

ORIGINAL RESEARCH ARTICLE



Long-Term Outcomes of Early Surgery Versus Conventional Treatment for Asymptomatic Severe Mitral Regurgitation: A Propensity Analysis

Sung-Ji Park MD, PhD*; Mijin Kim MD, PhD*; Jihee Son MD; Ha Hye Jo MD; Ga Yun Kim MD; Jihoon Kim, MD; Byung Joo Sun MD, PhD; Eun-Kyung Kim, MD, PhD; Sahmin Lee MD, PhD; Jae Suk Yoo MD, PhD; Sung-Cheol Yun, PhD; Sung-Ho Jung, MD, PhD; Jong-Min Song MD, PhD; Duk-Hyun Kang MD, PhD

BACKGROUND: The timing of surgery in asymptomatic severe mitral regurgitation remains controversial. This observational study sought to compare long-term outcomes of early surgery with a conventional treatment strategy in asymptomatic patients with severe mitral regurgitation.

METHODS: From 1996 to 2016, a total of 1063 consecutive asymptomatic patients (673 men; mean \pm SD age, 51 \pm 14 years) with severe degenerative mitral regurgitation and preserved left ventricular function were enrolled, and followed prospectively for a median of 12 years (interquartile range, 8–17 years). Early surgery was performed on 545 patients and the conventional treatment strategy was chosen for 518 patients. We compared overall and cardiac mortality rates between these 2 treatment strategies using propensity score adjustment.

RESULTS: In the early surgery group, no operative deaths occurred, and mitral valve repair was successfully performed in 97% of patients. During follow-up, 8 (1.5%) patients in the early surgery group and 54 (10.4%) in the conventional management group died from cardiovascular causes (hazard ratio, 0.17 [95% CI, 0.07–0.40]; $P<0.001$). A total of 74 (13.6%) deaths from any cause occurred in the early surgery group, whereas 116 (22.4%) occurred in the conventional management group (hazard ratio, 0.72 [95% CI, 0.52–0.99]; $P=0.046$). For the 358 propensity score matched pairs, the early surgery group had a significantly lower risk of cardiac mortality than the conventional treatment group (hazard ratio, 0.18 [95% CI, 0.08–0.43]; $P<0.001$) and significantly lower cardiac mortality rates (5.6% versus 17.4% at 20 years; $P=0.002$). Compared with the conventional treatment group, the early surgery group also had a significantly lower risk of overall mortality (hazard ratio, 0.66 [95% CI, 0.47–0.93]; $P=0.018$) and significantly lower overall mortality rates (28.2% versus 33.9% at 20 years; $P=0.015$).

CONCLUSIONS: Compared with conventional management, early surgery is associated with better long-term outcomes among asymptomatic patients with severe mitral regurgitation and preserved left ventricular function.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01703806.

Key Words: cardiac surgical procedures ■ mitral valve insufficiency ■ observation ■ outcome assessment ■ therapeutics ■ thoracic surgery

Editorial, see p 1218

Surgery is recommended for severe, degenerative mitral regurgitation (MR) in symptomatic and asymptomatic patients with left ventricular

(LV) dysfunction.^{1,2} However, controversy remains as to whether mitral valve (MV) repair should be performed in asymptomatic patients without LV dysfunction,^{3–5} and

Correspondence to: Duk-Hyun Kang, MD, PhD, Division of Cardiology, Asan Medical Center, College of Medicine, University of Ulsan, 388-1, Poongnap-dong, Songpa-gu, Seoul, Korea 138-736. Email dhkang@amc.seoul.kr

*S.-J. Park and M. Kim contributed equally.

Supplemental Material, the podcast, and transcript are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.125.074560>. Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

For Sources of Funding and Disclosures, see page 1217.

© 2025 American Heart Association, Inc.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- This prospective, observational study involving 1063 asymptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular systolic function demonstrated that compared with conventional treatment, early surgery is associated with better long-term outcomes.
- The clinical benefit of early surgical correction of asymptomatic severe mitral regurgitation was confirmed in a propensity cohort consisting of 358 matched pairs.

What Are the Clinical Implications?

- Conventional treatment (watchful observation with referral to surgery when surgical indications develop) appears to be a safe strategy, but early surgery may be a more effective treatment option for asymptomatic, severe mitral regurgitation at valve centers with >95% likelihood of successful mitral valve repair and an expected operative mortality rate of <1%.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
EDD	end-diastolic dimension
EF	ejection fraction
EROA	effective regurgitant orifice area
ESD	end-systolic dimension
HR	hazard ratio
LV	left ventricular
MR	mitral regurgitation
MV	mitral valve

the guidelines differ on indications for early surgery. The American Heart Association/American College of Cardiology guidelines recommend early surgery for asymptomatic patients with preserved LV function if the likelihood of a successful MV repair is >95%, but the 2021 European Society of Cardiology guidelines recommend watchful waiting for such patients.^{1,2}

The clinical outcomes of asymptomatic severe MR are heterogeneous,⁶ and asymptomatic patients with a flail MV or a larger effective regurgitant orifice area (EROA) of MR have shown poor outcomes under medical management.^{7,8} Among asymptomatic patients with flail MV, early surgery, compared with initial medical management, was associated with a significant survival benefit.⁹ However, according to a small observational study,¹⁰ the overall survival of such patients managed with a watchful waiting strategy was comparable to the expected survival of the

general population for up to 15 years. These controversial results underscore persistent uncertainty. Although a randomized clinical trial could provide definitive evidence, it is highly unlikely that a large, randomized trial will ever be conducted for asymptomatic MR. Data from large, carefully designed registries are needed to improve quality of care,¹ and we previously showed that early surgery was associated with reduced cardiac mortality rates, but not overall mortality rates, in asymptomatic severe MR.^{4,11} In the current study, we enrolled >1000 asymptomatic patients with degenerative MR (EROA of MR >0.4 cm²) and extended the duration of follow-up to >20 years. We sought to examine the hypothesis that early surgery is associated with better survival in these patients by comparing long-term cardiac mortality and all-cause mortality rates between early surgery and conventional treatment with the use of propensity score adjustment.

METHODS

Study Design

We conducted this prospective, multicenter, observational study involving asymptomatic patients with severe degenerative MR who were candidates for either early surgery or conservative management at 2 centers in Korea. The study protocol was designed by the principal investigator and approved by the institutional review board of each participating center. Because of data privacy restrictions, data from the current study are unable to be shared outside of the members of the executive committee.

Patient Selection

Eligibility criteria were 20 to 85 years of age; severe, degenerative MR without exertional dyspnea; LV ejection fraction (EF) >60%; and end-systolic dimension (ESD) <40 mm. Severe, degenerative MR should fulfill the following criteria: severe MV prolapse with loss of coaptation or flail leaflet and holosystolic MR with EROA >0.4 cm².¹

In accordance with the 2006 American Heart Association/American College of Cardiology guidelines on surgical indications for severe MR,¹² patients were excluded if they had exertional dyspnea or angina, LVEF ≤60%, LVEDD ≥40 mm, new onset of persistent atrial fibrillation (AF) secondary to MR, or substantial aortic valve disease.

Study Procedures

Eligibility was determined after each patient underwent a thorough evaluation of symptom status, medical records, and echocardiography results. After enrollment in the study, the treatment groups were not assigned randomly. Instead, the risks and benefits of early surgery and conventional treatment were explained to each patient, and the patients and attending physician collaborated to choose a management option that aligned with the individual patient's preferences and values, sharing responsibility for the decision of treatment. Informed consent was obtained from each patient and the study protocol was approved by the ethics committee of our institution.

The protocol specified that patients in the early surgery group should undergo MV surgery within 6 months of enrollment. Patients in the conventional treatment group were treated according to American Heart Association/American College of Cardiology guidelines^{1,12} and referred for surgery if they became symptomatic during follow-up, or if LVEF ≤60%, LVESD ≥40 mm, Doppler estimated pulmonary artery pressure >50 mmHg on follow-up echocardiography, or AF developed.

Echocardiographic evaluation was performed at baseline and annually during follow-up. End-diastolic dimension (EDD) and ESD of the left ventricle were measured from parasternal M-mode acquisitions, and end-systolic volume, end-diastolic volume, and EF of the left ventricle were calculated with the biplane Simpson method.¹³ Comprehensive echocardiographic evaluation of MR was performed using the integrated approach of 2-dimensional, Doppler, and color flow imaging. Preoperative transesophageal echocardiography was conducted for all patients undergoing MV surgeries to provide surgeons with a better understanding of the anatomic substrate for degenerative MR and the type of repair needed. The EROA was determined by dividing the regurgitant flow rate, calculated as $2\pi r^2 \times$ aliasing velocity, where r is the proximal isovelocity surface area radius, by peak MR velocity.¹⁴ A regurgitant volume was estimated as EROA multiplied by the velocity time integral of the MR jet. In cases of eccentric or multiple MR jets, for which the proximal isovelocity surface area method is less accurate, regurgitant volume and EROA were also obtained by volumetric methods based on quantitative Doppler measurement of mitral and aortic stroke volume.¹⁵

The protocol specified that all the study patients would be followed at 3 months, 6 months, and 1 year after enrollment, and at 6-month intervals thereafter until close-out of the study. Patients were also educated to report to a study coordinator or an investigator if they experienced exertional dyspnea or any symptoms. Adherence to scheduled follow-up was complete for 839 (79%) patients (394 [76.1%] in the conventional treatment group and 445 [81.7%] in the early surgery group), whereas 224 (21%) patients (124 [23.9%] in the conventional treatment group and 100 [18.3%] in the early surgery group; $P=0.026$) elected not to visit the heart valve clinic regularly, preferring to visit the clinic only when they experienced symptoms. For the 38 (7%) patients in the conventional treatment group and the 17 (3%) patients in the early surgery group who were lost to follow-up, data on vital status and dates and causes of death were obtained from the Korean national registry of vital statistics. The primary end point was cardiac death during follow-up and the secondary end point was all-cause death during follow-up. The causes of death were classified as cardiac or noncardiac on the basis of the medical records. Specific definitions of end points are provided in the *Methods* in the Supplemental Material.

Statistical Analysis

Analyses followed the intention-to-treat principle, in which all study patients were included in the treatment group originally assigned at the time of enrollment, and all deaths occurring after enrollment were included in the end points. Baseline clinical and echocardiographic characteristics were compared in the 2 treatment groups using the Student *t* test or the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables as appropriate. Given the potential

imbalance in baseline characteristics between enrolled patients in the treatment groups, outcomes were compared with the use of propensity score adjustment (propensity score matching and overlap propensity score weighting) to correct for selection biases and potential confounding.^{16,17} 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). A propensity score overlap plot is presented in Figure S1. The discrimination and calibration ability of the propensity score model was assessed by means of the *C* statistic ($C=0.73$) and the Hosmer-Lemeshow statistic ($\chi^2=3.67$, $df=8$, $P=0.89$). The propensity score-matched pairs were created by matching early surgery and conventional strategy participants on 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 After propensity score matching, we examined the similarity of early surgery and conventional strategy participants in the propensity score-matched sample by calculating standardized differences for each of the baseline variables listed in Table 1. All the standardized differences for each of the baseline variables were <0.10 (10%) after matching. Event-free survival curves were constructed with Kaplan-Meier estimates and compared using the stratified log-rank test.¹⁹ In the propensity score-matched cohort, the risks of mortality 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 overlap propensity score weighting. Overlap weighting is a propensity score method in which outliers do not dominate results and worsen precision.¹⁷ The proportional hazards assumption was checked by examination of $\log(-\log[\text{survival}])$ curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. In addition, the consistency of treatment effect was evaluated with tests for interaction among subgroups according to patient age, enrollment period, and compliance with the study protocol. All reported *P* values were 2 sided, and a *P* value <0.05 was considered statistically significant. SAS version 9.1 (SAS Institute, Inc.) and R package version 3.3.1 were used for statistical analyses.

RESULTS

Patient Characteristics

From 1996 to 2016, a total of 1063 consecutive asymptomatic patients with severe degenerative MR and preserved LV function were enrolled. The mean \pm SD age of the patients was 51.4 ± 13.7 years and 63.3% were men. Early surgery was performed on 545 patients and the conventional treatment strategy was chosen for 518 patients. The baseline clinical and echocardiographic characteristics of the early surgery group and the conventional treatment group were compared, as shown in Table 1. There were no significant differences between the 2 groups in terms of sex, body surface area, smoking, diabetes, hypertension, or EF. However, the early surgery group was older; had a higher comorbidity index; and had larger EROA of MR, LVESD, EDD, and left atrial

Table 1. Baseline Clinical and Echocardiographic Characteristics of the Study Patients According to Treatment Group

Characteristics	Overall cohort				Propensity score-matched cohort		
	Conventional (n=518)	Early surgery (n=545)	P value*	Standardized difference of mean, %	Conventional (n=358)	Early surgery (n=358)	Standardized difference of mean, %
Age, y	50.5±14.2	52.2±13.1	0.038	-12.7	51.6±14.5	51.2±13.7	-4.20
Male	340 (65.6)	333 (61.1)	0.125	9.4	221 (61.7)	224 (62.5)	-1.73
Body surface area, m ²	1.73±0.18	1.73±0.19	0.991	-0.1	1.72±0.18	1.72±0.19	0.53
Body mass index, kg/m ²	23.9±3.3	24.4±3.4	0.017	-14.7	24.0±3.2	24.1±3.3	-2.37
Smoking	127 (24.7)	136 (25.0)	0.926	-0.6	89 (24.9)	95 (26.5)	-3.84
Diabetes	32 (6.2)	34 (6.2)	0.967	-0.3	24 (6.7)	18 (5.0)	7.14
Chronic renal insufficiency	2 (0.4)	2 (0.4)	>0.999	0.3	1 (0.3)	1 (0.3)	0.00
Hypertension	185 (35.7)	200 (36.7)	0.739	-2.1	115 (32.1)	118 (33.0)	-1.79
Atrial fibrillation	4 (0.8)	14 (2.6)	0.023	-14.1	4 (1.1)	4 (1.1)	0.00
Drug therapy							
Angiotensin receptor blocker	88 (17.0)	162 (29.7)	<0.001	-30.5	70 (19.6)	73 (20.4)	-2.10
ACE inhibitor	30 (5.8)	37 (6.8)	0.499	-4.2	21 (5.9)	19 (5.3)	2.43
Calcium channel blocker	48 (9.3)	71 (13.0)	0.052	-12.0	33 (9.2)	30 (8.4)	2.96
β-blocker	43 (8.3)	85 (15.6)	<0.001	-22.6	38 (10.6)	30 (8.4)	7.63
Diuretic	61 (11.8)	135 (24.8)	<0.001	-34.1	55 (15.4)	57 (15.9)	-1.54
Nitrate	15 (2.9)	16 (2.9)	0.969	-0.2	12 (3.4)	8 (2.2)	6.78
Statin	28 (5.4)	60 (11.0)	<0.001	-20.5	24 (6.7)	22 (6.2)	2.28
EuroSCORE	1.06±1.39	1.20±1.41	0.041	-10.3	1.13±1.45	1.12±1.38	0.99
Charlson comorbidity index	0.71±1.21	0.96±1.10	<0.001	-21.7	0.79±1.31	0.81±1.01	-1.43
Reasons for echocardiography				44.9			6.24
Cardiac murmur alone	74 (14.3)	54 (9.9)			41 (11.5)	46 (12.9)	
Referral from other hospital	310 (59.9)	430 (78.9)			260 (72.6)	255 (71.2)	
Preoperative consultation†	16 (3.1)	11 (2.0)			11 (3.1)	11 (3.1)	
Cardiovascular health checkup	118 (22.8)	50 (9.2)			46 (12.9)	46 (12.9)	
Echocardiographic characteristics							
End-systolic dimension, mm	34.2±3.8	35.1±4.3	0.001	-20.0	34.7±3.7	34.7±4.3	0.33
End-diastolic dimension, mm	57.1±5.2	58.9±5.5	<0.001	-34.0	57.9±5.0	58.1±5.2	-3.97
Left atrial dimension, mm	45.3±6.9	47.0±6.4	<0.001	-24.7	46.0±7.2	46.1±6.5	-1.14
Left ventricular ejection fraction, %	66.0±4.7	66.4±4.9	0.125	-9.4	65.8±4.7	66.1±4.9	-5.81
EROA of MR, cm ²	0.73±0.31	0.79±0.31	<0.001	-19.3	0.76±0.33	0.76±0.29	0.64
Prolapsed segment			0.178	10.4			0.00
Anterior	111 (21.4)	97 (17.8)			73 (20.4)	71 (19.8)	
Posterior	280 (54.1)	324 (59.5)			199 (55.6)	201 (56.2)	
Both	127 (24.5)	124 (22.8)			86 (24.0)	86 (24.0)	

Values are mean±SD or n (%). ACE indicates angiotensin-converting enzyme; EROA, effective regurgitant orifice area; EuroSCORE, European System for Cardiac Operative Risk Evaluation score; and MR, mitral regurgitation.

*Conventional treatment versus early surgery.

†Preoperative consultation for noncardiac surgery.

diameter ($P<0.01$). Propensity score matching for the overall cohort yielded 358 matched pairs of patients. In the matched cohort, there were no longer any significant differences between the early surgery and conventional treatment groups for any covariates according to the use of statistical methods appropriate for matched data (Table 1).

Surgical Procedures

The procedures were performed with the use of standard cardiopulmonary bypass. Throughout the study period, MV repair was attempted whenever anatomically feasible. Triangular resection was more common in the earlier period, whereas new chordae formation became

increasingly favored over time. Use of the Da Vinci Surgical System for MV repair began in 2017. In the early surgery group, all the patients underwent surgery within 6 months after enrollment; the median time between enrollment and surgery was 29 days (interquartile range, 8.0 to 53.8). MV repair or replacement was performed successfully in 528 (96.9%) patients and 17 (3.1%) patients (9 men; 50.7±15.2 years of age), respectively, and there were no cases of operative mortality in the early surgery group. Concomitant maze operation or tricuspid valve repair was performed in 19 (3.5%) and 33 (6.1%) patients, respectively, and coronary artery bypass grafting operation was carried out in 33 (6.1%). The Da Vinci System was used in 165 (30.3%) patients. In the conventional treatment group, 234 patients underwent late MV surgery with MV repair (n=197) or MV replacement (n=37), and 3 patients were treated with transcatheter edge-to-edge repair of MV at a mean interval of 6.4±4.8 years after enrollment during follow-up. Concomitant maze operation, tricuspid valve surgery, or coronary artery bypass grafting operation were performed in 59 (25.2%), 34 (14.5%), and 13 (5.6%) patients, respectively. The Da Vinci System was used in 51 (21.8%) patients. There were 2 (0.8%) operative deaths in the conventional treatment group with late surgery, and the repair rate was significantly lower than that in the early surgery group (84.2% versus 96.9%; $P<0.01$). Details regarding surgical procedures and outcomes in the conventional treatment group are provided in the **Supplemental Results**.

Comparison of Outcomes in the Overall Cohort

Data collection ended in October 2024. The median follow-up was 12.0 years (interquartile range, 8.3–16.8). In an intention-to-treat analysis including all the study patients, 8 (1.5%) of 545 patients who underwent early surgery and 54 (10.4%) of 518 patients who chose conventional management died of cardiac causes (hazard ratio [HR] in the early surgery group, 0.17 [95% CI, 0.07–0.40]; $P<0.001$; Table 2). The cumulative incidence of the primary end point (cardiac mortality), as adjusted with the use of overlap weighting, was 0.4±0.2% at 10 years and 5.6±2.3% at 20 years in the early

surgery group compared with 5.5±1.0% at 10 years and 17.4±2.3% at 20 years in the conventional management group ($P<0.001$; Figure 1A). A total of 74 (13.6%) deaths from any cause occurred in the early surgery group and 116 (22.4%) in the conventional management group (HR, 0.72 [95% CI, 0.52–0.99]; $P=0.046$). The estimated actuarial mortality rates were significantly lower in the early surgery group than in the conventional management group (4.5% versus 11.3% at 10 years and 29.6% versus 33.9% at 20 years; $P=0.034$; Figure 1B). On sensitivity analyses with the use of adjusted Cox model, the risk of cardiac mortality and all-cause mortality was significantly lower in the early surgery group (Table S1). In the secondary per-protocol analysis that included 839 patients who completed scheduled follow-up, the early surgery group had a lower risk of cardiac mortality (HR, 0.16 [95% CI, 0.05–0.53]) and all-cause mortality (HR, 0.83 [95% CI, 0.56–1.25]) than the conventional treatment group. Among the 224 patients with incomplete adherence to scheduled follow-up, the early surgery group also had a lower risk of cardiac mortality (HR, 0.21 [95% CI, 0.07–0.61]) and all-cause mortality (HR, 0.51 [95% CI, 0.30–0.88]). The subgroup analysis according to adherence to scheduled follow-up (Tables S2 and S3) found no significant interactions in risk of cardiac mortality ($P_{\text{interaction}}=0.73$) or all-cause mortality ($P_{\text{interaction}}=0.16$) between the treatment groups, suggesting that the survival benefits of early surgery were consistent regardless of compliance with the study protocol.

During follow-up, hospitalization for heart failure occurred in 13 (2.4%) patients in the early surgery group and in 47 (9.1%) patients in the conventional treatment group (HR, 0.32 [95% CI, 0.17–0.58]; $P<0.001$), and stroke occurred in 18 (3.3%) patients in the early surgery group and in 22 (4.2%) patients in the conventional treatment group (Table S4). New-onset AF developed in 73 (13.4%) patients in the early surgery group and in 89 (17.2%) patients in the conventional treatment group. The risks of falsification end points such as hospitalization for infections or fractures did not differ significantly between the treatment groups (Table S5).

In the early surgery group, 38 (7.0%) patients had recurrences of moderate (n=30) or severe MR (n=8),

Table 2. Cox Proportional Hazards Regression Analysis for Mortality in Early Surgery Vs Conventional Treatment

Cause of death	Overall cohort				Propensity score-matched cohort			
	Number of events		Adjusted by overlap weighting		Number of events		Propensity score matching	
	Early surgery (n=545)	Conventional treatment (n=518)	HR (95% CI)	P value	Early surgery (n=358)	Conventional treatment (n=358)	HR (95% CI)	P value
All	74	116	0.716 (0.515–0.994)	0.046	48	80	0.660 (0.468–0.930)	0.018
Cardiac	8	54	0.172 (0.074–0.402)	<0.001	6	37	0.179 (0.075–0.428)	<0.001

HR indicates hazard ratio.

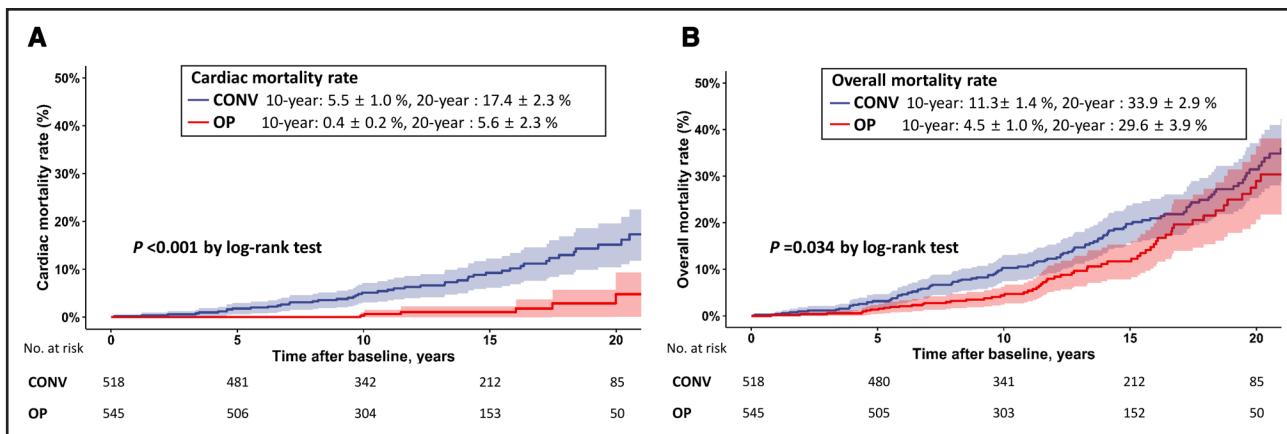


Figure 1. Comparison of conventional treatment and early surgery in terms of actuarially determined cardiac and overall mortality rates in the overall cohort.

Comparison of conventional treatment (CONV) and early surgery (OP) in terms of actuarially determined cardiac mortality rates (**A**) and overall mortality rates (**B**), adjusted by overlap weighting, in the overall cohort.

and 8 (1.5%) underwent repeat MV surgeries. In the conventional treatment group, 18 (7.7%) had recurrences of moderate ($n=11$) or severe MR ($n=7$), and 6 (2.6%) underwent repeat MV surgeries among 234 patients who underwent late MV surgeries (Table S4). The estimated actuarial 20-year rates of MR recurrence and repeat MV surgery in the early surgery group were $8.5 \pm 1.4\%$ and $3.7 \pm 1.5\%$, respectively; these values were $10.1 \pm 2.3\%$ and $3.6 \pm 1.5\%$, respectively, in the conventional treatment group.

Comparison of Outcomes in the Propensity-Matched Cohort

For the 358 propensity score-matched pairs, the median follow-up was 12.0 years (interquartile range, 8.1–16.7) in the early-surgery group and 13.3 years (interquartile range, 9.0–17.5) in the conservative management group ($P=0.13$). During follow-up, 6 (1.6%) patients in the

early surgery group and 37 (10.3%) in the conventional management group died from cardiac causes (Table 2). The early surgery group had a significantly lower risk of cardiac mortality than the conventional treatment group (HR, 0.18 [95% CI, 0.08–0.43]; $P<0.001$) and a significantly lower 20-year cardiac mortality rate ($5.6 \pm 2.8\%$ versus $17.4 \pm 3.1\%$; $P=0.002$; Figure 2A). A total of 48 (13.4%) deaths from any cause occurred in the early surgery group and 80 (22.3%) in the conventional management group. Compared with the conventional treatment group, the early surgery group had a significantly lower risk of overall mortality (HR, 0.66 [95% CI, 0.47–0.93]; $P=0.018$), and the estimated actuarial mortality rates were significantly lower in the early surgery group than in the conservative management group (3.9% versus 11.2% at 10 years and 28.2% versus 33.9% at 20 years; $P=0.015$; Figure 2B). In the subgroup analysis according to adherence to scheduled follow-up (Table S3), there were no significant interactions between the treatment

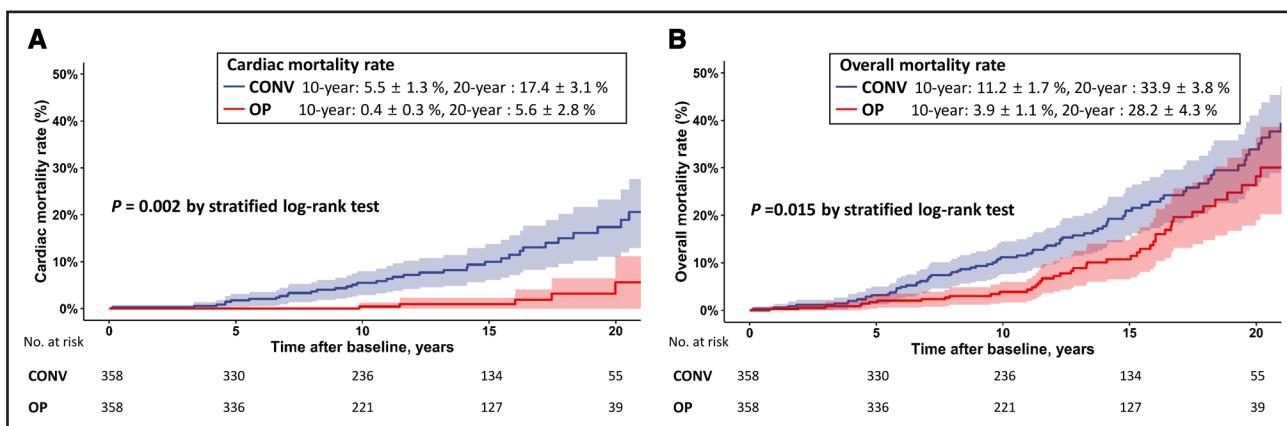


Figure 2. Comparison of conventional treatment and early surgery in terms of actuarially determined cardiac and overall mortality rates in the propensity-matched cohort.

Comparison of conventional treatment (CONV) and early surgery (OP) in terms of actuarially determined cardiac mortality rates (**A**) and overall mortality rates (**B**) in the propensity-matched cohort.

group and the risk of cardiac mortality ($P_{\text{interaction}} = 0.68$) or all-cause mortality ($P_{\text{interaction}} = 0.36$).

Subgroup Analysis

To address the effect of era changes on clinical practice and patients' preferences for early surgery, the enrollment period was divided into the first half (1996–2006) and the second half (2007–2016). The subgroup analysis found no significant interactions between the treatment groups and risk of cardiac mortality ($P_{\text{interaction}} = 0.48$) or all-cause mortality ($P_{\text{interaction}} = 0.44$) according to enrollment period in the overall cohort (Table S2). In the propensity-matched cohort, there were no significant interactions for risk of all-cause mortality ($P_{\text{interaction}} = 0.32$) according to enrollment period (Table S3). The subgroup analysis according to age (<50 versus ≥50 years) found no significant interactions between the treatment groups and risks of cardiac or all-cause mortality in the overall cohort (Table S2) or in the propensity-matched cohort (Table S3). Nonfatal outcomes were compared between the treatment groups according to enrollment period (Table S6) and patient age (Table S7). There were no significant interactions between the treatment groups and risks of recurrent hospitalization for heart failure according to enrollment period or age (Table S8). The incidences of MV replacement among the patients who underwent late MV surgeries in the conventional treatment group were significantly higher than those in the early surgery group across all subgroups of enrollment period and patient age (Table S9).

Longer follow-up results of our previous cohort of 610 patients¹¹ showed that compared with the conventional treatment group, the early surgery group had a significantly lower risk of cardiac mortality in the overall cohort (Table S10; Figure S2). For the 207 propensity score-matched pairs, the risk of cardiac mortality was also significantly lower in the early surgery group (Table S11; Figure S3). The risk of all-cause mortality did not differ significantly between treatment groups in the overall cohort or in the propensity-matched cohort.

DISCUSSION

The current study demonstrates that compared with conventional treatment, early surgery is associated with significant long-term reductions in primary and secondary end points among asymptomatic patients with severe MR and preserved LV systolic function. In our previous studies, we did not find a significant association between early surgery and improved survival,^{4,11} but enrollment of >1000 study patients and extending follow-up duration to >20 years provided the current study with sufficient power to detect a significant difference in overall mortality rates between the 2 management strategies in a propensity analysis. Analysis of the Mitral Regurgitation

International Database registry also showed that long-term survival rates were significantly higher in patients with early surgery than in those with initial medical management (86% versus 69% at 10 years), which was confirmed in a propensity-matched cohort.⁹ In contrast, watchful observation with a protocol of clinical and echocardiographic follow-up in the heart valve clinic may have improved outcomes of initial medical management,³ and a small observational study reported an overall survival rate of 85.6% at 10 years for patients managed with careful surveillance,¹⁰ which was similar to the survival rate of those who underwent early surgery in the Mitral Regurgitation International Database registry. Therefore, there is no consensus on the optimal management strategy.⁵ In the current study, overall survival in the conventional treatment group, which also followed a surveillance protocol, was 89% at 10 years, suggesting a similarly favorable prognosis of asymptomatic MR with careful surveillance. Our findings might appear to support the recommendation of the European Society of Cardiology guidelines that MV surgery can be safely deferred until symptoms or LV dysfunction (LVESD >40 mm or LVEF <60%) develop in asymptomatic patients with severe MR.² However, our results also present a compelling case for early surgery, potentially challenging the conventional watchful observation approach, because the early surgery group had higher overall survival rates (96% at 10 years) than the conventional treatment group, as confirmed in a propensity-matched cohort. To our knowledge, our study provides the strongest evidence supporting the American Heart Association/American College of Cardiology guidelines, which recommend early surgery for asymptomatic patients with preserved LV function and EROA of MR >0.4 cm².¹ A randomized clinical trial involving >1000 trial patients and requiring a follow-up duration of >20 years would be unfeasible.

Several prerequisites should be met before considering early surgery in asymptomatic patients with severe MR. First, early surgery should be performed at valve centers with >95% likelihood of successful MV repair and with an expected operative mortality rate of <1%; in our early surgery group, the repair rate was 97%, and the operative mortality rate was 0%. A recent cohort study using The Society of Thoracic Surgeons Adult Cardiac Surgical Database also reported that operative mortality for MV repair and risk of conversion to MV replacement were lower at higher-volume centers, with an operative mortality rate of 0.73% and conversion rate of 3.69%.²⁰ In contrast, the repair rate was 84% in the conventional treatment group of the current study, and an outcome study of the watchful waiting strategy reported that MV repair was performed in 86% of patients, with a reoperation rate of 6.3% resulting from failed repairs.¹⁰ Second, a durable repair should be provided with 95% freedom from reoperation and >80% freedom from recurrence of moderate or severe MR at 15 to 20 years after

surgery^{1,21,22}; the rates of MR recurrence and repeat MV surgery at 20 years were $8.5 \pm 1.4\%$ and $3.7 \pm 1.5\%$, respectively, in the early surgery group of the current study. In a recent report from Toronto General Hospital involving 1234 patients who had MV repair, the probability of recurrent moderate or severe MR was 12.5% at 20 years and the cumulative incidence of reoperation on the MV was 4.6% at 20 years.²³ The probability of developing new AF was 32.4% at 20 years and AF was associated with cardiac and noncardiac death in that study.²³ Because progressive remodeling of the left atrium associated with severe MR fosters the development of AF, early correction of MR may decrease the risk associated with new-onset AF. Third, quantitative assessment of MR has an important prognostic value,^{24,25} and the EROA of MR should be $>0.4 \text{ cm}^2$. Enriquez-Sarano et al⁸ reported that asymptomatic patients with EROA of MR $>0.4 \text{ cm}^2$ had excess mortality and that a survival benefit was associated with surgery for larger EROAs. The current study is the first to demonstrate a greater survival benefit of early surgery in asymptomatic patients with EROA $>0.4 \text{ cm}^2$ by directly comparing early surgery with a watchful waiting strategy. The enrollment criterion for severe, degenerative MR in the current study was severe MV prolapse with loss of coaptation or flail leaflet, with EROA of holosystolic MR $>0.4 \text{ cm}^2$. Fourth, a strategy of watchful waiting involves clinical and echocardiographic follow-up at a heart valve center every 6 months,¹⁰ and patient compliance with surveillance should also be considered for the decision of treatment. Considering that early MV repair eliminates the need for surveillance and also obviates the possibility of loss to follow-up,^{1,26} early surgery could be the preferred strategy for patients who are noncompliant with surveillance. In the current study, compared with conventional treatment, the risk reduction of all-cause mortality with early surgery was greater in the subgroup of patients who did not adhere to the study protocol than in the compliant subgroup, implying that the advantage of early surgery would be greater in patients without compliance. Considering that a community cohort study has revealed substantial undertreatment of severe MR,²⁷ early surgery might provide a much greater benefit than a watchful waiting strategy in real-world practice.

Study Limitations

The current study was subject to limitations resulting from the nonrandom assignment of treatment groups, which may have influenced the results because of selection bias and potential confounding. Propensity score matching and overlap weighting attempt to mimic important attributes of randomized clinical trials and adjust for biases related to treatment selection and imbalance in baseline characteristics.^{16,17} Although our robust study design and propensity-based statistical analyses

strengthen the internal validity of our results, no observational study can exclude residual confounding that may not be captured in the demographics, comorbidities, and echocardiographic variables presented.

Incomplete adherence to scheduled follow-up might delay recognition of surgical triggers and compromise outcomes in the conventional treatment group, although the subgroup analyses according to compliance found no significant interactions in outcomes between the treatment groups.

Surgical techniques changed over the 20-year study period, but the core principle of anatomic repair+annuloplasty and the core objective of complete leaflet coaptation remained consistent during the study period. The survival benefit of early surgery remained consistent over time, showing no significant interaction with the enrollment period. However, refinements in repair methods and the increased use of robotic-assisted approaches may reinforce the feasibility of safe, durable repairs. We included only patients with Carpentier type II degenerative MR, and the results of the current study are not applicable to Carpentier type III MR, which involves subvalvular fibrosis and scarring. Our study was conducted at 2 high-volume, experienced centers with demonstrated expertise in MV surgery. The high repair rate ($\approx 97\%$) and the low operative mortality rate observed throughout the study period may not be directly applicable to lower-volume surgical centers. When deciding to pursue early surgery for asymptomatic severe MR, it is important to carefully consider the surgeon's expertise, the patient's operative risk, and the institutional outcomes. Despite the early surgery group being older, with a higher comorbidity index and more severe MR, the incidence of noncardiac deaths was similar between the treatment groups. This may suggest a potentially protective effect of early surgery on the excess mortality associated with baseline imbalances. Intervention thresholds for degenerative MR may not be fully calibrated for Asian populations²⁸ and could contribute to undertreatment of MR in the conventional treatment group.

Conclusions

Compared with conventional management, early surgical correction of MR is associated with reduced long-term cardiac and all-cause mortality rates among asymptomatic patients with severe MR. The clinical benefit of early surgery was confirmed in a propensity-matched cohort. Although conventional management appears to be a safe strategy, early surgery may be a more effective treatment option for asymptomatic patients with severe MR at excellent heart valve centers.

ARTICLE INFORMATION

Received March 10, 2025; accepted July 7, 2025.

Affiliations

Division of Cardiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea (S-J.P., J.S., J.K., E.-K.K.). Division of Cardiology, Pusan National University Hospital, Pusan National University School of Medicine, Pusan, Korea (M.K.). Division of Cardiology, Hanyang Medical Center, Hanyang University College of Medicine, Seoul, Korea (H.H.J.). Division of Cardiology (G.Y.K., B.J.S., S.L., J.-M.S., D.-H.K.), Cardiac Surgery (J.S.Y., S.-H.J.), and Biostatistics (S.-C.Y.), Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Korea.

Sources of Funding

None.

Disclosures

None.

Supplemental Material

Methods

Results

Figures S1–S4

Tables S1–S12

Checklist

REFERENCES

- Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;143:e35–e71. doi: 10.1161/CIR.0000000000000932
- Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, et al; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632. doi: 10.1093/euroheartj/ehab395
- Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, Schemper M, Maurer G, Baumgartner H. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238–2244. doi: 10.1161/CIRCULATIONAHA.105.599175
- Kang DH, Kim JH, Rim JH, Kim M-J, Yun S-C, Song J-M, Song H, Choi K-J, Song J-K, Lee J-W. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation*. 2009;119:797–804. doi: 10.1161/CIRCULATIONAHA.108.802314
- Björn R, Strom JB, Lloyd G, Bhattacharya S. Asymptomatic severe degenerative mitral regurgitation. *Heart*. 2025;111:47–54. doi: 10.1136/heartjnl-2024-324739
- Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet*. 2009;373:1382–1394. doi: 10.1016/S0140-6736(09)60692-9
- Ling LH, Enriquez-Sarano M, Seward JB, Orszulak TA, Schaff HV, Bailey KR, Tajik AJ, Frye RL. Early surgery in patients with mitral regurgitation due to flail leaflets: a long-term outcome study. *Circulation*. 1997;96:1819–1825. doi: 10.1161/01.cir.96.6.1819
- Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005;352:875–883. doi: 10.1056/NEJMoa041451
- Suri RM, Vanoverschelde JL, Grigioni F, Schaff HV, Tribouilloy C, Avierinos JF, Barbieri A, Pasquet A, Huebner M, Rusinaru D, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA*. 2013;310:609–616. doi: 10.1001/jama.2013.8643
- Zilberszac R, Heinze G, Binder T, Laufer G, Gabriel H, Rosenhek R. Long-term outcome of active surveillance in severe but asymptomatic primary mitral regurgitation. *JACC Cardiovasc Imaging*. 2018;11:1213–1221. doi: 10.1016/j.jcmg.2018.05.014
- Kang D-H, Park S-J, Sun BJ, Cho EJ, Kim D-H, Yun S-C, Song J-M, Park SW, Chung C-H, Song J-K, et al. Early surgery versus conventional treatment for asymptomatic severe mitral regurgitation: a propensity analysis. *J Am Coll Cardiol*. 2014;63:2398–2407. doi: 10.1016/j.jacc.2014.02.577
- Bonow RO, Carabello BA, Kanu C, de Leon AC, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114:e84–231. doi: 10.1161/CIRCULATIONAHA.106.176857
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
- Enriquez-Sarano M, Miller FA, Hayes SN, Bailey KR, Tajik AJ, Seward JB. Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. *J Am Coll Cardiol*. 1995;25:703–709. doi: 10.1016/0735-1097(94)00434-R
- Grayburn PA, Weissman NJ, Zamorano JL. Quantitation of mitral regurgitation. *Circulation*. 2012;126:2005–2017. doi: 10.1161/CIRCULATIONAHA.112.121590
- Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550–560. doi: 10.1097/00001648-200009000-00011
- Thomas LE, Li F, Pencina MJ. Overlap weighting: a propensity score method that mimics attributes of a randomized clinical trial. *JAMA*. 2020;323:2417–2418. doi: 10.1001/jama.2020.7819
- Rosenbaum PR. *Observational Studies*. Springer-Verlag; 1995.
- Klein JP, Moeschberger KL. *Survival Analysis: Techniques for Censored and Truncated Data*. Springer-Verlag; 1997.
- Badhwar V, Chikwe J, Gillinov AM, Vemulapalli S, O'Gara PT, Mehaffey JH, Wyler von Ballmoos M, Bowdish ME, Gray EL, O'Brien SM, et al. Risk of surgical mitral valve repair for primary mitral regurgitation. *J Am Coll Cardiol*. 2023;81:636–648. doi: 10.1016/j.jacc.2022.11.017
- Lazam S, Vanoverschelde J-L, Tribouilloy C, Grigioni F, Suri RM, Avierinos J-F, de Meester C, Barbieri A, Rusinaru D, Russo A, et al; MIDA (Mitral Regurgitation International Database) Investigators. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: analysis of a large, prospective, multicenter, international registry. *Circulation*. 2017;135:410–422. doi: 10.1161/CIRCULATIONAHA.116.023340
- David TE, Armstrong S, McCrindle BW, Manlhot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Circulation*. 2013;127:1485–1492. doi: 10.1161/CIRCULATIONAHA.112.000699
- David TE, David CM, Tsang W, Lafreniere-Roula M, Manlhot C. Long-term results of mitral valve repair for regurgitation due to leaflet prolapse. *J Am Coll Cardiol*. 2019;74:1044–1053. doi: 10.1016/j.jacc.2019.06.052
- Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, et al; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802. doi: 10.1016/S0894-7317(03)00335-3
- Antoine C, Benfari G, Michelena HI, Maalouf JF, Nkomo VT, Thapa P, Enriquez-Sarano M. Clinical outcome of degenerative mitral regurgitation: quantitative assessment in routine practice. *Circulation*. 2018;138:1317–1326. doi: 10.1161/CIRCULATIONAHA.117.033173
- Enriquez-Sarano M, Suri RM, Clavel M-A, Mantovani F, Michelena HI, Pislaru S, Mahoney DW, Schaff HV. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation. *J Thorac Cardiovasc Surg*. 2015;150:50–58. doi: 10.1016/j.jtcvs.2015.04.009
- Dziadko V, Clavel MA, Dziadko M, Medina-Inojosa JR, Michelena H, Maalouf J, Nkomo V, Thapa P, Enriquez-Sarano M. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet*. 2018;391:960–969. doi: 10.1016/S0140-6736(18)30473-2
- Hamid N, Bursi F, Benfari G, Vanoverschelde JL, Tribouilloy C, Biagini E, Avierinos JF, Barbieri A, Fan Y, Guerra F, et al. Degenerative mitral regurgitation outcomes in Asian compared with European-American institutions. *JACC Asia*. 2024;4:468–480. doi: 10.1016/j.jacasi.2024.03.003