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Early and long-term results of surgery for secondary mitral regurgitation with a damaged heart

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Abstract

Background: Surgery for secondary mitral regurgitation is still controversial, especially when the left ventricle is damaged. The Mitra Clip has been shown to be safe and effective for certain patient groups but does not offer superior control of mitral regurgitation compared with the surgery. If performed safely, the surgery can provide greater benefits over the long-term. The objective of this study was to retrospectively investigate the early and long-term results of mitral valve surgery for secondary mitral valve regurgitation with a damaged, dilated left ventricle.

Methods: Patients with ejection fraction <40% and left ventricular end-diastolic/systolic diameter >50/40 mm who underwent mitral valve surgery for secondary mitral regurgitation were investigated retrospectively.

Results: The mean age of the 80 identified cases was 65.7 years, and 63 patients were male. Preoperative echocardiograms showed a mean ejection fraction of 25.2% and mean left ventricular diameters in diastole/systole of 64.5/56.9 mm, respectively. Mitral valve replacement was performed in 39 cases, and mitral valve plasty in 41 cases. The most common concomitant procedures were coronary artery bypass grafting and tricuspid valve surgery (41.3% each). Mitral regurgitation improved significantly from 3.5 to 0.83, and no operative or in-hospital deaths were encountered. Long-term results showed actual 1-, 3- and 5-year survival rates of 93.1%, 80.0%, and 64.7%, respectively (mean follow-up, 1264 days).

Conclusions: Early results of this study were good and long-term results were acceptable. Our results suggest that mitral valve surgery is feasible for secondary mitral valve regurgitation even in dilated, damaged hearts.

KEYWORDS
mitral valve surgery, secondary mitral regurgitation, valve repair/replacement

1 | INTRODUCTION

With the emergence of percutaneous transcatheter mitral valve repair, concerns about mitral valve regurgitation have been increasing.[1,2] A consensus has been reached regarding the utility of mitral valve surgery for primary severe mitral valve regurgitation because mechanically caused valve dysfunction can only be fixed with a mechanical solution.[3,4] On the other hand, surgery for secondary

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mitral valve regurgitation is still controversial, especially when the left ventricle is enlarged and damaged.[5-13] The controversy results from the fact that secondary mitral valve regurgitation results from an already damaged left ventricle and surgical correction of the regurgitation cannot address the pre-existing left ventricular damage.[3,13] However, in ischemic mitral valve regurgitation as a form of secondary mitral valve regurgitation, the presence of even moderate mitral regurgitation is associated with a worsened prognosis.[8,9] Correction of secondary mitral regurgitation is likely to be beneficial, although clear evidence remains lacking.

The Mitra Clip (Abbott Vascular, Menlo Park, CA) has been proven safe and effective for a certain subset of patients but does not seem to offer superior control of mitral regurgitation as compared with the surgery.[14] If accomplished without increasing perioperative mortality or morbidity in such ill patients, mitral valve surgery can provide greater benefits in the postoperative course over the long-term. Clarification of the early and long-term results of surgical correction for secondary mitral valve regurgitation in dilated, damaged hearts is very important.

The purpose of this study was to retrospectively investigate the operative and long-term results of mitral valve surgery for secondary mitral valve regurgitation with dilated reduced left ventricular function and to identify predictors of rehospitalization because of heart failure and death after mitral valve surgery.

2 | PATIENTS AND METHODS

Between November 2008 to October 2018, all cases of cardiac surgery performed at Nagoya Heart Center were screened and patients with preoperative echocardiographic ejection fraction <40%, left ventricular end-diastolic diameter >50 mm and end-systolic diameter >40 mm were identified. Of these, cases that underwent mitral valve surgery for secondary mitral valve regurgitation without the aortic valve procedure comprised the study group. Concerning echocardiographic evaluations, the dimensions of the cardiac chamber were measured using the standard M-mode method. The cardiac ejection fraction was calculated using the modified Simpson's method. Valve regurgitation was assessed using color-flow Doppler as “trivial”, “mild”, “moderate”, or “severe”. Postoperative transthoracic echography was performed on each patient before discharge.

Chronic obstructive pulmonary disease was defined as the percentage predicted forced expiratory volume in 1.0 seconds less than 75%, partial pressure of oxygen in arterial blood less than 60 mm Hg or provision of medical therapy. Liver dysfunction was defined as total bilirubin greater than 1.5 mg/dL or liver enzymes (aspartate aminotransferase or alanine aminotransaminase) greater than 100 U/L. Clinical data were gathered from medical records, operative records or the in-hospital surgical database.

Long-term results were assessed by direct contact or telephone interviews with patients, their families, or local doctors. Survival was assessed from April to October 2018.

The primary end-points were mortality and morbidity as early results, and mortality and hospitalization because of heart failure as long-term results. As sub-analyses, differences in results were assessed between mitral repair and replacement groups. We also investigated risk factors for mortality and hospitalization.

The data were analyzed using the SPSS version 22 statistical software (SPSS, Chicago, IL). Results are expressed as mean ± standard deviation. Continuous data were analyzed using the Mann-Whitney U test or *t* test as appropriate. Categorical data were analyzed using the χ^2 test. Multivariate analyses were performed using multiple logistic regression analysis with a forcible loading method. Survival analysis was performed using the Kaplan-Meier method. Results were considered to be significant for values of $P < .05$.

2.1 | Operative procedures and strategy

Our standard procedure was as follows. Through median sternotomy, the cardiopulmonary bypass was established with ascending aortic and bicaval cannulations. Concomitant coronary artery bypass grafting was performed in an on-pump beating fashion where possible to reduce cross-clamp time. Other procedures were performed under cardiac arrest with intermittent antegrade cold blood cardioplegia.

Our strategy for selecting repair or replacement was changed at the beginning of 2014, on the basis of the results of a randomized control study and the favorable results of chordal-sparing mitral valve replacement.[15,16] Before 2014, our first choice of mitral procedure was mitral plasty even in cases with reduced cardiac function. Mitral valve replacement was chosen when the left-ventricular diastolic diameter was greater than 70 mm, in redo cases, or in hemodialysis cases for which reverse remodeling was not expected. Since 2014, we have selected chordal-sparing mitral valve replacement as the first-line procedure in secondary mitral regurgitation with a damaged heart. Mitral plasty was applied in younger patients (early 60 s or younger), and the left-ventricular diastolic diameter was less than 60 mm.

Apart from this strategy, we have chosen mitral valve replacement for all patients for whom poor prognosis was anticipated, such as in patients with advanced age, fragility, or other critical illness.

In mitral valve plasty, an undersized annuloplasty full ring was used and whether or not the mitral sub-valvular apparatus procedure was performed was determined by the surgeon based on the findings from echocardiography, such as tethering height greater than 10 mm[17] or location of papillary muscles. Our sub-apparatus procedures consist of papillary muscle resuspension to the mitral anterior annulus with CV4. When the papillary muscle heads were separated, the anterior and posterior heads were combined together with the resuspension stitch, then re-suspended as previously reported.[18]

In mitral valve replacement, mitral leaflets were tucked in the annulus with stitches securing the prosthetic valve, and all chordae were preserved. This study was approved by the institutional ethics committee, and the need to obtain written consent from patients was waived because of the retrospective study design.

3 | RESULTS

During the observation period, 2306 cases of cardiac surgery were performed in our institution and 226 cases were identified as showing dilated, reduced left the ventricular function. Of these, 86 cases underwent mitral valve surgery without the aortic valve procedure. Six cases were excluded from the analysis, because of primary (organic) mitral valve regurgitation in three cases and congenitally corrected transposition of the great arteries in three cases. As a result, 80 cases comprised the study group and were investigated for early and long-term results. Preoperative characteristics of these 80 patients are shown in Table 1. Mean age of the 80 patients at the time of operation was 65.7 years, and 63 patients were male. Preoperative echocardiograms showed a severely dilated and damaged left ventricle, with a mean ejection fraction of 25.2%, and left ventricular diameters in diastole/systole of 64.5/56.9 mm, respectively.

In all but one case, who underwent surgery through a right thoracotomy under hypothermic ventricular fibrillation because severe adhesions were anticipated because of previous cardiac

TABLE 1 Characteristics of the 80 patients

Variable	*n* (%), mean ± SD
Age, y	65.7 ± 11.4
Males	63 (78.8%)
Body surface area, m^2	1.64 ± 0.20
Body mass index, kg/m^2	22.6 ± 4.3
NYHA III/IV	54 (67.5%)
IABP required	9 (11.1%)
Emergency	2 (13.3%)
Comorbidities	
Hypertension	35 (43.7%)
Dyslipidemia	46 (57.5%)
Diabetes	37 (46.3%)
Atrial fibrillation	25 (31.3%)
Hemodialysis	8 (10%)
COPD	33 (41.3%)
Smoking	47 (58.8%)
Liver dysfunction	19 (23.8%)
Carotid artery stenosis	1 (1.3%)
Peripheral artery disease	8 (10.0%)
Prior cardiac surgery	10 (12.5%)
Prior myocardial infarction	19 (23.8%)
Prior percutaneous coronary intervention	20 (25.0%)
Serous creatinine, mg/dL	1.75 ± 1.99
Hematocrit, %	40.0 ± 5.6
Total bilirubin, mg/dL	1.23 ± 0.68
Etiology	
Ischemic	38 (47.5%)
Non-ischemic	42 (52.5%)
Preoperative echocardiogram	
LV ejection fraction, %	25.2 ± 7.5
Left atrial diameter, mm	49.3 ± 8.3
LV diameter in diastole, mm	64.5 ± 8.2
LV diameter in systole, mm	56.9 ± 8.4
Mitral regurgitation	3.5 ± 0.6
Tricuspid regurgitation	2.4 ± 1.0

Abbreviations: COPD, chronic obstructive pulmonary disease; LV, left ventricle; NYHA, New York Heart Association functional classification; SD = standard deviation.

TABLE 2 Perioperative results in the 80 patients

Variables	*n* (%), mean ± SD
Mitral valve replacement	39 (48.8%)
Mitral valve plasty	41 (51.2%)
Subvalvular apparatus procedure	29 (36.3%)
Concomitant procedure	
Coronary artery bypass grafting	33 (41.3%)
Distal anastomosis/patient	2.8 ± 1.3
Tricuspid valve plasty	33 (41.3%)
Maze	23 (28.8%)
Left ventricular restore	7 (8.8%)
Aortic arch replacement	1 (1.3%)
Operation time	292.9 ± 88.6 min
Cardiopulmonary bypass	156.0 ± 53.6 min
Aortic cross clamp	90.7 ± 39.4 min
Transfusion	58 (72.5%)
Mean ventilation time, h	7.5 ± 5.6
Mean intensive care unit stay, d	1.3 ± 1.2
Mean postoperative hospitalization, d	21.9 ± 21.6
Morbidities	
Prolonged ventilation (>24 h)	1 (1.3%)
Re-intubation	3 (3.8%)
Re-exploration	2 (2.5%)
Require hemodialysis	4 (5.0%)
Cerebral infarction	1 (1.3%)
Transient ischemic attack	2 (2.5%)
Postoperative atrial fibrillation	32 (40.0%)
Deep wound infection	1 (1.3%)
Operative/in-hospital death	0 (0%)
Postoperative echocardiogram	
LV ejection fraction, %	27.4 ± 9.4
Left atrial diameter, mm	45.6 ± 7.3
LV diameter in diastole, mm	61.5 ± 8.9
LV diameter in systole, mm	54.4 ± 9.8
Mitral regurgitation	0.83 ± 0.88
Tricuspid regurgitation	1.6 ± 0.68

Abbreviations: LV, left ventricle; SD, standard deviation.

surgery, procedures were performed through median sternotomy. Perioperative results are shown in Table 2. Mitral valve replacement was performed in 39 cases, and mitral valve plasty in 41 cases. Among the cases of mitral valve plasty, 29 cases received subvalvular apparatus procedures. The most common concomitant procedures were coronary artery bypass grafting and tricuspid valve surgery (41.3% each). The Maze procedure was performed in 28.8% of cases. The mean operation time was 292.9 minutes, and the mean aortic cross-clamp time was 90.7 minutes. Transfusion was performed in 58 cases (72.5%).

One patient required prolonged Postoperative ventilation (>24 hours), but postoperative morbidity rates were relatively low, except for atrial fibrillation (40%). No cases of 30-day/in-hospital death were encountered and the mean duration of hospitalization from operation to discharge was 21.9 days.

Postoperative echocardiograms showed significantly improved mitral regurgitation from 3.5 (moderate to severe) to 0.83 (less than trivial, $P = .000$).

As a sub-analysis, we divided patients into two groups: a repair group, and a replacement group. Table 3 demonstrated the results of

TABLE 3 Comparison of characteristics between mitral repair versus replacement

Variable	Repair (41) *n* (%), mean ± SD	Replacement (39) n (%), mean ± SD	*P* value
Age, y	65.4 ± 9.5	65.9 ± 13.3	.647
Males	31 (75.6%)	32 (82.1%)	.481
Body surface area, m^2	1.63 ± 0.17	1.65 ± 0.22	.585
Body mass index, kg/m^2	22.8 ± 4.0	22.3 ± 4.5	.433
NYHA III/IV	26 (63.4%)	28 (71.8%)	.424
IABP required	5 (12.2%)	4 (10.3%)	.532
Emergency	2 (4.9%)	0 (0%)	.259
Comorbidities			
Hypertension	21 (51.2%)	14 (35.9%)	.167
Dyslipidemia	26 (63.4%)	20 (51.3%)	.273
Diabetes	20 (48.8%)	17 (43.6%)	.642
Hemodialysis	**1 (2.4%)**	**7 (17.9%)**	**.024**
COPD	19 (46.3%)	14 (35.9%)	.343
Smoking	21 (51.2%)	26 (66.7%)	.161
Liver dysfunction	**6 (14.6%)**	**13 (33.3%)**	**.049**
Carotid artery stenosis	1 (2.4%)	0 (0%)	.512
Peripheral artery disease	3 (7.3%)	5 (12.8%)	.328
Prior cardiac surgery	3 (7.3%)	7 (22.6%)	.136
Prior myocardial infarction	**15 (36.6%)**	**4 (10.3%)**	**.006**
Prior PCI	9 (22.0%)	11 (28.2%)	.518
Serous creatinine, mg/dL	**1.1 ± 0.6**	**2.4 ± 2.6**	**.000**
Hematocrit, %	40.2 ± 5.7	39.7 ± 5.5	.686
Total bilirubin, mg/dL	1.15 ± 0.6	1.32 ± 0.8	.378
Etiology			
Ischemic	20 (48.8%)	18 (46.2%)	.814
Preoperative echocardiogram			
LV ejection fraction, %	24.8 ± 7.3	25.6 ± 7.7	.645
Left atrial diameter, mm	48.1 ± 5.2	50.5 ± 10.5	.204
LV diameter in diastole, mm	63.3 ± 8.0	65.7 ± 8.2	.077
LV diameter in systole, mm	55.7 ± 8.8	58.1 ± 7.8	.122
Mitral regurgitation	3.4 ± 0.6	3.5 ± 0.6	.255
Tricuspid regurgitation	2.2 ± 1.0	2.6 ± 0.9	.080

Abbreviations: COPD, chronic obstructive pulmonary disease; LV, left ventricle; NYHA, New York Heart Association functional classification; PCI, percutaneous coronary intervention; SD, standard deviation.

TABLE 4 Comparison of perioperative results between mitral repair and replacement

Variables	Repair (41) *n* (%), mean ± SD	Replacement (39) n (%), mean ± SD	*P* value
Concomitant procedure			
Coronary artery bypass grafting	17 (41.5%)	16 (41.0%)	.968
Tricuspid valve plasty	13 (31.7%)	20 (51.3%)	.075
Maze	10 (24.4%)	13 (33.3%)	.377
Left ventricular restore	5 (12.2%)	2 (5.1%)	.237
Aortic arch replacement	0 (0%)	1 (2.7%)	.487
Operation time, min	**313.5 ± 80.9**	**271.2 ± 92.2**	**.015**
Cardiopulmonary bypass, min	**167.4 ± 49.1**	**144.1 ± 56.2**	**.028**
Aortic cross clamp, min	**98.4 ± 40.2**	**82.5 ± 37.3**	**.015**
Transfusion	**25 (61.0%)**	**33 (84.6%)**	**.018**
Mean ventilation time, h	8.6 ± 5.9	6.3 ± 5.1	.074
Mean intensive care unit stay, d	1.3 ± 0.7	1.4 ± 1.6	.793
Mean postoperative hospitalization, d	21.1 ± 17.7	22.8 ± 25.1	.787
Morbidities			
Re-intubation	2 (4.9%)	1 (2.6%)	.519
Re-exploration	0 (0%)	2 (5.1%)	.234
Require hemodialysis	1 (2.4%)	3 (7.7%)	.289
Cerebral infarction	0 (0%)	1 (2.6%)	.487
Transient ischemic attack	1 (2.4%)	1 (2.6%)	.741
Postoperative atrial fibrillation	14 (34.1%)	18(46.2%)	.273
Deep wound infection	1 (2.4%)	0 (0%)	.512
Operative/in-hospital death	0 (0%)	0 (0%)	
Postoperative echocardiogram			
LV ejection fraction, %	28.2 ± 10.2	26.6 ± 8.6	.588
Left atrial diameter, mm	44.7 ± 6.2	46.6 ± 8.3	.473
LV diameter in diastole, mm	59.9 ± 8.6	63.2 ± 9.1	.095
LV diameter in systole, mm	52.8 ± 9.8	56.1 ± 9.6	.135
Mitral regurgitation	**1.05 ± 1.01**	**0.59 ± 0.65**	**.038**
Tricuspid regurgitation	1.73 ± 0.81	1.53 ± 0.054	.277

Abbreviations: LV, left ventricle; SD, standard deviation.

sub-analysis. The replacement group showed significantly lower liver and renal functions, and tended to have a more dilated left ventricle than the repair group. In terms of operative results, operative time, perfusion time, and cross-clamp time were significantly shorter in the replacement group, despite identical concomitant procedures in both groups (Table 4). Postoperative results did not differ between groups.

The rate of a successful collection of follow-up data was 98.8%, with a mean follow-up of 1264 days (range, 19–3630 days). Figure 1 shows the survival curve for all-cause death. Actual 1-, 3- and 5-year survival rates were 93.1%, 80.0%, and 64.7%, respectively. Figure 2 demonstrates the survival curve for cardiac death, including sudden death, death from unknown cause, and cerebral infarction. Deaths from pneumonia (two cases) and cancer (two cases) were regarded as noncardiac deaths. The 1-, 3-, and 5-year survival rates were 93.1%, 81.3%, and 68.6%, respectively. Figure 3 shows the rate of freedom from Readmission because of heart failure. The 1-, 3-, and 5-year readmission-free rates were 82.6%, 68.4%, and 53.7%, respectively.

Table 5 indicates factor analyses for all-cause death and readmission because of heart failure. When multivariate analyses were performed, age was identified as an independent risk factor for all-cause death, and the left atrial dimension was significantly associated with postoperative heart failure.

Neither the mitral valve procedure nor etiology affected the long-term outcomes in this study.

4 | DISCUSSION

This was a single-center, retrospective report of the early and long-term results of mitral valve surgery for secondary mitral valve regurgitation with a dilated, damaged left ventricle. Early results of

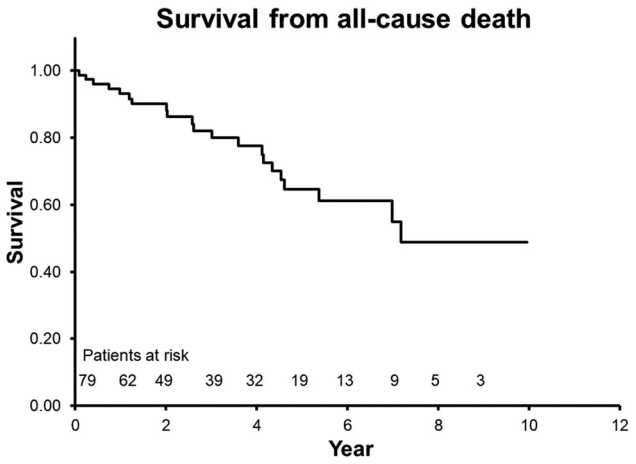

FIGURE 1 Kaplan-Meier analysis of survival from all-cause death

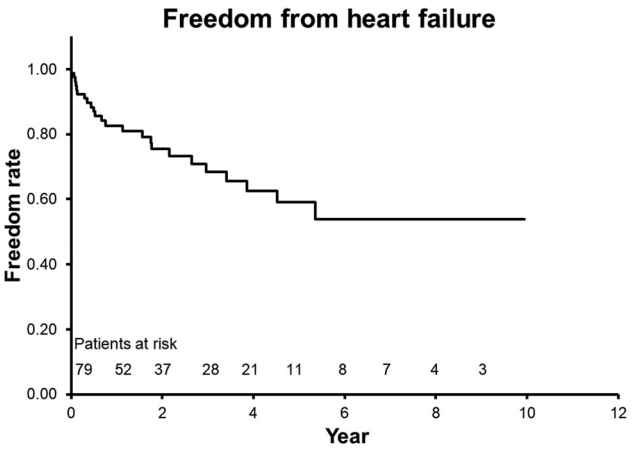

FIGURE 3 Kaplan-Meier analysis of freedom from heart failure

this study were excellent in terms of surgical mortality and good in terms of perioperative complications.

Long-term survival in this study was acceptable when considering the previous reports, in which the long-term results for secondary mitral valve regurgitation were dismal when only pharmacotherapy was provided.[19,20]

Feldman et al[1] suggested that the result of mitral valve surgery on reduced left ventricular systolic function was not superior to percutaneous treatment. They also commented that a less effective therapy could be acceptable if safety was improved. If mitral valve surgery proves safer in the early postoperative period, the procedure could be applicable to more candidates. Our results encourage the application of open surgery to secondary mitral regurgitation even under conditions of dilated, reduced cardiac function.

In this study, we applied both mitral repair and replacement. However, we chose valve replacement for more severe patients. As mitral valve replacement has been shown to require shorter operative, perfusion, and cross-clamp times, our strategy might contribute to good early results.

Although the postoperative morbidity rate was low, postoperative hospitalization was long, at almost 22 days. This is because patients with poor cardiac function show slow recovery and require a longer time to achieve optimal regimens for medications, such as angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers or beta-blockers.

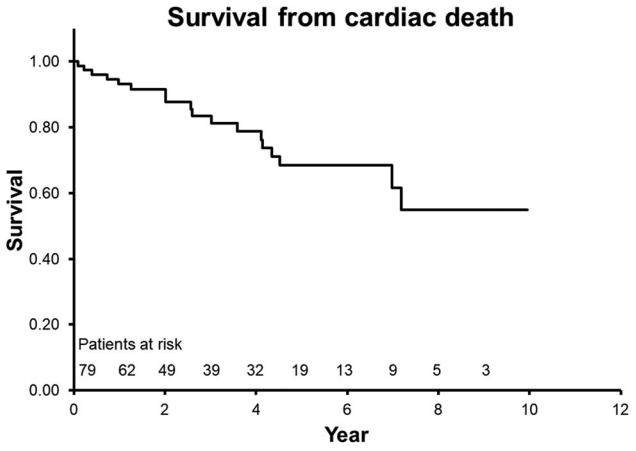

FIGURE 2 Kaplan-Meier analysis of survival from cardiac death

Long-term survival after open mitral valve surgery seems acceptable, but we could not find any independent predictors of death after surgery, except for increasing age. Multidisciplinary therapy might be needed, including pharmacotherapies, diet, rehabilitation, and cardiac resynchronization therapy, even after surgical correction of secondary mitral valve regurgitation.

Readmission rates were still high, at 31.6% at 3 years and 46.3% at 5 years. This may reflect the fact that even with good control of mitral regurgitation after open surgery, left ventricular dysfunction remains. The left atrial diameter was the only predictor of postoperative heart failure in the present study. Although we did not assess pulmonary artery pressure in this study, the left atrial diameter has been reported to be independently associated with pulmonary artery systolic pressure.[21] Our results suggest that patients who require readmission after mitral valve surgery have higher pulmonary artery pressure than those not hospitalized after surgery.

The present study had several limitations. First, the data in this study represent our clinical experience with a consecutive series of patients with secondary mitral regurgitation and dilated, reduced left the ventricular function. The number of patients was relatively small. Furthermore, when we selected open surgery for patients, a huge selection bias was present. However, our results imply that reduced cardiac function itself does not represent a contraindication for the surgery.

The second limitation was that we did not assess follow-up echocardiographic data. The extent to which regurgitation remained corrected in each patient over the long-term period remains unclear.

Finally, because of the retrospective nature of the investigation, this study did not include a control group. Whether surgical correction of secondary mitral regurgitation provides any mortality benefit over the long-term is unknown. However, considering that several articles have reported poor prognosis of secondary mitral regurgitation and our good operative results, we feel encouraged to provide open mitral valve surgery if the patient can tolerate the surgery.

TABLE 5 Analyses for all-cause death and heart failure

	Univariate			Multivariate		
All-cause death	**Yes n = 21**	**No n = 59**	***P* value**	**HR**	**95%CI**	***P* value**
Age, y	69.2 ± 11.6	64.4 ± 11.2	.097	**1.065**	**1.007-1.127**	**.026**
Male, n	19 (90.5%)	44 (74.6%)	.108	2.438	0.434-13.69	.311
Prior cardiac surgery, n	6 (28.6%)	4 (6.8%)	**.018**	4.342	0.92-20.6	.064
Left atrial dimension, mm	52.4 ± 7.3	48.1 ± 8.4	**.040**	1.058	0.985-1.136	.121
Heart failure after surgery	**Yes n = 24**	**No n = 56**				
Male, n	20 (83.3%)	43 (76.8%)	.512	0.679	0.134-3.440	.679
Age, y	64.5 ± 12.1	66.2 ± 11.2	.546	1.007	0.957-1.061	.782
Hypertension, n	15 (62.5%)	20 (35.7%)	**.027**	2.484	0.728-8.476	.146
COPD, n	15 (62.5%)	18 (32.1%)	**.011**	2.902	0.863-9.759	.085
Left atrial dimension, mm	52.8 ± 8.3	47.7 ± 7.9	**.011**	**1.102**	**1.014-1.197**	**.022**
Operation time, min	324.7 ± 72.7	279.3 ± 91.9	**.022**	1.005	0.998-1.013	.161

Note: Values represent number (%) or mean ± SD.
Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

5 | CONCLUSION

In conclusion, the early results of mitral valve surgery for secondary mitral valve regurgitation with a damaged left ventricle are good and the long-term results appear acceptable. Our results suggest that open mitral valve surgery could be applicable to secondary mitral valve regurgitation even in a dilated, damaged heart when the patient can tolerate the operation.

Further investigation, including controlled randomized trials, are needed to confirm the efficacy of mitral valve surgery for secondary mitral valve regurgitation in the long-term.

AUTHOR CONTRIBUTION

AK helped with the statistical analysis, YK helped in study design and data interpretation, and MT and YK contributed to the collection and analysis of the data.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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