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Heart Valve Disease

Early Surgery Versus Conventional Treatment for Asymptomatic Severe Mitral Regurgitation

A Propensity Analysis

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Objectives This study sought to compare long-term outcomes of early surgery with a conventional treatment strategy in asymptomatic patients with severe mitral regurgitation (MR).

Background The timing of surgery in asymptomatic severe MR remains controversial.

Methods From 1996 to 2009, 610 consecutive asymptomatic patients (364 men, 50 $\pm$ 14 years of age) with severe degenerative MR and preserved left ventricular function were evaluated prospectively. Early surgery was performed on 235 patients, and the conventional treatment strategy was chosen for 375 patients. We compared overall mortality, cardiac mortality, and cardiac events (operative mortality, cardiac mortality, repeat surgery, and urgent admission due to heart failure) between the 2 treatment strategies in the propensity score–matched cohort.

Results For the 207 propensity score–matched pairs, early surgery had a lower risk of cardiac mortality (hazard ratio [HR]: 0.109; 95% confidence interval [CI]: 0.014 to 0.836; $p = 0.033$) and cardiac events (HR: 0.216; 95% CI: 0.083 to 0.558; $p = 0.002$) than conventional treatment. On Cox proportional hazard model analysis, the risk of cardiac events was significantly lower in the early surgery group than in the conventional treatment group in patients aged 50 years of age and older (HR: 0.221; 95% CI: 0.086 to 0.567; $p = 0.002$), but not significantly different in those younger than 50 years of age ($p = 0.20$).

Conclusions Compared with conservative management, early surgery is associated with significant long-term reductions of cardiac mortality and cardiac events in asymptomatic severe MR. These benefits were evident among patients age 50 years of age and older. (J Am Coll Cardiol 2014;63:2398–407) © 2014 by the American College of Cardiology Foundation

Surgery is the only definitive therapy for severe mitral regurgitation (MR), and the guidelines recommend that severe MR in symptomatic or asymptomatic patients with left ventricular (LV) dysfunction should be managed with surgery (1,2). However, it remains unclear when asymptomatic patients with severe MR should undergo surgical intervention because randomized clinical trials comparing early surgery with watchful waiting have not been performed (3,4). The benefit of early surgery has been suggested in prospective, observational studies (5–8), whereas a watchful waiting strategy seemed to be safe and effective in another prospective study (9). The consensus guidelines for performing early surgery in asymptomatic patients with severe MR are different, reflecting controversy. The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend early surgery for asymptomatic patients if the success rate of mitral valve (MV) repair is expected to exceed 90%, but the 2012 European Society of Cardiology guidelines recommend watchful waiting for such patients (1,2).

The clinical outcomes of asymptomatic patients with MR are poorly defined (3), and it is important to identify

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high-risk patients in whom early surgery may be warranted. Older patients and those with a larger effective regurgitant orifice area (EROA) showed increased mortality with medical management (6,10), but it is controversial whether early surgery would improve clinical outcome of such patients because the performance of surgery in high-risk patients may be associated with increased operative risk.

We previously compared clinical outcomes of early surgery with those of conventional treatment in asymptomatic severe MR. In our previous single-center study, early surgery was significantly associated with a reduction in cardiac events, but no significant differences in all-cause or cardiac mortality were found in a propensity analysis (8). In the present study, we sought to examine the hypothesis that early surgery is associated with a significant decrease in all-cause and cardiac mortalities using a propensity analysis of greater registry data collected prospectively at 2 centers and to confirm whether early surgery would be more beneficial to older patients with a larger EROA.

Methods

Study population. A prospective registry, started in 1996 at Asan Medical Center and in 2001 at Samsung Medical Center, has included all consecutive patients with MR undergoing echocardiography at our hospitals. Case report forms, including patient demographics, clinical presentation, and echocardiographic data, were stored in an electronic database (8). Comorbidity was assessed using the Charlson comorbidity scale, which assigns weights to specific comorbid disease states (11). Clinical and echocardiographic follow-up data of study patients were collected annually and entered into the database. From 1996 to 2009, 1,505 patients had a diagnosis of severe degenerative MR at the time of enrollment, but 93 patients who had an EROA <0.4 cm^2 were not included in the analysis. Of the 1,412 patients who had an EROA ≥ 0.4 cm^2 and received a diagnosis of severe degenerative MR, 601 patients with exertional dyspnea were excluded; 811 patients were assessed for eligibility, 16 of whom were not candidates for surgery and 185 of whom were excluded according to the recommendations of the 2006 ACC/AHA guidelines for surgical indications of asymptomatic severe MR (1). Because the presence of coronary artery disease is an important prognostic factor, and concomitant coronary artery bypass graft operation may increase the operative risk, patients with a history of coronary artery disease or regional wall motion abnormalities were also excluded, but 25 patients with incidental coronary artery disease detected on pre-operative coronary angiography were not excluded. Of the 786 patients requiring surgery and excluded from the study, 649 (83%) underwent surgery with 9 (1.4%) operative mortalities. MV repair and replacement were performed in 503 (78%) and 146 (22%) patients, respectively (Online Table 1). Baseline clinical and echocardiographic characteristics of excluded patients are listed in Online Table 2. The primary cohort comprised 610 asymptomatic patients (364 men, 50 ± 14 years of age) with chronic severe degenerative MR who were potential candidates for early surgery (Fig. 1). The treatment groups were not assigned randomly. Instead, the choice of early surgery or conventional treatment for each patient was at the discretion of the attending physician, who explained the potential benefits and procedural risks of early surgery in detail and, most importantly, took the preferences of the individual patients into account. Early elective surgery was performed on 235 patients (early surgery group) within 6 months of the initial echocardiographic evaluation, and the conventional treatment strategy was chosen for 375 patients (conventional treatment group). Because in the absence of hypertension, there is no known indication for the use of medical therapy in asymptomatic patients with MR and preserved LV systolic function, patients in the conventional treatment group were observed without medical therapy and were referred for surgery if exertional dyspnea developed and they had an LV ejection fraction (EF) ≤ 0.60, LV end-systolic dimension ≥ 40 mm, Doppler estimated pulmonary artery pressure >50 mm Hg, or atrial fibrillation. Informed consent was obtained from each patient, and the study protocol was separately approved by the ethics committees of our institutions.

Abbreviations and Acronyms

ACC/AHA = American College of Cardiology/American Heart Association

CHF = congestive heart failure

EDD = end-diastolic dimension

EF = ejection fraction

EROA = effective regurgitant orifice area

LV = left ventricular

MR = mitral regurgitation

MV = mitral valve

PISA = proximal isovelocity surface area

Echocardiographic evaluation. Echocardiographic evaluation was performed at baseline and annually during follow-up. Two-dimensional echocardiography and Doppler color flow imaging were performed on all patients using a Hewlett-Packard Sonos 2500, 5500, or 7500 imaging system (Hewlett-Packard, Andover, Massachusetts) and a VIVID 7 or E9 ultrasound system (General Electric Healthcare, Little Chalfont, United Kingdom). End-diastolic dimension and end-systolic dimension of the left ventricle were measured from parasternal M-mode acquisitions, and the end-systolic volume, end-diastolic volume, and EF of the left ventricle were calculated with the biplane Simpson method (12). Comprehensive echocardiographic evaluation of MR was performed using the integrated approach of 2-dimensional, Doppler, and color flow imaging. With the simplified proximal isovelocity surface area (PISA) method, the degree of MR was graded as mild (PISA radius <4 mm), moderate (PISA radius <8 mm), and severe (PISA radius ≥ 8 mm) (13). Severe degenerative MR was defined as severe prolapse and/or flail leaflet of the MV with an EROA of holosystolic MR ≥ 0.4 cm^2. The EROA was determined by dividing the regurgitant flow rate, calculated as $2\pi r^2 \times$ aliasing velocity, where r is the PISA radius, by peak MR velocity (14). In the patients

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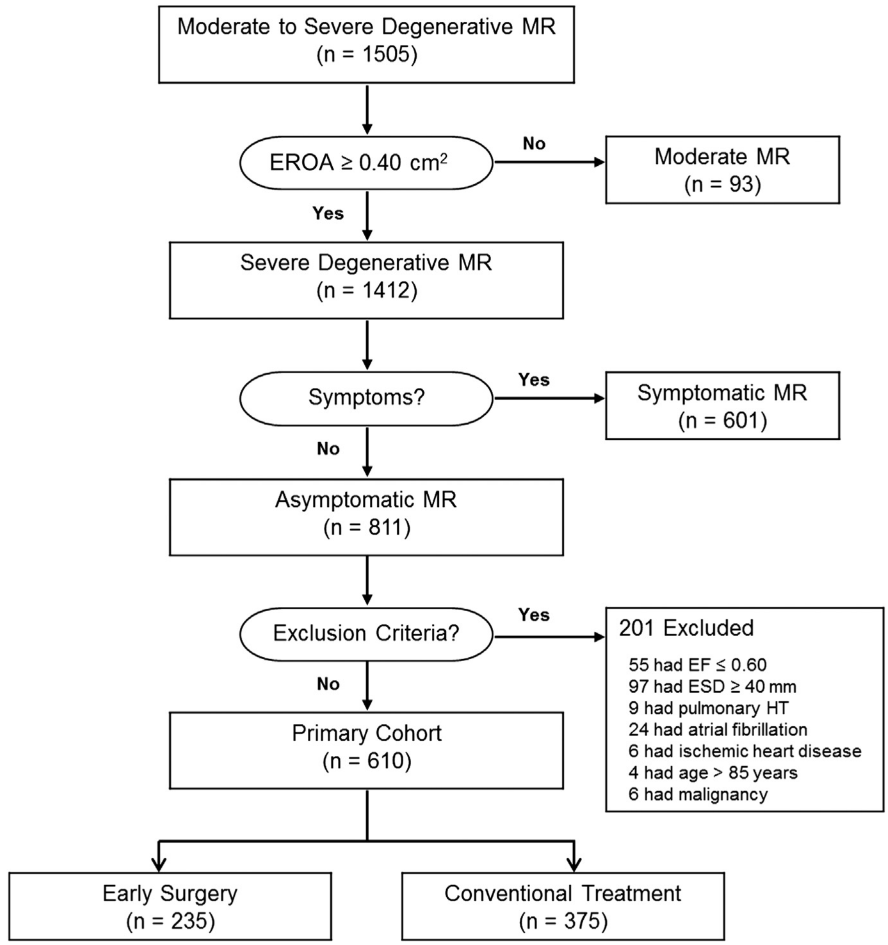

Figure 1 **Flow Diagram of Study Patients**

EF = ejection fraction; EROA = effective regurgitant orifice area; ESD = end-systolic dimension; HT = hypertension; MR = mitral regurgitation.

with eccentric or multiple MR jets for which PISA is less accurate, the EROA was also obtained by volumetric methods based on quantitative Doppler measurement of mitral and aortic stroke volumes (15,16). Regurgitant volume was also measured in 244 patients (40%) with an acceptable envelope of MR jet. Transesophageal echocardiography was performed in 452 patients (74%) to evaluate the functional anatomy of the MV in detail and to assess the feasibility of repair.

Surgical procedures. The procedures were performed with the use of standard cardiopulmonary bypass. In the early surgery group, MV repair and replacement were performed successfully in 222 (94%) and 13 (6%) patients, respectively, and concomitant coronary artery bypass grafting at the time of MV surgery was performed on 23 patients (10%), with bypass grafts of 2.1 ± 1.2 vessels. MV repair was performed with the following techniques singly or in combination: new chord formation, quadrangular resection, and commissuroplasty, and all but 2 patients also underwent annuloplasty with an annular ring, the mean size of which was 30.2 ± 2.2 mm.

Follow-up. All the study patients were asked to visit their attending physician regularly every 6 to 12 months, and the study coordinators called them if they missed their appointment for annual follow-up. Data were obtained during annual visits to the outpatient clinic or echocardiographic laboratory until March 2013. Operative mortality was defined as death within 30 days of surgery. Deaths were classified as cardiac or noncardiac on the basis of the medical records. Regular follow-up was complete for 514 patients (84%), and follow-up information was complemented by telephone interviews in 96 patients (16%) with irregular follow-up. Follow-up information was complete for 598 patients (98%). For the 8 patients (2%) in the conventional treatment group, and the 4 patients (2%) in the early surgery group who were lost to follow-up, data on the vital status, dates, and causes of death were obtained from the Korean National Registry of Vital Statistics.

The primary endpoint of the study was defined as cardiac death during follow-up, and the secondary endpoint was all-cause death and the composite of operative mortality, cardiac death, repeat MV surgery, and hospitalization due to congestive heart failure (CHF) during follow-up. A hospitalization for CHF was defined as an unplanned, urgent admission for the management of CHF. A patient admitted for CHF had to show resting dyspnea and radiological signs of pulmonary edema and require intravenous diuretics.

Statistical analysis. Categorical variables are presented as numbers and percentages and were compared using the chi-square test and Fisher exact test. Continuous variables are expressed as mean ± SD and were compared using the Student unpaired *t* test or the Mann-Whitney *U* test. Analysis of the clinical endpoint was performed on an intention-to-treat basis. Event-free survival curves were constructed with Kaplan-Meier estimates and compared by using the log-rank test. For Kaplan-Meier analysis, we analyzed all clinical events by time to first event and the patients in the conventional treatment group who developed criteria for MV surgery but refused to undergo surgery were censored at the time an indication for surgery developed. Cox proportional hazards analysis was performed to compare hazard rates of outcomes between the early surgery and conventional treatment groups.

To reduce the effect of treatment selection bias and potential confounding in this observational study, we performed rigorous adjustment for the differences in baseline characteristics using propensity-score matching (17). The propensity scores were estimated without regard to outcome variables, using multiple logistic regression analysis. All prespecified covariates were included in the full nonparsimonious models for treatment with early surgery versus conventional strategy (Table 1). The discrimination and calibration ability of the propensity-score model was assessed by means of the C statistic (C = 0.691) and the Hosmer-Lemeshow statistic (chi-square = 6.165, df = 8, p = 0.63). The propensity score–matched pairs were created by matching early surgery and conventional strategy subjects on

Table 1 Baseline Characteristics of Patients Who Underwent Early Surgery and Those Who Underwent Conventional Treatment

	Overall Cohort			Propensity Score–Matched Cohort		
	Early Surgery Group (n = 235)	Conventional Treatment Group (n = 375)	p Value	Early Surgery Group (n = 207)	Conventional Treatment Group (n = 207)	p Value
Age, yrs	50.5 ± 14.0	50.2 ± 14.6	0.82	50.5 ± 14.2	49.0 ± 14.1	0.28
Male	130 (55)	234 (62)	0.08	116 (56)	115 (56)	0.92
Body surface area, m^2	1.70 ± 0.19	1.72 ± 0.18	0.21	1.71 ± 0.19	1.72 ± 0.19	0.54
Body mass index, kg/m^2	24.0 ± 3.4	23.9 ± 3.3	0.67	24.1 ± 3.3	23.9 ± 3.4	0.53
Smoking	85 (36)	98 (26)	0.008	69 (33)	63 (30)	0.53
Diabetes	13 (6)	21 (6)	0.97	11 (5)	10 (5)	0.82
Chronic renal insufficiency	1 (0.4)	2 (0.5)	1.00	1 (0.5)	1 (0.5)	1.00
Hypertension	87 (37)	138 (37)	0.96	75 (36)	78 (38)	0.76
Drug therapy						
ACE inhibitor	19 (8)	19 (5)	0.13	15 (7)	11 (5)	0.41
Angiotensin receptor blocker	37 (16)	44 (12)	0.16	34 (16)	24 (12)	0.16
Calcium antagonist	21 (9)	30 (8)	0.68	17 (8)	13 (6)	0.45
Beta-blocker	16 (7)	22 (6)	0.64	14 (7)	8 (4)	0.19
Diuretics	34 (14)	32 (9)	0.02	30 (14)	20 (10)	0.13
Cholesterol, mg/dl	176 ± 48	177 ± 49	0.83	177 ± 47	175 ± 49	0.73
Additive EuroSCORE	1.10 ± 1.21	1.04 ± 1.31	0.26	1.09 ± 1.21	1.02 ± 1.21	0.39
Charlson comorbidity index	0.59 ± 0.90	0.54 ± 1.12	0.012	0.58 ± 0.87	0.54 ± 1.11	0.29
Reasons for echocardiography			0.12			0.66
Cardiac murmur alone	60 (26)	125 (33)		55 (27)	51 (25)	
Referral from other hospitals	167 (71)	237 (63)		147 (71)	148 (71)	
Pre-operative consultation*	8 (3)	13 (4)		5 (2)	8 (4)	
End-systolic dimension, mm	34.9 ± 4.1	34.4 ± 3.8	0.15	34.7 ± 4.1	34.7 ± 3.8	0.97
End-diastolic dimension, mm	58.8 ± 5.5	57.2 ± 5.1	<0.001	58.3 ± 5.6	58.3 ± 5.1	0.96
Left atrial dimension, mm	47.0 ± 6.8	45.6 ± 6.5	0.013	46.4 ± 6.7	46.4 ± 6.4	0.96
Ejection fraction, %	66.0 ± 5.2	65.6 ± 4.6	0.38	65.8 ± 5.0	65.6 ± 4.7	0.64
Prolapsed segment			0.81			0.83
Anterior	45 (19)	65 (17)		40 (19)	45 (22)	
Posterior	128 (54)	213 (57)		116 (56)	113 (55)	
Both	62 (26)	97 (26)		51 (25)	49 (24)	
EROA, cm^2	0.86 ± 0.37	0.76 ± 0.33	0.001	0.82 ± 0.34	0.81 ± 0.37	0.94

Values are mean ± SD or n (%). *Pre-operative consultation for noncardiac surgery.
ACE = angiotensin-converting enzyme; EROA = effective regurgitant orifice area; EuroSCORE = European System for Cardiac Operative Risk Evaluation score; MR = mitral regurgitation.

the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score (18). A Greedy matching was performed by using the %GMATCH macro; the Division of Biostatistics at the Mayo Clinic provides a set of SAS macros on its website (19) for propensity-score matching. After propensity-score matching, the baseline covariates were compared between the 2 groups with a paired *t* test or Wilcoxon signed rank test for continuous variables and the McNemar test or marginal homogeneity test for categorical variables (Table 1). We also examined the similarity of early surgery and conventional treatment strategy subjects in the propensity score–matched sample by calculating standardized differences for each of the baseline variables listed in Table 1. All of the standardized differences for each of the baseline variables were <0.10 (10%) after matching. In the propensity score–matched cohort, the risks of clinical endpoints were compared using Cox regression models with robust standard errors that accounted for the clustering of matched pairs. Moreover, we also adjusted for differences in baseline characteristics in the overall cohort by using weighted Cox proportional hazards regression models with inverse probability of treatment weighting method (20), with weights for patients receiving early surgery being the inverse of (1 − propensity score) and weights for patients receiving conventional treatment being the inverse of propensity score.

All reported p values were 2 sided, and a value of $p < 0.05$ was considered statistically significant. SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina), was used for statistical analyses.

Results

Baseline characteristics. The baseline clinical and echocardiographic characteristics of the early surgery and conventional treatment group were compared, as shown in Table 1. There were no significant differences between the 2 groups in terms of age, sex, body mass index, diabetes mellitus, hypertension, EF, EuroSCORE (European System for Cardiac Operative Risk Evaluation score), and location of prolapsed segments. However, the early surgery group had a significantly higher Charlson comorbidity index and a significantly larger EROA, LV dimensions, and left atrial diameter ($p < 0.05$). Regurgitant volume was also significantly larger in the early surgery group than in the conventional treatment group (96 ± 31 ml vs. 84 ± 31 ml, $p < 0.01$). Propensity-score matching for the overall cohort yielded 207 matched pairs of patients, the ages of whom ranged from 16 to 82 years. In the matched cohort, there were no longer any significant differences between the early surgery group and the conventional treatment group for any covariates, according to the use of statistical methods appropriate for matched data (Table 1).

Comparison of outcomes in the overall cohort. There were no cases of operative mortality in the early surgery group. The median follow-up was 7.5 years (interquartile range, 5.4 to 10.9 years) in the early surgery group and 8.2 years (interquartile range, 5.5 to 10.9 years) in the conventional treatment group ($p = 0.50$). The patients in the conventional treatment group in whom an indication for surgery developed, but who were not operated on, were censored at the time that they reached criteria for surgery, and 1 sudden death, 5 CHF deaths, and 1 noncardiac death that occurred after censoring were not counted in the endpoints. During follow-up, there were 1 cardiac and 14 noncardiac deaths in the early surgery group and 13 cardiac and 18 noncardiac deaths in the conventional treatment group. The estimated actuarial 12-year mortality rates were 9 ± 3% in the early surgery group and 12 ± 2% in the conventional treatment group ($p = 0.46$)) (Fig. 2A). The causes of noncardiac deaths were malignancy (n = 6), stroke (n = 5), infection (n = 1), suicide (n = 1), and trauma (n = 1) in the early surgery group, and malignancy (n = 12), stroke (n = 2), infection (n = 1), trauma (n = 2), and

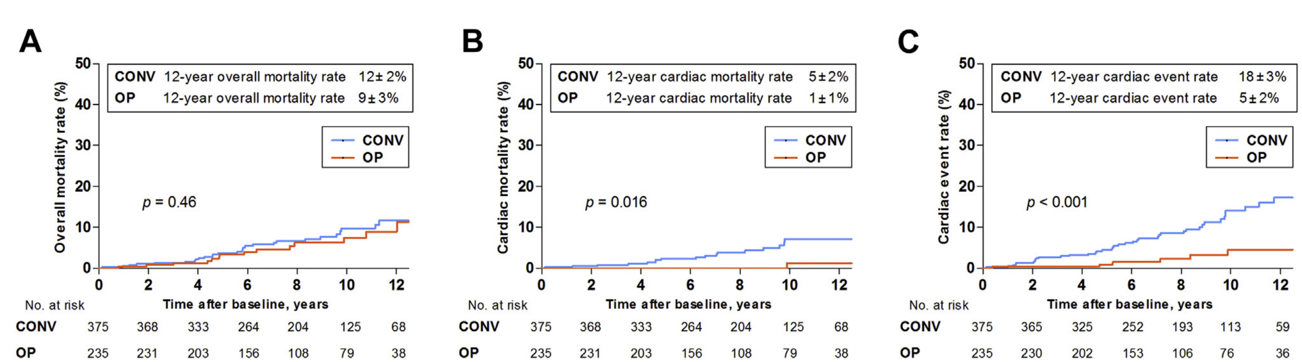

Figure 2 Comparison of Endpoints in the Overall Cohort

Kaplan-Meier curves for the cumulative probabilities of overall mortality **(A)**, cardiac mortality **(B)**, and cardiac event **(C)** according to treatment group in the overall cohort. CONV = conventional treatment group; OP = early surgery group.

Table 2 HRs for Clinical Outcomes of Early Surgery Compared With Conventional Treatment

	No. of Events		Unadjusted		Adjusted by IPTW	
	Early Surgery (n = 272)	CONV (n = 417)	HR (95% CI)	p Value	HR (95% CI)	p Value
All-cause death	15	31	0.791 (0.427–1.465)	0.46	0.613 (0.320–1.177)	0.14
Cardiac death	1	13	0.124 (0.016–0.944)	0.044	0.136 (0.018–1.028)	0.053
Cardiac event	6	40	0.240 (0.102–0.566)	0.001	0.205 (0.085–0.492)	< 0.001

CI = confidence interval; CONV = conventional treatment; HR = hazard ratio; IPTW = inverse probability of treatment weights.

dementia (n = 1) in the conventional treatment group. The causes of cardiac deaths in the conventional treatment group were sudden cardiac death in 8 patients, CHF in 1, operative mortality after late urgent surgery in 1, endocarditis in 2, and acute myocardial infarction in 1, whereas 1 cardiac death in the early surgery group was due to CHF related to a recurrence of severe MR. The mean ages of 14 patients who died of cardiac causes later were 65 ± 9 years at the time of enrollment. The risk of cardiac mortality was significantly lower in the early surgery group (HR: 0.124; 95% CI: 0.016 to 0.944; p = 0.044), and the estimated actuarial 12-year cardiac mortality rates were 1 ± 1% in the early surgery group and 5 ± 2% in the conventional treatment group (p = 0.016) (Fig. 2B). Four patients in the early surgery group and 1 patient in the conventional treatment group underwent repeat MV surgery, and 1 patient in the early surgery group and 26 patients in the conventional treatment group required hospitalization for CHF without cardiac mortality. Thus, 6 patients (2.6%) in the early surgery group and 40 patients (10.7%) in the conventional treatment group attained the composite endpoint, and the estimated actuarial 12-year event rate was 5 ± 2% in the early surgery group and 18 ± 3% in the conventional treatment group (p < 0.001) (Fig. 2C). The risk of a cardiac event was significantly lower in the early surgery group than in the conventional treatment group on unadjusted and adjusted Cox proportional hazard model analysis by the inverse probability of treatment weighting method (Table 2).

Although occurrences of atrial fibrillation and stroke were not pre-specified endpoints, persistent or post-operative paroxysmal atrial fibrillation occurred in 50 patients (21.2%) in the early surgery group and in 35 patients (9.3%) in the conventional treatment group during follow-up, nonfatal and fatal strokes occurred in 6 patients (2.6%) in the early surgery group, and in 7 patients (1.9%) in the conventional treatment group during follow-up.

In the conventional treatment group, 99 patients (26%) underwent late MV surgery with MV repair (n = 81) or MV replacement (n = 18) at the mean interval of 4.4 ± 3.1 years after enrollment. There was 1 operative mortality (1.0%) in the conventional treatment group with late surgery, and the repair rate was significantly lower than that in the early surgery group (82% vs. 94%, p < 0.001). The operative mortality and repair rate in the conventional treatment group with late surgery were similar to those of patients excluded due to the presence of symptoms or echocardiographic criteria for surgery. The early surgery group and the conventional treatment group with late surgery were compared in terms of the results of echocardiographic examinations performed after surgery and during follow-up (Table 3). The 2 treatment groups were similar in terms of LV dimensions, volumes, and EF at baseline, but the early surgery group had significantly smaller LV dimensions and volumes on immediate post-operative echocardiographic examinations. In the early surgery group, 12 patients (5.1%) had recurrences of moderate (n = 9) or severe (n = 3) MR, and 4 (1.5%) underwent repeat MV surgeries due to severe symptomatic MR (n = 2), infective endocarditis (n =1), or severe symptomatic mitral stenosis due to pannus formation at the annular ring (n = 1). The estimated actuarial 12-year rates of MR recurrence and

Table 3 Comparison of Echocardiographic Results Between the Early Surgery and Late Surgery Groups

	Early Surgery Group (n = 235)			Late Surgery Group (n = 99)		
	Baseline	Post-Operative	Follow-Up	Baseline	Post-Operative	Follow-Up
End-systolic dimension, mm	34.9 ± 4.1*	33.8 ± 4.8†	30.4 ± 4.3†	35.8 ± 3.0	36.4 ± 5.4	32.3 ± 5.0
End-diastolic dimension, mm	58.8 ± 5.5	49.5 ± 5.0†	48.2 ± 4.6	59.4 ± 4.4	51.8 ± 6.0	49.3 ± 5.4
End-systolic volume, ml	48.4 ± 18.4	40.8 ± 17.1†	37.9 ± 13.8	48.1 ± 15.2	49.6 ± 20.5	40.6 ± 13.8
End-diastolic volume, ml	139.2 ± 44.3	93.3 ± 31.9†	94.6 ± 29.0	141.3 ± 38.9	109.7 ± 33.2	101.1 ± 29.7
Ejection fraction, %	66.0 ± 5.2	56.8 ± 8.0	61.3 ± 5.6	66.2 ± 4.7	55.4 ± 8.0	60.1 ± 5.8
Recurrence of MR						
Moderate MR	—	—	9 (3.8)	—	—	1 (1.0)
Severe MR	—	—	3 (1.3)	—	—	1 (1.0)

Values are mean ± SD or n (%). *p < 0.05. †p < 0.01 versus late surgery group.
MR = mitral regurgitation.

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Table 4 HRs for Clinical Outcomes of Early Surgery Compared With Conventional Treatment in the Propensity Score-Matched Cohort

	No. of Events		Propensity Score Matching	
	Early Surgery (n = 207)	CONV (n = 207)	HR (95% CI)	p Value
All-cause death	11	22	0.509 (0.241–1.077)	0.078
Cardiac death	1	9	0.109 (0.014–0.836)	0.033
Cardiac event	5	23	0.216 (0.083–0.558)	0.002

Abbreviations as in Table 2.

repeat MV surgery in the early surgery group were 8 ± 2% and 3 ± 2%, respectively.

Comparison of outcomes in the propensity score–matched cohort. For the 207 propensity–score matched pairs, the early surgery group had a significantly lower cardiac mortality rate (1 ± 1% vs. 6 ± 2% at 12 years, p = 0.010) and cardiac event rate (4 ± 2% vs. 19 ± 4% at 12 years, p = 0.001) (Fig. 3). Cox regression model with robust SEs also revealed that the early surgery group had significantly lower risks of cardiac death (HR: 0.109; 95% CI: 0.014 to 0.836; p = 0.033) and cardiac events (HR: 0.216; 95% CI: 0.083 to 0.558; p = 0.002) than the conventional treatment group (Table 4).

Subgroup analysis according to age. Subgroup analysis was performed to determine the impact of early surgery on cardiac endpoint according to age. In the 283 patients younger than 50 years of age, there were 1 cardiac and 3 noncardiac deaths, and in the 327 patients 50 years of age and older, there were 13 cardiac and 29 noncardiac deaths. On Cox proportional hazard model analysis, the early surgery group had a significantly lower risk of cardiac mortality than the conventional treatment group in the patients 50 years of age and older, but the difference was not significant in terms of overall mortality (Table 5). In patients 50 years of age and older, the risk of a cardiac event was significantly lower in the early surgery group than in the conventional treatment group (p = 0.002), but not significantly different in those aged younger than 50 years of age (p = 0.20). In the propensity score–matched analysis of those 50 years of age and older, the early surgery group also had a significantly lower risk of cardiac mortality (HR: 0.120; 95% CI; 0.015 to 0.932; p = 0.043) and cardiac events (HR: 0.189; 95% CI; 0.066 to 0.543; p = 0.002) than the conventional treatment group. In patients 50 years of age and older, the early surgery group had a significantly lower cardiac mortality rate (2 ± 2% vs. 9 ± 3%, p = 0.017) and cardiac event rate (6 ± 3% vs. 26 ± 5%, p = 0.001) at 12 years (Fig. 4).

Discussion

Principal findings. In this propensity analysis of a large cohort of asymptomatic patients with severe MR and preserved LV systolic function, early surgery was associated with significant long-term reductions of cardiac mortality and cardiac events. We previously reported that early surgery was associated with an improved cardiac event rate at 7 years for the 127 propensity score–matched pairs, but significant reductions in cardiac mortality could not be demonstrated due to the small number of patients and insufficient follow-up duration (8). Merging prospective registry data of 2 centers and lengthening follow-up duration to 12 years provided our study with sufficient power to compare cardiac mortalities between the 2 management strategies in a propensity analysis. The larger number of study patients also made it possible to show that the risk-to-benefit ratios of

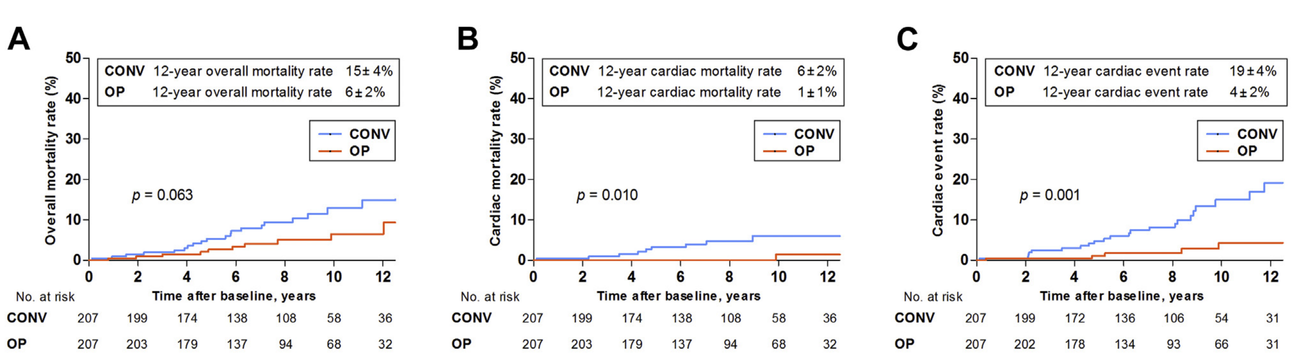

Figure 3 Comparison of Endpoints in a Propensity Score–Matched Cohort

Kaplan-Meier curves for the cumulative probabilities of overall mortality **(A)**, cardiac mortality **(B)**, and cardiac event **(C)** according to treatment group in a propensity score–matched cohort.

Table 5 HRs for Clinical Outcomes of Early Surgery Compared With Conventional Treatment According to Age

	No. of Events		Unadjusted	
	Early Surgery	CONV	HR (95% CI)	p Value
Age <50 yrs	n = 106	n = 177		
All-cause death	2	2	1.76 (0.25–12.51)	0.57
Cardiac death	0	1	NC	
Cardiac event	1	7	0.26 (0.03–2.08)	0.20
Age ≥50 yrs	n = 129	n = 198		
All-cause death	13	29	0.67 (0.35–1.30)	0.24
Cardiac death	1	12	0.125 (0.016–0.960)	0.046
Cardiac event	5	33	0.221 (0.086–0.567)	0.002

NC = not calculable; other abbreviations as in Table 2.

early surgery were significantly different according to age subgroups. Moreover, our previous study could not show a significant difference in repair rate between the early surgery group and the conventional treatment group with late surgery (8), but this study demonstrates that the repair rate of late surgery was significantly lower than early surgery.

Durability of early MV repair. Before early pre-emptive surgery can be recommended, it must be associated with very low operative mortality (<1%), high repair rates, and high durability of repair (21). The long-term benefit of early surgery has been questioned by previous reports suggesting increased risks of reoperation and recurrence of MR (22,23). The operative mortalities in asymptomatic patients who had MV repair ranged from 0% to 0.5% in experienced centers (24,25), and a recent study of early surgery (26) yielded long-term overall mortality rate of 14 ± 4% at 10 years, which is similar to that in the present study. Repair rates and durability of MV repair in large mitral repair centers are similar to those observed in the present study, reporting repair rates >90% with low reoperation rates <5% at 10 years (27–29). In addition to the very low operative mortality and high repair rate found in our previous study, the present study confirms the durability of early MV repair by showing very low long-term rates of reoperation and recurrence of MR.

Clinical implications. Early surgery was associated with a significant decrease in cardiac mortality and cardiac event for patients 50 years or age and older, but there were no significant differences between the early surgery and the conventional treatment groups in those younger than 50 years of age. A recent study that enrolled older patients (mean age, 65 ± 13 years) with flail mitral leaflets also reported that early surgery was associated with greater long-term survival and a lower risk of heart failure (30). Because aging is related to progression of MR and poor tolerance to MR (31), clinical outcomes were different in relation to the age of patients included in previous observational studies (6,9). The natural history of asymptomatic MR (10) also showed that 10-year cardiovascular morbidity was significantly higher for patients 50 years of age and older than for those younger than 50 years of age at diagnosis (45 ± 4% vs. 10 ± 2%). Considering that patients aged younger than 50 years of age have excellent outcomes and a conventional treatment strategy may decrease the number of surgeries performed, it is possible that a watchful waiting strategy may play a role in the initial management of such patients.

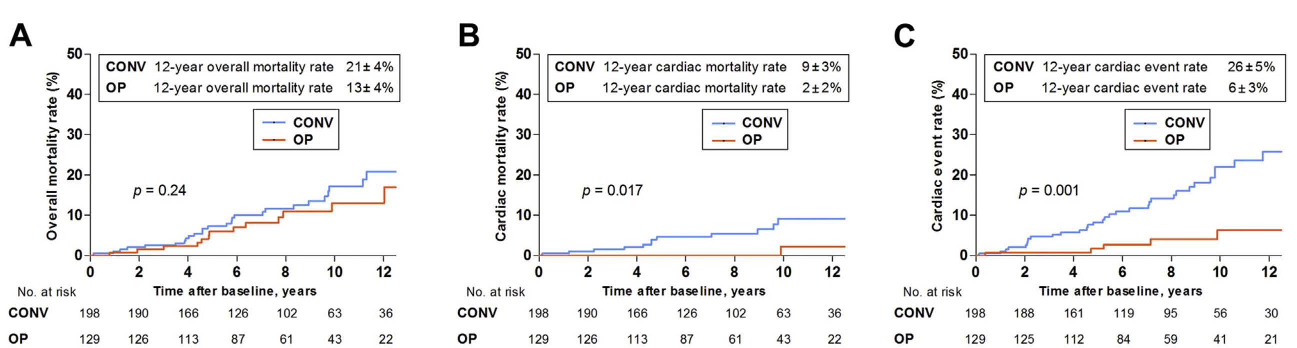

Figure 4 Comparison of Endpoints in Patients 50 Years of Age and Older

Kaplan-Meier curves for the cumulative probabilities of overall mortality **(A)**, cardiac mortality **(B)**, and cardiac event **(C)** according to treatment group in patients 50 years of age and older. Abbreviations as in Figure 1.

Furthermore, the clinical practice of valve repair is globally insufficient, and only 69% of patients undergo MV repair according to data from the Society of Thoracic Surgeons database (32). However, it should be noted that in these low-risk patients, early and late surgeries may differ significantly in terms of repair rates and post-operative LV dysfunction; moreover, compared with early surgery, conventional treatment of low-risk patients requires more frequent clinical and echocardiographic follow-up examinations and prompt referral to surgery once they reach surgical criteria (33). The current ACC/AHA guidelines suggest a medical management approach in elderly patients because operative mortality increases and survival is reduced in patients older than 75 years of age (1). Because the patients included in the propensity analysis ranged to 82 years, our results may not be applicable to elderly patients older than 75 years of age.

Quantitative assessment of MR is strongly recommended in the guidelines, and measurement of the EROA has an important prognostic value (34). In a large prospective study of MR, Enriquez-Sarano et al. (6) reported that patients with an EROA $\geq$0.4 cm^2 had excess mortality and that a greater survival benefit was associated with surgery for larger EROAs and suggested that patients with an EROA $\geq$0.4 cm^2 should promptly be considered for cardiac surgery. However, proponents of the watchful waiting argued that this study did not provide a basis for early surgery because early surgery was not compared directly with the watchful waiting strategy (23). Although randomized trials are required to establish indications for early surgery, ethical and financial constraints prevent us from conducting a randomized trial. Given the absence of randomized trials, a recent study by Suri et al. (30) and our study support the early surgery strategy by demonstrating significant differences in the rate of primary endpoints between groups in both risk-adjusted models and propensity score–matched cohorts and strongly suggest that early surgery should be considered for patients who are older than 50 years of age and have an EROA $\geq$0.4 cm^2 or flail mitral leaflets.

Study limitations. Comparison of treatment strategies was subject to the limitations inherent to nonrandomized assignment, and such limitations may have significantly affected our results due to selection bias and unmeasured confounders. To control for the inherent biases related to treatment selection and heterogeneity in baseline factors, we performed a propensity analysis, which consistently showed significantly lower rates of cardiac endpoints in the early surgery group. Although it would be desirable that prospective, randomized clinical trials confirm the efficacy of early surgery, in the absence of such studies, the results of the present study provide the strongest observational evidence that early surgery is effective for asymptomatic patients with severe MR.

Because the operative mortality was very low in the present study, our results may not be applicable to patients at high operative risk. Current guidelines recommend that asymptomatic patients with severe MR should be seen every 6 months (1,2) and annual follow-up was not enough for close monitoring of high-risk patients. Regular follow-up was partially complete, and not every patient in the conventional treatment group complied with a watchful waiting strategy during the entire follow-up. Although a differential impact of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers might have altered relative hazards between the 2 groups, it could not be analyzed. The large sample size of our study provided sufficient number of patients for a propensity analysis, but it was not possible in the subgroup analysis to analyze the heterogeneity of treatment effects on tests for interaction due to the small number of endpoints observed in the early surgery group. It might be considered a limitation that an analysis was not performed of this entire registry and was retrospectively limited to patients with an EROA $\geq$0.4 cm^2.

Conclusions

Compared with conservative management, early surgery is associated with an improved long-term outcome by decreasing cardiac mortality and cardiac events in asymptomatic patients with severe MR in a propensity analysis. Although early surgery is generally the preferred strategy for asymptomatic patients with severe MR, the difference in cardiac event rates was not significant among patients aged younger than 50 years of age.

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Key Words: echocardiography ▪ mitral valve ▪ regurgitation ▪ surgery.

APPENDIX

For supplemental material, please see the online version of this article.