



Original Investigation | Cardiology

Clinical Outcomes of Mitral Valve Surgery in Atrial Functional Mitral Regurgitation in the REVEAL-AFMR Registry

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Abstract

IMPORTANCE The characteristics and treatment strategies of atrial functional mitral regurgitation (AFMR) are poorly understood.

OBJECTIVE To investigate the prevalence, clinical characteristics, and outcomes of mitral valve (MV) surgery in AFMR.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study, called the Real-World Observational Study for Investigating the Prevalence and Therapeutic Options for Atrial Functional Mitral Regurgitation (REVEAL-AFMR), was conducted across 26 Japanese centers (17 university hospitals, 1 national center, 3 public hospitals, and 5 private hospitals). All transthoracic echocardiography procedures performed from January 1 to December 31, 2019, were reviewed to enroll adult patients (aged ≥ 20 years) with moderate or severe AFMR, defined by preserved left ventricular function, a dilated left atrium, and an absence of degenerative valvular changes. Data were analyzed from May 8, 2023, to May 16, 2024.

EXPOSURES Mitral valve surgery, with or without tricuspid valve intervention.

MAIN OUTCOMES AND MEASURES The primary composite outcome included heart failure hospitalization and all-cause mortality.

RESULTS In 177 235 patients who underwent echocardiography, 8867 had moderate or severe MR. Within this group, 1007 (11.4%) were diagnosed with AFMR (mean [SD] age, 77.8 [9.5] years; 55.7% female, of whom 807 (80.1%) had atrial fibrillation. Of these patients, 113 underwent MV surgery, with 92 (81.4%) receiving concurrent tricuspid valve surgery. Patients who underwent surgery were younger but had more severe MR (57.5% [n = 65] vs 9.4% [n = 84]; $P < .001$), a larger mean (SD) left atrial volume index (152.5 [97.8] mL/m² vs 87.7 [53.1] mL/m²; $P < .001$), and a higher prevalence of heart failure (according to the New York Heart Association class III [marked limitation of physical activity] or class IV [symptoms of heart failure at rest], 26.5% [n = 30] vs 9.3% [n = 83]; $P < .001$) than those who remained under medical therapy. During a median follow-up of 1050 days (IQR, 741-1188 days), 286 patients (28.4%) experienced the primary outcome. Despite a more severe disease status, only the surgical group showed a decrease in natriuretic peptide levels at follow-up and had a significantly lower rate of the primary outcome (3-year event rates were 18.3% vs 33.3%; log-rank, $P = .03$). Statistical adjustments did not alter these findings.

(continued)

Key Points

Question What are the prevalence, characteristics, and clinical outcomes of patients with atrial functional mitral regurgitation (AFMR) who undergo mitral valve (MV) surgery?

Findings In this cohort study of 177 235 adult patients who underwent clinical echocardiography, 8867 had significant mitral regurgitation, of which 1007 (11%) were identified with AFMR for the final cohort. Among patients with AFMR, those who underwent MV surgery had lower rates of heart failure hospitalization and all-cause mortality, despite presenting with more severe AFMR and more advanced cardiac remodeling compared with those managed medically.

Meaning These findings suggest that MV surgery was associated with lower rates of adverse clinical outcomes in patients with AFMR, underscoring the need for further clinical trials to investigate the influence of AFMR on cardiovascular medicine.

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE The findings of this cohort study suggest that in patients with AFMR, who were typically older and predominantly had atrial fibrillation, MV surgery was associated with lower rates of adverse clinical outcomes. Future studies are warranted to investigate a possible causal relationship to better regulate cardiovascular medicine.

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Introduction

Mitral regurgitation (MR) constitutes the leading cause of cardiac surgery in countries with abundant resources.^{1,2} It is typically classified as primary, originating from intrinsic mitral valve (MV) pathology, or functional, resulting from alterations in left ventricular geometry.³⁻⁶ In addition to these traditional classifications, atrial functional MR (AFMR) is emerging as a distinct entity characterized by the absence of MV pathology and normal left ventricular function, with atrial dilation and annular remodeling implicated as the primary mechanisms of MV leaflet malcoaptation.⁷⁻¹⁰

Despite advances in the pathophysiological understanding of AFMR,¹¹⁻¹³ the clinical understanding of AFMR remains limited.^{14,15} The prevalence and clinical outcomes of AFMR reported in the literature vary significantly, obscuring the true extent of its clinical implications.¹⁰ Several studies have demonstrated that patients with moderate or severe AFMR may have a higher risk of heart failure hospitalization and all-cause mortality,^{16,17} and various surgical interventions have been reported to effectively eliminate AFMR.¹⁸⁻²¹ However, these studies were limited by the single-center nature and their small sample sizes, rendering them underpowered for statistically adjusting for confounders. As a result, the prognostic implications of surgical interventions for patients with AFMR have not been thoroughly investigated with appropriate statistical adjustments, and accordingly, current guidelines do not provide a strong recommendation for the therapeutic strategy in this disease entity.²

In light of these limitations and the need for a comprehensive understanding of AFMR, we conducted a multicenter study to investigate the clinical characteristics of AFMR and identify associations between surgical interventions and patient outcomes.

Methods

Study Design

The Real-World Observational Study for Investigating the Prevalence and Therapeutic Options for Atrial Functional Mitral Regurgitation (REVEAL-AFMR) study aimed to investigate the prevalence, clinical characteristics, treatment methods, and outcomes of patients with AFMR. This cohort study's protocols complied with the Declaration of Helsinki²² and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline²³ and were approved by the institutional review board of Juntendo University, Japan, with each participating center approving the execution of the study. All enrolled individuals were informed about the study's details and were reassured that they could withdraw at any time. Written informed consent was waived because of the observational and retrospective nature of the study according to the ethical guidelines for medical and biological research involving human participants in Japan. Study information was provided in the University Hospital Medical Information Network Clinical Trials Registry public database before starting enrollment.

Patients who underwent transthoracic echocardiography from January 1 to December 31, 2019, at 26 participating centers (17 university hospitals, 1 national center, 3 public hospitals, and 5 private hospitals) in Japan were retrospectively screened. After reviewing all echocardiographic reports to identify adult patients (aged ≥ 20 years) with moderate or greater MR, at each center, cardiologists

who were echocardiography specialists reviewed all echocardiographic videos and classified individuals with MR as degenerative MR, ventricular functional MR, or AFMR. All specialists had received echocardiography training equivalent to or exceeding level III training outlined by the American College of Cardiology, the American Heart Association, and the American Society of Echocardiography.²⁴ In addition, 100 randomly selected videos were reviewed in the imaging core laboratory to confirm the diagnosis and the validity of the measurements. Transesophageal echocardiography was also reviewed when available for accurate disease classification.

Atrial functional MR was defined with a prerequisite of preserved left ventricular function (ejection fraction, $\geq 50\%$) and a dilated left atrium (left atrium volume index, ≥ 38 mL/m² for men and ≥ 41 mL/m² for women; if the left atrium volume index was not available, left atrium diameter, ≥ 40 mm for men and ≥ 37 mm for women; values were defined based on the previously reported normal values in the Japanese population).²⁵ The exclusion criteria for AFMR were degenerative changes in the MV, MR due to systolic anterior motion of the MV, and MR subsequent to MV surgery. Patients in the acute phase of decompensated heart failure were also excluded from the analysis.

Data Acquisition

Patient characteristics at baseline, at the most recent follow-up, and just before MV surgery were collected in a REDCap database between April and November 2022. For all patients, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was calculated to assess the risk of surgery.²⁶ Mitral annuloplasty, MV repair, and MV replacement were considered MV surgery. Transcatheter interventions for MR were not considered MV surgery in this study, and patients who underwent these procedures were censored at the time of the procedure.

Grading of MR was retrospectively evaluated by echocardiography specialists at each site, with a comprehensive approach as recommended in the guidelines.^{2,27} Moderate, moderate-to-severe, and severe MR were equivalent to grades II, III, and IV MR, defined in the published guidelines, respectively.²⁷ To ensure consistent findings, all echocardiography specialists reviewed shared examples of each patient's severity of AFMR before participating in the study. Additionally, a dedicated cloud application to share anonymized echocardiographic videos facilitated discussions when investigators were uncertain about their findings. The other echocardiographic data were extracted from clinical reports, while the core laboratory reanalyzed to confirm the data quality and the agreement in the grading of MR in a randomly selected group of 100 patients.

The primary end point was a composite of heart failure hospitalization and all-cause death. Heart failure hospitalization was defined in accordance with the published statement.²⁸ Telephone surveys were conducted with patients to confirm end points when more than 1 year had elapsed since the patient's last follow-up. For the outcome analysis, we performed a sensitivity analysis in the following subpopulations: excluding patients with moderate or severe aortic stenosis and severe aortic regurgitation and excluding patients with a dilated left ventricular end-diastolic volume (>150 mL) in addition to the aortic valve diseases specified in the first subpopulation.

Statistical Analysis

Data were analyzed from May 8, 2023, to May 16, 2024, and are presented as means (SDs) or medians (IQRs) for continuous variables as appropriate and as frequencies (percentages) for categorical variables. Baseline group differences were evaluated using *t* tests with the Welch correction or Mann-Whitney tests for continuous variables and the χ^2 test or Fisher exact tests for categorical variables.

In the data validation process, 100 randomly selected patients were reviewed at the core laboratory, and the diagnosis of AFMR was confirmed for all of those patients. Intraclass correlation coefficient and weighted Cohen κ were used to assess the concordance of the echocardiographic measurements by local laboratories and those conducted by the core laboratory (eTable 1 in Supplement 1). Paired *t* tests were used to test changes in log-transformed natriuretic peptides from baseline to follow-up. In addition to comparing patients who underwent MV surgery with those

treated medically, the characteristics and survival curves of patients who underwent MV repair and MV replacement were also investigated.

In this study, multiple approaches were used to assess the outcomes of surgical intervention for AFMR. First, univariable and multivariable Cox proportional hazards regression analyses were performed. Multivariable analyses included 25 covariates established as prognostic factors of cardiovascular diseases (eMethods in Supplement 1). In addition, another model including only MV surgery and EuroSCORE II was also tested. For patients who underwent MV surgery, variables recorded just before the surgery were used.

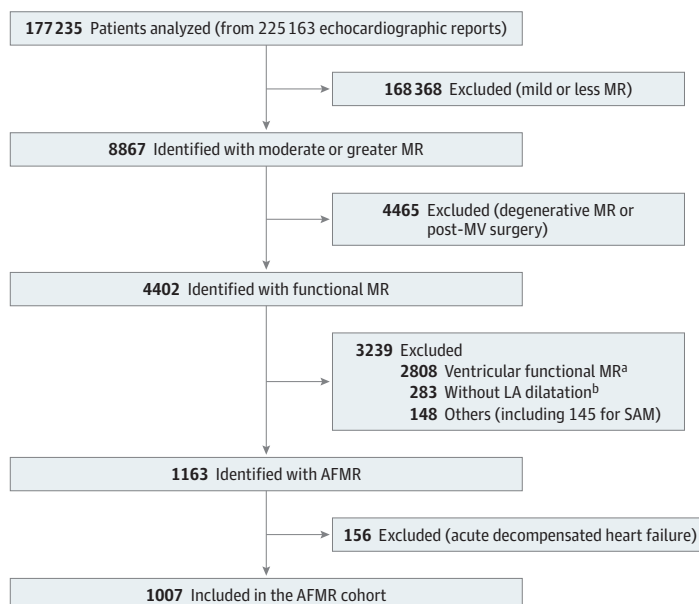
Although the multivariable Cox proportional hazards regression analyses consider influences of confounding factors, this method might introduce immortal time bias; patients who underwent MV surgery were those who could survive until the time of surgery, whereas those who died before the surgery were inevitably categorized into the medically treated group. We applied a propensity score-based time zero matching, which is detailed in the eMethods, eTable 2, and eFigure 1 in Supplement 1. The time zero matching technique was previously developed by other researchers and was shown to most effectively eliminate the immortal time bias compared with other methods.²⁹ In the matched cohort, Kaplan-Meier curves and log-rank tests were used. Additionally, to identify subgroups in which the association of MV surgery with clinical outcomes might be stronger, we calculated hazard ratios (HRs) in prespecified subgroups based on age, sex, MR severity, TR severity, and LA and LV size. We also assessed *P* values for interactions within these subgroups.

In all multivariable Cox proportional hazards regression analyses, robust SEs were calculated and used to yield *P* values to account for the clustering of patients within each institute. All statistical analyses were performed with R, version 4.3.2 (R Project for Statistical Computing). In all analyses, a 2-tailed *P* < .05 indicated statistical significance.

Results

Figure 1 summarizes the patient enrollment flowchart. Among a total of 225 163 echocardiographic reports, 177 235 patients who underwent transthoracic echocardiography were analyzed. After excluding those with mild or no MR, 8867 patients were identified with moderate or severe MR. Based on a detailed transthoracic and/or transesophageal echocardiography review process, 4465

Figure 1. Patient Flowchart



AFMR indicates atrial functional mitral regurgitation; LA, left atrium; MR, mitral regurgitation; MV, mitral valve; SAM, systolic anterior motion.

^a Defined as a left ventricular ejection fraction less than 50% and/or wall motion abnormality.

^b Defined as an LA volume index less than 38 mL/m² for men and less than 41 mL/m² for women (or an LA diameter <40 mm for men and <37 mm for women).

patients were excluded because they had degenerative MR or had already undergone MV surgery. An additional 2808 patients were excluded owing to ventricular functional MR (defined by a left ventricular ejection fraction less than 50% and/or wall motion abnormality), along with 283 patients who did not have LA dilatation, 145 who had systolic anterior motion, and 3 others. The final cohort consisted of 1007 patients with AFMR.

Patient Characteristics

The **Table** presents the baseline characteristics of the 1007 patients who were included in the study, comparing the medically treated group (n = 894) and the MV surgery group (n = 113). Overall, patients with AFMR were older (mean [SD] age, 77.8 [9.5] years; 55.7% female; 44.3% male); 807 patients (80.1%) had a history of atrial fibrillation and 200 patients (19.9%) did not. Patients in the MV surgery group were significantly younger than those in the medically treated group (mean [SD] age, 73.8 [8.7] years vs 78.3 [9.5] years; $P < .001$). The prevalence of New York Heart Association class III (marked limitation of physical activity) or IV (symptoms of heart failure at rest) (26.5% [n = 30] vs 9.3% [n = 83]; $P < .001$) and permanent atrial fibrillation (77.0% [n = 87] vs 60.6% [n = 542]; $P < .001$) was higher in the MV surgery group than in the medically treated group. Compared with the medically treated group, the MV surgery group had a significantly larger mean (SD) left ventricular end-diastolic diameter (53.2 [7.8] vs 48.4 [6.5]; $P < .001$), left ventricular end-systolic diameter (35.3 [6.3] vs 31.9 [5.4]; $P < .001$), left atrium diameter (61.3 [14.3] vs 49.9 [9.6]; $P < .001$), and left atrium volume index (152.5 [97.8] mL/m² vs 87.7 [53.1] mL/m²; $P < .001$) and a higher prevalence of severe MR (57.5% [n = 65] vs 9.4% [n = 84]; $P < .001$), as well as severe tricuspid regurgitation (38.1% [n = 43] vs 12.8% [n = 114]; $P < .001$).

In patients who underwent MV surgery, 25 were characterized as having moderate MR in a stable clinical condition prior to surgery. The indications for surgical referral for these patients included either persistent symptoms of heart failure accompanied by previous documentation of severe MR, which became apparent only during exercise or heart failure decompensation (n = 13) or coexisting indications for other cardiac surgical procedures (n = 12) (eTable 3 in [Supplement 1](#)).

Procedure and Natriuretic Peptides

Of the 113 MV procedures, 68 (60.2%) were MV repairs and 45 (39.8%) were MV replacements. The MV repairs consisted of 60 simple annuloplasties (88.2%) and 8 annuloplasties with leaflet augmentations (11.8%). No patient was treated with leaflet resection or artificial chords. Patients who underwent MV replacement exhibited lower serum levels of albumin, sodium, and cholesterol; had a larger left atrium; and were more likely to have severe tricuspid regurgitation compared with those who underwent MV repair (eTable 4 in [Supplement 1](#)).

A tricuspid valve surgery was performed simultaneously in 92 (81.4%) of the patients, of which 3 procedures (3.2%) were for valve replacement and the others were for annuloplasty. Other concomitant procedures included aortic valve replacement (n = 21), coronary artery bypass grafting (n = 9), left atrium appendage closure or resection (n = 88), and a Maze procedure (n = 21). There were 28 of 1007 patients (2.8%) who underwent transcatheter edge-to-edge repair for MV during the follow-up, and they were censored at the time of the procedure. Catheter ablation for atrial fibrillation was performed for 60 patients in those who were medically treated and only for 1 patient among those who underwent MV surgery. No procedure-related complications were reported for catheter ablation, and it is unlikely that patients who remained under medical therapy experienced adverse events owing to these procedures.

The most recent echocardiographic examinations were conducted after a median of 434 days (IQR, 46-752 days) from surgery among 103 patients. After MV repair, 8 of 61 patients (13.1%) had at least mild to moderate MR, and 1 of 41 patients (2.4%) experienced paravalvular leakage after MV replacement ($P = .04$). Among the 61 patients, severe MR was seen in only 2 (3.2%) after MV repair and in no patients after MV replacement ($P = .16$). Kaplan-Meier curves indicated similar clinical outcomes between these 2 groups (eFigure 2 in [Supplement 1](#)). Among the patients who remained

Table. Baseline Patient Characteristics

Characteristic	No.	Overall	Medically treated	Mitral valve surgery	P value
Total, No.	1007	1007	894	113	NA
Age, mean (SD), y	1007	77.8 (9.5)	78.3 (9.5)	73.8 (8.7)	<.001
Sex, No. (%)					
Female	1007	561 (55.7)	508 (56.8)	53 (46.9)	.06
Male	1007	446 (44.3)	386 (43.2)	60 (53.1)	.06
Clinical measurements, mean (SD)					
Body surface area, m ²	1002	1.54 (0.19)	1.53 (0.19)	1.59 (0.20)	.001
Body mass index ^a	1002	22.1 (3.5)	22.0 (3.4)	22.8 (4.1)	.06
Systolic BP, mm Hg	946	127.0 (19.9)	127.6 (19.6)	122.3 (21.6)	.02
Diastolic BP, mm Hg	946	70.2 (13.9)	70.3 (13.8)	69.8 (14.1)	.76
Heart rate, per min	996	72.5 (16.6)	72.5 (16.7)	72.8 (15.2)	.84
Laboratory values, mean (SD)					
Hemoglobin, g/dL	990	11.8 (2.0)	11.8 (2.0)	11.9 (1.8)	.60
Albumin, g/dL	877	3.74 (0.59)	3.73 (0.60)	3.85 (0.45)	.01
BUN, mg/dL	983	24.0 (13.7)	23.6 (13.1)	26.6 (17.7)	.08
Creatinine, mg/dL	991	1.26 (1.16)	1.25 (1.15)	1.37 (1.20)	.30
Sodium, mEq/L	983	140.3 (3.0)	140.4 (3.0)	139.8 (3.1)	.07
HDL cholesterol, mg/dL	686	55.8 (17.1)	56.0 (17.1)	55.1 (17.0)	.62
LDL cholesterol, mg/dL	718	93.3 (30.0)	94.2 (30.1)	88.0 (28.6)	.04
EuroSCORE II, mean (SD), % ^b	1007	3.49 (4.19)	3.48 (3.75)	3.57 (6.78)	.89
AF duration, median (IQR), mo	706	64.5 (17.0-144.0)	60.0 (13.0-125.0)	120.0 (72.0-228.0)	<.001
BNP, median (IQR), pg/mL	546	199.0 (112.3-368.3)	198.0 (113.8-370.0)	199.5 (109.5-319.3)	.86
NT-proBNP, median (IQR), pg/mL	347	1280.0 (563.0-2588.0)	1255.5 (545.8-2567.0)	1492.0 (888.5-2904.0)	.18
Comorbidities, No. (%)					
NYHA (III or IV)	1007	113 (11.2)	83 (9.3)	30 (26.5)	<.001
Current smoker	976	71 (7.3)	59 (6.8)	12 (11.0)	.12
Hypertension	1007	849 (84.3)	744 (83.2)	105 (92.9)	.006
Prior heart failure admission	1007	271 (26.9)	228 (25.5)	43 (38.1)	.007
Coronary artery disease	1007	143 (14.2)	129 (14.4)	14 (12.4)	.67
Dementia	1007	75 (7.4)	73 (8.2)	2 (1.8)	.02
Diabetes	1007	151 (15.0)	136 (15.2)	15 (13.3)	.68
Dialysis	1001	30 (3.0)	25 (2.8)	5 (4.4)	.37
COPD	1007	53 (5.3)	47 (5.3)	6 (5.3)	>.99
Loop diuretics	1007	554 (55.0)	469 (52.5)	85 (75.2)	<.001
ACE-I or ARB	1007	458 (45.5)	397 (44.4)	61 (54.0)	.06
Beta-blocker	1007	504 (50.0)	435 (48.7)	69 (61.1)	.02
MRA	1007	273 (27.1)	218 (24.4)	55 (48.7)	<.001
Anticoagulation drugs	1007	708 (70.3)	614 (68.7)	94 (83.2)	.001
Type of AF, No. (%)					
Paroxysmal	NA	141 (14.0)	137 (15.3)	4 (3.5)	<.001
Persistent	NA	37 (3.7)	33 (3.7)	4 (3.5)	
Permanent	NA	629 (62.5)	542 (60.6)	87 (77.0)	
Sinus rhythm	NA	200 (19.9)	182 (20.4)	18 (15.9)	
Echocardiographic values, mean (SD)					
IVSd, mm	1007	10.0 (2.0)	10.0 (2.0)	9.7 (1.8)	.13
LVDd, mm	1007	48.9 (6.9)	48.4 (6.5)	53.2 (7.8)	<.001
LVDs, mm	1007	32.3 (5.7)	31.9 (5.4)	35.3 (6.3)	<.001
LVEDV, mL	1007	97.5 (35.8)	95.0 (33.9)	117.6 (43.7)	<.001

(continued)

Table. Baseline Patient Characteristics (continued)

Characteristic	No.	Overall	Medically treated	Mitral valve surgery	P value
LVEDV index, mL/m ^{2c}	1002	63.1 (21.0)	62.1 (20.2)	71.3 (25.2)	<.001
LVESV, mL	1007	37.6 (16.0)	36.6 (15.1)	45.8 (20.1)	<.001
LVESV index, mL/m ^{2c}	1002	24.2 (9.1)	23.8 (8.9)	27.3 (10.5)	.001
LVEF, %	1007	61.8 (6.0)	61.8 (5.9)	61.6 (6.2)	.74
LV stroke volume, mL	770	59.6 (22.2)	60.3 (21.9)	54.8 (23.9)	.03
Cardiac index, L/min/m ^{2d}	761	2.64 (0.98)	2.68 (0.99)	2.42 (0.91)	.01
LA diameter, mm	1005	51.2 (10.8)	49.9 (9.6)	61.3 (14.3)	<.001
LAVI, mL/m ²	946	95.3 (63.6)	87.7 (53.1)	152.5 (97.8)	<.001
TR velocity, m/s	962	2.77 (0.46)	2.76 (0.46)	2.83 (0.46)	.14
MR ERO, cm ²	481	0.27 (0.12)	0.25 (0.09)	0.38 (0.16)	<.001
MR RVol, mL	567	44.9 (19.1)	42.8 (16.8)	55.4 (25.9)	<.001
Mitral E wave, cm/s	997	101.8 (28.2)	99.9 (27.0)	117.1 (32.4)	<.001
E/e'	944	16.0 (7.0)	16.1 (7.1)	15.3 (6.0)	.20
Deceleration time, ms	989	183.6 (55.4)	185.0 (55.6)	172.4 (52.4)	.02
Severe AS, No. (%)	1007	47 (4.7)	39 (4.4)	8 (7.1)	.23
Severe AR, No. (%)	1006	11 (1.1)	8 (0.9)	3 (2.7)	.12
Severe TR, No. (%)	1007	157 (15.6)	114 (12.8)	43 (38.1)	<.001
MR grades, No. (%)					
Moderate	NA	710 (70.6)	686 (76.7)	25 (22.1)	
Moderate to severe	NA	147 (14.6)	124 (13.9)	23 (20.4)	<.001
Severe	NA	149 (14.8)	84 (9.4)	65 (57.5)	

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AR, aortic regurgitation; ARB, angiotensin II receptor blocker; AS, aortic stenosis; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; E/e', early mitral inflow velocity divided by mitral annular early diastolic velocity; ERO, effective regurgitant orifice; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; HDL, high-density lipoprotein; IVSd, intraventricular septal thickness at diastole; LA, left atrium; LAVI, left atrial volume index; LDL, low-density lipoprotein; LV, left ventricle; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; RVol, regurgitant volume; TR, tricuspid regurgitation.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; albumin to grams per liter, multiply by 10; BUN to millimoles per liter, multiply by 0.357; creatinine to micromoles per liter, multiply by 88.4; sodium to millimoles per liter, multiply by 1.0; and HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259.

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

^b Scores predict in-hospital mortality and range from 0% to 5%, with higher scores indicating higher risk; scores of 0% to 2%, low risk; greater than 2% to 5%, moderate risk; and greater than 5%, high risk.

^c Calculated as LVEDV and LVESV divided by body surface area in square meters.

^d Calculated as cardiac output in liters per minute divided by body surface area in square meters.

under medical therapy, 450 of 560 (80.4%) had moderate or greater MR at the final echocardiographic examination (median, 765 days [IQR, 420-1013 days]) after the baseline examination vs the MV surgery group (9 of 103 [8.7%]; *P* < .001) (Figure 2). In addition, the log-B-type natriuretic peptide and the log-N-terminal pro-B-type natriuretic peptide decreased in patients who underwent MV surgery but did not decrease in patients who were medically treated (eFigure 3 in Supplement 1).

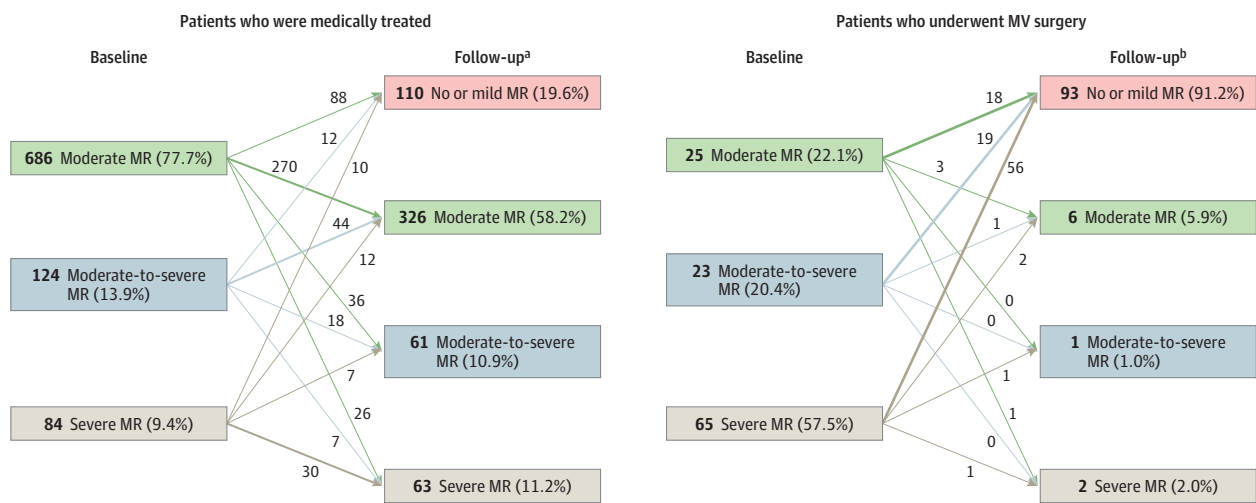
Primary Outcomes Between the Treatment Groups

During the median follow-up period of 1050 days (IQR, 741-1188 days), 286 of 1007 patients (28.4%) experienced the combined primary outcome (141 heart failure hospitalizations and 179 all-cause deaths). Patients who underwent MV surgery had a significantly lower event rate compared with those treated medically (3-year event rates were 18.3% vs 33.3%; log-rank, *P* = .03) (Figure 3A).

Multivariable Cox proportional hazards regression models revealed that MV surgery was associated with the primary outcome in a univariable model (HR, 0.62 [95% CI, 0.42-0.91]; $P = .01$), when adjusted for 25 variables (HR, 0.43 [95% CI, 0.29-0.64]; $P < .001$), and when adjusted by EuroSCORE II (HR, 0.55 [95% CI, 0.37-0.80]; $P = .002$) (eTable 5 in Supplement 1).

A propensity score-based time zero matching yielded 70 matched pairs (140 patients) with similar propensity scores, in which immortal time bias was minimized. Characteristics of these patients are shown in eTable 6 in Supplement 1, and the top parameters that were associated with MV surgical referral are summarized in eTable 7 in Supplement 1. Clinical and echocardiographic parameters were well-balanced between the treatment groups. The Kaplan-Meier curve analysis presented in Figure 3B and the multivariable Cox proportional hazards regression yielded a significant association of MV surgery with a lower event rate in this matched cohort (HR, 0.39 [95% CI, 0.20-0.78]; $P = .007$) (eTable 5 in Supplement 1). The associations with MV surgery and the

Figure 2. Changes in Mitral Regurgitation (MR) Severity by Treatment Group

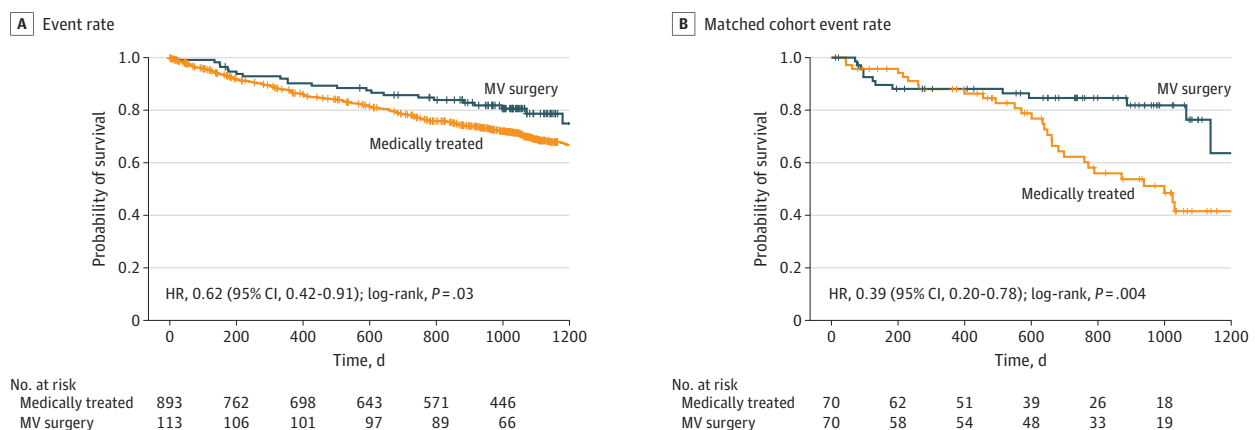


Atrial functional MR was well managed by surgery with only 1.9% ($n = 2$) of patients with recurrent severe MR, whereas 80.4% ($n = 450$) of patients who were medically treated presented moderate or severe MR at the latest follow-up. MV indicates mitral valve.

^a A total of 334 patients were lost to follow-up (266 with moderate MR, 43 with moderate-to-severe MR, 25 with severe MR).

^b A total of 11 patients were lost to follow-up (3 with moderate MR, 3 with moderate-to-severe MR, 5 with severe MR).

Figure 3. Kaplan-Meier Curve Analyses for Heart Failure Hospitalization and All-Cause Mortality



A, Patients who underwent mitral valve (MV) surgery had a significantly lower event rate compared with those treated medically. B, Propensity score time 0 matching to minimize immortal time bias showed similar results. HR indicates hazard ratio.

primary outcome remained significant when excluding patients with moderate or severe aortic stenosis or severe aortic regurgitation (eFigure 4 and eTable 8 in Supplement 1) and those with a left ventricular end-diastolic volume index greater than 150 mL (eFigure 5 and eTable 9 in Supplement 1).

Exploratory Subgroup Analysis

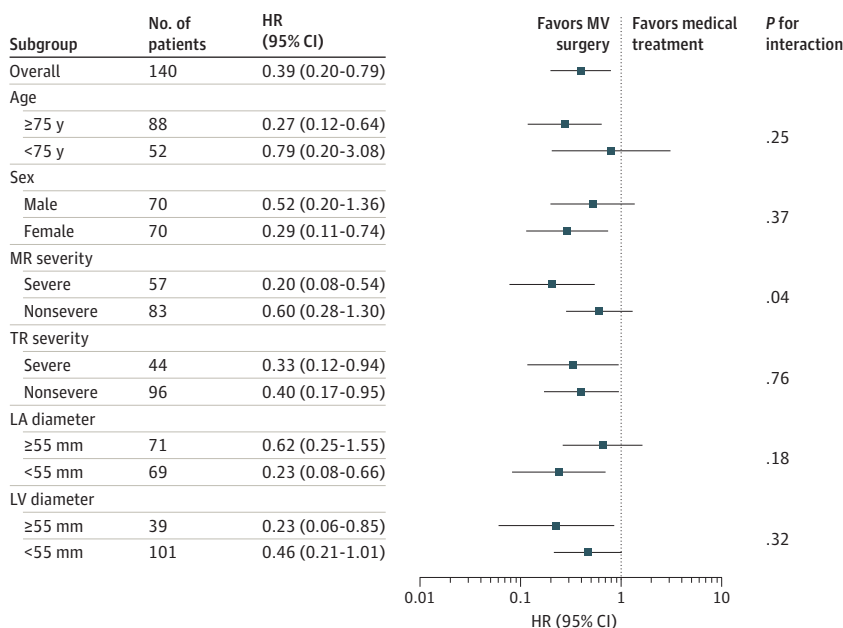
Subgroup analyses were performed in the matched cohort to investigate the potential associations with the surgical outcomes. While age, sex, the severity of tricuspid regurgitation, left atrium diameter, and left ventricular diameter were not associated with outcomes, outcomes favored treatment of patients with severe MR compared with those with nonsevere MR (Figure 4). The HRs were 0.20 (0.08-0.54) in patients with severe MR and 0.60 (0.28-1.30) in those with nonsevere MR (P for interaction = .04).

Discussion

In this large, retrospective, multicenter cohort study, significant AFMR was not uncommon (11.4% of all MR), and patients with AFMR were typically older with a high event rate. Mitral valve surgery for AFMR was associated with significant reductions in both MR severity and natriuretic peptide levels. The results of survival analyses suggest that MV surgery was associated with a lower event rate, consistent with the findings of multiple sensitivity analyses.

The clinical characteristics of AFMR have not been fully understood, mainly because of the lack of a large multicenter database. Most previous studies were conducted in a single center and their findings and the prevalence and the characteristics of AFMR showed significant variation among them.^{8,10} The present study is the first, to our knowledge, of AFMR in a large cohort from 26 centers including various kinds of hospitals. Thus, the present results may represent AFMR data in a clinical setting. The prevalence of 11.4% found in all kinds of MR is not negligible because the prevalence of significant MR in the general population is estimated to be 2.0% to 3.5%.^{30,31} In addition, the importance of AFMR will increase further as the general population ages, since the proportion of AFMR in MR increases in older people.³² Accordingly, the establishment of effective treatment strategies is an urgent demand.

Figure 4. Associations of Treatment Types With Outcomes in Subgroup Analyses in the Matched Cohort



Subgroups of age (≥75 years), sex, the severity of tricuspid regurgitation (TR), left atrium (LA) diameter (≥55 mm), and left ventricle (LV) diameter (end-diastolic; ≥55 mm) were not associated with outcomes. The treatment effect favored mitral valve (MV) surgery in patients with severe mitral regurgitation (MR) compared with those with nonsevere MR. Markers indicate hazard ratios (HRs); horizontal lines, 95% CIs.

Studies have shown that AFMR is associated with increased adverse events, including all-cause mortality and heart failure hospitalizations.¹⁶ Patients with AFMR typically have a small and stiff left ventricle, as confirmed in our present results of small left ventricular volumes and elevated early mitral inflow velocity divided by mitral annular early diastolic velocity. Additionally, AFMR may affect the hemodynamic condition in these patients because such small and stiff left ventricles cannot increase forward volume in the presence of significant MR. Thus, a reduction in AFMR via MV surgery might improve clinical outcomes in this population.

Successful control of MR should be the key element of MV surgery for MR. In previous studies, AMFR has been reported to be effectively reduced by simple MV surgical procedures.^{18,19} We found that patients in a clinical setting who underwent MV procedures had a significantly smaller amount of MR after midterm follow-up, with only a 3.2% recurrence rate of severe MR after MV repair and 0% after MV replacement. In relation to the clinical outcomes, a single-center observational study by Mesi et al¹⁷ showed that patients who underwent MV procedures had significantly fewer adverse events. However, this included only 16 patients who underwent MV surgery, and no statistical adjustment was possible. With a large number of patients, we investigated the association of MV procedures with rigorous statistical methods. The results from both traditional multivariable Cox proportional hazards regression models and propensity score-based time zero matching, which minimized the immortal time bias, showed that MV surgery was associated with the reduced rate of heart failure hospitalizations and all-cause deaths. The HRs were smaller when adjusted for covariates than they were in a univariable model, probably because MV surgery was performed for patients with higher risks.

The results from this study should serve as an important basis for the clinical and scientific understanding of AFMR. By identifying the prevalence and characteristics of AFMR in a clinical setting, along with the outcomes of surgical intervention, this study provides valuable insights into the literature and may offer useful information for clinicians and researchers. The low rate of recurrent MR after MV surgery and differences in event rates between the treatment groups will be crucial in planning future clinical trials. However, owing to the study design, the association between MV surgery and low event rates should not be interpreted as a causal relationship. Future studies to further clarify the benefits of MV procedures in patients with AFMR are warranted.

Limitations

This study has several limitations. First, despite the multicenter design, all patients were Japanese adults. Next, the diagnosis of AFMR was based dominantly on transthoracic echocardiography, although transesophageal echocardiography was also referred to when available. However, all transthoracic echocardiography in this study was carefully reviewed by experienced cardiologists who were specialized in echocardiography and underwent dedicated level III-equivalent echocardiography training. Moreover, we confirmed the diagnosis in randomly selected patients, all of whom were approved as significant AFMR. All patients who underwent MV surgery were diagnosed as AFMR during the surgery. In addition, the patient characteristics in this study were clearly different from typical characteristics of young patients with degenerative MR. Next, the echocardiographic analysis was dominantly performed at each site. However, the parameters used in this study were well-established standard parameters. Furthermore, we confirmed the measurements at the core laboratory, and these parameters showed excellent agreement with the original measurements at each site. Last, and most importantly, although we used multiple analyses with comprehensive statistical methods to mitigate the risk of potential biases, the retrospective design meant that there was a possibility of unmeasured residual confounders. These findings must be validated in future prospective studies, ideally with the use of randomization.

Conclusions

The findings of this cohort study suggest that in patients with AFMR, who were typically older and predominantly had atrial fibrillation, MV surgery was associated with lower rates of adverse clinical outcomes. The influence of AFMR on cardiovascular medicine in populations of older individuals should not be disregarded. Future clinical trials are warranted to investigate the causal relationship between MV surgery and clinical outcomes in patients with severe AFMR.

ARTICLE INFORMATION

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SUPPLEMENT 1.

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SUPPLEMENT 2.

Data Sharing Statement