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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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Editor's Page

Evolving the Subspecialty Cardiology Training

Sunanto Ng[1]
Editor-in-Chief

(Indonesian J Cardiol, 2025;46;137)

The subspecialty of cardiology training in Indonesia is still evolving. Indonesia's system is marked by a dualism between university-based (Sp-2) and hospital-based fellowship pathways, both of which operate without unified (yet) terminology or accreditation, resulting in conceptual and regulatory ambiguities. This mirrors the broader complexities found in Indonesia's approach to advanced medical education, where rapid expansion in cardiology has not always been matched by standardization or global recognition.

Timely and relevant to this current situation, Munawar M. et al provides comprehensive, well-contextualized review of the evolving structure of cardiology subspecialty training in Indonesia.[1] They highlighted regulatory gaps, the fragmented dual-track system, and policy challenges, and offer globally benchmarked recommendations. Importantly, the paper's recommendations for a hybrid, competency-based system and unified regulations are timely for Indonesia's ambitions to become a regional leader in cardiovascular training. The call for reforms is especially relevant given the context of Indonesia's healthcare evolution, emerging regional competition, and the growing need to align with international standards. Overall, this review not only addresses technical and policy gaps, but also situates the Indonesian experience in a global perspective—serving as a catalyst for ongoing improvement in subspecialty medical education.

While the pros and cons of university-based and hospital-based subspecialty training are not unique to Indonesia (it is indeed also found in most countries adopting this dual system), educational maturity can only be achieved if scientific and objective discussions take place. Serving as the peer journal of the Indonesian Heart Association, the Indonesian Journal of Cardiology (IJC) would like to contribute to this development by providing a platform for this kind of discussion.

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[1]Editor-in-Chief, Indonesian Journal of Cardiology.

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Editorial

Revisiting Subspecialty Training in Cardiology in Indonesia: Structural, Regulatory, and Global Perspectives

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Abstract

The rapid expansion of cardiology as a discipline has prompted the emergence of numerous subspecialties that require structured, competency-based training. In Indonesia, however, the development of subspecialty education remains inconsistent, divided between university-based programs known as *Spesialis-2* (Sp-2) and hospital-based clinical fellowships. The interchangeable use of the terms “fellowship” and “subspecialty” has generated conceptual ambiguity and regulatory uncertainty. Globally, cardiology subspecialty training follows a hospital-based apprenticeship model led by accredited teaching hospitals and regulated by national or regional professional boards such as the Accreditation Council for Graduate Medical Education (ACGME), the American College of Cardiology (ACC), or the European Society of Cardiology (ESC). Indonesia’s deviation from these international norms has implications for both the quality of advanced cardiovascular training and the nation’s potential to attract international fellows—a marker of global academic recognition. This review examines the current landscape of cardiology subspecialty training in Indonesia, compares it with global frameworks, and discusses academic, structural, and legal challenges, including those related to foreign trainees. A policy framework is proposed to harmonize Indonesia’s subspecialty education with global standards, thereby strengthening national capacity and international credibility.

(Indonesian J Cardiol, 2025;46;138-143)

Introduction

Cardiology has evolved rapidly into a diverse field that requires highly specialized expertise, encompassing interventional cardiology, electrophysiology, heart failure, cardiac imaging, and preventive cardiology. This global shift has been supported by structured subspecialty programs emphasizing clinical apprenticeship, procedural competency, and research engagement. The American College of Cardiology (ACC) and the American Heart Association (AHA) have repeatedly emphasized the importance of competency-based subspecialty training as the cornerstone of high-quality cardiovascular care.[1-2]

In Indonesia, subspecialty training remains fragmented and inconsistently defined. The term *Spesialis*-2 (Sp-2) refers to a formal academic pathway under university governance[3], whereas fellowship denotes hospital-based programs often initiated by tertiary cardiac centers.[4] The absence of unified terminology and accreditation criteria creates confusion among both professionals and regulators. Furthermore, unlike the standardized hospital-based apprenticeship model widely accepted globally, Indonesia's system remains largely university-centric.

The emergence of foreign physicians seeking advanced training in Indonesia would signify the maturity and competitiveness of Indonesian cardiology education. However, such progress demands legal certainty, institutional readiness, and global alignment in training standards. This review critically analyzes the existing system of subspecialty training in cardiology in Indonesia, examining its terminological, structural, and legal dimensions, and providing evidence-based recommendations for reform.

Historical Evolution of Subspeciality Training: Europe, the United States, and Indonesia

The concept of medical subspecialization emerged as a natural consequence of scientific progress and the growing complexity of clinical medicine. In Europe, structured postgraduate specialization began in the early twentieth century but became systematized in Spain after the 1950s. The Spanish Médico Interno Residente (MIR) system, established in 1955, marked a transition from informal apprenticeship to a nationally regulated, merit-based training structure. By the 1980s, legislation through the Royal Decree formally recognized residency as the only legitimate route to specialization, integrating training within university hospitals and linking it to continuous quality assessment and public accountability. This model inspired other European nations to adopt state-regulated, competency-based specialty programs that emphasized hospital-centered apprenticeships and standardized evaluation.[5]

In the United States, specialization and subspecialization evolved in parallel with scientific and institutional reforms. Following the influential Flexner Report of 1910, which called for research-based medical education, American medicine entered an era of structured specialization. The American Board of Ophthalmology became the first specialty board in 1917, followed by the American Board of Medical Specialties (ABMS) in 1933 and the American Board of Internal Medicine (ABIM) in 1936. By the 1970s, internal medicine had divided into multiple organ- and disease-based subspecialties, including cardiology, nephrology, and infectious disease. Over the subsequent decades, the ABIM approved further subspecialties, including interventional cardiology, electrophysiology, and advanced heart failure, reflecting the increasing technical complexity of care and the need for credentialed expertise. Cassel and Reuben observed that subspecialization, although driven by scientific advancements and societal needs, also raised concerns regarding professional fragmentation and the balance between generalist and specialist roles.[6]

In Indonesia, the origin of cardiology subspecialty training is less clearly documented, but it can be traced back to the early 1990s under the pioneering leadership of Dr. Otte J. Rachman, who initiated short-term fellowship-style programs in interventional cardiology. During this period, training typically lasted three to six months and was reserved for cardiologists affiliated with satellite hospitals, focusing primarily on the transfer of procedural skills rather than structured curricula.[7] The modern era of subspecialty education began in 2010, when a physician from Vietnam applied for fellowship training at Binawaluya Cardiac Center, marking the first international participation in an Indonesian cardiac fellowship. Subsequently, Professor Dr. Harmani Kalim, as Chairman of the *Kolegium Jantung dan Pembuluh Darah Indonesia* (KJPDI, Indonesian College of Cardiology), formally appointed Binawaluya as Indonesia's first official national training center for interventional cardiology. By 2012, a nationwide fellowship network was established across nine accredited training centers, each under the supervision of the KJPDI. This milestone marked the beginning of the National Fellowship Program in Interventional Cardiology, which opened access to all qualified cardiologists in Indonesia without institutional or regional discrimination. Other subspecialties were then established, including electrophysiology, echocardiography, and structural intervention. The establishment of this network not only standardized training but also symbolized Indonesia's commitment to developing a structured, equitable, and globally recognizable framework for cardiology subspecialties.

Global Standards in Cardiology Subspeciality Education

Internationally, subspecialty training in cardiology is guided by well-established frameworks. In the United States, the ACGME defines subspecialty training as a structured, hospital-based apprenticeship conducted after residency or general cardiology fellowship.[8] The 2023 ACC/AHA/SCAI Advanced Training Statement on Interventional Cardiology details competency domains, procedural requirements, and expected research output.[9] In Europe, the ESC and European Board for Accreditation in Cardiology (EBAC) accredit programs based on predefined curricula, mentorship models, and institutional capacity.[10]

These systems share key characteristics, including training within accredited hospitals, mentorship-driven apprenticeships, standardized competency assessments, and independent accreditation harmonized with national authorities. The apprenticeship model promotes direct skill transfer, mentorship, and early integration into multidisciplinary care.[11-12]

Indonesia's Dual System: University-Based versus Hospital-Based Pathways

Indonesia's postgraduate medical education system has evolved from a university-dominated framework where degrees are awarded through academic institutions. The Sp-2 system, administered by universities and accredited by the *Lembaga Akreditasi Mandiri Pendidikan Tinggi Kesehatan Indonesia* (LAM-PTKes, Indonesian Independent Accreditation Agency for Higher Education in Health), an independent regulatory body, continues formal academic pathways.[3] In contrast, hospital-based fellowship programs—usually offered by national cardiac centers—are designed to provide advanced, practical training without conferring an academic degree.

While the Sp-2 model ensures academic rigor and research exposure, it often suffers from bureaucratic rigidity and limited procedural experience due to constraints in patient volume and case diversity. Conversely, hospital-based fellowships are more responsive to clinical innovation and industry collaboration, yet often lack standardized national oversight. This dualism leads to uneven training quality, fragmented curricula, and uncertainty regarding professional recognition by regulatory bodies such as the *Konsil Kedokteran Indonesia* (KKI, Indonesian Medical Council) and the KJPDI.

Similar challenges were reported in surgery, where the introduction of hospital-based residency programs improved responsiveness to health system needs and reduced training bottlenecks.[5,13] Lessons from that reform suggest that cardiology could benefit from greater hospital autonomy under national accreditation supervision.

Apprenticeship as the Core of Subspecialty Training

The apprenticeship model, derived from centuries of medical tradition, remains the backbone of postgraduate clinical education. It emphasizes supervised experiential learning in real clinical environments rather than classroom-based instruction. In cardiology, this model is particularly critical given the rapid evolution of procedural technologies, device therapies, and multimodality imaging.

Studies from the United States and Europe highlight the superiority of apprenticeship-based subspecialty education in achieving procedural competency and in preparing for independent practice.[6,13] The ACGME and ESC frameworks require fellows to demonstrate mastery in procedural skills, clinical decision-making, and academic output before board certification.

In contrast, academic Sp-2 programs in Indonesia often emphasize coursework, thesis production, and theoretical examinations, which, although academically valuable, may not fully align with the skill-based demands of modern cardiology. Without sufficient procedural volume and exposure, trainees may graduate with limited hands-on proficiency.

A hybrid model integrating the strengths of both systems (academic rigor from universities and clinical apprenticeship from hospitals) could provide an optimal solution. Such a model would require coordinated accreditation, joint supervision, and shared competency benchmarks among the Ministry of Education, the Ministry of Health, and professional bodies such as the *Perhimpunan Dokter Spesialis Kardiovaskular Indonesia* (PERKI, Indonesian Heart Association), the *Pokja Intervensi Kardiologi Indonesia* (PIKI, Indonesian Society of Intervention Cardiology), the KJPDI, and the KKI. A comparison between university-based and hospital-based models, in conjunction with the global model, is depicted in Table 1.

Legal, Immigration, and Ethical Dimensions

Opening Indonesia's subspecialty programs to foreign physicians entails complex legal and ethical considerations. Current immigration and labour regulations do not specifically address foreign doctors in training programs. While temporary medical practice permits can be issued under supervision, there is no comprehensive framework governing academic or clinical apprenticeships for non-Indonesian physicians.

Table 1. Comparison of subspeciality training models.

Aspect	University-Based (Sp-2)	Hospital-Based Fellowship	Global Apprenticeship Model
Governing Body	University / Ministry of Education	Hospital / Specialist Society	Teaching Hospital under National Medical Board
Primary Focus	Academic / research-based	Clinical / procedural skills	Competency-based clinical mastery
Accreditation	Academic accreditation (LAM-PTKes)	Institutional / internal	Independent national / international accreditation
Certification	Academic degree (Sp-2)	Fellowship certificate (KJPDI)	Board certification
Flexibility and responsiveness	Low	Moderate	High
International Recognition	Limited	Low	High

Explanatory note: Flexibility and responsiveness indicate how quickly a subspecialty program adapts to changes in technology and clinical practice. University-based programs typically adapt more slowly due to academic processes, while hospital-based and global models can adjust curricula and clinical experiences more rapidly. International recognition refers to whether a program's training standards and certifications are recognized globally; LAM-PTKes: *Lembaga Akreditasi Mandiri Pendidikan Tinggi Kesehatan Indonesia* (Indonesian Independent Accreditation Agency for Higher Education in Health); KJPDI: *Kolegium Jantung dan Pembuluh Darah Indonesia* (Indonesian College of Cardiology).

This legal vacuum creates risks for both hosting institutions and trainees. Without clear rules on liability, malpractice coverage, or training status, hospitals may be reluctant to accept foreign fellows. Conversely, the absence of legal protection may discourage international participation. Comparative examples from Singapore, Malaysia, and Australia show that structured medical training visas and limited practice licenses can safely regulate international fellowships.[14-16]

Ethically, institutions must ensure equitable access for local physicians, transparent selection, and educational objectives consistent with patient safety. Balancing these concerns requires collaboration among ministries, immigration authorities, and professional associations.

Potential Global Recognition and Academic Diplomacy

The ability to attract international trainees is a recognized indicator of medical-education maturity. Nations such as Singapore, Thailand, and India have become regional hubs for subspecialty training due to harmonization with global standards and proactive academic diplomacy. If Indonesian institutions can provide accredited, transparent, and competency-based subspecialty programs, they could enhance regional cooperation and elevate Indonesia's academic reputation in cardiovascular medicine.

Beyond prestige, international fellows contribute to local innovation, joint research, and economic growth through tuition and service exchange. The broader impact includes strengthening Indonesia's soft power in global health and fostering collaboration at the ASEAN level. However, to achieve this, programs must be standardized, internationally benchmarked, and legally protected. Without such reforms, Indonesia risks remaining an educational consumer rather than a provider in the global medical ecosystem.

Policy Recommendations

Reform of subspecialty cardiology education in Indonesia requires multisectoral coordination. A unified terminology should clearly distinguish between academic Sp-2 programs and clinical fellowships while placing both under a national competency framework. An independent accreditation system—analogous to ACGME or EBAC—should be established under joint oversight by the KKI and KJPDI. Legal mechanisms must regulate the participation of foreign trainees, including visa, licensing, insurance, and institutional responsibility.

In the long term, Indonesia should pursue mutual-recognition agreements with international cardiology societies. Such reciprocity would enable exchange fellowships, collaborative research, and elevate Indonesia's role as a regional leader in cardiovascular education.

Limitation

This article is a narrative and policy-oriented analytical review that synthesizes publicly available regulatory documents, historical accounts, and international accreditation standards. No primary empirical data, surveys, or quantitative evaluations were collected. Accordingly, the analysis depends on the completeness and accuracy of existing policies and published literature. While the recommendations are grounded in comparative and normative frameworks, future empirical research—such as competency-based assessments, stakeholder interviews, systematic data collection from training centers, and quantitative evaluations of training outcomes and national workforce needs—is required to validate and refine the proposals presented in this manuscript.

Conclusion

Cardiology subspecialty education in Indonesia stands at a crossroads. While academic universities provide a robust scientific foundation, they lack the procedural dynamism and flexibility of hospital-based apprenticeship programs. The coexistence of university-based and hospital-based systems without a unified regulatory framework has resulted in ambiguity and fragmentation. To elevate Indonesia's position in global cardiovascular medicine, an integrated hybrid model—combining academic rigor, clinical apprenticeship, and international accreditation—is essential. Furthermore, legal reforms to support international trainees would enhance Indonesia's global recognition and reinforce the country's vision to become a center of excellence in cardiovascular training and innovation.

List of Abbreviations

ABIM	American Board Internal Medicine
ABMS	American Borad of Medical Specialties
ACC	American College of Cardiology
ACGME	Accreditation Council for Graduate Medical Education
AHA	American Heart Association
EBAC	European Board for Accreditation in Cardiology
ESC	European Society of Cardiology
KJPDI	Indonesian College of Cardiology
KKI	Indonesian Medical Council
LAM-PTKes	Indonesian Independent Accreditation Agency for Higher Education in Health
MIR	Médico Interno Residente
PERKI	Indonesian Heart Association
PIKI	*Pokja Intervensi Kardiologi Indonesia*
SCAI	Society for Cardiovascular Angiography & Interventions
Sp-2	*Spesialis-2*

Conflict of Interest Statement

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Editorial

Pulmonary Hypertension in Indonesia: An Urgent Call to Close the Gaps in Diagnosis and Care

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Abstract
Pulmonary Hypertension (PH) is a progressive disease marked by elevated pulmonary arterial pressure greater than 20 mmHg at rest, as measured by right heart catheterization. Despite the advancement of diagnostic and treatment in PH, diagnostic delay has been a challenge in Indonesia due to a lack of PH awareness, a fragmented referral system, limited diagnostic facilities, and PH-specific therapy, which leads to high mortality and rehospitalization. Guideline-directed combination therapy of PH is markedly constrained, with only PDE-5i and oral prostacyclin analogues covered by the Indonesian National Health Insurance (BPJS). True prevalence and incidence remain unknown nationally. Community support, a patient-based organization, also plays a crucial role in raising PH awareness, including promoting therapy adherence among PH patients. Creating PH centers is also in urgent need to execute an integrative and comprehensive management of PH. To close the gaps of diagnosis and care of PH patients, Indonesia should establish nationwide PH registries, expand access to echocardiography and catheterizations, broaden BPJS coverage on PH combination therapy, and develop PH centers and strengthen *Yayasan Hipertensi Pulmonal Indonesia* (YHPI, Pulmonary Hypertension Association of Indonesia) on addressing social burdens of PH patients.

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Introduction

Pulmonary hypertension (PH) remains a complex, progressive syndrome marked by elevated pulmonary arterial pressure and high morbidity and mortality. Diagnostic delay is a global issue, but its magnitude in Indonesia is especially alarming. Despite major advances in diagnostics and therapy worldwide, Indonesia continues to face structural barriers that cause significant delays in PH detection and treatment. International studies demonstrate that PH is frequently diagnosed 2–4 years after symptom onset[1], with a strong association with more advanced right ventricular dysfunction, higher mortality, and diminished long-term survival.[2] In Indonesia, these challenges are exacerbated by fragmented referral systems, a lack of routine screening, limited catheterization facilities, and restricted access to therapeutic options. Local data from the COHARD-PH registry, Indonesia's first adult congenital heart disease-related (CHD) PH registry, confirms that 77% of adults with CHD show echocardiographic signs of PH at first presentation, of which 66.9% are confirmed as pulmonary arterial hypertension (PAH) by right-heart catheterization (RHC).[3] These data reflect decades of underdiagnosis and delayed PH referral in children and adults.

Definition and Classification

Pulmonary hypertension is defined hemodynamically as a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg at rest, measured by RHC.[4-5] The current clinical classification classifies PH into five groups: (1) PAH; (2) PH associated with left heart disease; (3) PH associated with lung disease and/or hypoxia; (4) PH associated with pulmonary artery obstruction with Chronic Thromboembolic Pulmonary Hypertension (CTEPH) as its core; and (5) PH with unclear or multifactorial mechanisms. While this classification is universal, Indonesia faces difficulties with the classification due to limited diagnostic facilities.

Group 1 PAH in Indonesia is dominated by CHD-associated PAH. In the COHARD-PH registry, which enrolled 1,012 adults with septal defects and shunt lesions over a seven-year period, the majority of congenital heart lesions were secundum Atrial Septal Defects (ASD; 73.4%). Among patients with CHD-related PAH, 89.3% had ASD and 18.7% had already progressed to Eisenmenger syndrome at the time of diagnosis.[3] These data underscore the consequences of late CHD recognition and missed opportunities for early defect closure. Another important spectrum of group 1 PAH is idiopathic PAH, heritable PAH, associated PAH with drug and toxin, persistent PH of the newborn, and associated with several diseases, including connective tissue disease, HIV infection, portal hypertension, and schistosomiasis. Most of them are difficult to detect, either due to limited facilities for genetic and supported examination, as well as their high cost.

Group 2 PH is likely the most common PH subtype in Indonesia, given the high prevalence of hypertension, coronary disease, rheumatic heart disease, and heart failure. International data report 50-70% of PH prevalence in HFpEF and valvular heart disease.[4] However, systematic data are lacking, and few cardiac registries in Indonesia exclude this group from their registry.[6] This results in under-recognition of group 2 PH and limited understanding of its true burden.

Group 3 PH is highly relevant in Indonesia because of the country's substantial burden of Tuberculosis (TB), post-TB lung disease, Chronic Obstructive Pulmonary Disease (COPD), and interstitial lung disease. Post-TB lung disease, in particular, is increasingly recognized globally as a contributor to PH, yet PH screening in this population is not routinely performed in Indonesia.[6] Local data from Persahabatan Hospital reports that there were 30% PH among COPD patients examined by echocardiography, which needs to be confirmed by RHC.[7] This data is in line with our unpublished data of 14% TB-related-PH incidence in our hospital. Moreover, Hoeper et al reported a fairly large proportion of 30-48% of group 3 PH across the globe.[8] Therefore, we believe that this group might potentially become the largest number of PH in Indonesia.

Group 4 CTEPH remains vastly underestimated. International registry reports prevalence of 26-38 cases/million adults.[4] Ventilation–perfusion (V/Q) scanning, the key screening tool for CTEPH, is not widely available, and high-quality CT pulmonary angiography is limited to selected tertiary hospitals. Moreover, there is a lack of experts who are able to interpret these advanced imaging techniques. As a result, many potentially treatable CTEPH cases are never recognized.[6]

Epidemiology

Diagnostic delay is a major epidemiological challenge. In a large multinational survey, Small and colleagues reported a mean total delay of 17 months from first PAH symptoms to confirmed diagnosis, with patients seeing nearly three physicians on average and over 40% receiving at least one misdiagnosis.[1] Misdiagnoses frequently included asthma, COPD, and heart failure, reflecting the non-specific nature of PH early symptoms and limited awareness of PAH among primary care physicians.

The Indonesian situation is likely worse. In the COHARD-PH registry, adults with CHD typically presented in their mid-30s; a large proportion had been asymptomatic for decades and only sought care once dyspnea on exertion, fatigue, or cyanosis became limiting.[3] At first enrollment, 77.1% already had echocardiographic signs of PH, and 66.9% met invasive hemodynamic criteria for PAH.[3] These data point to a large, long-standing reservoir of undetected PAH that only becomes visible when the disease is advanced.

Nationally, the true prevalence and incidence of PH and PAH remain unknown. Indonesia does not yet have a nationwide PH registry, and the national health survey (RISKESDAS) does not include PH indicators.[4] Existing data come predominantly from single-center cohorts, such as COHARD-PH, and a limited number of specialized referral hospitals. Another single-center unpublished cohort registry in Universitas Indonesia Hospital reported 167 PH patients with distribution of 35% group 1 PH, 32% group II PH, 25% group III PH, and 7,1% group IV PH. A coordinated national registry effort by the Indonesia Pulmonary Hypertension (INA-PH) working group is currently taking place.

Diagnostic Limitations

Right-heart catheterization remains the gold standard for diagnosing and phenotyping PH for guiding treatment decisions. In Indonesia, however, access to RHC is limited to a small number of tertiary centers, and even in those, catheterization laboratories are often dominated by coronary interventions.[3,6] Facilities to measure pulmonary vascular resistance, perform vasoreactivity testing, and conduct serial hemodynamic monitoring are not uniformly available.

Transthoracic echocardiography is the main screening tool for PH, but access is uneven across health facilities in Indonesia. Operator expertise varies, and standardized PH-focused protocols, as recommended in international guidelines, are not consistently used.[6] Many patients with exertional dyspnea in primary care settings never undergo echocardiography at all.

Comprehensive risk stratification requires biomarkers such as NT-proBNP, exercise testing (6-minute walk distance), and detailed imaging of right ventricular structure and function, in addition to RHC hemodynamics. In the COHARD-PH registry, NT-proBNP was significantly higher in CHD-PAH compared with CHD without PAH (median 774 vs 121 pg/mL), and worse WHO functional class correlated with lower oxygen saturation, shorter walking distance, and more adverse hemodynamics.[3] Yet NT-proBNP assays and structured 6-minute walk testing are still not universally available across Indonesian centers.

Mortality

Pulmonary hypertension mortality varies across the globe. Recent global trend of PH mortality from 54 countries during 2001 to 2019 reports an average of 3-year crude mortality (per 100.000) of 1.6, with Georgia as the highest death of 16.51 and Nicaragua as the lowest of 0.13. This study also reported a global reduction of 3 years' crude mortality from 2.1 in 2001 to 1.6 in 2019. This reduction is due to the advancement of PH diagnosis and treatment. However, delayed diagnosis has direct prognostic implications for mortality. In a recent study of PAH patients, Kubota and colleagues demonstrated that longer time from symptom onset to diagnosis correlated with higher BNP, worse right ventricular function indices, and a significantly higher rate of death or PAH-related hospitalization during follow-up.[2] Patients diagnosed within three months of symptom onset were more likely to have lower mortality compared to those with delayed diagnosis.[2] These findings echo the broader international experience that untreated or late-treated PAH carries a poor long-term survival, particularly for patients diagnosed in WHO functional class III–IV. In Indonesia, CHD-PAH patients with worse functional class in COHARD-PH had lower oxygen saturation, shorter walking distance, higher NT-proBNP, and more severe hemodynamic derangements[3], all of which are established predictors of mortality.

Studies from the United States and Europe highlight the superiority of apprenticeship-based subspecialty education in achieving procedural competency and in preparing for independent practice.[6,13] The Accreditation Council for Graduate Medical Education (ACGME) and the European Society of Cardiology (ESC) frameworks require fellows to demonstrate mastery in procedural skills, clinical decision-making, and academic output before board certification.

Management

International guidelines recommend a risk-stratified approach to PAH therapy, with early use of combination regimens that target the endothelin, nitric oxide, prostacyclin pathways, and Activin-A signal inhibition. For most of the newly diagnosed patients, upfront dual therapy with an Endothelin Receptor Antagonist (ERA) plus a Phosphodiesterase-5 inhibitor (PDE5i) is now standard, whereas high-risk patients may benefit from initial triple therapy.

In Indonesia, however, therapeutic options are markedly constrained. There are two PAH-targeted drugs that are widely available, including a PDE-5 inhibitor (sildenafil) and oral prostacyclin analogues (beraprost), which fortunately currently reimbursed by the Indonesian National Health Insurance (BPJS). Inhaled prostacyclin analogues (iloprost) and ERA agents such as macitentan and ambrisentan require out-of-pocket payment.[6] Even further, ambrisentan is currently only accessible through a limited special-access program in Universitas Indonesia Hospital. These constraints prevent many Indonesian patients from receiving guideline-directed combination therapy.

Despite these limitations, local studies have shown that sildenafil-based regimens can improve symptoms, functional capacity, and quality of life in CHD-related PAH.[4] Structured cardiopulmonary rehabilitation and supervised exercise programs have also been shown to add benefits when combined with pharmacologic therapy.[6] Scaling these relatively low-cost interventions could provide significant improvements in outcomes, even before broader drug access is achieved.

Several types of PH patients might benefit from an interventional strategy. Patient with CHD should undergo their respective CHD repair if possible. However, they might miss the window of repair due to the development of CHD-PAH, which, unfortunately, is in line with the trend of more severe forms of CHD-PAH findings in COHARD-PH. Therefore, early screening for CHD is mandatory to prevent the development of CHD-PAH in the future.

Another type of PH that might benefit from an interventional strategy is group IV CTEPH. Robust international data revealed that the surgical procedure of Pulmonary Endarterectomy (PEA) and Interventional Balloon Pulmonary Angioplasty (BPA) reduced pulmonary vascular resistance and improved CTEPH mortality and morbidity.[10] Pulmonary endarterectomy is indicated for CTEPH with proximal thrombus in the main, interlobar, or proximal part of the segmental pulmonary artery, while BPA is indicated for cases with difficulty in performing PEA or segmental-subsegmental pulmonary artery. Despite these positive interventional outcomes, Indonesia is not yet able to offer these interventional strategies due to limited facilities and interventional experts.

Community Services and PH Centers

Beyond drugs and diagnostics, community and institutional structures play a crucial role in PH care. In Indonesia, the patient-based organization *Yayasan Hipertensi Pulmonal Indonesia* (YHPI) has emerged as an important partner in raising awareness, supporting patients and families, and promoting adherence and follow-up.[6] Such organizations help address the psychosocial burden of a chronic, life-limiting disease that is often diagnosed late.

At the health-system level, there is an urgent need to develop and accredit dedicated PH centers of excellence. International guidelines recommend that PH patients be managed in expert centers with access to RHC, advanced echocardiography, V/Q scanning or high-resolution CT, biomarker testing, exercise testing, and a multidisciplinary team including cardiology, pulmonology, rheumatology, imaging, and rehabilitation. Currently, only a handful of Indonesian institutions approach this standard.

Conclusion

Pulmonary hypertension in Indonesia remains underdiagnosed, underestimated, and undertreated. Structural limitations in diagnostic capacity and restricted access to PAH-specific therapies further amplify the burden.

Indonesia now has an opportunity and a responsibility to close these gaps. Priorities include establishing nationwide PH registries, integrating

PH indicators into national health surveys, expanding access to echocardiography and RHC, hopefully broadening BPJS coverage to include combination PAH therapy, developing PH centers of excellence, and strengthening collaboration with patient organizations. With coordinated action from clinicians, policymakers, and patient groups, it should be possible to shorten the diagnostic journey, improve access to effective treatment, and ultimately change the trajectory of PH in Indonesia.

List of Abbreviations

ABIM	American Board Internal Medicine
ACGME	Accrediation Council for Graduate Medical Education
ASD	Artial Septal Defects
BPA	Balloon Pulmonary Angioplasty
BPJS	Indonesian National Health Insurance
COPD	Chronic Obstructive Pulmonary Disease
CHD	Congenital Heart Disease
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
ERA	Endothelin Receptor Antagonist
ESC	European Society of Cardiology
INA-PH	Indonesia Pulmonary Hypertension
PAH	Pulmonary Arterial Hypertension
PDE5i	Phosphodiesterase-5 inhibitor
PEA	Pulmonary Endarterectomy
PH	Pulmonary Hypertension
RHC	Right-Heart Catheterization
RISKESDAS	National Health Survey
YHPI	Pulmonary Hypertension Association of Indonesia

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, analyses, or conclusions presented in this manuscript.

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Original Article

Electrocardiographic Remodeling Before and After Interventional Closure of Secundum Atrial Septal Defects

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Abstract

Background: Secundum atrial septal defect (ASD) is a common congenital cardiac lesion that produces left-to-right shunting and chronic right-sided volume overload, leading to geometric and electrical remodeling. Electrocardiography (ECG) provides a simple, non-invasive method to detect ASD-related electrical abnormalities and to assess reverse remodeling following defect closure. This study aimed to evaluate the short-term (<24 hours) and long-term (>6 months) electrical changes after Secundum ASD closure.

Methods: We conducted a prospective, single-center, observational cohort study of Secundum ASD patients who underwent percutaneous or surgical closure at RSUP Dr. Wahidin Sudirohusodo. A total of 54 eligible subjects were included. ECG measurements were performed at admission (pre-closure), within 24 hours post-closure, and at more than 6 months post-closure. ECG parameters were statistically compared using a paired T-test or Wilcoxon signed-rank test.

Results: Of the 54 ASD patients, the majority were female (66.7%) and adults (68.5%), with 33 patients (61.1%) undergoing percutaneous closure. Significant reductions were observed across all ECG parameters within 24 hours post-closure, including P-wave amplitude (0.19 ± 0.04 to 0.11 ± 0.03 mV; $p<0.001$), P-wave duration (97.78 ± 11.94 to 75.35 ± 13.36 ms; $p<0.001$), PR interval (182.89 ± 26.47 to 156.83 ± 21.81 ms; $p<0.001$), QRS duration (112.97 ± 14.84 to 88.31 ± 14.43 ms; $p<0.001$), QRS axis (107.94 ± 23.00 to 95.25 ± 24.62°; $p<0.001$), QTc interval (403.84 ± 30.85 to 396.80 ± 33.76 ms; $p=0.017$), and R-wave amplitude in V1 (0.74 ± 0.35 to 0.53 ± 0.24 mV; $p<0.001$). From <24 hours to >6 months post-closure, most parameters continued to decline significantly, with the exception of P-wave amplitude, which remained stable ($p=0.321$).

Conclusions: Interventional closure of Secundum ASD induces marked electrical reverse remodeling, evident both within hours of the procedure and during long-term follow-up. These findings underscore the value of ECG as an accessible and informative modality for tracking post-intervention cardiac recovery.

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Keywords: Secundum atrial septal defect, electrocardiogram, reverse remodeling, congenital heart disease, percutaneous closure, surgical closure

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Introduction

Atrial Septal Defect (ASD) is the second most common non-cyanotic congenital heart defect, with Secundum ASD accounting for over 80% of cases.[1] It causes a persistent left-to-right shunt, leading to chronic right-sided volume overload and progressive structural and electrical remodeling of the right atrium and ventricle.[2] Early surgical or device closure can reverse these changes by terminating the atrial shunt. However, many ASD patients remain asymptomatic until adulthood and are often diagnosed incidentally during routine cardiovascular assessment.[3]

Electrocardiography (ECG) is a convenient non-invasive tool for evaluating remodeling in ASD patients, as it is routinely performed before and after intervention. Characteristic ECG changes in ASD include Right Bundle Branch Block (RBBB), Right Ventricular Hypertrophy (RVH), Right Atrial Enlargement (RAE), Right Axis Deviation (RAD), the Crochetage sign, and, in more advanced cases, right ventricular strain patterns[4], reflect right-sided overload. Comparing ECG parameters before and after closure can help assess the effect of intervention on remodeling, with serial improvements serving as quantitative markers of recovery in cardiac structure and conduction. Prior studies, including those by Bernardo et al., have shown that ECG parameters correlate with defect severity and can track reverse remodeling after percutaneous or surgical closure.[5]

Despite these findings, evidence supporting ECG as a tool to assess reverse electrical remodeling after ASD closure remains limited. To date, no data are available for the Indonesian ASD population. This study aims to evaluate ECG parameter changes in Indonesian patients with Secundum ASD who underwent interventional closure. The findings may support the development of an ECG-based framework for monitoring postprocedural electrical remodeling and improving long-term management after ASD closure.

Methods

This study employed a prospective, observational pre–post cohort study to evaluate changes in ECG parameters in patients with Secundum ASD following transcatheter or surgical closure. Data were obtained from patients who underwent Secundum ASD closure at the Integrated Heart Center, Dr. Wahidin Sudirohusodo General Hospital. ECG parameters were assessed within 24 hours and 6 months post-intervention. Patients with concomitant congenital heart disease, alternative causes of pulmonary hypertension, or significant pre-existing arrhythmias were excluded.

Statistical analyses were performed using paired t-tests for normally distributed variables and Wilcoxon signed-rank tests for non-normally distributed variables. The study protocol was approved by the Health Research Ethics Committee

Table 1. Baseline patient characteristics (categorical variables).

Variable	Total (n=54)	Percentage
Gender		
Male	18	33.3
Female	36	66.7
Age Group		
> 16 years old	38	70.3
≤ 16 years old	16	29.7
Intervention Method		
Percutaneous	33	61.1
Surgical	21	38.9
Pre-intervention Medication		
Furosemide	21	38.9
ACE-Inhibitor/ARB	5	9.2
Beta Blocker	11	20.3
MRA	14	25.9
PDE-5 Inhibitor	4	7.4
Prostacyclin Analogue	10	18.5
Digitalis	4	7.4
Pre-intervention Medication		
ASA	10	18.5
P2YI2 Inhibitor	23	42.6

Furosemide	12	22.2
ACE-Inhibitor	3	5.5
Beta Blocker	5	9.2
MRA	10	18.5
PDE-5 Inhibitor	3	5.5
Prostacyclin Analogue	8	14.8
Digitalis	2	3.7

ACE-I: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin II Receptor Blocker; MRA: Mineralocorticoid Receptor Antagonist; PDE-5: Phosphodiesterase-5; ASA: Acetylsalicylic Acid.

of the Faculty of Medicine, Universitas Hasanuddin, and Dr. Wahidin Sudirohusodo General Hospital (Approval No. 423/UN4.6.4.5.31/PP36/2020; No. UH21060397).

Results

A total of 54 patients with Secundum ASD who underwent interventional closure were included in the analysis; nine patients were lost to follow-up at the 6-month evaluation. Baseline characteristics of the study population are summarized in Tables 1 and 2.

In the comparison between pre-closure and the early post-closure period (<24 hours), all evaluated ECG parameters demonstrated significant reductions: P-wave amplitude (0.19 ± 0.04 vs. 0.11 ± 0.03 mV; $p < 0.001$), P-wave duration (97.78 ± 11.94 vs. 75.35 ± 13.36 ms; $p < 0.001$), PR interval (182.89 ± 26.47 vs. 156.83 ± 21.81 ms; $p < 0.001$), QRS duration (112.97 ± 14.84 vs. 88.31 ± 14.43 ms; $p < 0.001$), QRS axis (107.94 ± 23.00 vs. 95.25 ± 24.62°; $p < 0.001$), QTc interval (403.84 ± 30.85 vs. 396.80 ± 33.76 ms; $p = 0.017$), and R-wave amplitude in V1 (0.74 ± 0.35 vs. 0.53 ± 0.24 mV; $p < 0.001$).

Table 2. Baseline characteristics of the study participants (numerical variables).

Variables	Min/Max (n = 54)	Mean ± SD or Median (Q1 – Q3)
Age (years)	2/58	24.6 ± 13.3
Body weight (kg)	11/80	45.1 ±16.1
Body height (cm)	83/179	148.9 ± 20.2
Body mass index (kg/m^2)	11.57/35.09	19.6 ± 4.5
Body surface area (m^2)	0.49/1.91	1.4 ± 0.3
Defect size (mm)		
TTE	8/43	20.7 ± 7.6
TEE	12/47	25.3 ± 8.1
Flow ratio	1.55/6.90	3.4 ± 1.5
Peripheral O_2 Saturation (%)	92/100	97.2 ± 1.9
mPAP (mmHg)	20/61	37.4 ± 9.9
PVR (WU)	0.20/4.50	2.3 ± 1.3
PVRI (WU/m^2)	0.12/3.39	1.7 ± 0.8
Haematology		
Leukocyte (*10^3/μL)	2.90/17.20	8.8 ± 2.7
Haemoglobin (gr/dL)	10.60/16/60	13.5 ± 1.5
Platelet (*10^3/μL)	150/527	296.3 ± 76.4
Renal functions		
Ureum (mg/dL)	10/57	20.9 ± 7.7
Creatinine (mg/dL)	0.10/1/06	0.6 ± 0.2
Liver function		
SGOT (U/L)	10/96	22.0 (17.8 – 29.3)

SGPT (U/L)	7/259	16.5 (12.0 – 25.3)
Coagulation		
PT (sec)	9.3/12.4	10.8 ± 0.7
INR	0.87/1.21	1.0 ± 0.07
APTT (sec)	22.3/36.3	28.2 ± 2.9
Electrolyte		
Natrium (mmol/L)	134/146	141.4 ± 2.6
Kalium (mmol/L)	3.1/4.7	4.0 ± 0.4
Chloride (mmol/L)	98/113	105.3 ± 3.1

Values are means ± SD or median (Q1-Q3). TTE: Trans-thoracal Echocardiography; TEE: Trans-esophagal Echocardiography; mPAP: mean Pulmonary Artery Pressure, PVR: Pulmonary Vascular Resistance; PVRI: Pulmonary Vascular Resistance Index; SGOT: Serum Glutamate Oxalat Transaminase; SGPT: Serum Glutamate Pyruvat Transaminase; PT: Prothrombin Time; INR: International Normalized Ratio; aPTT: activated Partial Tromboplastin Time, WU: Wood Units.

Table 3. Comparison of ECG parameters before and 24-hour after intervention.

ECG Parameters	Pre-intervention (n = 54)	<24 hour post intervention (n = 54)	ECG changes (Δ) mean difference (95% CI)	p-value
P wave amplitude (mv)	0.19 ± 0.04	0.12 ± 0.03	0.07 (0.06 – 0.08)	<0.001*
P wave duration (ms)	97.8 ± 11.9	75.4 ± 13.4	22.4 (19.6 – 25.3)	<0.001*
PR interval (ms)	182.9 ± 26.5	156.8 ± 21.8	26.1 (21.9 – 30.2)	<0.001*
QRS duration (ms)	113.0 ± 14.8	88.3 ± 14.4	24.7 (20.9 – 28.5)	<0.001*
QRS axis (°)	107.9 ± 23.0	95.3 ± 24.6	12.7 (10.1 – 15.2)	<0.001*
QTc interval (ms)	403.8 ± 30.9	396.8 ± 33.8	7.0 (0.5 – 13.6)	0.035*
R wave V1 amplitude (mv)	0.74 ± 0.35	0.53 ± 0.24	0.21 (0.14 – 0.28)	<0.001*

*p<0.05. Values are mean ± SD. Analyses were done using dependent t-test.

Hypothesis testing for pre- and post-intervention ECG differences is presented in Tables 3 and 4. When comparing the early (<24 hours) and late (>6 months) post-closure periods, these reductions were largely sustained across parameters. The only exception was P-wave amplitude (0.121 ± 0.03 vs. 0.119 ± 0.03 mV; p = 0.321), which showed no significant interval change.

We subsequently performed a subgroup analysis to compare changes in ECG parameters before and after closure intervention, specifically P-wave duration, P-wave amplitude, and PR interval, between adult and pediatric patients, as illustrated in Figure 1. Statistically significant reductions were observed in all assessed ECG parameters in both adults and pediatric patients (p < 0.001 for all comparisons).

Table 4. Comparison of ECG parameters 24-hour vs. 6-month after intervention.

ECG Parameters	<24 hour post intervention (n = 45)	6-month post intervention (n = 45)	ECG changes (Δ) mean difference (95% CI)	p-value
P wave amplitude (mv)	0.12 ± 0.03	0.12 ± 0.03	0.001 (-0.005 – 0.007)	0.779
P wave duration (ms)	75.1 ± 13.8	69.5 ± 11.8	5.6 (3.4 – 7.8)	<0.001*
PR interval (ms)	155.5 ± 22.8	148.3 ± 19.3	7.2 (3.1 – 11.4)	<0.001*
QRS duration (ms)	89.7 ± 14.0	85.4 ± 14.2	4.4 (2.2 – 6.5)	<0.001*
QRS axis (°)	94.8 ± 23.6	81.3 ± 22.9	13.5 (8.4 – 18.6)	<0.001*
QTc interval (ms)	396.2 ± 33.7	384.4 ± 37.9	11.8 (0.6 – 23.0)	0.040*
RV1 amplitude (mv)	0.51 ± 0.25	0.33 ± 0.22	0.18 (0.13 – 0.24)	<0.001*

*p<0.05. Values are mean ± SD. Analyses were done using dependent t-test.

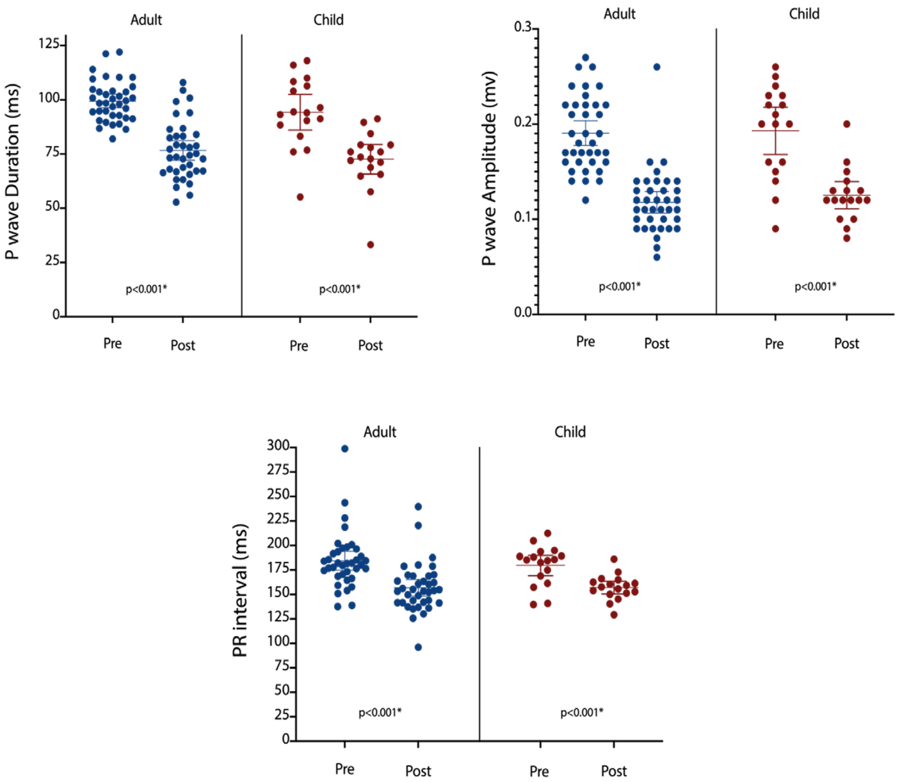

Figure 1. Subgroup analysis comparing ECG changes before and after ASD closure in adult vs. pediatric patients.

Discussion

This study demonstrates that closure of Secundum atrial septal defects induces rapid and sustained improvements in electrocardiographic parameters, reflecting the underlying structural and electrical remodeling of the right heart. Our findings highlight the dynamic interplay between anatomical reverse remodeling and electrophysiological normalization, emphasizing the utility of ECG not only as a diagnostic tool but also as a practical, non-invasive method to monitor post-procedural cardiac recovery. By evaluating both early (<24 hours) and late (>6 months) post-closure changes, this study provides novel insights into the timeline and magnitude of electrical remodeling, with important implications for patient management and long-term follow-up

Electrocardiography is increasingly recognized not only as a diagnostic tool but also as a valuable modality for guiding and assessing outcomes in patients with Secundum ASD following intervention.[6–8] Post-procedural ECG changes reflect the underlying anatomical and electrical remodeling that occurs after normalization of the right heart's volume load. This process, termed reverse remodeling, underpins the clinical benefits observed after ASD closure and begins almost immediately once the hemodynamic burden is relieved.[6-9,10]

The link between structural and electrical remodeling is well established. Echocardiographic studies consistently demonstrate that ASD closure results in rapid and significant reductions in right atrial and right ventricular dimensions.[9,11-12] For example, Bigdelu et al. (2023) reported marked decreases in right heart chamber size and pulmonary artery pressures within six months post-closure. As the right-sided chambers shrink, mechanical stretch on myocardial and conduction fibers is relieved, allowing normalization of conduction pathways, which is directly reflected on the ECG.[13] The reductions in QRS duration [6,8,13], leftward shift of the QRS axis[7,14], and decreased R-wave amplitude in V1[6,7] observed in our cohort correspond anatomically to the decreased right ventricular size and normalization of interventricular septal motion seen on echocardiography.

Advanced imaging modalities, such as cardiac magnetic resonance (CMR), have further corroborated this relationship. Mansour et al. (2022) demonstrated significant reductions in right atrial and ventricular volumes three months after ASD closure, which correlated closely with electrical remodeling observed on ECG.[6] Our observation of a significant reduction in P-wave amplitude and duration within 24 hours post-closure reflects the rapid unloading and decrease in right atrial size. While P-wave duration continued to improve at the >6-month follow-up, amplitude did not demonstrate further significant change, suggesting that the primary geometric remodeling occurs almost immediately. These findings are consistent with prior reports by Kamphuis et al. (2019).[7] Recent studies have also highlighted the clinical relevance of P-wave dispersion, the difference between the maximum and minimum P-wave duration, as a marker of intra-atrial conduction heterogeneity.[6-7,14] Evidence indicates that P-wave dispersion decreases significantly following ASD closure, potentially predicting a lower long-term risk of atrial arrhythmias.[6,15-16]

The observed reduction in PR interval aligns with previous studies and reflects improved atrioventricular conduction as the right atrial geometry normalizes.[6,14] Likewise, the progressive shortening of QRS duration at both early and late follow-up points indicates resolution of right ventricular conduction delay, often manifesting as a right bundle branch block pattern pre-closure.[14] These electrical improvements are directly attributable to the reduction in right ventricular size and pressure, resulting in more synchronous and efficient ventricular depolarization.[7,16]

The observed leftward shift of the QRS axis and the reduction in R-wave amplitude in lead V1 represent classic electrocardiographic markers of regressing right ventricular hypertrophy.[7,16] These electrical changes closely reflect structural reverse remodeling of the right ventricle, as documented in echocardiographic and CMR follow-up studies after ASD closure.[6,12] For instance, Saedi et al. (2022) reported significant improvements in right ventricular function using advanced echocardiographic parameters, including strain and strain rate, shortly after device closure, providing a functional correlate for the electrical changes observed. Resolution of these ECG abnormalities serves as a robust indicator of procedural success and is associated with favorable long-term outcomes.[17]

Our results underscore the utility of ECG as a straightforward, readily available, and informative method for tracking beneficial cardiac remodeling after ASD closure. Future prospective, multicenter investigations combining ECG and echocardiographic evaluations are needed to better define the relationship between structural and electrical reverse remodeling and to enhance post-procedural patient care.

This study has several limitations. As a single-center study, it is inherently susceptible to selection bias. A major limitation is the lack of concurrent long-term echocardiographic data to directly correlate with the observed ECG changes; such correlations would have strengthened the link between electrical and structural reverse remodeling and represent an important avenue for future research. Additionally, more advanced ECG parameters, including P-wave dispersion and T-peak to T-end interval, were not analyzed. These metrics have been shown in recent studies to provide valuable prognostic information regarding arrhythmia risk following ASD closure.

Conclusion

Interventional closure of Secundum ASD induces significant and sustained electrical reverse remodeling, as demonstrated by improvements across nearly all ECG parameters. These changes occur immediately post-procedure and continue to evolve over the long term. Our findings highlight ECG as a simple, widely accessible, and valuable tool for monitoring favorable cardiac remodeling following ASD closure.

List of Abbreviations

aPTT	activated Partial Thromboplastin Time
ASD	Atrial Septal Defect
CMR	Cardiac Magnetic Resonance
ECG	Electrocardiography
INR	International Normalized Ratio
mPAP	mean Pulmonary Artery Pressure
PT	Prothrombin Time
PVRI	Pulmonary Vascular Resistance Index
PVR	Pulmonary Vascular Resistance
RAD	Right Axis Deviation
RAE	Right Atrial Enlargement
RBBB	Right Bundle Branch Block
RVH	Right Ventricular Hypertrophy
SGOT	Serum Glutamate Oxalat Transaminase
SGPT	Serum Glutamate Pyruvat Transaminase
TEE	Trans-esophageal Echocardiography
TTE	Trans-thoracic Echocardiography
WU	Wood Units

Ethical Clearance

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No studies with animals was performed by any of the authors of this article.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

YP, AHA, and ARB conceived the initial idea. ARB, YP, and MA conducted data collection. ARB and AQ managed the data, performed data cleaning, and conducted the statistical analysis. ARB prepared the initial manuscript. AQ made critical revisions, additional data analysis, and prepared the final submitted manuscript. YP, AHA, II, MA, TDN, and IM reviewed and provided feedback for further revisions. All contributing authors approved the final draft.

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Conflict of Interest

All of the authors declare that they have no conflict of interest.

Availability of Data and Materials

The datasets generated and/or analysed during this study are not publicly available since they contain private data owned by multiple centers which were involved in this study. However, subject data are available from the corresponding author on reasonable request.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, ChatGPT (OpenAI, San Francisco, CA, USA) was used to assist with paraphrasing, proofreading, and improving language clarity. The authors reviewed and edited all content generated by the tool, and take full responsibility for the final version of the manuscript.

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Original Article

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

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Abstract
Background: The Coronary Artery Calcium Score (CACS) is widely used to assess coronary atherosclerosis. However, its utility in reflecting systemic atherosclerosis burden remains limited. Notably, no prior study has investigated the relationship between CACS and plaque morphology in the lower extremities. This research aims to address this gap by examining the association between CACS, Ankle-Brachial Index (ABI), and peripheral arterial plaque morphology as assessed by duplex ultrasonography.
Methods: One hundred consecutive patients who had lower extremity Doppler ultrasound and coronary CT angiography between November 2024 and May 2025 were included in this single-center, cross-sectional study. CACS was calculated using the Agatston method. ABI and Doppler-based plaque morphology were evaluated to determine the presence, severity, and complexity of Peripheral Artery Disease (PAD).
Results: CACS and ABI showed a moderately negative association ($r = -0.628$, $p < 0.001$), whereas CACS and plaque morphology showed a moderately positive correlation ($r = 0.619$, $p < 0.001$). CACS showed good discriminatory power for detecting peripheral plaque (AUC = 0.765), and excellent performance in identifying advanced plaque types (III-IV) at a threshold of 478.5 HU (AUC = 0.852; sensitivity 68%; specificity 91.7%).
Conclusions: This is the first study to demonstrate a direct association between coronary calcium burden and plaque morphology in the lower extremities. These findings highlight the potential role of CACS as a surrogate marker for systemic atherosclerosis and a valuable tool for identifying asymptomatic individuals who may benefit from peripheral arterial evaluation.

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Keywords: Coronary Artery Calcium Score, Peripheral Artery Disease, Plaque Morphology, Ankle-Brachial Index, Atherosclerosis

Introduction

Atherosclerosis is a systemic disease that affects the entire vascular system without boundaries, with a diffuse burden that extends beyond the coronary arteries. However, research and clinical interventions have overwhelmingly focused on Coronary Artery Disease (CAD), often at the expense of other equally significant manifestations, such as Peripheral Artery Disease (PAD).[1-2] Although PAD is a sign of extensive atherosclerosis and bears an equally high risk of cardiovascular morbidity and mortality, CAD is unquestionably a life-threatening condition. Consequently, the dominance of CAD research has led to PAD research–a clear indicator of systemic vascular dysfunction–remaining under-recognized, despite its devastating consequences.[3-4] More specifically, the link between coronary calcium burden and peripheral plaque morphology remains under-explored. More than 200 million people worldwide suffer from PAD, which can manifest as atypical leg discomfort, critical limb ischemia, intermittent claudication, and sporadic acute limb ischaemia.[1-2,5-6] Beginning with endothelial degradation and the atherosclerotic process, PAD releases inflammatory factors until calcium and lipid particles are deposited in the artery's intima layer, creating calcification. Thus, calcium plays a vital role as a marker of atherosclerosis burden.[7] One technique for identifying PAD is the assessment of the Ankle-Brachial Index (ABI), a measure of the lower limb blood vessels' functional capacity.[7-8] Despite underlying PAD, arterial calcification and advanced plaque characteristics in patients with diabetes mellitus or chronic renal disease can cause deceptively normal or high ABI results. This phenomenon may occur because arterial stiffness or non-compressibility masks true perfusion deficits that might only be revealed through exercise ABI testing. In such cases, duplex ultrasonography offers added diagnostic value by visualizing the location, severity, and plaque morphology, allowing for better assessment of PAD progression.[9–11]

A noninvasive imaging method called Coronary Artery Calcium Scoring (CACS) evaluates coronary artery calcification.[7,12] Derived using the Agatston method, CACS is able to provide predictive value for cardiovascular mortality and adverse events.[7,12-13] Recent studies have presented promising data on the involvement of CACS in the presence and severity of coronary atherosclerotic lesions. Actually, a higher Syntax score, a metric used to assess CAD complexity, was independently associated with higher CACS levels.[14–19] Despite the established use of CACS in assessing coronary atherosclerosis, its extrapolation to other vascular territories remains limited. PAD often remains undiagnosed, especially in asymptomatic individuals. Although CACS is now widely performed and routinely used to assess coronary arteries, its potential role in evaluating lower extremity arteries, especially plaque morphology, remains largely unexplored. It may serve as a valuable tool for identifying patients who would benefit from further assessment of lower-limb arterial disease.[18]

This study aims to bridge the gap by evaluating the relationship between CACS and the presence of PAD, as assessed through ABI measurements and Doppler ultrasonography of the lower extremity arteries. By integrating functional and imaging-based evaluations of peripheral circulation, this study seeks to provide a more comprehensive understanding of systemic atherosclerosis and its clinical implications.

Methods

Study Design, Ethical Consideration, and Sample Size

One hundred consecutive patients who underwent coronary CT angiography at Dr. Hasan Sadikin General Hospital in Bandung, Indonesia, between November 2024 and May 2025 were included in a single-center, cross-sectional, observational analytic study. In order to reduce selection bias and more accurately represent the real-world clinical population, consecutive sampling was employed. This approach is commonly applied in observational studies to enhance external validity while maintaining feasibility in routine clinical practice. Retrospective data collection was done using the patient's medical record and the hospital's imaging registry. The Dr. Hasan Sadikin General Hospital in Bandung, Indonesia's Research Ethics Committee provided ethical permission (DP.04.03/D.XIV.6.5/425/2024) with waiver of informed consent for this retrospective chart review, in accordance with the principles of the Declaration of Helsinki. No patient re-contact was performed for this retrospective analysis.

Inclusion and Exclusion Criteria

The study's inclusion criteria included: (1) patients treated at Dr. Hasan Sadikin General Hospital who were included in the time period undergoing Coronary CT Angiography examination. (2) Patients with complete medical records, including CACS, ABI, and duplex ultrasonography of lower extremities measurements. (3) Patients (or their legal representatives) must provide written informed permission to take part in the study. The following were the study's exclusion criteria: (1) incomplete medical record and registry data, (2) known PAD defined as prior formal diagnosis of PAD based on clinical symptoms (claudication, critical limb ischemia), prior lower extremity revascularization, or documented ABI <0.9 on prior lower extremity revascularization, or documented ABI <0.9 on previous examinations, and (3) patients who refused to provide written informed consent.

Data Collection Methods

Data were retrospectively obtained from the patient's Medical Records (MR) and imaging registry database. Variables collected included patient demographic data (e.g., age and gender) and risk factors (e.g., smoking status, menopause, family history, and obesity). Patient's objective clinical examination was collected, including physical examination (blood pressure in both arms and both legs) and Body Mass Index (BMI). Laboratory data on admission (Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, fasting blood glucose, ureum, creatinine and eGFR), Coronary CT Angiography report and duplex ultrasonography of lower extremities report.

Coronary CT imaging was performed using Siemens Scenario® preliminary multislice CT (128 slices, single source) with electrocardiogram-gated acquisition. Images were obtained after intravenous bolus injection of 70 mL of Ultravist. Data were transferred off line for 3D Multiplanar Reconstruction (MPR) and Maximum Intensity Projection (MIP) with post-processing of 75% of the cardiac cycle and a Dose Length Product (DLP) of 666.86 mGy. CACS acquisition was performed using a 3-mm slice thickness with retrospective ECG gating. The software (GE Healthcare SmartScore® Version 4.0) was used to determine the coronary artery calcium score. The Agatston technique was used to determine the calcium score level based on the presence of lesions that are automatically identified and colored by the software with an area larger than 1 mm^2 and a peak intensity more than 130 Hounsfield Units (HU). Using the Agatston method, the total CACS was determined for each marked lesion. During the procedure, all patients showed sinus rhythm, and patients with a heart rate above 60 beats per minute received beta-blockers to improve image quality.

ABI measurements were obtained after participants rested in a supine position for at least 5 minutes. Systolic blood pressure was recorded in both arms and both ankles using appropriately sized cuffs. In the lower limbs, pressure was measured over the dorsalis pedis and posterior tibialis arteries using a Philips Epiq CVx® machine equipped with a 12-3 MHz linear-array vascular transducer. The ABI was calculated by dividing the highest ankle systolic pressure by the highest brachial systolic pressure. The lower ABI value from both legs was used for analysis, with values below 0.9 or above 1.4 considered abnormal.[7] In addition, lower-extremity arterial evaluation was performed with the same ultrasound system. Duplex Doppler imaging enabled high-resolution visualization of the characterization of plaque morphology. The examination included a detailed assessment of the common femoral artery, proximal, mid, and distal segments of the Superficial Femoral Artery (SFA), as well as the popliteal artery and the anterior and posterior tibial arteries.[20]

Patients with a history of visits or treatment at Dr. Hasan Sadikin General Hospital will have data in their medical records, allowing their comorbidities to be traced. Patients who have possible comorbidities based on anamnesis (e.g., history of hypertension, diabetes mellitus, history of taking antihypertensive drugs or diabetes mellitus drugs), physical examination, or laboratory results will be consulted with an appropriate consultant or specialist for diagnosis. All data collected by cardiology residents during admission or during hospitalization will be checked and validated by the cardiology consultant and researchers. Missing data will be traced, but if not found or considered incomplete, then excluded from the study

Operational Definitions and Outcome Measures

CACS was performed using the Agatston method, which quantifies the total burden of coronary calcification by summing the area and peak attenuation (measured in Hounsfield units) of all calcified lesions within the coronary arteries. The total CACS was subsequently categorized into four groups: mild (CACS 1-100), moderate (CACS 101-300), severe (CACS 301-999), and extensive (CACS ≥1000).[13] The ABI was calculated by dividing the systolic blood pressure measured at the ankle by that of the upper arm, with values interpreted according to the 2017 European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of peripheral arterial disease. A normal ABI was defined as 0.9-1.4.[21]

Plaque characterization in lower extremity arteries was performed using duplex ultrasonography and classified according to grayscale and Doppler features, using a modified echogenicity-based system adapted from Sztajzel et al. (2005).[22] This classification system has been validated in carotid artery assessment and adapted for peripheral arteries.[23] No plaque was defined as a regular arterial segment with smooth walls, homogenous echogenicity, and laminar flow. Type I plaques were homogenously hypoechoic, indicating soft, lipid-rich content. Type II plaques showed predominantly hypoechoic areas mixed with echogenic spots, suggesting a combination of lipid and fibrous tissue. Type III plaques were predominantly echogenic with mixed echogenic and hypoechoic areas, reflecting fibrous or partially calcified tissue. Type IV plaques were uniformly hypoechoic with posterior acoustic shadowing, consistent with dense calcification. All Doppler evaluations were performed by a consultant cardiologist with expertise in vascular medicine, ensuring consistent, expert-level assessment. Nevertheless, this study did not include assessments of inter- and intra-observer variability, which should be acknowledged as a limitation. This classification supports a more detailed evaluation of atherosclerotic burden beyond the ABI.[22,23]

The medical history of all patients was recorded in detail. Systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg were considered indicators of hypertension. A fasting blood glucose level of >126 mg/dL was used to diagnose diabetes mellitus. Dyslipidemia was defined as total cholesterol ≥200 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL, and/or triglycerides ≥150 mg/dL. Smoking status was defined as never, former, and current smoker.[7,24–27]

Statistical Analysis

CACS was considered the independent variable in this study, while the ABI and plaque morphology were treated as dependent variables. Numerical data are presented as mean ± standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. Categorical variables were coded and presented as frequency distributions and percentages. Normality of To ascertain whether the numerical data had a normal distribution, the Shapiro-Wilk test was used. When comparing numerical variables between two groups, normally distributed data were analyzed using the independent t-test, while non-normally distributed data were analyzed using the Mann-Whitney U test. ANOVA for normally distributed data and the Kruskal-Wallis test for non-normally distributed data were employed for comparisons involving more than two groups. The Chi-square test or Fisher's exact test was used to assess associations between categorical variables in cases when the predicted cell counts were low. The Pearson correlation test for regularly distributed data and the Spearman rank correlation test for non-normally distributed data were used to evaluate correlations between numerical variables. The strength and direction of the correlations, as well as the p-values, were interpreted according to Guilford's criteria. Using Receiver Operating Characteristic (ROC) curve analysis, the discriminatory ability of CACS to identify plaque was assessed. The Youden index was used to determine the optimal cut-off value. Due to the small sample size and severe imbalance between groups (n=12 without plaque vs. n=88 with plaque). In addition, multivariable logistic regression analyses were conducted to assess the independent association between CACS and PAD. Two models were constructed: Model 1 examined the presence of any peripheral plaque (plaque vs. no plaque), while Model 2 evaluated the presence of advanced plaque (type III-IV vs type no plaque-II). Both models were adjusted for major confounders, including age, sex, smoking status, diabetes mellitus, hypertension, and LDL cholesterol. Odds ratios (OR) with 95% confidence intervals (CI) and p-values were reported. All analyses were conducted using SPSS version 26.0 for Windows and R Studio.

Results

A total of 100 consecutive participants were included in this study. The baseline characteristics are presented in Table 1 using a mean ± standard deviation format. The mean age was 61.49±10.03 years, with 57% male and 43% female. The average blood pressure readings were 87±8 mmHg for the diastolic and 136±17 mmHg for the systolic. Lipid profile measurements showed a mean total cholesterol of 207.38±24.19 mg/dL, LDL of 145.27±24.93 mg/dL, HDL of 42.78±6.37 mg/dL, and triglycerides of 156.17±13.57 mg/dL. Mean fasting blood glucose was 101±21.41 mg/dL. Renal function markers revealed a mean serum creatinine level of 1.35±0.43 mg/dL and eGFR of 79.57±20.34 mL/min/1.73 m^2. In terms of clinical risk factors, 65 participants (65%) had hypertension, 13 (13%) had diabetes mellitus, and 7 (7%) reported a positive family history of cardiovascular disease. Regarding smoking status, 42% had never smoked, 20% had smoked in the past, and 38% were now smokers. The mean ABI across the study population was 1.13±0.14.

Lower extremity arterial plaque characteristics, assessed by Duplex ultrasonography, revealed a diverse distribution of plaque type. While 12 participants (12%) showed no evidence of plaque, a significant portion demonstrated early to advanced stages of atherosclerotic changes. Type I and II plaques were each observed in 22% of participants. More advanced plaque morphologies, type III plaques, which are often associated with fibrous and calcified components, were found in 24%, and type IV plaques were observed in 20%. This distribution underscores a substantial presence of asymptomatic peripheral atherosclerosis, reflecting the potential utility of plaque characterization for cardiovascular risk assessment in routine clinical practice.

Among participants with atherosclerotic plaque detected in the lower extremities (n = 88), systolic blood pressure, LDL cholesterol, triglyceride levels, fasting blood glucose, and CACS values were significantly higher compared to those without plaque (n = 12). Interestingly, ABI was also lower in the plaque group (1.13±0.14 vs 1.15±0.10); however, this difference did not reach statistical significance ($p = 0.378$). These results show that ABI alone may not be sufficiently sensitive to detect early or subclinical atherosclerosis in this study.

Correlations between CACS and plaque type, and between CACS and ABI were evaluated using the Spearman correlation test, which yielded the following results: $r = -0.628$ ($p < 0.001$) and $r = 0.619$ ($p < 0.001$), respectively. This suggests a significant correlation with a negative correlation direction

Table 1. Baseline Characteristic

Characteristic	Total N = 100	Coronary Artery Calcium Score					Doppler-based Plaque Findings		
		Mild (CAC 1-100 HU) N = 20	Moderate (CAC 101-300 HU) N = 30	Severe (CAC 101-300 HU) N = 35	Extensive (CAC ≥1000 HU) N = 15	p-value	No Plaque N = 12	Plaque N = 88	p-value
Age, years	61.49 ± 10.03	59.7 ± 11.27	58,93 ± 10.53	62.51 ± 9.75	66.6 ± 5.36	0.074	59.41 ± 10.79	61.77 ± 9.95	0.448
Male sex	57 (57%)	8 (14.03%)	17 (29.82%)	20 (35.08%)	12 (21.05%)	0.133	6 (50%)	51 (57.95%)	0.832
BMI (kg/m²)	22.56 ± 3.54	21.77 ± 4.08	21.99 ± 2.96	22.84 ± 3.37	24.09 ± 3.97	0.290	22.47 ± 3.63	22.57 ± 3.54	0.988
Systolic blood pressure (mmHg)	136 ± 17	120.97 ± 12.39	131.22 ± 11.34	141.63 ± 17.44	150.96 ± 10.47	<0.001	127.75 ± 14.93	136.88 ± 16.93	0.078
Diastolic blood pressure (mmHg)	87 ± 8	78.71 ± 3.92	84.08 ± 6.76	91.39 ± 5.62	94.52 ± 5.41	<0.001	83.91 ± 5.77	87.59 ± 8.15	0.121
Total cholesterol (mg/dL)	207.38 ± 24.19	181.3 ± 12.99	198.9 ± 15.79	215.6 ± 18.98	239.93 ± 9.46	<0.001	195.75 ± 28.92	208.96 ± 23.22	0.081
LDL cholesterol (mg/dL)	145.27 ± 24.93	110.7 ± 9.31	139.53 ± 12.79	153.68 ± 12.35	183.2 ± 8.51	<0.001	133.83 ± 23.3	146.83 ± 24.48	0.090
HDL cholesterol (mg/dL)	42.78 ± 6.37	48.30 ± 5.18	44.86 ± 5.15	40.94 ± 4.80	35.53 ± 4.65	<0.001	44.58 ± 6.69	42.53 ± 6.32	0.298
Triglycerides (mg/dL)	156.17 ± 27.71	117.05 ± 13.57	153.3 ± 15.35	165.8 ± 17.08	191.6 ± 14.21	<0.001	135.92 ± 22.81	158.93 ± 27.27	0.006
Fasting blood glucose (mg/dL)	101 ± 21.41	84.3 ± 13.28	96.13 ± 17.61	103.74 ± 18.57	126.26 ± 19.23	<0.001	87.67 ± 19.57	102.76 ± 21.11	0.025
Ureum	36.6 ± 7.91	37.11 ± 9.23	38.27 ± 7.51	35.89 ± 7.14	34.23 ± 8.52	0.388	36.38 ± 9.48	36.64 ± 7.74	0.917
Creatinine	1.35 ± 0.43	0.98 ± 0.21	1.21 ± 0.25	1.43 ± 0.34	1.97 ± 0.47	<0.001	1.08 ± 0.36	1.40 ± 0.44	0.012
eGFR	79.57 ± 20.34	98.19 ± 5.63	90.96 ± 7.02	73.85 ± 11.6	45.31 ± 18.42	<0.001	90.5 ± 14.61	78.10 ± 20.58	0.021
Hypertension									
Yes	65 (65%)	5 (25%)	17 (56.6%)	29 (82.8%)	14 (93.3%)	<0.001	7 (58.33%)	58 (65.9%)	0.748
No	35 (35%)	15 (75%)	13 (43.4%)	6 (17.2%)	1 (6.7%)		5 (41.67%)	30 (34.09%)	

Diabetes Mellitus									
Yes	13 (13%)	0 (0%)	1(3.33%)	5 (14.2%)	7 (46.6%)	<0.001	0 (0%)	13 (14.77%)	0.356
No	87 (87%)	20 (100%)	29 (96.6%)	30 (85.7%)	8 (53.3%)		12 (100%)	75 (85.22%)	
Smoking Status									
Current	38 (38%)	5 (25%)	10 (33.3%)	15 (42.8%)	8 (53.3%)	0.198	3 (25%)	35 (39.77%)	0.239
Former	20 (20%)	2 (10%)	6 (20%)	8 (22.8%)	4 (26.6%)		1 (8.33%)	19 21.59%)	
No	42 (42%)	13 (65%)	14 (46.6%)	12 (34.2%)	3 (20%)		8 (66.67%)	34 (38.63%)	
Menopause									
Yes	40 (40%)	10 (50%)	12 (40%)	15 (42.9%)	3 (20%)	0.329	5 (41.7%)	35 (39.8%)	0.998
No	60 (60%)	10 (50%)	18 (60%)	20 (57.1%)	12 (80%)		7 (58.3%)	53 (60.2%)	
Family History									
Yes	7 (7%)	0 (0%)	3 (10%)	3 (8.6%)	1 (6.7%)	0.581	2 (16.7%)	5 (5.7%)	0.197
No	93 (93%)	20 (100%)	27 (90%)	32 (91.4%)	14 (93.3%)		10 (83.3%)	83 (94.3%)	
Ankle-brachial index	1.13 ± 0.14)	1.25 ± 0.10	1.16 ± 0.08	1.09 ± 0.12	0.98 ± 0.12	<0.001	1.15 ± 0.10	1.13 ± 0.14	0.378
Plaque type									
No plaque	12 (12%)	5 (25%)	4 (13.3%)	2 (5.7%)	1 (6.7%)	<0.001			0.002
I	22 (22%)	8 (40%)	7 (23.3%)	6 (17.1%)	1 (6.7%)				
II	22 (22%)	3 (15%)	9 (30%)	7 (20%)	3 (20%)				
III	24 (24%)	4 (20%)	5 (16.7%)	13 (37.2%)	2 (13.3%)				
IV	20 (20%)	0 (0%)	5 (16.7%)	7 (20%)	8 (53.3%)				
CACS									
Mild (1-100 HU)							5 (41.7%)	15 (17%)	0.002
Moderate (101-300 HU)							4 (33.3%)	26 (29.5%)	
Severe (301-999 HU)							2 (16.7%)	33 (37.5%)	
Extensive (≥1000 HU)							1 (8.3%)	14 (15.9%)	

Description: Categorical data is presented with the number/frequency and percentage, while numeric data is presented with the mean, median, standard deviation and range. P-value are unadjusted.

and moderate strength for CACS and ABI and positive correlation direction and moderate strength for CACS and plaque type based on the Guilford criteria.

Figure 1 shows the ROC curve analysis of CACS in detecting peripheral plaque. ROC analysis demonstrated that CACS had a good discriminatory ability in predicting the presence of any atherosclerotic plaque, with an AUC of 0.765 (95% CI: 0.671-0.859), a sensitivity of 73.86% and a specificity of 75% at an optimal threshold of 142.5 HU. However, the ability of CACS to identify type I and type II plaques morphology was limited, with a lower AUC of 0.678 (95% CI: 0.558-0.798), suggesting suboptimal discrimination between subjects without plaque and those with early plaque formation. In contrast, the performance of CACS in detecting type III and IV plaque was notably higher, with an AUC of 0.852 (95% CI: 0.776-0.928). At an optimal threshold 478.5 HU, the sensitivity was 68.2% and specificity was 91.7%, highlighting its stronger predictive value for more advance calcified plaque. Furthermore, Table 2 summarizes the ROC performance of CACS in detecting overall and type-specific peripheral plaques.

In the multivariable logistic regression for any plaque (Model 1), higher CACS (after square transformation to meet linearity assumption) remained a significant independent predictor of peripheral plaque (OR ≈ 1.00 per unit^2, p = 0.046), after adjustment for age, sex, smoking, diabetes mellitus, hypertension, and LDL cholesterol. None of the traditional risk factor were independently associated with plaque presence. For advanced plaque (Model 2) CACS was slso an independent predictor (OR 1.005, p = 0.003). Other clinical risk factors were not independently associated. The Nagelkerke R^2 of the models was 0.416 for Model 1 and 0.524 for model 2, indicating moderate explanatory power.

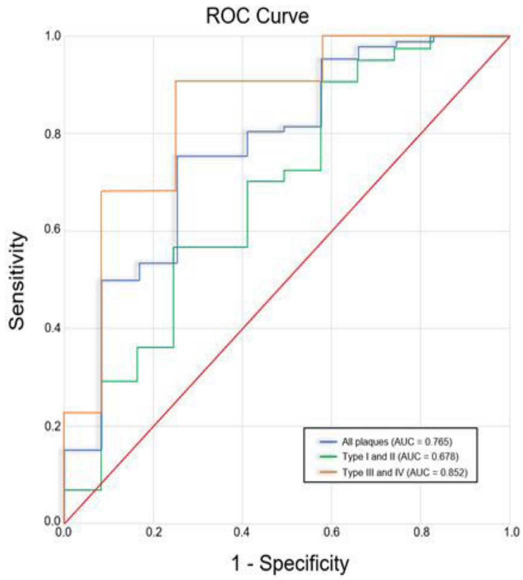

Figure 1. Receiver operating curve analysis of CACS in detecting peripheral plaque.

Table 2. ROC summary for CACS in detecting peripheral plaque.

Comparison	AUC	Std. Error[a]	Asymptotic 95% Confidence Interval[b]		Sensitivity (%)	Specificity (%)	Optimal Cut-off (HU)	p-value
			Lower	Upper				
CACS for plaque vs no plaque	0.765	0.077	0.615	0.916	73.86	75	142.5	<0.05
CACS for Type I and II plaques	0.678	0.094	0.494	0.862	90.9	41.7	35.5	0.06
CACS for Type III and IV plaques	0.852	0.068	0.718	0.986	68.2	91.7	478.5	<0.05

a. Under the nonparametric assumption
b. Null hypothesis: ture area = 0.5

Discussion

This study highlights three main findings. First, a statistically significant moderate inverse correlation was observed between CACS and ABI (r = -0.628, p < 0.001), underscoring the interplay between coronary and peripheral pathology. As previously acknowledged, arterial calcification and advanced plaque burden in specific populations may paradoxically coexist with preserved ABI values, potentially masking the diagnosis of PAD. In this study, ABI values were also lower in the plaque group, although the difference did not reach statistical significance. This subtle yet important observation underscores the limitations of ABI as a sole diagnostic tool in specific vascular phenotypes.[9–11]

Second, to further elucidate the phenomenon, we investigated the relationship between CACS and plaque morphology in the lower extremity arteries as assessed by duplex ultrasonography. The analysis revealed a moderate positive correlation (r = 0.619, p < 0.001), suggesting that increasing coronary calcium burden mirrors the progression of peripheral atherosclerotic plaque complexity.

Third, in a more granular exploration of this relationship, the ROC curve analysis revealed that CACS demonstrated good discriminatory power for detecting the presence of plaque in the lower extremities, with an AUC of 0.765, sensitivity of 73.86%, and specificity of 75% at an optimal threshold of 142.5 HU. This finding offers a novel perspective, suggesting that CACS may serve as a surrogate indicator of systemic atherosclerosis burden, particularly within the peripheral vascular territory. To further refine the diagnostic value of CACS, this study conducted a sub-analysis comparing its performance in identifying type I and II plaque morphology versus more advanced plaque (type III and IV) in the lower extremities.

Critically, the discriminatory ability of CACS for detecting softer plaques (type I and II) was suboptimal, with an AUC of only 0.678. This

Table 3. Multivariate logistic regression for association between CACS and PAD.

Variable	Odds Ratio (95% CI)	p-value
Model 1: Any plaque (plaque vs no plaque)		
CACS	1.00 (1.00–1.01)	0. 042
Age	0.999 (0.93–1.07)	0.98
Male sex	1.534 (0.22–10.71)	0.66
Hypertension	2.359 (0.45–12.24)	0.30
Diabetes mellitus	0.00 (0.00–Inf)	1.00
Smoking		
Current	0.00 (0.00–Inf)	1.00
Former	0.00 (0.00–Inf)	1.00
LDL cholesterol	0.097 (0.093–1.02)	0.28
Model 2: Advanced plaque (type III-IV vs no plaque-II)		
CACS(centered)	1.005 (1.002–1.009)	0.003
Age	0.98 (0.93–1.04)	0.656
Male sex	1.18 (0.289–4.892)	0.811
Hypertension	0.718 (0.208–2.473)	0.599
Diabtes mellitus	0.00 (0.00–Inf)	0.988
Smoking		
Current	5.062 (0.974–26.306)	0.054
Former	4.944 (0.561–20.188)	0.059
LDL cholesterol	1.00 (0.99–1.01)	0.726

represents a significant "blind spot" of CACS that has important clinical implications. This modest performance reflects the underlying pathophysiology: CACS, by definition, quantifies calcified plaque, which is often a marker of chronic, stable, long-standing atherosclerosis. However, acute cardiovascular events in both coronary and peripheral beds can arise from the rupture of non-calcified or minimally calcified, lipid-rich, vulnerable plaques. Therefore, a low or zero CACS score does not rule out the presence of potentially dangerous, non-calcified peripheral atherosclerotic disease. This limitation must be clearly understood when considering CACS as a screening tool for peripheral arterial disease. This modest performance may be attributed to the low calcium content typically present in lipid-rich or mixed soft plaques, which may not significantly elevate the overall coronary calcium score. In contrast, CACS exhibited markedly superior performance in predicting the presence of more advanced, calcified plaque (types III and IV), with an AUC of 0.852, a sensitivity of 68%, and a notably high specificity of 91.7% at an optimal threshold of 478.5 HU. While these findings provide evidence that CACS may reflect systemic vascular calcification in peripheral territories, the proposed threshold of 478.5 HU should be interpreted with caution due to the small sample size and lack of external validation. A more appropriate interpretation is that high CACS burden is associated with a higher likelihood of advanced peripheral plaque. It indicates a state of high systemic atherosclerotic burden, rather than recommending a specific clinical cutoff.

Atherosclerosis, a systemic arterial disease, is caused by endothelial dysfunction, lipid particle buildup, inflammatory cell recruitment, and intimal calcification. The development of atherosclerosis in the peripheral, carotid, or coronary arteries is consistent with the advancement of arterial calcification.[7,18] Although arterial calcification is widely studied and recognized as an independent risk factor for cardiovascular and cerebrovascular disease, the clinical relevance of coronary calcification in assessing lower extremity arterial disease remains largely unexplored.[18] Several studies have investigated the role of calcium scoring, whether derived from peripheral or coronary arteries, in the assessment of lower extremity PAD. In 2020, Yadav et al. conducted a comparative evaluation of a non-invasive technique, demonstrating that the arterial calcium scoring of lower extremities outperformed both color Doppler ultrasound and dual-energy CT (DECT) angiography in diagnosing PAD. Notably, a calcium score threshold >842.2 yielded robust sensitivity and specificity for detecting atheromatous lesions, underscoring the diagnostic potential of local vascular calcification quantification.[28] By shifting the focus from local to systemic vascular beds, the Multi-Ethnic Study of Atherosclerosis (MESA) provided landmark evidence linking CACS with both ABI and clinical PAD. Our study builds upon this systemic perspective by demonstrating a statistically significant inverse correlation between CACS and ABI ($r = -0.628$, $p < 0.001$). This aligns with findings from Bakhsi et al., who reported that a 1-unit increase in log-transformed CACS was independently associated with a 1.15-fold higher odds of developing an abnormal ABI over time ($p < 0.001$). Importantly, this relationship remained robust after adjustment for traditional cardiovascular risk factors, suggesting that CACS extends beyond coronary risk prediction to serve as a marker of diffuse atherosclerotic burden.[7] Most recently, Maahs et al. introduced a novel ultrasound-based scoring system of femoral artery calcification, which demonstrated strong concordance with CT-based calcium quantification ($r = 0.64$). Beyond anatomical correlation, elevated ultrasound-derived scores were independently associated with adverse limb outcomes, including reduced amputation-free survival. This pivotal study validates duplex ultrasound not only as a hemodynamic assessment tool but also as a morphological risk stratification modality, further reinforcing the growing clinical value of calcium scoring across vascular territories.[20]

Building upon these findings, our study is, to our knowledge, the first to explore the association between CACS and plaque morphology in the lower extremities. Beyond its established role in stratifying coronary risk, our result suggests that CACS may also serve as a valuable prompt to broaden clinical vigilance toward other vascular territories. Specifically, CACS may enhance awareness of lower extremity arterial disease, enabling earlier identification of PAD. This novel perspective positions CACS not merely as a cardiac metric but as a gateway marker for systemic atherosclerotic burden, with meaningful implications for more comprehensive vascular risk assessment.

Study Limitation and Further Research

This study has several significant limitations that must be acknowledged and directly impact the interpretation and generalizability of our findings. First, this investigation was conducted retrospectively using a single-center hospital's imaging registry, which is inherently biased. The clinical indications for ordering both a coronary CT and a lower extremity duplex ultrasound are not random, as this patient cohort is likely enriched with individuals suspected of having complex, multi-site vascular disease. This represents a specialized, high-risk diagnostic population rather than a general screening population, which may limit the external validity of these results. Second, the unequal distribution between participants without peripheral plaque (n=12) and those with plaque (n=88) represents a significant limitation that affects the precision of our diagnostic accuracy estimates. This imbalance particularly impacts the stability of ROC curve analysis and the reliability of the proposed CACS cut-off values, which should be validated in larger, more balanced cohorts before clinical application. The small control group size means our diagnostic thresholds require external validation in diverse populations.

Third, CACS demonstrated limited utility in predicting type I and II plaques, as reflected by the low AUC in the ROC analysis, representing a critical clinical limitation. Fourth, not all relevant clinical variables and potential confounders were collected, including information regarding patients' prior medication use, which may have influenced the observed associations. Fifth, while we used an established plaque classification system, we did not assess inter-observer and intra-observer variability for plaque classification, which affects the reproducibility of our primary outcome measure. Sixth, although multiple statistical comparisons were performed, no correction for multiple comparisons was applied, increasing the potential for type I error. Finally, the assessment of lower extremity arterial plaques was limited to selected arterial segments. However, the femoral and popliteal arteries' evaluation may reasonably reflect the atherosclerotic burden in the lower extremities due to their exposure to high shear stress.[29-30]

Future studies should adopt a prospective, multicenter design with larger and more diverse populations to improve the external validity of the findings. Inclusion of a broader range of clinical variables could further minimize bias and strengthen the analysis. Moreover, more comprehensive vascular imaging of the entire lower extremity arterial tree is recommended to better characterize arterial plaque distribution. Despite these limitations, this study provides valuable preliminary evidence for the association between CACS and peripheral plaque morphology, representing the first investigation of this relationship. The findings suggest potential clinical utility of CACS as a marker of systemic atherosclerotic burden, while highlighting areas that require further investigation before broader clinical application.

Conclusion

This study shows that CACS can reflect the systemic nature of atherosclerosis, including its presence in peripheral arteries. We found a moderate inverse relationship between CACS and ABI, a practical tool in daily clinical use. This study is the first to link CACS with plaque types in the lower extremities, as assessed by Doppler ultrasound. While CACS showed good discriminatory performance for detecting advanced peripheral plaque, it demonstrated significant limitations in identifying early, non-calcified plaques. A high CACS burden appears to be associated with advanced peripheral plaque and may indicate a high systemic atherosclerotic burden. However, the findings should be interpreted with significant caution due to the retrospective design, severe group imbalance, small sample size, and the specialized nature of the study population. The proposed CACS threshold requires external validation in larger, more balanced cohorts before any clinical application can be considered.

List of Abbreviations

ABI	Ankle-Brachial Index
AUC	Area Under Curve
BMI	Body Mass Index
CACS	Coronary Artery Calcium Score
CAD	Coronary Artery Disease
CT	Computed Tomography
DECT	Dual-Energy Computed Tomography
DLP	Dose Length Product
eGFR	estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein Cholesterol
HU	Hounsfield Units
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
MESA	Multi-Ethnic Study of Atherosclerosis
MHz	Megahertz
MIP	Maximum Intensity Projection
MPR	Multiplanar Reconstruction
MR	Medical Record
PAD	Peripheral Artery Disease
ROC	Receiver Operating Characteristic
SFA	Superficial Femoral Artery
SPSS	Statistical Package for the Social Sciences

Ethical Clearance

Ethical approval was obtained from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia (Approval No. DP.04.03/D.XIV.6.5/425/2024) with a waiver of informed consent in accordance with the Declaration of Helsinki.

Publication Approval

All authors have reviewed and approved the final version of the manuscript and consent to its publication in the Indonesian Journal of Cardiology.

Authors Contributions

MSA: Conceptualized the research, designed the study methodology, supervised data collection and analysis, interpreted imaging and statistical results, and drafted the main manuscript; NYK: Conducted patient data collection, performed coronary CT and Doppler ultrasound data analysis, and contributed to manuscript writing and figure preparation; SH: Conducted statistical analysis, validated data accuracy, performed correlation and regression modeling, and contributed to critical revision of the manuscript; RP: Provided methodological supervision, contributed to study design refinement, reviewed the literature, and critically reviewed and approved the final version for publication. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflict of Interest

The authors affirm that no financial or commercial ties that might be interpreted as a potential conflict of interest existed throughout the course of this investigation. No commercial entity provided financial assistance or funding for this study.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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The authors acknowledge the use of Artificial Intelligence (AI) and large language model (LLM) technologies to assist in the writing and revision process of this manuscript. Specifically, AI tools were utilized for:

a. Language enhancement and grammar correction
b. Structural organization of certain sections
c. Literature review formatting and citation management
d. Proofreading and consistency checks

The authors take full responsibility for the content, scientific accuracy, and integrity of all data and conclusions presented in this manuscript. All AI-generated content was thoroughly reviewed, edited, and validated by the authors. The use of AI did not involve the generation of scientific data, analysis, or conclusions, which remain entirely the work of the human authors. This disclosure is made in accordance with emerging guidelines for transparent reporting of AI-assisted academic writing.

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Review Article

Could Cardiac Shockwave Therapy Be the Breakthrough Solution for Refractory Angina? A Systematic Review and Meta-analysis

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Abstract
Refractory Angina (RA) is a chronic condition unresponsive to standard treatments like Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG), leaving limited options for many patients. Cardiac Shockwave Therapy (CSWT) is a novel, non-invasive modality that improves myocardial perfusion of stimulating microvascular regeneration. The present systematic review and meta-analysis were designed to assess the therapeutic efficacy of CSWT in patients with RA. Relevant studies were identified through a structured search of major electronic databases, including Cochrane, PubMed, and ScienceDirect, including comparative studies with controls that evaluated CSWT in RA patients between 2010 and 2024. Studies not in English, with irrelevant outcomes, or lacking full-text access, were excluded. Data were extracted and analyzed using a random-effects model to address heterogeneity. Seven studies with a total of 417 patients were analyzed. CSWT demonstrated significant improvements in multiple clinical outcomes. CSWT reduces angina severity in CSWT reduces angina severity in CCS grade (MD -0.76, 95% CI -0.97, -0.55, P < 0.00001) and in NYHA class (MD -0.62, 95% CI -0.95, -0.30, P = 0.0002), increased the 6-Minute Walk Test (6MWT) distance by 57.63 meters (MD 57.63, 95% CI 16.71, 98.54, P = 0.006), increased SAQ scores by 10.96 points (MD 10.96, 95% CI 1.66, 20.26, P = 0.02), improved Left Ventricular Ejection Fraction (LVEF) by 4.43% (MD 4.43, 95% CI: 2.66 to 6.21, P< 0.01), and decreased nitroglycerin usage by 1.62 intake per week (MD -1.62, 95% CI -2.61, -0.62, P = 0.001). However, there was no significant difference in LVEDD between the two groups. CSWT appears to be a promising therapeutic option for patients with RA, demonstrating improvement in Canadian Cardiovascular Society (CCS) angina class, New York Heart Association (NYHA) class, 6-minute walk test distances, SAQ score, LVEF, and reducing nitroglycerin usage.

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Keywords: Cardiac Shockwave Therapy, Refractory Angina, Non-invasive Cardiac Therapy, Chronic Angina Treatment, Innovative Angina Therapies

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Introduction

Atherosclerotic plaque buildup in the arterial lumen is a hallmark of Coronary Artery Disease (CAD), which impairs myocardial oxygenation and blood flow. It remains the primary global cause of mortality and a significant contributor to disability.[1] Standard management options for angina typically encompass pharmacological therapy with anti-anginal agents, Percutaneous Coronary Intervention (PCI), and surgical revascularization through Coronary Artery Bypass Grafting (CABG). While PCI and CABG restore blood flow of the main blood vessels, they fail to address microvascular occlusion, dysfunction, or loss. Furthermore, advanced CAD frequently leads to cardiac dysfunction due to chronic multivessel disease, resulting in extensive myocardial necrosis, fibrosis, and reduced ventricular compliance.

Refractory Angina (RA) is defined as a chronic syndrome, persisting for more than three months, in which patients experience ongoing anginal symptoms secondary to coronary insufficiency in the setting of CAD, despite optimal medical therapy, percutaneous angioplasty, or coronary bypass surgery.[2-3] Many RA patients have undergone multiple CABG or PCI procedures, often rendering them unsuitable for additional revascularization due to high procedural risks or diminished vascular integrity.[3] Patients with prior CABG, particularly those with graft degeneration or progressive atherosclerosis, frequently present with refractory angina or ischemic cardiomyopathy, yet are no longer viable candidates for PCI or repeat CABG due to vascular limitations or poor clinical prognosis. Consequently, alternative therapeutic approaches, such as gene therapy, transmyocardial revascularization, and spinal cord stimulation, have been explored, though they remain in clinical trials and are more invasive.[4] Another alternative is Cardiac Shock Wave Therapy (CSWT), which has emerged as a less invasive and novel strategy for managing RA, showing potential for improving heart disease treatment outcomes.[5]

CSWT has gained recognition as an emerging non-invasive therapy, utilizing focused shock waves to augment myocardial perfusion and relieve anginal symptoms in patients with RA. The technique applies controlled acoustic energy, delivered via a commercially available shockwave generator, directly to ischemic myocardial segments.[4] This biomechanical stimulation generates cavitation effects and shear stress within the myocardium, leading to the upregulation of angiogenic mediators such as Vascular Endothelial Growth Factor (VEGF) and Nitric Oxide (NO). Notably, VEGF is a central driver of microvascular neovascularization, thereby improving myocardial perfusion and reducing ischemic burden.[6-7]

Although its mechanistic rationale is increasingly understood, the role of CSWT in patients with refractory angina who have previously undergone revascularization remains insufficiently investigated. To our knowledge, no prior meta-analysis has systematically quantified its therapeutic impact and clinical applicability within this subgroup. Accordingly, we conducted a systematic review and meta-analysis to rigorously evaluate the efficacy and clinical outcomes of CSWT in the treatment of refractory angina.

Methods

The protocol for this study was prospectively documented in the International Prospective Register of Systematic Reviews (PROSPERO; Registration ID: CRD42024604283), with full details available at https://www.crd.york.ac.uk/prospero/. The conduct and reporting of the review adhered rigorously to the standards outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, available at http://www.prisma-statement.org/.[8]

Literature Search

The systematic review followed the PRISMA framework, incorporating a structured literature search across three primary databases: Cochrane, PubMed, and ScienceDirect. The search strategy utilized the terms ("cardiac shockwave therapy" OR "extracorporeal shockwave therapy") AND ("refractory angina" OR "severe angina pectoris") to maximize the identification of relevant studies. Additional Medical Subject Headings (MeSH) and supplementary keywords were integrated to refine retrieval. Eligible studies were limited to full-text, English-language publications between 2010 and 2025. Titles and abstracts of potentially relevant studies were screened, followed by qualitative analysis and full-text review.

Eligibility Criteria

Inclusion criteria required studies to: (1) involve participants diagnosed with refractory angina; (2) use cardiac shockwave therapy (low or high-intensity) as the intervention; (3) include a control group rather than a pre- and post-treatment comparison within the same participants; and (4) report outcomes related to refractory angina symptoms. Exclusion criteria comprised: (1) non-English studies; (2) studies lacking relevant data or results; (3) inaccessible full texts; and (4) non-original research formats such as editorials, letters, or reviews. All primary comparative studies, including randomized controlled trials (RCTs), quasi-experiments, and prospective and retrospective observational studies, were included if they met the criteria and statistically compared outcomes.

Comparators

Because inclusion required a concurrent control arm, we extracted the exact intervention received by the control groups in all included studies. Controls comprised either Optimal Medical Therapy (OMT) alone or sham procedures (device inoperative) superimposed on OMT.

Study Selection

Two reviewers (FDP and MRA) independently evaluated all retrieved records according to predefined inclusion and exclusion criteria. Each reviewer conducted a comprehensive assessment, and any discrepancies were resolved through collegial discussion. Studies deemed ambiguous underwent further deliberation before final decisions were made. Subsequently, all included articles were validated by consensus among the investigators. A structured data extraction form was then developed to consolidate and organize findings from the eligible studies systematically.

Data Extraction

Data extraction was conducted independently by two investigators (FDP and MRA) under the guidance and consultation of the senior author (MM). A standardized data extraction form was used to collect information, including the author's name, year of publication, study design, sample size, treatment details for cardiac shockwave therapy, and study outcomes. Titles and abstracts of retrieved studies were independently screened by the investigators, with discrepancies resolved through discussion and arbitration by the senior author following the removal of duplicates. Eligible studies were catalogued using a shared spreadsheet and subsequently assessed for inclusion until consensus was achieved. Priority was given to publications with the largest sample size and the most recent publication date when multiple sources discussed the same study. In cases of missing data, corresponding authors were contacted to obtain additional information.

Quality Assessment

The evaluation of study quality and potential bias was performed independently by FDP and MRA, with oversight from MM, utilizing established tools specific to the type of study. Randomized controlled trials were assessed using the Modified Jadad Scale, which examines key elements such as randomization methods, blinding procedures, and

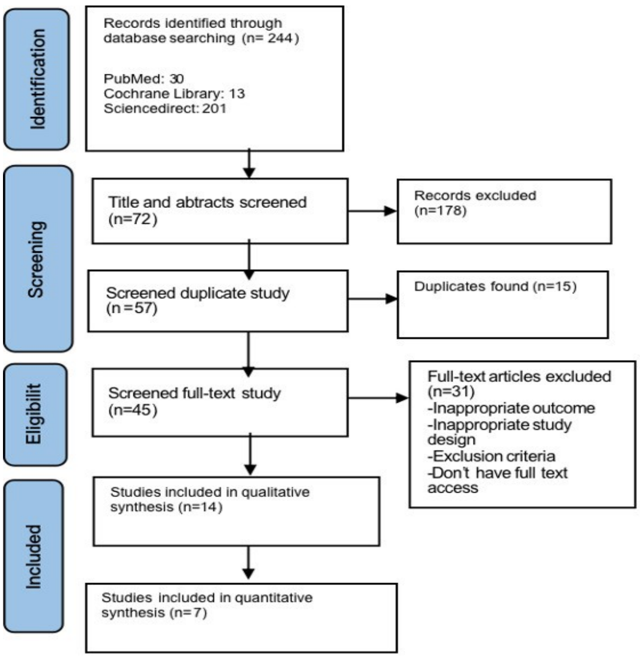

Figure 1. Diagram of study selection using PRISMA flowchart.

the management of participant withdrawals. Trials receiving scores of four or higher (out of eight) were deemed high quality, while those scoring below four were considered low quality. For observational studies, the Newcastle-Ottawa Scale (NOS) was employed, focusing on participant selection, group comparability, and the reliability of outcome or exposure measurements. Studies scoring above seven were categorized as high-quality. Any disagreements in the quality evaluation process were resolved through discussion, ensuring a consistent and thorough assessment under the guidance of the senior author.

Statistical Analysis

Meta-analyses were performed using Review Manager (RevMan) version 5.4. Continuous outcomes were synthesized as mean differences (MD) with corresponding 95% Confidence Intervals (CI). Statistical heterogeneity was examined using chi-square tests and quantified by the I^2 statistic, classified as low (below twenty-five percent), moderate (twenty-five to fifty percent), or high (more than fifty percent). In the presence of significant heterogeneity, a random-effects model was employed, and findings were illustrated using forest plots.

In addition to random-effects modeling when heterogeneity was present, we prespecified subgroup analyses by study design (Randomized Controlled Trials [RCTs] vs observational studies) and tested between-subgroup differences using χ^2 statistics. We further conducted sensitivity analyses by (i) excluding studies rated at high risk of bias, (ii) excluding studies rated high risk plus those with some concerns, and (iii) performing leave-one-out analyses for primary outcomes. We interpreted pooled effects cautiously when substantial heterogeneity ($I^2 > 50\%$) or significant subgroup differences were observed, and we withheld a single pooled estimate when subgroup effects differed.

Results

Search Results

The database search yielded 244 records (PubMed: 30; Cochrane Library: 13; ScienceDirect: 201). After title/abstract screening (n = 72) and duplicate removal (n = 15), 45 full texts were assessed for eligibility. Fourteen (14) studies met the inclusion criteria and were retained for the qualitative synthesis. Of these, seven studies provided comparable, adequately reported, two-arm data and were therefore included in the quantitative meta-analysis. The remaining seven studies were excluded from quantitative synthesis due to at least one of the following: non-eligible outcomes, non-comparative design (e.g., single-arm/pre–post), failure to meet exclusion criteria upon full-text assessment, or lack of full-text access. Figure 1 displays the PRISMA diagram for the study flow.

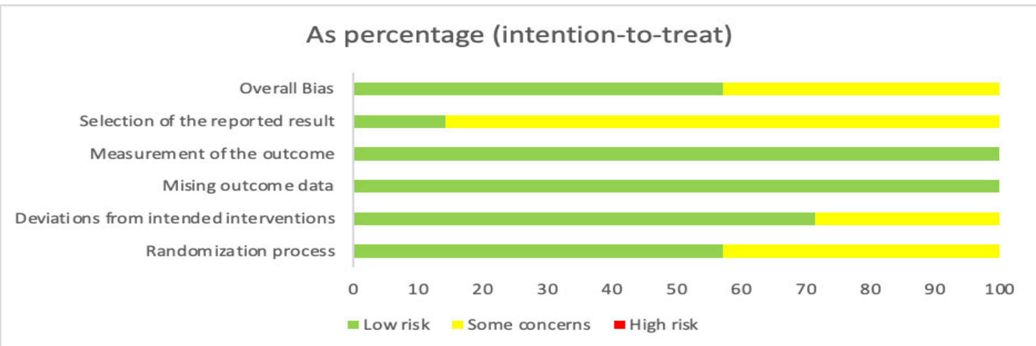

Figure 2-1. Risk of bias graph.

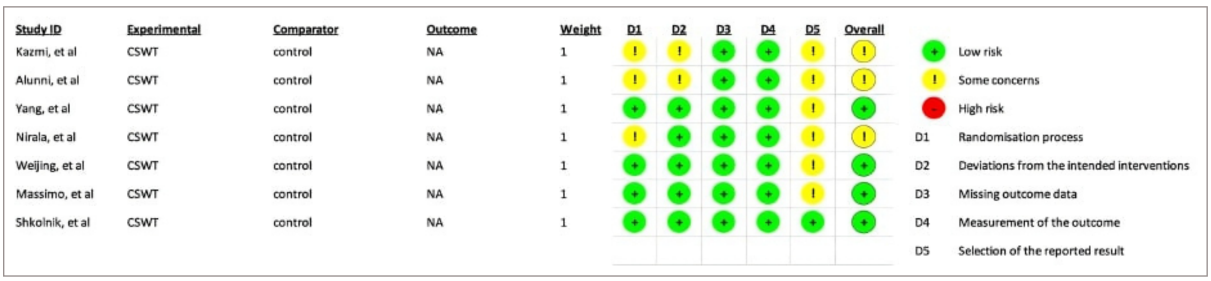

Figure 2-2. Risk of bias summary.

Risk of Bias Assessment

The appraisal of methodological quality, performed with the Cochrane Risk of Bias instrument, is illustrated in Figure 2.[9] Of the included trials, four demonstrated a low likelihood of bias, while three were judged to harbor moderate concerns regarding validity.

Summary of Included Studies

The sample sizes of the eligible studies ranged from 23 to 87 participants. An overview of the characteristics of selected studies is summarized in Table 1. The control group comprised either Optimal Medical Therapy (OMT) alone or sham procedures superimposed on OMT. Specifically: Liu Weijing 2021—OMT only (control); Shkolnik 2018—triple-blind sham procedure plus OMT; Ping Yang 2012—sham (device without energy) plus routine therapy; Alunni 2015, Slavich 2017, Kazmi 2012, and Nirala 2016—usual care/OMT without CSWT. Individuals presenting with acute myocardial infarction within the preceding three months, advanced chronic obstructive pulmonary disease, valvular pathology beyond grade II, intraventricular thrombus, pregnancy, or active malignancy were excluded.

The review identified seven eligible articles published between 2010 and 2025, comprising both qualitative and quantitative studies. Single-arm studies lacking control groups or using only pre- and post-treatment comparisons were excluded from the meta-analysis. Shockwaves were administered to ischemic myocardial regions identified through stress imaging tests. The principal clinical endpoints encompassed: (1) grading of angina according to the Canadian Cardiovascular Society (CCS) classification; (2) functional status based on the New York Heart Association (NYHA) class; (3) Left Ventricular Ejection Fraction (LVEF); (4) Left Ventricular End-Diastolic Diameter (LVEDD); (5) performance on the 6-Minute Walk Test (6MWT); (6) health-related quality of life assessed with the Seattle Angina Questionnaire (SAQ); and (7) frequency of weekly nitrate use.

Sensitivity Analysis

Risk-of-bias–informed sensitivity analyses supported the robustness of the CCS and NYHA findings: excluding the high-risk study did not change the direction or significance of the results. In contrast, 6MWT and SAQ proved less stable: effects remained significant within the RCT-only subset but attenuated or lost significance when “some concerns” studies were removed, reflecting the dispersion seen in Figure 2. These results justify interpreting 6MWT by study design rather than as a single pooled metric.

Table 1. Characteristics of selected studies.

Author (year)	Patients, CSWT/ control	Study design	Age (years)	Sex, male, n (%)	Follow up, months	BMI, kg/m^2	Hyper-tension	Diabetes	Control (Comparator)
Weijing, et al, 2021	46/41	RCT	68.1 ± 6.7/ 68.9 ± 6.6	70/71	6 months	24.7 ± 3.8/ 24.9 ± 3.7	27/23	52/56	Optimal medical therapy (OMT) only (no CSWT)
Gianluca, 2015	43/29	Cohort study, observational	70±5.3/ 71±5.3	83.7/79	6 months	Not stated	100/100	32.5/27	Usual care/ OMT without CSWT
S. Nirala, 2016	41/11	Cohort study, observational	63.4±10.8/ 71±6.52	35/8	6 months	23.9±2.7/ 23.21±2.35	Not stated	30.77	Usual care/ OMT without CSWT
Evgeny S., 2018	37/35	RCT, triple-blind	67.6±8.3/ 68.8±8.3	62.3/82.3	6 months	29.7±4.1/ 30.1±3.8	96.3/97.1	21.6/28.8	Sham procedure (device inoperative) + OMT
Massimo S., 2018	19/4	Cohort study, retrospective	69.79±10.22/ 65.25±5.74	79/75	6 months	Not stated	79%/100%	42%/75%	Usual care/ OMT without CSWT
Ping Y, 2012	14/11	RCT	63.7±8.60/ 66.45± 8.51	71.4/72.7	6 months	Not stated	57.1/45.5	42.9/45.5	Sham (device inoperative) + routine therapy
Waqar H, 2012	43/43	Cohort study	58.7±9.5/ 56.6±11.6	87/84	6 months	Not stated	56/44	77/74	Usual care/ OMT without CSWT

Canadian Cardiovascular Society (CCS) Grade

The analysis included six studies (n=345),[6,10–14] comprising two RCTs and four observational studies (Figure 3-1). Marked heterogeneity was detected across the trials (P = 0.009, I^2 = 67%), warranting the adoption of a random-effects analytical model. The pooled estimates demonstrated a statistically significant benefit of CSWT over control (MD = –0.76; 95% CI = –0.97 to –0.55; P < 0.00001). In practice, patients undergoing CSWT showed an average reduction of 0.76 points on the CCS angina severity scale compared with those receiving standard therapy.

Subgroup analysis by design showed consistent direction of benefit in both RCTs and observational studies; heterogeneity was primarily driven by smaller observational cohorts.

NYHA Class

Four studies (n = 235)[10,12–14] assessed changes in NYHA class between CSWT and control groups, comprising two randomized controlled trials (RCTs) and two observational studies (Figure 3-2). Substantial heterogeneity was detected (P < 0.0001, I^2 = 87%), necessitating a random-effects model. Pooled analysis demonstrated a significant improvement in NYHA class among CSWT-treated patients (MD –0.62; 95% CI –0.95 to –0.30; P < 0.0002), corresponding to an average improvement of 0.62 points compared with controls. No statistically significant difference between RCT and observational subgroups was detected; however, because of the high heterogeneity, we should assess the result carefully.

6-minute Walk Test

Three studies[11-12,14] (n = 188), including two RCTs and one observational trial, investigated the effect of CSWT on the 6MWT (Figure 3-3). Substantial inter-study heterogeneity was present (P = 0.03, I^2 = 73%), necessitating the use of a random-effects model. There were significant between-subgroup differences (forest-plot test for subgroup differences, P = 0.01). RCTs demonstrated a significant improvement (approximately MD ≈ 76 m), whereas the single observational study showed a small adverse effect (≈ −5 m). In view of this statistically substantial subgroup effect, we

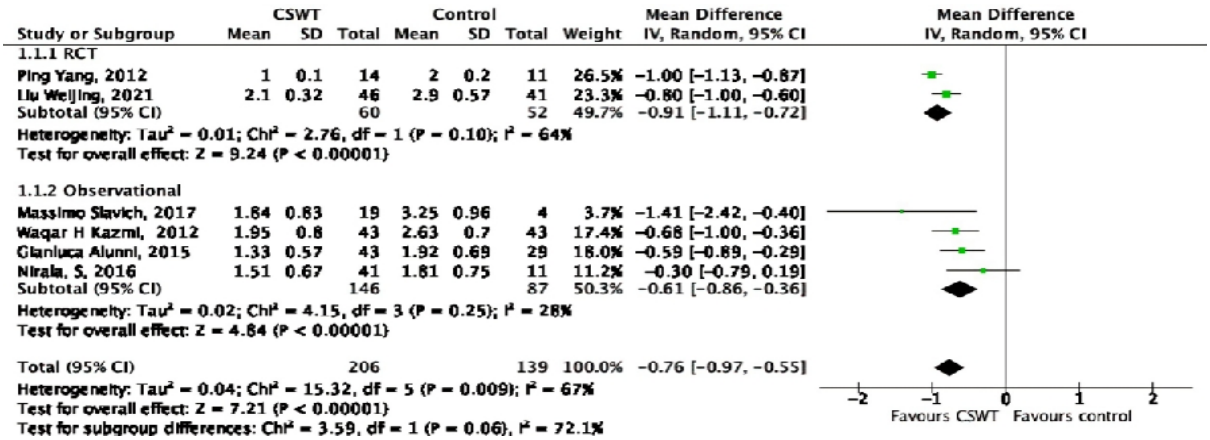

Figure 3-1. Forest plot of the CSWT group vs the control group-CCS score.

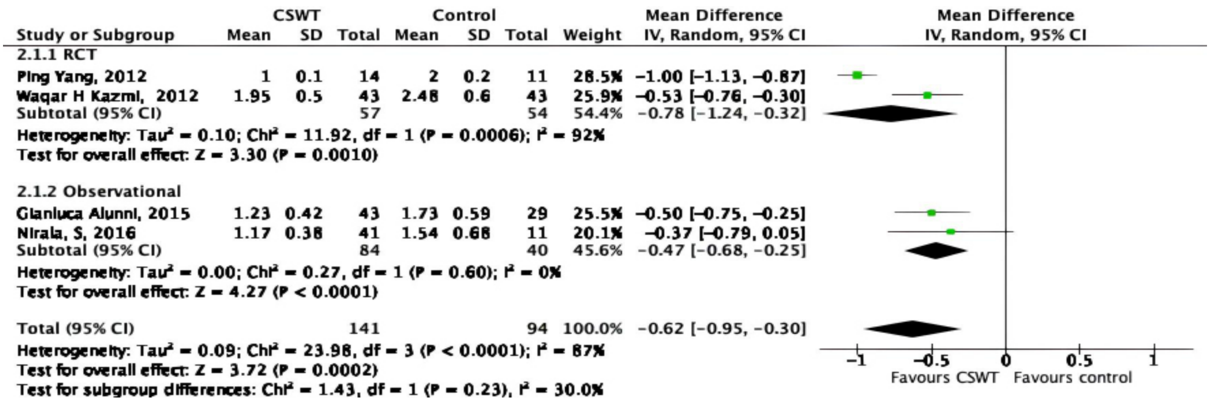

Figure 3-2. Forest plot of the CSWT group vs the control group-NYHA class.

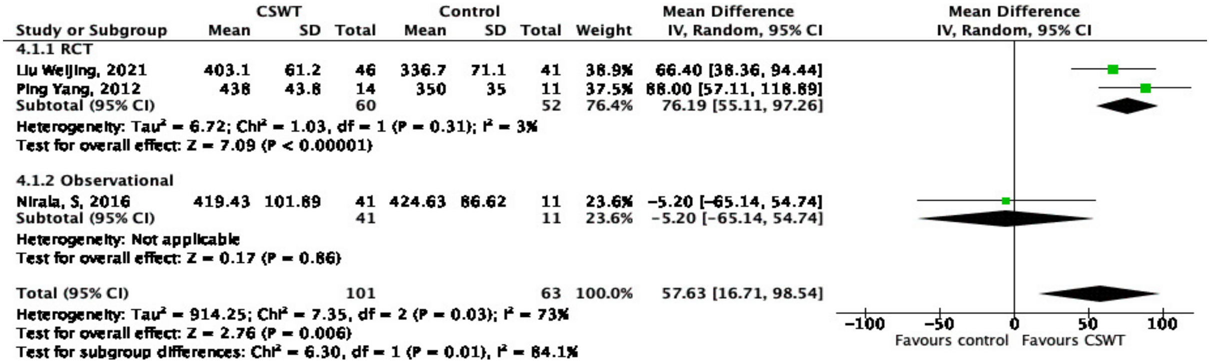

Figure 3-3. Forest plot of the CSWT group vs the control group-6 min walk test.

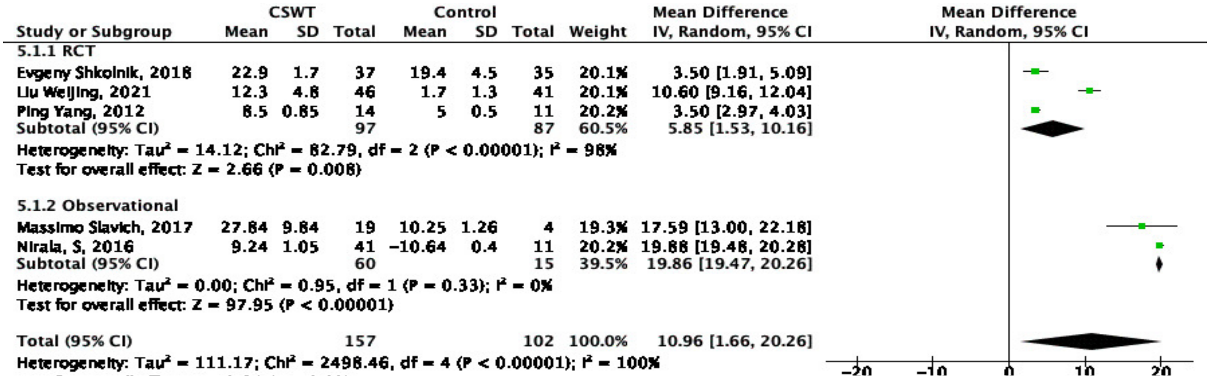

Figure 3-4. Forest plot of the CSWT group vs the control group-SAQ score.

refrain from presenting a single pooled estimate and interpret RCT and observational results separately.

SAQ Score

Five studies[6,11-12,14-15] (n = 259), including three RCTs and two observational studies, evaluated SAQ total scores following intervention (Figure 3-4). The result indicated a benefit with CSWT (pooled MD 10.96; 95% CI 1.66 to 20.26), but heterogeneity was extreme ($I^2 \approx 100\%$). Study design-based subgrouping did not resolve the dispersion/heterogeneity; effects were larger and more stable in RCTs and markedly variable in observational studies. These features lower certainty and warrant cautious interpretation.

Left Ventricular end Diastolic (LVEDD)

Three studies[6,11-12] (n = 135), including two randomized controlled trials (RCTs) and one observational study, assessed changes in Left Ventricular End-Diastolic Diameter (LVEDD) between CSWT and control groups (Figure 4-1). Meta-analysis revealed significant heterogeneity ($P< 0.00001$, $I^2=96\%$), necessitating the use of a random-effects model. The pooled estimate showed no statistically significant difference between groups (MD = –1.50 mm; 95% CI: –5.18 to 2.18; P = 0.42). No meaningful RCT–observational difference was detected.

Left Ventricular Ejection Fraction (LVEF)

Four studies[6,10–12] (n = 221), comprising two RCTs and two observational trials, investigated the impact of CSWT on Left Ventricular Ejection Fraction (LVEF) **(Figure 4-2)**. High heterogeneity was evident across the studies ($P < 0.00001$, $I^2 = 98\%$), warranting the application of a random-effects framework. Meta-analytic results demonstrated a significant elevation in LVEF favoring CSWT (MD=4.43%; 95%CI 2.66 to 6.21; $P<0.00001$). Subgroup analysis by study type demonstrated no statistically significant differences. The result should be interpreted carefully.

Weekly Nitroglycerin Used

Weekly nitroglycerin consumption was reported in four studies[11–14] (n = 236), including two RCTs and two observational studies **(Figure 4-3)**. High heterogeneity was identified ($P<0.00001$, $I^2= 98\%$), for which a random-effects model was utilized. The synthesis of available data indicated a significant reduction in nitrate use in the CSWT group compared with controls (MD –1.62 doses/week; 95%CI –2.61 to –0.62; P=0.001). Subgroup analyses by study design showed no significant between-group differences. Because of the high heterogeneity, the result should be interpreted carefully.

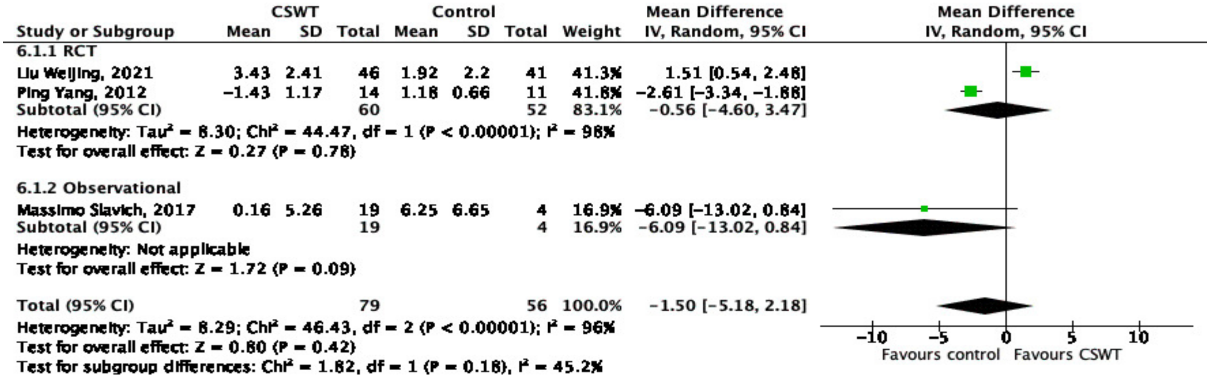

Figure 4-1. Forest plot of the CSWT group vs the control group-LVEDD.

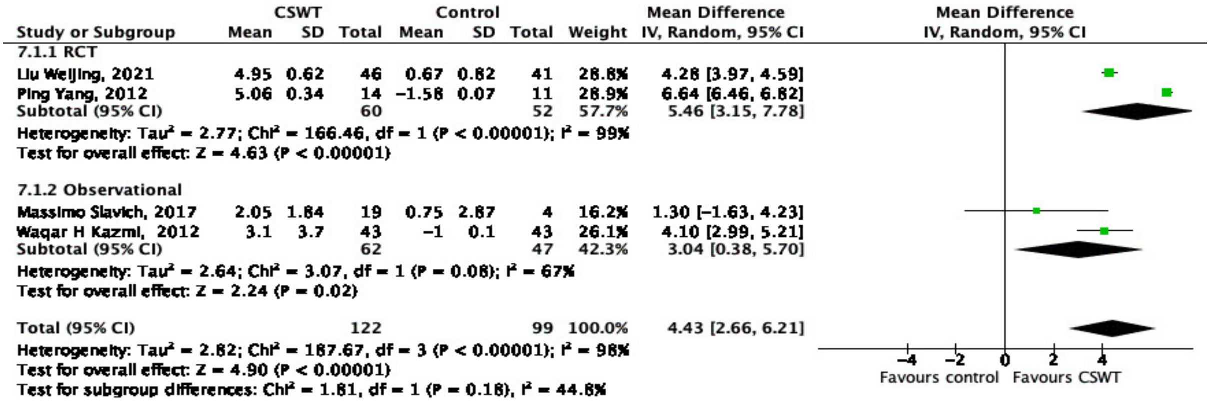

Figure 4-2. Forest plot of the CSWT group vs the control group-LVEF.

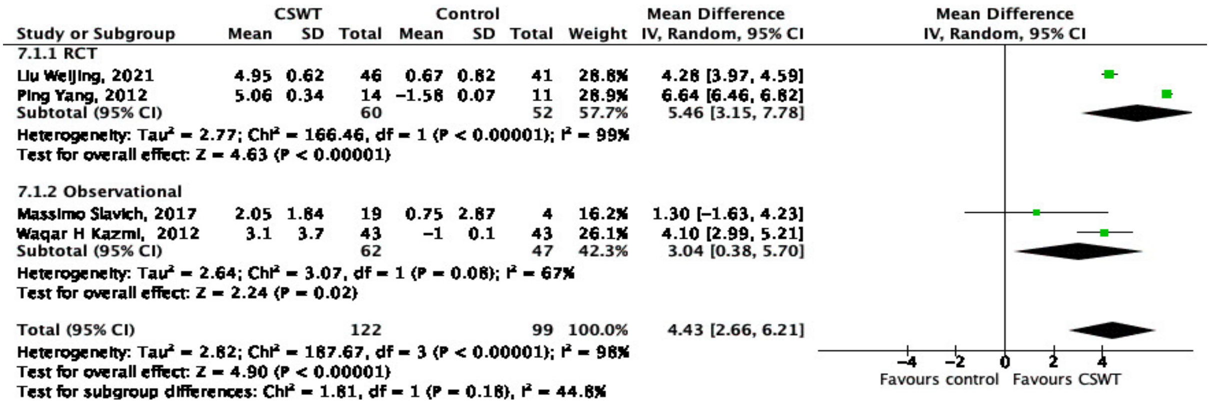

Figure 4-3. Forest plot of the CSWT group vs the control group-Nitroglycerin used.

Discussion

Mechanistically, CSWT is a non-invasive modality that enhances myocardial perfusion and mitigates anginal symptoms by delivering focused shockwave pulses to ischemic myocardial regions, typically localized via imaging.[4] Its therapeutic effect is mediated by shockwave-induced mechanotransduction, which stimulates angiogenesis through vasodilation, neocapillarization, and upregulation of multiple angiogenic signaling pathways.[16-17]

The magnitude of effect observed here is clinically relevant. A mean CCS reduction of 0.76 classes approximates a one-category improvement, often translating into fewer anginal episodes and less rescue nitrate use in daily life. The 6MWT gain in RCTs (~70–80 m) clearly exceeds the typical minimal clinically important difference reported for cardiopulmonary populations (~25–45 m), indicating a tangible improvement in functional capacity. A ~11-point increase in SAQ corresponds to a noticeable improvement in health-related quality of life for stable angina. However, the pronounced heterogeneity and instability observed in the sensitivity analyses, especially for the 6MWT and SAQ, indicate that the most reliable evidence comes from randomized controlled trials, whereas findings from observational studies should be interpreted with caution.

Clinically plausible explanations for the 6MWT discrepancy include: (i) rigorous stabilization of background therapy and mitigation of expectation effects in sham-controlled RCTs versus usual-care controls in observational designs; (ii) residual confounding and selection in non-randomized cohorts; and (iii) small-study effects. Therefore, we prioritize subgroup-specific interpretation for 6MWT and integrate risk-of-bias–guided sensitivity analyses, as recommended by contemporary evidence-synthesis standards.

Angiogenesis and vasculogenesis are the predominant mechanisms underlying CSWT, culminating in myocardial repair and functional recovery. The underlying biological effects are predominantly mediated through the upregulation of Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF), both of which serve as pivotal regulators of angiogenic remodeling and tissue repair.[18] Moreover, CSWT induces a phenomenon often referred to as the "cavitation effect," wherein microscopic bubbles form within myocardial tissue. Their subsequent oscillation and collapse generate mechanical forces, specifically shear stress, that act directly upon cellular membranes. Notably, Fluid Shear Stress (FSS) has been identified as an important trigger of arteriogenesis, particularly after arterial occlusion or severe stenosis, thereby enhancing blood flow and vessel formation in the affected regions.[19]

CSWT is delivered via a generator integrated with cardiac ultrasound for precise targeting of ischemic regions, and is synchronized with the Electrocardiogram (ECG) to avoid electrical impulses during myocardial repolarization, thereby reducing arrhythmogenic risk. Each session typically delivers 1,000 shocks across targeted areas, with a standard protocol of 9 sessions. The procedure is well tolerated and associated with minimal side effects, although poor acoustic windows and left ventricular thrombus are relative contraindications.[16]

By combining the most recent research and examining a range of clinical outcomes, to our knowledge, this is the updated meta-analysis specifically addressing the impact of CSWT in patients with RA. The principal observations can be summarized as follows: (1) CSWT attenuates the frequency of anginal episodes, reflected in reduced nitrate utilization, lower CCS grading, and enhanced SAQ scores; (2) CSWT augments left ventricular performance, demonstrated by improvements in LVEF; (3) CSWT ameliorates overall cardiac function, evidenced by favorable shifts in NYHA classification, thereby translating into tangible gains in daily activity and functional status; and (4) CSWT enhances exercise tolerance, as indicated by an increased distance covered during the 6-minute walk test. However, LVEDD was not statistically significant.

Our results are broadly consistent with earlier evidence syntheses. Xinze Wu et al.[20] in a meta-analysis encompassing 19 trials with 1,254 subjects, reported substantial benefits in functional capacity, angina classification, nitrate requirement, and LVEF, although no significant differences were observed for SAQ scores or exercise duration. Another meta-analysis by Hai Tao Yang in 2020, including 26 studies and involving 781 patients, concluded that CSWT offers pronounced improvements in anginal symptomatology, exercise endurance, quality of life, nitrate consumption, and myocardial perfusion. Together, these findings highlight the multifaceted benefits of CSWT, particularly in enhancing myocardial perfusion and functional recovery.[5]

The first clinical trial of the application of CSWT in refractory angina was conducted by Yoshihiro et al. in protocols employing low-intensity shockwave delivery (4,000–8,000 shocks over 20–40 spots) thrice during the initial week. Remarkably, without anesthesia or analgesic requirements, investigators observed symptomatic relief, reduced nitroglycerin dependence, and enhanced myocardial perfusion in ischemic regions, all without procedure-related complications or adverse sequelae.[6] Subsequent studies confirmed that CSWT significantly enhances left ventricular function in patients with Ischemic Heart Disease (IHD).[21] Another use of shockwave therapy is in the perioperative context, where prophylactic low-energy SWT facilitates wound healing following saphenous vein harvesting for CABG. The proposed mechanisms include upregulation of VEGF and Flt-1, stimulation of angiogenesis, and enhanced production of nitric oxide via nonenzymatic pathways.[23]

CSWT may be especially valuable for patients with Multiple-Vessel Coronary Artery Disease (MVD) who are candidates for PCI or CABG. In such patients, extensive myocardial necrosis, fibrosis, or impaired ventricular compliance limits the efficacy of conventional revascularization strategies. The therapeutic principle of CSWT relies on the delivery of low-energy, high-frequency shockwaves to ischemic myocardial tissue. These pulses induce mechanical shear stress, cavitation, and microstreaming, thereby stimulating angiogenesis and microvascular remodeling. The precision of this intervention is enhanced by echocardiography-guided localization, with shockwave delivery synchronized to the R wave of the electrocardiogram during the absolute refractory period, thereby ensuring procedural safety.[5]

Despite its promising outcomes, several limitations exist regarding the clinical application of CSWT. First, a restricted acoustic window limits treatment to accessible myocardial regions, most often the anterior wall. Second, concerns have been raised regarding potential pulmonary injury due to adjacent tissue exposure. As an alternative, an epicardial approach during surgical procedures has been proposed to optimize energy delivery. Recent intraoperative studies combining CSWT with CABG have demonstrated encouraging results, including significant improvements in LVEF and exercise capacity among patients with ischemic cardiomyopathy.[22-23] These findings suggest that hybrid strategies may broaden the therapeutic scope of CSWT and improve its clinical utility.

Most trials included in this analysis are relatively small, single-center, single-arm studies, and some lack sufficient methodological transparency and result reporting. The predominance of high heterogeneity across outcomes necessitates a cautious interpretation of the pooled findings. This meta-analysis specifically focused on RA patients and double-arm (controlled) studies to provide more robust evidence. CSWT has not yet been widely adopted in clinical practice, despite its excellent tolerability, minimal side effects, significant symptomatic benefits, and non-invasive nature. This limited adoption may be attributed to the need for specialized, high-cost equipment, advanced expertise in ultrasound scanning and CSWT application, and the considerable time commitment required for the full course of treatment.[24] Nevertheless, CSWT represents a promising adjunctive treatment for managing RA, offering an effective and innovative treatment option.[25]

Conclusion

Patients with RA may benefit from the new, non-invasive treatment known as CSWT. It appears to enhance exercise tolerance through multiple pathways: by diminishing the frequency of anginal episodes, as evidenced by reductions in CCS grading and nitrate use; by yielding higher SAQ scores; and by augmenting left ventricular performance, reflected in measurable gains in LVEF, improves cardiac performance, as shown by the decrease in NYHA classification, and can increase the distance of a 6-minute walk. LVEDs were not statistically significant, nevertheless. CSWT may be a promising, safe, and effective cardioprotective strategy that should be further explored in patients with refractory angina. It is hoped that this procedure will lessen the need for re-revascularization following PCI/CABG. However, substantial heterogeneity and a statistically significant RCT-versus-observational divergence for 6MWT warrant cautious interpretation and emphasis on sham- or OMT-controlled randomized evidence. Furthermore, information on its long-term effectiveness in relieving symptoms, improving cardiac function, and reducing mortality rates remains insufficient. Therefore, future multicentre RCTs with standardized comparators and transparent reporting of control interventions are needed to consolidate indications and optimize CSWT protocols in refractory angina.

List of Abbreviations

6MWT	6 Minute Walking Test
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCS	Canadian Cardiology Society
CI	Confidence Interval
CSWT	Cardiac Shock Wave Therapy
ECG	Electrocardiogram
FSS	Fluid Shear Stress
IHD	Ischemic Heart Disease
LVEDD	Left Ventricular End Diastolic Dimension
LVEF	Left Ventricular Ejection Fraction
MD	Mean Differences
MVD	Multiple-Vessel Coronary Artery Disease
NO	Nitric Oxide
NYHA	New York Heart Association
PCI	Pecutaneous Coronary Intervention
PlGF	Placental Growth Factor
PRISMA	Preffered Reportinf Items for Systematics Review and Meta-Analysis

PROSPERO	Prospective Register for Systematic Reviews
RA	Refractory Angina
RCT	Randomized Controlled Trial
SAQ	Seattle Angina Quetionnaire Score
SD	Standard Deviation
VEGF	Vascular Endothelial Growth Factor

Ethical Clearance

Not applicable.

Publication Approval

All authors have read, critically revised, and approved the final version of the manuscript for submission and publication.

Authors Contributions

FDP and MRA developed the concept for the project and formulated the methodology. FDP managed the study protocol. Both FDP and MRA conducted the literature review, study selection, data collection, and bias risk assessment. FDP carried out the formal data analysis. FDP created visual representations of the results. FDP and MRA analyzed and interpreted the findings. FDP, MRA, and MM prepared the initial draft of the manuscript. They also collaboratively reviewed, validated, and finalized the manuscript, with MRA editing it for submission. MM was responsible for overarching project supervision. All contributors critically evaluated and endorsed the final version of the manuscript for submission.

Acknowledgments

None.

Conflict of Interest

All authors (FDP, MRA, MM) of the study declare no conflict of interest.

Availability of Data and Materials

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Review Article

Accuracy of the YEARS Algorithm Compared to Thoracic Imaging for the Diagnosis of Pulmonary Embolism in Pregnant and Postpartum Patients

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Abstract
Pulmonary Embolism (PE) continues to carry substantial morbidity and mortality, with recent data suggesting a rising trend. Diagnosis during pregnancy and the postpartum period is particularly complex because clinical features often overlap with normal physiological changes. The pregnancy-adapted YEARS algorithm, which integrates clinical probability assessment with D-dimer testing, has been proposed as a strategy to rule out PE while avoiding thoracic imaging and unnecessary radiation. In this systematic review and meta-analysis, we investigated the diagnostic accuracy of the pregnancy-adapted YEARS algorithm in pregnant and postpartum women suspected of PE. Eligible studies were identified through comprehensive searches of PubMed, Scopus, and Cochrane and required the use of CT Pulmonary Angiography (CTPA) or Ventilation–Perfusion (V/Q) scanning as the diagnostic reference standard. The quality of the included studies was assessed using the QUADAS-2 tool. Data from the eligible trials were synthesized in Meta-Disc with a random-effects model. In total, five studies involving 1,036 participants were analyzed, all of which showed a low risk of bias. The pooled results indicated a sensitivity of 1.00 (95% CI: 0.94–1.00), a specificity of 0.12 (95% CI: 0.10–0.14), and an AUC of 0.72, suggesting that the algorithm performs well in excluding PE but is less reliable for confirming the diagnosis. These results indicate that the pregnancy-adapted YEARS algorithm may serve as a safe screening approach to minimize radiation exposure for both mother and fetus. However, confirmatory thoracic imaging remains necessary in patients with positive findings.

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Keywords: YEARS algorithm, pregnancy, postpartum, pulmonary embolism, CT Pulmonary Angiography, V/Q scan.

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Introduction

Pulmonary Embolism (PE), a major contributor to maternal morbidity and mortality, accounts for up to 20% of maternal deaths.[1] Among pregnant women and those in the postpartum period, the risk of venous thromboembolism increases four- to five-fold due to physiological changes such as hypercoagulability, venous stasis, and vascular injury. However, clinical diagnosis is challenging because symptoms such as dyspnea and leg swelling often mimic normal physiological changes of pregnancy.

In the general population, diagnostic evaluation for PE typically includes clinical assessment, D-dimer testing, and thoracic imaging. However, these strategies are less reliable during pregnancy because D-dimer concentrations rise physiologically with gestation, leading to frequent reliance on imaging in suspected cases.[2] Since CT Pulmonary Angiography (CTPA) and Ventilation–Perfusion (V/Q) scans expose patients to ionizing radiation, their use during pregnancy raises safety concerns for maternal and fetal health.[3] To address this, the pregnancy-adapted YEARS algorithm was developed, integrating clinical criteria with D-dimer thresholds adjusted for gestational age. This strategy aims to reduce the need for thoracic imaging by safely excluding suspected PE in many cases. Although several studies have investigated its application in pregnant populations, the findings have been inconsistent.[4]

A prior meta-analysis evaluated the diagnostic accuracy of the YEARS algorithm in the general population. That review included nearly 14,000 patients across 10 studies and reported a sensitivity of 96%, specificity of 50%, and a 22% reduction in advanced imaging.[5] These findings support the safety of the YEARS algorithm as a rule-out tool while showing its limited value for ruling in PE. Notably, that analysis did not include pregnant women, leaving uncertainty about whether its diagnostic accuracy extends to pregnancy, a setting where physiological changes affect both pre-test probability and D-dimer interpretation.[6]

This systematic review and meta-analysis examines pregnant and postpartum women with suspected PE and assesses the diagnostic accuracy of the pregnancy-adapted YEARS algorithm compared with thoracic imaging as the reference standard

Methods

Strategy and Study Selection

This study was conducted as a systematic review and meta-analysis in accordance with PRISMA guidelines. The search strategy covered three major databases (PubMed, Scopus, and the Cochrane Library) and included the keywords "pregnancy," "YEARS algorithm," and "pulmonary embolism." Duplicate records were removed prior to screening. Two reviewers (HA and RM) independently evaluated titles and abstracts to exclude ineligible

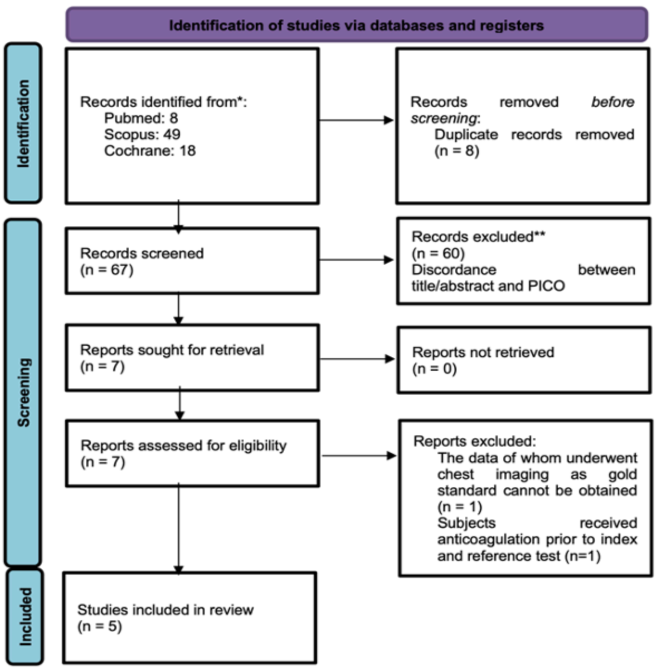

Figure 1. PRISMA flowchart.

Table 1. Study characteristics.

Author	Design	Population	Inclusion criteria	Exclusive criteria	Index text	Reference text	Mean age (y)	Obstetric period	PE Prevalence	Reported D-dimer	Number of subjects	Risk of bias
Langlois E, 2019[5]	Retro-spective cohort	Pregnant women suspected of PE	Outpatient pregnant women presenting with a suspected PE at 11 centers in France and Switzerland between August 2008 and July 2016	• Decline to participate • Unable to provide consent • Allergy to contrast • On full-dose anticoagu-lation • No D-dimer test	YEARS algorithm	CTPA	31.1 + 6.1	1st trimester: 21.8%, 2nd: 43.9%, 3rd: 35.3%	6.5%	Not reported	294	Low risk
Mileto A, 2024[6]	Retro-spective cohort	Pregnant women suspected of PE	Pregnant patients ≥18 years of age who presented to the ED with chief complaints consistent with a suspected PE	• Did not receive a D-dimer test as part of their clinical workup • Worked up for a PE out-side their pregnancy period	YEARS algorithm	CTPA	27.9 (19–38)	1st trimester: 21.6%, 2nd: 36.4%, 3rd: 41.9%	2.7%	Not reported	35	Low risk
Oweidat KA, 2020[4]	Cross-sectional	Pregnant women suspected of PE	Pregnant woman age >18 years	• Missing data needed to deter- mine YEARS criteria • Anticoagulation treatment before doing D-dimer • Diagnosis of deep vein thrombosis with Doppler ultrasound	YEARS algorithm	CTPA or ventila-tion-per-fusion (V/Q) scan	30.4 ± 5.7	1st trimester: 4.5%, 2nd: 15,2%, 3rd: 80.4%	4.5%	Median: 0.3/0.4/ 1.32 μg/mL (1st/2nd/3rd trimester)	112	Low risk
Potgieter R, 2022[3]	Cross-sectional	Pregnant and post-partum women suspected of PE	In-patients presenting with suspected pulmonary embolism in the pregnancy and puerperal periods who underwent CT pulmonary angiogram at Kalafong Provincial Tertiary Hospital Radiology Department from 1 June 2017 to 1 June 2020	D-dimer was not performed	YEARS algorithm	CTPA	Not reported	Pregnancy & puerperium	5.9%	Not reported	101	Low risk
van der Pol, 2019[7]	Pro-spective cohort	Pregnant women suspected of PE	Consecutive pregnant women with clinically suspected pulmonary embolism screened at the 18 participating hospitals	• Received anticoagulant treatment >= 24 hour be-fore eligibility assessment •Were not pregnant • Had contraindication for CTPA • Did not undergo d-dimer testing	YEARS algorithm	CTPA	30 ± 5.8	1st trimester: 15%, 2nd: 39%, 3rd: 46%	4%	Median: 505/730/ 1120 ng/mL (1st/2nd/3rd trimester)	494	Low risk

studies, followed by full-text assessment using predefined inclusion and exclusion criteria. The search was finalized on 31 August 2025, and the selection process is illustrated in Figure 1.

Inclusion and Exclusion Criteria

This review included studies that evaluated pregnant women with suspected PE using the pregnancy-adapted YEARS algorithm. The algorithm integrates D-dimer testing with three clinical items: the presence of DVT signs, hemoptysis, and the physician's judgment that PE was the most likely diagnosis. A diagnosis of PE was ruled out when D-dimer values were <1000 ng/mL in the absence of all criteria, or <500 ng/mL when at least one criterion was present. Patients who did not meet these criteria were referred for CTPA or V/Q scanning, which served as the diagnostic reference standard. To be eligible, studies had to apply thoracic imaging as the comparator and report diagnostic accuracy outcomes. Exclusion applied to studies enrolling patients already receiving anticoagulants, those limited only to postpartum women, or those lacking thoracic imaging as a reference. Methodological quality was judged using QUADAS-2, and pooled analyses were performed with a random-effects model in Meta-Disc.

Data Extraction

From each eligible study, data were extracted on study characteristics (author, year, design, sample size, and population features) and details of the index test, including application of the pregnancy-adapted YEARS algorithm, clinical items, and D-dimer thresholds. CTPA or V/Q scanning was considered the reference standard. Outcomes of interest included sensitivity, specificity, and predictive values, with follow-up information noted when available. Extraction was performed independently by two reviewers, with a third author consulted in cases of disagreement.

Statistical Analysis

The statistical analyses were performed using MetaDiSc version 1.4 (Hospital Ramón y Cajal, Madrid, Spain). Sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–), and Diagnostic Odds Ratios (DOR) were pooled with a random-effects model. To display overall diagnostic performance, a Summary Receiver Operating Characteristic (SROC) curve was generated, and the corresponding Area Under the Curve (AUC) was reported. Heterogeneity across studies was examined using the I^2 statistic and Cochran's Q test, where I^2 values above 50% or p-values less than 0.05 were interpreted as significant. Publication bias was not formally evaluated because only a small number of studies were available. All tests were conducted as two-tailed, with $p < 0.05$ considered statistically significant.

Results

Study Selection

The initial search identified 75 records from PubMed, Scopus, and Cochrane databases. After removing eight duplicates, 67 articles were screened based on title and abstract. Of these, 60 were considered irrelevant to the research question and were excluded. Seven full-text articles were retrieved for eligibility assessment. Two were excluded: one for not using thoracic imaging as the reference standard and another for including patients on anticoagulant therapy. Ultimately, five studies were included in the review (Figure 1).

Study Characteristics

A total of five studies, published between 2019 and 2024, were included. The research was conducted across Europe, the Middle East, and Africa. Study designs comprised one prospective cohort, two retrospective cohorts, and two cross-sectional investigations. All included studies assessed pregnant or postpartum women with suspected PE using the pregnancy-adapted YEARS algorithm as the index test, with CTPA or V/Q scanning as the reference standard. Sample sizes ranged from 35 to 494, giving a total of 1,036 participants. The key characteristics of these studies are summarized in Table 1.

Table 2. Risk of bias assessment.

Study	Risk of bias			
	Patient selection	Index test	Reference standard	Flow and timing
Langlois E, 2019[5]	✓	✓	?	✓
Mileto A, 2024[6]	✓	✓	?	✓
Oweidat KA, 2020[4]	✓	✓	✓	✓
Potgieter R, 2022[3]	✓	✓	✓	✓
van der Pol, 2019[7]	✓	✓	?	✓

Risk of Bias

Risk of bias was assessed using the QUADAS-2 tool. Overall, a low risk of bias was observed across all domains (Table 2).

Pooled Diagnostic Accuracy

The pooled analysis showed that the pregnancy-adapted YEARS algorithm had a sensitivity of 1.00 (95% CI: 0.94–1.00), confirming its strong ability to rule out PE. However, specificity was much lower at 0.12 (95% CI: 0.10–0.14), indicating that the tool provides limited confirmation of the disease. The likelihood ratios were 1.13 (95% CI: 1.02–1.25) for LR+ and 0.35 (95% CI: 0.10–1.16) for LR–, while the diagnostic odds ratio reached 3.47 (95% CI: 0.95–12.75). Overall diagnostic performance, illustrated by the SROC curve, yielded an AUC of 0.72, consistent with moderate discriminative capacity (Figures 2–7).

Sensitivity

Sensitivity was consistently high across all included studies, with a pooled estimate of 1.00 (95% CI: 0.94–1.00). No heterogeneity was observed (I^2 = 0.0%, p = 1.000), supporting the robustness of this finding.

Specificity

Specificity was low at 0.12 (95% CI: 0.10–0.14), with marked heterogeneity (I^2 = 95.1%, p < 0.0001). This indicates a tendency to misclassify patients without PE, resulting in a high false-positive rate.

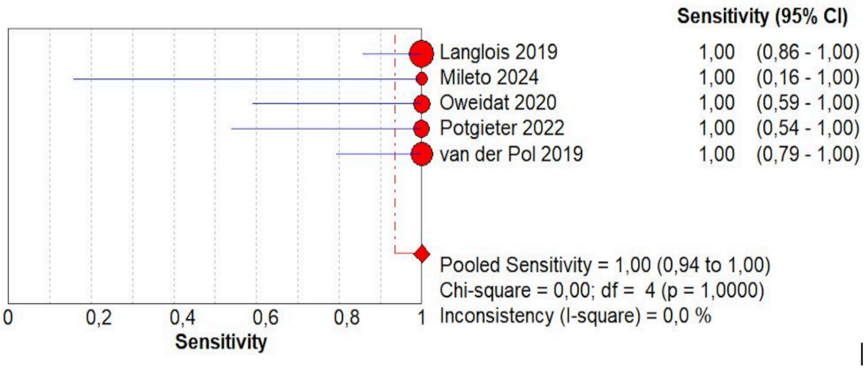

Figure 2. The pooled sensitivity of the pregnancy-adapted YEARS algorithm.

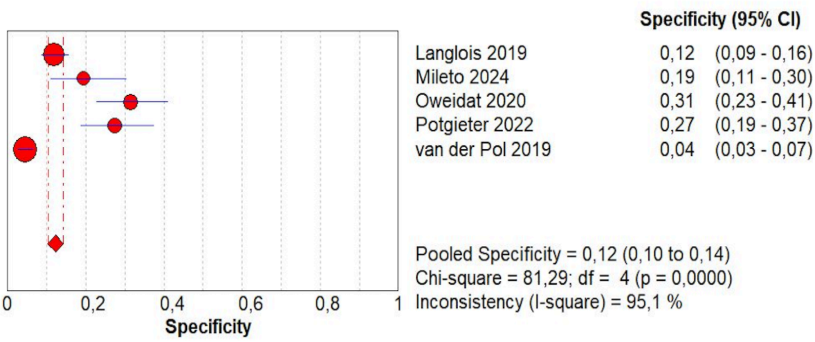

Figure 3. The pooled specificity of the pregnancy-adapted YEARS algorithm.

Likelihood Ratios

The pooled LR+ was 1.13 (95% CI: 1.02–1.25), offering little value in confirming PE. In contrast, the LR– was 0.35 (95% CI: 0.10–1.16), supporting its utility as a rule-out tool.

DOR and SROC

The DOR was modest at 3.47 (95% CI: 0.95–12.75), with no significant heterogeneity (I^2 = 0.0%, p = 0.8675). The SROC analysis yielded an AUC of 0.72, indicating moderate overall discriminative ability of the algorithm.

Discussion

This review analyzed five studies involving 1,036 pregnant and postpartum women suspected of having pulmonary embolism to evaluate the diagnostic performance of the pregnancy-adapted YEARS algorithm. This review found that the pooled analysis demonstrated excellent sensitivity (100%) but low specificity (12%), with an AUC of 0.72. These findings confirm that the algorithm is highly effective for ruling out PE but has limited value for confirming the diagnosis.

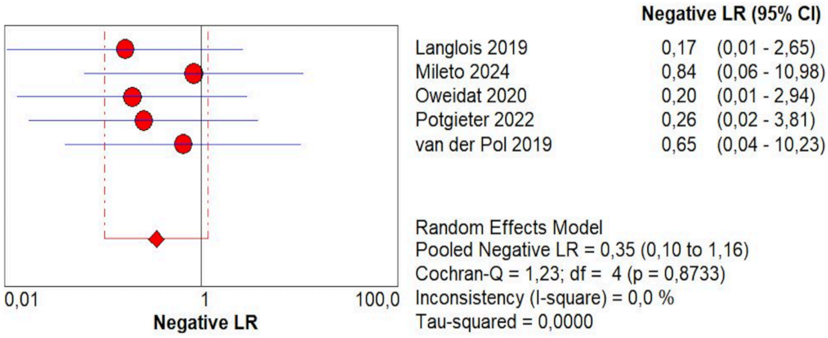

Figure 4. Pooled LR- of the studies.

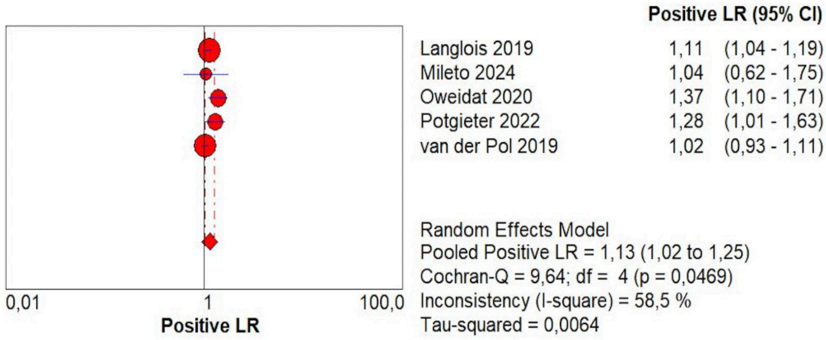

Figure 5. Pooled LR+ of the studies.

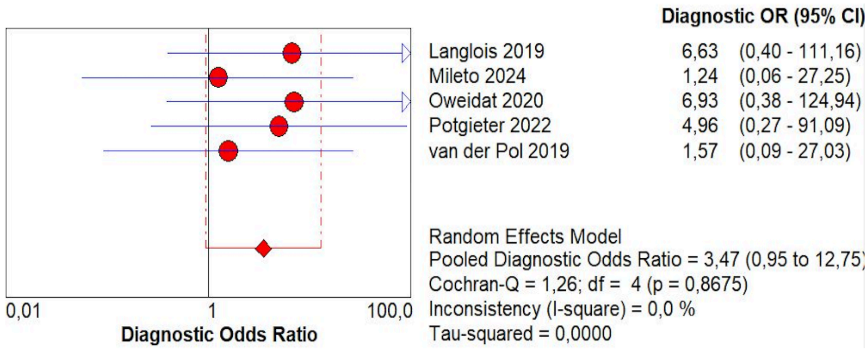

Figure 6. The diasnotic odds ratio of the studies.

Compared with broader populations, our findings are consistent with prior evidence from non-pregnant populations. In the largest meta-analysis to date, Te Haara et al.[5] pooled nearly 14,000 participants. They reported a sensitivity of 96% (95% CI 93–98%) and specificity of 50% (33–67%), alongside a 22% reduction in advanced imaging (RR 0.78, 95% CI 0.67–0.90). These results similarly support the YEARS algorithm as a safe rule-out tool while highlighting its modest rule-in utility. The lower specificity observed in our pregnancy-focused review (12% vs ~50% in the general population) likely reflects pregnancy-specific factors, including physiologically elevated D-dimer levels, the use of lower D-dimer thresholds in adapted protocols, and variations in PE prevalence.[7]

The consistently high sensitivity across both pregnant and non-pregnant cohorts is clinically reassuring, as underdiagnosis of PE in pregnancy can lead to severe maternal and fetal outcomes.[7-8] This aligns with earlier multicentre studies, which showed that combining YEARS criteria with D-dimer testing maintains patient safety while reducing unnecessary imaging.[2,9] However, the very low specificity in pregnancy means that many women without PE will still require confirmatory

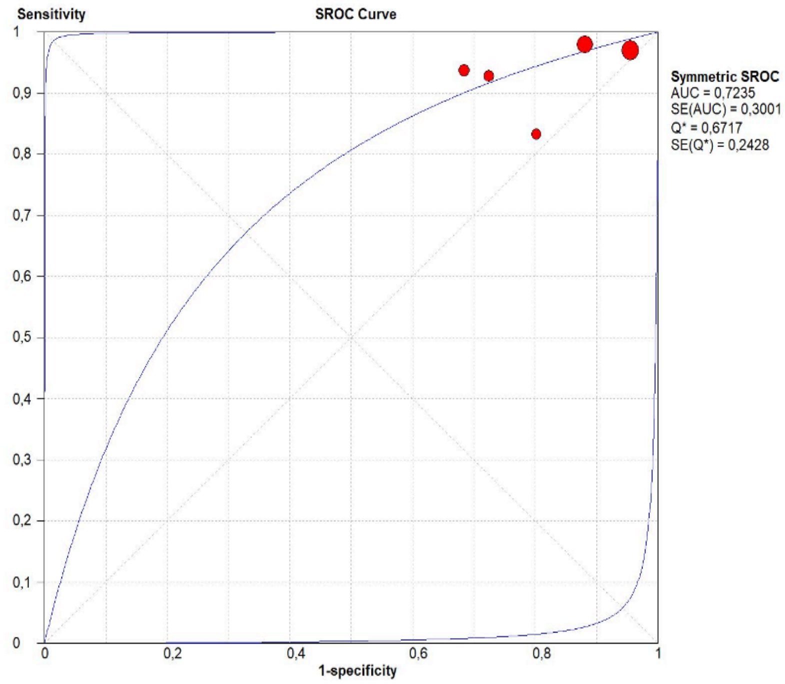

Figure 7. The ROC of the pregnancy-adapted YEARS algorithm.

thoracic imaging. Thus, while the algorithm safely excludes PE, it cannot substitute for imaging when results are positive. [3-4,8]

From a clinical perspective, our findings indicate that the pregnancy-adapted YEARS algorithm can safely defer imaging in women with low pre-test probability, thereby reducing unnecessary radiation exposure. This is particularly important because the breast receives the highest organ dose from CTPA, with an estimated 94 future cancer cases per million CTPA procedures.[10] In settings with limited access to CTPA or V/Q scans, such as Indonesia, the algorithm can help protect low-risk women while conserving scarce resources. Positive cases, however, still require confirmatory imaging, and decisions must balance their excellent sensitivity with low specificity and the constraints of healthcare infrastructure.

Compared with other clinical prediction rules, such as the Wells score for DVT or the revised Geneva score for PE, the pregnancy-adapted YEARS algorithm offers a simpler, more pragmatic approach. Traditional scores were not explicitly designed for pregnancy and have demonstrated limited validation in this population, often leading to poor specificity and higher imaging rates.[10-11] By contrast, the YEARS algorithm, while still limited in specificity, maintains nearly perfect sensitivity and a streamlined diagnostic pathway that is more practical for use in pregnant and postpartum women.

The generalizability of these findings also requires cautious interpretation. The included studies were mainly conducted in Europe, the Middle East, and Africa, across diverse healthcare systems and diagnostic capacities. Because most of the data rely on CTPA as the reference standard, their applicability to low-resource settings where such imaging is less available may be limited. In countries like Indonesia, where diagnostic infrastructure is variable, large-scale prospective studies are needed to validate the relevance of the YEARS algorithm in these environments.

It is also important to note discrepancies across the included studies. Reported PE prevalence varied considerably, from as low as 2.7% in the U.S. study by Mileto et al.[9] to 6.5% in the French–Swiss cohort by Langlois et al., eight while the ARTEMIS trial reported 4.0%.[7] Study populations differed, with Al-Oweidat et al.[4] including predominantly third-trimester patients and Potgieter et al.[3] reporting all PE cases during the puerperium, in contrast to van der Pol et al.,[7] who enrolled women across all trimesters. Differences in design (prospective vs retrospective), D-dimer assays, and reference standards (CTPA, V/Q) also contributed to heterogeneity in findings, particularly specificity estimates. These variations highlight the need for harmonized diagnostic protocols and large-scale multicentre validation.

By focusing exclusively on pregnant and postpartum cohorts, this review builds on earlier analyses by confirming the safety of the YEARS algorithm for ruling out PE while highlighting its limitations as a confirmatory tool. Future studies should directly compare the YEARS algorithm with other clinical prediction models to refine diagnostic strategies for this high-risk population.

Limitations

This review is subject to several limitations. The number of available studies was small (n = 5), and sample sizes were modest, which may reduce statistical power and the precision of pooled estimates. Considerable heterogeneity was observed, particularly in specificity, likely due to differences in study design, patient selection, and reference standards. Most trials relied on CTPA as the reference test, with limited use of V/Q scans, which restricts generalizability to settings where nuclear medicine is more commonly used. This limitation is especially relevant in low-resource environments, including Indonesia, where access to advanced thoracic imaging is limited and confirmation of positive YEARS results may be challenging. Variation in D-dimer assays and threshold values across studies may also have influenced diagnostic accuracy. Publication bias could not be formally assessed because of the small number of included studies; more minor negative or inconclusive studies may remain unpublished, potentially inflating estimates of diagnostic safety. Although the literature search covered PubMed, Scopus, and Cochrane, it remains possible that some studies were missed, particularly unpublished or non-English reports. Finally, as all included studies were observational, residual confounding and selection bias cannot be excluded. To strengthen the evidence base, future large-scale, prospective, multicenter studies are needed to validate the diagnostic accuracy of the pregnancy-adapted YEARS algorithm across diverse healthcare settings, including those with limited resources.

Conclusion

The pregnancy-adapted YEARS algorithm showed excellent sensitivity (100%) for ruling out PE in pregnant and postpartum women, yet its specificity remained low (12%), limiting its usefulness for diagnostic confirmation. It may be safely applied to reduce unnecessary imaging and radiation exposure in low-risk patients, although imaging remains essential for positive cases. Validation through large-scale, prospective studies is needed to strengthen these findings and guide optimal management strategies in this high-risk population.

List of Abbreviations

AUC	Area Under the Curve
CI	Confidence Interval
CTPA	Computed Tomography Pulmonary Angiography
DOR	Diagnostic Odds Ratio
DVT	Deep Vein Thrombosis
LR+	Positive Likelihood Ratio
LR-	Negative Likelihood Ratio
PE	Pulmonary Embolism
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
ROC	Receiver Operating Characteristic
SROC	Summary Receiver Operating Characteristic
V/Q	Ventilation-Perfusion (scan)

Ethical Clearance

Not required. This work is a systematic review and meta-analysis of previously published studies; no new human participants were recruited and no individual level, identifiable data were collected.

Authors Contributions

HA, RM, and LKP conceived the study idea and concept. HA and RM contributed to study design and preparation of figures. VR supervised the project. HA and RM drafted the manuscript. All authors reviewed, commented, and approved the final version of the manuscript.

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Case Reports

From Benign Origins to Final Moments: Right Ventricular Outflow Tract Premature Ventricular Complexes Culminating in Asystole on Holter Monitoring

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Abstract

Background: Premature Ventricular Complexes (PVCs) are a common cardiac arrhythmia, typically of a benign nature. Their origin in the right ventricular outflow tract (RVOT) is often of interest due to its implications for treatment strategies. While the vast majority of PVC RVOT cases remain uneventful, isolated incidents challenge this common perception. Continuous monitoring methods, such as the Holter monitor, have provided invaluable insights into the real-world dynamics of arrhythmias, capturing rare events that can be of paramount clinical significance.

Case Illustration: A 60-year-old female presented to Harapan Kita Hospital Jakarta, in May with palpitations. Over several visits, physical examinations consistently indicated a heart within normal parameters, free of murmurs or gallop. Successive ECGs revealed persistent PVCs of RVOT origin. Despite medical intervention, her arrhythmic pattern persisted. By September, her symptoms had diversified, including occasional chest pain, nausea, and dyspnea. An ECG, yet again, confirmed PVCs with RVOT origin. During a Holter monitoring session in September, a distressing sequence of events was captured. The monitor initially registered a non-sustained Ventricular Tachycardia (VT), which escalated to sustained VT, ventricular fibrillation, and culminated in asystole, marking the patient's final moments.

Conclusions: The pathophysiological journey from benign PVCs of RVOT origin to a fatal arrhythmic event underscores the unpredictability and inherent dangers of cardiac arrhythmias. This case is a reminder of the critical importance of persistent monitoring, timely interventions, and the nuanced understanding of conditions conventionally deemed 'benign'.

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Keywords: Premature Ventricular Complex, Right Ventricular Outflow Tract, Ventricular Tachycardia, Sudden Cardiac Death, Holter Monitoring

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Introduction

Ectopic beats originating from the ventricles are identified as Premature Ventricular Complexes (PVCs). These are prevalent and can manifest in numerous clinical contexts and among a broad spectrum of individuals.[1-3] In the past, PVCs were generally viewed as harmless. While some patients may not exhibit any symptoms, others may present acute symptoms directly related to PVCs or gradual symptoms resulting from the sustained impact of frequent PVCs on the heart's ability to contract.[2,4] PVCs are widely distributed, with most individuals demonstrating their presence during extended ambulatory assessments.[5-6] Factors like advancing age, greater stature, elevated blood pressure, prior heart conditions, decreased physical activity, and smoking habits tend to increase the likelihood of PVC occurrence.[1] While the core origins of PVCs are not definitively understood, potential triggers might encompass spontaneous activity, inherent automaticity, or reentrant pathways. Often, these PVCs might go unnoticed, but they can also manifest through symptoms like heart palpitations, shortness of breath, near fainting, and fatigue.[4-5]

Diagnosing and evaluating PVCs critically relies on a combination of patient history, physical examination, and 12-lead ECG. In instances where there are explicit symptoms or an unusually high frequency of PVCs, an echocardiogram is recommended.[6] Further, cardiac magnetic resonance imaging becomes pivotal when there's an indication of accompanying structural heart anomalies. To gauge the regularity of PVCs, ambulatory monitoring becomes indispensable.[3] The long-term outlook for individuals with PVCs ranges widely. Specific key indicators that might predict unfavourable outcomes remain ambiguous. However, a high frequency of PVCs can potentially lead to heart complications or even mortality.[7]

Case Illustration

A 60-year-old female, weighing 53 kg and standing at a height of 147 cm, initially presented to the National Cardiovascular Center Harapan Kita Jakarta with palpitations. Physical examinations revealed normal heart sounds without any murmur or gallop. Pulmonary auscultation was vesicular with no signs of wheezing or rhonchi. The ECG identified PVCs, as showcased in Figure 1, which illustrated a PVC with QRS morphologies of Left Bundle Branch Block (LBBB) and inferior axis, suggesting an origin from the Right Ventricular Outflow Tract (RVOT) on sinus rhythm.

On her follow-up visits, the patient presented with a stable condition. The RVOT-origin PVCs remained consistent on her ECG. The treatment strategy at this time was optimized medical treatment. However, during one visit, the patient reported occasional epigastric pain, nausea, and shortness of breath, but no palpitations. Physical examinations remained consistent with previous results. The ECG still displayed PVCs of RVOT origin. Given these findings, a Holter monitoring was planned along with the scheduling of ablation. During the Holter monitoring, a catastrophic event occurred. The patient experienced an episode of nonsustained VT, as shown in Figure 2, transitioning from sinus rhythm to nonsustained monomorphic VT and then to sustained monomorphic VT. The situation continued, transitioning from monomorphic VT to Ventricular Fibrillation (VF) and finally to asystole, as shown in Figure 3 and Figure 4.

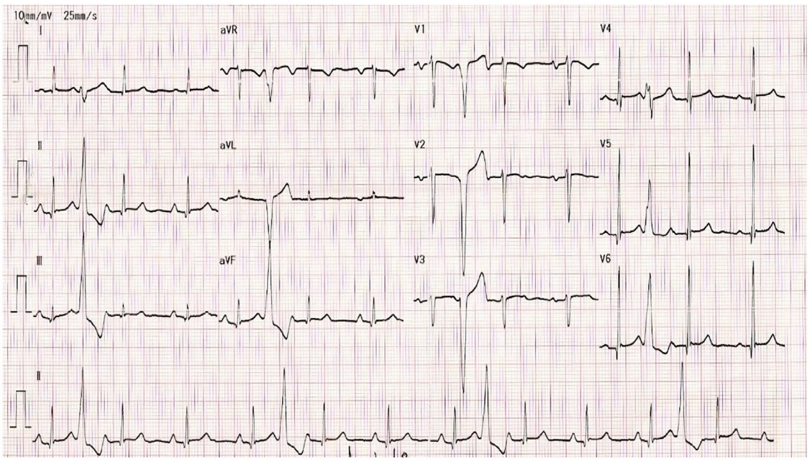

Figure 1. Electrocardiogram displaying PVC originating from RVOT on sinus rhythm.

It is worth noting that a year before the first reported episode, the patient was referred with a history of monomorphic VT. Her complaints were intermittent palpitations without any associated syncope. Past medical history and risk factors were non-contributory. Physical examinations revealed normal heart and lung findings. The ECG at that time demonstrated frequent PVCs originating in the RVOT.

She was planned for VT ablation; however, at the beginning of the ablation procedure, she remained asymptomatic. Notably, baseline ECG showed no PVC or VT. Provocative agents Isuprel up to 2 mcg/kg/min and epinephrine up to 0.15 mcg/kg/min failed to induce any PVC or VT during the session. After 20 minutes of observation, no PVCs reappeared, and the planned ablation was cancelled. The discharge medications included Concor 1.25 mg, Candesartan 8 mg, Simvastatin 20 mg, and Miniaspi 80 mg. Then, the patient was advised to schedule a follow-up and continue her medications as prescribed.

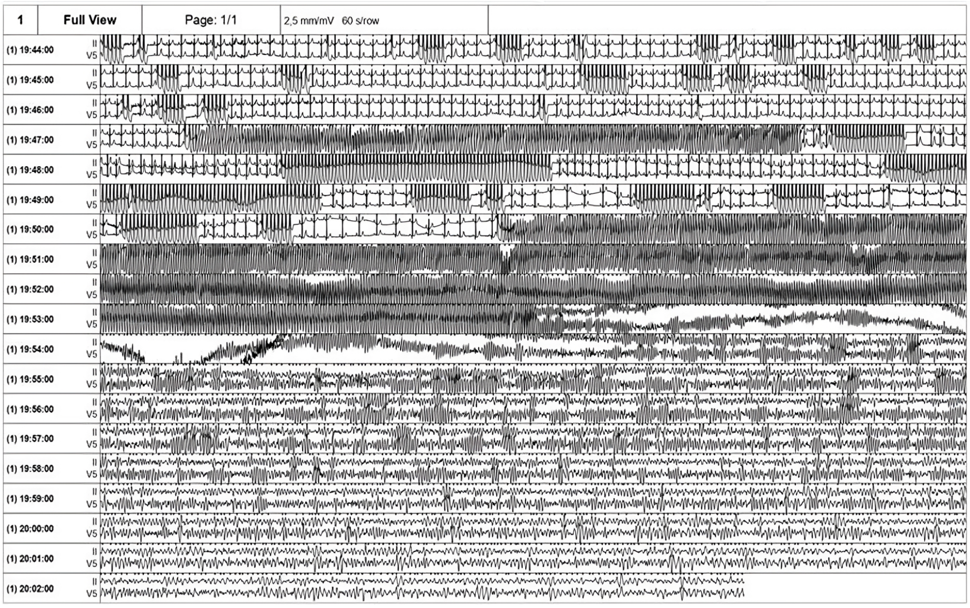

Figure 2. Electrocardiographic progression from sinus rhythm to non-sustained monomorphic VT and subsequently into sustained monomorphic VT.

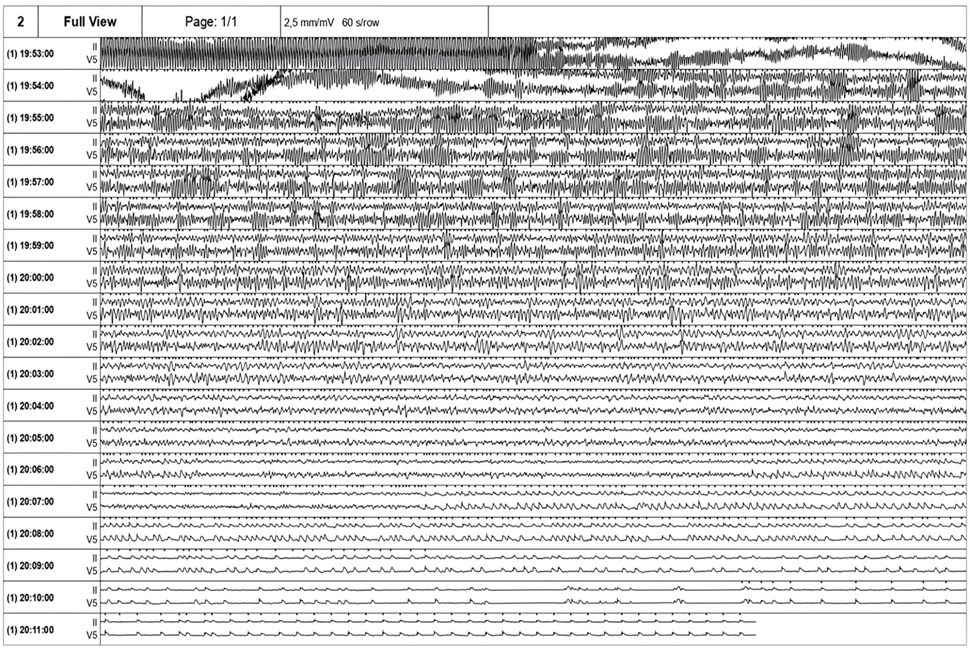

Figure 3. Transition from monomorphic VT to polymorphic VT, ventricular fibrillation, and bradycardia.

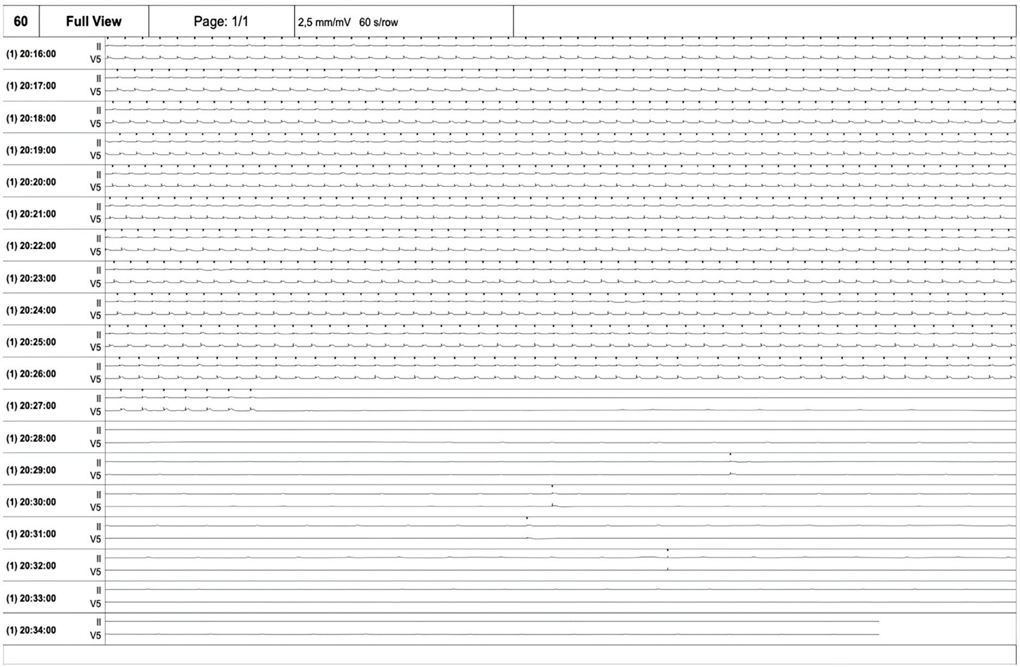

Figure 4. Transition from bradycardia to asystole.

Following the cancelled ablation, the patient was discharged on bisoprolol 1.25 mg, candesartan 8 mg, simvastatin 20 mg, and aspirin 80 mg, and was advised regular follow-up. During this period, she continued to experience intermittent palpitations without syncope. Several months later, her symptoms evolved to include epigastric pain, nausea, and dyspnea, while her ECG consistently showed PVCs of RVOT origin. During a Holter monitoring session, these arrhythmias progressed from non-sustained VT to sustained VT, then VF, and ultimately asystole, resulting in her death.

This case exemplifies the deceptive nature of RVOT-origin PVCs, which are often regarded as benign. The patient's trajectory from presenting with simple palpitations to a critical asystole episode captured on Holter, alongside the detailed figures, emphasizes the importance of vigilant monitoring and aggressive intervention when indicated. The progression displayed in the statistics is rare on continuous Holter monitoring, underscoring the crucial and invaluable insights it can offer, even when the patient remains asymptomatic.

Discussion

Holter monitoring is a valuable tool of assessing PVCs, providing insights into their frequency, burden, and potential risks.[8] This case highlights the significance of Holter monitoring findings, particularly when PVCs originate from the RVOT, and underscores the importance of continuous surveillance in patients with seemingly benign PVCs.

Benign PVCs are typically considered harmless, but in rare cases, they can lead to life-threatening arrhythmias.[8] Literature reports have documented extreme outcomes associated with PVCs of RVOT origin, including ventricular fibrillation and sudden cardiac death.[9-10] Although such events are infrequent, they remind us of the need for vigilance when managing patients with PVCs, even when these arrhythmias appear benign.

In this case, although the initial ventricular arrhythmia was monomorphic VT consistent with RVOT origin, the Holter strip demonstrated a transition to polymorphic VT, possibly torsades-like, likely precipitated by an R-on-T phenomenon. This highlights the potential for PVCs to trigger polymorphic VT through afterdepolarization mechanisms. The recording concluded with electrical silence consistent with asystole. This evolution underscores the complexity and unpredictability of PVC-related arrhythmogenesis.

The transition from benign PVCs to fatal arrhythmias remains a subject of investigation. In some patients, underlying structural heart disease or genetic factors might play a role.[11-12] PVCs occurring in patients with a history of Myocardial Infarction (MI) have long been associated with poor prognosis, due to increased risk of VT, VF, and sudden cardiac death in this group. Moreover, growing studies observed beneficial outcomes of cardiac ablation in patients with a high PVC burden and decreased left ventricular function with structural heart diseases.[13] Additionally, the excessive burden of PVCs, as observed on Holter monitoring, can lead to electrical and mechanical remodelling of the myocardium, potentially precipitating arrhythmogenic events.[14] Furthermore, frequent occurrences of PVCs also increase the likelihood of developing PVC-induced cardiomyopathy, whether or not there is pre-existing structural heart disease.[13,15] According to a study by Keles et al., patients with frequent PVCs showed lower early diastolic strain rate than healthy individuals, increasing the risk of left ventricular diastolic dysfunction.[16] The origin of the PVC has also been postulated to affect the risk of developing cardiomyopathy.[14] In a study with a median follow-up time of 5.2 years, the mortality rate in the PVC group was 5.7 per 1000 person-years, significantly lower than the 11.9 per 1000 person-years observed in the control group of the general population without PVC in the absence of structural heart disease.[17]

High-risk PVC morphologies are characterized by short coupling intervals, multifocal origin, or the ability to trigger R-on-T phenomena, all of which predispose to malignant arrhythmias. In our patient, the progression from monomorphic RVOT PVCs to polymorphic VT was most likely facilitated by an R-on-T event, placing this case within the high-risk spectrum despite the initially benign morphology. This highlights the importance of recognizing PVC characteristics that may signal increased arrhythmic risk. Short coupling intervals of 350 ms are considered a high-risk feature.[18] However, in our case, we found that longer coupling intervals, as shown in Figure 5, caused torsades due to the R-on-T phenomenon, whereas shorter coupling intervals, as shown in Figure 6, did not. This underlines the need to re-evaluate the threshold for defining malignant PVC coupling intervals.

Managing patients with benign-seeming PVCs involves a multidimensional approach. Reassurance is often sufficient, but it is crucial to assess the impact of symptoms on a patient's quality of life.[5] In cases where symptoms persist or worsen, medical therapy or catheter ablation may be considered.[2,9] Beta-blockers and calcium channel blockers are commonly used as first-line medications, with catheter ablation demonstrating superior effectiveness.[10] However, the choice between medical therapy and ablation should be guided by patient preference and individual characteristics.

This case offers several lessons for clinicians. First, it underscores the importance of continuous monitoring and thorough examinations in patients with PVCs, even when these arrhythmias initially appear benign. Second, it highlights the need for risk stratification to identify those at higher risk of adverse outcomes.[11] Finally, it emphasizes the evolving nature of PVC management, with ongoing research providing insights into better strategies and interventions.

While this case study provides valuable insights, it has its limitations. The rarity of extreme outcomes in patients with benign PVCs makes it challenging to draw definitive conclusions. Additionally, the case's retrospective nature limits our ability to establish

Figure 5. PVC with coupling interval of 426 ms induces Torsades de pointes.

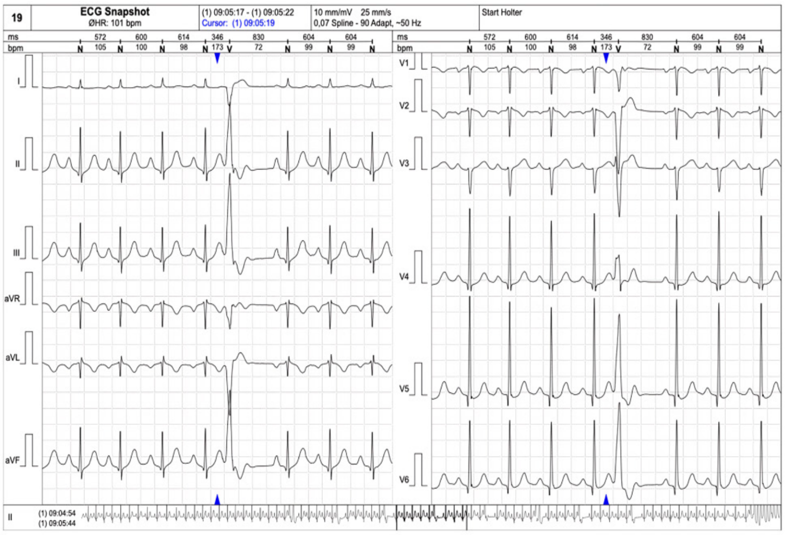

Figure 6. PVC with coupling interval of 346 ms.

causal relationships and generalize findings. There was a lack of evidence to confirm the absence of preexisting structural heart disease in the patient. A significant limitation of this report is the absence of echocardiographic data and a treadmill test, which would have been essential to exclude structural or ischemic heart disease and to assess the potential indication for ICD implantation. This absence restricts the ability to characterize the patient's substrate fully and highlights the need for comprehensive evaluation in similar cases.

Conclusion

In conclusion, this case of benign PVCs ultimately leading to asystole on Holter monitoring serves as a stark reminder of the potential risks associated with these seemingly harmless arrhythmias. Although PVCs are often regarded as benign, especially those originating from the RVOT, they can evolve into life-threatening arrhythmias, as demonstrated in this patient. This case exemplifies the complexity of PVC management and underscores the importance of ongoing advances in diagnostic tools and therapeutic strategies.

List of Abbreviations

ECG	Electrocardiogram
ICD	Implantable Cardioverter Defibrillator
LBBB	Left Bundle Branch Block
MI	Myocardial Infarction
PVC	Premature Ventricular Complex
R-on-T	R-on-T Phenomenon
RVOT	Right Ventricular Outflow Tract
Torsades	Torsades de Pointes
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

Ethical Clearance

Not Applicable.

Publication Approval

All authors approve the manuscript for publication.

Authors Contributions

SBR was the main author who conceptualized the case, provided clinical supervision, and made critical contributions to the manuscript's writing and final revision. SVR and AP assisted with literature searching and manuscript writing. DAH, DYH, and YY provided valuable clinical input, reviewed the manuscript, and offered additional insights on the case details and clinical implications discussed in the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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Copyright/Permissions for Figures

Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

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Case Reports

Antiphospholipid Syndrome Manifesting as Myocardial Infarction: A Case Report and Review of the Literature

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Abstract

Background: Antiphospholipid Syndrome (APS) is characterized by the presence of antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies, and β2-glycoprotein I. These antibodies target phospholipids and associated proteins, leading to diverse clinical manifestations such as stroke, myocardial infarction, and deep vein thrombosis. Acute myocardial infarction caused by arterial thromboembolism is a rare first manifestation of APS.

Case Illustration: We present a case study of a 37-year-old female with a history of Deep Vein Thrombosis (DVT) and no identifiable risk factors, who, a decade ago and recently, experienced a sudden Myocardial Infarction (MI) due to arterial thrombosis. The angiographic appearance and the need for angioplasty were challenging at presentation, as the clot was migratory and had moved between coronary vessels. We conducted a thrombophilia evaluation due to the unusual site of thrombosis and the patient's age at presentation, which led us to establish the diagnosis of APS.

Conclusions: This case highlights the rare but essential association between APS and recurrent MI, as well as the unique angiographic behavior of APS-related coronary thrombi that can complicate percutaneous coronary intervention. While long-term vitamin K antagonist therapy remains standard for secondary prevention, clinicians should recognize APS as a potential cause of MI in young patients and anticipate procedural and therapeutic challenges beyond anticoagulation alone.

(Indonesian J Cardiol, 2025;46;196-206)

Keywords: Antiphospholipid Syndrome, Acute Coronary Syndrome, Myocardial Infarction, Thrombosis.

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Introduction

Antiphospholipid Syndrome (APS) is an autoimmune disorder characterized by the presence of antiphospholipid (aPL) antibodies, which increase the risk of thrombotic events in both veins and arteries.[1-2] These antibodies, including Lupus Anticoagulant (LA), anticardiolipin antibodies (aCL), and β2-glycoprotein I (β2GPI), target phospholipids and associated proteins, leading to diverse clinical manifestations such as stroke, Myocardial Infarction (MI), and Deep Vein Thrombosis (DVT).[1,3-4] This case report underscores the complexities of managing acute myocardial infarction in the context of APS, exemplified by a 37-year-old woman with a history of DVT, presenting with severe chest pain and hypotension at Tehran Heart Center. Her clinical journey, marked by multiple thrombotic events and the eventual identification of aPL, highlights the intersection of APS with acute coronary syndromes and the imperative for comprehensive thrombophilia screening in similar cases. This report addresses the gap in understanding the relationship between thrombophilia and coronary artery disease, emphasizing the importance of greater clinical awareness and personalized treatment approaches to manage such complex clinical situations.

Case Illustration

A 37-year-old woman presented to the emergency department with an acute onset of severe chest pain and hypotension. Electrocardiography revealed ST-segment elevation in leads V1–V2, which corresponds to the septal wall region (Figure 1). The patient had a history of DVT 10 years ago, which had been treated with anticoagulation therapy. In the emergency department, her vital signs showed hypotension and tachycardia, and a physical exam revealed an S3 gallop sound and clear lungs. Emergency coronary angiography showed single-vessel disease with complete occlusion of the Left Anterior Descending (LAD) artery (Figure 2). Following successful wire passage through the

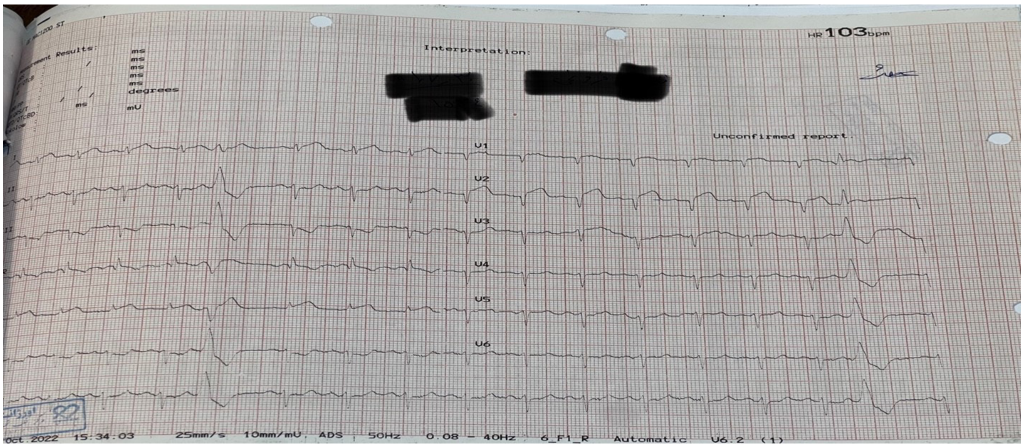

Figure 1. Electrocardiogram upon arrival of the patient to the emergency department.

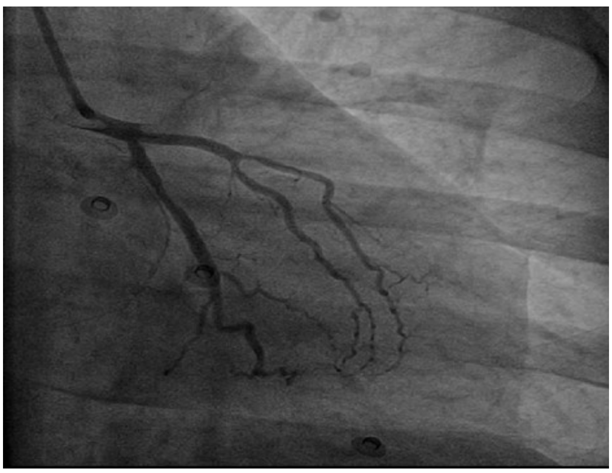

Figure 2. Coronary angiogram revealed that the Left Anterior Descending (LAD) artery is occluded from the ostioproximal.

affected artery, a significant clot was identified as the cause of the LAD artery occlusion. Although a thrombectomy was performed, the chest pain persisted, leading us to place a stent in the proximal LAD. However, shortly after the initial treatment, the patient experienced a recurrence of severe chest pain, similar in intensity to her initial symptoms. Continuous monitoring revealed the development of ventricular tachycardia. Synchronized cardioversion was promptly and successfully delivered with a 200-joule electrical shock. Following this intervention, a repeat examination of the coronary arteries revealed a new occlusion in the proximal segment of the Left Circumflex (LCx) artery and the mid part of the LAD, as depicted in Figure 3. The thrombus in the LAD artery appeared to have migrated and now obstructed the LCx artery. A wire was promptly navigated through the LCx occlusion, and a decision was made to deploy a stent at this location. Following balloon dilation to expand the arteries, a drug-eluting stent was placed in the proximal LAD and LCx, achieving successful reperfusion with TIMI grade 3 flow. The final angiograms from both the initial LAD intervention and the subsequent LCx Percutaneous Coronary Intervention (PCI) demonstrated adequate stent apposition, no residual stenosis in the treated segments, and restoration of distal flow (TIMI Flow = 3) without evidence of thrombus or dissection (Figure 4). Following the post-dilation of the LCx stent, the patient experienced a recurrence of chest pain. A subsequent coronary angiogram revealed a significant stenosis in the midsection of the Ramus Intermedius (RI) artery (Figure 4), which was treated with balloon angioplasty. After these interventions, the patient was transferred to the Coronary Care Unit (CCU) without reporting any further chest pain and with stable vital signs. However, laboratory

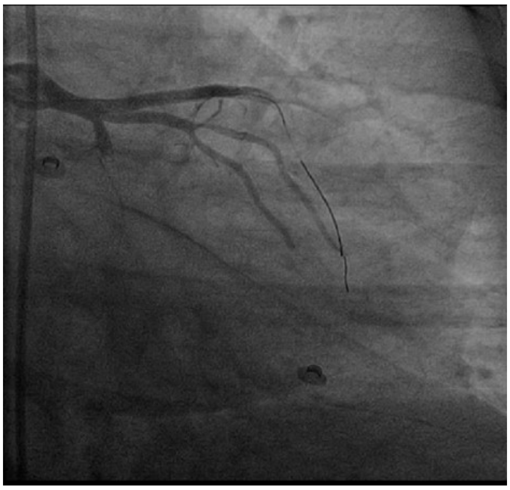

Figure 3. Coronary angiogram revealed left circumflex (LCx) artery occlusion.

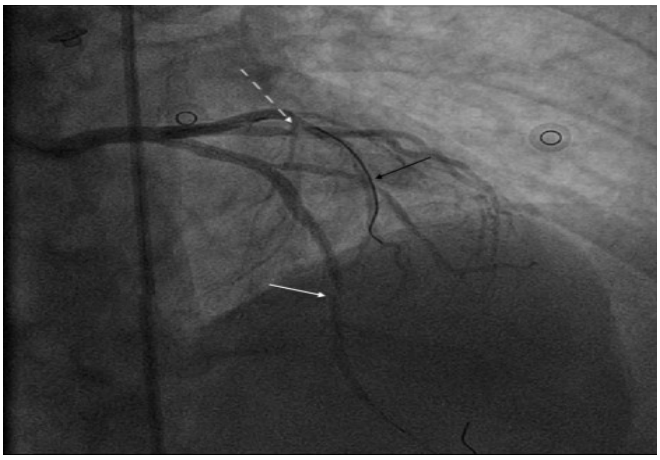

Figure 4. Coronary angiogram showed significant stenosis of the mid portion of the Ramus Intermedius (RI) artery. Black arrow: LCx is patent; there is a wire in LCx. White arrow: The LAD is patent; the wire is shown in the LAD. Dashed arrow: Significant stenosis in RI.

tests revealed a significantly elevated cardiac enzyme level, with a troponin T level of 47,300 ng/L, indicating substantial myocardial damage. Notably, despite the patient's denial of diabetes mellitus or dyslipidemia, laboratory results showed elevated total cholesterol (220 mg/dL), Low-Density Lipoprotein (LDL) cholesterol (170 mg/dL), and a hemoglobin A1c level of 11%, suggesting poorly controlled glycemic levels. Additional laboratory tests were conducted to determine the possibility of a thrombophilia disorder due to the patient's history of DVT and recent acute myocardial infarction caused by a clot. The results showed positive findings for anticardiolipin IgM (19 U/ml), anti-beta2 glycoprotein-1 antibody IgM (22 U/ml), and lupus anticoagulant (62 U/ml). These tests were repeated 12 weeks later, yielding consistent results. Based on these findings, we initiated an intensive antithrombotic treatment regimen to reduce the risk of future thrombotic events. The patient was prescribed a combination of Acetylsalicylic Acid (ASA, also known as aspirin), clopidogrel, and warfarin for one month, followed by clopidogrel and warfarin for an additional year. Long-term warfarin therapy was planned to be continued indefinitely to manage the risk of arterial thrombosis, with a target International Normalized Ratio (INR) of 2.5-3.5 to ensure optimal anticoagulation.

Discussion

APS is characterized by a state of hypercoagulability secondary to circulating antiphospholipid antibodies, which promote thrombus formation via several mechanisms. These antibodies induce endothelial dysfunction, activate platelets, and stimulate coagulation cascades, leading to increased fibrin generation and impaired fibrinolysis. As a result, patients with APS are at heightened risk for migratory and recurrent arterial thromboses, even within coronary vessels during interventional procedures.[5-6]

This case illustrates the procedural dilemmas posed by APS during PCI, particularly the need to balance anticoagulation to prevent new thrombus formation without precipitating bleeding complications or stent thrombosis. Initial management involved attempts at thrombus aspiration, which proved unsuccessful. Due to ongoing hemodynamic instability, coronary stenting was selected to restore flow. Alternative strategies, such as intracoronary thrombolytics, could be considered. Using IIb/IIIa inhibitors and follow-up angiography could also be considered, but was less optimal given the patient's instability.

Thrombotic events associated with APS can affect arteries and veins, leading to diverse symptoms and sequences of thrombotic events

Table 1. A review of the literature on patients with antiphospholipid syndrome who experienced myocardial infarction

	Semczuk-Kaczmarek et al.	Prandi et al.	Marti et al.	Qiu et al.	Cranley et al.	González-Cordero et al.	Ayan et al.	Smukowska-Gorynia et al.	Snipelisky et al.	Pervez et al.	Faizal et al.
Year	2020	2022	2014	2023	2018	2019	2019	2015	2013	2019	2021
Gender	Male	Male	Male	Male	Female	Male	Male	Female	Male	Female	Female
Age	25	51	47	35	51	26	23	43	55	27	46
Past medical history	SLE	No	Inferior MI, PTE, APS	ORIF (lumbar)	APS	No	No	Hx of heavy bleeding	No	Chronic pain syndrome	No
Other risk factors	Overweight (BMI = 29)	Smoking	Hypercoagulability	Smoking	No	No	Smoking, Family history of premature CAD	Smoking	No	No	No
History of VTE	Yes	No	Yes	No	No	Yes	No	No	No	Yes	No
Known case of APS	Yes	No	No	No	Yes (CAPS)	No	No	No	No	Yes	No
MI localization	Anterior	Anterior	Inferior	Inferior	Inferior	Anterolateral	Anterolateral	Anterolateral. Anterior-Inferior (recurrent)	Lateral	Anterior (v4 through v6) and inferior (II, III, aVF)	Anterior-wall
Number of vessels	2	2	1	1	0	1	1	2	1	1	1

Target vessel	LAD and the left marginal artery	LM and ostial LAD	RCA	Posterior descending RCA	Slow flow in RCA	Proximal LAD	Distal LAD	LAD, CX, proximal LAD (recurrent)	RCA	Proximal LAD	Distal LAD
LVEF	47	40	N/A	N/A	N/A	<30	35-40	45	50	Preserved	N/A
Reccurrent MI during admission	No	No	No	Yes	No	Yes	No	Yes	Yes	No	No
Pharmacother spy during admission	DAPT, eptifibatide	Eptifibatide, DAPT	Heparin, abciximab, enoxaparin, DAPT	TT, tirofiban (discontinue), bivalirudin (replaced by fondaparinux), methylprednisolone	LMWH, warfarin, corticosteroid replacement therapy (due to adrenal crisis)	LMWH, nitrates, enalapril, metoprolol succinate, DAPT, eptifibatide	Warfarin, heparin, and anti-ischemic medications	DAPT, statin, eptifibatide ACE II inhibitor, beta-blocker, abciximab, TNG, UFH (replaced by LMWH), methylprednisolone followed by prednisone	Warfarin	TT	Enoxaparin, switched to oral anticoagulation with warfarin
Post-discharge treatment	TT	LMWH, clopidogrel and warfarin	DAPT, acenocoumarol, and atorvastatin	TT	TT, corticosteroid replacement	TT, hydroxychloroquine, high-dose statin, carvedilol, and enalapril	Not mentioned	TT, beta-blocker, ACE II inhibitor, pantoprazole, statin, and prednisone	Warfarin	TT	Enoxaparin was switched to oral anticoagulation with warfarin

SLE: Systemic Lupus Erythematosus; MI: Myocardial Infarction; PTE: Pulmonary Thromboembolism; APS: Antiphospholipid Syndrome; ORIF: Open Reduction and Internal Fixation; CAPS: Catastrophic Antiphospholipid Syndrome; CAD: Coronary Artery Disease; Hx: History; DAPT: Dual Antiplatelet Therapy; TT: Triple Therapy (Oral Anticoagulant Such As Warfarin + DAPT); LMWH: Low Molecular Weight Heparin; ACE II: Angiotensin-Converting Enzyme II; TNG: Trinitroglycerin; UFH: Unfractionated Heparin; RCA: Right Coronary Artery; LAD: Left Anterior Descending; LM: Left Main Artery.

depending on the number of vessels involved or the affected organ. The leading cardiac symptoms of APS include valve disease, myocardial infarction, and intracardiac thrombus. Table 1 demonstrates a review of the literature on the topic. The reported cases span young to middle-aged adults (early 20s to mid-50s) with a slight male predominance, and only a minority had a prior APS diagnosis or classical cardiovascular risk factors. Smoking and a history of venous thromboembolism were the most frequent additional risks. Our patient also had diabetes mellitus and dyslipidemia despite her denial in her past medical history. Diabetes and high cholesterol significantly increase cardiovascular risk and promote endothelial dysfunction in APS, thereby raising the likelihood and severity of arterial thrombosis and atherosclerosis progression. These conditions act synergistically with APS to accelerate vascular events, such as myocardial infarction and stroke, necessitating the aggressive control of both blood glucose and lipids.[7] Infarcts involved both anterior and inferior territories, most often affecting the LAD or right coronary arteries, with single-vessel disease predominating. Left ventricular function ranged from preserved to severely reduced, and recurrent infarction during the same admission occurred in several patients. Management varied but typically combined dual antiplatelet therapy and anticoagulation, often triple therapy with warfarin, alongside steroids or immunomodulation when catastrophic APS or adrenal crisis was suspected. These findings underscore the heterogeneous presentation of APS-related myocardial infarction and highlight the importance of early recognition and aggressive, tailored antithrombotic therapy to prevent recurrence and improve outcomes. A study by Cervera[1] investigated the prevalence of arterial thrombosis in a cohort of 1000 individuals diagnosed with APS. The results showed that 5.5% of these patients experienced MI, whereas only 2.8% of them presented with MI as the initial manifestation of APS.[1] Furthermore, Cervera et al. reported that antiphospholipid antibodies were present in approximately 11% of patients with MI, highlighting the potential role of APS in the pathogenesis of MI.[1] One of the most challenging issues in managing patients with APS is treating those with vascular thrombosis. In our case, the patient presented with acute MI, and Initial thrombus aspiration was attempted as a clot removal strategy; however, it failed to restore adequate coronary flow. Given the ongoing instability and the critical nature of the lesion, stent implantation was selected to promptly re-establish vessel patency, secure the lesion, and minimize the risk of further flow compromise. The LCx occlusion could represent either a) procedure-related embolization of thrombotic material from the LAD during PCI or b) de novo in-situ thrombosis related to the hypercoagulable state of APS. The immediate temporal relationship to LAD manipulation and the abrupt angiographic appearance favor an embolic complication, whereas APS likely enhanced the thrombotic milieu and prolonged the occlusion. We have acknowledged both possibilities, but consider procedure-related embolization on a background of APS the most plausible explanation.[8] Consequently, we opted for a triple antithrombotic therapy regimen consisting of ASA, clopidogrel, and warfarin for an initial period of one month, followed by clopidogrel and warfarin for one year. After that, we decided to continue warfarin therapy indefinitely, with a target INR of 2.5-3.5. However, a significant challenge in treating APS patients is the use of warfarin or Direct Oral Anticoagulants (DOACs), which requires careful consideration and monitoring to balance the risk of thrombosis with the risk of bleeding.

Initially, it is essential to stratify APS patients into high-risk and low-risk groups. A history of arterial thrombosis or triple positivity for LA, aCL, and β2GPI[9] typically characterizes high-risk patients. The Trial of Rivaroxaban in Antiphospholipid Syndrome (TRAPS) revealed that rivaroxaban was associated with an increased incidence of adverse events in high-risk APS patients without providing any significant benefits and, instead, introducing additional risks.[10] Consequently, the 2019 European Society of Cardiology guidelines recommend against the use of DOACs in patients with APS, regardless of the APS subtype or the number of positive tests. Furthermore, a meta-analysis revealed that DOACs significantly increased the risk of subsequent arterial thrombosis, with a 5-fold higher risk than vitamin K antagonists (VKAs)[9], leading to a recommendation to use VKAs instead of DOACs for anticoagulation treatment and secondary prophylaxis of arterial thrombosis in APS patients.[11] A comprehensive review of case reports underscores the difficulties in managing APS in patients who have experienced MI. Despite aggressive treatment regimens, including triple therapy, a significant proportion of patients (3 out of 7) experienced recurrent MI. This high recurrence rate highlights the complexity of achieving optimal outcomes in patients with APS and MI. It emphasizes the critical importance of post-discharge treatment choices in long-term disease management. Established guidelines recommend indefinite treatment with VKAs for patients with APS.[11]

Conclusion

In conclusion, personalized management strategies are essential for patients with thrombophilia conditions. The recurrence of MI despite aggressive treatment underscores the complexities of treatment and the need for ongoing, tailored management. Further research is necessary to refine therapeutic approaches and improve outcomes for patients with APS who have cardiovascular complications.

List of Abbreviations

ACE II	Angiotensin-Converting Enzyme II
aCL	Anticardiolipin
aPL	Antiphospholipid
APS	Antiphospholipid Syndrome
ASA	Acetylsalicylic Acid
β2GPI	β2-glycoprotein I
BMI	Body Mass Index
CAD	Coronary Artery Disease
CAPS	Catastrophic Antiphospholipid Syndrome
CCU	Coronary Care Unit
CX	Circumflex Artery
DAPT	Dual Antiplatelet Therapy
DOACs	Direct Oral Anticoagulants
DVT	Deep Vein Thrombosis
Hx	History
INR	International Normalized Ratio
LA	Lupus Anticoagulant
LAD	Left Anterior Descending
LCx	Left Circumflex
LDL	Low-Density Lipoprotein
LM	Left Main Artery
LVEF	Left Ventricular Ejection Fraction
LMWH	Low-Molecular Weight Heparin
MI	Myocardial Infarction
ORIF	Open Reduction And Internal Fixation
PCI	Percutaneous Coronary Intervention
PTE	Pulmonary Thromboembolism
RCA	Right Coronary Artery
RI	Ramus Intermedius
SLE	Systemic Lupus Erythematosus
TIMI	Thrombolysis in Myocardial Infarction
TNG	Trinitroglycerin
TRAPS	The Trial of Rivaroxaban in

	Antiphospholipid Syndrome
TT	Triple Therapy (Oral Anticoagulant Such As Warfarin + DAPT)
UFH	Unfractionated Heparin
VTE	Venous Thromboembolism

Ethical Clearance

The participant in this case report has provided written informed consent to publish her clinical information, and any identifying information has been removed or anonymized to protect her privacy.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

SS Conceptualized, drafted, and revised the manuscript critically for important intellectual content; SN drafted and revised the article; AM drafted and revised the article; HA conceptualized, designed, and critically revised the article for important intellectual content. All authors approved the final version to be published.

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Generative AI and AI-Assisted Technologies in the Writing Process

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Case Reports

Breaking Bad News to A Terminally-diseased Physician in ICCU: A Case Study of Ethical and Cultural Dilemma

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Abstract

Background: Breaking bad news is one of the most problematic tasks for physician. Moreover, local guidelines or recommendations about this is not well established in Indonesia and its practice still varies between physicians.

Case Illustration: This paper presents a case of a fellow physician admitted to ICCU with terminal cardiac condition whose family wished to keep the bad news away from the patient. The physician team were in a difficult situation when the patient asked about his condition, but they decided to respect and commit to the family's decision to not giving information about his terminal state.

Conclusions: In performing such problematic task, balancing non-maleficence and autonomy principle is the key. Cultural background differences should also be considered when dealing with such cases. Other important factor that can affect this practice is lack of legal support in Indonesia. Combination of all those factors should always be considered for the best interest of both parties.

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Keywords: Breaking Bad News, Terminal Disease, Bioethics, Autonomy, Non-Maleficence.

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Introduction

The physician-patient relationship used to be a one-way communication with a paternalistic characteristic.[1-2] Physicians acted as the sole decision-makers for the medical treatment of the patients, while patients were not involved in the decision-making process.[1] They were also commonly concealed from the diagnosis and prognosis. Patient did not even bother trying to understand their disease because they believed that the physician was giving their best to cure them. Such a condition persisted worldwide until the advancement of bioethics. Methods of treating patients were finally shifted from a paternalistic approach to an individualistic approach.[1-3] Informing diagnosis and treatment planning is now a common practice worldwide, even in Eastern cultures. Patients are also encouraged to participate actively in choosing the treatment options for their disease. This progress aligns with the recognition of patients' right to information, which is part of the autonomy principle in modern bioethics.[1,4]

The paradigm shift in truth-telling was evident in an older publication from 1979.[5-6] It was observed from a survey conducted in the US between 1961 and 1979. In 1961, 88% of physicians did not routinely discuss the diagnosis of cancer with patients. Surprisingly, in 1979, 98% of physicians discussed the diagnosis of cancer with patients.[5] However, telling the truth about life-threatening prognosis to patients is still a controversial topic, especially in the eastern part of the world.[6-7] Despite the emerging trend to disclose important information regarding the patient's condition throughout the world, many countries still prefer the non-disclosure principle in their medical practice.[3,6,8] A survey performed in 2000 declared that only 17% Japanese physicians agreed that a doctor should inform patients of a cancer diagnosis.[6] From another perspective, in a different Asian country, only 48% hospitalized Iranian cancer patients were aware that they had cancer.[1,9] Cultural aspects play an essential role in this area.[3] In asian perspectives, patients' family members are decision-makers. Therefore, information regarding the patient's disease and its prognosis is commonly given to them.[3,8]

Indonesian culture regarding breaking bad news to patients is similar to that of Japan and Iran. Truth-telling had been encouraged since the development of palliative care medicine in Indonesia in 1992. However, the progress had been very slow and varied across the country. Communication between doctor and patient is still somewhat paternalistic. Patients perceive doctors to be of higher status and avoid disrespect by not asking too many questions.[10] This trend is gradually shifting towards modern bioethics principles in which the patients hold a significant role in deciding treatment options for themselves. On the other hand, unlike most developed countries, there were no local guidelines or recommendations for physicians on breaking bad news in Indonesia.[11] Therefore, the practice of telling the truth to patients varies greatly among physicians. Currently, the decision on whether to disclose comprehensive information about the disease to patients or their families primarily rests with the physician.

Case Illustration

Mr. NH, a 79-year-old male, presented to the emergency room in National Cardiovascular Center Harapan Kita (NCCHK) with chest pain in the last 3 days before admission. The patient, who was a physician in a local hospital, demonstrated signs and symptoms of shock with low cardiac output. Interventricular Septal (IVS) Rupture due to acute ST-Elevation Myocardial Infarct (STEMI) was confirmed by echocardiography (Figure 1). The defect was identified as a discontinuity of the apical ventricular septum. Color Doppler image revealed a turbulent jet at that specific region, consistent with left-to-right shunting. The ECG result is shown in Figure 2. ST-segment elevation was obvious on precordial leads (V1-V4). The subsequent evolution of the ECG was also observed, with the development of a pathological Q wave. Cardiogenic shock due to a mechanical complication was the initial main problem. An Intra-Aortic Balloon Pump (IABP) was applied, and the patient was admitted to the Intensive Cardiovascular Care Unit (ICCU) immediately. IABP gave a temporary solution for the hemodynamic problem. However, definitive treatment was needed. A multidisciplinary discussion with a cardiovascular surgeon decided that the patient required surgical closure of the IVS rupture with a synthetic patch. A synthetic patch for IVS rupture closure was not available at that time. An effort was made to provide the patch from various parts of the country, with no satisfying result. The neighboring country could also not help with patch availability. IABP could not be maintained for more than 13 days for the patient due to the development of Acute Limb Ischemia (ALI). IABP needed to be removed while no definitive treatment can be done. At this point, deterioration of the clinical condition and death were inevitable. This would be the appropriate time to deliver the bad news.

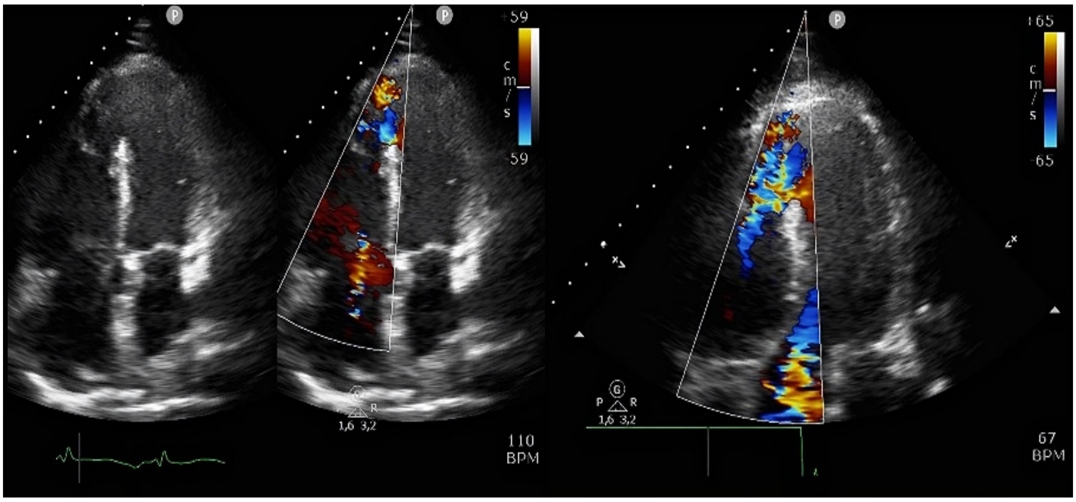

Figure 1. Echocardiographic image of IVS rupture.

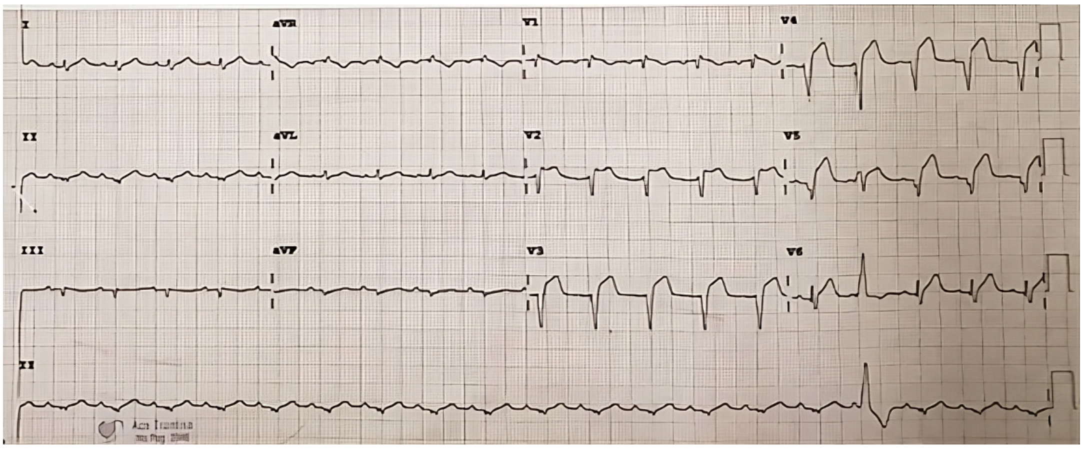

Figure 2. Patient's ECG.

The bad news was delivered not to the patient but to his family. A formal meeting with five family members was held. At this meeting, the family decided that the patient should not be informed of the poor prognosis. The patient remained conscious until several hours before death. The patient tried to understand his condition by asking some doctors and medical staff, but no one answered directly. Most medical staff were comforting the patient, assuring them that they were making their best effort. Considering the poor prognosis and unavailability of a definite treatment, the Do Not Resuscitate (DNR) option was offered to the family. The patient later died under DNR status.

Discussion

The development of modern bioethics principles in recent decades, especially autonomy, has changed both physicians' and patients' perceptions of communication in medicine. The patient's role is getting bigger and more balanced with the physician's role. Physicians' dominance is no longer acceptable in medical practice, even in Eastern countries.[1] Despite such progress in all parts of the world, physicians' attitude towards information disclosure still varies greatly among different cultures.[1,3] Research about truth-telling practice was numerous in various parts of the world. It is well established that different cultures influence this practice. The difference between Western countries and Eastern cultures regarding this issue is conspicuous. Western countries uphold the value of the individual, while Eastern cultures place more emphasis on the important role of the family.[1,7-8] Indonesia is a large country in Southeast Asia whose culture resembles most eastern civilizations.

The most common topic in reviews and research regarding truth-telling is about cancer patients.[3,5,7,9] However, breaking bad news is not limited only to such a diagnosis. The scope is much bigger. Any news related to permanent changes of an individual is actually considered bad news. Some diagnoses considered as bad news are cancer, coronary artery disease, diabetes, mental illness, genetic disease, and incurable fatal disease.[10-12] The worst kind of news involves information about imminent death. The ethical aspect of truth-telling about imminent death is similar for both cancer and other incurable fatal diseases.[12] Therefore, ethical analysis of truth-telling in cancer patients applies to other fatal diseases.

Modern Bioethic Principle and Truth Telling

The principles of modern bioethics were initially described by Beauchamp and Childress in 1979.[13] It recently passed its fortieth anniversary, with numerous research and reviews polishing the concept of modern bioethics.[14] Those principles, as depicted in Figure 3, are beneficence, non-maleficence, autonomy, and justice.[3-4] Beneficence obliges to promote the well-being of patients, which must always be encouraged. Non-maleficence is the fundamental principle of avoiding harm and not inflicting further harm on patients. Justice means that every action planned for patients is impartial and fair. Autonomy entails respecting and appreciating the rights of patients as individuals to determine what course of action is best for themselves.[3-4] Balancing all these aspects is the key to implementing the ideal practice of modern bioethics. All those principles are valuable tools for analyzing ethical problems in medical practice, including breaking bad news. Beneficence and justice play a minor role in truth-telling. Non-maleficence and autonomy are essential aspects in analyzing ethical issues in breaking bad news.[3]

Respecting the patient's autonomy means respecting their right to know what is wrong with their body and their right to decide which course of treatment they are willing to undergo. Applying autonomy means telling the truth to the patients, including an explanation of the disease and its terminal nature.[4,8,13] Patient's characteristics are an important part of applying the autonomy principle. Both internal and external factors influence it. Internal factors are mental capacity, stress, and the capability to understand medical information. External factors are culture and socioeconomic class.[1,8] Considering all internal factors in upholding the autonomy principle, physicians need to be certain that the patient is lucid and has the capacity to receive bad news and make decisions based on this condition.[2] However, one can argue whether, once the patient knows his terminal state, he will be depressed and no longer have the ability to decide the next course of action. All those factors influence a physician's reasoning to determine how deeply they respect the patient's autonomy. A physician might give full disclosure of all information, reveal the diagnosis but not the terminal nature, or conceal both the diagnosis and the prognosis.[3,7]

Upholding the non-maleficence principle is what keeps physicians away from revealing the disease and its terminal nature to the patients.[8] The most important justified reason not to disclose important information regarding terminal disease was the fear of causing new psychological morbidity to the patients.[3] Psychological comorbidity is not a rare finding in terminal patients. It usually comes as depression, and it can be as advanced as suicidal thoughts or the intention to hasten death.[15] The prevalence of depression among cancer patients is 5-20%.[15-16] This prevalence increases with more advanced stages of cancer, which resembles a more imminent death.[15] A study in 2013 recorded that more than half of terminally ill patients in the Netherlands (50.4%) were taking psychotropic medication to cope with psychological morbidity.[16] A comparison of the quality of life between patients who knew their cancer di-

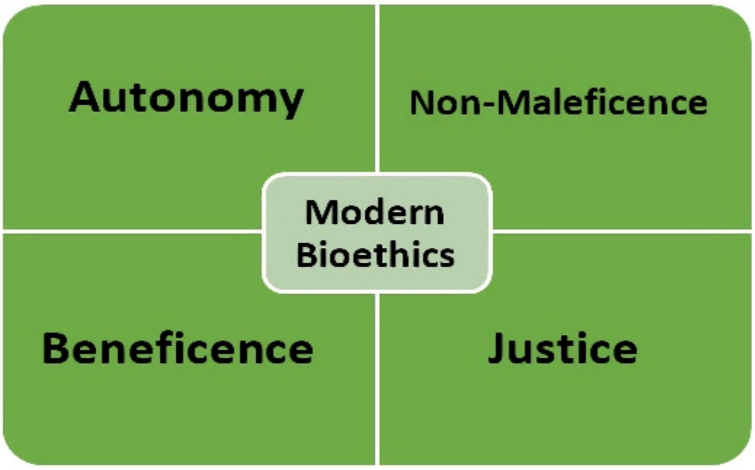

Figure 3. The four pillars of modern bioethics.[4,13]

agnosis and those who did not revealed that the first group had a significantly lower degree of emotional and social functioning.[9]

Despite the obviously higher number of psychological morbidities in terminal patients, a direct correlation between breaking bad news and depressive symptoms has not yet been established.[2-3] Furthermore, it is still debatable whether concealing the truth can serve as an effort to prevent depression in terminal disease patients.[2]

Not telling the truth to patients may harm them in many ways. It may not harm patients medically, but it may do so from a holistic point of view. Patients who do not know what their disease is might ignore important symptoms and are reluctant to seek medical attention.[1,17] They may make major decisions about their lives that they would not make if they knew the truth. They can be frustrated to be the one kept out of a big secret.[1-2] Their trust in doctors and their families will dissipate.[17] Patients with terminal disease may miss the opportunity to say goodbye and leave a meaningful farewell for their loved ones. Moreover, for a religious person, the opportunity to make peace with God in the face of imminent death can provide a significant sense of closure if they know they do not have much time left.[1] These consequences are often ignored and neglected by both physicians and families. When considering breaking bad news, these factors should be acknowledged.

Physician's Point of View

Analysis suggests that physicians' reluctance to tell the truth to terminally ill patients is mainly influenced by their attempt to balance autonomy and non-maleficence.[3] Multiple factors from the physician's point of view also influence the practice of information disclosure to terminally ill patients. Both internal and external factors can drive it.[1,12] These factors have been reviewed in multiple publications, and several solutions have already been established.

Breaking bad news is not an easy task for physicians. It places a significant burden on physicians, as if they were taking hope away from patients' minds.[3,11] Moreover, breaking bad news is a stressful action where patients and families might respond negatively and blame the doctors for any dissatisfaction.[11] A survey conducted in 2002 analyzed how patients perceived the event of having bad news broken to them. Among 106 participants, 26% were dissatisfied with how their doctors told them the truth.[18] Another survey in 2018 in Poland explored that a bad experience in receiving bad news often stems from the doctor's attitude and lack of emotional support during the truth-telling event. This issue comes from the physician's lack of skill in delivering bad news.[12] It has been addressed recently, and physicians are recommended to acquire this specific skill to manage such a stressful environment. The modern curriculum of medicine has been integrating skills of communication and how to perform breaking bad news with empathy.[3,11-12] This effort might reduce physicians' worry and prevent them from concealing information out of fear.[11]

Feedback from patients who received bad news also indicated that their unpleasant experience was due to an insufficient amount of time given for communication.[12] Physicians at the hospital are always busy. Most of their time in the hospital is spent on appointments with numerous patients in the outpatient clinic and on visits to many patients in the ward.[3] A survey of patients receiving bad news in Poland described that 42% patients felt that physicians did not devote enough time to communication.[12] A survey of physicians revealed that the average time for a physician to perform good-quality breaking bad news is 27 minutes.[19] Although it is understandable that sparing more than 15 minutes of a physician's time exclusively for meetings with patients and families is difficult, sufficient time allocated for breaking bad news is crucial for the patients and families.

Medical practice is vulnerable to lawsuits. A simple miscommunication or minor dissatisfaction from either patients or families might end up in court. This drives physicians to be very careful in handling communication with both patients and families. Breaking bad news is a grey area that is not regulated by law. A lack of legal and ethical guidelines can also be why many physicians are confused about what action to take. Some countries have addressed this problem and published formal recommendations for use.[3,7,12,20-21] However, Indonesia still lacks of guidelines.[11] This put Indonesian physicians in a difficult situation, resulting in their hesitation to give full information disclosure for patients.[10-11]

Lack of skill, lack of time, and lack of legal support are obstacles, from the physician's perspective, to deciding whether to deliver bad news to patients.[1,12] These internal and external factors create doubt in the minds of physicians. Considering Indonesian culture as an eastern culture, physicians prefer to defer the decision to families to clear their doubts.

Family's Role in Deciding Truth Telling

In contrast to Western culture, which respects an individual's values in full, Eastern culture emphasizes the family's role.[1,8] Family plays a vital part in deciding which treatment options should be selected for the patient. As a country in the eastern hemisphere with a similar culture, disease is considered a family matter in Indonesia. Hence, the decision-making process is made by family discussion.[10-11] Patients tend to comply with the family's decision, even when it contradicts their own wishes. With that much role of the family, family is frequently the first part being informed about the disease and the nature of the disease in this part of the world.[1,7-8]

In most Asian countries, the family is given the privilege to decide to what extent the patients should be informed of their disease and its prognosis.[3,8] The most common practice is informing the patient's family of both the diagnosis and the prognosis first, and then letting them decide whether the physician should also inform the patient or not.[1] On some occasions, the bad news was delivered to the patient by a family member without the physician's presence.[3] Resistance to disclose information might come from the family. Usually, this decision is taken because they believe it will only cause psychological trouble for the patient without any benefit.[3,8] Families tend to believe that a poor prognosis would extinguish the patient's hope and generate depression. Therefore, families prefer to protect their beloved member from the truth of the illness.[7-8,10]

Family members often state multiple other reasons to conceal the information from patients. First, the family did not know how to tell the truth. Second, the family did not think it necessary to say to the patient the truth. Third, they believe that the patients would be better or happier if they didn't know the truth.[1] The first reason is based on a lack of skill to perform such an action. This lack of skill can be covered by the physician, who was trained to deliver bad news.[11-12] The second and third reason is based on assumptions and feelings.

The significant role of the family in deciding whether the patient should be informed does not always align with the patient's desire. Patients' preferences toward full disclosure differ from one culture to another.[1] Survey of patients revealed that 83-99% patients would like to be informed of their diagnosis in Western countries.[2] The numbers were lower in non-Western countries (24-74%).[2,6-8] Survey of Japanese patients revealed that only 65% patients agreed that physicians should inform the family first about their patient's terminal disease and let them decide whether the patient should be told or not.[6] Although this number represents the majority of Asian patients whose desire is to let the family decide, the minority is not small in proportion. The same survey elaborated more by describing that 24% Japanese patients preferred that physicians should inform the patients about their terminal state, even if their family decided not to tell.[6] The same contradictory phenomenon was also observed in Hong Kong, affirming that there was no academic evidence to support that breaking bad news should be performed to the family instead of the patient.[8] Whether the family's interest represents what the patient really wants or not needs to be questioned and researched.

ICCU Setting

ICCU settings are known as battlegrounds in the fight against numerous medical emergencies. Spaces for comfortable discussion with families are usually nonexistent. Such discussions usually take place in the aisle between beds. Moreover, information is conveyed in a limited time due to the physician's rush to attend to another medical emergency for other patients.[21] This setting does not encourage full disclosure of terminal disease. Lack of time and an appropriate place to deliver bad news are also essential factors in breaking bad news.[3,19]

A poor environment for breaking bad news should not be an excuse not to do so. No matter how busy the physician was during emergency procedures, they should always make time for communication after the storm passed. When a comfortable, private room for breaking bad news is unavailable in ICCU, cooperation with other units that have such a meeting place is urged. Hospital management should be encouraged to understand that patients' beds and medical equipment are not the only infrastructure needed in ICCU.[21] Meeting room or conference room is also essential.

Case Analysis

There were no problems in the diagnostic process of the disease. The diagnostic process, from anamnesis to supportive examination, was thorough and timely. Problems arose when the ideal solution for the patient could not be put into practice. The main problem discussed in this paper is the consequences of this condition: Should we tell the patient?

Modern bioethics encourages thorough analysis in dealing with various problems of ethics. The four main pillars represent multiple perspectives in analyzing such a condition. Balancing the principles of non-maleficence and autonomy is key to telling patients the truth.[3] Should we uphold the autonomy principle as most Western countries do, we need to tell the patient about his condition and his terminal state.[1] Our patient explicitly asked about how his disease is progressing. Our medical staff decided to respect and commit to the family's decision not to give him information about his terminal state. Arguably, our medical staff neglected the autonomy principle of the patient. However, the autonomy principle is complicated. Internal and external factors influence it.[1,4] Cultures and social relations in particular render autonomy not only limited to "always tell everything to the patients."[4] It has been suggested that notifying unprepared patients of a bad prognosis, whose cultural practice is to avoid painful medical truth, is actually not respectful to their autonomy.[1-2] Forcing the truth on unprepared patients can also damage the trust the patient has placed in the physician and break the relationship.[2] This notion of cultural sensitivity is important to discuss.

Formal breaking bad news was performed in a conference room to family members. This practice is common in Indonesia. In such a conference, some decisions are made. It often involves selecting the course of treatment for the patient. In difficult cases, the conference also decides whether the physician should tell the patient about his imminent death.[7] Respecting the family's preference is the main characteristic of medical practice in Eastern cultures.[1,3,6,8] However, this decision should be made only after the physician explains both the consequences of revealing and concealing the truth to the family.[3] The family decided that the patient should not be told about his terminal state. The family requested that all medical staff comply. This is a common but difficult situation for a physician. Western and Eastern cultures reacted differently in this situation. A survey from 2000 comparing Japanese and US physicians exhibits such a phenomenon. When the family requested that no information be given to the patient, 79% of US physicians still gave it anyway. Only 8% Japanese physicians agreed to do the same thing.[6] We reacted the same way in accordance with our Eastern cultures.

The objective of ethical practice in this condition is to discern the patient's preference without conflicting with the family's interests. Asking whether the patient wants to be told about the truth of their disease is the best course of action.[1,8] It is common for patients in Western countries to have a surrogate decision maker. Such patients do not wish to hear or receive information about their disease, so they choose someone they trust to perform that important task.[1-2] This option is legally supported as long as the patients' wishes and chosen surrogates are well documented in the medical record. Should the patient choose no surrogate, what the patient wanted trumps what the family wishes for. Whatever options the patient chooses, his autonomy is maximized.[1] The important issue is when we ask the question. Asking whether the patients want to choose someone as their surrogate when their condition deteriorates might imply that their disease is terminal. This consequence contradicts the family's desire that the patient feel everything will be fine. Family might be against such action and blame doctors afterwards. The hardest part is knowing the patient's preference without asking them at an improper time.

Lack of legal support in Indonesia is an important negative factor in breaking bad news to patients.[10] This condition causes physicians to be too careful because of the fear of legal lawsuits. When physicians tell the truth to patients and respect their wishes, they might incur the family's rage for not complying with their wishes. Local ethical guidelines might serve as a benchmark for physicians nationwide in deciding how to handle difficult ethical issues in breaking bad news.[7,20] This guideline will be the standard for physicians on when to tell the patients directly or when to tell the family first.[20] This legal support can also cover the issue of a surrogate decision maker, which is currently uncommon in Indonesia.

Conclusion

Breaking bad news is one of the most problematic tasks for physicians. While many factors played a role in analyzing ethical problems in breaking bad news, balancing beneficence, non-maleficence, autonomy, and the principle of justice is the key. Carefully handling communication with both patients and families is essential; forcing the truth may cause psychological morbidity, but withholding the truth may also harm them in many ways. A step-by-step approach in a controlled and comfortable environment is needed to prepare patients and families for breaking bad news. It is encouraged for physicians to perform good-quality breaking bad news in sufficient amounts of time, and to respect the patient's right to know and the patient's right not to know about their condition. Legal support from local ethical guidelines is needed, as it will serve as the standard of care for physicians when dealing with ethical cases. This legal support will provide guidance on when and how to disclose the true situation to the patient, address the issue of the surrogate decision-maker, and serve as strong grounds and protection for the physicians.

List of Abbreviations

ALI	Acute Limb Ischemia
DNR	Do Not Resuscitate
ECG	Electrocardiography
IABP	Intra-aortic Balloon Pump
ICCU	Intensive Cardiovascular Care Unit
IVS	Interventricular Septal
NCCHK	National Cardiovascular Center Harapan Kita
STEMI	ST-Elevation Myocardial Infarction

Ethical Clearance

Not Applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

Conception and the framework of the manuscript was initiated by TMHP and DAJ. Manuscript was drafted by TMHP, FPA, WF, and FT. TMHP, BEP, and DAJ critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Erratum

Erratum: The Impact of Tricuspid Annular Plane Systolic Excursion (TAPSE) After Mitral Valve Surgery on Long Term Mortality

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Erratum

Erratum: The Incidence of Persistent Symptom and Echocardiographic Findings in Survivors of COVID-19 Infection with Mild Symptoms

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Erratum

Erratum: When Positive Ischemic Response on Treadmill Test Implies Otherwise: One Overlooked Pitfall on TMT

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Erratum

Erratum: Management of Acute Coronary Syndrome in Indonesia: Insight from One ACS Multicenter Registry

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Erratum

Erratum: Validation and Comparison of Zwolle, TIMI, and GRACE Risk Scores for STEMI Patients Undergoing Primary Percutaneous Coronary Intervention in The Indonesian Population

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Erratum

Erratum: C-Reactive Protein to Albumin Ratio Predict In-Hospital and Long-term Outcome of ST-Segment-Elevation Myocardial Infarction Patients with SARS-CoV2 Infection Underwent Fibrinolytic Therapy

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Erratum

Erratum: Cardiogenic Shock

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In "Cardiogenic Shock" (Indonesian Journal of Cardiology, 43(2), 90-9. https://doi.org/10.30701/ijc.1505), there are an errors noted.

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[1] Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada - Sardjito General Hospital, Yogyakarta
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The affiliations have been corrected to:
[1] Department of Cardiology and Vacular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada - Sardjito General Hospital, Yogyakarta, Indonesia
[2] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia - National Cardiovascular Center Harapan Kita, Jakarta Indonesia
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Erratum

Erratum: Management of Decongestion in Acute Heart Failure: Time for a New Approach?

Miftah Pramudyo[1], Iwan Cahyo Santosa Putra[1], Edrian Zulkarnain[2], Siska Suriadanda Danny[3], Hendry Purnasidha Bagaswoto[4], Setyasih Anjarwani[5], Irmaliyas Mazwar[3], Dafsah Ariza Juzar[3], Vireza Pratama[6], Faisal Habib[7], Akhtar Fajar Muzakkir Ali Ispar[8], Bambang Widyantoro[3]

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In “Management of Decongestion in Acute Heart Failure: Time for a New Approach?” (Indonesian Journal of Cardiology, 43(2), 77-89. https://doi.org/10.30701/ijc.1381), there is an error noted.

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Erratum

Erratum: Does Chronic Inflammation Play a Role in Rheumatic Mitral Valve Restenosis after Percutaneous Transvenous Mitral Commissurotomy?

Maruli Butarbutar[1], Amiliana M. Soesanto[1], Doni Firman[1], Rina Ariani[1], Amir Aziz Alkatiri[1], Sony Hilal Wicaksono[2]

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In "Does Chronic Inflammation Play a Role in Rheumatic Mitral Valve Restenosis after Percutaneous Transvenous Mitral Commissurotomy?" (Indonesian Journal of Cardiology, 43(3), 101-107. https://doi.org/10.30701/ijc.1398), there is an error noted.

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Erratum

Erratum: Hemodynamic and Clinical Outcomes of Milrinone Compared to Dobutamine in Cardiogenic Shock: A-Systematic Review and Meta-Analysis

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In "Hemodynamic and Clinical Outcomes of Milrinone Compared to Dobutamine in Cardiogenic Shock: A-Systematic Review and Meta-Analysis" (Indonesian Journal of Cardiology, 43(3), 108-15. https://doi.org/10.30701/ijc.1296), there is an error noted.

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Erratum

Erratum: High Degree AV Block in Infants

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In "High Degree AV Block in Infants" (Indonesian Journal of Cardiology, 43(3), 116-22. https://doi.org/10.30701/ijc.1244), there are errors noted.

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Erratum

Erratum: An Acute Anterior Reinfarction Complicating with Transient Symptomatic Total Atrioventricular Block

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In "An Acute Anterior Reinfarction Complicating with Transient Symptomatic Total Atrioventricular Block" (Indonesian Journal of Cardiology, 43(3), 130-6. https://doi.org/10.30701/ijc.1216), there is an error noted.

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In the original published version of this article, there is an error in the author's name. The author's name has been changed to "Mochamad Rizky Hendiperdana" from the previous "Rizky Hendiperdana."

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Erratum

Erratum: The Importance of Hyperthyroid Screening in Acute Decompensated Heart Failure with Persistent Tachycardia Despite Optimal Decongestion: A Case Report

Risalina Myrtha[1], Matthew Aldo Wijayanto[2], Nurhasan Agung Prabowo[3]

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In “The Importance of Hyperthyroid Screening in Acute Decompensated Heart Failure with Persistent Tachycardia Despite Optimal Decongestion: A Case Report” (Indonesian Journal of Cardiology, 43(3), 123-9. https://doi.org/10.30701/ijc.1328), there is an error noted.

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Erratum

Erratum: Simplified Selvester QRS Score as an Infarct Size Parameter in STEMI Patients Undergoing Pharmacoinvasive or Primary Percutaneous Coronary Intervention

Arif Eka Prasetia[1], Anggoro Budi Hartopo[1], Nahar Taufiq[1], Hendry Purnasidha Bagaswoto[1], Budi Yuli Setianto[1]

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In "Simplified Selvester QRS Score as an Infarct Size Parameter in STEMI Patients Undergoing Pharmacoinvasive or Primary Percutaneous Coronary Intervention" (Indonesian Journal of Cardiology, 43(4), 150-8. https://doi.org/10.30701/ijc.1186), there is an error noted.

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Erratum

Erratum: Mayo Cardiac Intensive Care Unit Admission Risk Score (M-CARS) Validation Test to Assess Mortality During Treatment in Cardiovascular Care Unit (CVCU) Patients at Haji Adam Malik Hospital

Basten Jeremiah Siahaan[1], Refli Hasan[1], Andika Sitepu[1]

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In "Mayo Cardiac Intensive Care Unit Admission Risk Score (M-CARS) Validation Test to Assess Mortality During Treatment in Cardiovascular Care Unit (CVCU)Patients at Haji Adam Malik Hospital" (Indonesian Journal of Cardiology, 43(4), 137-43. https://doi.org/10.30701/ijc.1261), there is an error noted.

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Erratum

Erratum: Predictors of Acute Kidney Injury in Critically Ill Patient at Intensive Cardiac Care Unit

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In "Predictors of Acute Kidney Injury in Critically Ill Patient at Intensive Cardiac Care Unit" (Indonesian Journal of Cardiology, 43(4), 144-9. https://doi.org/10.30701/ijc.1322), there is an error noted.

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Erratum

Erratum: A Broken Heart Coexisting with Obstructive Coronary Artery Disease: Double Trouble

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In "A Broken Heart Coexisting with Obstructive Coronary Artery Disease: Double Trouble" (Indonesian Journal of Cardiology, 43(4), 168-73. https://doi.org/10.30701/ijc.1368), there is an error noted.

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Erratum

Erratum: A Rare Case of Ventricular Standstill and High-Grade AV Block in Patient with Thyrotoxicosis

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In "A Rare Case of Ventricular Standstill and High-Grade AV Block in Patient with Thyrotoxicosis" (Indonesian Journal of Cardiology, 43(4), 159-67. https://doi.org/10.30701/ijc.1299), there is an error noted.

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Erratum

Erratum: Added Value of CHA2DS2-VASc Score to Safe Contrast Volume for Contrast Induced Nephropathy Prediction after Percutaneous Coronary Intervention

Wael Ali Khalil[1], Mohammad Gouda Mohammad[1], Mohammad Hossam Alshaer[1], Mohammad Gamal Abd El Mageed[1]

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In "Added Value of CHA2DS2-VASc Score to Safe Contrast Volume for Contrast Induced Nephropathy Prediction after Percutaneous Coronary Intervention" (Indonesian Journal of Cardiology, 44(1), 1-9. https://doi.org/10.30701/ijc.1516), there is an error noted.

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Erratum

Erratum: Usefulness of The CHADS2 and CHA2DS2-VASc Scores in Predicting In-Hospital Mortality in Acute Coronary Syndrome Patients: A Single-Center Retrospective Cohort Study

Miftah Pramudyo[1], Iwan Cahyo Santosa Putra[1], Fahmi Bagus Pratama[1], Raymond Pranata[1]

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In "Usefulness of The CHADS2 and CHA2DS2-VASc Scores in Predicting In-Hospital Mortality in Acute Coronary Syndrome Patients: A Single-Center Retrospective Cohort Study" (Indonesian Journal of Cardiology, 44(1), 17-27. https://doi.org/10.30701/ijc.1294), there is an error noted.

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Erratum

Erratum: The Sub-Analysis of HFmrEF and HFrEF Group in CORE-HF Registry: When being Good is Not Enough

Trisulo Wasyanto[1], Irnizarifka[1,2], Titus H. Chau[2], Habibie Arifianto[1,2]

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In "The Sub-Analysis of HFmrEF and HFrEF Group in CORE-HF Registry: When being Good is Not Enough" (Indonesian Journal of Cardiology, 44(1), 10-6. https://doi.org/10.30701/ijc.1545), there is an error noted.

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Erratum

Erratum: Hyperkalemia Mimicking Anteroseptal Myocardial Infarction: a Rare Feature that Confuses Clinicians

Raka Aldy Nugraha[1], Auliya Husen[1], Hary Sakti Muliawan[2], Dian Zamroni[2]

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In "Hyperkalemia Mimicking Anteroseptal Myocardial Infarction: a Rare Feature that Confuses Clinicians" (Indonesian Journal of Cardiology, 44(1), 28-32. https://doi.org/10.30701/ijc.1297), there is an error noted.

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Erratum

Erratum: Factors Influencing Mortality of Thoracic Aortic Surgery in The Third World Country

Rienna Diansari[1], Dicky Aligheri[1], Bagus Herlambang[1], Sony Hilal Wicaksono[1], Brian Mendel[2], Amir Aziz Alkatiri[1], Hananto Andriantoro[1], Suko Adiarto[1]

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In “Factors Influencing Mortality of Thoracic Aortic Surgery in the Third World Country” (Indonesian Journal of Cardiology, 44(2), 41-52. https://doi.org/10.30701/ijc.1494), there are several errors noted.

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Erratum

Erratum: PEACH Score Validation of Postoperative In-Hospital Mortality in Adult Congenital Heart Disease Patients at Haji Adam Malik General Hospital Medan

Juang Idaman Zebua[1], Ali Nafiah Nasution[1], Andre Pasha Ketaren[1], Harris Hasan[1], Nizam Zikri Akbar[1]

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In "PEACH Score Validation of Postoperative In-Hospital Mortality in Adult Congenital Heart Disease Patients at Haji Adam Malik General Hospital Medan" (Indonesian Journal of Cardiology, 44(2), 61-7. https://doi.org/10.30701/ijc.1546), there is an error noted.

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Erratum

Erratum: Correlation between Peak Left Atrial Longitudinal Strain and The Severity of Mitral Valve Disease at Haji Adam Malik General Hospital Medan

Dina Ryanti[1], Andre Pasha Ketaren[1], Zulkifli Mukhtar[2], Nizam Zikri Akbar[1], Anggia Chairuddin Lubis[1], Tengku Winda Ardini[1]

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In "Correlation between Peak Left Atrial Longitudinal Strain and The Severity of Mitral Valve Disease at Haji Adam Malik General Hospital Medan" (Indonesian Journal of Cardiology, 44(2), 68-74. https://doi.org/10.30701/ijc.1541), there is an error noted.

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Erratum

Erratum: Impact of Acute Kidney Injury in Patients with Acute Decompensated Heart Failure: Cardiorenal Syndrome

Sagar Tandel[1], Ashish Mishra[2], Sharad Jain[3], Vishal Sharma[3], Kewal Kanabar[3], Pooja Vyas[3], Krutika Patel[3], Nisarg Desai[3], Aman Kedia[3]

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In "Impact of Acute Kidney Injury in Patients with Acute Decompensated Heart Failure: Cardiorenal Syndrome" (Indonesian Journal of Cardiology, 44(2), 75-86. https://doi.org/10.30701/ijc.1561), there are an errors noted.

An error has been found in the PDF version of this article. The DOI printed in the PDF is incorrect. The correct DOI is https://doi.org/10.30701/ijc.1561. The error occurs only in the PDF; the DOI listed in the article metadata is already correct.

An error was also found in the author's name Sagar Tandel. We have corrected the author name from "Sager Tandel" to "Sagar Tandel".

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Erratum

Erratum: Triglyceride Glucose Index as a Predictor of 30-Day Readmission and 6 Months Mortality After Hospitalization in Acute Decompensated Heart Failure

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In "Triglyceride Glucose Index as a Predictor of 30-Day Readmission and 6 Months Mortality After Hospitalization in Acute Decompensated Heart Failure" (Indonesian Journal of Cardiology, 44(2), 53-60. https://doi.org/10.30701/ijc.1380), there are an errors noted.

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An error also occurred in the author's name. We have corrected the author's name from "Vienna Rossiamarina" to "Vienna Rossimarina."

There is also an error in the page numbering on the first page of the article. At the top, it says "57-64," but we have changed it to the correct page numbers (53-60).

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Erratum

Erratum: Transcatheter Closure for Ventricular Septal Defect (VSD): Unveiling Key Predictors in Pediatric Interventions

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In "Transcatheter Closure for Ventricular Septal Defect (VSD): Unveiling Key Predictors in Pediatric Interventionse" (Indonesian Journal of Cardiology, 44(3), 95-102. https://doi.org/10.30701/ijc.1571), there is an error noted.

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Erratum

Erratum: Exploring Clinical and Echocardiographic Factors in EHRA Type 2 Atrial Fibrillation for Predicting Ischaemic Stroke: A Search for Unrevealed Insights

Jessica Putri Natalia Simbolon[1], Sunu Budhi Raharjo[1], Anwar Santoso[1], Lies Dina Liastuti[1], Dony Yugo Hermanto[1], Vienna Rossimarina[1], Armalya Pritazahra[1], Dicky Armein Hanafy[1], Yoga Yuniadi[1]

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In "Exploring Clinical and Echocardiographic Factors in EHRA Type 2 Atrial Fibrillation for Predicting Ischaemic Stroke: A Search for Unrevealed Insights" (Indonesian Journal of Cardiology, 44(3), 87-94. https://doi.org/10.30701/ijc.1562), there is an error noted.

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Erratum

Erratum: Modified STEMI protocol for PPCI during COVID-19 Pandemic: Does it prolong Door-To-Balloon performance?

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In "Modified STEMI protocol for PPCI during COVID-19 Pandemic: Does it prolong Door-To-Balloon performance?" (Indonesian Journal of Cardiology, 44(3), 103-10. https://doi.org/10.30701/ijc.1325), there is an error noted.

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Erratum

Erratum: Utility of Ischemic Signs from Initial ECG in Detecting Culprit Vessels in NSTE-ACS Patients

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In "Utility of Ischemic Signs from Initial ECG in Detecting Culprit Vessels in NSTE-ACS Patients" (Indonesian Journal of Cardiology, 44(3), 111-9. https://doi.org/10.30701/ijc.1321), there are several errors noted.

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In addition, there was an error in the title of Table 2. The title of the table has been corrected to "Baseline characters."

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