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# Recovery of left ventricular function after surgery for aortic and mitral regurgitation with heart failure

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ABSTRACT

*Background:* Severe aortic regurgitation (AR) and mitral regurgitation (MR) can lead to left ventricular (LV) systolic dysfunction; however, there are limited data about recovery of LV after surgery for AR or MR. Little is known to guide the management of combined AR and MR (mixed valvular heart disease [VHD]). This study is sought to investigate the predictors of postoperative LV function recovery in left-sided regurgitant VHD with reduced left ventricular ejection fraction (LVEF), especially for mixed VHD.
*Methods:* From 2010 to 2020, 2053 adult patients underwent aortic or mitral valve surgery at our center. The patients with valvular stenosis, infective endocarditis, concomitant revascularization, and preoperative LVEF ≥40 % were excluded. A total of 127 patients were included in this study: 22 patients with predominant AR (AR group), 64 with predominant MR (MR group), and 41 with combined AR and MR (AMR group).
*Results:* The mean preoperative LVEF was 32.4 %, 30.7 %, and 30.2 % ($p = 0.44$) in the AR, MR, and AMR groups, respectively. The AR group was more likely to have postoperative LVEF recovery. The cut-point of left ventricular end-systolic diameter (LVESD) for better recovery was 49 mm for the MR group and 58 mm for the AMR group.
*Conclusion:* LV dysfunction due to combined AR and MR has similar remodeling reserve as AR, and better recoverability than MR. Thus, double-valve surgery is recommended before the LVESD is > 58 mm.

## 1. Introduction

The prevalence of degenerative heart valve disease has increased [1–3], and severe aortic regurgitation (AR) or mitral regurgitation (MR) can lead to left ventricular (LV) dilatation and systolic dysfunction [4,5]. The surgical timing for repair of AR or MR is not clear [6], even with defined criteria to increase the probability of LV function recovery, or to avoid LV dysfunction. The LV ejection fraction (LVEF) and LV end-systolic diameter (LVESD) are the 2 most crucial echocardiographic parameters mentioned in the class I surgical indications for asymptomatic patients [7,8]. Even following guideline recommendations, postoperative LV dysfunction can still occur after timely surgery for mixed valvular heart disease (VHD; AR and MR). For patients with mixed VHD, especially those with impaired LV contractility, the surgical option is seldom seriously treated [9]. In mixed severe AR and MR, once the LV dysfunction develops there are fewer surgical treatment options that if surgery was performed before the development of LV dysfunction.

Evidence to guide the management of combined AR and MR is limited. Gentles et al. [10] suggested that the LV mechanics in combined AR and MR closely resemble that of AR, but combined AR and MR is associated with a higher risk of postoperative LV dysfunction. On the other hand, in a study of young patients with rheumatic AR and MR, Skudicky et al. [11] found an initial postoperative decline in LVEF may be followed by normalization at 1 year after double-valve replacement. Unlike in pediatric or young rheumatic heart disease patients, a degenerative etiology of MR or AR is more prevalent in the adult population, especially in the seventh decade of life. For the elderly, the coexistence of severe AR and MR is poorly tolerated and immediate valve surgery is usually needed, even with a normal LVEF.

However, the valve surgery may not be performed at an optimal

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time. For example, it is possible that moderate AR can progress to functional MR such that both contribute to the development of LV dysfunction. Consequently, even with regular follow-up some patients with moderate AR may not reach the class I surgical indication until the LVEF declines and more than moderate MR develops. This may preclude valve surgery under the concern of postoperative LV dysfunction after mitral valve (MV) surgery according to the surgical indication for MR. Furthermore, when LV dysfunction is present it is hard to clarify the etiology of MR into binary categories (i.e., organic or functional), which further complicates the surgical timing and method.

This study is sought to investigate the predictors of postoperative LV function recovery in left-sided regurgitant VHD with reduced LVEF.

## 2. Materials and methods

### 2.1. Patients

From 2010 to 2020, 2053 adult patients had aortic valve (AV) and/or MV surgery at our tertiary cardiovascular referral center in northern Taiwan. Eligible patients for this study were older than 18 years of age, and had elective surgical procedures. Patients with valvular stenosis, isolated right-sided valve disease, and infective endocarditis were excluded. To investigate the relation of valvular regurgitation and LV dysfunction, patients with a history of percutaneous coronary intervention (PCI) and those with coronary bypass surgery (CABG) were also excluded. In order to observe recovery of LV dysfunction, only patients with a preoperative LVEF <40 % were included. The inclusion algorithm is summarized in Fig. 1.

The Institutional Review Board approved this study protocol, and waived the requirement to obtain informed consent due to the retrospective study design (CHGH-IRB; number (523)104-59).

### 2.2. Echocardiography

All echocardiograms were performed with an EPIQ 7C system equipped with an S5-1 or X7-2t transducer (Philips Medical Systems, Andover, MA, USA), and were acquired according to suggested guidelines [12–14]. The LVESD, LV end-diastolic diameter (LVEDD), LV septal wall thickness (IVSd), LV posterior wall thickness (LVPWd), aortic root diameter, and left atrial (LA) anteroposterior diameter were measured from 2D transthoracic parasternal long axis views. Right ventricular (RV) systolic pressure was measured as the peak tricuspid regurgitation pressure gradient plus estimated right atrial pressure. Vena contracta width of AR, MR, and the direction of regurgitant jets were measured and observed by transesophageal echocardiogram performed immediately before surgery.

### 2.3. Statistical analysis

Categorical variables were presented as number and percentage, and were compared using the chi-square test. Continuous variables were expressed as the mean ± standard deviation, and were compared using ANOVA and Student's *t*-test. Receiver operating characteristic (ROC) curves were constructed to determine the optimal cut-off of chosen variables, and the area under the ROC curve (AUC). All statistical analyses were performed using SPSS Statistics for Windows, version 17.0 (IBM SPSS Inc., Chicago, IL, USA). All *p*-values were 2-tailed, and *p* values $< 0.05$ were considered to be statistically significant.

## 3. Results

### 3.1. Patient characteristics and echocardiographic parameters

A total of 127 patients met the inclusion criteria, and baseline data are summarized in Table 1. There were 22 patients with isolated more than moderate AR (AR group), 41 patients with both more than moderate AR and MR (AMR group), and 64 patients with more than moderate MR, but no significant AR (MR group).

Of the 22 AR patients, 2 received the David procedure, 1 the Bentall procedure, 1 the Cabrol procedure, and 18 received AV replacement (1 with concomitant tricuspid repair). Of the 41 AMR patients, all received AV replacement (except for 1 patient who received the David procedure), 11 received MV replacement, 27 MV repair, and 3 had no surgical treatment of the MV; 8 of the patients also underwent concomitant tricuspid repair. Of the 64 MR patients, 23 received MV replacement, 41 underwent MV repair, and 18 received concomitant tricuspid repair.

The AR group has the largest LV chamber size, LV wall thickness, and aortic root diameter; the MR group had smallest chamber size, thinnest LV wall thickness, largest left atrial (LA) size, and highest percentage of right ventricle (RV) dysfunction and atrial fibrillation. There was no significant difference of LVEF among the 3 groups. For the AMR group and MR group, although most mitral pathologies were attributed to

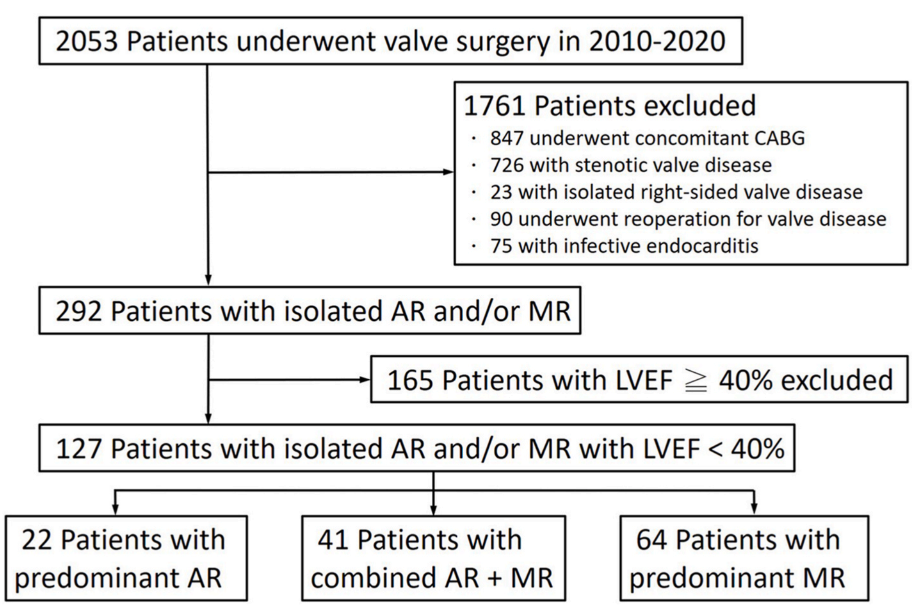


**Fig. 1.** Flow diagram of patient inclusion.

**Table 1**
Echocardiographic parameters and comorbidities in groups with different regurgitation diseases.

| | AR (n = 22) | AMR (n = 41) | MR (n = 64) | *F/ Chi²* | *p* |
|---|---|---|---|---|---|
| Age (years) | 56.7 ± 15.1 | 63.7 ± 11.9 | 62.0 ± 9.0 | 2.83 | 0.063 |
| LVEDD (mm) | 68.9 ± 6.7 | 63.3 ± 8.6 | 59.3 ± 7.2 | 13.75 | <0.001 |
| LVESD (mm) | 55.4 ± 7.2 | 52.4 ± 9.6 | 48.5 ± 7.6 | 6.70 | 0.002 |
| LVEF (%) | 32.4 ± 6.8 | 30.2 ± 6.4 | 30.7 ± 6.4 | 0.82 | 0.441 |
| IVSd (mm) | 11.5 ± 2.0 | 10.9 ± 1.6 | 9.8 ± 1.6 | 10.89 | <0.001 |
| LVPWd (mm) | 11.3 ± 1.8 | 10.5 ± 1.6 | 9.6 ± 1.6 | 9.88 | <0.001 |
| RWT (%) | 33.5 ± 6.7 | 34.3 ± 6.7 | 33.3 ± 7.4 | 0.25 | 0.777 |
| LAd (mm) | 47.4 ± 8.5 | 51.8 ± 6.9 | 56.8 ± 8.5 | 12.63 | <0.001 |
| Aortic root (mm) | 43.8 ± 10.0 | 37.7 ± 7.8 | 30.9 ± 4.1 | 33.93 | <0.001 |
| RVSP (mmHg) | 35.9 ± 13.6 | 49.1 ± 16.4 | 47.3 ± 14.1 | 5.84 | 0.004 |
| Eccentric MR | N/A | 14 (26.8 %) | 32 (50 %) | N/A | N/A |
| Functional MR | N/A | 38 (92.7 %) | 51 (79.7 %) | N/A | N/A |
| Eccentric AR | 17 (77.3 %) | 23 (56 %) | N/A | N/A | N/A |
| VC width of AR (mm) | 8.2 | 8.0 | N/A | N/A | 0.618 |
| VC width of MR (mm) | N/A | 6.9 | 7.3 | N/A | 0.309 |
| RV dysfunction | 7 (31.8 %) | 24 (58.5 %) | 51 (79.7 %) | 17.36 | <0.001 |
| Atrial fibrillation | 3 (13.6 %) | 14 (34.1 %) | 38 (59.4 %) | 16.02 | <0.001 |
| DM | 1 (4.5 %) | 7 (17.1 %) | 12 (18.8 %) | 2.57 | 0.277 |
| HTN | 4 (18.2 %) | 12 (29.3 %) | 15 (23.4 %) | 1.02 | 0.600 |
| CKD | 4 (18.2 %) | 11 (26.8 %) | 32 (50 %) | 9.80 | 0.007 |
| LVEF recovery | 20 (90.9 %) | 35 (85.4 %) | 40 (62.5 %) | 10.59 | 0.005 |

AMR: combined aortic and mitral regurgitation; AR: aortic regurgitation; CKD: chronic kidney disease; DM: diabetes mellitus; HTN: hypertension; IVSd: left ventricular septal wall thickness; LAd: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVPWd: left ventricular posterior wall thickness; MR: mitral regurgitation; RV: right ventricular; RVSP: right ventricular systolic pressure; RWT: relative wall thickness; VC: vena contracta.

functional MR, the MR jet directions were eccentric in nearly half of the patients. The echocardiographic parameters of the AMR group were mostly between the values of the AR and MR group, but the AMR group had the highest RV systolic pressure (RVSP). The AR and AMR groups had higher recovery rates of LVEF than the MR group.

### *3.2. Differences between groups with and without recovery of LVEF*

Recovery of the LVEF was observed in 95 patients (Table 2). There was no significant difference of the LVEDD between the recovery and non-recovery groups, but the recovery group had a smaller LVESD, and thus higher preoperative LVEF.

The recovery group also had thicker LV wall, smaller LA size, and larger aortic root diameter. Patients with AR were more likely to have postoperative recovery of LVEF, while there was no significant difference between patients with or without MR.

**Table 2**
Echocardiographic parameters in groups with or without LVEF recovery.

| | No recovery (n = 32) | Recovery (n = 95) | *p* |
|---|---|---|---|
| Age (years) | 59.2 ± 10.6 | 62.5 ± 11.6 | 0.159 |
| LVEDD (mm) | 64.1 ± 7.0 | 61.6 ± 8.6 | 0.154 |
| LVESD (mm) | 54.8 ± 6.8 | 49.7 ± 8.8 | 0.004 |
| LVEF (%) | 27.7 ± 6.1 | 31.9 ± 6.2 | 0.001 |
| IVSd (mm) | 9.8 ± 1.9 | 10.6 ± 1.7 | 0.020 |
| LVPWd (mm) | 9.5 ± 1.9 | 10.4 ± 1.6 | 0.007 |
| RWT (%) | 30.2 ± 5.3 | 34.8 ± 7.2 | 0.001 |
| LAd (mm) | 58.1 ± 9.2 | 52.0 ± 8.1 | <0.001 |
| Aortic root (mm) | 32.0 ± 5.2 | 36.4 ± 8.5 | 0.008 |
| AR≥3 | 8 (25 %) | 55 (57.9 %) | 0.001 |
| MR ≥ 3 | 30 (93.8 %) | 75 (78.9 %) | 0.056 |

AR: aortic regurgitation; IVSd: left ventricular septal wall thickness; LAd: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVPWd: left ventricular posterior wall thickness; MR: mitral regurgitation; RWT: relative wall thickness.

### *3.3. Prediction of postoperative LVEF recovery by ROC analysis*

The preoperative LVESD and LVEF were used in the ROC analysis to predict postoperative LVEF recovery in each group (Table 3). The LVESD was of limited predictive value in the AR group, but exhibited good predictive value in the AMR group (AUC 0.83, best cut-off 58 mm, sensitivity 83 %, specificity 77 %) (Fig. 2), and the MR group (AUC 0.81, best cut-off 49 mm, sensitivity 79 %, specificity 68 %) (Fig. 3). The predictive value of preoperative LVEF was only modest in all 3 groups. The smaller number of patients and high recovery rate of LVEF in the AR group lead to an unremarkable AUC, and there was little predictive valve of LVESD or LVEF. Thus, we pooled the AR and AMR groups for ROC analysis as a suboptimal surrogate to minimize the sample size effect with a better predictive valve of LVESD (AUC 0.69, best cut-off 56 mm, sensitivity 75 %, specificity 66 %) (Fig. 4).

## 4. Discussion

### *4.1. Recovery of the LV function in non-ischemic left-sided regurgitant VHD-related heart failure with reduced ejection fraction (HFrEF)*

Postoperative LV dysfunction is a major concern in patients undergoing heart valve surgery. With the development of transcatheter AV replacement, aortic stenosis can be treated in previously inoperable patients, and recovery of LV function in patients with a low LVEF has been reported [15,16]. Unlike aortic stenosis, the optimal timing of

**Table 3**
Predictive ability of LVESD and LVEF in LVEF recovery by ROC analysis.

| Parameter | Group | Best cut-off | Sensitivity (%) | Specificity (%) | AUC |
|---|---|---|---|---|---|
| LVESD (mm) | AR | 56 | 50 | 55 | 0.39 |
| LVESD (mm) | AR + AMR | 56 | 75 | 66 | 0.69 |
| LVESD (mm) | AMR | 58 | 83 | 77 | 0.83 |
| LVESD (mm) | MR | 49 | 79 | 68 | 0.81 |
| LVEF (%) | AR | 22 | 100 | 50 | 0.68 |
| LVEF (%) | AR + AMR | 32 | 44 | 52 | 0.42 |
| LVEF (%) | AMR | 27 | 71 | 60 | 0.70 |
| LVEF (%) | MR | 28 | 85 | 53 | 0.70 |

AMR: combined aortic and mitral regurgitation; AR: aortic regurgitation; AUC: area under the curve; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; ROC: receiver operating characteristic.

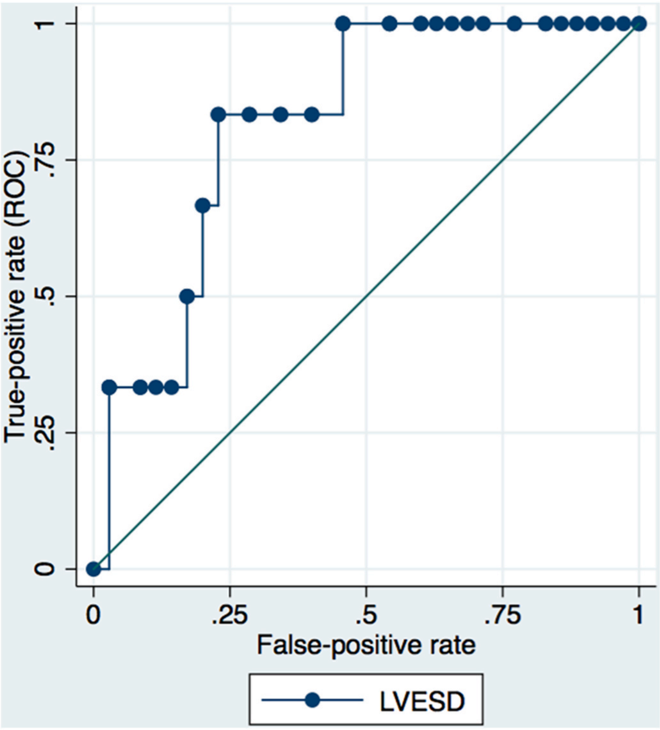


**Fig. 2.** ROC analysis of LVESD for prediction of LVEF recovery in patients with combined AR and MR. AR: aortic regurgitation; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; ROC: receiver operating characteristic.

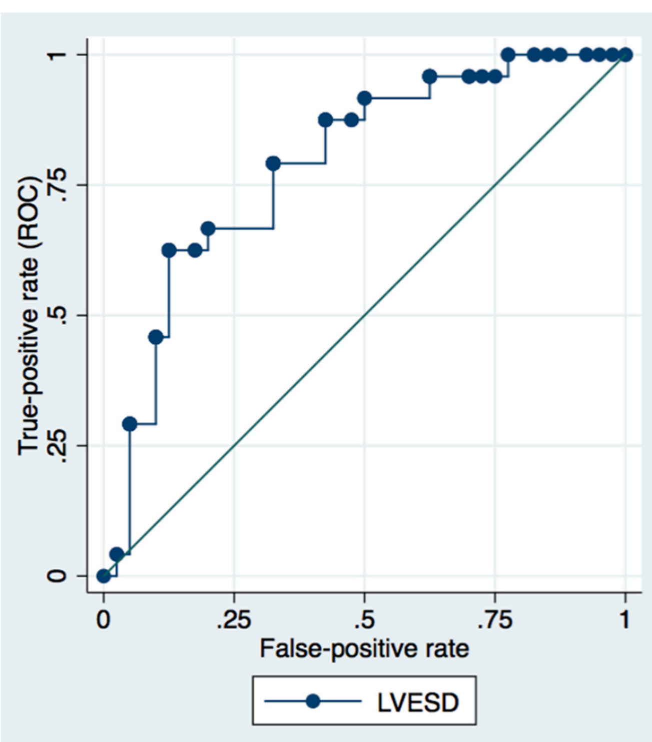


**Fig. 3.** ROC analysis of LVESD for prediction of LVEF recovery in patients with MR. LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; ROC: receiver operating characteristic.

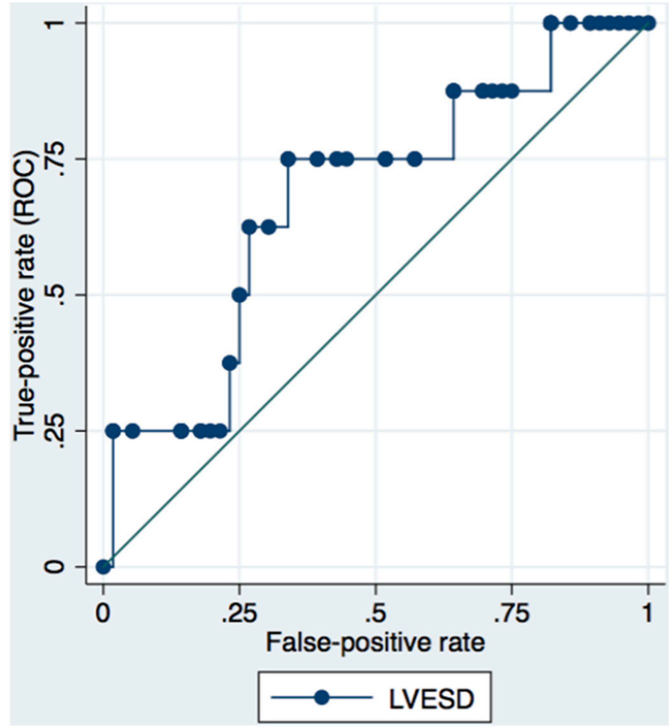


**Fig. 4.** ROC analysis of LVESD for prediction of LVEF recovery in patients with AR, and combined AR and MR. AR: aortic regurgitation; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; ROC: receiver operating characteristic.

surgery for isolated AR or MR remains controversial, and postoperative LV function recovery is unpredictable, with the greatest variability in patients with HFrEF receiving combined AR and MR surgery.

We focused on non-ischemic HFrEF patients (LVEF <40 %, no concomitant bypass surgery, no prior PCI), and retrospectively compared the outcomes between 3 different groups; AR, AMR, and MR. We found that 74.8 % (95 of 127) of patients had recovery of LVEF to the normal range (> 55 %) in a mean follow-up period of 17.7 months. Of the 3 groups, the AR group had the highest percentage of postoperative LVEF normalization. Although the AMR group had a larger LV size and comparable vena contracta width to the MR group, patients had a greater probability of a normal postoperative LVEF.

In general, patients prefer medical treatment over surgery and thus delay surgery past the optimal time. In the era of transcatheter valve therapy, patients commonly delay surgical treatment and patients presenting with refractory symptoms and poor LV function is not uncommon. One of the reasons that we focused on patients with a LVEF <40 % was to investigate the cardiac morphology at the critical time when patients are finally willing to accept surgery due to physical intolerance of symptoms.

For left-sided regurgitant VHD, the recovery of LVEF after surgery is actually the “reverse” remodeling of LV chamber size, especially for the end-systolic dimension. The ROC analysis showed that LVESD could significantly predict postoperative normalization of LVEF in the AMR and the MR groups, and the cut-point to predict recoverability for the MR group was 49 mm, larger than the recommended value in current guidelines, which suggests broader surgical indications. Moreover, the cut-point was larger for the AMR group (58 mm) than the MR group (49 mm), which was not expected and might imply a distinct remodeling mechanism and myocardial reserve for recovery.

### 4.2. *Remodeling reserve*

Due to the different pathophysiology and remodeling mechanism (smaller LVESD and higher LVEF), MV surgery should be considered earlier [7,8], while surgery for AR is always recommended when severe, irrespective of LVEF. The results of this study suggest that MR is less tolerable, even at a smaller LV chamber size. On the contrary, AR-related eccentric LV remodeling with a higher mass-volume ratio ameliorates wall tension as well as symptoms, such that patients often present with an extremely large LV at the time of surgery, but there is better reserve for recovery. More interestingly, we found that the AMR group had a similar cardiac morphology as the AR group at the time of surgery, even with smaller LVEDD and aortic root, and higher RVSP than the AR group, but better remodeling reserve than the MR group.

### *4.3. Etiology of combined AR and MR*

The primary cause of multiple valve disease has shifted from rheumatic heart disease to degenerative pathophysiology.[1] Current guidelines recommend surgical methods based on isolated valve dysfunction. For regurgitant mixed VHD, however, the interaction and timing of the development of AR and MR might be more complex and important. Beaudoin et al. [17] reported a low prevalence of functional MR in patients with chronic AR (46 of 816, 5.6 %), and proposed that the MV is significantly enlarged to reduce functional MR. On the contrary, Regeer et al. [18] reported that even with similar LV volumes, geometrical change of the mitral apparatus can still lead to significant MR (28 of 120, 23 %).

In patients with combined AR and MR, once LV dysfunction develops it is difficult to classify the MR into primary or secondary [19–21]. Degenerative MR could mimic functional MR in the scenario of concomitant AR because LV dysfunction might occur earlier, before the MR becomes severe. Hence, there should be caution considering significant MR as functional due to LV dysfunction, since the remaining untreated valve could further degenerate and thus lead to the need of an additional surgery, or the optimal surgical timing might be missed.

### *4.4. Surgery for combined AR and MR with HFrEF*

Numerous studies have investigate the optimal timing of surgery for AR and MR [22–25]. LV function, dimensions, valve reparability, and clinical symptoms are the most mentioned reasons for performing surgery. Although an observational study of combined AR and MR secondary to rheumatic heart disease suggested that lower preoperative LVEF is a more acceptable indication for double-valve surgery than of isolated MR [26], there is no evidence for the timing of treatment for patients with HFrEF secondary to mixed degenerative AR and MR.

In the AMR group, although 38 of 41 patients had functional MR there were 14 patients with eccentric regurgitation jets; thus patients may have had underlying mixed etiologies. Since AR-induced LV dysfunction has better reverse remodeling reserve than MR-induced LV dysfunction, even with primary MR in the AMR group, surgery for AR allows coexistent MR to be treated earlier, resulting in better outcomes than in patients with isolated MR. The development of functional MR has been reported to be an ominous sign for patients with chronic, severe AR [27].

Since functional MR can be improved by medical treatment for HFrEF [28], surgical correction of the adverse effect of AR on LV, as well as surgical reduction of MR, should provide better reverse remodeling. As such, the coexistence of functional MR should not preclude the surgery for AR, even at an LVEF <40 %. Thus, based on the results of this study, for non-ischemic HFrEF with combined severe AR and MR aggressive treatment with double-valve surgery is recommended, and the recovery of LV function can be expected.

### *4.5. Study limitations*

As a retrospective study patient inclusion and surgical method selection bias could not be completely avoided. Obtaining postoperative echocardiograms was decided by individual physicians, with variability in time intervals. Although ischemic heart disease was excluded, detailed ischemic burden and myocardial viability evaluation for patients with non-ischemic VHD should be investigated by reliable cardiovascular imaging. Finally, since the study is focused on the postoperative recoverability and predictors of LVEF, survival outcomes and cardiac events were not analyzed.

## 5. Conclusions

Our results showed a remarkable recovery rate of LV function after surgery for left-sided regurgitant VHD, and thus suggest broader surgical indications than in current guidelines. Combined AR- and MR-induced LV dysfunction has similar reverse remodeling reserve as AR, with greater physical tolerance and a better recovery rate than MR. Therefore, for patients with non-ischemic HFrEF and combined severe AR and MR, double-valve surgery is recommended before the LVESD becomes >58 mm.

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None.

## CRediT authorship contribution statement

**Wei-Tsung Lai:** Data curation, Writing – original draft, Writing – review & editing. **I-Chen Chen:** Data curation, Writing – original draft. **Ming-Chon Hsiung:** Data curation. **Ting-Chao Lin:** Data curation. **Kuan-Chih Huang:** Conceptualization, Supervision, Methodology. **Chung-Yi Chang:** Data curation. **Jeng Wei:** Data curation.

## Declaration of competing interest

All authors stated that there is no conflict of interest.

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