endocarditis. Turbulent blood flow from a high-pressure chamber to a low-pressure chamber, or through a narrow defect, can injure the endothelium and promote thrombus formation, resulting in a sterile platelet and fibrin clot known as nonbacterial thrombotic endocarditis. This condition provides an ideal environment for bacterial adherence and the formation of infected vegetations. Endothelial lesions are usually located on the low-pressure side, so vegetations are often found on the atrial side of the AV valves or distal to the descending aorta in cases of aortic coarctation.[10]

In this case, TTE also showed left atrial and left ventricular dilation. These findings may be related to chronic hemodynamic disturbances in congenital heart disease. In VSD, abnormal shunting can increase pulmonary blood flow and pulmonary venous return, resulting in left-sided volume

overload. As tissue metabolic demands increase, the left ventricle may compensate by increasing stroke volume and heart rate determines LA and LV dilation.[11]

Diagnosing DCRV in adulthood is particularly challenging and frequently misinterpreted as pulmonary stenosis. Symptoms are often absent, leading to misdiagnosis. Patients with DCRV are reported to remain asymptomatic until they become symptomatic due to progressive obstruction, which eventually creates a high gradient between the two chambers.[7,12] In this case, the patient reported no symptoms and maintained normal activities, only occasionally experiencing palpitations and blurred vision due to his history of hypotension. DCRV was incidentally discovered when the patient presented with abdominal pain. A study by Malone et al. (2024) also reported that two-thirds of DCRV patients were asymptomatic.[2] Two-dimensional TTE and Doppler imaging are capable of reliably identifying DCRV in both pediatric and adult populations. In one series, TTE confirmed the diagnosis in 26 out of 32 patients (81%), demonstrating its value in characterizing structural abnormalities and estimating intraventricular pressure gradients.[2] Nevertheless, despite its utility, TTE does not always provide optimal anatomical visualization. In such situations, Transesophageal Echocardiography (TEE) offers more detailed imaging of cardiac structures, subpulmonic gradients, valve motion, and subinfundibular narrowing. Nevertheless, TTE remains the preferred initial modality for detecting DCRV.[9]

Surgical resection of intraventricular obstruction is an effective and durable treatment for patients with DCRV.[2] According to the latest American Heart Association and American College of Cardiology (AHA/ACC) guidelines, operative intervention is recommended for symptomatic adults with congenital heart disease who present with moderate Right Ventricular Outflow Tract (RVOT) obstruction, indicated by a Doppler velocity of ≥3.0 m/s or a peak gradient of ≥36 mmHg. Evidence from other studies also highlights that surgery is commonly undertaken in patients with DCRV when the Right Ventricular Pressure (RVP) gradient exceeds 40 mmHg, or in the presence of significant left-to-right shunting due to severe VSD (Qp/Qs ≥ 2.0). Surgical repair should aim to eliminate the obstruction by resecting the hypertrophied muscular bundles in the RVOT to reduce pressure gradients. The obstruction in DCRV can lead to increased proximal chamber pressure, resulting in significant clinical symptoms such as dyspnea or heart failure. Therefore, the most common management is surgical resection of the abnormal muscular bundle causing the obstruction.[9]

At the 12-month follow-up, continuous-wave Doppler across the mid-RV obstruction showed Vmax of 3.29 m/s (peak = 43 mmHg), meeting commonly cited operative thresholds for DCRV (≥40 mmHg). This was discussed with the patient, and surgery was declined. Because TEE adequately delineated the obstructing bundle with reproducible Doppler measurements, and the patient declined further work-up and surgery, TEE/CMR/CT Cardiac was not performed. Acknowledging that Doppler may overestimate intracavitary gradients relative to catheterization, invasive confirmation will be obtained if a future operative decision hinges on gradient magnitude.

However, since the obstruction in DCRV is dynamic, pharmacological treatment can also be used to help manage this condition. Beta-blockers and calcium channel blockers can help reduce RVP by decreasing myocardial contractility and slowing the HR. Nevertheless, the effectiveness of these medications is limited, and they are generally considered as temporary management or for patients who cannot undergo immediate surgery.[9]

Beta blockers are recommended as first-line therapy for patients with Heart Failure and Reduced Left Ventricular Ejection Fraction (HFrEF), including those with Dilated Cardiomyopathy (DCM). For DCRV, the recommendation is similar, but caution is advised in cases of severe RV dysfunction or acute heart failure, as beta blockers may worsen hemodynamics in these settings. Several landmark trials and meta-analyses have shown that beta blockers improve survival and reduce hospitalizations in patients with HFrEF, including those with DCM.[13]

Because DCRV obstruction has a dynamic component, pharmacologic therapy may assist symptom control when surgery is deferred. β-blockers can control DCRV with dynamic obstruction. In this patient who declined surgery and had preserved biventricular function (LVEF 72%, TAPSE 20 mm), we initiated a low-dose beta blocker to reduce HR/contractility and thereby blunt the dynamic gradient.[3] Given a PR interval of 0.22–0.24 s (first-degree AV block), β-blocker therapy was started cautiously, with ECG/clinical monitoring and avoidance of additional AV nodal blocking agents, recognizing that first degree AV block is not an absolute contraindication, yet AV

nodal drugs can worsen conduction or precipitate higher-degree block, treatment would be withheld if PR prolongation, symptomatic bradycardia, or hypotension occurred. In line with the 2018 ACC/AHA/HRS bradycardia guideline, first-degree "marked" AV block is defined as a PR interval > 0.30 ms. Because β-blockers are listed among medications that can induce/exacerbate bradycardia or conduction disorders, their use in first-degree AV block is not absolutely contraindicated but warrants careful ECG surveillance and continued avoidance of other AV-nodal blockers.[14]

Conclusion

DCRV is an unusual congenital heart condition where abnormal thickening of the muscular bundles within the ventricle divides the RV into two chambers that operate under different pressures. In this case, a 37-year-old male with a history of unrepaired VSD was incidentally found to have type 2 DCRV on echocardiography, without evidence of a VSD, possibly due to spontaneous closure. Diagnosis of DCRV in adulthood is often mistaken for pulmonary stenosis, especially in patients with mild or asymptomatic presentations. TTE and Doppler studies are essential for identifying and confirming the diagnosis, although TEE or advanced imaging may be needed in more complex cases. Management includes symptomatic treatment, such as the use of beta-blockers, and further evaluation to determine the need for surgical intervention. This case emphasizes the value of prompt diagnosis and comprehensive assessment of congenital heart disease in adults.

List of Abbreviations

AV Atrioventricular
BMI Body Mass Index
BP Blood Pressure
CTR Cardiothoracic Ratio
DCM Dilated Cardiomyopathy
DCRV Double-Chambered Right Ventricle
ECG Electrocardiography
EF Ejection Fraction
HFrEF Heart Failure and Reduced Left Ventricular Ejection Fraction
HR Heart Rate
MPV Mean Platelet Volume
NYHA New York Heart Association
RBBB Right Bundle Branch Block
RV Right Ventricle/Ventricular
RVOT Right Ventricular Outflow Tract
TAPSE Tricuspid Annular Plane Systolic Excursion
TEE Transesophageal Echocardiography
TTE Transthoracic Echocardiography
VSD Ventricular Septal Defect

Ethical Clearance

Not applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

DAY conceptualized and designed the study, conducted clinical data acquisition, drafted and critically revised the manuscript; PDA drafted and critically revised the abstract and manuscript; PIMY provided clinical data support, conducted the literature review, and revised the manuscript; RRI assisted with the discussion section, refined, proofread, and revised the manuscript; NN provided clinical supervision, validated supporting diagnostic findings, and critically revised the manuscript. All authors approved the final version

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Conflict of Interest

The authors declare no conflicts of interest.

Availability of Data and Materials

Not applicable.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

Generative AI was used solely to improve the language (grammar and phrasing). The authors reviewed, edited, and take full responsibility for the content, including the accuracy of all clinical information, interpretations, and references.

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Corrigendum

Corrigendum: The Role of Coronary Artery Calcium Score as a Systemic Marker of Atherosclerosis: A Cross-sectional Imaging Study

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Following publication of this article, the authors notified the Editorial Office of an error in the order of authorship. The order of the author is wrong and should have been:

Mohammad Sidqi Aulia, Raymond Pranata, Syarief Hidayat, Nuraini Yasmin Kusumawardhani

All authors have provided written consent to approve the revised authorship order. Thea authorship order has now been corrected in the published article. The authors apologizes for any inconvenience caused by this error.

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