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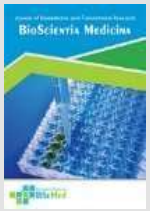

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Rheumatic Heart Disease in East of Bali Indonesia

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A B S T R A C T

Background: Rheumatic heart disease remains to be the most acquired heart disease among people aged <25 years. Despite improvements in high sociodemographic countries, low and low-middle sociodemographic countries have been less successful in lowering the burden of RHD.1 However, data of patient with RHD is still lacking in Indonesia, especially in Bali. Karangasem is a rural area, one of the regencies in the eastern part of Bali. **Methods:** This retrospective study was performed between January 2023 and January 2024 at two hospitals in Karangasem Regency, Karangasem Regional General Hospital and BaliMed Karangasem Hospital. These two hospitals were the only hospital in Karangasem regency. The study population comprised all patients who were diagnosed with RHD. Patient characteristics and echocardiographic parameters were collected retrospectively from medical records. **Results:** Data from 101 patients with RHD were collected. They were predominantly female (73.3%) young adults (mean ages 41.97 years), graduated from primary school (58.4%), unemployed (26.7%), and mostly from the Karangasem subdistrict (34.7%). Mitral stenosis and mitral regurgitation were the same counts (65.3%), with mixed valve lesions (mitral and aortic) as the most common lesion (45.5%). Fifty-eight patients (57.4%) had secondary tricuspid regurgitation, with 6 patients with TR V-Max >3.4m/s. Atrial fibrillation was a common complication (47.5%). Most patient with RHD had preserved Left Ventricular Ejection Fraction (LVEF >50%). Only a quarter of patients had reduced RV contractility (TAPSE <17mm). All of the patients with AF were given warfarin. All under 40-year-old patients were given a benzathine penicillin G injection. Only 7 patients had a history of valve surgery. **Conclusion:** Mixed valve lesion (mitral and aortic) was the most observed condition of valve lesion in RHD with the same count of mitral stenosis and mitral regurgitation. Characteristic of patients in this study were predominantly female, young adult, graduated from primary school, unemployed, had preserved LV function, normal RV contractility, high prevalence of AF with all prescribed warfarin, all of under 40 years were given antibiotics prophylaxis.

1. Introduction

Indonesia is an endemic country of rheumatic heart disease (RHD), and becomes the fourth most prevalent country in the world (after China, India, and Pakistan) with 1.18 million cases per year in 2015.[1] Rheumatic fever mostly affects children and adolescents in low and middle-income countries, especially where poverty is widespread and access to health services is limited. People who live in overcrowded and poor conditions are at greatest risk of developing the disease.[2,3] Without intervention, RHD progresses to heart failure and increases the risk of cerebrovascular accident, bacterial endocarditis, and arrhythmia. Despite RHD's enormous global public health burden, there have been few publications and conference reports on the disease. [2,3] This study aimed to describe the characteristic and valvular involvement of RHD patients attending two hospitals in Karangasem Regency. Karangasem is one of the districts in Bali. It is the third largest district,

with 8 subdistricts and 75 villages, most of the region is dry land area.[4] The region faces some of the least favourable socioeconomic indicators among 9 regencies in Bali.[5]

2. Methods

This study was a retrospective study of demography, and echocardiography data from all patients with RHD in Karangasem regency. This study was performed in two hospitals in Karangasem Regency, Bali, Indonesia. Karangasem Regional General Hospital and BaliMed Karangasem Hospital, seated in the town of Amlapura. Almost all of the public health centers in subdistricts in Karangasem refer patients who require further examination to these two hospitals. The study population comprised 101 patients with diagnosis of RHD on the medical record, who had undergone transthoracic echocardiography at Karangasem Regional General Hospital and BaliMed Karangasem Hospital. Echocardiography was performed by cardiologist. Patient characteristics and echocardiography parameters were collected respectively from medical records and hospital information systems. Demographic parameters included in this study were sex, age, education, occupation, and subdistrict where the patients lived. The history of receiving Benzathine Penicillin G injection, history of receiving warfarin, history of valve replacement, and other complications are also included in this study.

Echocardiography parameters obtained were type of valvular lesions, left ventricular ejection fraction (LVEF), left atrial diameter, tricuspid annular plane systolic excursion (TAPSE), peak tricuspid regurgitation velocity (TR Vmax). Diagnosis and grading severity of valve abnormality were performed based on 2021 European Society of Cardiology (ESC) guidelines for the management of valvular heart disease.[6] Left atrial diameter was categorized as a gender-specific variable, such that left atrial enlargement was defined as a left atrial diameter of 4.1 cm or greater in men, or 3.9 cm or greater in women; a left atrial diameter below these values defined in normal left atrial size.[7] TAPSE <17mm is highly suggestive of RV systolic dysfunction.[8] The TR Vmax cut off value was obtained from 2022 ESC/European Respiratory Society guideline for the diagnosis and treatment of pulmonary hypertension.[9] Other findings in echocardiography were also obtained such as pericardial effusion, spontaneous echocontrast, and thrombus. Data management was performed using the SPSS software version 26 (IBM Corp., USA). Descriptive statistic was used to describe and summarize the data.

3. Results

Baseline characteristics of the patients can be found in Table 1. There were triple as many females as male participants (74 females vs. 27 males). The ages ranged from 11 to 77 years (mean 41.97 years). Half of the sample only graduated from primary school (58.4%), and most were unemployed (26.7%). Thirty-five of the samples lived in the Karangasem subdistrict (34.7%), followed by the Abang subdistrict (23.8%) and Kubu subdistrict (13.9%).

Among all patients with RHD, we found the same count of mitral stenosis and mitral regurgitation (65.3%), followed by aortic regurgitation (45.5%). Aortic stenosis was the least valve abnormality (10.9%). Tricuspid regurgitation in conjunction with left-sided valvular lesions was found in more than half of the patients (57.4%). No cases of rheumatic tricuspid stenosis and involvement of pulmonary valve lesions were found in this study. Other findings secondary to MS, there are 2 patients with left atrial thrombus, 2 patients with spontaneous echocontrast (SEC), and 3 patients with pericardial effusion. Further analysis of valvular involvement is shown in Table 3. Mixed valve lesion (mitral and aortic) was the most common valve lesion observed in this study (45.5%), followed by isolated mitral stenosis (22.8%). No isolated aortic stenosis was found in this study.

Patients with isolated mitral regurgitation tended to be younger than other groups (mean age 29.157). Half of the patients with mixed valve lesions also had atrial fibrillation (50%). AF was not found in isolated

aortic regurgitation patients. Significant dilatation of the left atrium was found more in mitral stenosis patients (82.6%) than in patients with mitral regurgitation (42.1%). Patients with mitral stenosis (isolated MS or MS with MR) had mostly reduced RV contractility (TAPSE <17mm). High tricuspid regurgitation maximum velocity (TR Vmax) was seen in all of the mitral valve lesion groups, signifying the probability of underlying pulmonary hypertension.

Table 1. Baseline characteristics of study samples.

Variable	Category	N (%)
Gender	Female	74 (73.3)
	Male	27 (26.7)
Age		
	11-20	14 (13.9)
	21-30	15 (14.9)
	31-40	17 (16.8)
	41-50	21 (20.8)
	51-60	21 (20.8)
	61-70	11 (10.9)
	>70	2 (2.0)
	Mean	41.97
Education		
	None	1 (1.0)
	Primary	59 (58.4)
	Secondary (junior)	5 (5.0)
	Secondary (senior)	25 (24.8)
	University	11 (10.9)
Occupation		
	Student	11 (10.9)
	Teacher	1 (1.0)
	Housewife	19 (18.8)
	Farmer	6 (5.9)
	Trader	12 (11.9)
	Self-employed	14 (13.9)
	Civil servants	8 (7.9)
	Unemployed	27 (26.7)
	Craftsman	2 (2.0)
	Midwife	1 (1.0)
Subdistrict		
	Abang	24 (23.8)
	Bebandem	15 (14.9)
	Karangasem	35 (34.7)
	Kubu	14 (13.9)
	Manggis	9 (8.9)
	Selat	4 (4.0)
	Rendang	0 (0.0)
	Sidemen	0 (0.0)

Table 2. Echocardiography findings.

Valvular lesion	Category	N (%)
	MS	66 (65.3)
	MR	66 (65.3)
	AR	46 (45.5)
	AS	11 (10.9)
	TR	58 (57.4)
Pericardial effusion		3 (2.9)
SEC in LA		2 (1.9)
Thrombus in LA		2 (1.9)

Table 3. Characteristic of valvular involvement.

Parameters	Mixed valve 46 (45.5%)	Isolated MS 23 (22.8%)	Isolated MR 19 (18.8%)	MS and MR 13 (12.9%)	Isolated AR 1 (1%)
Female	28 (60.9%)	19 (82.6%)	17 (89.5%)	10 (76.9%)	0 (0%)
Male	18 (39.1%)	4 (17.4%)	2 (10.5%)	3 (23.1%)	1 (100%)
Age (mean)	44.06	42.13	29.15	53.07	0 (0%)
AF	23 (50%)	10 (43.5%)	3 (15.8%)	12 (92.3%)	0 (0%)
EF					
≤40%	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
41%-49%	3 (6.5%)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)
≥50%	42 (91.3%)	23 (100%)	19 (100%)	12 (92.3%)	1 (100%)
Dilated LA	38 (82.6%)	19 (82.6%)	8 (42.1%)	12 (92.3%)	0 (0%)
TAPSE					
<17 mm	9 (19.6%)	9 (39.1%)	2 (10.5%)	6 (46.2%)	0 (0%)
TR Vmax					
No TR	24 (52.2%)	8 (34.8%)	11 (57.9%)	5 (38.5%)	1 (100%)
<2.8 m/s	16 (34.8%)	10 (43.5%)	4 (21.1%)	4 (30.8%)	0 (0%)
2.8-3.4 m/s	5 (10.9%)	2 (8.7%)	3 (15.8%)	3 (23.1%)	0 (0%)
>3.4 m/s	1 (2.2%)	3 (13%)	1 (5.3%)	1 (7.7%)	0 (0%)

Table 4. Clinical complications of RHD.

Variable	N (%)
AF	48 (47.5)
Stroke	1 (1.0)
DVT	1 (1.0)
ALI	1 (1.0)

Table 5. Medication history.

Variable	Category	N (%)
Warfarin		
	Yes	49 (48.5)
	No	51 (51.5)
Antibiotics		
	BPG injection	40 (39.6)
	Phenoxymethyl penicillin oral	2 (2.0)
	No	59 (58.4)

Table 4 shows the clinical complication of RHD found in our study. Almost 50% of patients had atrial fibrillation. Table 5 shows medication history of the patients. All of 48 patients with AF were prescribed warfarin. One patient was receiving warfarin because of having deep vein thrombosis. Among 101 patients, all patients under 40 years old were prescribed penicillin for streptococcal prophylaxis, and 39.6% had Benzathine Penicillin G injection. Only 2 patients refused to have injection, and preferred oral phenoxymethylpenicillin, mostly because of fear of painful injection. Other 58.4% of patients did not have injections of BPG, with age more than 40 years old when diagnosed with RHD. From Table 6, 7 patients had a history of valve surgery, 5 with a history of mitral valve replacement, 1 with double valve replacement (mitral and aortic), and 1 with aortic valve replacement.

Table 6. History of surgery.

Variable	Category	N
Surgery		
	MVR	5
	DVR	1
	AVR	1

4. Discussion

A shortage of healthcare resources, poverty, malnutrition, poor housing, and overcrowding, are still prevalent in Indonesia, including in Bali and Karangasem regency. Karangasem Regency area has a tropical wet and dry climate.[4] RHD have been documented to be more common in the Karangasem subdistrict, especially in Seraya village, Abang subdistrict, and Kubu subdistrict, the area that tends to be dry and hot. This happened probably because *Streptococcus pyogenes* are carried easily in the dry air.[10] Apart from that, access to hospitals is closer, so this disease is more commonly detected in the Karangasem subdistrict. Rendang and Sidemen subdistricts had zero cases of RHD, this is probably because the nearest access was another hospital in another regency (Klungkung regency). In many populations, RHD is more common in females than males, this also have been shown in this study. Females were predominant in all spectra of valve involvement. Whether this trend is a result of innate susceptibility, increased exposure to *Streptococcus pyogenes* because of greater involvement of women in child rearing, or reduced access to preventive medical care for women is unclear.[10,11] In our study, most of the patients were middle-aged and elderly, as mitral stenosis is increasingly frequent in patients from the fourth to the sixth decade of life.[11] This finding reflects the pathogenesis of RHD that mitral stenosis usually develops later than mitral regurgitation after the episode of rheumatic fever. Involvement of the aortic valve alone was not common. Most patients with aortic valve lesions had it combined with mitral valve lesions. It is known that the tricuspid valve is rarely affected by rheumatic carditis, but functional tricuspid regurgitation may accompany mitral valve disease.[10] As in this study, tricuspid regurgitation was seen in 58 patients (57.4 %).

Left atrium (LA) enlargement frequently as a result of mitral valve and to a lesser extent aortic valve disease.[10] Increased LV end-diastolic pressure may be responsible for the increased LA size. Increased LA pressure occurred with subsequent dilatation and remodelling that eventually triggered atrial fibrillation.[7] AF was explained by the large majority of patients having left atrial diameter greater than 40mm.[12] Atrial fibrillation (AF) may complicate LA enlargement and was seen in 48 (47,5%) of the patients. AF leads to a loss of organised mechanical activity of LA and increases the tendency to develop thrombus.[10] Two patients had thrombus in LA and other two had SEC in LA. Interestingly, stroke rates remained low despite the high prevalence of atrial fibrillation. This could be explained by the fact all of patients with AF were prescribed warfarin, with monitoring of the international normalized ratio (INR).

Most RHD patients in this study had preserved LVEF. This finding may be caused by volume overload.[11] Twenty-four patients had reduced RV contractility, mostly in mitral valve involvement (isolated MS, mixed valve, and MS with MR). RV dysfunction mostly occurs because of long-standing pulmonary hypertension, secondary to left-sided valve lesions or significant tricuspid valve regurgitation. In mitral valve lesions, LA is directly affected by increased pressure or volume that is subsequently transmitted to the pulmonary circulation, RV, and RA. This triggered maladaptive remodelling and dilatation of RV, leading to decreased contractility, leading to symptomatic right heart failure, and impaired survival.[9,13]

Pulmonary hypertension (PH), develops early and is usual in patients with mitral valve disease. Pulmonary hypertension is a common finding in patients with left-sided long-standing rheumatic heart disease. The major pathomechanism is the retrograde transmission of pressure from LA due to forward flow. However active resistance resulting from pulmonary vascular vasoconstriction and remodelling may also contribute to pulmonary hypertension in long-standing left heart disease. Gradually, patients also develop right ventricular (RV) dysfunction and dilatation, and severe chronic pulmonary hypertension may result in irreversible changes.[13-15] In this study, 53 of the patients had a probability of PH. Intramuscular benzathine penicillin G injection is the mainstay of treatment among patients with chronic rheumatic heart disease. Penicillin is given every 4 weeks reducing the rate of recurrence of acute rheumatic fever. With good adherence to penicillin, the prognosis of RHD has been observed to be improved.[13] Mixed valve lesion (mixed mitral and aortic lesion) was the most common echocardiographic finding, showing an advanced stage of the disease. This may be caused by lack of primary health care facilities; most patients came to secondary and tertiary hospital when they already have advanced disease. Another reason may be that early detection of rheumatic fever is missed by many physicians. Then, the patients present on their first visit with already established rheumatic heart disease. Poverty, illiteracy, and lack of awareness and education, also contribute in a way to rheumatic fever becoming late to be diagnosed.[12] Primary prevention of acute rheumatic fever needs identification of group A streptococcal infection by means of throat swab culture, especially in primary health care. This job is important to do, but still very difficult to do in our setup. Most of the patients were middle-aged and elderly, many of whom already had severe disease at presentation, requiring surgical intervention. Only a few of the patients had valve surgery. Most patients with severe valve disease refuse to have surgery because of fear and far access to a tertiary hospital in Bali.

5. Conclusion

In conclusion, rheumatic heart disease is still a common problem. Patients with RHD and mitral valve lesions tended to have AF, dilated LA, lower RV contractility, higher pulmonary pressure, and tricuspid regurgitation compared with the isolated aortic regurgitation group. Mixed valve lesion was the most common pattern of valve lesion in RHD, with the same count of MS and MR. Preserved LVEF was a common finding in this population. Patients were predominantly female, young adult and elderly, unemployed, with a lower education background (primary school), and mostly from the Karangasem subdistrict. Primary prevention, early detection of diagnosis in primary health care, and timely referral to the tertiary hospital are essential to reduce morbidity and mortality.

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