



Original Investigation | Cardiology

Early Mitral Valve Surgery and Survival in Asymptomatic Severe Primary Mitral Regurgitation

Juhee Ahn, PhD; Soongu Kwak, MD, PhD; Jaehyun Lim, MD; Kyu Kim, MD; Jihoon Kim, MD; Byung Joo Sun, MD, PhD; Dae-Hee Kim, MD, PhD; Kyung Hwan Kim, MD, PhD; Chi Young Shim, MD, PhD; Sung-Ji Park, MD, PhD; Sungho Won, PhD; Seung-Pyo Lee, MD, PhD

Abstract

IMPORTANCE The optimal timing of mitral valve (MV) surgery in patients with asymptomatic severe primary mitral regurgitation (MR) remains uncertain because randomized clinical trials are lacking.

OBJECTIVE To evaluate the association of early MV surgery with long-term survival in patients with asymptomatic severe primary MR using a target trial emulation framework.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used a clinical valve registry from 3 tertiary hospitals in South Korea between 2000 and 2022. Patients with asymptomatic severe primary MR were analyzed using a clone-censor-weight approach to emulate a target trial. A 6-month grace period after diagnosis was used to define treatment strategies. This analysis was conducted from September 2024 to January 2025.

EXPOSURE Early MV surgery (within 6 months of diagnosis) vs watchful waiting.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality and the secondary outcome, a composite of all-cause mortality or heart failure hospitalization. Inverse probability of censoring-weighted estimates of the per-protocol effect size included restricted mean survival time (RMST) differences as the primary measure and hazard ratios (HRs) as secondary measures.

RESULTS Among 802 patients (mean [SD] age, 55 [16] years; 476 men [59%]), 344 underwent early surgery, and 458 received watchful waiting. During a median (IQR) follow-up of 7.4 (4.1-11.6) years, 27 deaths occurred in the early surgery group and 103 in the watchful waiting group. At 5 years, early surgery was associated with an RMST gain of 66 days (95% CI, 19-129 days). The survival benefit persisted up to 15 years. Early surgery was also associated with a lower risk of all-cause mortality compared with watchful waiting (HR, 0.69; 95% CI, 0.41-0.94; $P = .02$). Similar associations were observed in patients without left ventricular decompensation (HR, 0.61; 95% CI, 0.31-0.96; $P = .04$) and in those with degenerative MR (HR, 0.66; 95% CI, 0.36-0.98; $P = .04$).

CONCLUSIONS AND RELEVANCE In this multicenter cohort study with a target trial framework, early surgery was associated with improved long-term survival among patients with asymptomatic severe primary MR. These findings support consideration of earlier surgical intervention in contemporary clinical practice.

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Key Points

Question Is early mitral valve surgery associated with improved survival compared with watchful waiting in asymptomatic patients with severe primary mitral regurgitation (MR)?

Findings In this cohort study of 802 patients with severe primary MR, early surgery within 6 months was associated with a survival benefit compared with watchful waiting, with 66 additional survival days at 5 years. The benefit was consistent among patients without left ventricular decompensation and those with degenerative MR.

Meaning These findings suggest that early surgical intervention improves survival in patients with asymptomatic severe primary MR, even before left ventricular decompensation develops.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Introduction

Severe primary mitral regurgitation (MR) leads to progressive left ventricular (LV) enlargement and systolic dysfunction, predisposing patients to adverse clinical events.¹ Therefore, timely surgical intervention is essential to prevent irreversible ventricular dysfunction and improve clinical outcomes. However, current guideline recommendations regarding the optimal timing of intervention, particularly in patients who are asymptomatic, remain debatable.^{2,3}

This uncertainty may be attributable to the limited evidence from randomized clinical trials (RCTs). Several observational studies have suggested that early MV surgery may be associated with improved survival and a reduced risk of heart failure.⁴⁻¹² However, most were limited by inadequate consideration of the waiting time to surgery, an important factor in clinical practice. Additionally, surgical expertise has substantially improved in the contemporary era, with successful MV surgery now associated with survival rates approaching those of the general population.¹³

Conducting RCTs to establish clear recommendations remains challenging,¹⁴⁻¹⁶ given the risks of valve surgery and increasing comorbidities in the aging population.¹⁷ Therefore, there is a need to assess the impact of early surgical intervention in patients with asymptomatic significant MR by leveraging high-quality health record data and advanced statistical methods. Target trial emulation has emerged as a framework for approximating RCTs, thereby mitigating confounding by indication and immortal time bias.¹⁸⁻²⁰

In this study, we conducted data analysis of patients with asymptomatic severe primary MR using a large-scale multicenter valve registry in South Korea. Applying target trial emulation, we aimed to investigate whether early MV surgery improves survival compared with watchful waiting.

Methods

Data Source

A multicenter registry was constructed to collect data on consecutive patients diagnosed with valvular heart disease from 3 major tertiary hospitals in Seoul, Korea, between 2000 and 2022: Seoul National University Hospital, Samsung Medical Center, and Severance Hospital.^{21,22} The index date was defined as the date of echocardiography on which significant valvular heart disease was diagnosed. Standardization was achieved by harmonizing the terminology and data structure across hospitals. Electronic medical records were integrated and validated through quality control procedures. All data were anonymized to ensure confidentiality of each patient.

This cohort study complied with the Declaration of Helsinki and was approved by the Seoul National University Hospital Ethics Committee, which waived informed consent owing to the retrospective nature of the anonymized database. This study followed Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) reporting guidelines for observational studies emulating target trials.²³

Study Population

We focused exclusively on patients with asymptomatic severe primary MR from the multicenter registry (Figure 1). MR severity was determined at each participating institution using a multiparametric assessment, including relevant MR quantification parameters.²⁴ Symptom status, such as dyspnea, peripheral edema, and chest discomfort or pain attributable to severe MR, was evaluated through clinical assessments performed by cardiologists or cardiothoracic surgeons within dedicated heart valve teams at each participating center.

We included patients with primary MR, such as degenerative (leaflet prolapse or flail motion of the MV), rheumatic, or congenital MR. Patients with symptoms attributable to severe MR were excluded. Other exclusion criteria were as follows: (1) previous valve surgery or intervention (ie, percutaneous balloon commissurotomy), (2) concomitant left-sided valvular heart disease of

moderate or greater degree, including mitral stenosis, (3) functional (secondary) MR, and (4) incomplete clinical information for target trial emulation.

Target Trial Emulation

In addition to following the TARGET guideline,²³ we followed prespecified key components of the hypothetical trial (eTables 1 and 2 in Supplement 1).^{19,20,25} Follow-up began once eligibility was met and continued until outcome occurrence or administrative censoring at 15 years.

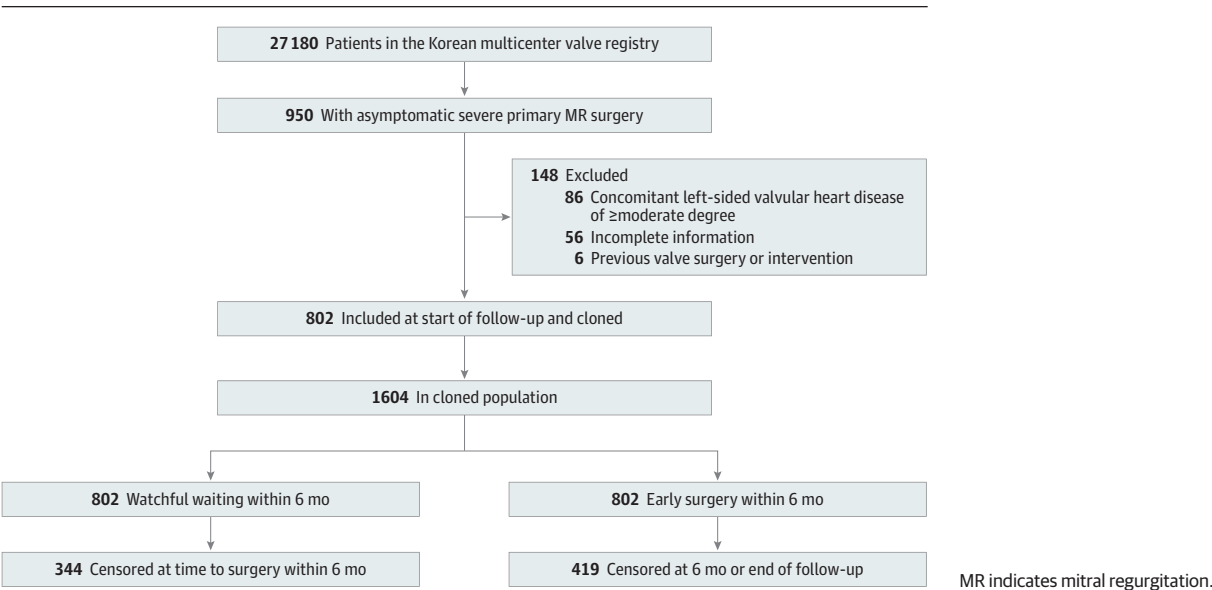
Patients were assigned to either watchful waiting or early surgery. The grace period was defined as 6 months from the diagnosis of severe MR.^{5,7,9} The early surgery group included patients undergoing MV repair or replacement within 6 months, whereas the watchful waiting group included those without surgery during this period, including those who underwent surgery later. In this approach, each eligible patient was assigned to both treatment strategies through cloning, so that all patients could contribute to both groups or strategies at baseline. Clones were then artificially censored if their observed treatment deviated from the assigned strategy during the grace period. Details are provided in the eAppendix in Supplement 1.

The primary outcome was all-cause mortality, obtained from electronic medical records and official national death records provided by Statistics Korea. The secondary outcome was a composite of all-cause mortality and admission for heart failure. To estimate the per-protocol effect of early surgery,²⁶ we primarily assessed difference in restricted mean survival time (RMST), with hazard ratios (HRs) as secondary measures.

Statistical Analysis

The clone-censor-weight approach was implemented (eFigure 1 in Supplement 1). To account for artificial censoring, the stabilized inverse probability of censoring weights (IPCWs) was applied. Baseline confounders were selected from established risk factors for mortality in severe MR, subject to data availability: age, sex, institutions, LV end-systolic diameter (LVESD), LV ejection fraction (LVEF), left atrial dimension, comorbidities (hypertension, diabetes, atrial fibrillation or atrial flutter [AF], myocardial infarction, and cerebrovascular events), and medications (renin-angiotensin system blockers, beta blockers, diuretics, and oral anticoagulants). We evaluated the distribution of stabilized IPCWs at the clone level (eTable 1 in Supplement 1). Additional details are provided in eMethods in Supplement 1.

Figure 1. Flowchart of the Entire Analysis



Continuous variables are summarized as mean (SD) and categorical variables as counts (percentages). Welch *t* tests or the χ^2 test was used for baseline comparisons. Covariate balance after artificial censoring was assessed using weighted absolute standardized mean differences (ASMDs) among clones remaining at risk at the end of the 6-month grace period. Patients with incomplete information for target trial emulation were excluded and missingness for other clinical characteristics is provided in eFigure 2 in [Supplement 1](#).

Kaplan-Meier curves with 95% CIs were estimated without weighting in the noncloned dataset and with weighting in the cloned dataset. The log-rank test was conducted only for the unweighted curves. The proportional hazards assumption was evaluated using Schoenfeld residuals tests and graphical diagnostics. RMST differences were estimated at 1, 3, 5, 10, and 15 years. A weighted Cox model was used to estimate HRs. The nonparametric bootstrap method (1000 resamples)—stratified by institution to preserve the institution-specific composition of the cohort—was used to estimate 95% CIs and *P* value.

Sensitivity analyses were performed in 3 prespecified subcohorts: (1) patients without evidence of LV decompensation, defined as preserved LV systolic function (LVEF higher than 60% and LVESD less than 40 mm); (2) patients with degenerative MR, defined by MR attributable to leaflet prolapse and/or flail leaflet; and (3) patients without baseline AF (eTable 2 in [Supplement 1](#)). Furthermore, we repeated the analyses by 3- and 12-month grace period.

All effect estimates are presented with 95% CIs, and 2-sided *P* < .05 was considered statistically significant. Analyses were conducted using R version 3.6.3 (R Foundation for Statistical Computing) from September 2024 to January 2025.

Results

Patients Characteristics

A total of 802 patients were included in the final analysis (mean [SD] age, 54.5 [15.9] years; 476 male [59.4%]) ([Table 1](#)). Using a 6-month grace period, 344 and 458 patients were assigned to the early surgery and watchful waiting groups, respectively. Patients in the watchful waiting group were older than those in the early surgery group (mean [SD] age, 56.8 [16.6] vs 51.5 [14.4] years; *P* < .001) and had a higher prevalence of diabetes (42 of 458 [9.2%] vs 16 of 344 [4.7%]; *P* = .02), while AF was more prevalent in the early surgery group (67 of 344 [19.5%] vs 46 of 458 [10.0%]; *P* < .001). The mean (SD) LVEF was 64.9% (7.4%) in the entire cohort. In contrast, the left atrial dimension was larger in the early surgery group than in the watchful waiting group (mean [SD] left atrial dimension, 50.0 [10.6] mm vs 47.0 [9.8] mm; *P* < .001).

Regarding the type of surgery, 227 patients (66.0%) underwent MV repair and 117 patients (34.0%) underwent MV replacement in the early surgery group. After the 6-month grace period, 86 patients (18.8%) in the watchful waiting group subsequently underwent surgery, including 21 patients within 1 year of severe MR diagnosis.

During the cloning process, 802 patients were duplicated, resulting in 1604 cloned records ([Figure 1](#)). After applying IPCWs, all weighted ASMDs for baseline covariates were less than 0.10, indicating adequate covariate balance ([Table 1](#)).

Survival Following Early Surgery in the Entire Cohort

A follow-up period of at least 5 years from diagnosis or until death was completed for 635 patients (79%). During the median (IQR) follow-up of 7.4 (4.1-11.6) years, 27 deaths occurred in the early surgery group and 103 deaths in the watchful waiting group. In the unweighted survival curves, the early surgery group showed higher survival than the watchful waiting group (*P* < .001 by the log-rank test) ([Figure 2A](#)). The weighted survival curves demonstrated an attenuation of early separation and a survival benefit in the early MV surgery group compared with the watchful waiting group, with 5-year survival rates of 91.9% (95% CI, 87.6-96.0%) vs 85.4% (95% CI, 82.0-88.7%) ([Figure 2A](#)). The weighted survival benefit in the early surgery group became more pronounced over time, up to 15

Table 1. Baseline Characteristics of the Study Population by Randomization Emulated Group

Characteristics	Patients, No. (%)			P value	ASMD before cloning	Weighted ASMD at 6 mo
	Total (N = 802)	Watchful waiting (n = 458)	Early surgery (n = 344)			
Age, mean (SD), y	54.5 (15.9)	56.8 (16.6)	51.5 (14.4)	<.001	0.341	0.046
Sex						
Female	326 (40.6)	196 (42.8)	130 (37.8)	.18	0.102	0.009
Male	476 (59.4)	262 (57.2)	214 (62.2)			
Year of MR diagnosis						
<2010	210 (26.2)	128 (27.9)	82 (23.8)	.12	NA	NA
2010-2020	573 (71.4)	316 (69.0)	257 (74.7)			
>2020	19 (2.4)	14 (3.1)	5 (1.5)			
Degenerative MR	677 (84.4)	400 (87.3)	277 (80.5)	.01	NA	NA
Type of surgery during 6-mo grace period						
MV repair	227 (66.0)	NA	227 (66.0)	NA	NA	NA
MV replacement	117 (34.0)	NA	117 (34.0)			
Body mass index, mean (SD) ^a	23.0 (3.5)	23.1 (3.5)	22.9 (3.5)	.59	NA	NA
Body surface area, mean (SD), m ²	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	.44	NA	NA
Institutions						
Severance Hospital	404 (50.4)	234 (51.1)	170 (49.4)	.81	0.033	0.041
Samsung Medical Center	203 (25.3)	112 (24.5)	91 (26.5)		0.046	0.004
Seoul National University Hospital	195 (24.3)	112 (24.5)	83 (24.1)		0.008	0.051
Laboratory examination, mean (SD)						
Hemoglobin, g/dL	13.2 (2.1)	13.2 (2.2)	13.2 (2.0)	.87	NA	NA
eGFR, mL/min/1.73 m ²	90.5 (23.3)	88.1 (23.1)	93.2 (23.3)	.003	NA	NA
Echocardiography, mean (SD)						
LVEDD, mm	57.8 (6.6)	56.5 (6.3)	59.6 (6.5)	<.001	NA	NA
LVESD, mm	36.4 (5.6)	35.5 (5.4)	37.5 (5.7)	<.001	0.343	0.017
LVEF, %	64.9 (7.4)	64.8 (7.5)	65.0 (7.3)	.65	0.033	0.039
IVSD, mm	9.4 (1.8)	9.5 (2.0)	9.3 (1.5)	.10	NA	NA
LVPWD, mm	9.3 (1.5)	9.3 (1.6)	9.3 (1.5)	.79	NA	NA
Left ventricular mass index, g/m ²	128.9 (34.7)	124.8 (34.8)	133.9 (34.0)	<.001	NA	NA
Left atrial dimension, mm	48.3 (10.2)	47.0 (9.8)	50.0 (10.6)	<.001	0.296	0.030
E wave, m/s	1.2 (0.3)	1.1 (0.3)	1.3 (0.3)	<.001	NA	NA
e' Wave, cm/s	8.5 (2.8)	8.1 (2.9)	9.0 (2.6)	<.001	NA	NA
E/e' ratio	15.1 (6.6)	15.2 (7.2)	15.0 (5.9)	.63	NA	NA
Maximal tricuspid regurgitation velocity, m/s	2.6 (0.5)	2.6 (0.5)	2.7 (0.5)	.51	NA	NA
MR EROA, cm ²	0.5 (0.2)	0.4 (0.2)	0.6 (0.2)	<.001	NA	NA
MR regurgitant volume, mL	73.6 (26.1)	68.3 (22.5)	79.9 (28.6)	<.001	NA	NA
Comorbidities						
Hypertension	239 (29.8)	145 (31.7)	94 (27.3)	.21	0.095	0.021
Diabetes	58 (7.2)	42 (9.2)	16 (4.7)	.02	0.179	0.042
Atrial fibrillation or atrial flutter	113 (14.1)	46 (10.0)	67 (19.5)	<.001	0.268	0.013
Myocardial infarction	8 (1.0)	4 (0.9)	4 (1.2)	.96	0.029	0.003
Cerebrovascular events	51 (6.4)	33 (7.2)	18 (5.2)	.32	0.082	0.006
Medications						
RAS blocker	242 (30.2)	124 (27.1)	118 (34.3)	.03	0.157	0.045
β-Blocker	47 (5.9)	21 (4.6)	26 (7.6)	.10	0.125	0.048
Diuretics	176 (21.9)	79 (17.2)	97 (28.2)	<.001	0.264	0.008
Oral anticoagulants	92 (11.5)	25 (5.5)	67 (19.5)	<.001	0.434	0.060
Clinical outcomes						
All-cause death	130 (16.2)	103 (22.5)	27 (7.8)	<.001	NA	NA
Heart failure	77 (9.6)	42 (9.2)	35 (10.2)	.72	NA	NA
Follow-up periods, mean (SD), y	7.8 (4.5)	7.3 (4.7)	8.3 (4.1)	.002	NA	NA

Abbreviations: ASMD, absolute standardized mean difference; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; IVSD, interventricular septum thickness; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVPWD, left ventricular posterior wall thickness; MR, mitral regurgitation; MV, mitral valve; NA, not applicable; RAS, renin-angiotensin system.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.

^a Calculated as weight in kilograms divided by height in meters squared.

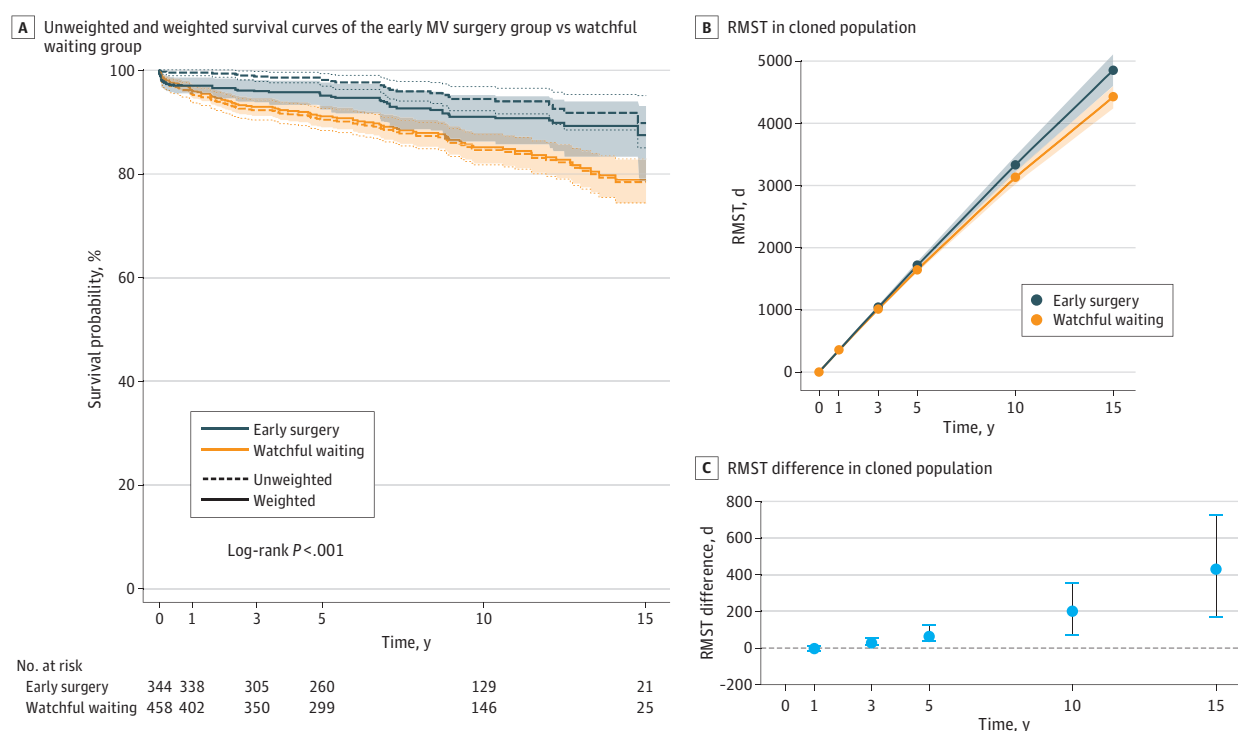
years, compared with the watchful waiting group (15-year survival rate, 79.6% [95% CI, 65.3%-88.7%] vs 65.7% [95% CI, 58.3%-71.9%]).

The IPCW-adjusted RMST at 5 years was longer in the early surgery group compared with the watchful waiting group (1717 days [95% CI, 1667-1772 days] vs 1651 days [95% CI, 1609-1691 days]) (Figures 2B and C). The absolute survival difference at 5 years favored early surgery within the 6-month grace period (66 days; 95% CI, 19-129 days) (Figure 2C). This survival benefit increased from 3 to 15 years postrandomization, with early surgery demonstrating improved all-cause mortality at 15 years (IPCW-adjusted HR, 0.69; 95% CI, 0.41-0.94; $P = .02$) (Table 2). The Schoenfeld residuals did not provide strong evidence against the PH assumption for the treatment strategy; graphical diagnostics are shown (eFigure 3 in Supplement 1).

Sensitivity Analyses in Prespecified Subcohorts

Of the 802 patients, 503 (62.7%) had no evidence of LV decompensation. Within this subgroup, 201 patients underwent early surgery, and 302 patients were managed with watchful waiting within the 6-month grace period (eTable 2 in Supplement 1). During the follow-up, 15 deaths occurred in the early surgery group and 66 deaths occurred in the watchful waiting group. In this subgroup, the weighted survival curve again showed higher survival in the early surgery group than in the watchful waiting group, with 5-year survival rates of 94.6% (95% CI, 89.8%-98.1%) vs 85.3% (95% CI, 80.7%-89.1%) (Figure 3A). The absolute survival difference at 5 years was 79 days (95% CI, 14-145 days) (Figure 3B and C) in favor of early surgery for this subcohort, with an IPCW-adjusted HR of 0.61 (95% CI, 0.31-0.96; $P = .04$) (Table 2). The results were also consistent among patients with

Figure 2. Kaplan-Meier Curve for Overall Survival and Line Graph and Dot Plot for Restricted Mean Survival Time (RMST) in the Entire Asymptomatic Severe Primary Mitral Regurgitation (MR) Patients According to Treatment Strategy



MV indicates mitral valve. A, Dashed lines indicate unweighted survival curves before cloning and solid lines indicate weighted survival curves after clone-censor-weight approach. Dotted boundary lines indicate bootstrap 95% CIs for the unweighted curves and shaded areas indicate 95% CIs for the weighted curves. The log-rank test was performed only for the unweighted curves. B, Point estimates of the RMSTs are visually

represented as circles, and their 95% CI are depicted as shades. C, Point estimates of the difference in RMST between early surgery and watchful waiting groups are visually represented as circles, and their 95% CIs are depicted as whiskers. Early surgery was defined as an operation performed within 6 months after the diagnosis of severe MR, and watchful waiting as medical management or operation beyond 6 months.

degenerative MR (5-year RMST difference, 77 days [95% CI, 22-136 days]; IPCW-adjusted HR, 0.66 [95% CI, 0.36-0.98]; $P = .04$) (eTable 3 and eFigure 4 in Supplement 1) and after excluding patients with baseline AF (eTable 4 in Supplement 1).

Sensitivity Analyses With Different Grace Periods

Sensitivity analyses using different grace periods of early surgery (3 months and 12 months) showed consistent results favoring early surgery (Table 2; eTable 5 in Supplement 1). Findings were also

Table 2. Association of Early Surgery With All-Cause Mortality According to Different Grace Period Definitions

Grace period (months)	Entire cohort (N = 802)		Subcohort without LV decompensation (n = 503) ^a	
	IPCW-adjusted HR (95% CI) ^b	P value ^c	IPCW-adjusted HR (95% CI) ^b	P value ^c
3 mo				
Early surgery group	0.64 (0.37-0.88)	.01	0.57 (0.26-0.95)	.03
Watchful waiting group	1 [Reference]	NA	1 [Reference]	NA
6 mo				
Early surgery group	0.69 (0.41-0.94)	.02	0.61 (0.31-0.96)	.04
Watchful waiting group	1 [Reference]	NA	1 [Reference]	NA
12 mo				
Early surgery group	0.68 (0.44-0.93)	.03	0.66 (0.38-1.00)	.05
Watchful waiting group	1 [Reference]	NA	1 [Reference]	NA

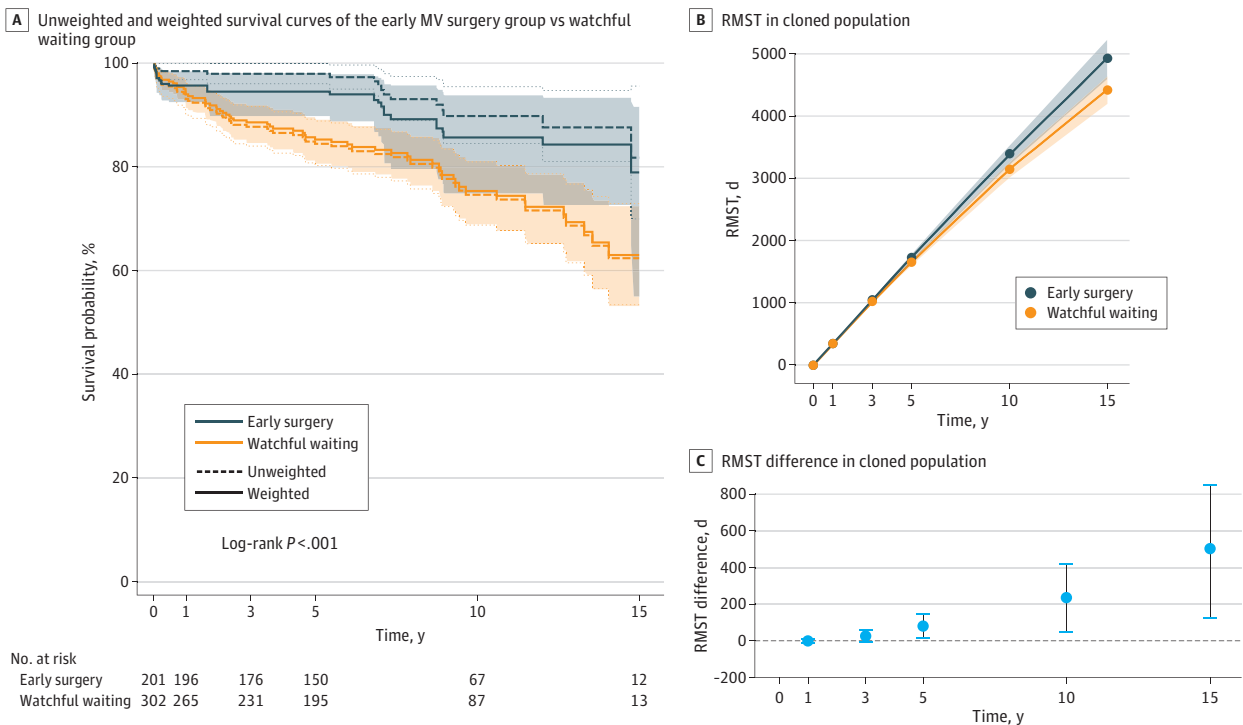
Abbreviations: HR, hazard ratio; IPCW, inverse probability of censoring weighting; LV, left ventricular; NA, not applicable.

^a LV decompensation was defined as an LV ejection fraction of 60% or less or an LV end-systolic dimension of 40 mm or greater.

^b 95% CIs were calculated using 1000 bootstrap samples stratified by institutions.

^c Two-sided P values were derived from the bootstrap empirical distribution on the log-HR scale.

Figure 3. Kaplan-Meier Curve for Overall Survival and Line Graph and Dot Plot for Restricted Mean Survival Time (RMST) in the Asymptomatic Severe Primary Mitral Regurgitation (MR) Patients Without Evidence of Left Ventricular (LV) Decompensation According to Treatment Strategy



LV decompensation was defined as either LV ejection fraction (LVEF) of 60% or below or LV end-systolic diameter (LVESD) 40 mm or higher. A, Dashed lines indicate unweighted survival curves before cloning and solid lines indicate weighted survival curves after clone-censor-weight approach; dotted boundary lines indicate bootstrap 95% CIs for the unweighted curves and shaded areas indicate 95% CIs for the weighted curves. The log-rank test was performed only for the unweighted curves. Patients who were asymptomatic with severe MR without evidence of LV decompensation were

included. B, The point estimates of the RMSTs are visually represented as circles, and their 95% CI are depicted as shades. C, Point estimates of the difference in RMST between early surgery and watchful waiting groups are visually represented as circles, and their 95% CIs are depicted as whiskers. Early surgery was defined as an operation performed within 6 months after the diagnosis of severe MR, and watchful waiting as medical management or operation beyond 6 months.

robust among patients without LV decompensation and in those with degenerative MR (Table 2; eTables 4 and 7 in [Supplement 1](#)).

Early Surgery and the Composite Outcome of Mortality and Heart Failure

During follow-up, 35 patients in the early surgery group and 42 patients in the watchful waiting group developed heart failure (Table 1). For the composite of all-cause mortality and heart failure admission events, the 5-year RMST difference favored early surgery by 83 days (95% CI, 32-161 days) (eTable 7 in [Supplement 1](#)). The IPCW-adjusted HR was 0.73 (95% CI, 0.45-0.95; $P = .02$), indicating that early surgery was associated with a lower risk of death or heart failure hospitalization.

Discussion

Using a large clinical valve registry involving major tertiary referral centers, we demonstrated that early MV surgery significantly improved overall survival in patients with asymptomatic severe primary MR. Compared with watchful waiting, the absolute survival benefit of early surgery remained significant in the RMST analysis for up to 15 years. Importantly, this benefit was consistently observed across patients without evidence of LV decompensation, those with degenerative MR, and those without AF. Sensitivity analyses across different grace periods yielded consistent results, underscoring the robustness of our findings. A notable strength of this study is the application of the clone-censor-weight approach within a target trial emulation framework, which enables a causal interpretation of the treatment effect in a clinical setting. The main study findings are illustrated in eFigure 5 in [Supplement 1](#).

We constructed a comprehensive multicenter valve registry in Korea and collected high-quality electronic medical records–based data from major tertiary hospitals with specialized expertise in MV surgery. Due to the significance of the surgical procedure and the need for multidisciplinary collaboration,^{16,27-30} MV surgeries in Korea are predominantly performed at a limited number of high-volume tertiary centers. These centers have collaborated to improve data quality and reliability while ensuring a large sample size. Our study included more than 800 patients with asymptomatic severe primary MR, including more than 500 patients without evidence of LV decompensation, providing sufficient statistical power for robust analyses.

We leveraged a target trial emulation approach with participant cloning and demonstrated that early surgery was associated with improved survival compared with watchful waiting. A limitation of previous conventional observational studies is that surgery is performed in patients who survive until the scheduled surgery, creating immortal-time bias that may overestimate the benefits of surgery.^{31,32} By mitigating this bias, target trial emulation strengthens causal inference and provides insights readily applicable to clinical decision-making.^{26,33} However, the watchful waiting strategy should be interpreted as initial conservative management during the grace period in which later surgery was allowed if clinically indicated and feasible, rather than as permanent medical management. Nevertheless, delayed surgery occurred only in a subset of patients and the similar results obtained using a 1-year grace period support the robustness of study findings.

In this study, we used the difference in RMST as the primary estimand and HR as a complementary measure. Although there was no strong evidence against the PH assumption for treatment strategy, the HR was considered a less straightforward measure to interpret the effect of early surgery given the long-term follow up and possible time-varying nature of treatment effects over time. In this context, RMST provides a more robust and clinically interpretable measure of treatment effect.^{34,35}

With these approaches, our results are consistent with previous observational studies that have investigated the potential protective effect of early MV surgery among asymptomatic or minimally symptomatic patients with MR.^{4,5,7,9,10,12} A meta-analysis of these studies further supported this association.³⁶ In our analysis, the RMST gain associated with early surgery was approximately 2

months in a 5-year follow-up window. However, this survival benefit exceeded 1 year at 15 years, indicating that the advantage may accumulate over long-term follow-up. This pattern suggests a meaningful long-term survival benefit for patients who are asymptomatic undergo early MV surgery for severe MR, whereas the short- to mid-term absolute survival difference may be relatively smaller in very low-risk individuals who are asymptomatic.

Relative and absolute measures of treatment effect provide complementary information. Although the IPCW-adjusted HR suggested a lower relative risk of all-cause mortality with early surgery, the RMST difference quantifies the absolute survival benefit. At 5 years, this benefit was modest, with an RMST difference of 66 days. This finding may partly reflect the relatively low mortality in the watchful waiting group over 5 years. RMST may be particularly useful for clinical decision-making because it expresses the expected survival gain on an absolute time scale. Furthermore, it can be weighed against patient-specific clinical considerations.

In our study, the benefit of early surgery was also observed in specific subgroups, including patients who are asymptomatic and without LV decompensation (LVEF above 60% and LVESD less than 40 mm), for whom watchful waiting remains an option under the current guidelines. Patients with normal ventricular function may derive benefit from early surgery,^{6,11} as LVEF deterioration and severe symptoms are predictors of long-term adverse clinical events.^{2,3} We also observed consistent benefits in the subgroup with degenerative MR. Earlier surgical intervention may prevent progressive degenerative changes of MV by eliminating the abnormal mechanical stress imposed on the MV apparatus, which could lead to preserve native valve anatomy and function of myocardium. Although our study was conducted at high-volume tertiary valve centers, accurate determination of MR severity and appropriate referral, particularly in the community setting, remain important considerations. Overall, our findings suggest the potential importance of optimizing surgical timing before LV systolic dysfunction occurs to maximize survival benefits.

Limitations

This study had several limitations. First, because this study used an observational database, unobserved or incompletely measured factors—including surgeon experience, physician judgement, patients' socioeconomic status, health literacy, and treatment preferences—could not be fully accounted for.²⁶ Nevertheless, the clone-censor-weight approach helped reduce bias from treatment assignment and artificial censoring. Second, longitudinal clinical and echocardiographic changes after the time zero were not available across institutions. Residual bias may remain; therefore, future studies with longitudinal follow-up may strengthen the evidence supporting early surgery. Third, this study did not include transcatheter edge-to-edge repair, as the majority of the study population was drawn from the period before this technique was introduced. Fourth, to avoid overfitting, we were unable to perform subgroup analyses, such as sex.³⁷ Fifth, because this study was conducted at tertiary referral centers with expertise in the diagnosis and management of MR, findings may not be fully generalizable to other clinical settings where accurate identification of severe MR and timely referral may be more challenging. Finally, data on postoperative complications were not collected. However, with only 4 deaths within 1 year after MV surgery, early postoperative mortality or complications are unlikely to have influenced the long-term outcomes.

Conclusions

In this target trial emulation study of patients with asymptomatic severe primary MR, we demonstrated the significant survival benefits of early MV surgery in a clinical setting, including those without evidence of LV decompensation and those with degenerative MR. These findings support earlier surgical intervention for asymptomatic primary MR in contemporary clinical practice.

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Corresponding Author: Seung-Pyo Lee, MD, PhD, Professor, Department of Internal Medicine, Seoul National University College of Medicine & Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea (sproll1@snu.ac.kr); Sunggho Won, PhD, Professor, Department of Public Health Science, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea (won1@snu.ac.kr).

Author Affiliations: Division of Data Science, University of Suwon, Hwaseong, Republic of Korea (Ahn); Institute of Health and Environment, Seoul National University, Seoul, Republic of Korea (Ahn, Won); Division of Cardiology and Cardiovascular Center, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea (Kwak, Lim, Lee); Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea (K. Kim, Shim); Division of Cardiology, Heart Vascular Stroke Institute, Sungkyunkwan University School of Medicine and Samsung Medical Centre, Seoul, Republic of Korea (J. Kim, Park); Division of Cardiology, College of Medicine, University of Ulsan and Asan Medical Centre, Seoul, Republic of Korea (Sun, D.-H. Kim); Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul, Korea (K. H. Kim); Department of Public Health Sciences, Seoul National University, Seoul, Republic of Korea (Won); Interdisciplinary Program of Bioinformatics, Seoul National University, Seoul, Republic of Korea (Won); RexSoft Inc, Seoul, Republic of Korea (Won); Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea (Lee); Center for Precision Medicine, Seoul National University Hospital, Seoul, Republic of Korea (Lee).

Author Contributions: Drs Lee and Won had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ahn and Kwak contributed equally as cofirst authors.

Concept and design: Ahn, Kwak, J. Kim, Lee.

Acquisition, analysis, or interpretation of data: Ahn, Kwak, Lim, K. Kim, Sun, D.-H. Kim, K. H. Kim, Shim, Park, Won, Lee.

Drafting of the manuscript: Ahn, Kwak, Won, Lee.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Ahn, Kwak, Won, Lee.

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Supervision: Lim, J. Kim, D.-H. Kim, K. H. Kim, Shim, Park, Won, Lee.

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SUPPLEMENT 1.

- eAppendix. Target trial emulation using the clone-censor-weight approach
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SUPPLEMENT 2.

- Data sharing statement