Incidence and Predictors of Long-Term Adverse Outcomes in Patients with Rheumatic Mitral Stenosis in Sinus Rhythm

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Background: *Rheumatic fever and rheumatic heart disease remain important health problems in developing countries. Mitral stenosis (MS) is the most common form of rheumatic heart disease. The aim of this study was to investigate incidence and echocardiographic predictors of long-term adverse outcomes in patients with rheumatic mitral stenosis in sinus rhythm.*
Material and Method: *We retrospectively reviewed medical records of patients diagnosed with isolated rheumatic MS of any severity at Siriraj Hospital between 1996 and 2013. Demographic data, echocardiographic data, and long-term adverse outcomes were collected. Long-term adverse outcomes included all-cause mortality, hospitalization due to heart failure, new-onset atrial fibrillation, and/or embolic stroke during follow-up.*
Results: *One hundred eighty five patients (aged 41.9±13.2 years, 81.1% female) were included during the median follow-up period of 12.6 years (95% CI: 11.2-14.0). MS was classified as mild, moderate, and severe in 8.6%, 27.6%, and 63.8% of patients, respectively. Average mitral valve score was 8.25±1.5. Most patients (61.6%) underwent percutaneous balloon mitral valvulotomy. Incidence of long-term adverse outcome was 43.2% (95% CI: 36.0-50.7%) and included mortality in two patients (1.1%, 95% CI: 0.13-3.9%), hospitalization due to heart failure in 20 patients (10.8%, 95% CI: 6.7-16.2%), new-onset atrial fibrillation in 71 patients (38.4%, 95% CI: 31.3-45.8%), and embolic stroke in 14 patients (7.6%, 95% CI: 4.2-12.4%). Echocardiographic parameters associated with long-term adverse outcomes were left atrial dimension greater than 50 mm (HR 2.61, 95% CI: 1.08-6.30; p = 0.03) and left ventricular end-systolic dimension less than 28 mm (HR 3.06, 95%CI: 1.25-7.49; p = 0.01).*
Conclusion: *Long-term adverse outcomes are common in patients with rheumatic MS in sinus rhythm. Long-term adverse outcomes were found to correlate with left atrial dimension and left ventricular end-systolic dimension.*

Keywords: *Echocardiography, Left atrium, Mitral stenosis, Rheumatic heart disease*

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Rheumatic heart disease is a major and often long-term sequel to a case of rheumatic fever. While incidence of rheumatic fever and rheumatic heart disease is declining in the western world, it remains a common disease in developing countries[1]. In Thailand, physicians commonly encounter patients with rheumatic heart disease in daily clinical practice, but incidence of rheumatic heart disease remains uncertain. However, incidence of rheumatic heart disease is however, considered to be significant. Echocardiography plays an important role in the assessment of rheumatic heart disease, including diagnosis, determination of severity, detection of complications, and decision-making for treatment options[2]. The most common site of rheumatic cardiac involvement is the mitral valve and its apparatus, leading predominantly to mitral stenosis. Valvular abnormalities in rheumatic mitral stenosis include thickening, calcification, and fusion of mitral commissure and leaflet tips, leading to limitation of the leaflet tips and narrowing of the mitral orifice. The mitral subvalvular apparatus is also involved in the rheumatic process with a resulting fusion, shortening, fibrosis, and calcification of the chordae tendinae. Anatomical changes caused by the rheumatic disease process provide echocardiographic characteristics for diagnosis of rheumatic heart disease[3-5]. Despite widespread use of echocardiography and continued health concern regarding rheumatic mitral stenosis, data regarding incidence, and predictors of long-term adverse outcomes, such as mortality, congestive heart failure, mitral valve interventions, and/or new-onset atrial fibrillation in patients with rheumatic mitral stenosis are still lacking.

At Siriraj Hospital, echocardiographic data are capably, consistently, and comprehensively collected. Accordingly, the authors endeavored to conduct a retrospective cohort study among patients

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with rheumatic heart disease who underwent comprehensive echocardiography to determine incidence and predictors of long-term adverse outcomes in patients with rheumatic mitral stenosis in sinus rhythm.

Material and Method

Patients

We retrospectively reviewed medical records and echocardiographic data of patients diagnosed with or evaluated for isolated rheumatic mitral stenosis in the echocardiography laboratory at Siriraj Hospital between 1996 and 2013. Patients were identified from the echocardiographic database and were included in the study if they were older than18 years old and were diagnosed with isolated mitral stenosis in sinus rhythm. Patients with incomplete data, history of previous mitral valve intervention, poor echocardiographic image quality, and patients lost to follow-up were excluded.

Echocardiographic data were derived from a comprehensive transthoracic echocardiographic examination and echocardiographic measurements from an average of three to five consecutive cardiac cycles were used for analysis. Severity of rheumatic mitral stenosis was classified as mild, moderate, or severe, according to recently published guidelines regarding mitral valve area and transvalvular pressure gradient[6]. Regarding morphologic change of mitral stenosis, mitral valve was scored according to Wilkins-Abascal scoring system[7]. Left atrial (LA) diameter, left ventricular (LV) end-systolic, and LV end-diastolic dimensions were measured by M-mode echocardiography in parasternal short axis view, as recommended by the American Society of Echocardiography[8]. LA volume and LV ejection fraction were determined using biplane area-length method and modified Simpson's rule (biplane), respectively[8]. Tricuspid regurgitant velocity obtained by continuous-wave Doppler study was used to calculate pulmonary artery systolic pressure using simplified Bernoulli equation[9]. Pulmonary hypertension was defined as pulmonary artery systolic pressure greater than 50 mmHg.

Data collection

Patient data collected included demographic data, symptoms at presentation, and current medications. Echocardiographic parameters of interest included LV ejection fraction, LA diameter and volume, LV systolic and diastolic dimensions, pulmonary artery pressure, and presence of LA thrombus. Long-term adverse outcomes included all-cause mortality, hospitalization due to heart failure, new-onset atrial fibrillation, and embolic stroke. Follow-up data regarding adverse outcomes of interest were obtained via review of patient medical records.

Statistical analysis

Descriptive statistics, including frequency and percentage, were used for categorical variables. Continuous variables were reported as mean ± standard deviation for normally distributed variables and median (minimum and maximum) for non-normally distributed variables. Normality of distribution of variables was examined by Kolmogorov-Smirnov test. Comparisons of categorical variables between patients with and without adverse outcomes were performed using Chi-square test or Fisher's exact test. Continuous variables were compared using Student's t-test or Mann-Whiney U test. Factors affecting long-term adverse outcomes were compared using log-rank test and presented by Kaplan-Meier survival curve. Multivariate predictors of long-term adverse outcomes were evaluated using Cox proportional hazards analysis (backward stepwise method) and presented as hazard ratio (HR) (95% confidence interval [CI]). For all tests performed, a two-tailed *p*-value of less than 0.05 was considered to be statistically significant. PASW Statistic version 18.0 (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Results

Medical records of 2,014 patients with rheumatic heart disease that sought treatment at Siriraj Hospital between 1996 and 2013 were reviewed. Of these, 460 patients were diagnosed with isolated rheumatic mitral stenosis. Only patients in sinus rhythm were included in the study (Fig. 1). As such, 185 patients with isolated rheumatic mitral stenosis in sinus rhythm (age 41.9±13.2 years, 81.1% female) were included in the study. Median follow-up period was 12.6 years (95% CI: 11.2-14.0 years). One hundred forty five patients were symptomatic at the time of echocardiography. History of transient ischemic attack or stroke was reported in 11 (5.9%) patients. A majority of patients underwent mitral valve intervention during follow-up, including percutaneous balloon mitral valvulotomy and mitral valve replacement in 114 (61.6%) and 27 (14.6%) patients, respectively. Baseline characteristics and echocardiographic data of the study population are presented in Table 1. Current

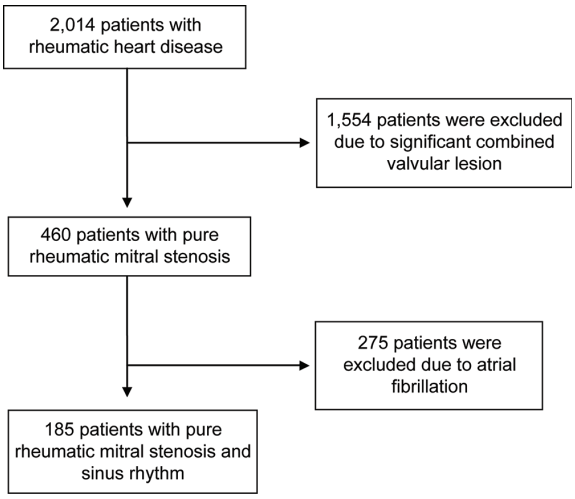

Fig. 1 Study population.

Table 1. Baseline and echocardiographic characteristics of patients with isolated rheumatic mitral stenosis in sinus rhythm

Patient characteristics & factors	n = 185
Age (year)	41.9±13.2
Male gender	35 (18.9)
History of heart failure	24 (13.0)
Severity of mitral stenosis	
Mild	16 (8.6)
Moderate	51 (27.6)
Severe	118 (63.8)
Mitral valve score	8.2±1.5
Spontaneous echocardiographic contrast in left atrium	10 (5.5)
Left ventricular ejection fraction (%)	65.9±9.2
Left ventricular systolic dimension ≥28.0 mm	95 (51.6)
Left ventricular diastolic dimension ≥44.2 mm	102 (55.4)
Left atrial diameter ≥50.0 mm	93 (51.7)
Pulmonary end-diastolic pressure (mmHg)	17.5±9.0

Data presented as mean ± standard deviation or number (percentage)

medications were beta-blockers, diuretics, penicillin V, digoxin, warfarin, and aspirin in 157 (84.9%), 139 (75.1%), 65 (35.1%), 28 (15.1%), 19 (10.3%), and 15 (8.1%) patients, respectively. Mean LV systolic and diastolic dimensions were 9.1±1.9 and 44.8±6.1 mm, respectively. Mean LA diameter, volume, and volume index were 49.3±8.2 mm, 101.2±32.4 ml, and 64.0±22.4 ml/m^2, respectively. Mean pulmonary artery systolic pressure was 49.7±22.5 mmHg. Pulmonary hypertension was reported in 61 (35.9%) patients and LA thrombus was observed in five (2.7%) patients.

Incidence of long-term adverse outcome was 43.2% (95% CI: 36.0-50.7%), as follows, mortality in two patients (1.1%, 95% CI: 0.13-3.9%), embolic stroke in 14 patients (7.6%, 95% CI: 4.2-12.4%), hospitalization due to heart failure in 20 patients (10.8%, 95% CI: 6.7-16.2%), and new-onset atrial fibrillation in 71 patients (38.4%, 95% CI: 31.3-45.8%). Patients having spontaneous echocardiographic contrast in LA, LV systolic dimension less than 28 mm, and/or LA diameter greater than 50 mm had higher incidence of long-term adverse outcome (Table 2). Univariate and multivariate factors associated with long-term adverse outcomes in patients with isolated rheumatic mitral stenosis in sinus rhythm are described in Table 3. LV systolic dimension less than 28 mm and LA diameter greater than 50 mm were found to be independent predictors of long-term adverse outcome (Fig. 2).

Discussion

Incidence of isolated rheumatic mitral stenosis with atrial fibrillation and sinus rhythm in the present

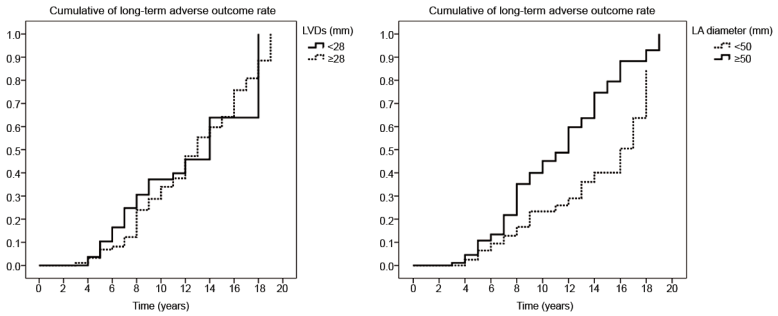

Fig. 2 Cumulative of long-term adverse outcome rate according to left ventricular systolic dimension (LVDs) and left atrial (LA) diameter.

Table 2. Comparison between patients with and without long-term adverse outcomes

Patient characteristics & factors	Long-term adverse outcomes		*p*-value
	With (n = 80)	Without (n = 105)	
Age (years)	43.5±13.8	40.7±12.7	0.167
Male gender	18 (51.4)	17 (48.6)	0.278
History of heart failure	14 (58.3)	10 (41.7)	0.110
Severity of mitral stenosis			0.175
Mild	6 (37.5)	10 (62.5)	
Moderate	17 (33.3)	34 (66.7)	
Severe	57 (48.3)	61 (51.7)	
SEC in LA	8 (80.0)	2 (20.0)	0.022
Mitral valve score	8.4±1.5	8.1±1.4	0.157
LV systolic dimension <28.0 mm	58 (65.2)	31 (34.8)	0.022
LV diastolic dimension ≥44.2 mm	50 (49.0)	52 (51.0)	0.091
Pulmonary end-diastolic pressure (mmHg)	18.2±8.2	17.1±9.7	0.596
Mitral valve intervention			0.071
None	13 (29.5)	31 (70.5)	
Percutaneous balloon valvulotomy	52 (45.6)	62 (54.4)	
Mitral valve replacement	15 (55.6)	12 (44.4)	
LV ejection fraction (%)	64.6±9.0	66.9±9.3	0.103
LA diameter ≥50 mm	54 (58.1)	39 (41.9)	<0.001

LA = left atrium; LV = left ventricle; SEC = spontaneous echocardiographic contrast
Data presented as mean ± standard deviation or number (percentage)

Table 3. Univariate and multivariate factors associated with long-term adverse outcomes

Factors	Univariate HR (95% CI)	*p*-value	Multivariate HR (95% CI)	*p*-value
History of heart failure	1.85 (1.03-3.31)	0.039	NS	NS
MS severity				
Mild	1	0.054	NS	NS
Moderate	0.36 (0.14-0.93)			
Severe	0.63 (0.28-1.48)			
SEC in LA	3.78 (1.79-7.99)	<0.001	NS	NS
Mitral valve score	1.25 (1.08-1.46)	0.004	NS	NS
LVDs <28 mm	1.08 (0.68-1.71)	0.750	3.06 (1.24-7.49)	0.014
LVDd ≥44.2 mm	1.25 (0.79-1.98)	0.337	NS	NS
PAEDP	1.06 (1.02-1.10)	0.006	NS	NS
Mitral intervention				
None	1	0.024	NS	NS
PBMV	0.84 (0.46-1.56)			
MVR	1.93 (0.92-4.08)			
LV ejection fraction	1.01 (0.98-1.04)	0.573	NS	NS
LA diameter ≥50 mm	2.27 (1.41-3.67)	0.001	2.61 (1.08-6.30)	0.033

LA = left atrium; LV = left ventricle; LVDd = left ventricular diastolic dimension; LVDs = left ventricular systolic dimension; MS = mitral stenosis; MVR = mitral valve replacement; NS = non-significant; PAEDP = pulmonary artery end-diastolic pressure; PBMV = percutaneous balloon mitral valvulotomy; SEC = spontaneous echocardiographic contrast

study was 22.8% and 9.2%, respectively. Long-term adverse outcomes occurred in 43.2% of patients. While prevalence remains low in developed countries, previous studies from developing countries, where there is a high prevalence of rheumatic fever, have reported a high prevalence of mitral stenosis[10-14]. It is

impractical and unsound to compare incidence and/or prevalence of mitral stenosis among studies due to differences in many aspects, including study population, geographical area, severity of disease, and social and demographic characteristics.

Data regarding predictors of long-term adverse outcomes in patients with isolated rheumatic mitral stenosis in sinus rhythm are limited. A pilot study in patients with newly diagnosed rheumatic heart disease of all types by Zhang et al demonstrated that LA diameter greater than 49 mm increased risk of adverse cardiac events[15]. That finding is consistent with the finding from our study, although differences existed in the study populations. The present study found that patients with isolated mitral stenosis in sinus rhythm with LA diameter greater than 50 mm or LV systolic dimension less than 28 mm are at risk of long-term adverse outcomes, such as mortality, embolic stroke, hospitalization due to heart failure, and new-onset atrial fibrillation. Although some previous studies assessed only one individual adverse outcome, such as development of atrial fibrillation or risk of embolic stroke as the primary endpoint, they reported the concordant finding that LA diameter was an important predictor of adverse outcome[16-19]. Therefore, this patient population should receive close clinical follow-up to facilitate early detection of possible complications or as a prevention strategy. For example, embolic stroke occurred in 7.6% of patients in the present study despite all patients being in sinus rhythm. Similarly, Coulshed et al reported that 8% of patients in sinus rhythm had systemic embolism[20]. Accordingly, risk of transient atrial fibrillation and the role of oral anticoagulant should be discussed with the patient in clinical practice.

Conclusion

Long-term adverse outcomes are common in patients with rheumatic mitral stenosis in sinus rhythm. Long-term adverse outcomes were found to correlate with left atrial dimension and left ventricular end-systolic dimension.

Limitations

Given that this was a retrospective study, we have some concerns about the completeness of data, especially the long-term follow-up data. Some patients with mitral stenosis may have had paroxysmal atrial fibrillation that was not detected by physical examination or electrocardiogram at presentation. In addition, the present study was performed in a national tertiary care center, which makes referral bias a possibility.

What is already known on this topic?

Mitral stenosis is the most common type of rheumatic heart disease. Serious complications associated with rheumatic mitral stenosis are atrial fibrillation, systemic embolism, pulmonary hypertension, and heart failure. Prevalence of rheumatic mitral stenosis varies worldwide, with higher prevalence in developing countries and lower prevalence in developed countries. Several clinical and echocardiographic variables, including age, severity of mitral stenosis, left atrial spontaneous echo contrast, LA diameter, and biomarkers have all been shown to predict adverse outcome.

What this study adds?

The present study describes incidence of isolated rheumatic mitral stenosis, regardless of cardiac rhythm, and predictors of serious complications. Consistent with previous studies, increase in LA diameter is associated with increased risk of poor outcome. Moreover, smaller LV systolic dimension is a predictor of long-term adverse outcome.

Acknowledgements

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Potential conflicts of interest

None.

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การศึกษาอุบัติการณ์และปัจจัยทำนายการเกิดผลลัพธ์ทางคลินิกที่ไม่พึงประสงค์ ในผู้ป่วยโรคลิ้นหัวใจไมตรัลตีบจากโรครูมาติกที่มีจังหวะการเต้นของหัวใจปกติ

พัษดี น่าชม, นิธิมา รัตนสิทธิ์

วัตถุประสงค์: *โรคหัวใจรูมาติกเป็นปัญหาสำคัญของกลุ่มประเทศกำลังพัฒนา เช่น ประเทศไทย โดยเฉพาะโรคลิ้นหัวใจไมตรัลตีบ ซึ่งเป็นผลจากไข้รูมาติกที่พบบ่อยที่สุด การศึกษานี้มีจุดประสงค์เพื่อศึกษาอุบัติการณ์ และปัจจัยทำนายการเกิดผลลัพธ์ทางคลินิกที่ไม่พึงประสงค์ในผู้ป่วยโรคลิ้นหัวใจไมตรัลตีบจากโรครูมาติกที่มีจังหวะการเต้นของหัวใจปกติ*

วัสดุและวิธีการ: *รูปแบบการศึกษาเป็นการศึกษาย้อนหลังแบบพรรณนา โดยรวบรวมข้อมูลในผู้ป่วยเฉพาะลิ้นหัวใจไมตรัลตีบและจังหวะการเต้นของหัวใจปกติ ที่เข้ารับการรักษาในโรงพยาบาลศิริราช ตั้งแต่ พ.ศ. 2539-2556 ผลลัพธ์ทางคลินิกที่ไม่พึงประสงค์ประกอบด้วย การเสียชีวิตรวมทุกสาเหตุ ภาวะหัวใจวายที่ต้องนอนรักษาในโรงพยาบาล ภาวะหัวใจห้องเอเตรียมเต้นผิดจังหวะแบบพลิ้ว และภาวะหลอดเลือดสมองอุดตันจากก้อนเลือดจากหัวใจ*

ผลการศึกษา: *จากการรวบรวมข้อมูลพบว่ามีผู้ป่วยโรคลิ้นหัวใจไมตรัลตีบจากโรครูมาติก ที่มีจังหวะการเต้นของหัวใจปกติทั้งหมด 185 ราย ระยะเวลาของการติดตามการรักษาโดยเฉลี่ย 12 ปี (ร้อยละ 95 ช่วงเชื่อมั่น 11.2-14.0) ผู้ป่วยส่วนใหญ่เป็นโรคลิ้นหัวใจไมตรัลตีบระดับรุนแรง ค่าคะแนนการเปลี่ยนแปลงทางรูปร่างของลิ้นหัวใจไมตรัล เฉลี่ย 8.25±1.5 ผู้ป่วยส่วนใหญ่ได้รับการรักษาด้วยวิธีถ่างขยายลิ้นหัวใจด้วยบอลลูน อุบัติการณ์ของการเกิดผลลัพธ์ทางคลินิกที่ไม่พึงประสงค์พบร้อยละ 43.2 (ร้อยละ 95 ช่วงเชื่อมั่น 36.0-50.7) โดยจำนวนผู้ป่วยที่เสียชีวิตรวมทุกสาเหตุร้อยละ 1.1 (ร้อยละ 95 ช่วงเชื่อมั่น 0.13-3.9) ภาวะหัวใจวายที่ต้องนอนรักษาในโรงพยาบาลร้อยละ 10.8 (ร้อยละ 95 ช่วงเชื่อมั่น 6.7-16.2) การเกิดหัวใจห้องเอเตรียมเต้นผิดจังหวะแบบพลิ้วร้อยละ 38.4 (ร้อยละ 95 ช่วงเชื่อมั่น 31.3-45.8) และภาวะหลอดเลือดสมองอุดตันจากก้อนเลือดจากหัวใจร้อยละ 7.6 (ร้อยละ 95 ช่วงเชื่อมั่น 4.2-12.4) ปัจจัยทำนายการเกิดผลลัพธ์ทางคลินิกที่ไม่พึงประสงค์คือ ขนาดห้องหัวใจเอเตรียมซ้ายมากกว่า 50 มิลลิเมตร และขนาดของหัวใจห้องล่างซ้ายขณะบีบตัวน้อยกว่า 28 มิลลิเมตร*

สรุป: *ผลลัพธ์ทางคลินิกที่ไม่พึงประสงค์ในผู้ป่วยโรคลิ้นหัวใจไมตรัลตีบจากโรครูมาติกที่มีจังหวะการเต้นของหัวใจปกติพบได้บ่อย และสัมพันธ์กับขนาดห้องหัวใจเอเตรียมซ้ายและขนาดของหัวใจห้องล่างซ้ายขณะบีบตัว*