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# 대동맥 판막 역류 환자에서의 수술 후 좌심실 질량 감소 및 그 임상적 의미에 대한 연구

Prognostic Impact of Left Ventricular Mass Regression after Aortic Valve Surgery in Severe Aortic Regurgitation

울산대학교 대학원

의 학 과

박 성 희

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지 도 교 수  김 대 희

이 논문을 의학석사 학위 논문으로 제출함

2024년 2월

울산대학교 대학원

의 학 과

박 성 희

박성희의 의학석사 학위 논문을 인준함

심사위원　　송 종 민　　인

심사위원　　김 대 희　　인

심사위원　　김 호 진　　인

울 산 대 학 교　대 학 원

2024년 2월

국문 요약

연구 배경: 만성 대동맥판막 역류 환자들은 병이 진행할수록 용적 부하에 의해 점차 진행하는 좌심실 재형성을 겪게 된다. 이 환자들에서 대동맥 판막 수술을 시행한 후, 좌심실 역재형성이 보고되었고, 이 좌심실 역재형성을 겪은 환자들은 더 좋은 경과를 겪게 된다. 하지만, 좌심실 역재형성의 정의에 대해서는 연구마다 차이가 있는데, 승모판막 역류와는 달리 대동맥판막 역류의 경우 압력 부하와 용적부하 모두가 문제가 되기 때문에 좌심실 질량 및 그 변화를 고려하는 것이 중요하다고 하겠다. 따라서 본 연구는 좌심실 역재형성을 좌심실 질량감소로 정의하고, 고도 대동맥판막 역류 환자에서 판막수술을 시행한 뒤 발생하는 좌심실 역재형성이 임상경과와 관계가 있는지를 규명하고자 하였다. 추가로, 본 연구는 좌심실 질량감소를 결정하는 인자들에 대해서도 분석하였다.

연구 방법: 2006년부터 2020년까지 서울아산병원에서 대동맥 판막 수술을 시행 받은 고도 대동맥판막 역류 환자들을 후향적으로 분석하였다. 분석의 최종 목표는 사망률과 심부전으로 인한 재입원의 합계로, 2차 목표는 사망률, 심부전으로 인한 재입원 각각으로 설정했다. 좌심실 역 재형성은 수술 전과 시행 1년 후 심장 초음파 결과를 비교하여 좌심실질량지수(left ventricular mass index)변화로 정의하였다. Time dependent ROC analysis를 통해 확인한 좌심실 역재형성값을 기준으로 변화가 큰 군과 작은 군으로 나누어 최종목표와의 연관성을 분석하였다.

연구 결과: 총 563명의 환자 중 312명이 역재형성이 큰 군, 253명이 역재형성이 작은 군에 배정되었고, 수술 후 추적관찰기간의 평균 값은 2768일 (사분위수 1328-4107일)이었다. 관찰기간 중 총 10.1% (55명)가 사망했으며 5.7% (32명)가 심부전으로 재입원하였다. 최종목표는 역재형성이 큰 군에서 9.3% (29명), 역재형성이 작은 군에서 20.1% (51명) 발생하여 다변량 콕스 분석 결과 역재형성이 큰 경우 조정 위험률 (adjusted hazard ratio) 0.42 (95% 신뢰구간 0.26 – 0.69, p<0.001)로, 역재형성이 큰 환자들에서 사망과 심부전으로 인한 재입원을 더 적게 경험하였다. 이 결과는 LV mass index 변화를 연속변수로 변환하여 분석했을 때도 변하지 않았다. 또한 고혈압은 좌심실질량지수의 감소를 예측하는 유일한 임상 변수였으며, 심장초음파 지표 중에서는 좌심방직경, 기저 좌심실질량지수, 좌심실 박출률, 그리고 대동막판막 최고속도가 좌심실질량지수 감소와 유의한 연관성을 보였다.

연구 결론: 본 연구결과 좌심실질량지수변화를 좌심실 역재형성의 지표로 설정하고 분석하였을 때, 좌심실 역재형성을 더 많이 경험한 환자들이 사망 및 심부전 악화로 인한 재입원을 경험하는 비율이 유의하게 더 적었고, 이는 임상경과 개선을 시사한다. 또한 고혈압이 좌심실 역재형성 감소를 초래하며, 기저 좌심실질량지수, 박출률, 그리고 대동맥판막 최고속도 역시 역재형성 정도 감소와 관계가 있었다.

# Contents

# List of Tables and Figures

## 1. Backgrounds

Severe aortic regurgitation (AR) leads to progressive left ventricular (LV) remodeling due to volume overload [1]. Although compensatory eccentric hypertrophy initially normalizes ventricular wall stress, LV function deterioration or symptoms can develop as a result of decompensation [2]. LV decompensation is associated with poor clinical outcomes and requires surgical intervention. The 2021 European Society of Cardiology/European Association for Cardiothoracic Surgery guideline recommends aortic valve (AV) surgery not only for patients with symptomatic AR but also for those with asymptomatic AR with severely dilated or dysfunctional LV (LV end-systolic diameter (LVESD) > 50 mm or LV ejection fraction (LVEF) ≤ 50%) [3].

LV reverse remodeling (LVRR), which is associated with improved clinical outcomes in patients with chronic AR, usually occurs after AV surgery [4, 5]. However, a considerable heterogeneity exists in the definition of LVRR. Most previous studies have attempted to define LVRR as an increase in LVEF or reduction in indexed LV diameter [6-9].

When dealing with AR, it is important to consider LV mass and its regression as AR causes both pressure and volume overload, unlike chronic mitral regurgitation. However, previous studies on LV mass regression have mainly focused on severe aortic stenosis instead of AR; therefore, more evidence on LVRR and LV mass regression following AV surgery in patients with chronic AR are warranted. In addition, long-term data on the prognostic impact of LVRR following AV surgery in patients with severe AR is limited. Therefore, this study aimed to investigate the impact of LVRR, as defined by LV mass regression, on the long-term clinical outcomes of patients with severe AR undergoing AV surgery. It also explored the determining factors of LV mass regression following AV surgery.

## 2. Methods

### 2.1. Study population and data collection

In this retrospective study, consecutive patients who underwent AV replacement or repair at Asan Medical Center in Seoul, Republic of Korea, due to severe AR between January 2006 and December 2020 were reviewed. Only those who had both baseline and 1-year follow-up transthoracic echocardiography (TTE) data were included in the study. Patients' demographic information, clinical characteristics, laboratory data, and imaging test results, including echocardiographic findings, were obtained from the electrical medical records at Asan Medical Center. Patients with symptomatic AR were defined as those who suffered from dyspnea on exertion (New York Heart Association Functional

Class 2 or higher). Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate ≤ 60 mL/min/1.73 $m^2$ according to the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-mineral and bone disorder. Patients with coronary artery disease (CAD) were defined as those who had already received percutaneous coronary intervention or were not deemed suitable for coronary artery bypass grafting (CABG) by the heart surgery team. People with atrial fibrillation (AF) were defined as those who experienced paroxysmal events and decided not to undergo a Maze operation. The exclusion criteria were patients who underwent concomitant CABG, other valve surgery, Maze operation, or redo operation; patients with infective endocarditis, aortitis, and aortic dissection; and patients with no available pre or postoperative echocardiographic data. Patients with combined moderate or severe aortic stenosis were also excluded. The study protocol was approved by the Institutional Review Board of Asan Medical Center.

### 2.2. Echocardiographic evaluation

As aforementioned, all patients underwent baseline TTE both before and 1 year after AV surgery. The average time from preoperative TTE to AV surgery was 37.5 days (interquartile range [IQR] 49.5, 6.0–55.5 days), and only experienced sonographers captured the images. Subsequently, echocardiographic specialists from Asan Medical Center reviewed the images, which included 2D color Doppler data in parasternal, apical, subcostal, and suprasternal notch views. The 2017 American Society of Echocardiography (ASE) guidelines were adopted to grade AR severity, with comprehensive diagnostic criteria defining severe AR [10]. The 2014 ASE recommendation was used to evaluate AS [11]. Furthermore, LV end-diastolic and end-systolic volumes and LVEF were measured in apical two and four-chamber views using the biplane Simpson method. Interventricular septal thickness, LV posterior wall thickness, and left atrial (LA) dimensions were measured in a parasternal long-axis view. LV mass was calculated according to the 2015 ASE guidelines and indexed to body surface area (BSA) [12, 13]. Tricuspid regurgitation peak velocity more than 3.0 m/s was considered to indicate the presence of pulmonary hypertension.

### 2.3. Outcomes and follow-up

The patients were advised to schedule appointments with their physicians every 1 to 6 months and undergo follow-up echocardiography. LVRR was defined as regression of the LV mass index (LVMi), calculated as the ratio of the baseline LVMi to that of the 1-year follow-up

($^{LVMi\ follow-up}/_{LVMi\ baseline}$) [13]. The patients were then divided into two groups based on their LVMi regression, namely, lesser regression (equal to or below the cutoff) group and greater regression (above the cutoff) group, with the cutoff value determined via time-dependent receiver-operating characteristic (ROC) curve analysis.

The primary outcome was a composite of all-cause mortality and rehospitalization due to heart failure over the follow-up period, whereas the secondary outcomes included the individual components of the primary outcome. The potential determining factors of LV mass regression were also investigated.

### 2.4. Surgical procedures

The surgical indication for this study was in accordance with the internationally recognized American College of Cardiology/American Heart Association guideline and determined at the physician's discretion. The approach to the procedure was decided by the operator, followed by AV replacement or repair via cardiopulmonary bypass and antegrade or retrograde cardioplegia infusion. The type of prosthesis (biological or mechanical) was determined before surgery, considering the guideline recommendations (usually based on the patient's age) and the patient's preferences. After AV replacement or repair, cardiopulmonary bypass was gradually reduced, and intraoperative transesophageal echocardiography was performed before cessation.

### 2.5. Statistical analyses

Continuous variables were expressed as means and standard deviations, whereas continuous variables were expressed as medians and IQRs. On the other hand, categorical variables were expressed as numbers and percentages. To compare baseline clinical and echocardiographic values, Pearson's chi-squared test and Wilcoxon's rank-sum test were employed for categorical and continuous variables, respectively. The researchers conducted a Cox proportional-hazards analysis to evaluate the effects of each covariate and divided the patients into the greater and lesser LVMi regression groups based on the value calculated from the survival ROC curve. The primary and secondary outcomes were analyzed using Kaplan–Meier estimations of up to 10 years. Univariate Cox regression models were used to calculate hazard ratios (HRs) for both primary and secondary outcomes, whereas multivariate Cox regression analysis was conducted using multiple clinical and preoperative echocardiographic factors considered to be associated with the univariate analysis outcomes. To account for collinearity, LV mass regression was put into binary and continuous variables, and Cox regression was performed on each

variable. Finally, logistic regression tests and a stepwise selection method were employed to determine the probable determining factors of LV mass regression. All statistical analyses were conducted using the R software (version 4.0.5), and the reported *p*-values were two-sided. *P*-values of 0.05 were considered statistically significant.

## Results

### 3.1. Study populations

A total of 1053 patients who underwent AV surgery at Asan Medical Center between January 2006 and December 2020 due to severe AR were reviewed. Of these patients, 391 met the exclusion criteria and were thus excluded. Among the excluded patients, 45 underwent concomitant CABG, 60 underwent other valve surgeries, 105 had a maze operation, and 96 previously underwent AV surgery. Furthermore, 13 patients were diagnosed with infective endocarditis and 28 suffered from aortitis or aortic dissection. In total, 24 patients had no available postoperative echocardiography, 64 had concurrent moderate or higher degree of aortic stenosis, and 55 missed their follow-up appointments at the outpatient clinic. Ultimately, 563 patients were included in the final analysis (Figure 1).

After LVRR assessment, the Kaplan–Meier method was employed and a time-dependent ROC analysis was conducted to calculate the cutoff value. The marker time was set to 10 years, and the optimal cutoff value was determined to be 63.519% (sensitivity 67.6%, specificity 66.3%) (Figure 2). Using this technique, 312 of the 563 patients were allocated into the greater regression group and the remaining 251 patients into the lesser regression group.

**Figure 1. Study flow diagram**

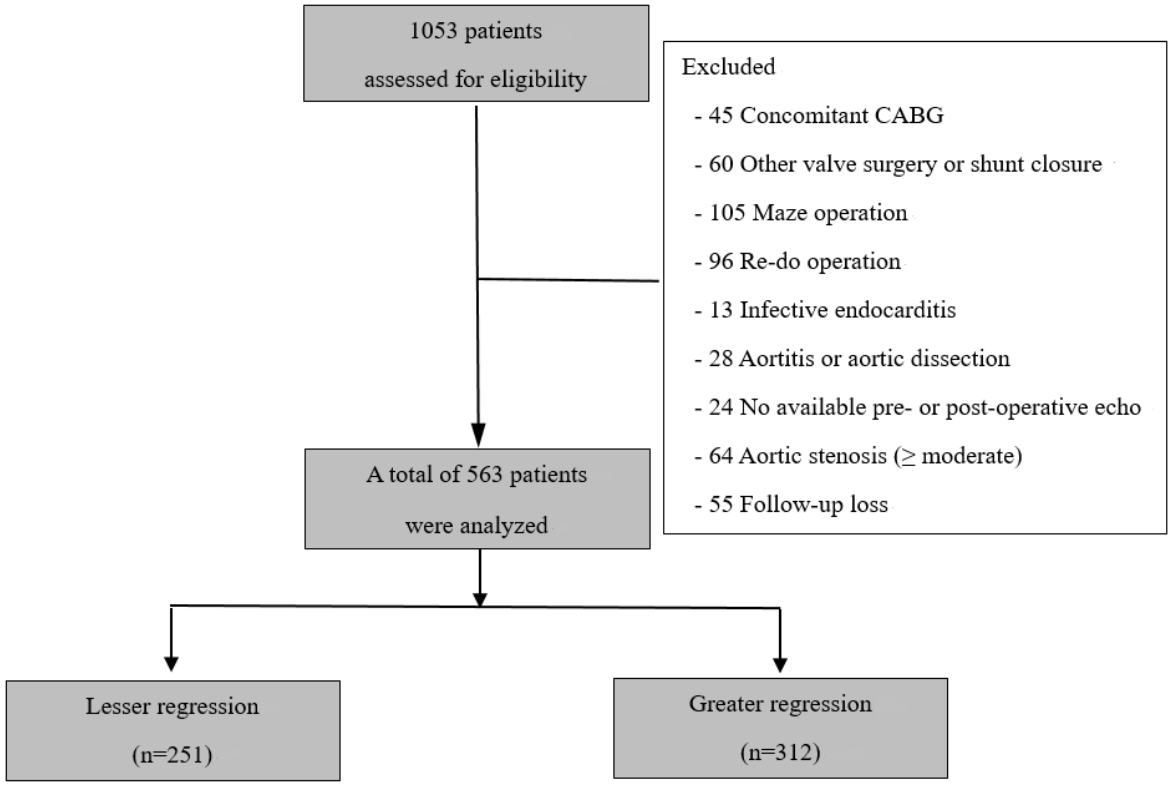
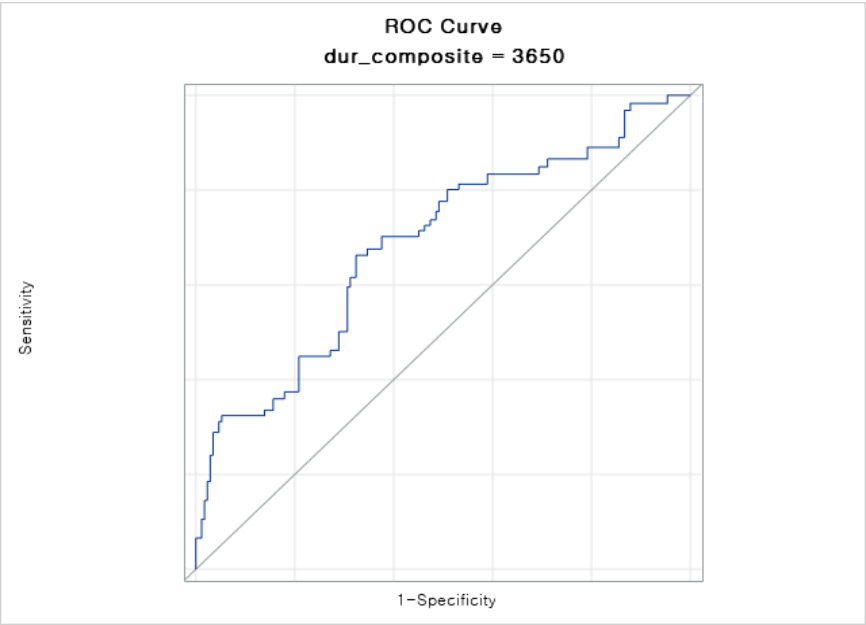



**Figure 2. Survival ROC curve**



### 3.2. Baseline characteristics

The baseline clinical characteristics of the enrolled patients are listed in Table 1. No significant differences were observed in baseline clinical characteristics between the two groups, except for the medical history of diabetes mellitus (DM). Of the patients, 447 underwent AV replacement whereas the remaining 137 underwent AV repair, which included those who underwent the David operation (valve-sparing aortic root replacement) and were included in the AV repair group. The type of surgery (AV replacement or repair), type of valve (mechanical or bioprosthetic valve), and valve size did not significantly differ between the groups.

**Table 1. Baseline clinical characteristics**

| | Overall (N = 563) | Lesser regression (N = 251) | Greater regression (N = 312) | p-value |
|---|---|---|---|---|
| **Preoperative factors** | | | | |
| Age, years | 54.9 ± 14.3 | 55.1 ± 13.7 | 54.7 ± 14.8 | 0.741 |
| Sex (%) | | | | 0.340 |
| Female | 169 (30) | 81 (32.3) | 88 (28.2) | |
| Male | 394 (70) | 170 (67.7) | 224 (71.8) | |
| BSA, $m^2$ | 1.7 ± 0.2 | 1.7 ± 0.2 | 1.7 ± 0.2 | 0.255 |
| Atrial fibrillation (%) | 11 (2.0) | 6 (2.4) | 5 (1.6) | 0.715 |
| Hypertension (%) | 256 (45.5) | 123 (49.0) | 133 (42.6) | 0.154 |
| Diabetes mellitus (%) | 33 (5.9) | 22 (8.5) | 11 (3.6) | 0.014 |
| CAD (%) | 13 (2.3) | 6 (2.4) | 7 (2.2) | > 0.999 |
| CKD (%) | 11 (2.0) | 7 (2.8) | 4 (1.3) | 0.328 |
| History of stroke (%) | 6 (1.1) | 3 (1.2) | 3 (1.0) | > 0.999 |
| Current smoker (%) | 67 (11.9) | 22 (8.8) | 45 (14.4) | 0.054 |
| NYHA 3/4 dyspnea (%) | 24 (4.3) | 9 (3.6) | 15 (4.8) | 0.430 |
| **Intraoperative factors** | | | | |
| AV replacement, n (%) | 446 (79.4) | 194 (77.6) | 252 (80.8) | 0.414 |
| Valve type, n (%) | | | | 0.240 |
| Mechanical | 312 (69.8) | 130 (66.7) | 182 (72.2) | |
| Bioprosthetic | 135 (30.2) | 65 (33.3) | 70 (27.8) | |
| Valve size, mm | 24.8 ± 2.6 | 24.5 ± 2.6 | 24.9 ± 2.6 | 0.109 |

Data are presented as the mean ± standard deviation, number (proportion).

Abbreviation: AV, aortic valve; BSA, body surface area; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease (Glomerular filtration rate <60mL/min/1.73$m^2$); NYHA, New York Heart Association

Echocardiographic data at baseline and 1 year postoperatively is presented in Table 2. In general, the greater regression group had a higher LVMi (158.2 ± 43.7 g/m² vs. 202.0 ± 50.2 g/m² in the lesser and greater regression groups, respectively; *p*-value < 0.001) and AV peak velocity (2.1 ± 0.6 m/s vs. 2.3 ± 0.6 m/s; $p < 0.001$) as well as larger LV chamber (LVIDd; 64.7 ± 8.0 mm vs. 69.8 ± 8.2 mm; $p < 0.001$). However, no significant difference was observed in LVEF (52.7 ± 11.2% vs. 51.8 ± 10.0%; $p = 0.317$) and LA dimension (40.8 ± 7.0 mm vs. 40.7 ± 7.2 mm; $p = 0.795$) between two groups.

Both groups exhibited improved echocardiographic parameters following AV surgery. The LVMi decreased from an average of 182.5 to 111.5 g/m$^2$, and the LVEF increased from an average of 52.2% to 57.5%. The greater regression group experienced a more significant change, despite starting with a larger LVMi and LV dimension. After surgery, the greater regression group exhibited smaller LVMi and LV dimension. Furthermore, while the baseline LVEF was similar between the groups (52.1% and 51.8% in the lesser and greater regression groups, $p = 0.317$), it was higher in the greater regression group following valve surgery (56.2% and 58.7% in the lesser and greater regression groups, $p < 0.001$).

**Table 2. Echocardiographic characteristics at baseline and 1 year after aortic valve surgery**

| | Overall (N = 563) | Lesser regression (N = 251) | Greater regression (N = 312) | p-value |
|---|---|---|---|---|
| **Baseline echocardiography** | | | | |
| LV mass index, $\mathbf{g/m^2}$ | 182.5 ± 52.2 | 158.2 ± 43.7 | 202.0 ± 50.2 | < 0.001 |
| LV ejection fraction, % | 52.2 ± 10.6 | 52.7 ± 11.2 | 51.8 ± 10.0 | 0.317 |
| LVIDs, mm | 47.6 ± 9.4 | 45.8 ± 9.6 | 49.0 ± 9.0 | < 0.001 |
| LVIDd, mm | 67.5 ± 8.5 | 64.7 ± 8.0 | 69.8 ± 8.2 | < 0.001 |
| LVPWs, mm | 15.0 ± 2.4 | 14.5 ± 2.3 | 15.4 ± 2.3 | < 0.001 |
| LVPWd, mm | 10.0 ± 1.8 | 9.7 ± 1.5 | 10.6 ± 1.9 | < 0.001 |
| LA dimension, mm | 40.7 ± 7.1 | 40.8 ± 7.0 | 40.7 ± 7.2 | 0.795 |
| E/e’ | 11.9 ± 5.7 | 12.2 ± 6.2 | 11.6 ± 5.4 | 0.212 |
| AV peak velocity, m/s | 2.2 ± 0.6 | 2.1 ± 0.6 | 2.3 ± 0.6 | < 0.001 |
| Pulmonary hypertension*, n (%) | 76 (13.5) | 38 (15.1) | 38 (12.2) | 0.369 |
| **1-year after aortic valve surgery** | | | | |
| Duration to f/u echo (days) | 327.6 ± 112.0 | 320.0 ± 109.6 | 333.8 ± 113.7 | 0.149 |
| LV mass index, $\mathbf{g/m^2}$ | 111.5 ± 31.6 | 122.7 ± 35.2 | 102.0 ± 24.4 | < 0.001 |
| LV ejection fraction, % | 57.5 ± 8.3 | 56.1 ± 9.9 | 58.7 ± 6.6 | < 0.001 |

| | | | | |
|---|---|---|---|---|
| LVIDs, mm | 34.1 ± 7.4 | 36.1 ± 8.6 | 32.5 ± 5.8 | < 0.001 |
| LVIDd, mm | 50.8 ± 6.5 | 53.1 ± 7.0 | 49.0 ± 5.4 | < 0.001 |
| LVPWs, mm | 15.2 ± 2.3 | 15.3 ± 2.4 | 15.0 ± 2.1 | 0.162 |
| LVPWd, mm | 10.0 ± 1.4 | 10.2 ± 1.4 | 9.9 ± 1.5 | < 0.001 |
| LA dimension, mm | 40.4 ± 21.7 | 41.2 ± 18.6 | 39.8 ± 23.9 | 0.457 |
| E/e’ | 11.2 ± 5.1 | 11.5 ± 5.4 | 10.9 ± 4.9 | 0.202 |

Data are presented as mean ± standard deviation

Abbreviation: IVSd, interventricular septum thickness (diastole); IVSs, interventricular septum thickness (systole); LV, left ventricle; LVIDd, LV internal dimension diastole; LVIDs, LV internal dimension systole; LVMi, LV mass index; LVPWd, LV posterior wall thickness (diastole); LVPWs, LV posterior wall thickness (systole)

* TR peak velocity ≥ 3.0m/s was considered as the presence of pulmonary hypertension[14].

### 3.3. Clinical outcomes

Detailed description of the primary outcome and its individual components are presented in Table 3. After AV surgery, the average follow-up period was 2768 days (IQR 2779, 1328–4107 days). During this period, there were 55 (10.1%) all-cause deaths and 32 (5.7%) rehospitalizations due to heart failure exacerbation. Of the 55 deaths, 33 were in the lesser regression group and 22 in the greater regression group (HR 0.41; 95% confidence interval [CI] 0.24–0.71; $p$ = 0.001). Similarly, there were 26 rehospitalizations in the lesser regression group and only 8 in the greater regression group (HR 0.23; 95% CI 0.10–0.50, $p < 0.001$). Overall, the primary outcome occurred inasmuch as 36% of the greater regression group in the lesser regression group. To further evaluate the effect of LVMi regression on the primary outcome and each composite of the outcome, Kaplan–Meier analysis was employed (Figure 3). Notably, a significant difference was observed in the primary outcome between the two groups ($p <$ 0.001).

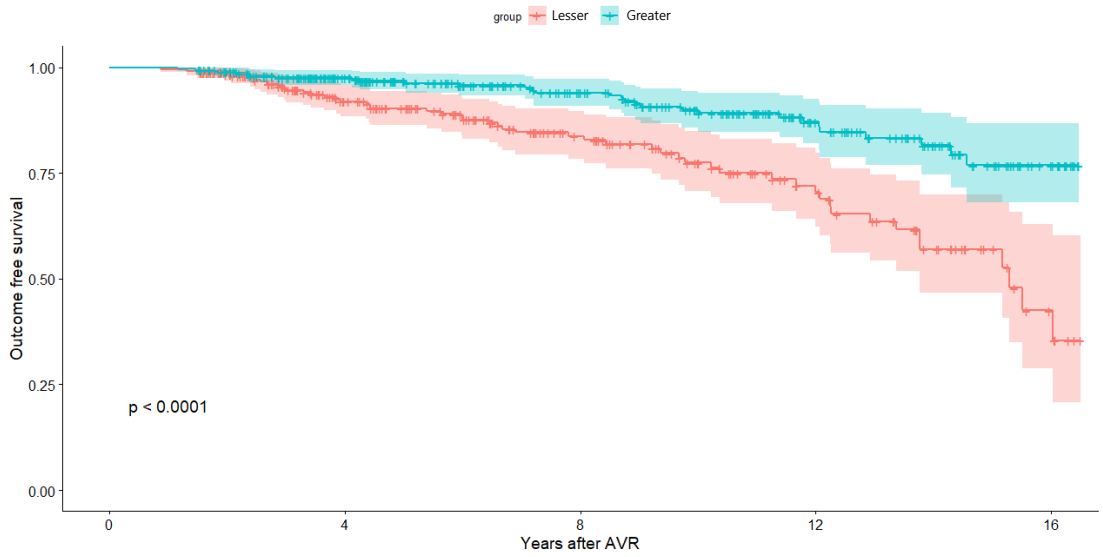
**Table 3. Primary and secondary endpoints**

| | **Overall (N = 563)** | **Lesser regression (N = 251)** | **Greater regression (N = 312)** | **Unadjusted HR** | **95% CI** | **p-value** |
|---|---|---|---|---|---|---|
| Primary composite outcome, n (%) | 80 (14.2) | 51 (20.4) | 29 (8.9) | 0.36 | 0.23-0.57 | < 0.001 |
| All-cause death | 55 (10.1) | 33 (13.1) | 22 (7.1) | 0.59 | 0.33 - 1.06 | 0.076 |
| Re-hospitalization | 32 (5.7) | 24 (9.6) | 8 (2.6) | 0.23 | 0.10-0.50 | < 0.001 |

Referent group: Lesser regression group, Data were shown as number (proportion)

Abbreviations: HR, Hazard ratio; CI, Confidence interval

**Figure 3. Kaplan-Meier curve for primary outcome**




The predictors of the primary outcome were investigated via univariate Cox proportional-hazards analysis (Table 4). LV mass regression, baseline LVID, LVEF, age, and certain patient histories, such as CAD and CKD, were all associated with better primary composite outcomes. Multivariate Cox proportional-hazards analysis was conducted on the related factors from the univariate analysis ($p \leq 0.05$). Among the parameters, age, combined CAD, baseline LVID (diastole), and LVEF were significantly associated with improved clinical results. LVRR, defined as LVMi regression, was also identified as an independent determinant of the primary outcome (HR 1.02; 95% CI 1.00–1.03; $p = 0.008$). Model 1 analyzed LV regression as a binary variable, divided into greater and lesser regression groups based on the cutoff value calculated in the time-dependent ROC analysis. In both univariate and multivariate analyses, the greater LV mass regression group showed a greater improvement in the primary outcome. Furthermore, age, CAD, baseline LVID (diastole), LVEF, and presence of pulmonary hypertension significantly affected the primary outcome.

**Table 4.** Association between the primary outcome and clinical characteristics, baseline echocardiographic parameter, and LVMi regression

**a. Model 1 (Binary variable)**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| LV mass index regression group | | | | | | |
| Lesser regression | Referent | | | Referent | | |
| Greater regression | 0.36 | 0.23 - 0.54 | <0.701 | 0.42 | 0.26 - 0.69 | <0.001 |
| | | | | | | |
| Age | 1.04 | 1.02 - 1.05 | <0.001 | 1.02 | 1.00 - 1.04 | 0.026 |
| Sex (Male) | 1.09 | 0.67 - 1.79 | 0.7 | | | |
| Atrial fibrillation | 3.23 | 1.31 - 8.00 | 0.011 | 1.21 | 0.43 - 3.44 | 0.7 |
| Hypertension | 1.05 | 0.68 - 1.64 | 0.8 | | | |
| Diabetes mellitus | 1.19 | 0.43 - 3.25 | 0.7 | | | |
| CAD | 4.24 | 1.54 - 11.7 | 0.005 | 4.11 | 1.43 - 11.8 | 0.009 |
| CKD | 9.89 | 4.21 - 23.2 | <0.001 | 2.23 | 0.75 – 6.61 | 0.15 |
| Stroke | 8.44 | 2.61 - 27.3 | <0.001 | 4.00 | 0.87 – 18.4 | 0.075 |
| Smoking | 0.61 | 0.29 - 1.27 | 0.2 | | | |
| Dyspnea | 1.10 | 0.88 – 1.37 | 0.4 | | | |
| | | | | | | |
| Baseline LVIDd | 0.96 | 0.94 - 0.99 | 0.009 | 0.96 | 0.92 - 0.99 | 0.020 |
| Baseline LVPWd | 1.07 | 0.95 - 1.20 | 0.3 | | | |
| Baseline LA | 1.04 | 1.01 - 1.07 | 0.019 | 1.01 | 0.98 - 1.04 | 0.5 |
| E/e’ | 1.05 | 1.02 -1.08 | <0.001 | 1.02 | 0.99 - 1.06 | 0.2 |
| Baseline LVMi | 1.00 | 0.99 - 1.00 | 0.5 | | | |
| Baseline LVEF | 0.98 | 0.96 - 1.00 | 0.038 | 0.97 | 0.95 - 1.00 | 0.029 |
| AV peak velocity | 0.81 | 0.56 - 1.18 | 0.3 | | | |
| Pulmonary HTN | 2.96 | 1.82 - 4.80 | <0.001 | 1.86 | 1.07 - 3.23 | 0.029 |

Abbreviation: HR, hazard ratio; IVSd, interventricular septum thickness (diastole); IVSs, interventricular septum thickness (systole); LA, left atrium; LV, left ventricle; LVIDd, LV internal dimension diastole; LVIDs, LV internal dimension systole; LVMi, LV mass index; LVPWd, LV posterior wall thickness (diastole); LVPWs, LV posterior wall thickness (systole); pulmonary HTN; pulmonary hypertension, meaning TR $V_{max}$≥ 3.0m/s

**b. Model 2 (Continuous variable)**

In Model 2, the regression for the LVMi was set as a continuous variable. Similarly, a decrease in LV mass index was included as an independent variable. Additionally, other significant factors identified in Model 1, such as coronary artery disease, LVIDd, and LVEF, were retained in the analysis as continuous variables.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| LVMi regression | 1.03 | 1.01 - 1.04 | <0.001 | 1.02 | 1.00 - 1.03 | 0.008 |
| Age | 1.04 | 1.02 - 1.05 | <0.001 | 1.02 | 1.00 - 1.04 | 0.039 |
| Sex (Male) | 1.09 | 0.67 - 1.79 | 0.7 | | | |
| BSA | 0.35 | 0.10 - 1.19 | 0.092 | 1.12 | 0.26 - 4.87 | 0.9 |
| Atrial fibrillation | 3.23 | 1.31 - 8.00 | 0.011 | 1.25 | 0.45 - 3.45 | 0.7 |
| Hypertension | 1.05 | 0.68 - 1.64 | 0.8 | | | |
| Diabetes mellitus | 1.19 | 0.43 - 3.25 | 0.7 | | | |
| CAD | 4.24 | 1.54 - 11.7 | 0.005 | 3.98 | 1.38 - 11.5 | 0.011 |
| CKD | 9.89 | 4.21 - 23.2 | <0.001 | 2.07 | 0.70 - 6.12 | 0.2 |
| Stroke | 8.44 | 2.61 - 27.3 | <0.001 | 4.49 | 1.04 - 19.5 | 0.045 |
| Smoking | 0.61 | 0.29 - 1.27 | 0.2 | | | |
| Dyspnea | 1.10 | 0.88 – 1.37 | 0.4 | | | |
| Baseline LVIDd | 0.96 | 0.94 - 0.99 | 0.009 | 0.96 | 0.92 - 1.00 | 0.035 |
| Baseline LVPWd | 1.07 | 0.95 - 1.20 | 0.3 | | | |
| Baseline LA | 1.04 | 1.01 - 1.07 | 0.019 | 1.01 | 0.97 - 1.04 | 0.7 |
| E/e’ | 1.05 | 1.02 -1.08 | <0.001 | 1.03 | 0.99 - 1.06 | 0.2 |
| Baseline LVMi | 1.00 | 0.99 - 1.00 | 0.5 | | | |
| Baseline LVEF | 0.98 | 0.96 - 1.00 | 0.038 | 0.97 | 0.95 - 1.00 | 0.041 |
| AV peak velocity | 0.81 | 0.56 - 1.18 | 0.3 | | | |
| Pulmonary HTN | 2.96 | 1.82 - 4.80 | <0.001 | 1.98 | 1.14 - 3.44 | 0.016 |

HR, hazard ratio; IVSd, interventricular septum thickness (diastole); IVSs, interventricular septum thickness (systole); LA, left atrium; LV, left ventricle; LVIDd, LV internal dimension diastole; LVIDs, LV internal dimension systole; LVMi, LV mass index; LVPWd, LV posterior wall thickness (diastole); LVPWs, LV posterior wall thickness (systole); pulmonary HTN, pulmonary hypertension, defined as TR peak velocity ≥ 3.0m/s

### 3.4. Secondary outcomes

The association between each component of the primary outcome, all-cause mortality and rehospitalization due to heart failure, and various explanatory factors is depicted in Tables 5 and 6. Univariate Cox proportional-hazards analysis revealed an association between LVMi regression and all-cause mortality. However, multivariate analysis showed that LV mass regression only exhibited a statistical tendency of association with all-cause mortality but that it was not statistically significant. Other clinical factors associated with all-cause mortality were age, CAD, and CKD. The baseline echocardiographic parameters that were correlated with all-cause mortality were LVIDd, LV ejection fraction, and pulmonary hypertension.

On the other hand, Table 6 shows that LVMi regression has a significant statistical correlation with the rate of rehospitalization in both models 1 and 2. Of the baseline echocardiographic parameters, only E/e', indicating diastolic function, was associated with the rate of rehospitalization (significant in model 1 and marginally significant with a *p*-value of 0.054 in model 2).

**Table 5. Relationship between all-cause death and clinical characteristics, baseline echocardiographic values, and LVMi regression**

**a. Model 1 (binary)**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| LV mass index regression group | | | | | | |
| Lesser regression | Referent | | | Referent | | |
| Greater regression | 0.44 | 0.25 - 0.75 | 0.003 | 0.59 | 0.33 - 1.06 | 0.076 |
| Age | 1.06 | 1.03 - 1.09 | < 0.001 | 1.04 | 1.02 -1.07 | 0.001 |
| Sex (Male) | 0.79 | 0.45 - 1.37 | 0.4 | | | |
| BSA | 0.10 | 0.02 - 0.45 | 0.003 | 0.61 | 0.10 - 3.58 | 0.6 |
| Atrial fibrillation | 4.76 | 1.89 - 12.0 | < 0.001 | 1.35 | 0.44 - 4.12 | 0.6 |
| Hypertension | 1.15 | 0.67 - 1.95 | 0.6 | | | |
| Diabetes mellitus | 1.35 | 0.42 - 4.33 | 0.6 | | | |
| CAD | 4.84 | 1.50 - 15.7 | 0.008 | 4.54 | 1.32 - 15.7 | 0.017 |
| CKD | 16.7 | 6.91 - 40.4 | <0.001 | 3.01 | 0.92 - 9.86 | 0.069 |
| Stroke | 13.9 | 4.21 - 16.0 | <0.001 | 4.46 | 0.84 - 23.8 | 0.080 |
| Smoking | 0.66 | 0.28 - 1.55 | 0.3 | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Dyspnea | 1.14 | 0.88 - 1.48 | 0.3 | | | |
| Baseline LVIDd | 0.95 | 0.92 - 0.98 | 0.003 | 0.93 | 0.89 - 0.98 | 0.005 |
| E/e’ | 1.07 | 1.03 - 1.10 | < 0.001 | 1.04 | 0.99 - 1.08 | 0.12 |
| Baseline LA | 1.05 | 1.01 - 1.08 | 0.010 | 1.02 | 0.98 - 1.06 | 0.3 |
| Baseline LVMi | 1.00 | 0.99 - 1.00 | 0.8 | | | |
| Baseline LVEF | 0.97 | 0.95 - 1.00 | 0.8 | 0.96 | 0.93 - 0.99 | 0.011 |
| AR peak velocity | 0.91 | 0.59 - 1.41 | 0.7 | | | |
| Pulmonary HTN | 3.88 | 2.22 - 6.76 | <0.001 | 2.10 | 1.10 - 4.00 | 0.024 |

Abbreviations: CI, confidence interval; HR, hazard ratio

**b. Model 2 (continuous variable)**

| | **Univariate analysis** | | | **Multivariate analysis** | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value |
| LVMi regression | 1.02 | 1.01 - 1.03 | 0.004 | 1.01 | 0.99 - 1.02 | 0.4 |
| Age | 1.06 | 1.03 - 1.09 | < 0.001 | 1.04 | 1.01 - 1.07 | 0.005 |
| Sex (Male) | 0.79 | 0.45 - 1.37 | 0.4 | | | |
| BSA | 0.10 | 0.02 - 0.45 | 0.003 | 0.63 | 0.11 - 3.78 | 0.6 |
| Atrial fibrillation | 4.76 | 1.89 - 12.0 | < 0.001 | 1.35 | 0.45 - 4.04 | 0.6 |
| Hypertension | 1.15 | 0.67 - 1.95 | 0.6 | | | |
| Diabetes mellitus | 1.35 | 0.42 - 4.33 | 0.6 | | | |
| CAD | 4.84 | 1.50 - 15.7 | 0.008 | 4.24 | 1.23 - 14.7 | 0.022 |
| CKD | 16.7 | 6.91 - 40.4 | < 0.001 | 3.14 | 0.93 - 10.6 | 0.064 |
| Stroke | 13.9 | 4.21 - 46.0 | < 0.001 | 4.68 | 0.91 - 24.0 | 0.064 |
| Smoking | 0.66 | 0.28 - 1.55 | 0.3 | | | |
| Dyspnea | 1.14 | 0.88 - 1.48 | 0.3 | | | |
| Baseline LVIDd | 0.95 | 0.92 - 0.98 | 0.003 | 0.93 | 0.88 - 0.98 | 0.004 |
| Baseline LVPW | 1.08 | 0.95 - 1.24 | 0.2 | | | |
| E/e’ | 1.07 | 1.03 - 1.10 | < 0.001 | 1.04 | 0.99 - 1.08 | 0.11 |
| Baseline LA | 1.05 | 1.01 - 1.08 | 0.010 | 1.02 | 0.98 - 1.06 | 0.3 |
| Baseline LVMi | 1.00 | 0.99 - 1.00 | 0.8 | | | |
| Baseline LVEF | 0.97 | 0.95 - 1.00 | 0.017 | 0.96 | 0.93 - 0.99 | 0.012 |
| AR peak velocity | 0.91 | 0.59 - 1.41 | 0.7 | | | |
| Pulmonary HTN | 3.88 | 2.22 - 6.76 | <0.001 | 2.14 | 1.13 - 4.08 | 0.020 |

**Table 6. Relationship between re-hospitalization and clinical characteristics, baseline echocardiographic values, and LVMi regression**

**a. Model 1 (binary)**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| LV mass index regression group | | | | | | |
| Lesser regression | Referent | | | | | |
| Greater regression | 0.17 | 0.07 - 0.40 | <0.001 | 0.18 | 0.07 - 0.43 | <0.001 |
| | | | | | | |
| Age | 0.99 | 0.97-1.02 | 0.5 | | | |
| Sex (Male) | 1.80 | 0.74 - 4.37 | 0.2 | | | |
| BSA | 3.14 | 0.48 - 20.5 | 0.2 | | | |
| Atrial fibrillation | 3.41 | 0.81 - 14.3 | 0.093 | 3.41 | 0.81 - 14.4 | 0.094 |
| Hypertension | 0.89 | 0.44 - 1.80 | 0.7 | | | |
| Diabetes mellitus | 0.65 | 0.09 - 4.76 | 0.7 | | | |
| CAD | 2.24 | 0.30 -16.5 | 0.4 | | | |
| CKD | 2.90 | 0.39 - 21.6 | 0.3 | | | |
| Stroke | 0.00 | 0.00 | > 0.9 | | | |
| Smoking | 0.39 | 0.09 - 1.65 | 0.2 | | | |
| Dyspnea | 1.13 | 0.79 - 1.62 | 0.5 | | | |
| | | | | | | |
| Baseline LVIDd | 0.99 | 0.95 - 1.04 | 0.8 | | | |
| E/e’ | 1.06 | 1.01 - 1.11 | 0.012 | 1.05 | 1.01 - 1.10 | 0.028 |
| Baseline LA | 1.02 | 0.98 - 1.07 | 0.3 | | | |
| Baseline LVMi | 1.00 | 0.99 - 1.01 | 0.8 | | | |
| Baseline LVEF | 0.98 | 0.95 - 1.01 | 0.2 | | | |
| AR peak velocity | 0.77 | 0.42 – 1.40 | 0.4 | | | |
| Pulmonary HTN | 2.01 | 0.87 - 1.03 | 0.2 | | | |

**b. Model 2 (continuous variable)**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| LVMi regression | 1.04 | 1.02 – 1.05 | < 0.001 | 1.03 | 1.02 - 1.05 | <0.001 |
| Age | 0.99 | 0.97-1.02 | 0.5 | | | |
| Sex (Male) | 1.80 | 0.74 – 4.37 | 0.2 | | | |
| Atrial fibrillation | 3.41 | 0.81 – 14.3 | 0.093 | 3.15 | 0.75 - 13.3 | 0.12 |
| Hypertension | 0.89 | 0.44 – 1.80 | 0.7 | | | |
| Diabetes mellitus | 0.65 | 0.09 – 4.76 | 0.7 | | | |
| CAD | 2.24 | 0.30 -16.5 | 0.4 | | | |
| CKD | 2.90 | 0.39 – 21.6 | 0.3 | | | |
| Stroke | 0.00 | 0.00 | > 0.9 | | | |
| Smoking | 0.39 | 0.09 – 1.65 | 0.2 | | | |
| Dyspnea | 1.13 | 0.79 – 1.62 | 0.5 | | | |
| Baseline LVIDd | 0.99 | 0.95 - 1.04 | 0.8 | | | |
| E/e’ | 1.06 | 1.01 - 1.11 | 0.012 | 1.04 | 1.00 - 1.09 | 0.054 |
| Baseline LA | 1.02 | 0.98 - 1.07 | 0.3 | | | |
| Baseline LVMi | 1.00 | 0.99 - 1.01 | 0.8 | | | |
| Baseline LVEF | 0.98 | 0.95 - 1.01 | 0.2 | | | |
| AR peak velocity | 0.77 | 0.42 – 1.40 | 0.4 | | | |
| Pulmonary HTN | 2.01 | 0.87 - 4.66 | 0.10 | | | |

### 3.5. Determining factors for LVMi regression

Clinical characteristics and preoperative echocardiographic parameters for identifying the key factors contributing to LV mass regression are presented in Table 7. Of the examined clinical characteristics, hypertension emerged as the sole predictive factor (odds ratio [OR] 0.65; 95% CI 0.44–0.96; $p = 0.0306$). As for preoperative echocardiographic parameters, LA diameter (OR 0.95; CI 0.93–0.98; $p = 0.0025$), baseline LVMi (OR 1.03; CI 1.00–1.05; $p < 0.001$), LVEF (OR 1.03; CI 1.02–1.03; $p = 0.0149$), and AV peak velocity (OR 1.41; CI 1.02–1.95; $p = 0.0358$) were independently associated with greater LV mass regression.

**Table 7. Possible determining factors for LV mass index regression**

| | Coefficient | SE | Pr(>\|z\|) | Multivariate analysis (stepwise selection) | | |
|---|---|---|---|---|---|---|
| | | | | OR | Confidence interval | p-value |
| Age | 0.012003 | 0.008104 | 0.13855 | | | |
| Sex (Male) | -0.314968 | 0.263857 | 0.23259 | | | |
| Atrial fibrillation | -0.294359 | 0.691450 | 0.67032 | | | |
| HTN | -0.471979 | 0.212025 | 0.02601 | 0.65 | 0.44-0.96 | 0.0306 |
| DM | -0.544160 | 0.441308 | 0.21755 | | | |
| CAD | 0.440352 | 0.609302 | 0.46985 | | | |
| CKD | -0.711532 | 0.808569 | 0.37887 | | | |
| Stroke | 0.212366 | 1.193298 | 0.85875 | | | |
| Smoking | 0.447542 | 0.0337842 | 0.18527 | | | |
| Dyspnea | -0.067992 | 0.133110 | 0.60949 | | | |
| | | | | | | |
| LVIDd | 0.023731 | 0.024992 | 0.34234 | | | |
| LVPWd | -0.014814 | 0.093762 | 0.87446 | | | |
| E/e’ | -0.017878 | 0.019347 | 0.35545 | | | |
| LA | -0.040995 | 0.016092 | 0.01085 | 0.95 | 0.93-0.98 | 0.0025 |
| LV ejection fraction | 0.025853 | 0.011856 | 0.02922 | 1.03 | 1.00-1.05 | 0.0149 |
| Baseline LVMi | 0.024320 | 0.004950 | 8.94e-07 | 1.03 | 1.02-1.03 | <0.001 |
| AV peak velocity | 0.327954 | 0.171330 | 0.05560 | 1.41 | 1.02-1.95 | 0.0358 |
| Pulmonary HTN | -0.119996 | 0.315611 | 0.70379 | | | |

Logistic regression was done to illustrate predictive factors of LV mass index regression.

Abbreviations: SE, Standard error; OR, Odds ratio; CAD, coronary artery disease; CKD, chronic kidney disease; LVIDd, LV internal dimension diastole; LVPWd, LV posterior wall thickness (diastole); LA, Left atrium; LVMi, left ventricular mass index; HTN, hypertension.

## 4. Discussion

Our study demonstrated a strong association between LVRR following surgery and improved clinical outcomes in patients with chronic AR who underwent AV surgery. In particular, those who experienced greater LVMi regression 1 year following AV surgery had lower rates of hospitalization due to heart failure and a composite of all-cause mortality and rehospitalization. Independent factors contributing to LVMi regression were the presence of hypertension, baseline LA diameter, LVEF, AV peak velocity, and baseline LVMi.

### 4.1. Preceding studies about LV reverse remodeling after aortic valve surgery

Previous studies have demonstrated that AV replacement is the most effective approach to improving survival in patients suffering from severe symptomatic AR [15-17]. However, for high-risk patients who cannot tolerate surgery, deciding to perform AV surgery is challenging. Therefore, in addition to established guidelines, this study focused on factors predicting postoperative outcomes. Recent studies have figured out that a larger preoperative LVMi is a strong predictor of outcomes following AV replacement in patients with AS and AR [17-19]. This may be because LV hypertrophy, measured by the LVMi, reflects the degree of LV remodeling resulting from pressure overload [8, 20, 21]. We hypothesized that the new LVRR, defined by changes in LVMi, could potentially serve as an indicator of postoperative outcome.

A recent study analyzed the impact of aortic valve replacement (AVR) on LV mass regression and LV global longitudinal strain in 211 patients diagnosed with severe AS and AR who exhibited varying degrees of LV remodeling (mainly due to pressure versus volume overload) [8]. The study found that patients with AR experienced a more significant decrease in LV mass regression than those with AS after the relief of volume overload. However, LVMi regression occurred at a slower rate in patients with AR than in those with AS. Notably, the study did not directly assess the association between these findings and the patients' prognoses. Furthermore, the study only included 79 patients with AR, thus limiting its generalizability. To address these limitations, we focused on LV mass regression as a measure of LVRR and examined its association with the clinical outcomes.

Koga-Ikuta et al. discovered that patients who underwent LVRR 1 year after AVR had significantly improved long-term outcomes, with LVEF and LVEDD being crucial predictors of long-term major adverse cardiovascular events (MACEs) [4]. Our own research corroborated their findings, as we also found that LVRR, measured by LVMi regression at 1 year postoperatively, was a significant determinant

of late clinical outcome. However, the definitions of LVRR between studies were different. While Koga-Ikuta et al. defined it as a binary factor based on postoperative LVEF and LVESDi values, we aimed to view it as both a continuous and binary variable as measured by LV mass regression.

### 4.2. LVMi regression

Patients who exhibited greater LVMi regression had a lower incidence of the primary outcome, which is a composite of all-cause mortality and rehospitalization due to heart failure. When the outcomes were separately analyzed, a consistent association between LV mass regression and rehospitalization rate was observed whereas the association with all-cause mortality showed only a tendency. These findings are consistent with those of previous studies showing that improvements in LVEF and LV size reduction following AVR were beneficial in reducing the incidence of adverse cardiovascular events and improving long-term clinical outcomes in patients with chronic AS and AR [4]. Regardless of the method employed to define LVRR, it is evident that such reverse remodeling is associated with improved clinical outcomes.

Improved prognosis associated with greater LV mass regression may be attributed to myocardial fibrosis. Chronic AR can lead to progressive volume and pressure overload in the LV, even if LVEF is preserved and patients are asymptomatic. Recent studies have used diagnostic tools such as global longitudinal strain to demonstrate LV pressure and volume overload in patients with AV disease [22, 23]. This process is associated with myocardial fibrosis through myocardial apoptosis [24], which can vary depending on factors such as age, sex, and underlying medical conditions. The fibrotic changes that occur in the left ventricle with chronic AR are thought to contribute to lesser LV mass regression following AV surgery and a higher rate of rehospitalization due to heart failure. LV hypertrophy is the most prevalent myocardial structural abnormality that is associated with heart failure with preserved EF.

The study found that LV mass regression is effective in improving the primary outcome, particularly on readmission due to heart failure. The association between LV mass regression and primary outcome was largely influenced by the rate of readmission due to heart failure, suggesting that LVMi regression is more focused on heart-related issues. Previous studies have established an association between LV mass regression and MACEs. Unfortunately, our study did not obtain cardiovascular mortality data, but further analysis of cardiac mortality could help compensate for the lack of association with all-cause mortality.

### 4.3. Determining factors for LV reverse remodeling

As demonstrated in Table 7, patients with hypertension had less LVRR. The study also showed that greater LVRR was associated with smaller LA, higher EF, baseline LVMi, and AV peak velocity, although the table only showed a significant difference in the prevalence of DM between the lesser and greater LVMi regression groups. Both diabetes and hypertension can lead to myocardial damage and fibrotic changes, resulting in stiffened hearts and smaller LVMi regression. The increase in LA size is a hallmark of the structural remodeling process, which is associated with diastolic dysfunction, LV hypertrophy, and systemic hypertension [25, 26]. Furthermore, patients with diabetes and hypertension are likely to experience diastolic dysfunction. This finding is reinforced by the correlation between the E/e' ratio and the outcome in our study.

The independent predictive parameter of greater LVMi regression was identified as baseline LVEF. Impaired LVEF can be associated with myocardial damage and fibrotic changes, which can hinder LV hypertrophy regression. This study also established that trans-aortic AV peak velocity is a predictive factor for greater LVRR, although patients with significant aortic stenosis were excluded from the analysis. A higher AV peak velocity may indicate pressure overload, which can lead to adaptive compensatory LV hypertrophy and an increase in baseline LVMi [27].

### 4.4. Limitations

This study has a few limitations. First, due to the retrospective nature of the data, it was difficult to determine the extent to which all-cause mortality was caused by cardiovascular reasons. Furthermore, an evaluation of heart failure medication was lacking. The study demonstrated that guideline-based medical therapy, which includes ACE inhibitors, ARBs, and sacubitril–valsartan, improved the survival of patients with heart failure; therefore, there is a possibility of unforeseen confounding variables [18]. Lastly, as we only enrolled patients who underwent follow-up echocardiography 1 year after surgery, patients who died within a year were excluded. It is possible that this also acted as a bias. Despite these limitations, the study enrolled a significant number of patients with severe AR before and after AVR, suggesting that LVRR can have a long-term effect on patients' quality of life. This study is also one of the few investigations that followed up AR patients for an extended period.

## 5. Conclusion

This study investigated the impact of LVRR on clinical outcomes in patients with severe AR who underwent AV surgery. Our findings indicated that patients who had greater LVRR, as measured by LVMi regression, were less likely to be readmitted due to heart failure exacerbation, suggesting a more positive prognosis. The study also found that hypertension was a risk factor for reduced LVRR, whereas baseline LVMi, EF, and trans-aortic peak velocity were crucial in LVMi regression.

**List of abbreviations**

| | |
|---|---|
| AR | Aortic regurgitation |
| ASE | American Society of Echocardiography |
| AV | Aortic valve |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| DM | Diabetes mellitus |
| HR | Hazard ratios |
| LA | Left atrial |
| LV | Left ventricular |
| LVEF | LV ejection fraction |
| LVRR | LV reverse remodeling |
| MACE | Major adverse cardiovascular events |
| ROC | Receiver-operating characteristic |

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## Abstract

**Background:** Severe aortic regurgitation (AR) leads to progressive left ventricular (LV) remodeling due to volume overload. LV reverse remodeling (LVRR), which is associated with improved clinical outcomes in chronic AR patients, usually occurs following aortic valve (AV) surgery. However, a considerable heterogeneity exists in the definition of LVRR; thus, it is important to consider LV mass and its regression when dealing with AR as it causes both pressure and volume overload, unlike chronic mitral regurgitation. This study aimed to investigate the impact of LVRR, as defined by LV mass regression, on the long-term clinical outcomes of patients with severe AR undergoing AV surgery. It also explored the determining factors of LV mass regression following AV surgery.

**Methods:** This retrospective study included patients who underwent AV surgery at the Asan Medical Center, Seoul, Republic of Korea, from 2006 to 2020 due to severe AR. The primary outcome was a composite of all-cause mortality and rehospitalization due to heart failure, whereas the secondary outcomes were the individual components of the primary outcome. LVRR was defined as the degree of LV mass index regression in 1-year follow-up echocardiography following AV surgery compared with the baseline image. The patients were divided into two groups, namely, greater regression and lesser regression groups, based on the cutoff value calculated via time-dependent receiver-operating characteristic curve analysis. The effect of LVRR on outcomes was then analyzed.

**Findings:** Of the 563 patients, 302 were allocated into the greater reverse remodeling group and 259 into the lesser reverse remodeling group. The average duration of follow-up after surgery was 2768 days, with an interquartile range of 1328–4107 days. During the follow-up period, 55 (10.1%) patients died whereas 32 (5.7%) were readmitted due to heart failure. The primary outcome was observed in 29 (9.3%) patients in the greater regression group and 51 (20.1%) in the lesser regression group. Multiple Cox regression analysis revealed that the greater regression group had a lower risk of all-cause mortality and readmission due to heart failure (adjusted hazard ratio, 0.42; 95% confidence interval, 0.26 - 0.69, $p < 0.001$). This result remained consistent even when the LV mass index change was considered a continuous variable. The study identified hypertension as the sole clinical predictive factor and left atrial diameter, baseline LV mass index (LVMi), LV ejection fraction, and AV peak velocity as independent echocardiographic predictors of LVMi regression.

**Conclusion:** Patients who exhibited greater LVRR, as determined by LVMi regression, had a lower likelihood of readmission due to heart failure exacerbation, suggesting a more favorable prognosis.

Furthermore, hypertension posed a risk for reduced LVRR, whereas baseline LVMi, EF, and trans-aortic peak velocity played a crucial role in LV mass index reduction.

## 8. Supplementary Data

**Supplementary table 1. Summary of time-dependent ROC analysis**

| LVMi regression | Specificity | Sensitivity | youden index = specificity + sensitivity |
|---|---|---|---|
| 60 | 0.57803 | 0.70174 | 0.27977 |
| 60.0174216 | 0.57803 | 0.70174 | 0.27977 |
| 60.10971787 | 0.57803 | 0.70174 | 0.27977 |
| 60.12931034 | 0.57803 | 0.70174 | 0.27977 |
| 60.23029229 | 0.57803 | 0.70174 | 0.27977 |
| 60.4747162 | 0.57803 | 0.70174 | 0.27977 |
| 60.48144433 | 0.57803 | 0.70174 | 0.27977 |
| 60.48239848 | 0.57803 | 0.70174 | 0.27977 |
| 60.53128314 | 0.58382 | 0.70174 | 0.28556 |
| 60.60126582 | 0.58382 | 0.70174 | 0.28556 |
| 60.64120055 | 0.58382 | 0.70174 | 0.28556 |
| 60.67278287 | 0.58382 | 0.70174 | 0.28556 |
| 60.68414038 | 0.5896 | 0.70174 | 0.29134 |
| 60.74821319 | 0.59538 | 0.70174 | 0.29712 |
| 60.89219331 | 0.59538 | 0.70174 | 0.29712 |
| 60.89703095 | 0.60116 | 0.70174 | 0.3029 |
| 60.89778259 | 0.60116 | 0.70174 | 0.3029 |
| 60.90838323 | 0.60694 | 0.70174 | 0.30868 |
| 60.98489796 | 0.61272 | 0.70174 | 0.31446 |
| 61.3903241 | 0.61272 | 0.70174 | 0.31446 |
| 61.41030608 | 0.6185 | 0.70174 | 0.32024 |
| 61.47947677 | 0.62428 | 0.70174 | 0.32602 |
| 61.51133501 | 0.62428 | 0.67559 | 0.29987 |
| 61.62695152 | 0.62428 | 0.67559 | 0.29987 |
| 61.67146974 | 0.63006 | 0.67559 | 0.30565 |
| 61.70906719 | 0.63006 | 0.67559 | 0.30565 |
| 61.82158453 | 0.63006 | 0.67559 | 0.30565 |
| 61.82846371 | 0.63006 | 0.67559 | 0.30565 |
| 62.18535469 | 0.63006 | 0.67559 | 0.30565 |
| 62.22080408 | 0.63584 | 0.67559 | 0.31143 |
| 62.25511537 | 0.63584 | 0.67559 | 0.31143 |
| 62.25959437 | 0.64162 | 0.67559 | 0.31721 |
| 62.30031949 | 0.6474 | 0.67559 | 0.32299 |
| 62.49073388 | 0.6474 | 0.67559 | 0.32299 |
| 62.53357207 | 0.6474 | 0.67559 | 0.32299 |

| | | | |
|---|---|---|---|
| 62.58278146 | 0.6474 | 0.67559 | 0.32299 |
| 62.65292981 | 0.6474 | 0.67559 | 0.32299 |
| 62.73525721 | 0.6474 | 0.67559 | 0.32299 |
| 62.75277234 | 0.6474 | 0.67559 | 0.32299 |
| 62.81725888 | 0.6474 | 0.67559 | 0.32299 |
| 62.92090838 | 0.6474 | 0.67559 | 0.32299 |
| 62.92495189 | 0.6474 | 0.67559 | 0.32299 |
| 62.95856626 | 0.65318 | 0.67559 | 0.32877 |
| 62.99831555 | 0.65318 | 0.66254 | 0.31572 |
| 63.04700162 | 0.65896 | 0.66254 | 0.3215 |
| 63.23987539 | 0.65896 | 0.66254 | 0.3215 |
| 63.25407699 | 0.66474 | 0.66254 | 0.32728 |
| 63.29830234 | 0.67052 | 0.66254 | 0.33306 |
| 63.36415676 | 0.67052 | 0.66254 | 0.33306 |
| 63.38582677 | 0.67052 | 0.66254 | 0.33306 |
| 63.38962606 | 0.67052 | 0.66254 | 0.33306 |
| 63.5186823 | 0.6763 | 0.66254 | 0.33884 |
| 63.52530541 | 0.6763 | 0.66254 | 0.33884 |
| 63.64892882 | 0.6763 | 0.66254 | 0.33884 |
| 63.77816291 | 0.6763 | 0.64633 | 0.32263 |
| 63.79310345 | 0.6763 | 0.62941 | 0.30571 |
| 63.82575758 | 0.6763 | 0.62941 | 0.30571 |
| 63.83169203 | 0.6763 | 0.61569 | 0.29199 |
| 63.83412644 | 0.6763 | 0.61569 | 0.29199 |
| 63.90306122 | 0.68208 | 0.61569 | 0.29777 |
| 63.90428212 | 0.68786 | 0.61569 | 0.30355 |
| 64 | 0.68786 | 0.61569 | 0.30355 |
| 64.15489273 | 0.68786 | 0.61569 | 0.30355 |
| 64.15929204 | 0.68786 | 0.61569 | 0.30355 |
| 64.28155905 | 0.68786 | 0.59539 | 0.28325 |
| 64.32403433 | 0.68786 | 0.59539 | 0.28325 |
| 64.35675329 | 0.69364 | 0.59539 | 0.28903 |
| 64.36583261 | 0.69364 | 0.58434 | 0.27798 |
| 64.44141689 | 0.69364 | 0.56862 | 0.26226 |
| 64.49814126 | 0.69364 | 0.55079 | 0.24443 |
| 64.4993498 | 0.69364 | 0.53973 | 0.23337 |