의 학 석 사 학 위 논 문

중증 승모판 질환의 유형에 따른 승모판 치환술 후 장기 사망률의 차이 : 승모판 협착증 대 승모판 폐쇄부전

Differences in long-term mortality after mitral valve replacement according to the type of severe mitral valve disease : mitral stenosis vs. mitral regurgitation

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이 논문을 의학석사 학위 논문으로 제출함

2022 년 2 월

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나태준의 의학석사 학위 논문을 인준함

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Abstract

Background: Although the mitral valve is the most commonly affected site in rheumatic valve disease, few studies to date have addressed the long-term mortality associated with the type of mitral valve disease. We here assessed long-term mortality outcomes following a mitral valve replacement (MVR) according to the type of severe rheumatic mitral valve disease.

Methods: We retrospectively reviewed 459 patients who underwent MVR for either severe mitral stenosis (MS) or regurgitation (MR). These subjects were divided into three groups as follows: an MS group in which severe MS was combined with a mild MR at most; an MR group in which severe MR was combined with a mild MS at most; and an MSR group in which severe MS was combined with severe MR. The primary outcome was all-cause mortality after MVR. Multivariable Cox hazard regression analyses were performed with and without stratification by percutaneous mitral valvuloplasty (PMV).

Results: Among the study population, 386 (84.1%) patients were assigned to Group MS, 44 (9.6%) to Group MR, and 29 (6.3%) to Group MSR. The long-term mortality was highest in Group MSR, followed by Group MR and Group MS. Sixty six of the study patients died during a median follow-up of 98 months. The MSR subjects were considered to be the reference group. Multivariable analyses indicated that the Group MS cases had a significantly lower long-term mortality (hazard ratio, 0.37; 95% confidence interval, 0.17-0.79, P =0.010), an association that remained after multivariable analysis with stratification by PMV (hazard ratio 0.40; 95% confidence interval, 0.18-0.88; P = 0.023).

Conclusions: The higher long-term mortality in patients with both severe MS and severe MR compared with cases of severe MS only is significant after adjusting for covariates, and remains significant even after conducting multivariate analyses stratified by a previous PMV.

Keywords: Rheumatic mitral valve disease, mitral valve replacement, long-term mortality

Table of Contents

Tables and Figures

Introduction

Rheumatic heart disease (RHD) has important public health implications as it affects about 33 million people worldwide and results in 3 million deaths annually.[1] Valve involvement in patients with acute rheumatic fever occurs as a result of autoimmune responses in the presence of a pharyngeal infection by a Group A streptococcus.[2] Among the instances of valve involvement with RHD, it most commonly occurs with the mitral valve, about 50% of cases, although the proportion varies with age.[3] Mitral valve involvement can cause congestive heart failure, pulmonary hypertension, atrial fibrillation, and stroke that are associated with the onset of symptoms,[2] and symptomatic patients need surgical intervention such as mitral valve replacement (MVR).[4]

Mitral valve disease presents as either mitral stenosis (MS), mitral regurgitation (MR), or a combination of both. A previous study has reported that MR was associated with higher in-hospital mortality in patients undergoing MVR, but this association did not remain after adjustment for covariates.[5] A significant MR has been associated with a composite of mortality, MVR, heart failure admission, and stroke in asymptomatic patients with mixed mitral valve disease.[6] Mixed mitral valve disease has been further reported to account for 46.5% of the rheumatic mitral valve disease cases,[7] with variations arising in the combinations of stenosis and regurgitation. The type of mitral valve disease also varies among patients who undergo MVR, although most of these cases are MS alone. Notably however, it has not yet been investigated whether the type of mitral valve disease affects the long-term outcomes in patients undergoing MVR.

We aimed in our present study to investigate the impact of the mitral valve disease type on the long-term mortality rates in patients undergoing MVR for this condition. We compared patients with severe MS, severe MR, and with a combination of these two conditions.

Methods

Study design and participants

This retrospective observational study included all patients aged ≥ 20 years who had undergone MVR at our institution between January 2005 and December 2019 for rheumatic mitral valve disease involving at least one of severe MS or MR. Patients were excluded if they had (1) infective endocarditis; (2) aortic stenosis (≥ moderate) or aortic regurgitation (≥ moderate), combined with mitral valve disease; (3) required the use of a device for preoperative mechanical assistance; (4) underwent redo- or trido-cardiac surgery; or (5) underwent coronary artery bypass graft surgery (CABG) simultaneously. To evaluate the effects of the type of mitral valve disease on mortality outcomes, patients were divided into three groups as follows: an MS group in which the severe MS was combined with only a mild MR at most; an MR group in which severe MR was combined with a mild MS at most; and an MSR group in which severe MS was combined with severe MR. All clinical data was obtained from the Asan Medical Center Cardiovascular Surgery and Anesthesia Database and from a retrospective review of the subjects' electronic medical records (Asan Medical Center Information System Electronic Medical Record). This study was conducted in accordance with Strengthening the Reporting of Observational Studies in Epidemiology and approved by the Institutional Review Board of our Asan Medical Center (AMC IRB 2021-1449), which waived the requirement for informed consent due to the retrospective nature of the analyses.

The primary outcome was all-cause mortality after MVR, calculated as the time from the day of the MVR to the death from any cause before the last follow-up. The cut-off date for the follow-ups was June 19, 2021.

Echocardiographic evaluation

All of the included study patients underwent a transthoracic echocardiographic examination both prior to surgery and during the follow-up period after MVR. The preoperative echocardiographic data obtained closest to the day of the surgery were used in the present analyses. Postoperative echocardiographic data were obtained before discharge.

Echocardiographic evaluations at Asan Medical Center are conducted in accordance with the standards and techniques recommended by the American Society of Echocardiography. Two-dimensional echocardiography and Doppler color flow imaging were performed in all of the patients using a Hewlett-Packard Sonos 2500, 5500, or 7500 imaging system (Hewlett-Packard, Andover, MA) and a VIVID 7 or E9 ultrasound system (General Electric Healthcare, Little Chalfont, UK) with a 2.5 MHz probe. The dimensions of the left ventricle (LV) and left atrium (LA) were measured from the parasternal M-mode acquisitions. The mitral valve area (MVA) was measured via direct planimetry of the mitral orifice, and the MS severity was graded as mild, moderate, or severe when the MVA was > 1.5 cm^2, 1.0-1.5 cm^2, or < 1.0 cm^2, respectively.[4] Comprehensive echocardiographic evaluations of MR were performed using an integrated approach including 2-dimensional, Doppler, and color flow imaging. The proximal isovelocity surface area (PISA) was determined from the proximal flow convergence that was measured by lowering the imaging depth and reducing the Nyquist limit at mid-systole. Various views were evaluated for optimal visualization of the PISA. The baseline shift was used to adjust the aliasing velocity to about 40 cm/sec. With the simplified PISA method, the MR severity was graded as mild, moderate, or severe by a PISA radius < 4 mm, 4-8 mm, or ≥ 8 mm, respectively.[4]

Statistical analysis

The study sample size was determined to be all patients included in the study, with no *a priori* power analysis performed. Continuous data are presented as mean ± standard deviation or median

(interquartile range), and categorical data are presented as frequencies (percentages). Categorical data were compared using the chi-square test or Fisher's exact test, as appropriate. Analysis of variance was used to compare normally distributed data among the three groups, with the Tukey test used for equal variance and the Games-Howell test for nonequal variance as post-hoc tests. The Kruskal-Wallis test was used to compare non-normally distributed data among the three groups, and a Bonferroni correction was used as the post-hoc test. Survival probability was calculated using the Kaplan-Meier method and differences in survival were evaluated using log-rank sum tests, followed by Bonferroni corrections as post-hoc tests.

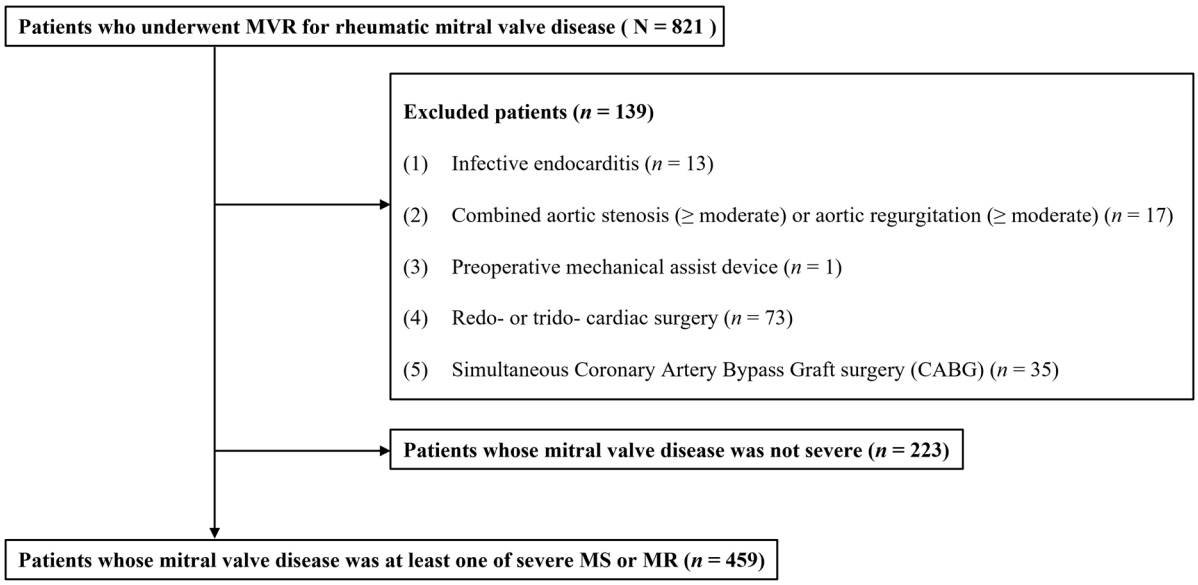
Missing values were replaced using the Markov chain Monte Carlo method. Univariate and multivariable Cox proportional hazard regression models were utilized to identify factors potentially prognostic of long-term mortality. Variables with P values < 0.10 in univariate analyses were entered into the multivariable analyses. The final model was determined by a backward elimination process. In addition, to correct the effects of MR caused by a previous percutaneous mitral valvuloplasty (PMV), patients were stratified according to a previous PMV, and then univariate and multivariable Cox proportional hazard regression models were constructed. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for multivariable regression analyses were calculated.

All reported P values are two sided, with P values < 0.05 considered statistically significant. Statistical analyses were performed using SAS® Version 9.4 (SAS Institute Inc., Cary, NC) and IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY) software.

Results

Of the 821 patients who underwent an MVR between January 1, 2005, and December 31, 2019 at our hospital, 459 cases were eligible for inclusion in the present study (Figure 1). These 459 patients included 135 (29.4%) men and 324 (70.6%) women, with a median age of 57 years (IQR, 48–65 years). The median follow-up period was 98 months (IQR, 53–152 months).

Figure 1. Flow diagram of patient inclusion



MVR, mitral valve replacement; MS, mitral stenosis; MR, mitral regurgitation.

Preoperative characteristics and perioperative echocardiographic findings by study group are presented in Tables 1 and 2. Among the total study population, 386 (84.1%) patients were included in Group MS, 44 (9.6%) in Group MR, and 29 (6.3%) in Group MSR. There were no significant differences in terms of patient age and sex between these groups. Group MS cases were more likely to have a history of cerebrovascular disease and the use of angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) medications than the patients in Group MR. In addition, the patients in Group MS were less likely to have undergone concomitant tricuspid valve replacement (TVR) than those in Group MR.

Table 1. Baseline characteristics of the study patients

Variables	Group MR (*n* = 44)	Group MS (*n* = 386)	Group MSR (*n* = 29)	*P*- value
Age (years)	53.4 ± 10.5	56.5 ± 10.7	57.2 ± 13.7	0.180
Female	33 (75)	272 (70.5)	19 (65.5)	0.679
BMI (kg/m^2)	22.5 ± 3.3	22.7 ± 3.1	23.0 ± 3.8	0.852
Comorbidity				
Hypertension	12 (27.3)	72 (18.7)	10 (34.5)	0.063
Diabetes mellitus	2 (4.6)	37 (9.6)	3 (10.3)	0.563
Dyslipidemia	21 (47.7)	161 (41.7)	13 (44.8)	0.731
Cerebrovascular disease	2 (4.6)	67 (17.4)*	1 (3.5)	**0.015**
Peripheral vascular disease	0 (0)	5 (1.3)	0 (0)	1.0
COPD	1 (2.3)	11 (2.9)	0 (0)	1.0
Renal failure	1 (2.3)	1 (0.3)	0 (0)	0.293
Chronic kidney disease	3 (6.8)	22 (5.7)	4 (13.8)	0.196
Atrial fibrillation	30 (68.2)	282 (73.1)	23 (79.3)	0.576
Coronary artery disease	1 (2.3)	19 (4.9)	2 (6.9)	0.658
Unstable angina	0 (0)	2 (0.5)	0 (0)	1.0
Previous MI	0 (0)	2 (0.5)	0 (0)	1.0
Previous PCI	0 (0)	7 (1.8)	0 (0)	1.0
Previous CABG	1 (2.3)	1 (0.3)	0 (0)	0.293
Congestive heart failure	5 (11.4)	25 (6.5)	4 (13.8)	0.157

New Euroscore	2.10 ± 1.67	2.04 ± 1.46	2.66 ± 2.27	0.371
Medication				
ACEi or ARB	19 (43.2)	77 (20.0)*	9 (31.0)	**0.001**
Beta blocker	14 (31.8)	95 (24.6)	8 (27.6)	0.562
Calcium channel blocker	9 (20.5)	83 (21.5)	6 (20.7)	0.983
Insulin	3 (6.8)	18 (4.7)	1 (3.5)	0.808
OHA	2 (4.6)	44 (11.4)	4 (13.8)	0.332
Lipid lowering drug	10 (22.7)	88 (22.8)	6 (20.7)	0.966
Aspirin	9 (20.5)	57 (14.8)	4 (13.8)	0.595
Clopidogrel	1 (2.3)	6 (1.6)	0 (0)	0.705
Digoxin	19 (43.2)	168 (43.5)	17 (58.6)	0.284
Procedure-related factors				
Mechanical valve	42(95.5)	336 (87.1)	23 (79.3)	0.114
Operation for tricuspid valve	21 (47.7)	180 (46.6)*	15 (51.7)	**0.041**
TAP	16 (36.4)	172 (44.6)	14 (48.3)	
TVR	5 (11.4)	8 (2.1)*	1 (3.5)	**0.007**
Maze operation	28 (63.6)	252 (65.3)	18 (62.1)	0.56
Previous PMV	11 (25)	71 (18.4)	6 (20.7)	

Data are presented as mean ± SD or as a number (percentage). Group MS: patients with severe MS combined with at most a mild MR; Group MR: patients with severe MR combined with at most a mild MS; Group MSR: patients with severe MS combined with severe MR; BMI: body mass index; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; Euroscore: European System for Cardiac Operative Risk Evaluation; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; OHA: oral hypoglycemic agent; TAP: tricuspid annuloplasty; TVR: tricuspid valve replacement; PMV: percutaneous mitral valvuloplasty;

*$P < 0.0167$ versus Group MR in a pairwise comparison after ANOVA.

Table 2. Preoperative echocardiographic findings in the study patients undergoing mitral valve replacement for mitral valve disease.

Variables	Group MR (*n*=44)	Group MS (*n*=386)	Group MSR (*n*=29)	*P*-value*
Left ventricle				
LVIDs (mm)	37.1 ± 6.7	32.6 ± 5.8	36.2 ± 6.5	0.193
LVIDd (mm)	55.4 ± 6.4	47.5 ± 5.8	53.6 ± 6.5	**<.0001**†
LVPWs (mm)	13.4 ± 2.4	12.9 ± 1.8	13.4 ± 1.9	0.807
LVPWd (mm)	8.8 ± 1.3	8.6 ± 1.2	9.0 ± 1.4	0.756
RWT	0.3 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.178
LVMI (g/m^2)	114.8 ± 31.0	85.8 ± 22.7	110.9 ± 27.2	**0.007**†
ESV (ml)	50.5 ± 21.7	36.6 ± 18.9	49.3 ± 23.5	0.615
EDV (ml)	116.4 ± 34.4	80.9 ± 27.7	110.4 ± 37.0	**<.0001**†§
LVEF (%)	57.3 ± 9.6	55.6 ± 7.9	56.6 ± 9.1	**0.0002**†§
LA (mm)	60.5 ± 11.0	56.3 ± 8.3	64.0 ± 9.1	**0.0003**†§
Mitral valve				
E (cm/s)	241.2 ± 52.5	249.4 ± 46.1	261.8 ± 56.0	0.839
A (cm/s)	150.3 ± 44.8	228.3 ± 58.4	210.0 ± 64.8	**<.0001**†
S´(septal) (cm/s)	6.0 ± 1.3	5.5 ± 1.2	5.4 ± 1.7	**0.007**†
E´(septal) (cm/s)	5. 3± 1.4	4.7 ± 1.5	4.7 ± 1.2	**0.043**

A´(septal) (cm/s)	5.0 ± 1.6	5.6 ± 1.4	5.3 ± 1.7	0.324
E/A ratio	1.5 ± 0.6	1.1 ± 0.3	1.4 ± 0.2	0.073
E/E' ratio	46.4 ± 16.5	55.9 ± 20.4	57.6 ± 19.8	0.258
PG max (mmHg)	24.4 ± 8.4	26.3 ± 8.3	30.8 ± 10.3	0.116
PG mean (mmHg)	11.1 ± 4.6	14.9 ± 5.6	16.3 ± 6.0	**0.002**†‡
Tricuspid valve				
Peak TR vel (m/s)	3.2 ± 0.6	3.2 ± 0.6	3.5 ± 0.8	0.063
TVPG (mmHg)	42.4 ± 16.9	41.2 ± 15.4	50.7 ± 23.9	**0.022**§

Data are presented as a number (percentage) or mean ± SD. Group MS: patients with severe MS combined with at most a mild MR; Group MR: patients with severe MR combined with at most a mild MS; Group MSR: patients with severe MS combined with severe MR; s: systolic phase of left ventricle; d: diastolic phase of left ventricle; LVID: left ventricular internal dimension; LVPW: left ventricular posterior wall; RWT: relative wall thickness; LVMI: left ventricular mass index; ESV: end-systolic volume; EDV: end-diastolic volume; LVEF: left ventricular ejection fraction; LA: left atrial diameter; E: peak early diastolic velocity of mitral inflow; A: peak late diastolic velocity of mitral inflow; S´: peak systolic velocity of mitral annulus; E´: peak early-diastolic velocity of mitral annulus; A´: peak late-diastolic velocity of mitral annulus; PG max: maximal pressure gradient across mitral valve; PG mean: mean pressure gradient across mitral valve; Peak TR vel: peak velocity of tricuspid regurgitation; TVPG: systolic pressure gradient of tricuspid valve; ***** means *P*-value for ANOVA.

In post-hoc analysis with the Bonferroni method: †$P < 0.0167$, Group MS vs. MR, ‡$P < 0.0167$ when Group MR vs. MSR and §$P < 0.0167$ Group MS vs. MSR.

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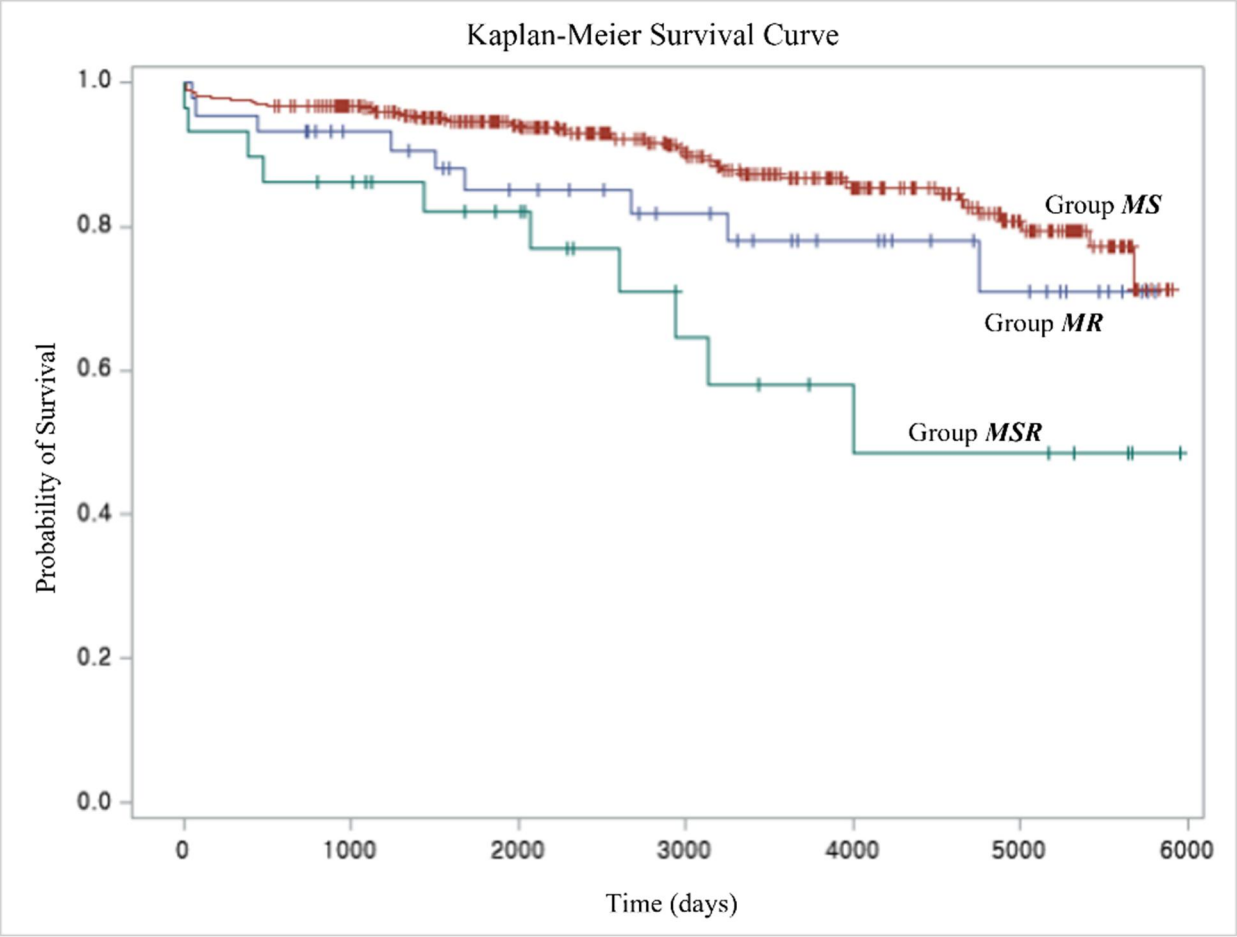
In perioperative echocardiographic findings, each group showed significant changes in several variables after surgery. All groups showed a significant decrease in the LA volume post-operation. The LA volume further decreased in both Group MR and MSR compared with Group MS, with no difference between the MR and MSR patients. The LV End-diastolic volume (LVEDV) was significantly increased in Group MS and decreased in Group MR. The LVEF was significantly decreased in both Group MR and MSR, with no change in Group MS. The mean pressure gradient of the mitral valve showed a significant decrease in all three groups, but the degree of decrease was greater in Group MS and MSR than in Group MR.

Figure 2. Kaplan-Meier survival curves for the three study groups.



Group MS: patients with severe MS combined with at most a mild MR; Group MR: patients with severe MR combined with at most a mild MS; Group MSR: patients with severe MS combined with severe MR;

Kaplan-Meier analysis revealed that the 5-, 10- and 15-year survival rates were lowest in Group MSR and higher in both Group MR and MS (Figure 2). We considered Group MSR to be a reference group for this analysis. Univariate Cox regression analysis indicated that Group MS but not Group MR was associated with decreased long-term mortality (HR, 0.30; 95% CI 0.15–0.59; $P<0.001$ vs. 0.48; 95% CI 0.19–1.17; $P=0.107$, respectively). An independent association between Group MS and decreased long-term mortality still remained after adjusting for several covariates (HR, 0.37; 95% CI 0.17–0.79; $P=0.010$; Table 3). Similar results were obtained when we stratified these univariate and multivariable Cox regression analyses by a previous PMV procedure as Group MS was still found to

be associated with decreased long-term mortality compared with Group MSR (unadjusted HR, 0.30; 95% CI 0.15–0.60, *P* <0.001 and adjusted HR, 0.40; 95% CI, 0.18–0.88; *P*=0.023; Table 3).

Table 3. Univariate & multivariable Cox regression analysis

Group	Univariate Cox				Multivariable Cox			
			Stratified				Stratified	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Group MR	0.476 (0.193-1.174)	0.107	0.497 (0.201-1.225)	0.129	0.506 (0.183-1.399)	0.190	0.539 (0.193-1.503)	0.238
Group MS	0.298 (0.150-0.589)	<0.001	0.301 (0.151-0.601)	<0.001	0.368 (0.172-0.788)	0.010	0.403 (0.184-0.882)	0.023
Group MSR	Reference	0.002	Reference	0.002				

Univariate and multivariable Cox regression analyses were performed for Group MS and MR, compared with Group MSR**.** Group MS: patients with severe MS combined with at most a mild MR; Group MR: patients with severe MR combined with at most a mild MS; Group MSR: patients with severe MS combined with severe MR; HR: hazard ratio; CI: confidence interval;

Other variables found to be associated with long-term mortality included age, chronic obstructive pulmonary disease (COPD), diabetes mellitus on insulin therapy, aspirin medication, and concomitant TVR (Table 4).

Table 4. Other variables associated with long-term mortality

			Stratified	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.06 (1.03-1.09)	<0.001	1.06 (1.02-1.09)	<0.001
LA	1.02 (0.99-1.05)	0.162	1.02 (0.99-1.05)	0.159
Euroscore	1.13 (0.99-1.30)	0.076	1.13 (0.99-1.30)	0.080
COPD	4.96 (1.71-14.43)	0.003	4.76 (1.63-13.90)	0.004
DM on Insulin	3.66 (1.30-10.31)	0.014	3.77 (1.32-10.81)	0.014
Aspirin	1.95 (1.13-3.36)	0.016	2.00 (1.15-3.47)	0.014
TVR	2.99 (1.08-8.26)	0.035	2.98 (1.08-8.28)	0.036

HR: hazard ratio; CI: confidence interval; LA: left atrium diameter; Euroscore: European System for Cardiac Operative Risk Evaluation; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; TVR: tricuspid valve replacement;

Discussion

Our present study findings have indicated that the type of severe mitral valve disease can affect the long-term mortality outcomes following an MVR procedure. Long-term mortality in our present patient series was highest in Group MSR, followed by Group MR, and lowest in Group MS. Compared with Group MSR, our Group MS cases showed a statistically significantly lower long-term mortality, which remained after adjustment for covariates and stratification for PMV.

It is noteworthy from data that a rheumatic etiology accounts for 85%-95% of MS cases.[8] Increased LA pressure causes LA enlargement, leading to a high risk of atrial arrhythmia and pulmonary hypertension. In addition, cardiac output is reduced due to impaired LV filling.[9] LV systolic function has also been reported to decrease upon an impaired long-axis function of the myocardium in patients with MS.[10] On the other hand, in MR cases that can also be attributed to a rheumatic etiology, part of the LV volume returns to LA in the systolic phase, so that both LA and LV are in steady volume-overload state. LV systolic dysfunction is often masked by a large ejection volume in patients with significant MR.[11]

Significant MS and MR can arise together, and this mixed mitral valve disease is particularly common in rheumatic heart disease.[3] When experiencing both significant MS and MR, the outcomes for the heart will vary depending on the underlying mechanisms that have disrupted valve function. This manifests as different combinations of severities in terms of stenosis and regurgitation. Accordingly, patients with MS, MR, and mixed mitral valve disease may experience different processes of remodeling and reverse remodeling of the heart, which are associated with clinical outcomes.[12-15] There has been no study to date that has focused on the impact of different types of mitral valve disease on patient outcomes, even in the short-term. This clinically significant issue thus remains unresolved as the lack of investigations precludes evidence-based recommendations. Current guidelines provide only general principles for doctors to follow when different valves are simultaneously involved,[4] and clinicians will therefore often follow the recommendations corresponding to the dominant lesion.[4,6]

Our present results showed that long-term mortality was higher in the MSR cases, and the difference in long-term mortality between the MSR and MS groups remained after adjusting for covariates.

From our preoperative echocardiographic findings, the LVEDV was significantly larger in both Group MR and MSR compared to Group MS, in which it had decreased after the MVR surgery. In several previous studies, it was reported that the volume-overload caused by MR induces myocardial fibrosis which results in structural and functional changes to the LV.[16-22] In a prior animal study of mice with severe MR, it was revealed that eccentric LV dilatation is caused by changes in the myocardial collagen and matrix metalloproteinases, and that this may contribute to extracellular matrix breakdown.[16] Moreover, myocardial fibrosis had been found to influence the outcomes of interventions for MR[23-25] In a previous observational cohort study of patients with chronic MR undergoing mitral valve repair, the presence of myocardial fibrosis on a cardiac magnetic resonance image was independently associated with postoperative clinical adverse events.[24] Myocardial fibrosis is also observed in rheumatic MS.[26-30] In this disorder, myocardial fibrosis is thought to be the result of myocardial damage from chronic inflammation in RHD. [26,27] LV myocardial fibrosis, quantified by late gadolinium enhancement using cardiac magnetic resonance, is associated with LV systolic function[28] and also the outcomes of mitral valve surgery in rheumatic MS patients.[29,30] Our current Group MSR cases may thus have been affected by a combination of both volume overload and rheumatic disease progression, resulting in the highest long-term mortality compared to the other groups, although the underlying mechanisms for the different mortality rates observed in our results cannot be elucidated.

Our Group MR and MSR patients did not show a statistically significant difference in terms of their long-term mortality outcomes. In a prior retrospective study on significant rheumatic MS (MVA $\leq$ 1.5cm^2) with at least a moderate MR, the results of univariate analysis of a subgroup of asymptomatic patients indicated that an increased risk of adverse events (all-cause mortality, MVR, heart failure admission, and stroke) was correlated with significant MR but no significant MS.[6] The presence of MS may therefore not add a substantial risk to the occurrence of poor clinical outcomes when

significant MR also exists. Because the numbers of patients in our MR and MSR groups were limited, further studies that incorporate larger sample sizes are needed.

PMV is one of the main treatment options for rheumatic mitral stenosis. However, despite advances in the technical aspects of these procedures and in optimizing patient selection, MR remains one of the major procedure-related complications, with an incidence of as high as 15% according to the present literature.[31-33] A previous systemic review and meta-analysis study have described, with regard to the long term duration (> 6 months) after PMV, a pooled overall incidence of severe MR and need for mitral valve surgery of 5.5% and 11.5% respectively.[34] We speculated from this that there may be possible differences between newly developed MR after PMV and chronically progressed MR in terms of the impact on the heart and outcomes of an MVR. Hence, we here performed multivariable Cox hazard regression analysis, stratified by a PMV prior to the MVR operation, and observed similar results to those without this stratification. This suggested that PMV-related MR had not had an impact on the long-term mortality differently from rheumatic MR in our present cohort.

Aside from the type of mitral valve disease, we further found in our current series that aspirin use before surgery was associated with a higher long-term mortality rate after surgery. Because the cause of death was not separately investigated in our present analyses however, it was difficult to clearly determine the effects of aspirin. Several studies have reported that aspirin use is not associated with postoperative bleeding events.[35,36] Hence, our result may have been due to comorbidities among the patients taking aspirin rather than the effects of aspirin itself. The same explanation is likely for concomitant TVR. In general, a tricuspid annuloplasty is the first intervention to be considered for tricuspid valve disease, and TVR is performed for structural tricuspid valve disease in cases where repair is not feasible.[37] A previous study reported that patients with a tricuspid valve disease of rheumatic origin who underwent TVR had a perioperative mortality rate of 27% and a 10-year survival rate of only 41%, which were explained by the presence of a pre-existing right ventricular dysfunction and structural abnormalities that were difficult to repair.[38] Further research is needed to determine whether TVR itself is a factor influencing mortality or if it just reflects a more progressed

disease of the tricuspid valve.

This study had several limitations of note. First, this was a retrospective study with the inherent limitations imposed by this design. Despite the adjustments for several covariates in our model, we could not adjust for unmeasured and unknown confounding factors. Second, we did not have any information on mitral valve disease-related symptoms, symptom duration, or the interval between the onset of symptoms and MVR among our study subjects, all of which could potentially affect the outcomes of the MVR. Third, we included only patients with severe rheumatic mitral valve disease. Additional studies that include cases of moderate rheumatic mitral valve disease are thus needed. Fourth, our analyses were based on data from our tertiary hospital only, and future multicenter studies are warranted to expand on our findings and improve their wider applicability.

Conclusion

Among patients undergoing an MVR procedure, cases with severe MSR experience a higher long-term mortality rate than those with severe MR, and a far higher rate than patients with severe MS. The differences in the long-term mortality outcomes between patients with severe MSR and those with severe MS are significant, and remain significant even after stratifying these subjects by the receipt of a previous PMV.

References

1. Watkins DA *et al*. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. N Engl J Med. 2017 Aug 24;377(8):713-722.
2. Karthikeyan G, Guilherme L. Acute rheumatic fever. Lancet. 2018 Jul 14;392(10142):161-174.
3. Zühlke L *et al*. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J. 2015 May 7;36(18):1115-22a.
4. Alec Vahanian *et al*. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. Ehab39.
5. Moreira JL, Barletta PHAAS, Baucia JA. Morbidity and Mortality in Patients Undergoing Mitral Valve Replacement at a Cardiovascular Surgery Referral Service: a Retrospective Analysis. Braz J Cardiovasc Surg. 2021 Apr 1;36(2):183-191.
6. Cho IJ, Lee SE, Jeong H, Chang HJ. Determinants of clinical outcomes in patients with mixed mitral valve disease. Echocardiography. 2020 Aug;37(8):1164-1170.
7. Manjunath CN, Srinivas P, Ravindranath KS, Dhanalakshmi C. Incidence and patterns of valvular heart disease in a tertiary care high-volume cardiac center: a single center experience. Indian Heart J. 2014 May-Jun;66(3):320-6.
8. Iung B *et al*. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003 Jul;24(13):1231-43.
9. Harb SC, Griffin BP. Mitral Valve Disease: a Comprehensive Review. Curr Cardiol Rep. 2017 Aug;19(8):73.
10. Dogan S, Aydin M, Gursurer M, Dursun A, Onuk T, Madak H. Prediction of subclinical left ventricular dysfunction with strain rate imaging in patients with mild to moderate rheumatic mitral stenosis. J Am Soc Echocardiogr. 2006 Mar;19(3):243-8.
11. Acar C, de Ibarra JS, Lansac E. Anterior leaflet augmentation with autologous pericardium for

mitral repair in rheumatic valve insufficiency. J Heart Valve Dis. 2004 Sep;13(5):741-6.

12. Fukui M *et al*. Left Ventricular Remodeling After Transcatheter Mitral Valve Replacement With Tendyne: New Insights From Computed Tomography. JACC Cardiovasc Interv. 2020 Sep 14;13(17):2038-2048.
13. Uretsky S, Shah DJ, Lasam G, Horgan S, Debs D, Wolff SD. Usefulness of Mitral Regurgitant Volume Quantified Using Magnetic Resonance Imaging to Predict Left Ventricular Remodeling After Mitral Valve "Correction". Am J Cardiol. 2020 Jun 1;125(11):1666-1672.
14. Samaan AA *et al*. Left Ventricular Remodeling Following Balloon Mitral Valvuloplasty in Rheumatic Mitral Stenosis: Magnetic Resonance Imaging Study. Front Cardiovasc Med. 2021 Jun 4;8:674435.
15. Soesanto AM, Desandri DR, Haykal TM, Kasim M. Association between late gadolinium enhancement and global longitudinal strain in patients with rheumatic mitral stenosis. Int J Cardiovasc Imaging. 2019 May;35(5):781-789.
16. Corporan D, Onohara D, Hernandez-Merlo R, Sielicka A, Padala M. Temporal changes in myocardial collagen, matrix metalloproteinases, and their tissue inhibitors in the left ventricular myocardium in experimental chronic mitral regurgitation in rodents. Am J Physiol Heart Circ Physiol. 2018 Nov 1;315(5):H1269-H1278.
17. Li S *et al*. Mechanism of Eccentric Cardiomyocyte Hypertrophy Secondary to Severe Mitral Regurgitation. Circulation. 2020 Jun 2;141(22):1787-1799.
18. Van De Heyning CM *et al*. Late gadolinium enhancement CMR in primary mitral regurgitation. Eur J Clin Invest. 2014 Sep;44(9):840-7.
19. Liu B *et al*. Myocardial fibrosis in asymptomatic and symptomatic chronic severe primary mitral regurgitation and relationship to tissue characterisation and left ventricular function on cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2020 Dec 14;22(1):86.
20. Podlesnikar T, Delgado V, Bax JJ. Cardiovascular magnetic resonance imaging to assess myocardial fibrosis in valvular heart disease. Int J Cardiovasc Imaging. 2018 Jan;34(1):97-112.

21. Edwards NC *et al*. Quantification of left ventricular interstitial fibrosis in asymptomatic chronic primary degenerative mitral regurgitation. Circ Cardiovasc Imaging. 2014 Nov;7(6):946-53.
22. Constant Dit Beaufils AL *et al*. Replacement Myocardial Fibrosis in Patients With Mitral Valve Prolapse: Relation to Mitral Regurgitation, Ventricular Remodeling, and Arrhythmia. Circulation. 2021 May 4;143(18):1763-1774.
23. Velu JF *et al*. Myocardial fibrosis predicts adverse outcome after MitraClip implantation. Catheter Cardiovasc Interv. 2019 May 1;93(6):1146-1149.
24. Chaikriangkrai K *et al*. Prognostic value of delayed enhancement cardiac magnetic resonance imaging in mitral valve repair. Ann Thorac Surg. 2014 Nov;98(5):1557-63.
25. Podlesnikar T, Delgado V, Bax JJ. Cardiovascular magnetic resonance imaging to assess myocardial fibrosis in valvular heart disease. Int J Cardiovasc Imaging. 2018 Jan;34(1):97-112.
26. Lee YS, Lee CP. Ultrastructural pathological study of left ventricular myocardium in patients with isolated rheumatic mitral stenosis with normal or abnormal left ventricular function. Jpn Heart J. 1990 Jul;31(4):435-48.
27. Choi EY *et al*. Detection of myocardial involvement of rheumatic heart disease with contrast-enhanced magnetic resonance imaging. Int J Cardiol. 2006 Nov 10;113(2):e36-8
28. Soesanto AM, Desandri DR, Haykal TM, Kasim M. Association between late gadolinium enhancement and global longitudinal strain in patients with rheumatic mitral stenosis. Int J Cardiovasc Imaging. 2019 May;35(5):781-789.
29. Putra TMH *et al*. Prognostic Value of Late Gadolinium Enhancement in Postoperative Morbidity following Mitral Valve Surgery in Rheumatic Mitral Stenosis. Int J Angiol. 2019 Dec;28(4):237-244.
30. Putra TMH *et al*. Left Ventricular Dimension after Mitral Valve Surgery in Rheumatic Mitral Stenosis: The Impact of Myocardial Fibrosis. J Tehran Heart Cent. 2020 Jul;15(3):119-127.
31. Iung B *et al*. Temporal trends in percutaneous mitral commissurotomy over a 15-year period. Eur Heart J. 2004 Apr;25(8):701-7.

32. Kim MJ *et al*. Long-term outcomes of significant mitral regurgitation after percutaneous mitral valvuloplasty. Circulation. 2006 Dec 19;114(25):2815-22.
33. Elasfar AA, Elsokkary HF. Predictors of developing significant mitral regurgitation following percutaneous mitral commissurotomy with inoue balloon technique. Cardiol Res Pract. 2011;2011:703515.
34. Abu Rmilah AA *et al*. Efficacy and safety of percutaneous mitral balloon valvotomy in patients with mitral stenosis: A systematic review and meta-analysis. Int J Cardiol Heart Vasc. 2021 Apr 1;33:100765.
35. Zhang H, Dong Y, Ao X, Fu B, Dong L; CLIATHVR (Chinese Low Intensity Anticoagulant Therapy After Heart Valve Replacement) multicenter clinical study team. Comparison of Antithrombotic Strategies in Chinese Patients in Sinus Rhythm after Bioprosthetic Mitral Valve Replacement: Early Outcomes from a Multicenter Registry in China. Cardiovasc Drugs Ther. 2021 Feb;35(1):1-10.
36. Durães AR *et al*. Impact of aspirin use in the incidence of thromboembolic events after bioprosthesis replacement in patients with rheumatic disease. Rev Bras Cir Cardiovasc. 2013 Jul-Sep;28(3):347-52.
37. Veen KM, Quanjel TJM, Mokhles MM, Bogers AJJC, Takkenberg JJM. Tricuspid valve replacement: an appraisal of 45 years of experience. Interact Cardiovasc Thorac Surg. 2020 Jun 1;30(6):896-903.
38. Iscan ZH, Vural KM, Bahar I, Mavioglu L, Saritas A. What to expect after tricuspid valve replacement? Long-term results. Eur J Cardiothorac Surg. 2007 Aug;32(2):296-300.

국문 요약

연구 배경

류마티스 판막 질환에서 승모판은 가장 흔하게 영향을 받는 부위임에도 불구하고, 승모판 질환의 유형에 따른 장기 사망률에 관한 연구는 거의 없다. 이 연구의 목적은 중증 류마티스 승모판 질환의 유형에 따라 승모판 치환술 이후 장기 사망률을 비교하는 것이다.

연구 방법

우리는 중증 승모판 협착 또는 폐쇄부전 중 하나 이상으로 승모판 치환술을 받은 459명의 환자를 후향적으로 연구하였다. 중증 승모판 협착과 경증 이하의 폐쇄부전을 가진 환자를 MS군, 중증 승모판 폐쇄부전과 경증 이하의 협착을 가진 환자를 MR군, 중증 승모판 협착과 폐쇄부전 모두를 가진 환자를 MSR군으로 분류하였다. 연구의 주요 결과는 승모판 치환술 이후의 모든 원인에 의한 사망률이었다. 다변수 콕스 위험 회귀분석이 경피적 승모판 판막성형술 여부에 따른 층화 후 시행되었다.

연구 결과

연구 대상 중 386명이 MS군, 44명이 MR군, 그리고 29명이 MSR군으로 분류되었다. 장기 사망률은 MSR군에서 가장 높았고, 그 다음으로 MR군, MS군 순이었다. 98개월 중앙값의 추적 관찰 기간 동안 총 66명의 환자가 사망하였다. MSR군을 기준으로 설정하였을 때, 다변수 분석은 MS군이 유의미하게 낮은 장기 사망률과 관련되어 있고, 이러한 연관성은 경피적 승모판 판막성형술 과거력에 대해 층화 분석을 시행한 이후에도 남아있음을 보여주었다.

결론

승모판 치환술을 받은 환자 중 중증 승모판 협착과 폐쇄부전을 모두 가진 군에서 장기 사망률이 가장 높았고, 중증 승모판 폐쇄부전을 가진 군이 그 뒤를 이었으며, 중증 승모판 협착을 가진 군에서 가장 낮았다. 중증 승모판 협착과 폐쇄부전을 모두 가진 군과 중증 승모판 협착을 가진 군 사이의 장기 사망률 차이는 공변량을 보정한 이후에도 유의미하였으며, 경피적 승모판 성형술 과거력에 따른 층화 분석을 시행한 이후에도 유의미했다.