

Outcome in children with newly diagnosed rheumatic heart disease in Indonesia

by Indah Kartika Murni

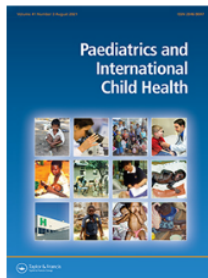
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Outcome in children with newly diagnosed rheumatic heart disease in Indonesia

Indah K. Murni^{a,b}, Nadya Arafuri^a, Andrew C. Steer^{c,d,e}, M. Taufik Wirawan^a, Fransisca G. W. Remi^a, Noormanto Noormanto^a and Sasmito Nugroho^a

^aDepartment of Child Health, Dr Sardjito Hospital/Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; ^bCentre for Child Health - Paediatric Research Office, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; ^cDepartment of Paediatrics, Centre for International Child Health, University of Melbourne, Melbourne, Australia; ^dGroup A Streptococcal Research Group, Murdoch Childrens Research Institute, Melbourne, Australia; ^eDepartment of General Medicine, Royal Children's Hospital, Melbourne, Victoria, Australia

ABSTRACT

Background: Rheumatic heart disease (RHD) is associated with high morbidity and mortality, especially in those with severe RHD or progression of valvular disease (VD). Evaluation of the factors that predict valvular progression is important in order to improve clinical outcome.

Aim: To evaluate outcome and clinical predictors of valvular progression in children with newly diagnosed RHD.

Methods: A retrospective cohort study was conducted in children with newly diagnosed RHD at Dr Sardjito Hospital, Yogyakarta, Indonesia during 2013–2020. Clinical and echocardiography data at the time of diagnosis were collected and patients were followed up for 1 year. Echocardiography evaluations were undertaken to determine the progression of VD. Independent predictors of valvular progression were identified by Cox regression analysis.

Results: A total of 77 patients were recruited, 36 (46.7%) of whom were male, and the median age (range) was 12.3 years (5.9–17.8). Thirty-three (42.8%) had progression of VD in the year after diagnosis. By multivariable analysis, an age at diagnosis of >10 years and high C-reactive protein (CRP) were independently associated with an increased risk of valvular progression with an adjusted hazard ratio (95% CI) of 3.23 (1.09–9.60) and 3.69 (1.45–9.67), respectively.

Conclusion: After only 1 year of follow-up, approximately four in 10 children with newly diagnosed RHD developed progression of VD. An increased risk of valvular progression was associated with being over 10 years of age and a high level of CRP.

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Introduction

Rheumatic heart disease (RHD) carries a considerable risk of morbidity and mortality, particularly in low- and middle-income countries [1,2]. Mortality is highest in those with severe RHD [3–6] and early detection of valvular progression in these patients is important in order to improve outcome.

There are few studies of the factors which might predict progression of RHD in children. One study identified predictors of valvular disease (VD) progression in children with RHD in Brazil which included moderate-to-severe carditis, recurrence of acute rheumatic fever and poor maternal education [7]. A study in Fiji evaluated valvular progression in young people with latent RHD diagnosed by echocardiographic screening and found that it had progressed in 70% of those with definite RHD [8].

There is a substantial burden of RHD in Indonesia. A study in Jakarta of children and young adults with RHD found that hospital admission related to congestive heart failure and pulmonary hypertension occurred in 11% of children and 20% of young adults

[9]. There are no studies of factors associated with VD progression in children with RHD in Indonesia. This study aimed to describe early outcome in children with newly diagnosed RHD in Yogyakarta and to identify the clinical predictors of VD progression.

Methods

Study population, time and setting

A retrospective cohort study was undertaken in Dr Sardjito Teaching Hospital, Yogyakarta, a referral teaching hospital for Yogyakarta and the southern part of the Central Java provinces in Indonesia. Patients with newly diagnosed RHD attending the paediatric cardiology clinic and the general paediatric wards between 1 January 2013 and 31 December 2020 were eligible for enrolment.

A baseline echocardiogram at diagnosis and a follow-up echocardiogram at 1 year were undertaken in eligible patients. Survival analysis with longitudinal data beyond 1 year were included. Subjects with no worsening of the valve lesion by 31 June 2021 or who

36 were lost to follow-up were removed from the study. After 1 year of follow-up, the severity of valvular involvement in those with RHD and whether there had been progression of VD were determined. Whether a series of epidemiological and clinical factors was associated with progression was also determined.

Echocardiographical examination

The RHD was diagnosed by experienced paediatric cardiologists on the basis of echocardiographical findings using previously published World Heart Federation (WHF) criteria [10]. Patients with RHD were categorised into definite or borderline RHD, as per the WHF criteria [10]. The paediatric cardiologists agreed the definitions of valvular disease severity.

Patients were assigned to the categories of mild, moderate or severe RHD. The grading for severity of valvular regurgitation included assessment of the regurgitant jet area, regurgitant fraction, regurgitant flow deceleration slope, and the size of the corresponding heart chamber. For valvular stenosis, the following were assessed: valvular orifice area by planimetry, forward flow mean pressure gradient and pre-stenotic heart chamber size [11]. Mild RHD was defined when the thickened valve and regurgitation of the heart valve lesion were considered to be mild without any corresponding chamber enlargement and no dilated valve annulus, and valve coaptation was good. Moderate RHD was when the heart valve lesion was considered to be moderate with mild chamber enlargement and mildly dilated valve annulus with mildly thickened or calcified valves with no reduced leaflet motion or congestive heart failure. Severe RHD was when the heart valve lesion was severe or moderate-to-severe, but there was congestive heart failure with thickened or calcified valves with reduced leaflet motion or a need for valve surgery [1,12].

Progression of RHD was defined as an increase in severity (from mild to moderate or severe, or from moderate to severe) when measured 1 year after enrolment, or a need for valve surgery within 1 year of enrolment [8].

Factors associated with progression

Demographic and clinical information was collected at enrolment. The demographic factors included age, sex, household income and household crowding. The clinical information included recurrence of rheumatic fever at the first diagnosis and during follow-up, the C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), haemoglobin, nutritional status, aortic valve involvement, severity of RHD at diagnosis, and adherence to secondary penicillin prophylaxis.

Low income was defined as a family income less than the regional minimum income. Overcrowding was defined as more than five persons sharing one bedroom. Anaemia was haemoglobin <11 g/dL. CRP was considered to be elevated when it was >5 mg/L and ESR when it was >15 mm/hr in males and >20 mm/hr in females. Nutritional status was determined using WHO criteria [13]. Malnutrition was defined as a Z-score <3 SD below the 50th centile for weight and height, adjusted for gender.

All patients diagnosed with RHD were prescribed oral penicillin prophylaxis which could be taken at their nearest district hospital. Echocardiographical evaluation of all RHD patients every 3–6 months at outpatient clinics was scheduled. At each subsequent visit, the medical staff asked patients to self-report adherence to penicillin prophylaxis. Patients were classified as having adhered adequately to secondary prophylaxis when they said they had consumed more than 80% of the prescribed oral penicillin for 12 months. Adherence was considered to be poor when patients reported having taken less than 80% of the oral penicillin. Patients who did not attend appointments for more than 12 months were considered to be lost to follow-up.

Statistical analysis

11 Data are presented as means and standard deviations (SD) for normally distributed data, or medians with a range of non-normal data, or proportions, as appropriate. Univariable analysis was performed to determine the significance and strength of the association between each factor and VD progression; $p < 0.05$ indicated statistical significance.

Kaplan–Meier survival curves and logrank tests were used to evaluate differences between patients with and without valvular progression. Cox hazard regression analysis was undertaken to determine the predictive factors which were independently associated with VD progression. All significant variables in the univariable analysis were entered into a multivariable regression analysis. The results were reported as adjusted hazard ratios with 95% confidence intervals. Data were analysed using STATA version 12.1 (StataCorp LP, Texas).

Ethics

The Medical and Health Research Ethics Committee of Universitas Gadjah Mada approved this study (KE/FK/0914/EC/2019). The committee did not require individual patient consent.

Results

During the study period, there were 127 children with newly diagnosed RHD, 11 (8.7%) of whom died during

hospitalisation, all with severe congestive heart failure as a result of severe RHD.

Thirty-nine (30.7%) were lost to follow-up at 1 year, and therefore 77 patients were in the final cohort for analysis. Of these, 24 (31.2%) had mild or moderate RHD. The mitral valve was involved in all children with RHD (Table 1). In the 39 lost to follow-up, the RHD was mild in six (15.4%), moderate in six (15.4%) and severe in 27 (69.2%).

Table 1. Characteristics of 77 children with rheumatic heart disease.

Baseline characteristics	Progression n = 33 (%)	No progres- sion n = 44 (%)	p-value
Sex			
Male	12 (63.6)	24 (54.5)	0.48
Female	21 (36.4)	20 (45.5)	
Age, y			
<10	3 (9.1)	15 (34.1)	0.01
>10	30 (90.9)	29 (65.9)	
Maternal education, y			
<9	18 (54.5)	30 (68.2)	0.24
>9	15 (45.5)	14 (31.8)	
Paternal education, y			
<9	17 (51.5)	29 (65.9)	0.24
>9	16 (48.5)	15 (34.1)	
Income			
Low	20 (60.6)	27 (61.4)	1.00
Middle and high	13 (39.4)	17 (38.6)	
Overcrowded			
Yes	6 (18.2)	9 (20.5)	1.00
No	27 (81.8)	35 (79.5)	
Recurrence of ARF at first diagnosis			
Yes	22 (66.7)	25 (56.8)	0.48
No	11 (33.3)	19 (43.2)	
Recurrence of ARF during follow-up			
Yes	7 (21.2)	2 (4.5)	0.03
No	26 (78.2)	42 (95.5)	
CRP			
Normal	6 (18.2)	27 (61.4)	<0.0001
High	27 (81.8)	17 (38.6)	
ESR			
Normal	11 (33.3)	27 (61.4)	0.02
High	22 (66.7)	17 (38.6)	
Anaemia			
No	19 (57.6)	35 (79.5)	0.04
Yes	14 (42.4)	9 (20.5)	
Nutritional status			
Normal	23 (69.7)	35 (79.5)	0.42
Malnutrition	10 (30.3)	9 (20.5)	
Aortic valve involvement	15 (45.5)	20 (45.5)	1.00
Severity of RHD at diagnosis			
Mild	1 (3.0)	5 (11.4)	0.03
Moderate	12 (36.4)	6 (13.6)	
Severe	20 (60.6)	33 (75.0)	
Number of valves involved			
1	10 (30.3)	16 (36.4)	0.17
2	13 (39.4)	20 (45.4)	
3	8 (24.2)	3 (6.8)	
4	2 (6.1)	5 (11.4)	
Adherence to penicillin			
Adequate	27 (81.8)	38 (86.4)	0.75
Poor	6 (18.2)	6 (13.6)	

ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RHD, rheumatic heart disease.

Anaemia: Hb <11 g/dL; high ESR, male >15 mm/h, female >20 mm/h; high CRP, >5 mg/dL.

Malnutrition: Z-score <3 SDs below the 50th centile for weight and height, adjusted for gender.

p-values in bold type are statistically significant.

By 1-year follow-up, 33 (42.8%) patients had developed progression of VD, 23 by 2 years, and 17 by 3 years. The survival analysis of VD progression of RHD after diagnosis is presented in Figure 1, and the survival analysis of progression of RHD according to severity of valvular heart disease at diagnosis in Figure 2. The inter-rater agreement among the cardiologists who assessed the severity of RHD was 0.89.

In the univariable analysis, the following variables were associated with progression: age >10 years, recurrence of rheumatic fever during follow-up, high levels of CRP and ESR, anaemia and moderate RHD at first diagnosis. In the multivariable regression analysis, age >10 years and CRP >5 mg/dL remained independently associated with valvular progression (Table 2).

Discussion

In this cohort of children with RHD in Yogyakarta, four in ten developed progression of VD after just 1 year. As far as we know, this is one of the first studies in Indonesia to evaluate outcome in children with newly diagnosed RHD and the factors associated with progression.

Two factors were found to be associated with valvular progression: age >10 years and high levels of CRP. Moderate RHD at first diagnosis predicted VD progression to be twice more likely than in mild RHD, but this was not statistically significant in the multivariable analysis. Although the odds ratio was lower, the results were in general agreement with a previous study that found that moderate RHD was associated with a 16-fold increase in the risk of valvular progression in children with RHD [7].

CRP is an independent predictor of progression of calcific aortic valve disease, coronary artery disease and atheroma formation [14]. A previous study also found that patients with RHD and a high plasma CRP level were more likely to develop atrial fibrillation and to progress to mitral stenosis [15]. This study raises the possibility that, after untreated rheumatic fever, chronic inflammation of the cardiac valves may continuously occur and lead to more rapid progression of valvular damage [16]. In this study, recurrence of acute rheumatic fever was not associated with valve progression. It is well known that recurrence of acute rheumatic fever is an important factor in valvular progression in RHD [7] and is the reason why secondary antibiotic prophylaxis is recommended for patients with RHD [7,17]. A meta-analysis found that intramuscular benzathine penicillin G was the antibiotic of choice for preventing recurrence of acute rheumatic fever [18,19]. At this hospital, however, benzathine penicillin G is unavailable and so daily oral phenoxymethylpenicillin is used for secondary prophylaxis. Adherence to daily oral penicillin is known to be poor [18]. It was not possible to measure adherence

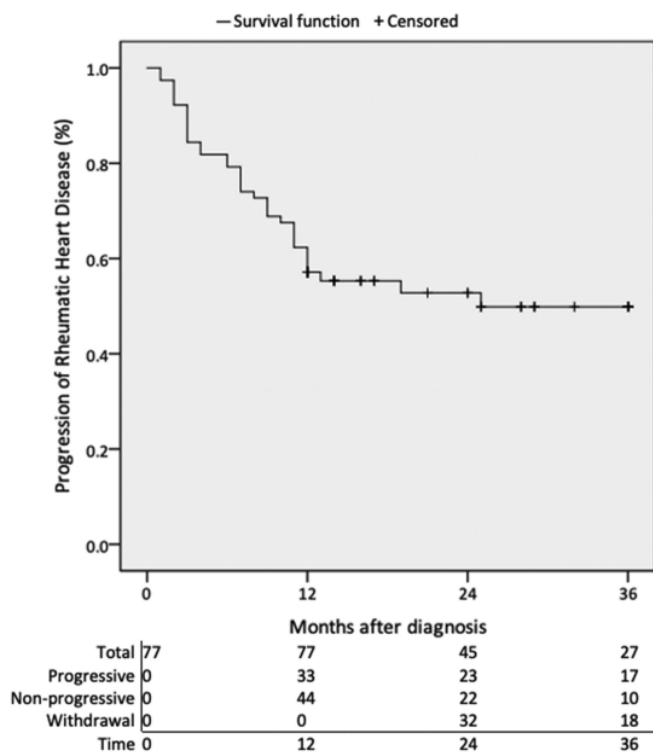


Figure 1. Survival analysis of valvular disease progression of rheumatic heart disease after diagnosis.

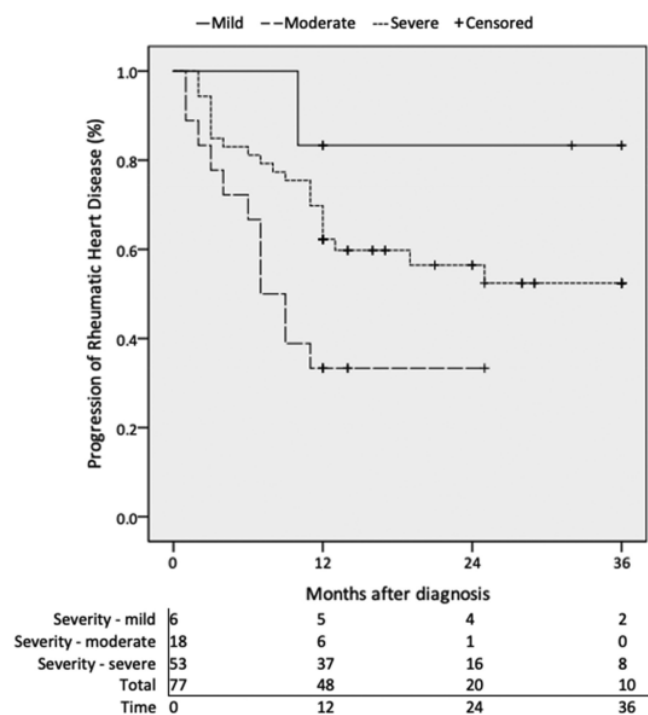


Figure 2. Survival analysis of progression of rheumatic heart disease according to severity of valvular heart disease at diagnosis.

Table 2. Predictors of valve disease progression in rheumatic heart disease.

Predictors	Hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Age at diagnosis >10 years	3.01 (1.06–8.55)	0.03	3.23 (1.09–9.60)	0.03
Male sex	1.43 (0.72–2.84)	0.30		
Low income	1.12 (0.58–2.17)	0.74		
Overcrowding	0.96 (0.42–2.20)	0.93		
Recurrence of ARF at first diagnosis	1.13 (0.58–2.20)	0.73		
Recurrence of ARF during follow-up	2.31 (1.01–5.28)	0.04	0.84 (0.41–1.73)	0.63
High CRP	3.58 (1.63–7.88)	0.01	3.69 (1.45–9.37)	0.01
High ESR	2.08 (1.05–4.10)	0.03	1.07 (0.48–2.39)	0.86
Anaemia	2.20 (1.14–4.25)	0.01	1.39 (0.68–2.83)	0.37
Malnutrition	1.44 (0.69–2.99)	0.33		
Aortic valve involvement	1.06 (0.55–2.04)	0.86		
Moderate RHD at first diagnosis	2.18 (1.08–4.40)	0.03	2.05 (0.96–4.35)	0.06
Poor adherence to penicillin	1.32 (0.54–3.20)	0.54		

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ARF, acute rheumatic fever; HR, hazard ratio; CI, confidence interval. Anaemia: Hb <11 g/dL; high ESR: male >15 mm/h, female >20 mm/h; high CRP: >5 mg/dL. Malnutrition was defined as a Z-score <3 SD below the 50th centile for weight and height, adjusted for gender. p-values in bold type are statistically significant.

properly in this study because children are managed by their district hospital after discharge which makes data collection challenging [9].

In addition to the high proportion of children with disease progression, there was an in-hospital mortality rate of 8.7%. Similar to a previous study [20], all who died had severe RHD and presented with severe congestive heart failure. Taken together, these findings reveal a considerable public health problem which requires a comprehensive approach to improve outcome. Such a strategy might include improved diagnosis and treatment of streptococcal pharyngitis, early detection of mild cases of RHD or acute rheumatic fever, a reliable referral system, echocardiographical screening programmes for RHD in school-age children and a credible cardiac surgery and critical care programme for those who require valve surgery [2].

The study has some limitations. Firstly, it was relatively small and lacked sufficient power to detect the

association between a number of factors and outcome. Secondly, it was not possible to track those lost to follow-up. Thirdly, the study was limited to Yogyakarta and so the results can not be generalised to other children with RHD in other low- and middle-income countries.

The study demonstrates a considerable burden of disease progression and mortality in children with RHD. Age >10 years and a high CRP at diagnosis were associated with valve progression. The study highlights the need for better clinical and public health efforts to control RHD in young people in Indonesia.

Abbreviations

ARF, acute rheumatic fever; CRP, C-reactive protein; RHD, rheumatic heart disease; SD, standard deviation; VD, valvular disease; WHF, World Heart Federation; WHO, World Health Organization

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Notes on contributors

Indah K Murni is a consultant paediatrician and paediatric cardiologist at DR Sardjito Hospital in Yogyakarta, Indonesia. Assoc Prof Murni is a lecturer in the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada. She is a principal research fellow at the Centre for Child Health - Paediatric Research Office, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada.

Nadya Arafuri is a consultant paediatrician and paediatric cardiologist at the Dr Sardjito Hospital. She is lecturer and researcher in the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada.

Andrew Steer is a consultant paediatrician and paediatric infectious diseases physician at the Royal Children's Hospital. He is principal research fellow at the Centre for International Child Health in the Department of Paediatrics at the University of Melbourne, as well as Group Leader of the Group A Streptococcal Research Group at MCRI. Prof Steer holds a current NHMRC/NHF career development fellowship.

M Taufik Wirawan is undergoing his paediatric residency training program and master program in the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/DR Sardjito Hospital.

Fransisca GW Remi is paediatrician and she undertook her residency training program in the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/DR Sardjito Hospital. She did her master program in the same institution.

Noormanto is a consultant paediatrician and paediatric cardiologist at the DR Sardjito Hospital. He is lecturer in the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada.

Sasmito Nugroho is a consultant paediatrician and paediatric cardiologist at the DR Sardjito Hospital. He is lecturer in the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada.

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