

Advancing Rheumatic Heart Disease Management in Indonesia: Strengthening Early Detection, Targeted Screening, and Prevention Strategies

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ABSTRACT

Background: Indonesia ranks fourth globally in rheumatic heart disease (RHD) prevalence, with a mortality rate of 4.8 per 100,000—higher than malaria. Despite global progress in RHD management, Indonesia lacks a comprehensive national prevention program. Secondary prevention strategies could significantly improve outcomes in high-risk populations by targeting disease progression. **Method:** This systematic review and meta-analysis examined the impact of secondary prevention on echocardiographic outcomes in Indonesian RHD patients. The review included randomized controlled trials, observational studies, quasi-experimental designs, and case-control studies, emphasizing the role of secondary prevention in mitigating disease progression. **Results:** Six studies meeting inclusion criteria underwent full-text analysis, with four eligible for meta-analysis. These studies revealed that secondary prevention improved echocardiographic markers, demonstrating its potential to alter disease trajectories in resource-limited settings. **Conclusion:** Indonesia faces challenges in RHD management due to geographical and healthcare constraints. Echocardiographic screening, a sensitive and specific diagnostic tool, is vital for early detection and monitoring. With technological advancements, cost-effective screening is increasingly feasible, even in remote areas. Strengthening early detection, targeted screening, and secondary prevention strategies is critical for reducing the RHD burden in Indonesia.

Keywords: ARF, Indonesia, RHD, secondary prevention

INTRODUCTION

Rheumatic heart disease (RHD) remains a leading cause of preventable cardiovascular deaths in developing regions, disproportionately affecting children and young adults in their most productive years. Indonesia is a high-burden country for RHD, ranking fourth globally in prevalence after China, India, and Pakistan, with an estimated 1.18 million cases annually as of 2015.^{1,2} The mortality rate associated with RHD in Indonesia stands at approximately 4.8 per 100,000 individuals at risk, a figure notably higher than the mortality rate from malaria in the same period, which was 3.02 per 100,000.³ These figures highlight the critical need for effective interventions, particularly as global initiatives to reduce RHD have demonstrated success in other regions, yet Indonesia remains without a comprehensive national program for RHD prevention and control.

Globally, significant reductions in RHD-related mortality

have been observed from 1990 to 2015 in countries with dedicated prevention and control programs. For instance, countries like Australia, New Zealand, India, and members of the African Union have implemented national initiatives focused on the prevention, control, and eradication of RHD, leading to substantial declines in disease burden.⁴⁻⁷ In contrast, Indonesia has not established a comparable national strategy, partly due to underreporting and the absence of centralized RHD data. Historical studies reflect this gap: one investigation in a tertiary hospital in Indonesia's capital city in 1995 found a 10-year survival rate of only 69.1% among children diagnosed with RHD, underscoring the long-standing need for enhanced disease management and prevention.⁸

Since 1995, Indonesia has seen notable socioeconomic and healthcare improvements, potentially translating into better outcomes for RHD patients if aligned with targeted interventions. Research indicates that advancements in healthcare infrastructure and economic status are

associated with improved RHD prognosis in other countries, suggesting that Indonesia might benefit from similar strategies.^{9,10} In light of these factors, we conducted a study to evaluate the echocardiographic outcomes of RHD patients in Indonesia, comparing those who received secondary prevention measures with those who did not. This analysis aims to clarify the role of secondary prevention in improving RHD management and reducing morbidity and mortality rates in Indonesia's high-risk population.

METHODS

This systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Our research question was structured in advance using the PICO (Population, Intervention, Comparator, and Outcome) framework. The defined parameters were: Population: individuals at risk for or diagnosed with rheumatic heart disease (RHD); Intervention: secondary prevention

measures for RHD; Comparator: individuals with RHD who did not receive secondary prevention; Outcome: echocardiographic assessment of disease progression in RHD. This approach ensured a thorough and focused examination of the efficacy of secondary prevention in managing RHD.

Eligibility Criteria

This systematic review and meta-analysis will include studies with varied designs—such as randomized controlled trials (RCTs), observational studies, quasi-experimental studies, and case-control studies—that examine echocardiographic outcomes in individuals with rheumatic heart disease (RHD) with and without secondary prevention interventions in Indonesia. Studies must specifically address the impact of secondary prevention on echocardiographic outcomes in this context.

The eligible population includes individuals at risk for or already diagnosed with RHD, without restrictions on age, gender, or geographic location. Studies will be

excluded if they do not focus directly on RHD, lack original data, or fail to provide echocardiographic comparison as a central outcome.

In this review, eligible studies must include a comparison group, examining echocardiographic outcomes with and without secondary prevention interventions. Studies lacking a comparison group or comparing different impacts on echocardiographic outcomes unrelated to secondary prevention will be excluded.

The primary outcome measure is echocardiographic comparison in the context of secondary prevention for RHD. Studies that report outcomes unrelated to this focus will be excluded. These criteria ensure the inclusion of studies that rigorously explore the echocardiographic impact of secondary prevention in RHD, supporting a comprehensive systematic review and meta-analysis of the literature.

Data Sources and Search Strategy

To investigate the echocardiographic comparison of RHD with and without secondary

prevention in Indonesia, a comprehensive search strategy was employed. The authors systematically searched key bibliographic databases—namely PubMed, The Lancet, Google Scholar, and ScienceDirect—to ensure a thorough collection of relevant studies for review.

Study Selection

Two independent investigators screened titles and abstracts to assess eligibility, selecting studies that met predefined criteria. Full-text articles of eligible studies were then retrieved and reviewed in detail. Any disagreements in study selection were resolved through consensus among all authors, ensuring a rigorous and unbiased selection process.

Data Extraction

Data extraction from eligible studies was conducted independently by two authors using full-text articles to ensure accuracy and consistency. Extracted data included the total number of events and controls for echocardiographic comparisons of rheumatic heart disease with and

without secondary prevention in Indonesia. Data presented in tables served as the primary source for this extraction process.

Risk of Bias

The quality of evidence was evaluated using the GRADE system, which considers the risk of bias and study design limitations. Randomized controlled trials (RCTs) were categorized as high-quality evidence, while observational studies were classified as low-quality. Each study was carefully assessed for potential biases and limitations, and these factors were systematically analyzed for each outcome across studies.

Heterogeneity

Heterogeneity was assessed by examining the consistency of point estimates, the degree of overlap in confidence intervals, and statistical measures. Subgroup analyses were conducted to identify possible sources of variability among the study results.

Evaluating the Quality of Evidence

The GRADE approach was used to assess and enhance the quality

of evidence, taking into account factors such as the magnitude of pooled effects, the relationship between interventions, and the presence of potential confounders.

Table 1. Search Strategy

<i>Database</i>	<i>Search Strategy</i>	<i>Hits</i>
Pubmed	<i>“Echocardiographic” AND “ Rheumatic Heart Disease” OR “Secondary Prevention” AND “ Indonesia”</i>	78
Science Direct	<i>“Echocardiographic” AND “ Rheumatic Heart Disease” AND “Secondary Prevention” AND “ Indonesia”</i>	18
Sagepub	<i>“Echocardiographic” AND “ Rheumatic Heart Disease” AND “Secondary Prevention” AND “ Indonesia”</i>	20



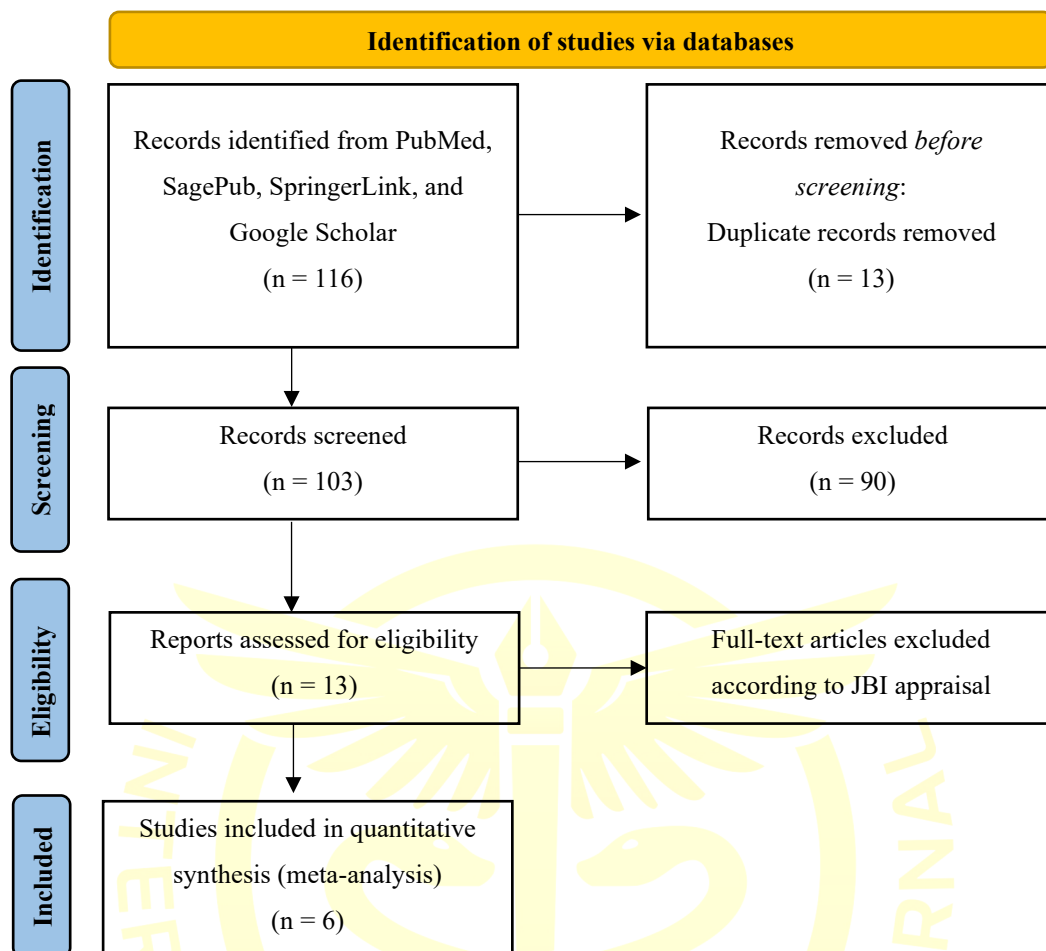


Figure 1. Search strategy and selection of studies for the meta-analysis.

Table 2. Critical appraisal of Study

Parameters	(Sastroas- moro et al., 1995)	(Rodriguez- Fernandez et al., 2015)	(Lilyasar i et al., 2020)	(Soesant o et al., 2020)	(Arafuri et al., 2022)	(Rudikty o et al., 2022)
1. Bias related to temporal precedence						
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation						
Was there a control group?	No	No	No	No	No	No
3. Bias related to confounding factors						
Were participants included in any comparisons similar?	Yes	Yes	Yes	No	Yes	Yes
4. Bias related to administration of intervention/exposure						
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No	No	No	No	No	No
5. Bias related to assessment, detection, and measurement of the outcome						
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	No	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	No	Yes	Yes
6. Bias related to participant retention						
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	No	No.	No.	No.	No.	No
7. Statistical conclusion validity						
Was appropriate statistical analysis used?	Yes	Yes	Yes	No	Yes	Yes

RESULT

Following a rigorous three-tiered screening process, six articles directly relevant to this systematic review were chosen for detailed examination through full-text analysis. These selected studies align closely with the research objectives and provide valuable insights pertinent to the study focus. Table 3 presents an overview of these articles, detailing each publication year and highlighting the distribution of publication years across the selected literature. This table offers a comprehensive snapshot of the temporal trends in the available research on this topic, supporting a deeper understanding of the progression and focus of studies within this field over time.

Table 3. Characteristics of studies included in the meta-analysis

Author	Origin	Method	Sample Size	Outcome	Result
Sastroasmoro, et al. ⁸ (1995)	Indonesia	We examined the survival curves of patients with established rheumatic heart disease treated at the Division of Cardiology, Department of Child Health, Faculty of Medicine University of Indonesia Cipto Mangunkusunto Hospital, Jakarta during the period of January 1983 until December 1992.	359 participants	Comparisons of several curves based on certain characteristics showed that age at the time of diagnosis and the number of valves involved were associated with survival.	A study of 177 patients with chronic heart disease confirmed the results of previous analyses, concluding that age at diagnosis and the number of valves in the ventricular tract are insufficient deterrents for children's prognosis.
Rodriguez-Fernandez, et al. ¹¹ (2015)	Indonesia	In order to identify and extract data on all rheumatic fever (RF) and RHD cases admitted to two hospitals in Papua between 2008 and 2013, clinical records of 15,608 mining workers (96.4% male,	83 participants	Basic demographics, employment history and echocardiographic findings.	Between 2008 and 2013, 83 RHD cases and 3 RF cases were identified, with an increased risk in individuals aged 35-44 and 45-68. The incidence density was 6.84 per 10,000 person years of follow-up. Mitral stenosis was the most common

		mean age 36.3±7.4 years) were retrospectively reviewed. The collected data included basic demographics, employment history, and echocardiographic findings.			valvular lesion at initial presentation (41.0%), with 6.0% being multivalvular.
Lilyasari, et al. ¹² (2020)	Indonesia	This was a hospital-based retrospective study conducted at the National Cardiovascular Center Harapan Kita, Indonesia; we retrieved relevant data from patients diagnosed with RHD between 2012 and 2018.	279 participants	The study aims to identify the clinical characteristics and patterns of RHD in children and young adults, emphasize its clinical significance, and provide a comprehensive understanding of RHD.	Rheumatic heart disease (RHD) is a prevalent condition in children and young adults, with a higher prevalence in females. Complications like congestive heart failure and pulmonary hypertension are common in children, while reactivation occurs in 17.2% of cases. The mitral valve is the most affected organ in children and young adults, with isolated mitral regurgitation and isolated mitral stenosis more common in children. Valve repair and replacement are more common in children and young adults, with low in-hospital mortality.
Soesanto, et al. ¹³ (2020)	Indonesia	The World Heart Federation aims to reduce premature deaths from ARF and RHD among individuals under 25 by 2025 through primary and primary prophylaxis, focusing on preventing ARF and limiting RHD	-	This encompasses the assessment of the pathological regurgitation flow and the morphological characteristics of RHD using 2D, color, and spectral Doppler criteria.	Rheumatic heart disease (RHD), a preventable disease resulting from acute rheumatic fever (ARF), is a significant health issue in developing countries. The World Heart Federation aims to reduce premature deaths from ARF and RHD by 25% by 2025. Early detection is crucial for

		progression and consequences.			prophylaxis strategies. In 2012, the WHF introduced new echocardiographic criteria to identify early stages of RHD. In Indonesia, a developing country with over 250 million people, a simplified echocardiographic criterion is needed for RHD screening.
Arafuri, et al. ¹⁴ (2022)	Indonesia	A retrospective cohort study was conducted on children under 18 years old with RHD at Dr. Sardjito Hospital, Indonesia, from 2011-2021. The study estimated survival time from diagnosis to endpoint, using Kaplan-Meier curves, log-rank test, and Cox-regression analysis for survival analysis and predictors.	155 participants	To examine the long-term consequences of RHD, with a particular emphasis on the predictors and survival rates.	A study involving 155 patients with RHD reported 14 deaths, with a mean age of 11.9 ± 2.9 years. The median follow-up period was 16 months. Survival rates were 93%, 86.1%, and 60% at 1, 4, and 8 years, with lower survival in patients with severe valve lesions and NYHA functional class III-IV at diagnosis.
Rudiktyo, et al. ¹⁵ (2022)	Indonesia	The study, conducted between 2016 and 2019, analyzed patients with valve disease aged 18+ in Jakarta, Indonesia, using medical records and hospital information systems. Patients were categorized based on valve disease etiologies.	2.333 participants	The purpose of this investigation was to describe the clinical and echocardiographic characteristics of patients with various types of valvular lesions in RHD in the Indonesian population.	A study of 2,333 patients with RHD, primarily female and younger, found that atrial fibrillation was the most common rhythm disorder and isolated mitral stenosis was the most common valve lesion. Most patients had preserved left ventricular ejection fraction, but half had reduced right ventricular contractility.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arafuri, 2022	+	?	+	?	+	+	+
Lilyasari, 2020	+	?	+	+	-	+	?
Rodriguez-Fernandez, 2015	+	?	+	+	?	+	-
Sastroasmoro, 1995	+	?	?	?	+	+	?

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

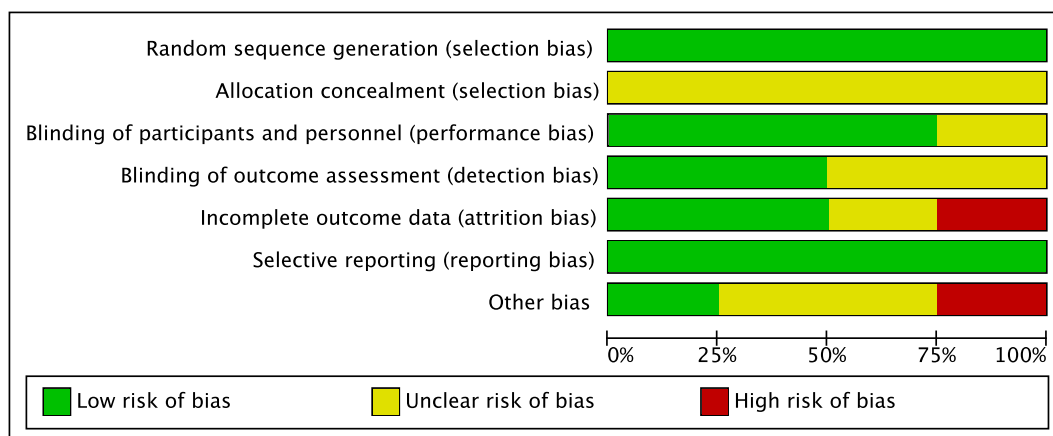


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

The primary objective of this analysis is to evaluate the impact of secondary prevention on echocardiographic outcomes in patients with RHD. Figure 4 presents forest plots that display the odds ratio (OR) for improved echocardiographic findings associated with secondary prevention compared to a control group. Specifically, out of 389 patients who received secondary prevention measures, a proportion demonstrated favorable echocardiographic outcomes. In contrast, the control group comprised 487 patients who did not undergo secondary prevention. The OR for achieving improved echocardiographic outcomes in the secondary prevention group versus the control was 0.38, with a 95% confidence interval (CI) of 0.16 to 0.91 and a p-value of 0.03. These findings indicate a statistically significant difference in echocardiographic improvement between the groups, favoring the secondary prevention group.

The odds ratio of 0.38 suggests that patients receiving secondary prevention interventions had a lower likelihood of adverse echocardiographic outcomes than those without such preventive measures. The confidence interval supports this finding, as it does not cross the threshold of 1.0, reinforcing the statistical significance of secondary prevention in enhancing echocardiographic results. This result underscores the potential clinical benefits of implementing secondary prevention strategies in patients with RHD.

Moreover, an I^2 heterogeneity test yielded a value of 0%, indicating no significant variability in effect sizes across studies. This homogeneity suggests consistent findings across the selected studies, reinforcing the robustness of the observed association between secondary prevention and improved echocardiographic outcomes in patients with RHD.

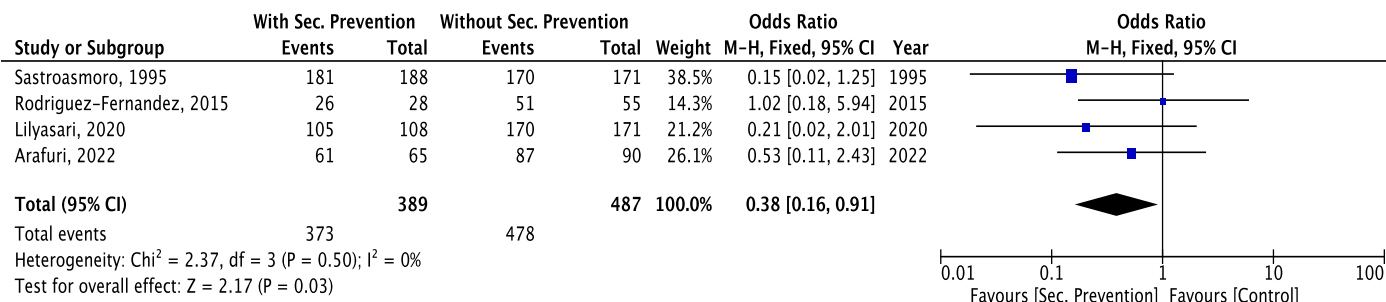


Figure 4. Forest Plot of Related Findings

DISCUSSION

Indonesia, the world's largest archipelago with over 17,000 islands and a population exceeding 267 million, faces significant challenges in tracking RHD and acute rheumatic fever (ARF) due to its complex geography and limited healthcare resources. The country lacks official nationwide data on the incidence of ARF and the prevalence of RHD, making it difficult to assess the full extent of these diseases. The scarcity of research is largely due to challenging access to remote islands, a shortage of healthcare workers, and

logistical constraints that impede large-scale screening efforts. Regional data, such as a meta-analysis from Asia reporting an RHD rate of 28.0 per 1,000 individuals, lacks representation from Indonesia.¹⁶ Historical data from 1970 to 1990 suggest an RHD prevalence of less than 1% in Indonesia¹⁷, yet more recent localized studies indicate some regions may have elevated rates of the disease.^{11,18}

Localized studies illustrate varying prevalence and highlight Indonesia's need for broader epidemiological data. For instance, a cohort study among miners in Papua

Province identified 83 RHD cases out of 15,608 workers, with an incidence density of 6.84 per 10,000 person-years and a high occurrence of mitral stenosis.¹¹ Another study conducted in Bandung's cardiac center reported an RHD prevalence of 2.3% (108 out of 4,682 patients) among cardiac patients, predominantly affecting women with a mean age of 44 years. This study noted common mitral and aortic valve involvement, with isolated mitral stenosis in 17.6% of cases.¹⁸ In contrast, a recent RHD screening in a rural Bali school setting among adolescents yielded only three borderline cases and no definitive RHD cases, despite high referral rates of adult RHD cases from this area.¹⁹ These findings underscore the need for a comprehensive, population-based screening strategy to more accurately determine the prevalence of RHD across Indonesia, facilitating better-targeted interventions for disease prevention and control.

Despite the application of several treatment options for ARF and RHD, the evidence supporting these therapies remains limited. Few studies have rigorously compared

outcomes in treated versus untreated individuals, and to date, only three randomized controlled trials have evaluated the effectiveness of penicillin treatment for RHD, each presenting methodological limitations.²⁰ In one trial, penicillin appeared to lower RHD recurrence; however, around 25% of participants did not complete follow-up, raising concerns about the reliability of the findings.²¹ Another notable study included 10,220 Ugandan children and adolescents with subclinical RHD and found that two-year penicillin prophylaxis (benzathine benzylpenicillin) significantly slowed disease progression in the treated group compared to controls.²² This finding highlights the potential of secondary antibiotic prophylaxis, yet further research is essential to confirm its benefits, particularly for patients with subclinical RHD. Moreover, the ideal duration for prophylaxis remains uncertain, though recent guidelines recommend that individuals with moderate RHD continue prophylaxis until 30-35 years of age, and those with severe RHD continue until 40.²³ At present,

there is no validated anti-inflammatory or immunosuppressive therapy proven to prevent or slow RHD progression. Randomized controlled trials are urgently needed to explore alternative treatments, and innovative genomic and proteomic methods may hold promise in preventing the tissue damage linked to ARF and RHD. Early research into plasma and tissue proteomic markers shows potential for advancing therapeutic strategies, offering a hopeful avenue for future ARF and RHD interventions.²⁴

Echocardiography has become an essential noninvasive diagnostic tool for detecting RHD, offering greater sensitivity and specificity compared to traditional auscultation methods.²⁵ It is particularly valuable for identifying subclinical RHD, which can occur in the absence of clinical signs of valvular regurgitation. Advances in echocardiography technology, such as the development of portable devices, have made it more accessible and cost-effective, even in remote or underserved areas.²⁶ These technological improvements have

facilitated early detection of RHD, which can be critical in reducing morbidity and mortality associated with the disease. However, while echocardiographic screening for RHD is not universally recommended, it may be warranted in populations where the incidence of RHD is suspected to be high or in areas experiencing clusters of ARF cases.²⁷

Subclinical RHD is defined by the presence of echocardiographic evidence of RHD without symptoms or a history of ARF.²⁵ Detecting this form of RHD early, through echocardiography, and administering secondary preventive measures, such as penicillin, can significantly reduce the risk of progression to more severe cardiac damage.²⁸ For instance, a study in Turkey found that the incidence of ARF in 2016 was 8.84 per 100,000 population, and through echocardiographic screening of school-aged children, 15 per 1,000 children were identified with subclinical RHD. These children were then able to receive secondary preventive therapy, which is estimated to prevent up to 80% of RHD progression in high-risk

populations. The study underscores the importance of targeted screening in areas with moderate to high RHD risk, where secondary prevention can make a substantial impact. In such areas, the rate of rheumatic valvular heart disease after negative echocardiographic screening was relatively low (5.9%-13.0%), suggesting that repeated screening could detect new cases of subclinical and definitive RHD, as well as prevent further disease progression.²⁹

In addition to detecting subclinical RHD, echocardiographic screening has the added benefit of identifying asymptomatic congenital heart defects, such as atrial septal defects, patent ductus arteriosus, and bicuspid aortic valves, which might otherwise remain undiagnosed.³⁰ Despite its advantages, the 2012 World Heart Federation (WHF) criteria for diagnosing RHD using echocardiography have some limitations. These criteria were designed to distinguish mild RHD from normal findings but rely on 2D, color Doppler, and continuous-wave Doppler echocardiography, which may not always capture the full extent

of valve pathology. More advanced echocardiographic methods are available to better assess the severity of valvular damage, yet the WHF criteria can be difficult to apply, especially for less experienced echocardiographers. Furthermore, there is a risk of misinterpreting benign variations, such as interscallop separations of the mitral valve, as signs of RHD, potentially leading to misdiagnosis.³¹ These challenges highlight the need for skilled echocardiographers and more refined diagnostic criteria to enhance the accuracy of RHD detection and improve the effectiveness of secondary prevention strategies.

CONCLUSION

Indonesia faces significant challenges in tracking RHD and ARF due to its complex geography and limited healthcare resources. The country lacks official nationwide data on the incidence of ARF and the prevalence of RHD, making it difficult to assess the full extent of these diseases. Echocardiographic screening has become an essential noninvasive diagnostic tool for

detecting RHD, offering greater sensitivity and specificity compared to traditional auscultation methods. Advances in echocardiography technology have made it more accessible and cost-effective, even in remote or underserved areas. However, echocardiographic screening for RHD is not universally recommended, and it may be warranted in populations where the incidence of RHD is suspected to be high or in areas experiencing clusters of ARF cases. The 2012 World Heart Federation criteria for diagnosing RHD using echocardiography have some limitations, and more advanced echocardiographic methods are available to better assess the severity of valve pathology.

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