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Risk Stratification and Mortality in Mitral Stenosis Patients

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ABSTRACT

Background: Rheumatic mitral stenosis is the most common valvular abnormalities found in developing countries. Mortality risk in those populations was poorly investigated. In addition, hemodynamic, morphological, and mechanical factors that influence or predict outcome of rheumatic mitral stenosis have not been identified.

Aims: To determine predictive factors affecting outcome in rheumatic mitral stenosis patients.

Method: This retrospective cohort study was conducted at the National General Hospital Dr. Sardjito, Yogyakarta, Indonesia. The study recruited patients from the Valvular Heart Disease Registry from May 2014 to November 2020. New York Heart Association (NYHA) functional classification, invasive or surgical treatment, and incidence of death were recorded. The baseline rhythm from electrocardiography (ECG) was categorized as sinus rhythm and atrial fibrillation or atrial flutter. Based on the findings of trans thoracal echocardiography (TTE), subjects who had moderate to severe pure rheumatic mitral stenosis (or followed by mitral regurgitation and / or less significant tricuspid regurgitation as a natural history) and subjects with rheumatic mitral stenosis with a combination of other heart valve problems (of which severity more significantly) classified as groups I and II. The mitral valve area (MVA), mitral valve gradient (MVG), left atrial diameter (LA), and mean pulmonary artery pressure (mPAP) were then analyzed.

Results: A total of 477 patients (mean age 44.08 ± 10.93 years; 71.5% female) were enrolled in this study. There were 61 deaths during the median follow-up of 393 days of which 35 deaths occurred in group I and 26 deaths occurred in group II. Kaplan Meier curve shows the 1 year survival rate is higher in group I than group II which is 92.5% and 92%, respectively. Bivariate followed by multivariate analysis showed MVG and mPAP were predictive risk factors for mortality in group I with p = 0.020 and p = 0.021. MVG parameter values evaluated from echocardiography with a cut-off of more than 10 mmHg and mPAP parameters with a cut-off of more than 50 mmHg were independent predictive risk factors for mortality. Thus, patients were at higher risk of death if MVG> 10 mmHg and mPAP> 50 mmHg..

Conclusion: One year survival rate in group I was higher than group II. MVG and mPAP were risk factors for predicting mortality in group I.

INTISARI

Latar Belakang: Stenosis mitral rematik merupakan kelainan katup yang paling sering ditemukan di negara berkembang, termasuk Indonesia.

Penelitian terkait stenosis mitral rematik terutama risiko kematian masih belum banyak dilakukan. Selain itu, faktor hemodinamik, morfologi dan mekanik yang mempengaruhi atau memprediksi luaran pasien stenosis mitral belum teridentifikasi.

Tujuan: Menentukan faktor prediktor yang berpengaruh terhadap kematian pasien stenosis mitral rematik yang mempunyai nilai prognostik.

Metode: Penelitian ini merupakan studi kohort retrospektif yang dilakukan di RSUP Dr. Sardjito, Yogyakarta, Indonesia. Subyek penelitian diperoleh dari data registri Valvular Heart Disease RSUP Dr. Sardjito Yogyakarta sejak bulan Mei 2014 hingga November 2020. Data klinis yang dikumpulkan antara lain klasifikasi kelas fungsional NYHA, tatalaksana invasif atau prosedur bedah yang dilakukan, dan kejadian kematian. Selain itu rekaman EKG (data irama dasar) dan hasil pemeriksaan ekokardiografi transthorakal (MVA, MVG, diameter atrium kiri, dan mPAP) dianalisis. Subyek dikelompokkan menjadi 2 grup berdasarkan pemeriksaan ekokardiografi, yaitu grup I yang terdiri dari subyek dengan stenosis mitral rematik murni sedang atau berat (atau kombinasi dengan regurgitasi mitral yang lebih ringan dan atau regurgitasi trikuspid sebagai kelanjutan perjalanan alamiah dari stenosis mitral tersebut) dan grup II (stenosis mitral dengan kombinasi penyakit katup jantung lain dengan derajat keparahan yang lebih berat).

Hasil: Empat ratus tujuh puluh tujuh (477) pasien direkrut sebagai subyek penelitian dengan usia rata-rata 44.08±10.93 tahun. Sebanyak 61 kematian tercatat yang terdiri dari 35 kematian dari grup I dan 26 dari grup II. Berdasarkan hasil analisis Kaplan-Meier didapatkan bahwa kesintasan tahun ke-1 pada grup I dan II masing-masing sebesar 92,5% dan 92%. Hasil analisis bivariat dan multivariat menggunakan Cox regression dari parameter MVA, MVG, mPAP, dan diameter atrium kiri, didapatkan hasil bahwa MVG dan mPAP merupakan faktor prediktor terhadap luaran subyek dengan p=0.020 dan p=0.021. Subyek mempunyai resiko kematian ketika nilai MVG > 10 mmHg atau mPAP > 50 mmHg.

Kesimpulan: Kesintasan tahun ke-1 pada grup I lebih tinggi daripada grup II. MVG dan mPAP merupakan faktor risiko independen terhadap kejadian kematian pada grup I.

Introduction

Mitral stenosis is a condition where there is a thickening of the mitral valve that blocks blood flow from the left atrium to the left ventricle. Mitral stenosis is the most common valve disorder found in developing countries such as Indonesia.¹ Developing countries has a high prevalence of rheumatic fever and rheumatic heart disease which constitute two-thirds of the world's population, causing a high incidence of mitral stenosis in the world.²

The clinical course of patients with mitral stenosis varies. Some patients show no or little change in the course of the disease over a long period of time, while some patients show a progressive course of disease leading to rapid death.³ Poor prognosis such as right heart failure and systemic congestion and even death can occur if a patient with mitral stenosis is not treated properly. Unfortunately, optimal management is often delayed or not performed in patients with mitral stenosis. Risk stratification is necessary to determine the appropriate timing of treatment and predict the patient's prognosis.⁴

Research on mitral stenosis, particularly the risk of mortality, is very limited. In addition, the hemodynamic, morphological, and mechanical factors that influence or predict the outcome in patients with rheumatic mitral stenosis have not all been identified. This cohort study was conducted to determine predictive factors that influence mortality in patients with rheumatic mitral stenosis. The results of the study, in the form of prognostic value for patients with rheumatic mitral stenosis, are expected to be a reference in determining the right time for intervention handling.

Methods

This retrospective cohort study evaluated data from the Valvular Heart Disease Registry of the National General Hospital (RSUP) Dr. Sardjito, Yogyakarta, Indonesia from May 2014 to November 2020. Adult patients diagnosed with rheumatic mitral stenosis who underwent invasive intervention (balloon mitral valvulotomy) or mitral valve surgery during the study period were enrolled as subjects. Patients with incomplete data and a history of pacemaker implantation were excluded. Clinical, ECG, and TTE data were obtained. The New York Heart Association (NYHA)

functional classification, invasive or surgical treatment, and events of death were recorded. The baseline rhythm of the ECG is categorized as sinus rhythm and atrial fibrillation / flutter.

All patients underwent TTE by a trained sonographer using the available echocardiography machines (Phillips Electrical General Medical System and Vivid 6® / Vivid 7®). Based on the findings of TTE, subjects who had pure moderate to severe rheumatic mitral stenosis (or followed by less significant mitral regurgitation and / or tricuspid regurgitation as a natural history) and subjects with rheumatic mitral stenosis with combination of other heart valve problems (which more significant severity) classified as groups I and II respectively. To determine the severity of rheumatic mitral stenosis in group I, MVA cut off <1 cm2, MVG> 10 mmHg, and mPAP > 50mmHg were considered negative predictive factors for the risk of death in patients with mitral stenosis according to the 2014 ACC / AHA Guidelines.⁵ For LA diameter parameters, the median is used as the intercept.6

Ethical permission is issued by the Medical and Health Research Committee of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University. All patients were asked for consent. Ethical clearance was released by Medical and Health Research Committee Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada. All patients provided informed consent.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation, while categorical variables are presented as percentages. The Kolmogorov-Smirnov test was used to evaluate the normality of the distribution of continuous variables. The Kaplan-Meier test was used to estimate event-free outcomes in inferring patient follow-up outcomes. Cox regression is used to evaluate the ability of certain variables to estimate outcomes. A p value <0.05 indicates statistical significance.

Results

A total of 584 rheumatic mitral stenosis patients enrolled in valvular heart disease registry in Sardjito General Hospital Yogyakarta. There were 60 patients excluded because incomplete database and 1 patient with pacemaker implantation. A number of 46 patients were dropped out because lost to follow up. Thus, the total number of patients who enrolled as subjects in this study were 477 subjects (mean age of 44.08 ± 10.93 years old; 71.5% female). Later these patients classified into 2 groups, there were 278 subjects (mean age of 44.31 ± 10.61 years old; 73% female) and 199 subjects (mean age of 43.77 ± 11.36 years old; 69.3% female) in group I and II respectively.

In this study, the median follow-up time for groups I and II was 388 and 400 days, respectively. Nearly all subjects were symptomatic (95%), and the majority were in the NYHA II functional class (72.5%). ECG parameters showed atrial fibrillation in 211 subjects (75.9%) group I and 134 subjects (67.3%) group II. There were 38 (13.7%) subjects

and (14) 7% who underwent BMV in groups I and II. Mitral valve surgery was performed in 39 (14%) of group I and 39 (19.6%) of group II.

Table 1.
Baseline characteristics

Variable	Value (n=477)
Age (year), mean ± SD	44.08 ± 10.93
Follow up (days), median	393
Gender	
Female, n (%)	341 (71.5%)
Male, n (%)	136 (28.5%)
Type of mitral stenosis	
Group I, n (%)	278 (58.3%)
Group II, n (%)	199 (41.7%)
NYHA Functional Class, n (%)	
I	24 (5%)
II	346 (72.5%)
III	105 (22%)
IV	2 (0.4%)
Electrocardiography, n (%)	
Atrial fibrillation	345 (72.3%)
Sinus rhythm	132 (27.7%)
Echocardiography Findings	
MVA (cm ²), median	0.8
MVG (mmHg), median	11.6
Left Atrial Diameter (mm), median	52
mPAP (mmHg), median	36
Management, n (%)	
Balloon mitral valvuloplasty	52 (10.9%)
Mitral valve surgery	78 (16.4%)
Survival, n (%)	
Survive	416 (87.2%)
Died	61 (12.8%)

MVA: mitral valve area; MVG: mitral valve gradient; mPAP: mean pulmonary arterial pressure.

There were 61 deaths during the study period where 35 (12.6%) deaths occurred in group I and 26 (13.1%) deaths occurred in group II (Table 2). Kaplan Meier curve shows one-year survival rate is higher in group I than group II which is 92.5% and 92%, respectively. Based on TTE findings; median MVA, MVG, mPAP, and LA diameter in group I were 0.8 cm2, 12 mmHg, 36 mmHg, and 53 mm.

Bivariate analysis using Cox regression showed that MVG \leq 10 mmHg (hazard ratio 0.602, 95% CI: 0.268-1355, p = 0.220), mPAP \leq 50 mmHg (hazard ratio 1.802, 95% CI: 0.678– 4.786, p = 0.238), and LA diameter (hazard ratio 0.673, 95% CI: 0.400-1.129, p = 0.134) statistically significant with p <0.25 (Table 3). Meanwhile, MVA was not statistically significant. Therefore, these three statistically significant parameters were also evaluated by multivariate analysis.

From the multivariate analysis using Cox regression, the parameter values of MVG and mPAP values were independent predictive risk factors for mortality (p = 0.020 and p = 0.021, respectively). Patients with an MVG of \leq 10 mmHg had hazard ratio 0.44 (95% CI: 0.225 - 0.878) compared in subjects with MVG > 10 mmHg daily. Meanwhile, patients with mPAP \leq 50 mmHg had hazard ratio 0.48 (95% CI: 0.261 - 0.895) compared in subjects

with mPAP > 50 mmHg daily (Table 4). Thus, patients were at higher risk of death if MVG > 10 mmHg or mPAP > 50 mmHg.

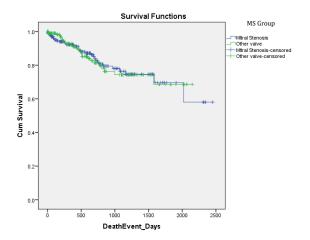


Figure 1. Kaplan Meier survival analysis

Table 2.Raseline characteristics based on Diagnosis

Baseline characteristics based on Diagnosis.				
	Group I	Group II		
Variables	(n=278)	(n=199)		
Age (year), mean ± SD	44.31±10.61	43.77±11.36		
Follow up, median	388	400		
Gender				
Female, n (%)	203 (73%)	138 (69.3%)		
Male, n (%)	75 (27%)	61 (30.7%)		
NYHA Functional Class, n (%)				
I	17 (6.1%)	7 (3.5%)		
II	201 (72.3%)	145 (72.9%)		
III	58 (20.9%)	47 (23.6%)		
IV	2 (0.7%)	0 (0%)		
Electrocardiography, n (%)				
Atrial Fibrillation	211 (75.9%)	134 (67.3%)		
Sinus Rhythm	67 (24.1%)	65 (32.7%)		
Echocardiography Findings				
MVA (cm ²), median	0.8			
MVG (mmHg), median	12			
Left Atrial Diameter (mm),				
median	53			
mPAP (mmHg), median	36			
Management, n (%)				
Baloon mitral valvulotomy	38 (13.7%)	14 (7%)		
Mitral valve surgery	39 (14%)	39 (19.6%)		
Survival, n (%)				
Survive	243 (87.4%)	173 (86.9%)		
Died	35 (12.6%)	26 (13.1%)		

MVA: mitral valve area; MVG: mitral valve gradient; mPAP: mea pulmonary arterial pressure

Table 3. Bivariate analysis for mortality predictive factors using Cox regression

	Hazard		
Variables	Ratio	95%CI	p
MVG ≤10 mmHg	0.602	0.268- 1.355	0.220*
mPAP ≤50 mmHg	1.802	0.678-4.786	0.238*
Left Atrial			
Diameter ≥ 53			
mm	0.673	0.400 - 1.129	0.134*

MVG: mitral valve gradient; mPAP: mean pulmonary arterial pressure

Table 4.

Multivariate analysis for mortality predictive factors

Variables	Hazard Ratio	95%CI	р	
MVG ≤10 mmHg	0.444	0.225 - 0.878	0.020*	
mPAP ≤50 mmHg	0.483	0.260 - 0.895	0.021*	
Left Atrial Diamete				
≥53mm	0.696	0.414 - 1.169	0.171	

MVG: mitral valve gradient; mPAP: mean pulmonary arterial pressure

Discussion

Our study classified all patients into two groups namely group I (only moderate to severe rheumatic mitral stenosis which can be followed by less significant mitral regurgitation and / or tricuspid regurgitation as its natural history) and group II (rheumatic mitral stenosis with combination of other heart valve problems that have more significant severity). According to our study, group I had a higher percentage in the 1-year survival rate compared to group II. We evaluated the correlation of survival rates with TTE parameters namely MVA, MVG, mPAP, and LA diameter. In the multivariate analysis, MVG and mPAP had proven a significant role as predictors of mortality.

The most common etiology for mitral stenosis is rheumatic fever.⁷ Jung et al. (2017) in the Euro Heart Survey stated that 85% of mitral stenosis is caused by rheumatic fever and about 12% is caused by a degenerative process.⁸ According to WHO, the estimated global prevalence of rheumatic heart disease is 15.6 million cases where 79% of cases originate from developing countries.⁹ The estimated prevalence of all age groups in these developing countries is 2.5 - 3.5 cases / 1000 population, while in developed countries it is 0.3 cases / 1000 population. In general, the cause of cardiovascular death due to rheumatic heart disease is 2%.¹⁰

A California study (1984-1998) involving 24,265 echocardiographic procedures found that mitral stenosis was more common in women than men (1.6% vs 0.4%, p <0.001).\(^{11}\) Bo Yang et al. (2016) studied 317 mitral stenosis patients who underwent mitral valve replacement surgery or mitral valve repair from 1994 to 2014 in Dallas, United States. Analysis of the study data showed the mean age of the subjects was 61 years and 77% of them were women.\(^{12}\) Other references also suggest that mitral stenosis is more common in women with symptom onset occurring in the third or fourth decade of life.\(^{7}\) According to several research, the majority of the subjects in this study were women (71.5%), while the mean age of the subjects was 44.08 \(^{1}\) 10.93 years.

In rheumatic heart disease, the frequency of atrial fibrillation is mostly experienced by patients with mitral stenosis reaching 29%, then mitral regurgitation (16%), and aortic valve disease (1%).¹³ Similarly, the results of this study indicate that atrial fibrillation occurs in 72, 3%

of research subjects. A hospital-based study of mitral valve abnormalities in Pakistan showed that atrial fibrillation was significantly more common in patients who died than in survivors (P = 0.007).¹⁴ According to that study, 355 patients with AF were pooled prospectively and compared with 379 patients with normal sinus rhythm (NSR). The result was that patients with AF had worse immediate and long-term outcomes.¹⁵ In contrast, our study showed that AF had no significant impact on the survival rate of patients with valve abnormalities. This data needs to be further analyzed, considering that the diagnosis of atrial fibrillation in our study was based on 12 lead ECG, so maybe many patients with paroxysmal atrial fibrillation are likely to go undetected.

Mitral stenosis can lead to group II pulmonary hypertension. One study, in which patients with varying degrees of mitral stenosis underwent cardiac catheterization, showed that 32% of patients had mild pulmonary hypertension, 14% had moderate pulmonary hypertension, and 9.6% had severe pulmonary hypertension. 16 There are still few studies evaluating morbidity and mortality in mitral stenosis patients with pulmonary hypertension. The current guidelines also do not mention pulmonary hypertension as an indication for intervention in mitral stenosis because there is no supporting research evidence. Bo Yang et al. (2016) stated that the 10 and 12 year survival rates in mitral stenosis patients with moderate to severe pulmonary hypertension who underwent surgical intervention were 58% and 51%. Meanwhile, the survival rates for patients without pulmonary hypertension and light pulmonary hypertension group reached 83% and 79% (p = <0.05 for 10- and 12-year mortality).12 In our study, median mPAP obtained by TTE was 36 mmHg. The results of the multivariate analysis showed that mPAP was statistically significant as a predictive risk factor for mortality in this study.

Post et al. (2016) published a sizable cohort study with 1004 degenerative mitral stenosis patients. The mean age of the study subjects was 73 ± 14 years, 73% were female, 49% had comorbid coronary artery disease and 50% had diabetes mellitus. The results showed that the survival rates for 1 and 5 years reached 78% and 47%, respectively. Several factors that have been shown to significantly influence mortality include age, atrial fibrillation, renal insufficiency, mitral regurgitation, tricuspid regurgitation, increased right atrial pressure, aortic stenosis, and low serum albumin levels. ¹⁷ In contrast to the results of this study, we demonstrated that the 1-year survival rates for pure mitral stenosis group and mitral stenosis with combination other heart valve disease were 92.5% and 92%, respectively.

In our study, MVA became an insignificant predictor of survival in patients with valve abnormalities. Consistent with our results, a cohort study of 1187 patients in South Korea showed that pre-operative MVA was not significantly associated with long-term clinical outcome. In addition, the postoperative cut-off MVA value of 1.76 cm2 indicates satisfactory predictive power (AUC: 0.63, 95%

CI: 0.587–0.672, sensitivity: 66%, specificity: 56%, p <0.001). A study of 532 patients from 1987 to 2011 also showed that postoperative MVA was consistently identified as a predictor of restenosis and has a strong prognostic impact on event-free survival as components for optimal outcome. 19

A research conducted at Siriraj Hospital between 1996 and 2013 aimed to find predictor factors which related to long-term adverse outcome in isolated rheumatic mitral stenosis. This study analysed 185 subjects and found that LA diameter greater than 50 mm (HR 2.61, 95% CI: 1.08-6.30; p = 0.03) were associated with an effect long-term side such as death, hospitalization, new onset atrial fibrillation, and or embolic stroke.²⁰ But our results suggest that LA diameter has no significant effect on the survival rate of patients with pure rheumatic mitral stenosis. Some echocardiographic parameters to assess LA enlargement in mitral stenosis, other than diameter, may need to be evaluated to describe LA function in more detail in terms of prognosis and mortality.

Limitations

The follow-up period in this study was relatively short to determine the survival rate. The duration of follow-up needs to be extended to reflect long-term survival rates. The high rate of loss to follow-up in our study was also a limitation of our study. This was because the subject no longer regularly comes to our hospital and could no longer be contacted by telephone (inactive or invalid phone number).

Conclusion

The one-year survival rate in the pure mitral stenosis group was higher than in the mitral stenosis group with the combination valve problem group. MVG values with a cut-off value of more than 10 mmHg and mPAP parameters with a cut-off value of more than 50 mmHg were independent predictive risk factors for mortality in subjects with pure mitral stenosis. Thus, patients were at higher risk of death if MVG > 10 mmHg and mPAP > 50 mmHg.

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Disclosures and ethics

Authors whose names appear on submission have contributed sufficiently to design the study and acquired, analyzed, and interpreted data. The authors declare that there are no conflicts of interest.

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