# Predictors of Long-Term Outcome of Isolated Surgical Aortic Valve Replacement in Aortic Regurgitation With Reduced Left Ventricular Ejection Fraction and Extreme Left Ventricular Dilatation

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**The management of severe aortic regurgitation (AR) in patients with reduced left ventricular function and extreme left ventricular dilatation presents a therapeutic dilemma. This study aims to assess risk factors of aortic valve replacement (AVR) for these particular population based on its performances. Two hundred twelve severe AR patients accompanied by left ventricular ejection fraction (LVEF) <50% and left ventricular end-diastolic dimension (LVEDD) ≥70 mm who underwent isolated AVR between January 2007 and December 2016 were identified retrospectively. Logistic regression and receiver operating characteristic were used to analyze prognostic indicators for in-hospital mortality while Kaplan−Meier analysis for long-term survival. Mean age was 56 ± 13 years with mean LVEF 40 ± 7% and LVEDD 78 ± 6 mm. In-hospital mortality rate was 7%, and survival rates at 5 and 10 years were 88 ± 4% and 73 ± 10%, respectively. Logistic regression analysis indicated in-hospital mortality was associated with preoperative age and LVEF. Receiver operating characteristic analysis showed LVEF = 35% was the best cut-off value at which to predict in-hospital death. Kaplan−Meier analysis revealed patients with markedly reduced LV function (LVEF <35%) had lower survival rates compared with other patients with moderate LV dysfunction (LVEF 36% to 50%) (1-, 5-, and 10-year: 90 ± 4%, 64 ± 7%, and 55 ± 14%, vs 97 ± 1%, 94 ± 3%, and 76 ± 7%, p <0.001). An age-matched analysis showed similar trend (p = 0.020). In Conclusion, AVR may be unsafe for severe AR patients with markedly reduced LV function (LVEF <35%) and extreme left ventricular dilatation (LVEDD >70 mm) due to poor postoperative early- and long-term outcomes.**  **(Am J Cardiol 2020;125:1385−1390)**

Management of severe aortic regurgitation (AR) in patients with reduced left ventricular function and extreme left ventricular dilatation presents a therapeutic dilemma.[1] Current American College of Cardiology/American Heart Association guideline and European Society of Cardiology/European Association of Cardiac and Thoracic Surgery guidelines recommend surgical intervention in severe AR patients with left ventricular ejection fraction (LVEF) of less than 50% as class I level.[2,3] However, earlier studies have shown clear association between the lower preoperative LVEF and reduced rates of postoperative survival in severe AR patients.[1,4,5−14] How to identify a high-risk group in the setting of severe AR is unclear, and the very definition of thresholds for defining marked reduction of LV function is controversial. The aim of our study was to assess the postoperative outcomes of patients with severe AR, reduced left ventricular function, and extreme left ventricular dilatation after AVR and identify prognostic indicators in such patients undergoing AVR.

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## Methods

The protocol of this study was approved by the Ethical Committee of Tongji Medical College affiliated with Huazhong University of Science and Technology. The methods used were in accordance with the approved guidelines, and informed consent was provided by each subject.

This retrospective cohort study reviewed 212 consecutive patients with severe AR whose LVEF was <50% and left ventricular end-diastolic dimension (LVEDD) was ≥70 mm and who underwent isolated AVR between January 2007 and December 2016 at the Department of Cardiovascular Surgery of Wuhan Union Hospital, China. All the patients enrolled were diagnosed to have severe AR (grade 3 or 4) by

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transthoracic echocardiographic. Initially, we retrieved 3,413 consecutive patients who underwent AVR from our database. Of these, 836 patients underwent AVR and had LVEF <50% and LVEDD ≥70 mm. We excluded 67 patients who had moderate or greater aortic stenosis, 521 patients who had concomitant coronary artery bypass grafting or mitral valve surgery or aortic root surgery and treatment of congenital heart disease 19 patients with previous surgery history and 17 patients with acute AR, including aortic dissections or infective endocarditis (Figure 1).

Preoperative clinical characteristics, operation variables, and postoperative in-hospital mortality were acquired from the medical records. Patients were followed up by telephone interview and clinical re-examination. Completeness of follow-up was 95%, with 10 patients lost connection after hospital discharge. The median follow-up time of this cohort is 59 months (mean: 60 ± 31 months). The major outcome measures were in-hospital mortality and long-term survival.

The Statistical Package for Social Sciences, version 19.0 and GraphPad Prism 6 were used for data storage and analysis, with $p$ <0.05 as the criterion for significance. Continuous variables are reported as the mean± standard deviation and categorical variables as percentages. Continuous variables were compared using Student's $t$ tests or Manne-Whitney U test, and categorical variables were compared using Fisher's exact tests. Binomial logistic regression analysis was used to determine the independent factors associated with postoperative death. The odds ratios with 95% confidence intervals were calculated. The receiver operating characteristic (ROC) curve analysis was adopted to evaluate cut-off values of independent continuous variables for predicting in-hospital mortality by calculating the area under the ROC. The cut-off values of LVEF were calculated corresponding to the maximum area under the ROC. The Youden index was used to identify the best cut-off value (J = sensitivity + specificity − 1). Kaplan-Meier analysis was used to determine the survival rate, and the difference between the overall group and age-matched group were analyzed using the log-rank test. The individual matching method was adopted to achieve age-matched group.

## Results

The overall cohort consisted of 212 severe AR patients with LVEF <50%, and LVEDD ≥70 mm. The mean age was 56 ± 13 years, and 61% were male. The mean LVEF was 40 ± 7% and the mean LVEDD was 78 ± 6 mm, respectively. Preoperative characteristics are summarized in Table 1.

Fifteen patients died during hospitalization (7%). The cause of death included low cardiac output syndrome (5 patients), malignant arrhythmia (2), or multiple organ failure (8). Logistic regression analyses were used to identify potential risk factors associated with postoperative death and we found age and preoperative LVEF were associated with increased risk of in-hospital mortality (Table 2). ROC curves showed best cut-off value for predicting in-hospital mortality after AVR for patients with severe AR, reduced left ventricular function, and left ventricular dilatation was preoperative LVEF = 35% (Figure 2).

Among the discharged patients, 187 patients were followed up. During the follow-up period, 26 patients died of various causes, including 15 congestive heart failure, 4 sudden cardiac death, 2 infective endocarditis, 2 intracerebral hemorrhage, and 3 other reasons. The overall survival rate was 95 ± 2% at 1 year, 85 ± 5% at 5 years, and 70 ± 10% at 10 years (Figure 3). Patients were stratified into two groups: severe LV dysfunction group (LVEF <35%) and moderate LV dysfunction group (35 ≤ LVEF <50%) (Table 3). In moderate LV dysfunction group, the 1-, 5-, and 10-year survival estimates were 97 ± 1%, 94 ± 3%, and 76 ± 7%, respectively; while they were 89 ± 4%, 64 ± 7%, and 55 ± 14%, in severe LV dysfunction group ($p$ < 0.001) (Figure 4). Additionally, after matching age, patients with LVEF ≤35% still performed

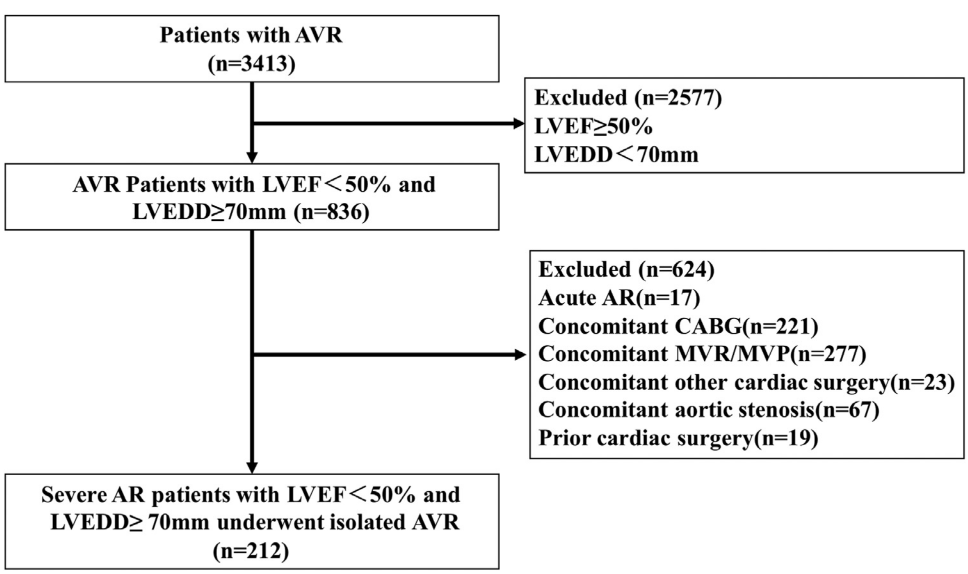



Figure 1. Selection of study cohort. AR: aortic regurgitation; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; MVP = mitral valve repair; MVR = mitral valve replacement.

Table 1
Preoperative and operative characteristics of overall cohort (n = 212)

| Variables | Overall cohort |
|---|---|
| Age (years) | 56 ± 13 |
| Men | 130(61%) |
| Hypertension | 40(19%) |
| Diabetes mellitus | 15(7%) |
| Chronic hepatic dysfunction | 18(9%) |
| Renal insufficiency | 10(5%) |
| Chronic obstructive pulmonary disease | 31(15%) |
| Atrial fibrillation | 28(13%) |
| Previous stroke | 6(3%) |
| NYHA class III−IV | 52(24%) |
| Bicuspid aortic valve | 28(13%) |
| Left ventricular ejection fraction (%) | 40 ± 7 |
| Left ventricular fractional shortening (%) | 20 ± 4 |
| Left ventricular end-diastolic dimension (mm) | 78 ± 6 |
| Left ventricular end-systolic dimension (mm) | 40 ± 5 |
| Left atrial diameter (mm) | 46 ± 7 |
| Interventricular septal thickness (mm) | 11 ± 1 |
| Posterior wall thickness (mm) | 10 ± 2 |
| Aortic root diameter (mm) | 44 ± 4 |
| Mechanical/Bioprosthetic valve | 171(81%)/41(19%) |
| Perfusion time (minutes) | 90 ± 36 |
| Cross-clamp time (minutes) | 52 ± 22 |
| Mechanical ventilation time (hours) | 49 ± 19 |
| In-hospital mortality | 15(7%) |
| Follow-up mortality | 26(13%) |

significantly worse in their short or long-term postoperative survival (p = 0.020) (Figure 5) (Table 3).

## Discussion

This is the first study to systematically analyze and follow-up the cohort of severe AR patients with reduced LV function (LVEF <50%) and extreme left ventricular dilatation (LVEDD >70 mm). The main finding of this study is that AVR may be an unsafe option for severe AR patients with LVEF <35% and LVEDD >70 mm, which could lead to poor postoperative in-hospital and long-term outcomes.

Table 2
Logistic regression analyses for predicting in-hospital mortality after aortic valve surgery in patients with severe aortic regurgitation, LVEF <50%, and LVEDD ≥70 mm

| Variables | OR (95% CI) | p Value |
|---|---|---|
| Age (years) | 1.612(1.414-1.837) | 0.030 |
| Men | 1.864(0.936-3.713) | 0.147 |
| Hypertension | 1.030(1.001-1.060) | 0.818 |
| Diabetes mellitus | 1.079(1.029-1.131) | 0.597 |
| Chronic hepatic dysfunction | 3.474(0.742-16.25) | 0.110 |
| Renal insufficiency | 1.505(0.228-9.934) | 0.519 |
| Chronic obstructive pulmonary disease | 1.929(0.415-8.953) | 0.319 |
| Atrial fibrillation | 3.122(0.669-14.58) | 0.137 |
| NYHA Classes III and IV | 3.362(0.630-17.94) | 0.135 |
| Left ventricular ejection fraction (%) | 0.783(0.566-0.912) | <0.001 |
| Left ventricular fractional shortening (%) | 0.816(0.779-1.322) | 0.152 |
| Left ventricular end-diastolic dimension (mm) | 2.105(0.774-4.123) | 0.129 |
| Left ventricular end-systolic dimension (mm) | 1.329(0.815-2.953) | 0.332 |
| Left atrial diameter (mm) | 2.120(0.958-5.575) | 0.233 |
| Interventricular septal thickness (mm) | 1.062(1.019-1.107) | 0.664 |
| Posterior wall thickness (mm) | 1.222(0.884-1.465) | 0.512 |

LVEF has been used as a traditional indicator to assess LV dysfunction.[15] Severe AR increases LV volume overload and impacts LV diastolic filling. Subsequently, the LV undergoes progressive and eccentric hypertrophy with augment in its dimensions to counter high LV wall stress. In addition, the LV is exposed to a higher afterload, resulting in further LV hypertrophy.[16] Eventually, the LV fails to maintain this compensated state, with a resultant increase in end-diastolic pressure and a decrease in LVEF. Previous studies have shown extremely decreased LVEF is a poor prognostic indicator for AVR in severe AR patients[17,18]; it remains unclear whether operating on patients with extremely decreased LVEF is safe and which patients are at prohibitive surgical risk. Several studies have evaluated the outcomes after AVR for patients with severe AR and extremely decreased LVEF, but their cut-off value for extremely decreased LVEF was different and the results were inconsistent. Chaliki et al reported patients with severe AR and LVEF <35% incurred excessive operative mortality, in-hospital mortality, and incidence of congestive heart failure after AVR.[1] Kaneko et al found that patients with markedly reduced LV function had similar postoperative outcomes and survival to those with moderate LV dysfunction or preserved LV function.[7] Chukwuemeka et al reported that AVR for patients with severe AR and LVEF <40% could be performed with low perioperative morbidity and mortality.[14] In our present study, the ROC curve was used to define the cut-off value of LVEF, and the extremely decreased LVEF was determined objectively. We revealed LVEF was the independent prognostic factor of the outcome after AVR, and ROC curve analysis showed LVEF =35% was the best cut-off value for predicting postoperative in-hospital mortality.

Our present study shows that the mid-long term survival rates after AVR were much lower in LVEF ≤35% group than 35% <LVEF <50%. Several studies have shown LV contractility and efficiency were still impaired in mid-long term after AVR for severe AR patients with impaired LV function; worsening LV efficiency after AVR is critical in these specific patients and contributes to the poor mid−long term outcome. Chaliki et al examined 450 patients over 15 years and patients were subdivided into three groups based on EF: group 1 (LVEF <35%); group 2 (35% <LVEF <50%), and group 3 (LVEF ≥50%).[1] They found postoperative LVEF could be improved only in the patients with LVEF ≥50%. Tanoue et al reported that LV contractility and efficiency in the low-EF AR group were still impaired 1 year after AVR,[9] and Amano et al demonstrated that LV end-diastolic diameter, LV end-systolic diameter, and LVEF at 1 year after AVR might be useful predictors of long-term cardiac death.[19]

Finally, the present study revealed other clinically important risk factors that were associated with worsened postoperative survival, such as NYHA classes III and IV[20,21] and older age,[22] which are consistent with other published reports. Until now, no randomized controlled trial

Table 3
Comparison of baseline clinical characteristics between 35% < LVEF < 50% group and LVEF ≤35% in overall population and age-matched group

| Characteristic | Overall population | | | Age-matched group | | |
|---|---|---|---|---|---|---|
| | 35% < LVEF <50% n = 152 | LVEF ≤35% n = 60 | p Value | 35% < LVEF <50% n = 57 | LVEF ≤35% n = 57 | p Value |
| Age (years) | 55 ± 11 | 58 ± 13 | 0.03 | 57 ± 10 | 58 ± 13 | 0.22 |
| Men | 105(67%) | 25(68%) | 0.94 | 48(65%) | 25(68%) | 0.78 |
| Hypertension | 27(17%) | 8(22%) | 0.52 | 15(20%) | 8(22%) | 0.87 |
| Diabetes mellitus | 10(6%) | 4(11%) | 0.34 | 7(10%) | 4(11%) | 0.82 |
| Chronic hepatic dysfunction | 12(8%) | 4(11%) | 0.53 | 9(12%) | 4(11%) | 0.83 |
| Renal insufficiency | 7(4%) | 2(5%) | 0.81 | 6(8%) | 2(5%) | 0.60 |
| Chronic obstructive pulmonary disease | 20(13%) | 7(19%) | 0.39 | 11(15%) | 7(19%) | 0.58 |
| Atrial fibrillation | 20(13%) | 6(16%) | 0.67 | 10(14%) | 6(16%) | 0.67 |
| Previous stroke | 4(3%) | 1(3%) | 0.96 | 3(4%) | 1(3%) | 0.70 |
| NYHA class III−IV | 32(20%) | 24(41%) | 0.01 | 24(32%) | 24(42%) | 0.39 |
| Bicuspid aortic valve | 20(13%) | 5(14%) | 0.90 | 13(18%) | 5(14%) | 0.58 |
| Left ventricular end-diastolic dimension (mm) | 75 ± 4 | 79 ± 7 | 0.03 | 79 ± 6 | 79 ± 7 | 0.34 |
| Left atrial diameter (mm) | 46 ± 6 | 46 ± 7 | 0.68 | 46 ± 7 | 47 ± 7 | 0.70 |
| Interventricular septal thickness (mm) | 11 ± 1 | 11 ± 2 | 0.27 | 11 ± 1 | 11 ± 2 | 0.97 |
| Posterior wall thickness (mm) | 10 ± 1 | 10 ± 2 | 0.51 | 10 ± 1 | 10 ± 2 | 0.59 |
| Aortic root diameter (mm) | 44 ± 5 | 44 ± 5 | 0.22 | 44 ± 5.2 | 44 ± 5 | 0.78 |
| Perfusion time (minutes) | 88 ± 33 | 93 ± 38 | 0.33 | 91 ± 34 | 93 ± 38 | 0.53 |
| Cross-clamp time (minutes) | 52 ± 23 | 54 ± 23 | 0.19 | 53 ± 23 | 54 ± 23 | 0.67 |

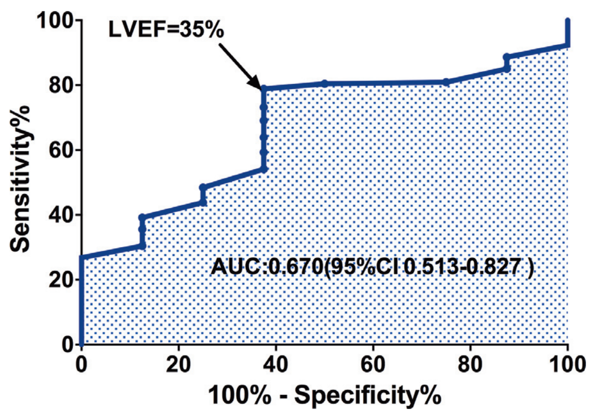
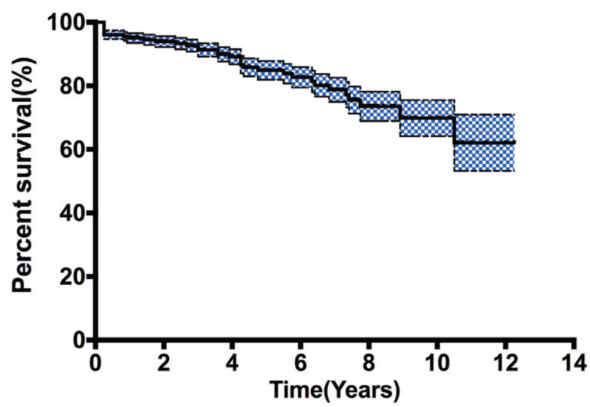


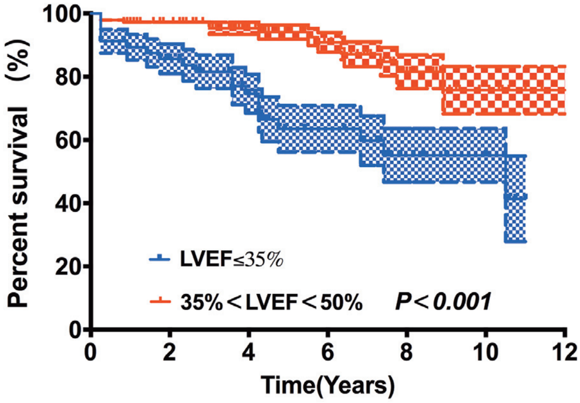

Figure 2. Receiver operating characteristic curve analyses of LVEF for predicting in-hospital mortality after AVR in patients with severe AR, reduced left ventricular function, and extreme left ventricular dilatation. AR = aortic regurgitation; AUC = area under the curve; AVR = aortic valve replacement; CI = confidence interval; LVEF = left ventricular ejection fraction.




| Years | 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| Patients at risk | 212 | 158 | 115 | 71 | 32 | 14 |

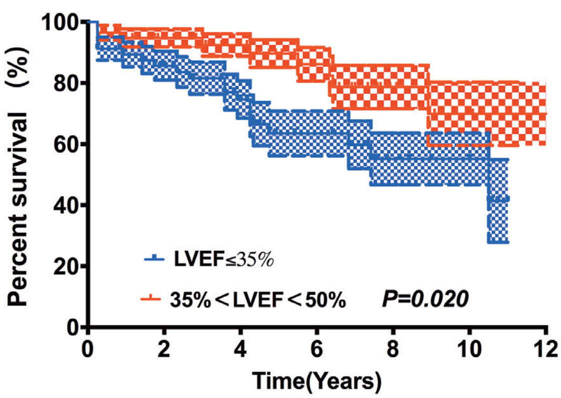
Figure 3. Long-term survival after aortic valve replacement for patients with severe AR, LVEF <50%, and LVEDD ≥70 mm. Confidence band was consistent with 1 standard error. AR aortic regurgitation; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction.

study has evaluated the optimal timing of surgical management for severe AR with reduced left ventricular function and extreme left ventricular dilatation. Understanding which factors preclude patients from being AVR candidates would be of tremendous utility in informing treatment decisions. In addition, identifying predictors of in-hospital mortality and long-term survival is particularly important with the advent of novel technology. Transcatheter aortic valve replacement could serve as an alternative option for high-risk patients with AR, reduced left ventricular function, and extreme left ventricular dilatation.[23,24] However, purely severe, native aortic valve regurgitation without aortic stenosis remains a contraindication to transcatheter aortic valve replacement, and it is not recommended in the guidelines for patients with predominant AR or noncalcified valve.[3] Another potential therapeutic option for patients with severe AR and extremely decreased LVEF is heart transplantation. The International Society for Heart and Lung Transplantation reported 1- and 5-year overall survival rates of heart transplant reached 70% to 80% and 60% to 70%, respectively, which is comparable to those with AVR.[25] Of note in our center, the 5-year survival estimate after heart transplantation was better than AVR for patients with severe AR, extreme low LVEF, and larger LVEDD. The mid-term mortality after heart transplantation was much higher than in those who received AVR once LVEF ≤35% and LVEDD ≥70 mm. Considering the extremely decreased LVEF, together with the extremely larger




| Years | 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 35% < LVEF < 50% | 152 | 117 | 85 | 53 | 23 | 9 |
| LVEF≤35% | 60 | 45 | 30 | 19 | 10 | 5 |

Figure 4. Comparison of long-term survival after AVR in the LVEF ≤35% group (blue) and the LVEF 35% to <50% group (red), among patients with severe AR, reduced left ventricular function, and extreme left ventricular dilatation. Log-rank p value was shown and confidence band was consistent with 1 standard error. AR = aortic regurgitation; AVR = aortic valve replacement; LVEF = left ventricular ejection fraction. (Color version available online.)




| Years | 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 35% < LVEF < 50% | 57 | 46 | 35 | 24 | 11 | 7 |
| LVEF≤35% | 57 | 45 | 30 | 19 | 10 | 5 |

Figure 5. Comparison of the overall survival curves in the LVEF ≤35% group (Blue) and the LVEF 35% to <50% group (red) in the age-matched study. Log-rank p value was shown and confidence band was consistent with 1 standard error. AR = aortic regurgitation; AVR = aortic valve replacement; LVEF = left ventricular ejection fraction. (Color version available online.)

LVEDD, it appears reasonable to favor heart transplantation as the first surgical option in this population.

Our study has several limitations**.** First**,** this was a retrospective, single-center observational study and, as such, is subject to limitations. Despite major efforts, as with any observational analysis, unmeasured confounders may influence the accuracy of the reported comparisons. Second, follow-up could not be obtained in all patients, the data of LVEF and LVEDD at mid- long term could not be reported. Third, the follow-up period was limited. Fourth, no preoperative right ventricle systolic pressure data.

In conclusion, AVR may be an unsafe option for severe AR patients with markedly reduced LV function (LVEF <35%) and extreme left ventricular dilatation (LVEDD >70 mm) with poor in-hospital and long-term outcomes. Reduced LVEF may be a contraindication to AVR for such patients, and other treatment options such as heart transplantation could be considered.

## Disclosures

The authors have no conflicts of interest to disclose.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