J Chin Med Assoc

ORIGINAL ARTICLE

Surgery for severe mitral regurgitation: The etiology matters

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Abstract

Background: While surgery has been the standard treatment for patients with severe primary mitral regurgitation (PMR), the role of surgery for severe secondary mitral regurgitation (SMR) remained debated. We therefore investigated the prognostic differences of surgery for patients with either severe PMR or SMR.

Methods: Subjects hospitalized for heart failure were enrolled from 2002 to 2012. The severity of MR was assessed by continuity equation, and an effective regurgitant orifice area of ≥40 mm^2 was defined as severe. Long-term survival was then identified by the National Death Registry.

Results: A total of 1143 subjects (66.4 ± 16.6 years, 65% men, and 59.7% PMR) with severe MR were analyzed. Compared with PMR, patients with SMR were older, had more comorbidities, greater left atrial and ventricular diameter, and less left ventricular ejection fraction (all $p < 0.05$). While 47.8% of PMR patients received mitral valve surgery, only 6.9% of SMR patients did. Surgical intervention crudely was associated with 54% reduction of all-cause mortality in PMR (hazard ratio, 0.46; 95% confident interval, 0.32-0.67), and 48% in the subpopulation with SMR (0.52, 0.30-0.91). Propensity score matching analysis demonstrated the survival benefits of mitral valve surgery was observed in patients with PMR (log rank $p = 0.024$), but not with SMR. Among the unoperated subjects, age, renal function, and right ventricular systolic pressure were common risk factors of mortality, regardless of MR etiology.

Conclusion: Mitral valve surgery for patients with heart failure and severe MR was associated with better survival in patients with PMR, but not in those with SMR.

Keywords: Medical therapy; Severe mitral valve regurgitation; Surgery

1. INTRODUCTION

Mitral regurgitation is the most common valvular heart disease, which may require surgical intervention. The feasibility of mitral valve surgery majorly depends on the etiology of severe mitral regurgitation,[1] while subjects with primary mitral regurgitation (PMR) but not secondary mitral regurgitation (SMR) may get truly survival benefits after surgery.[2–9] The indication of surgical intervention for severe PMR involves the presence of heart failure symptoms or left ventricular remodeling.[10] In contrast, subjects with severe SMR would be suggested mitral valve surgery as a concomitant open-heart procedure.[10] Moreover, the surgical risks related to age, comorbidities and left ventricular function may further affect the surgeon's willingness to do the operations.[11]

Goel et al[4] have demonstrated the dismal clinical outcomes of a total of 1095 unoperated patients with severe symptomatic mitral regurgitation. The majority of unoperated patients had SMR and the mortality rate elevated during the follow-up. In the meantime, the proportion of the survival patients hospitalized for heart failure increased from 41% in the first year to 90% by 5 years, which implied these patients were at greater risks of mortality.[4,12] However, the comparison of clinical impact of surgery between different mechanisms of severe MR and the determinants of long-term survival who were unwilling to receive surgery has yet been elucidated. We therefore investigated the clinical outcomes of patients with either severe PMR or SMR, hospitalized for heart failure in a tertiary medical center. We further analyzed the prognostic factors of the unoperated patients in the present study.

2. METHODS

2.1. Study population

The study population was drawn from the HARVEST registry that patients hospitalized for heart failure in Taipei Veterans

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 869-875.

Received March 12, 2023; accepted July 11, 2023.

doi: 10.1097/JCMA.0000000000000977.

General Hospital between 2002 and 2012 were eligible. All the participants have received comprehensive echocardiographic studies, and those with severe mitral regurgitation, defined by an effective regurgitation orifice area (EROA) of ≥40 mm^2 were enrolled in this analysis.[13] Patients who were younger than 18 years old have prior open-heart surgery, active infectious diseases, active malignancies, or concomitant cardiac or coronary abnormalities required surgery were excluded. Data of demographic characteristics, comorbidities, biochemistry, and hemogram were obtained. Estimated glomerular filtration rate (eGFR) was calculated using the Chinese Modification of Diet in Renal Disease equation.[14] An eGFR of <60 mL/min/1.73 m^2 was defined as chronic kidney disease. Medications, including renin-angiotensin system inhibitors, β-blockers, and mineralocorticoid receptor antagonists, were recorded. The investigation was conformed to the principles outlined in the Declaration of Helsinki. The institutional review committee of Taipei Veterans General Hospital approved the use of the registry data for research purposes, and the informed consent was waived.

2.2. Echocardiography

The transthoracic echocardiographic study was conducted by experienced technicians according to the recommendations from the American Society of Echocardiography.[15] Left atrial (LA) dimension, left ventricular internal diameter at end-diastole (LVIDd), and end-systole (LVIDs) were measured by M-mode. LVEF was calculated from the LV end-diastolic volume and end-systolic volume estimates by bi-plane Simpson's method. Right ventricular systolic pressure (RVSP) was estimated using Doppler echocardiography by calculating trans-tricuspid pressure gradient during systole and right atrial pressure by the dimension and collapsibility of inferior vena cava.

The quantification of mitral regurgitation was measured by adopting the proximal isovelocity hemispheric surface area of the flow convergence on the ventricular side in apical four chamber view with an aliasing velocity of color Doppler of 30 cm/s. Severe mitral regurgitation was defined by an EROA of ≥40 mm.[2,10] PMR is referred to the presence of excessive motions of mitral leaflets with or without ruptured chordae, causing significant regurgitation of blood during systolic phase. Otherwise, mitral leaflet morphology is normal in SMR, while leaflet tethering and/or annulus dilation hinder leaflet coaptation due to papillary muscle displacement or dysfunction.[10]

2.3. Statistical analysis

Categorical variables were expressed as percentages, and descriptive continuous variables were expressed as means ± standard deviations. Student's *t* test was used to compare continuous variables and the χ^2 test was used to compare categorical data.

Because of the heterogenous baseline characteristics between the operated and unoperated subjects, we performed 1:1 and 3:1 propensity score matching for PMR and SMR, respectively. A multivariate logistic regression analysis was conducted to evaluate the independent associations of the variables, which were significantly different between the operated and the unoperated subjects, with the decision of surgery. Propensity score was then estimated using a multivariate logistic regression model, including age, eGFR, LVIDs for PMR, and age, eGFR, LVEF and LA dimension for SMR. The calipers of 0.1 and 0.01, without replacement, were applied for PMR and SMR matching, respectively. The Kaplan–Meier survival curve analysis was used to assess the prognostic difference between the operated and unoperated subjects. Cox proportional hazards models were used to evaluate the determinants of the clinical outcomes.

All statistical analyses were performed on SPSS software (SPSS, version 24.0.0.0, IBM Corporation, Armonk, NY, USA). All tests were two-sided and a p value of <0.05 was considered statistically significant.

3. RESULTS

3.1. Baseline characteristics

A total of 1143 patients (mean age 66.4 ± 16.6 years; 65.1% men) with severe MR were analyzed, while 682 subjects (59.7%) of them had PMR and 461 had SMR. The baseline characteristics were demonstrated in Table 1. Patients with severe SMR were older, more male predominantly, and had lower eGFR and more comorbidities, including hypertension, diabetes, prior heart failure, coronary artery disease, stroke, and chronic obstructive pulmonary disease (COPD) than those with PMR. Patients with SMR also have greater LA dimension, LVIDd, LVIDs, and RVSP, but lower LVEF and EROA than those with PMR. In addition, subjects with SMR were treated with more renin-angiotensin system inhibitors, β-blockers, and mineralocorticoid antagonists. During a mean follow-up duration of 3.3 ± 2.7 years, 359 subjects with PMR (31.4%) and 236 subjects with SMR (55.1%) died. The Kaplan survival curve analysis suggested a better survival in patients with PMR than those with SMR (Fig. 1).

There were 47.8% of PMR patients (n = 326) and 6.9% of SMR patients (n = 32) receiving mitral valve surgery. Among patients with PMR, the operated subjects were younger, had better eGFR, less hypertension or COPD, and greater LVIDs and EROA than the unoperated subjects (Table 1). Majority of the operated PMR subjects underwent mitral valve replacement, and only 88 patients (27%) underwent mitral valve repair (Table 2). The operated PMR patients deemed to have better survival than their counterpart (Fig. 2A). In the subpopulation with SMR, the operated subjects were younger, had better eGFR, and less hypertension, diabetes or coronary artery disease, and better LVEF than the unoperated subjects (Table 1). The distribution of the operated patients stratified by LVEF is illustrated in Fig. 3. Among subjects with preserved LVEF, there was only 7.9% of them would receive surgery. Among the operated SMR patients, 19 (59.3%) of them received mitral valve repair, 9 (21.9%) underwent mitral valve replacement, and 4 (12.5%) accepted heart transplantation (Table 2). The mortality rates were similar in SMR subjects with or without surgical intervention (Fig. 2B).

The propensity score matching cohort is demonstrated in Table 3. Among the matched PMR subpopulation, the operated subjects remained a bit younger, has less hypertension or COPD, larger EROA, and more prescriptions of RAS inhibitors. Mitral valve surgery was associated with better long-term survival in PMR patients (Fig. 4A, log rank p = 0.024). The Cox proportional hazards model showed mitral valve surgery was significantly associated with less mortality (hazard ratio, 0.63; 95% confidence intervals, 0.40-0.99), after accounting for age, EROA, and the presence of hypertension and COPD in the matched PMR cohort.

In the matched SMR cohort, the operated subjects still had less hypertension than the unoperated patients. However, the Kaplan–Meier survival curve analysis demonstrated similar survival probabilities of them (Fig. 4B, log rank p = 0.097). The multivariate Cox regression analysis suggested the surgical intervention in the matched SMR cohort did not correlate with better long-term survival (HR, 0.67, 95% CIs, 0.35-1.28), after accounting for the presence of hypertension.

Among the 356 unoperated PMR patients, age, RVSP, and presence of hypertension, diabetes and COPD were positively and eGFR was negatively associated with all-cause mortality (Table 4). The multivariate Cox regression analysis indicated the increased age and RVSP, decreased eGFR, and presence of

Table 1

Characteristics of the study population, stratified by primary or secondary cause

		PMR			SMR		
	Overall (n = 1143)	Subtotal (n = 682)	Operated (n = 326)	Unoperated (n = 356)	Subtotal (n = 461)	Operated (n = 32)	Unoperated (n = 429)
Age	66.4 ± 16.6	62.4 ± 17.2[a]	58.3 ± 15.6[b]	66.2 ± 17.7	72.4 ± 13.7	63.5 ± 12.5[b]	73.1 ± 13.5
Male, %	745 (65.1)	440 (64.5)[a]	212 (65.0)	228 (64.0)	305 (66.2)	26 (81.3)	279 (65.0)
Creatinine, mg/dL	1.75 ± 1.75	1.38 ± 1.35[a]	1.3 ± 1.4	1.49 ± 1.2	2.22 ± 2.06	2.15 ± 2.85	2.22 ± 2.0
eGFR, mL/min/1.73 m^2	59.8 ± 29.2	69.4 ± 27.6[a]	74.6 ± 26.2[b]	63.6 ± 28.1	46.7 ± 26.0	57.1 ± 24.9[b]	45.9 ± 25.9
Comorbidities, n (%)							
Hypertension	419 (36.7)	213 (31.2)[a]	82 (25.2)[b]	131 (36.8)	206 (44.7)	5 (15.6)[b]	201 (46.9)
Diabetes mellitus	185 (16.2)	69 (10.1)[a]	27 (8.3)	42 (11.8)	116 (25.2)	3 (9.4)[b]	113 (26.3)
Coronary artery disease	331 (29.0)	137 (20.1)[a]	59 (18.1)	78 (21.9)	194 (42.1)	7 (21.9)[b]	187 (43.6)
Chronic kidney disease	111 (9.7%)	38 (5.6%)[a]	16 (4.9)	22 (6.2)	73 (15.8)	2 (6.3)[b]	71 (16.6)
Atrial fibrillation	125 (10.9)	73 (10.7)	29 (8.9)	44 (12.4)	52 (11.3)	3 (9.4)	49 (11.4)
Stroke	69 (6.0)	30 (4.4)[a]	12 (3.7)	18 (5.1)	39 (8.5)	1 (3.1)	38 (8.9)
COPD	204 (17.8)	95 (13.9) [+]	34 (10.4)[b]	61 (17.1)	109 (23.6)	5 (15.6)	104 (24.2)
Echocardiogram							
LVEF, %	56.4 ± 18	65.8 ± 11[a]	65.9 ± 11	65.8 ± 11	42.5 ± 17	48.8 ± 16[b]	42.0 ± 17
EF <50%, %	352 (30.8)	54 (7.9)[a]	27 (8.3)	27 (7.6)	298 (64.5)	19 (59.4)	279 (65.0)
LAD, mm	50.2 ± 10.5	49.9 ± 10.9[a]	50.5 ± 10.9	49.3 ± 11.0	50.6 ± 9.	58.8 ± 12.9[b]	50.0 ± 9.2
LVIDd, mm	59.1 ± 9.5	56.5 ± 8.0[a]	57.9 ± 8.2[b]	55.1 ± 7.6	63.0 ± 10.1	65.2 ± 10.3	62.8 ± 10.1
LVIDs, mm	39.0 ± 12.3	33.0 ± 7.7[a]	34.0 ± 8.1[b]	32.1 ± 7.2	47.8 ± 12.5	46.7 ± 18.2	47.9 ± 12.5
RVSP, mmHg	47.0 ± 19.9	45.4 ± 20.7[a]	46.2 ± 21.5	44.7 ± 19.9	49.5 ± 18.5	46.6 ± 18.2	49.7 ± 18.5
EROA, mm^2	64.8 ± 40.8	72.5 ± 43.2[a]	78.8 ± 44.9[b]	66.9 ± 41.0	47.8 ± 28.3	50.6 ± 19.8	47.5 ± 29.0
Medication, n (%)							
RAS inhibitors	573 (50.2)	315 (46.3)[a]	140 (42.9)	175 (49.2)	258 (56.0)	14 (43.8)	244 (56.9)
Beta-blockers	31 (2.7)	22 (3.2)[a]	10 (3.1)	12 (3.4)	9 (2.0)	0 (0.0)	9 (2.1)
MRA	267 (23.4)	116 (17.0)[a]	56 (17.2)	60 (16.9)	151 (32.8)	9 (28.1)	142 (33.1)

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; LVIDd = ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole; MRA = mineralocorticoid antagonist; PMR = primary mitral regurgitation; RAS = renin-angiotensin system; RVSP = right ventricular systolic pressure; SMR = primary mitral regurgitation.

[a]*p* value < 0.05, compared with SMR group.

[b]*p* value < 0.05, compared with the unoperated subjects.

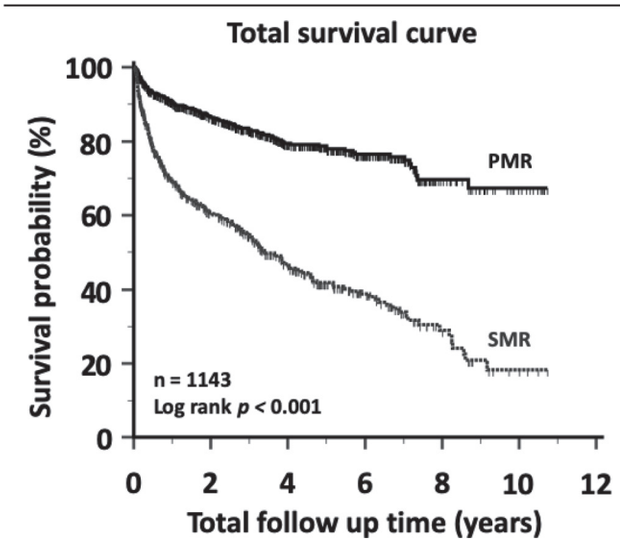

Fig. 1 The Kaplan–Meier survival curve analysis of the study population, stratified by PMR or SMR. PMR = primary mitral regurgitation; SMR = secondary mitral regurgitation.

diabetes were independent risk factors of mortality. In contrast, age, eGFR, coronary artery disease, LVEF, and RVSP were all related to the survival in the unoperated SMR patients (Table 4). In the multivariate Cox regression analysis, increased age and RVSP, and decreased eGFR and LVEF remained associated with all-cause mortality.

Table 2

Types of surgical interventions

	Primary MR (n = 326)	Secondary MR (n = 32)	*p*
Valve repairment, %	88 (27.0)	19 (59.3)	0.001
Valve replacement, %	238 (73.0)	9 (21.9)	<0.001
Heart transplantation, %	0 (0.0)	4 (12.5)	<0.001

MR = mitral regurgitation.

4. DISCUSSION

The present single-center study suggested patients with severe MR and heart failure were associated with dismal clinical outcomes, and the median survival of the study population was 33.6 months. While half of the PMR patients have undergone mitral valve surgery, only 6.9% of FMR patients would do so. When age, renal function, and lung disease were the determinants of operation among subjects with PMR, diabetes, coronary artery disease, and LA and ventricular sizes also affected the surgical decisions. However, mitral valve surgery might only extend the lives of PMR patients but not those with SMR. Among the unoperated patients, age, renal function, and RVSP were independently related to the long-term survival, regardless of the MR etiologies. In addition, diabetes in PMR patients and LVEF in FMR patients were also predictive of mortality, if left unoperated.

It has been well known that mitral valve surgery was indicated for symptomatic PMR patients to improve the long-term survival, which was also true for asymptomatic patients with a dilated left ventricle and/or abnormal LVEF.[4,11] In addition, mitral valve repair has outperformed mitral valve replacement

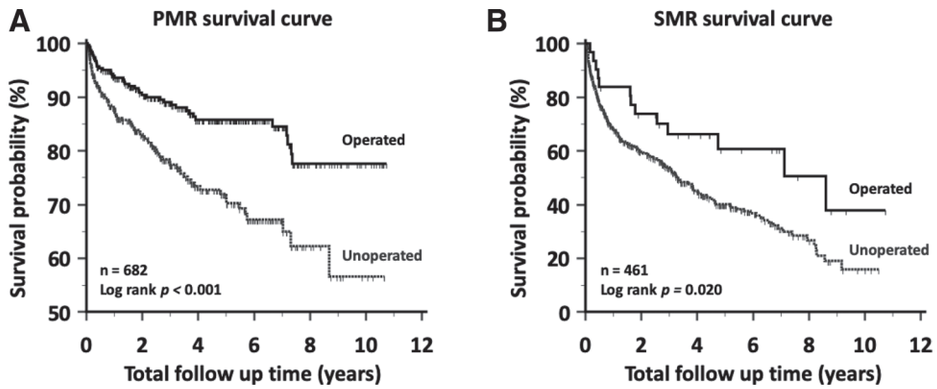

Fig. 2 The Kaplan–Meier survival curve analysis of patients with primary mitral regurgitation (A) or secondary mitral regurgitation (B), stratified by surgery. PMR = primary mitral regurgitation; SMR = secondary mitral regurgitation.

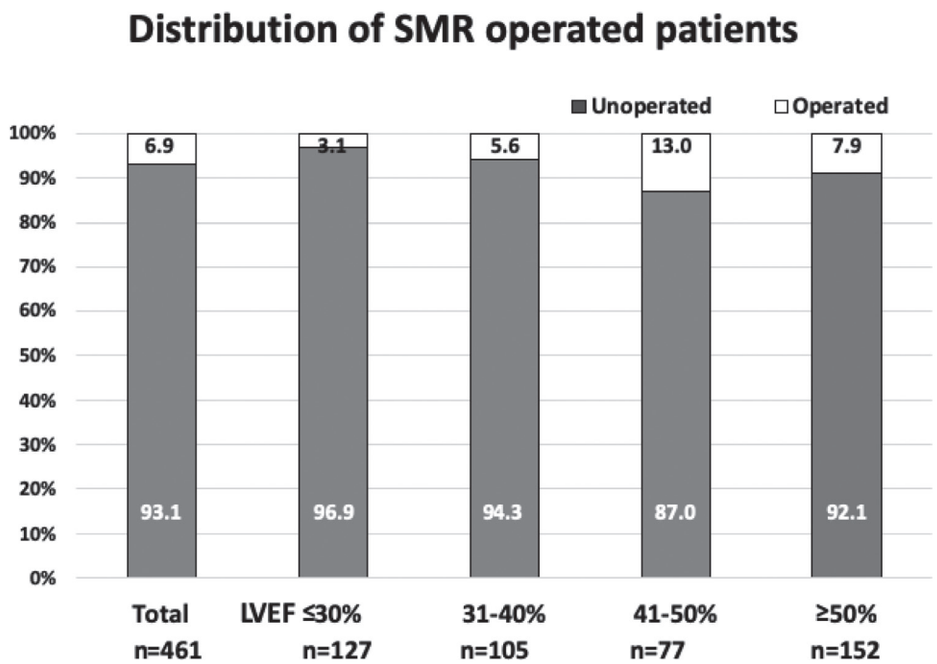

Fig. 3 The distribution of patients with secondary mitral regurgitation and mitral valve surgery, stratified by LVEF. LVEF = left ventricular ejection fraction; SMR = secondary mitral regurgitation.

in those subjects.[9] As the study population have been hospitalized for heart failure, those with PMR were deemed to require mitral valve surgery. But only 46.8% of PMR subjects received surgery. The undertreated were prevalent in Asians. Even vast majority of the operated subjects underwent mitral valve replacement, there was still a substantial improvement in long-term survival after the surgery. In addition to the well-known prognostic factors, including age and comorbidities, RVSP was also independently correlated with mortality in PMR patients. The results may support the guideline recommended pulmonary hypertension as one of the surgical indications.[10]

Although SMR is strongly associated with the outcome of patients with HF,[16] the role of surgical intervention remains in debates that the decline in LVEF and left ventricular remodeling may continue even after surgery.[3,5] The Cardiothoracic Surgical Trials Network (CSTN) has demonstrated coronary bypass surgery plus mitral valve repair in patients with moderate ischemic MR did not improve the survival neither reduce hospitalizations, compared with bypass surgery alone.[8] A meta-analysis of 1161 subjects with ischemic MR further confirmed the futile attempt of mitral valve repair in addition to bypass surgery to prolong the survival.[13] Moreover, Wu et al[2] also showed no mortality benefit conferred by mitral valve repair for SMR, regardless of the ischemic etiology. Even though CSTN has recommended chordal-sparing mitral valve replacement rather than mitral valve repair in concomitant coronary bypass surgery for severe ischemic MR,[6,17] mitral valve replacement was associated with numerically increased short-term mortality and similar 2-year adverse event rates.[6,17] These may explain majority of SMR patients would receive conservative treatment, regardless of heart failure symptoms.[4] In the present study, only 6.9% of patients with heart failure and SMR received surgery. However, the long-term survival was not different in SMR patients with or without surgery. The results may reflect the dilemma of managing patients with heart failure and SMR and the need for transcatheter therapy. In addition to age, renal function, and RVSP, LVEF was also an independent predictor of mortality in majority of SMR patients, treated conservatively. In other words, patients

Table 3

Characteristics of the propensity score matching cohorts, stratified by primary or secondary cause

	PMR		SMR	
	Operated (n = 233)	Unoperated (n = 233)	Operated (n = 32)	Unoperated (n = 81)
Age, y	63.7 ± 13.9[a]	66.6 ± 15.7	63.1 ± 12.6	67.9 ± 14.5
Male, %	163 (70.0)	159 (68.2)	27 (84.4)	57 (70.4)
Creatinine, mg/dL	1.26 ± 1.31	1.33 ± 1.20	1.99 ± 2.61	2.02 ± 2.28
eGFR, mL/min/1.73 m^2	71.1 ± 24.8	68.4 ± 27.6	57.2 ± 24.9	54.0 ± 27.8
Comorbidities, n (%)				
Hypertension	67 (28.8)[a]	97 (41.6)	5 (15.6)[a]	36 (44.4)
Diabetes mellitus	26 (11.2)	30 (12.9)	3 (9.4)	20 (24.7)
Coronary artery disease	50 (21.5)	54 (23.2)	7 (21.9)	30 (37.0)
Chronic kidney disease	10 (4.3)	16 (6.9)	2 (6.3)	9 (11.1)
Atrial fibrillation	25 (10.7)	25 (10.7)	3 (9.4)	10 (12.3)
Stroke	9 (3.9)	14 (6.0)	1 (3.1)	5 (6.2)
COPD	30 (12.9)[a]	47 (20.2)	5 (15.6)	17 (21.0)
Echocardiogram				
LVEF, %	66.4 ± 10.7	65.7 ± 10.8	48.8 ± 16.8	46.4 ± 17.6
EF< 50%, %	18 (7.7)	18 (7.8)	19 (59.4)	43 (53.1)
LAD, mm	51.0 ± 10.9	49.6 ± 11.4	58.9 ± 13.0	55.6 ± 8.4
LVIDd, mm	57.5 ± 8.3	55.4 ± 7.8	65.1 ± 10.3	63.3 ± 10.5
LVIDs, mm	33.6 ± 8.0	32.7 ± 7.8	46.3 ± 13.4	46.5 ± 13.4
RVSP (mmHg)	51.3 ± 20.5	47.7 ± 18.1	51.6 ± 15.3	54.7 ± 16.2
EROA, mm^2	74.2 ± 34.6[a]	62.7 ± 34.1	50.7 ± 19.9	45.7 ± 14.8
Medication, n (%)				
RAS inhibitors	102 (43.8)[a]	130 (55.8)	14 (43.8)	47 (58.0)
Beta-blockers	7 (3.0)	9 (3.9)	0 (0.0)	2 (2.5)
MRA	37 (15.9)	46 (19.7)	9 (28.1)	27 (33.3)

ACEi or ARB = angiotensin converting enzyme inhibitor or angiotensin II receptor blocker; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; LVIDd = ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole; PMR = primary mitral regurgitation; RVSP = right ventricular systolic pressure; SMR = secondary mitral regurgitation.

[a]*p* value < 0.05, compared with the unoperated subjects.

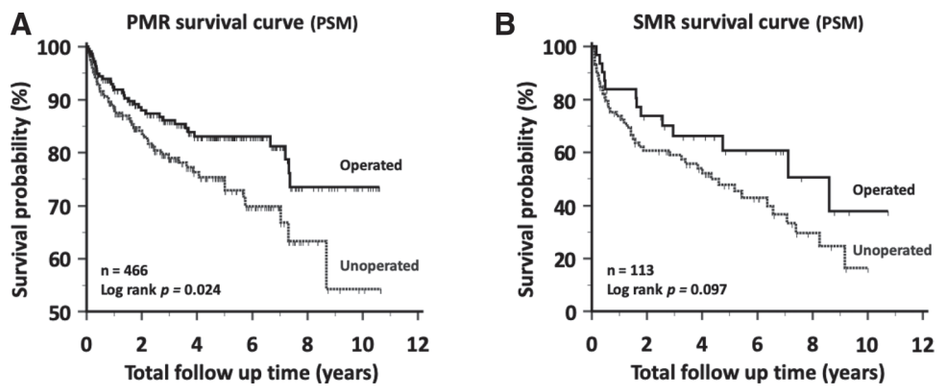

Fig. 4 The Kaplan–Meier survival curve analysis of the propensity score matching cohorts with primary mitral regurgitation (A) or secondary mitral regurgitation (B), stratified by surgery. PMR = primary mitral regurgitation; PSM = propensity score matching; SMR = secondary mitral regurgitation.

with old age, impair renal function, low LVEF, or elevated RVSP may have urgent needs for transcatheter mitral valve repair in the modern era.

Among the study population of heart failure and severe MR, the long-term clinical outcomes were dismal if left without surgical intervention. Patients undergone surgery were generally younger, have better renal or cardiac function, and less comorbidities than their counterpart, which may have overstated the surgical benefits. By propensity score matching analysis, the study clearly demonstrated PMR but not SMR patients did get true clinical benefits from surgery. In other words, symptomatic PMR patients with manageable surgical risks should be encouraged to receive mitral valve surgery. For patients with heart failure and SMR, guideline-directed medical therapy should be aggressively attempted if transcatheter therapy was not available.

Given the nature of an observational study, there were some study limitations. First, the selection bias due to unobserved variables may largely confound the study results. We therefore conducted propensity score matching analysis to evaluate the surgical benefits. Given age was so much discrepant between operated and unoperated subjects, the match on age would seriously deprive the case number and jeopardize the statistical power. We did not apply propensity score stabilized weighting method to increase the case number, because the baseline characteristic would even be unequal. Due to the limited cases of the matched SMR cohorts, the statistical power was not sufficient to exclude the survival benefits of mitral valve surgery among

Table 4

Predictors of mortality in the unoperated subjects

	PMR (n = 356)		SMR (n = 429)	
	Univariate	Multivariate	Univariate	Multivariate
Age, y	1.07 (1.05-1.09)[a]	1.05 (1.02-1.08)[a]	1.02 (1.01-1.03)[a]	1.02 (1.01-1.03)[a]
Gender	0.98 (0.62-1.55)		1.07 (0.80-1.43)	
eGFR, mL/min/1.73 m^2	0.97 (0.96-0.98)[a]	0.98 (0.96-0.99)[a]	0.98 (0.98-0.99)[a]	0.98 (0.98-0.99)[a]
Hypertension	1.96 (1.27-3.03)[a]	1.17 (0.70-1.95)	1.26 (0.97-1.65)	
Diabetes mellitus	2.04 (1.20-3.49)[a]	2.19 (1.21-3.95)[a]	1.25 (0.94-1.67)	
Coronary artery disease	1.15 (0.69-1.91)		1.52 (1.16-1.98)[a]	1.15 (0.86-1.55)
Atrial fibrillation	1.53 (0.86-2.73)		0.80 (0.52-1.24)	
Stroke	1.72 (0.79-3.74)		1.30 (0.84-2.03)	
COPD	1.70 (1.02-2.82)[a]	0.76 (0.42-1.36)	1.25 (0.92-1.69)	
LVEF, %	0.81 (0.14-4.55)		0.36 (0.17-0.76)[a]	0.33 (0.14-0.77)[a]
LAD, mm	1.02 (0.99-1.04)		0.99 (0.98-1.01)	
LVIDd, mm	0.98 (0.95-1.01)		1.00 (0.99-1.02)	
LVIDs, mm	0.99 (0.96-1.03)		1.01 (0.99-1.02)	
RVSP, mmHg	1.03 (1.02-1.04)[a]	1.02 (1.00-1.03)[a]	1.02 (1.01-1.03)[a]	1.01 (1.00-1.02)[a]
EROA, mm^2	0.98 (0.96-1.00)		0.99 (0.98-1.01)	

The values are displayed as hazard ratio and 95% confidence intervals.

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; LVIDd = ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole; PMR = primary mitral regurgitation; RVSP = right ventricular systolic pressure; SMR = secondary mitral regurgitation.

[a]$p < 0.05$.

subjects with SMR. Second, the MR severity was assessed by PISA method, which may underestimate EROA in subjects with SMR and overestimate in those with PMR and non-central pathology. Third, the study has excluded patients who needed concomitant coronary bypass surgery to estimate the prognostic values of mitral valve surgery per se. However, the clinical impacts of concomitant tricuspid annuloplasty was not evaluated in this study. Finally, evidence has indicated mitral valve repairment was superior to mitral valve replacement in patients with PMR. While the majority of PMR patients in this study underwent mitral valve replacement, the survival benefits could be further magnified in the modern era.

In conclusion, patients with heart failure and severe MR, the etiology of MR is important to allocate therapeutic strategy. Subjects with PMR but not SMR were urged to receive mitral valve operation while the surgical risks were appropriate.

ACKNOWLEDGMENTS

This work received support from Ministry of Health and Welfare, Taiwan (Nos. MOHW110-TDU-B-211-124001, MOHW111-TDU-B-211-134001, and MOHW112-TDU-B-211-144001), National Science and Technology Council Science and Technology of Taiwan (Nos. NSTC111-2314-B-A49-010 and NSTC112-2314-B-A49-042), Taipei Veterans General Hospital-National Taiwan University Hospital Joint Research Program (VN111-04, VN112-05) and Taipei Veterans General Hospital (V107C-027, V108-133).

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