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ORIGINAL RESEARCH

Prognostic Markers and Long-Term Outcomes After Aortic Valve Replacement in Patients With Chronic Aortic Regurgitation

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BACKGROUND: The objectives of the present study were (1) to evaluate the echocardiographic prognostic factors associated with improved left ventricular (LV) systolic function after aortic valve replacement, and (2) to compare the long-term outcomes after aortic valve replacement in chronic aortic regurgitation (AR) patients with or without LV dysfunction.

METHODS AND RESULTS: A total of 280 patients who underwent aortic valve replacement because of chronic aortic regurgitation were studied. Patients with reduced LV systolic function (LV ejection fraction [LVEF] <50%; group reduced LVEF [rEF]; N=80) were compared with those with preserved LV systolic function (LVEF ≥50%; group preserved LVEF; N=200). Postoperative clinical outcomes, overall survival, and freedom from cardiac death were compared. Postoperative echocardiographic examinations were reviewed, and changes in echocardiographic parameters were analyzed. The parameters related to LVEF improvement or normalization were evaluated, and risk factors affecting long-term survival were identified. Follow-up was complete in 100% of patients, with a median follow-up of 104.8 months. Overall and cardiac mortality-free survival rates at postoperative 10 years were 80.1% and 92.9% and 87.3% and 97.2% in groups rEF and preserved LVEF, respectively (P=0.036 and P=0.058, respectively). LVEF tended to decrease in the early postoperative period but improved thereafter in both groups. Preoperative early diastolic transmitral flow velocity/mitral annular tissue velocity ratio was a parameter of postoperative improvement or normalization of LVEF in all patients (area under the curve, 0.719; P=0.003) and in group rEF patients (area under the curve, 0.726; P=0.011) with a cutoff value of 12.73. Preoperative early diastolic transmitral flow velocity/mitral annular tissue velocity ratio also was the parameter of overall survival in all patients (hazard ratio [HR], 1.08; P=0.001) and in group rEF patients (HR, 1.08; P=0.005).

CONCLUSIONS: Long-term outcomes and survival after aortic valve replacement were related to preoperative LV function in patients with chronic aortic regurgitation. Preoperative early diastolic transmitral flow velocity/mitral annular tissue velocity ratio was correlated with the postoperative improvement or normalization of LVEF and long-term survival, especially in group rEF patients.

Key Words: aortic valve replacement ■ left ventricular dysfunction ■ long-term follow-up

Aortic valve replacement (AVR) is recommended in patients with symptomatic chronic aortic regurgitation (AR) and in asymptomatic patients with AR with left ventricular (LV) dysfunction or dilatation.[1] Although previous studies have shown that AVR in these patients is related to better survival than expected from the natural progression of the disease,[2,3] preoperative LV dysfunction and enlarged

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CLINICAL PERSPECTIVE

What Is New?

- This study is the first study evaluating the relevance of preoperative tissue Doppler early diastolic transmitral flow velocity/mitral annular tissue velocity ratio to the postoperative improvement of left ventricular function and long-term outcomes after aortic valve replacement in patients with chronic aortic regurgitation.
- Preoperative early diastolic transmitral flow velocity/mitral annular tissue velocity ratio was correlated with the postoperative improvement or normalization of left ventricular ejection fraction and long-term survival.
- Long-term outcomes after aortic valve replacement were related to preoperative left ventricular function in patients with chronic aortic regurgitation.

What Are the Clinical Implications?

- Early surgical treatment before the progression of left ventricular diastolic dysfunction may improve long-term outcomes in patients with chronic aortic regurgitation.
- Preoperative early diastolic transmitral flow velocity/mitral annular tissue velocity ratio value might provide valuable information in determining the optimal timing of surgical treatment for chronic aortic regurgitation, especially in patients with reduced left ventricular ejection fraction.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
AVR	aortic valve replacement
E/e'	early diastolic transmitral flow velocity/mitral annular tissue velocity ratio
LVEDD	left ventricular end-diastolic diameter
LVESD	left ventricular end-systolic diameter
LVFS	left ventricular fractional shortening
pEF	preserved left ventricular ejection fraction
rEF	reduced left ventricular ejection fraction

LV dimensions were known to be negative prognostic indicators for patients undergoing surgery.[4,5] Recent studies showed that the prognosis after AVR in patients with severe AR with preoperative LV dysfunction was similar to that in patients without LV dysfunction, and that LV function increased postoperatively in patients with LV dysfunction.[6,7] However, LV dysfunction in patients with chronic AR is likely to span a spectrum of disease severity because LV dysfunction gradually worsens, and identifying the timing of irreversible LV dysfunction is an important consideration. Current guidelines for treatment of chronic AR might be insufficient for detecting if the irreversible LV dysfunction has taken place. Little is known of when the irreversible dysfunction takes place and about the optimal timing of AVR in patients with chronic AR because the development of LV dysfunction frequently precedes the onset of symptoms.[8] The parameters of preoperative AR quantification or LV function have not yet been thoroughly investigated, and their relevance to the postoperative prognosis has been little studied.[9,10]

The aims of the present study were (1) to evaluate the echocardiographic prognostic factors associated with improved LV systolic function after AVR and (2) to compare the long-term outcomes after AVR in patients with chronic AR with or without LV dysfunction.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

The study protocol was reviewed by the Institutional Review Board and approved as a minimal-risk retrospective study (approval No. 4-2019-0337) that did not require individual consent on the basis of the institutional guidelines for waiving consent.

Among 919 patients who underwent AVR without another valve surgery from January 2001 to December 2014, 280 who underwent AVR because of chronic AR were included in this study. Patients who underwent concomitant coronary artery bypass grafting (N=21) or ascending aortic surgery (N=51) were included. Patients who had acute AR caused by aortic dissection or aortic valve perforation caused by endocarditis (N=92), greater than moderate aortic valve stenosis (N=399), combined mitral valvular disease (N=104), a history of previous valve surgery (N=11), and missed echocardiographic data (N=33) were excluded. The patients were divided into the reduced LV ejection fraction (LVEF) group (group rEF; LVEF <50%) and preserved LVEF group (group pEF; LVEF ≥50%), according to preoperative LVEF (Figure 1).

Patients underwent regular postoperative follow-up examinations through the outpatient clinic at 3- to 4-month intervals, and their survival status or reporting of cardiovascular events was collected by reviewing electronic medical records. In addition, data for the vital statistics and death from cardiovascular diseases were obtained from death certificates

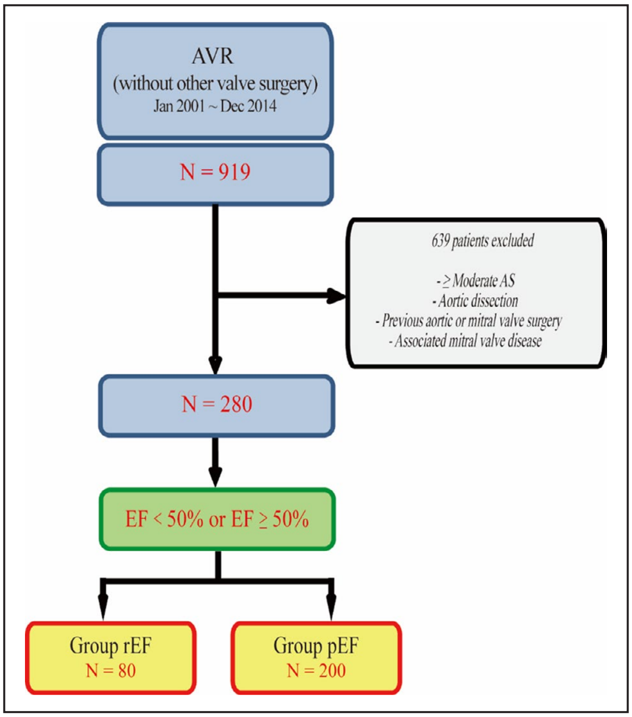

Figure 1. Summary flow diagram of patients.
AS indicates aortic stenosis; AVR, aortic valve replacement; EF, ejection fraction; pEF, preserved left ventricular EF (EF ≥50%); and rEF, reduced left ventricular EF (EF <50%).

available at Statistics Korea, a central organization for statistics under the Ministry of Strategy and Finance. The clinical and echocardiographic follow-up examinations were closed on July 31, 2019. The follow-up data were complete in 100% (280/280) of patients, with a median follow-up duration of 104.8 (interquartile range, 72.7–152.2) months. Postoperative clinical outcomes, overall survival, freedom from cardiac death, and cardiac events were compared between the groups. Operative death was defined as death occurring within 30 days after AVR or during the same hospital stay. Cardiac death was defined as any death related to cardiac events, including sudden death during the follow-up. Cardiac event was defined as readmission because of heart failure, reoperation because of prosthetic valve failure, a need for cardiac intervention, such as percutaneous coronary intervention or coronary artery bypass grafting, pacemaker implantation, or cardiac death.

Early (median, 6.0 [interquartile range, 4.0–7.0] days), 1-year (median, 11.1 [interquartile range, 7.0–13.2] months), 3-year (median, 35.9 [interquartile range, 30.4–41.3] months), and 5-year (median, 65.6 [interquartile range, 58.5–76.8] months) postoperative echocardiographic examinations were performed in 96.4% (270/280), 78.6% (220/280), 65.0% (182/280), and 67.5% (189/280) of patients, respectively. The echocardiographic parameters included LVEF calculated by modified Simpson method, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), LV fractional shortening (LVFS; [LVEDD−LVESD/LVEDD]×100), and the early diastolic transmitral flow velocity/mitral annular tissue velocity (E/e′) ratio. We used septal E/e′ rather than lateral E/e′ to indicate patient's LV diastolic function. Preoperative E/e′ was not available in 16 patients. The parameter of LVEF improvement or normalization was evaluated, and risk factors affecting long-term survival were identified.

Statistical Analysis

Statistical analysis was performed with R software, version 3.6.0. Continuous data were expressed as the mean±SD for normally distributed variables or as medians (interquartile ranges) for nonnormally distributed variables, according to the Shapiro-Wilk test; and categoric data were expressed as counts (percentages). Comparisons between continuous variables were made using Student *t* test for normally distributed data or the Wilcoxon rank-sum test for nonnormally distributed data, on the basis of the Shapiro-Wilk test. Categoric variables were compared using a χ^2 test. When ≥20% of expected counts were ≤5, however, the Fisher exact test was used.

The differences between preoperative and postoperative echocardiographic parameters were calculated, and the differences over time between groups were analyzed using repeated measures of ANOVA. Each model included the group, time, and interaction term between group and time variables (stats package).

Increased LVEF >10 percentage points compared with preoperative LVEF or LVEF ≥50% at 3 years or later after postoperative echocardiography was regarded as "improved or normalized LVEF" based on previous studies analyzing serial changes in LV volumes or LVEF in patients with heart failure,[11,12] and used as an outcome variable in receiver operating characteristic curve analysis. The receiver operating characteristic curve analysis of preoperative parameters for postoperative LVEF improvement or normalization was performed, and cutoff values of preoperative parameters and area under the curve (AUC) were identified (Epi package and pROC package).

Overall survival, freedom from cardiac death, and freedom from cardiac event were analyzed using Kaplan-Meier survival curves, and comparisons between the groups were performed using the log-rank test. Univariable and multivariable Cox proportional hazard models were used to identify risk factors that affected long-term survival. Appropriate variables in the multivariable model were selected using backward elimination procedure.

RESULTS

Patient Characteristics

A total of 280 patients were divided into group rEF (N=80) and group pEF (N=200), according to preoperative LVEF. There were no differences in preoperative patient characteristics between the 2 groups, except for a lower New York Heart Association functional class in group rEF than in group pEF (*P*=0.001) (Table 1).

Operative Data and Early Clinical Outcomes

There were 5 operative mortalities, and intergroup differences were not found between the groups rEF and pEF (*P*=0.943). The median cardiopulmonary bypass time and aortic cross-clamp time were 98.5 (interquartile range, 84.0–117.3) minutes and 70.0 (interquartile range, 60.0–86.0) minutes, respectively (*P*=0.926 and *P*=0.245, respectively). Mechanical prosthetic valves were more frequently implanted in group pEF than in group rEF (*P*=0.008). Combined operations were performed in 78 patients (coronary artery bypass grafting, N=21; surgery on ascending aorta, N=51; ventricular septal defect closure, N=2; atrial septal defect closure, N=1; coronary arteriovenous fistula closure, N=1; sinus of Valsalva aneurysm repair, N=1; and Cox-Maze III procedure, N=1), and showed no intergroup difference (*P*=0.598). The intensive care unit stay was significantly longer in group rEF than in group pEF (*P*=0.033) (Table 2).

Postoperative Changes in Echocardiographic Parameters

The LVEF was directly correlated with LVFS (*P*<0.001), and inversely correlated with LVEDD (*P*<0.001), LVESD (*P*<0.001), and E/e′ (*P*=0.005) preoperatively (Figure S1). The LVEF and LVFS tended to decrease in the early postoperative period and increased at ≥1 year during the follow-up period, and LVEDD and LVESD tended to decrease after AVR. In contrast, E/e′ showed no significant differences during the postoperative periods. When the changes of echocardiographic parameters over time between groups were compared, group rEF patients showed higher changes in improved LVEF and LVFS and decreased LVEDD and LVESD than group pEF patients (*P*<0.001). However, the changes of E/e′ over time were not significantly different between the 2 groups (*P*=0.416) (Table 3).

Table 1. Comparison of the Patients' Preoperative Demographic Data Between the rEF and pEF Groups

Variable	Group rEF (N=80)	Group pEF (N=200)	*P* Value
Age, y	60.9 (52.9–68.6)	59.0 (47.0–66.8)	0.100
Women	23 (28.8)	66 (33.0)	0.584
BMI, kg/m^2	23.3 (20.8–25.1)	23.6 (21.8–25.8)	0.170
BSA, m^2	1.7±0.2	1.7±0.2	0.294
Smoking			0.953
Nonsmoker	50 (62.5)	124 (62.0)	
Ex-smoker	12 (15.0)	28 (14.0)	
Current smoker	18 (22.5)	48 (24.0)	
Atrial fibrillation	8 (10.0)	10 (5.0)	0.204
Hypertension	41 (51.2)	103 (51.5)	>0.999
Diabetes mellitus	7 (8.8)	23 (11.5)	0.647
Chronic renal failure	6 (7.5)	10 (5.0)	0.597
Preoperative creatinine, mg/dL	1.0 (0.9–1.2)	0.9 (0.8–1.1)	0.146
History of stroke	5 (6.2)	12 (6.0)	>0.999
Coronary artery disease	14 (17.5)	29 (14.5)	0.656
Peripheral vascular obstructive disease	2 (2.5)	5 (2.5)	>0.999
Chronic obstructive lung disease	7 (8.8)	13 (6.5)	0.687
NYHA class			0.001
1	0 (0.0)	6 (3.0)	
2	15 (18.8)	78 (39.0)	
3	56 (70.0)	106 (53.0)	
4	9 (11.2)	10 (5.0)	
Preoperative AR grade			0.382
2	4 (5.0)	18 (9.0)	
3	38 (47.5)	101 (50.5)	
4	38 (47.5)	81 (40.5)	
Bicuspid aortic valve	19 (23.8)	41 (20.5)	0.662

Data are given as median (interquartile range) or number (percentage). AR indicates aortic regurgitation; BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; pEF, preserved left ventricular ejection fraction (left ventricular ejection fraction ≥50%); and rEF, reduced left ventricular ejection fraction (left ventricular ejection fraction <50%).

Echocardiographic Parameters Associated With Postoperative LVEF Improvement or Normalization

Improved or normalized LVEF was observed in 92.7% (215/232) of all patients. Optimum cutoff values of preoperative LVEDD, LVESD, LVFS, and E/e′ for improvement or normalization of LVEF were 74 mm (sensitivity, 59.1%; specificity, 76.5%), 52 mm (sensitivity, 50.7%; specificity, 94.1%), 25% (sensitivity, 71.2%; specificity, 82.4%), and 12.73 (sensitivity, 68.3%; specificity, 76.5%), respectively. Preoperative LVEDD, LVESD, LVFS, and E/e′ were significantly associated with postoperative improvement or normalization of LVEF,

Table 2. Comparison of the Patients' Operative Data and Early Clinical Outcomes Between the rEF and pEF Groups

Variable	Group rEF (N=80)	Group pEF (N=200)	*P* Value
Cardiopulmonary bypass time, min	99.0 (87.5–112.5)	98.0 (82.0–119.0)	0.926
Arterial cross-clamp time, min	69.0 (59.5–79.5)	71.0 (60.0–91.5)	0.245
Mechanical prosthesis	46 (57.5)	149 (74.5)	0.008
Co-operations	20 (25.0)	58 (29.0)	0.598
Length of ICU stay, d	2.0 (2.0–3.0)	2.0 (1.0–2.0)	0.033
Length of hospital stay, d	11.0 (8.0–15.5)	9.0 (8.0–14.0)	0.162
Operative mortality	2 (2.5)	3 (1.5)	0.943

Data are given as median (interquartile range) or number (percentage). ICU indicates intensive care unit; pEF, preserved left ventricular ejection fraction (left ventricular ejection fraction ≥50%); and rEF, reduced left ventricular ejection fraction (left ventricular ejection fraction <50%).

with AUC of 0.733 (*P*<0.001), 0.794 (*P*<0.001), 0.794 (*P*<0.001), and 0.719 (*P*=0.003), respectively (Figure 2). In group rEF, improved or normalized LVEF was observed in 78.5% (51/65) of patients at 3 years or later postoperatively. Of preoperative echocardiographic parameters for group rEF, E/e′ was associated with improved or normalized LVEF postoperatively (AUC, 0.726; *P*=0.011), and the optimum cutoff value was 12.73 (sensitivity, 70.2%; specificity, 78.6%). Other parameters, such as LVEDD, LVESD, and LVFS, failed to show relation with improved or normalized LVEF postoperatively (Figure 3).

Overall Survival, Freedom From Cardiac Death, and Freedom From Cardiac Events

All-cause mortality occurred in 44 patients (group rEF versus pEF, 18/80 versus 26/200), including 9 cardiac deaths (group rEF versus pEF, 5/80 versus 4/200), during the follow-up period. Overall postoperative survival rates at 5 and 10 years were 86.2% and 80.1% in group rEF, respectively, and 94.0% and 87.3% in group pEF, respectively (*P*=0.036), although statistical significance became marginal after age adjustment (*P*=0.058) (Figure 4). Cardiac mortality-free postoperative survival rates at 5 and 10 years were 94.5% and 92.9% in group rEF, respectively, and 98.4% and 97.2% in group pEF, respectively. A significant intergroup difference in cardiac mortality-free survival rates was found between the groups after age adjustment (*P*=0.028). Freedom from postoperative cardiac event rates at 5 and 10 years was 88.7% and 78.9% in group rEF, respectively, and 95.0% and 87.2% in group pEF, respectively. No significant difference in freedom from cardiac events was found between the groups after age adjustment (*P*=0.099) (Figure 4). Multivariable analysis by Cox proportional hazard model revealed that age (*P*<0.001), creatinine level (*P*=0.007), combined coronary artery disease (*P*<0.001), and New York Heart Association class (*P*=0.001) were significant parameters of all-cause mortality in all study patients (Table 4). Multivariable analysis in group rEF showed E/e′ to be a significant parameter of all-cause mortality (*P*=0.005) (Table 5).

Echocardiographic Parameters Associated With Postoperative LVEF Improvement or Normalization in Late-Referral Group

Subgroup analysis was performed with "late-referral group" that included patients with New York Heart Association class ≥3 (N=89) or LVESD >50 mm (N=181) other than group rEF patients.

In patients with New York Heart Association class ≥3, optimum cutoff values of preoperative LVEDD, LVESD, LVEF, and E/e′ for improvement or normalization of LVEF were 68 mm (sensitivity, 64.7%; specificity, 75.0%), 46 mm (sensitivity, 47.8%; specificity, 91.7%), 49% (sensitivity, 70.6%; specificity, 83.3%), and 12.73 (sensitivity, 63.3%; specificity, 83.3%), respectively. Preoperative LVEDD, LVESD, LVEF, and E/e′ were significantly associated with postoperative improvement or normalization of LVEF in these patients with AUC of 0.731 (*P*=0.008), 0.726 (*P*=0.009), 0.720 (*P*=0.012), and 0.718 (*P*=0.013), respectively (Figure S1). In patients with LVESD >50 mm, optimum cutoff values of preoperative LVEDD, LVESD, LVEF, and E/e′ for improvement or normalization of LVEF were 82 mm (sensitivity, 85.2%; specificity, 27.3%), 55 mm (sensitivity, 34.4%; specificity, 90.9%), 47% (sensitivity, 47.5%; specificity, 90.9%), and 9.67 (sensitivity, 41.1%; specificity, 100.0%), respectively. Only preoperative E/e' was associated with postoperative improvement or normalization of LVEF in these patients, with a marginal significance (AUC, 0.669; *P*=0.080). Other parameters were not associated with postoperative improvement or normalization of LVEF (Figure S2).

DISCUSSION

This study demonstrated 4 main findings. First, the LVEF decreased in the early postoperative period and increased at ≥1 year during the follow-up period. Second, the reduced LVEF group showed lower overall postoperative survival and cardiac mortality-free survival rates than the preserved LVEF group at

Table 3. Changes in Echocardiographic Parameters

Variable	Preoperative	Early Postoperative (270/280) (rEF, 78/80; pEF, 192/200)	1 y (220/280) (rEF, 65/80; pEF, 155/200)	3 y (182/280) (rEF, 54/80; pEF, 128/200)	5 y (189/280) (rEF, 53/80; pEF, 136/200)	*P* Value*
		(Median, 6.0 [IQR, 4.0–7.0] d)	(Median, 11.1 [IQR, 7.0–13.2] mo)	(Median, 35.9 [IQR, 30.4–41.3] mo)	(Median, 65.6 [IQR, 58.5–76.8] mo)	
LVEF, %						
All patients	56.60±12.55	49.16±13.33	59.30±10.67	62.58±8.68	62.67±9.10	
Group rEF	39.95±8.15	36.19±10.38	50.58±11.77	57.04±10.88	57.91±10.90	<0.001
Group pEF	63.26±6.21	54.42±10.51	62.95±7.88	64.86±6.37	64.53±7.56	
LVEDD, mm						
All patients	65.95±8.44	55.68±8.14	50.72±6.01	49.47±5.66	49.67±5.16	
Group rEF	70.68±7.56	61.08±8.59	53.40±7.73	50.98±6.95	51.62±5.87	<0.001
Group pEF	64.06±8.04	53.48±6.84	49.58±4.71	48.85±4.93	48.90±4.67	
LVESD, mm						
All patients	47.13±9.13	42.28±9.35	35.47±6.85	33.76±6.03	33.92±5.85	
Group rEF	56.10±7.54	50.31±9.24	39.91±8.70	36.74±8.11	37.00±7.42	<0.001
Group pEF	43.55±7.01	39.01±7.18	33.60±4.82	32.54±4.42	32.72±4.62	
LVFS, %						
All patients	28.93±6.86	24.70±7.16	30.45±6.36	32.05±5.55	32.01±6.09	
Group rEF	20.73±4.76	18.02±5.70	25.84±6.66	28.53±6.39	28.86±7.19	<0.001
Group pEF	32.21±4.37	27.43±5.78	32.39±5.13	3.50±4.44	33.23±5.13	
E/e′						
All patients	12.55±5.55	13.13±5.79	11.79±4.85	11.91±6.11	12.80±5.29	
Group rEF	13.39±6.58	14.38±7.34	12.01±4.31	11.57±5.94	13.17±5.58	0.416
Group pEF	12.22±5.05	12.62±4.96	11.70±5.07	12.06±6.19	12.65±5.19	

Data are given as mean±SD. E/e′ indicates early mitral inflow velocity/mitral annular early diastolic velocity ratio; IQR, interquartile range; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVFS, left ventricular fractional shortening; pEF, preserved LVEF (LVEF ≥50%); and rEF, reduced LVEF (LVEF <50%).

**P* values of interaction between group and time obtained by 2-way repeated measures of ANOVA.

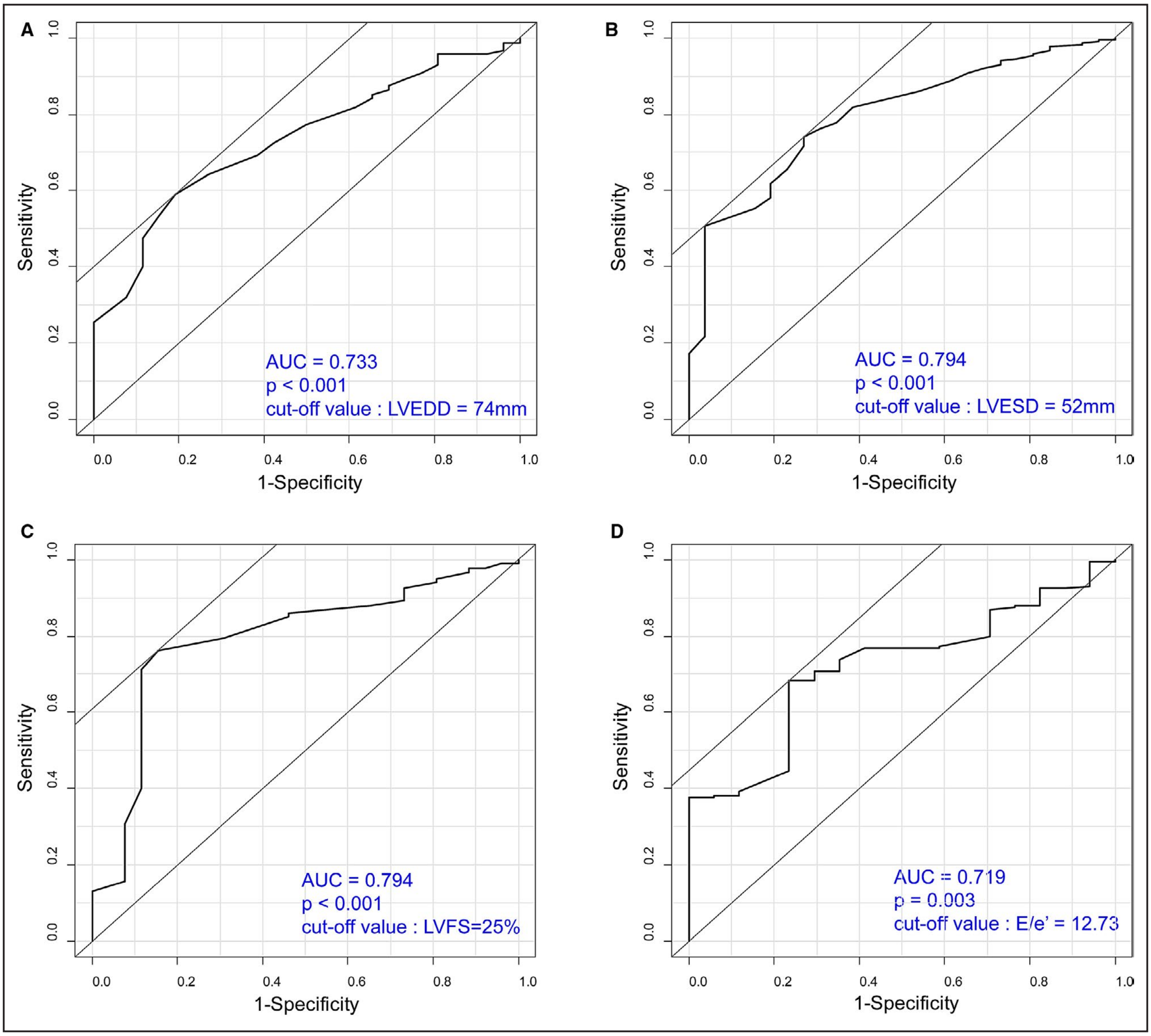

Figure 2. Receiver operating characteristic (ROC) curves in all patients.
ROC curves were calculated to determine a cutoff value of preoperative left ventricular end-diastolic diameter (LVEDD) (**A**), preoperative left ventricular end-systolic diameter (LVESD) (**B**), preoperative left ventricular fractional shortening (LVFS) (**C**), and preoperative early diastolic transmitral flow velocity/mitral annular tissue velocity ratio (E/e′) (**D**) for improvement or normalization of left ventricular function. AUC indicates area under the curve.

5 and 10 years. Third, preoperative E/e′ was associated with postoperative improvement or normalization of LVEF and all-cause mortality in the reduced LVEF group.

Current treatment guidelines for patients with chronic AR recommend that AVR is indicated for patients with severe AR patients with symptoms or LV systolic dysfunction (LVEF <50%), is reasonable to be performed in asymptomatic patients with AR with normal LV systolic function (LVEF ≥50%) but with LVESD >50 mm or indexed LVESD >25 mm/m^2, and may be considered in asymptomatic patients with AR with normal LV systolic function but LVEDD >65 mm.[1] However, current guidelines might be too conservative and hence mistime surgery because AVR is a safer procedure than in the past and there are evolving surgical options, such as rapid deployment AVR with newly designed bioprosthetic valve to reduce implantation time. Therefore, the optimal timing for AVR in patients with chronic AR needs to be reevaluated and reassessed.[13,14] One recent study by Mentias et al, which included 1417 patients with greater than grade 3 chronic AR and preserved LVEF, showed that the mortality in nonsurgical patients with chronic AR significantly and continuously increased when indexed LVESD was >20 mm/m^2 and proposed

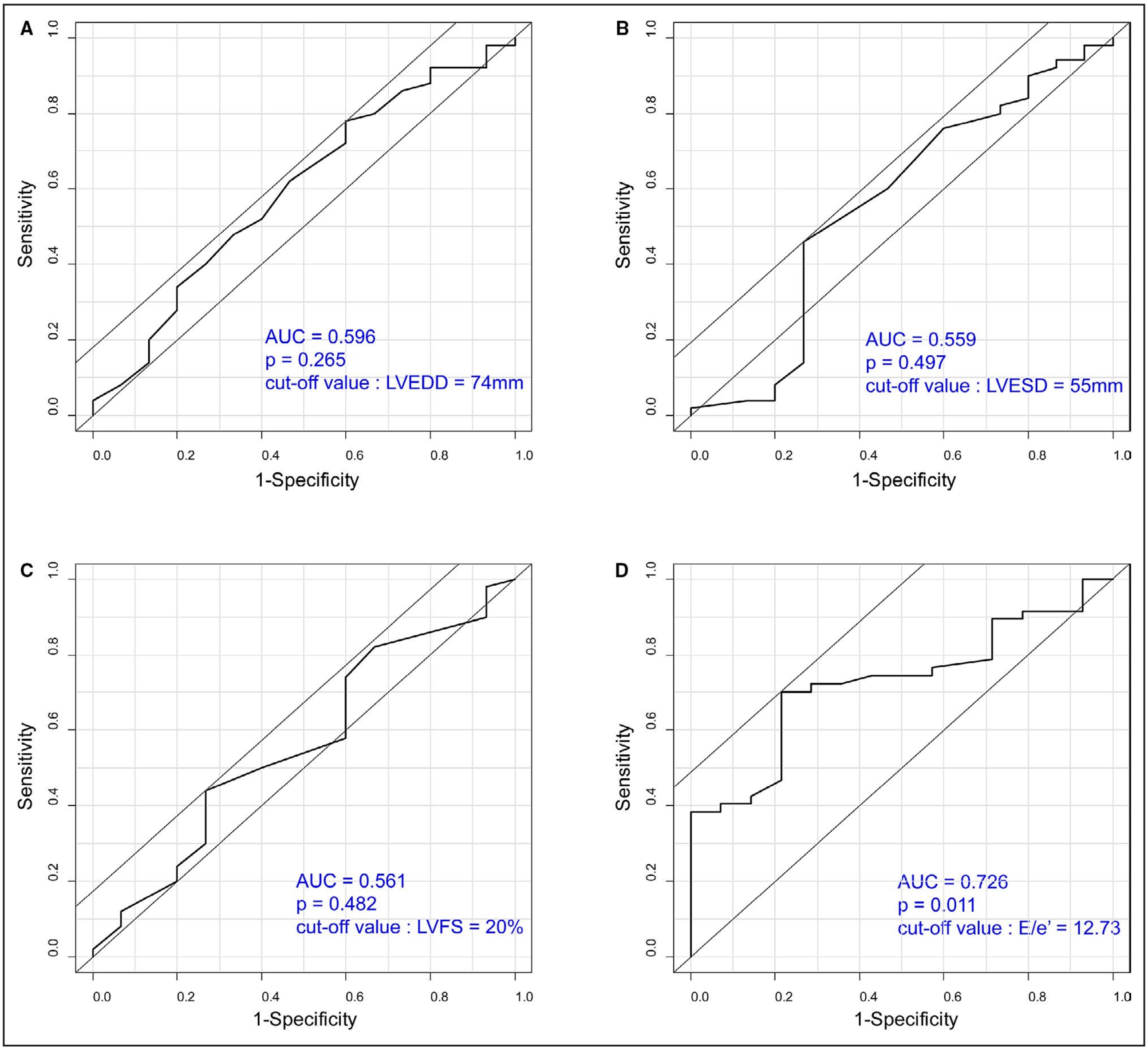

Figure 3. Receiver operating characteristic (ROC) curves in patients with left ventricular (LV) systolic dysfunction (preoperative LV ejection fraction <50%).
ROC curves were calculated to determine a cutoff value of preoperative left ventricular end-diastolic diameter (LVEDD) (**A**), preoperative left ventricular end-systolic diameter (LVESD) (**B**), preoperative left ventricular fractional shortening (LVFS) (**C**), and preoperative early diastolic transmitral flow velocity/mitral annular tissue velocity ratio (E/e′) (**D**) for improvement or normalization of LV function. AUC indicates area under the curve.

a possibility for reassessment of current recommendations for AVR in these patients.[15] Another study by Yang et al, which included 748 patients with greater than moderate chronic AR, showed that the indexed LVESD was associated with all-cause mortality and the ideal cutoff of the value was less than previously recommended.[16] Wang et al, in their study of 192 patients with severe AR, normal LVEF, and severe LV dilatation, revealed satisfactory outcomes in these patients, but found that LVEF <55% was related to poorer prognosis.[17]

One previous study by Borer et al demonstrated that 3 years was necessary for the recovery of LV performance in terms of LVEF after AVR for AR.[18] The present study included 280 patients who underwent AVR because of chronic AR and showed similar results that LVEF tended to decrease in the early postoperative period and increased thereafter after AVR. In the current study, patients with chronic AR with grade 2 or higher, most of whom underwent AVR during concomitant coronary artery bypass grafting or ascending aortic surgery, were included to reflect

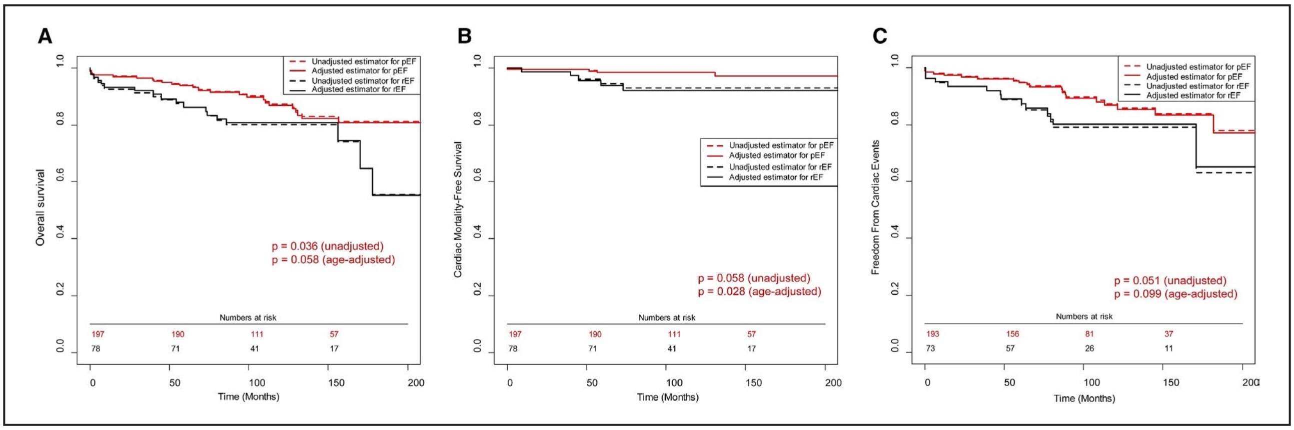

Figure 4. Comparison of overall survival (A), cardiac mortality-free survival (B), and freedom from cardiac events (C) between preserved left ventricular ejection fraction (LVEF ≥50%) (pEF) and reduced LVEF (LVEF <50%) (rEF) groups, before and after age adjustment.

surgeons' interest in real world. Group rEF patients needed a longer intensive care unit stay and showed worse overall survival and cardiac mortality-free survival when compared with group pEF patients. This study supports that earlier surgery before the patient's LVEF decreases <50% might have a positive prognostic impact on the patient's long-term clinical outcomes.

Previous studies have identified preoperative parameters associated with the prognosis after AVR in patients with chronic AR and suggested that preoperative diastolic function may have an importance in predicting outcomes.[19–23] The present study demonstrated that the optimum cutoff values of LVEDD, LVESD, LVFS, and E/e′ for improvement or normalization of LV systolic function were 74 mm, 52 mm, 25%,

Table 4. Univariable and Multivariable Parameters of All-Cause Mortality in All Patients

Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Female sex	1.03 (0.55–1.94)	0.927		
Age	1.05 (1.02–1.07)	0.001	1.05 (1.02–1.08)	<0.001
BMI	0.96 (0.89–1.04)	0.306		
Smoking	1.24 (0.90–1.72)	0.192		
Hypertension	1.28 (0.70–2.32)	0.422		
Diabetes mellitus	1.95 (0.91–4.21)	0.088		
Chronic renal failure	2.71 (1.06–6.89)	0.037		
Preoperative creatinine level	1.20 (1.05–1.38)	0.009	1.20 (1.05–1.37)	0.007
History of stroke	2.94 (1.15–7.48)	0.024		
Coronary artery disease	3.11 (1.66–5.81)	<0.001	3.99 (2.10–7.58)	<0.001
Peripheral vascular obstructive disease	2.36 (0.57–9.78)	0.235		
Chronic obstructive lung disease	1.26 (0.39–4.08)	0.706		
NYHA class	2.43 (1.48–3.99)	<0.001	2.51 (1.47–4.29)	0.001
LVEF	0.98 (0.96–1.00)	0.117		
LVEDD	0.99 (0.96–1.03)	0.677		
LVESD	1.01 (0.98–1.04)	0.642		
LVFS	0.97 (0.93–1.02)	0.212		
E/e′	1.08 (1.03–1.13)	0.001		

BMI indicates body mass index; E/e′, early mitral inflow velocity/mitral annular early diastolic velocity ratio; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVFS, left ventricular fractional shortening; and NYHA, New York Heart Association.

Table 5. Univariable and Multivariable Parameters of All-Cause Mortality in Patients With LV Systolic Dysfunction (Preoperative LVEF <50%)

Variable	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Female sex	1.53 (0.55–4.25)	0.416		
Age	1.01 (0.97–1.06)	0.477		
BMI	0.93 (0.80–1.07)	0.288		
Smoking	1.33 (0.80–2.20)	0.269		
Hypertension	1.96 (0.75–5.13)	0.169		
Diabetes mellitus	1.02 (0.23–4.46)	0.977		
Chronic renal failure	1.59 (0.36–6.99)	0.536		
Preoperative creatinine level	1.43 (0.96–2.14)	0.079		
History of stroke	0.82 (0.11–6.21)	0.847		
Coronary artery disease	2.57 (0.96–6.91)	0.060		
Peripheral vascular obstructive disease	4.54 (0.60–34.66)	0.144		
Chronic obstructive lung disease	3.16 (0.89–11.25)	0.075		
NYHA class	2.64 (1.12–6.24)	0.027		
LVEF	0.96 (0.91–1.01)	0.118		
LVEDD	1.04 (0.98–1.10)	0.169		
LVESD	1.05 (0.99–1.11)	0.099		
LVFS	0.93 (0.84–1.03)	0.161		
E/e′	1.08 (1.02–1.15)	0.005	1.08 (1.02–1.15)	0.005

BMI indicates body mass index; E/e′, early mitral inflow velocity/mitral annular early diastolic velocity ratio; HR, hazard ratio; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVFS, LV fractional shortening; and NYHA, New York Heart Association.

and 12.73, respectively, in all patients. Of the preoperative variables, the cutoff values of LVEDD, LVESD, and LVFS were similar to the current guidelines, and performing AVR before the parameters reach these cutoff values may be warranted. Measurement of tissue Doppler E/e′, a ratio between early transmitral flow velocity and early diastolic mitral annular tissue velocity, is known to be the most reproducible noninvasive method for estimation of LV filling pressure, and is one of the key variables recommended for assessment of LV diastolic function.[24–26] Lateral E/e′ >12 or septal E/e′ >15 is known to be associated with a higher likelihood of increased LV filling pressure.[26] In the previous study, Egbe et al demonstrated that preoperative E/e’ >14 was the risk factor of cardiac death after AVR.[22] Similarly, the present study revealed E/e’ to be related to all-cause mortality as well as cardiac mortality after AVR, and its relevance increased in patients with reduced LV systolic function.

The cutoff value of septal E/e′ associated with the improvement of normalization of LVEF, 12.73, was lower than the known threshold value of LV diastolic dysfunction, and this might imply that the earlier consideration of surgical treatment is warranted because diastolic dysfunction is known to be associated with unfavorable outcomes in various cardiac pathological conditions.[24,27] In group rEF patients, only E/e′ was associated with the improvement or normalization of LV systolic function, and other parameters failed to show relationship with LV systolic function improvement or normalization. The cutoff value of E/e′ associated with LV systolic function improvement or normalization in group rEF was 12.73, which was identical to the value in all patients. In addition, E/e′ was a multivariable parameter of all-cause mortality in group rEF.

To the best of our knowledge, this study is the first to evaluate the relevance of preoperative tissue Doppler E/e′ on post-AVR outcomes and LV function in patients with chronic AR. E/e′ appears to be a robust and useful measure that is associated with postoperative normalization of LV systolic function and overall survival in all patients and in patients with LV systolic dysfunction. Furthermore, E/e’ was analyzed to be a useful parameter in patients with chronic AR with symptoms or LVESD >50 mm as well. E/e’ was more strongly associated with postoperative improvement of LV systolic function than other parameters, and the cutoff value of E/e’ associated with improvement or normalization of LVEF was lower in patients with LVESD >50 mm than other patients (9.67 versus 12.73). Further study is warranted to clear out this result.

This study has limitations that must be recognized. First, it was a retrospective study performed at a single institution. Second, relatively small sample size, short echocardiographic follow-up, and absence of strain measurement, such as global longitudinal strain, might be limitations to generalize this study finding in the daily practice. Third, the determined optimal cutoff values of parameters were not validated or tested in an independent population. Fourth, long-term outcomes, including overall survival, could be affected by confounding factors because of the group heterogeneity, although we performed age-adjusted log-rank tests for the overall survival to overcome this limitation. Fifth, using E/e' alone might have a pitfall in the measurement of LV diastolic function, especially in circumstances such as combined mitral regurgitation, although E/e' is one of the important variables used for assessment of LV diastolic dysfunction.[25] We excluded patients with prior valve surgery or combined mitral valve disease to make the study population more homogeneous. However, further studies on the impact of other parameters related to LV diastolic dysfunction on the post-AVR outcomes may be warranted.

CONCLUSIONS

In patients with chronic AR, long-term clinical outcomes and survival after AVR were related to preoperative LV function. Preoperative E/e′ was strongly correlated with the postoperative improvement or normalization of LVEF and long-term survival, especially in patients with LVEF <50%. We suggest that these data support earlier surgical treatment before the progression of LV diastolic dysfunction.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Figures S1–S2

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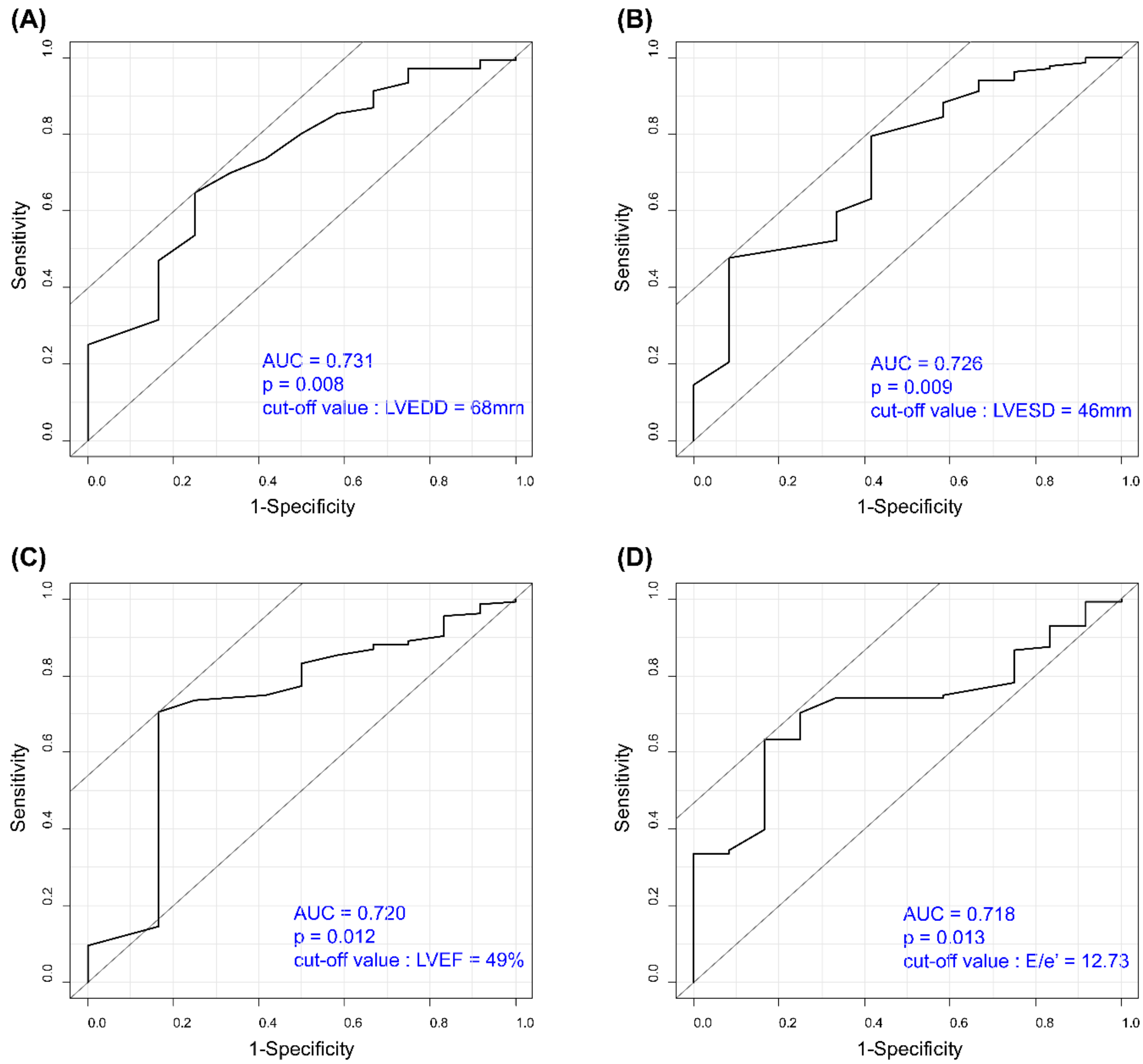
SUPPLEMENTAL MATERIAL

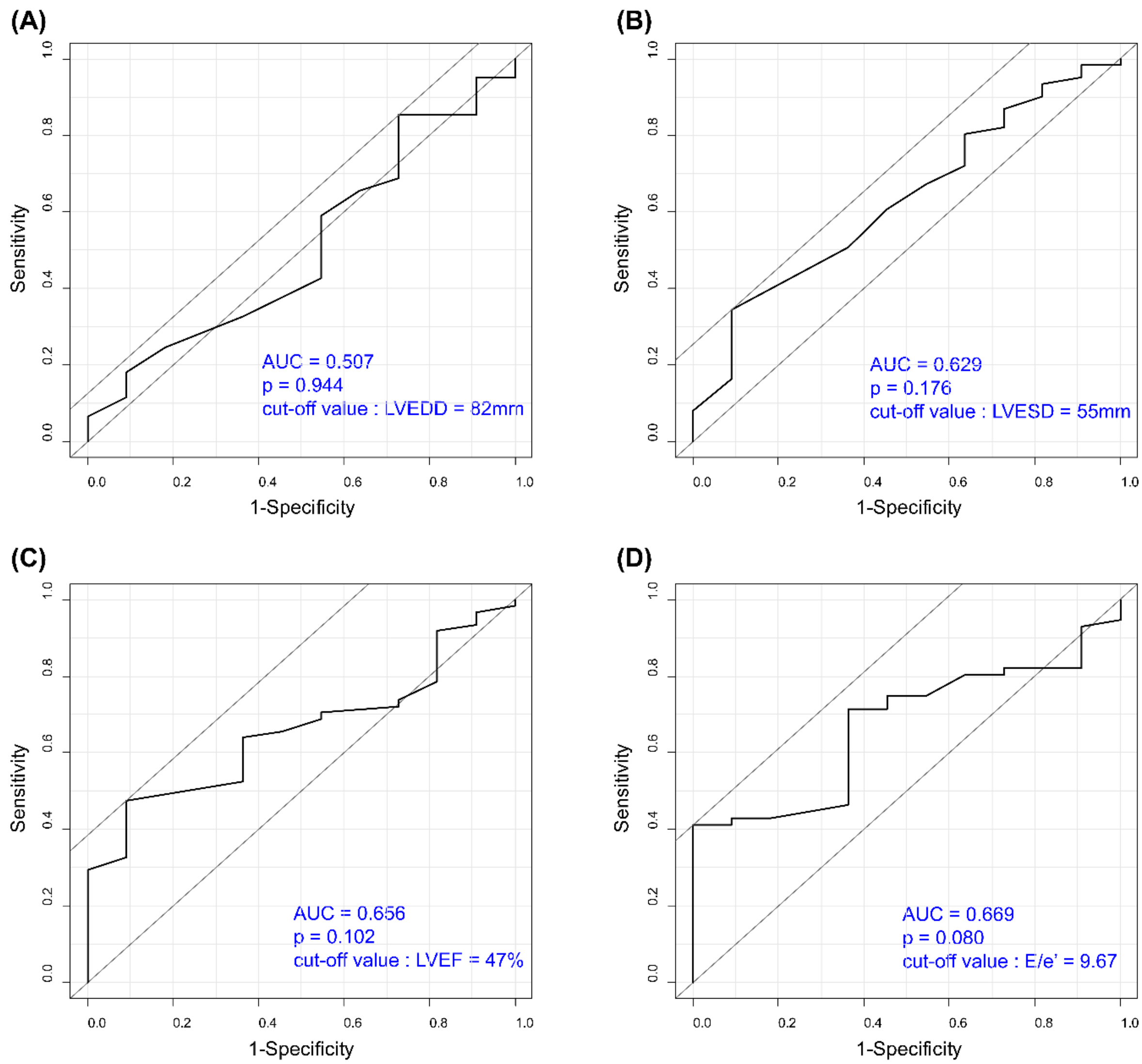
Figure S1. Receiver Operating Characteristic (ROC) curves in patients with NYHA class ≥ 3.



ROC curves were calculated to determine a cutoff value of (A) preoperative LVEDD, (B) preoperative LVESD, (C) preoperative LVEF, and (D) preoperative E/e′ for improvement or normalization of LV function.

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVFS, left ventricular fractional shortening.

Figure S2. Receiver Operating Characteristic (ROC) curves in patients with LVESD>50mm.



ROC curves were calculated to determine a cutoff value of (A) preoperative LVEDD, (B) preoperative LVESD, (C) preoperative LVEF, and (D) preoperative E/e′ for improvement or normalization of LV function.
LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVFS, left ventricular fractional shortening.