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# Outcomes After Transcatheter Edge-to-Edge Mitral Valve Repair According to Mitral Regurgitation Etiology and Cardiac Remodeling

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## ABSTRACT

**BACKGROUND** Transcatheter edge-to-edge repair (TEER) has been increasingly used for selected patients with mitral regurgitation (MR), but limited data are available regarding clinical outcomes in patients with varied etiology and mechanism of MR.

**OBJECTIVES** The aim of this study was to evaluate the outcomes of TEER according to etiology and left ventricular (LV) and left atrial remodeling.

**METHODS** Consecutive patients who underwent TEER between 2007 and 2020 were included in the analysis. Among patients with functional MR (FMR), those with predominant LV remodeling were classified as having ventricular FMR (v-FMR), whereas those without LV remodeling but predominant left atrial remodeling were classified as having atrial FMR (a-FMR). The primary outcome was a composite of all-cause mortality and heart failure hospitalization at 2 years and was compared among patients with degenerative MR (DMR), a-FMR, and v-FMR.

**RESULTS** A total of 1,044 patients (11% with a-FMR, 48% with v-FMR, and 41% with DMR) with a mean Society of Thoracic Surgeons score of 8.6 $\pm$ 7.8 underwent TEER. Patients with a-FMR had higher rates of atrial fibrillation and severe tricuspid regurgitation with larger left and right atria, whereas patients with v-FMR had lower LV ejection fractions with larger LV dimensions. Residual MR more than moderate at discharge was not significantly different among the 3 groups (5.2% vs 3.2% vs 2.6%; $P = 0.37$). Compared with patients with DMR, 2-year event rates of the primary outcome were significantly higher in patients with a-FMR and v-FMR (21.6% vs 31.5% vs 42.3%; log-rank $P < 0.001$).

**CONCLUSIONS** Despite excellent procedural outcomes, patients with a-FMR and v-FMR had worse clinical outcomes compared with those with DMR. (J Am Coll Cardiol Intv 2022;15:1711–1722) © 2022 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is the most common valvular heart disease in developed countries, accounting for 7.1% among patients aged 75 years or older.[1] There are 2 types of MR: degenerative mitral regurgitation (DMR) (also called primary MR) and functional mitral regurgitation (FMR) (also called secondary MR). DMR is caused by abnormal mitral valve anatomy, such as leaflet prolapse and flail, while FMR is the consequence of geometric changes (dilatation) of the left ventricle and mitral annulus. FMR is generally

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**ABBREVIATIONS AND ACRONYMS**

**a-FMR** = atrial functional mitral regurgitation

**DMR** = degenerative mitral regurgitation

**EROA** = effective regurgitant orifice area

**FMR** = functional mitral regurgitation

**LA** = left atrial

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**MR** = mitral regurgitation

**RV** = right ventricular

**TEER** = transcatheter edge-to-edge repair

**TR** = tricuspid regurgitation

**v-FMR** = ventricular functional mitral regurgitation

caused by left ventricular (LV) dysfunction and subsequent LV dilatation (referred to as ventricular FMR [v-FMR]) and is associated with poor long-term prognosis.[2,3] However, FMR is a heterogeneous condition with varied etiologies and mechanisms of MR. Recent data showed that patients with significant MR caused by mitral annular enlargement (secondary to atrial enlargement, often as a consequence of atrial fibrillation), referred to as atrial FMR (a-FMR), accounted for 27% of patients diagnosed with significant MR and had a poor prognosis despite preserved LV systolic function.[4,5]

Transcatheter edge-to-edge repair (TEER) using the MitraClip device (Abbott Vascular) has become an important treatment for symptomatic patients with DMR who are at prohibitive or high surgical risk.[6] In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, TEER was associated with reductions in mortality and heart failure hospitalization and subsequent geometric changes of the left ventricle in patients with FMR and LV dysfunction.[7,8] Accordingly, current American and European guidelines on FMR recommend the use of TEER in selected patients with v-FMR.[9,10] However, a-FMR has been underrecognized and undertreated, with limited available clinical data, and thus, this population has not been addressed in the current guidelines.[9] In the present study, we aimed to evaluate and compare the baseline clinical and echocardiographic characteristics and outcomes after TEER among patients with a-FMR, v-FMR, and DMR.

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## METHODS

**STUDY POPULATION.** Patients who had moderate to severe or severe MR and underwent TEER at Cedars-Sinai Medical Center were included in the present study. For patients with structurally normal mitral valves, MR was classified as FMR, while patients with valvular abnormalities explaining the MR were classified as having DMR. Patients with both structural and functional deformation were classified as having mixed MR.

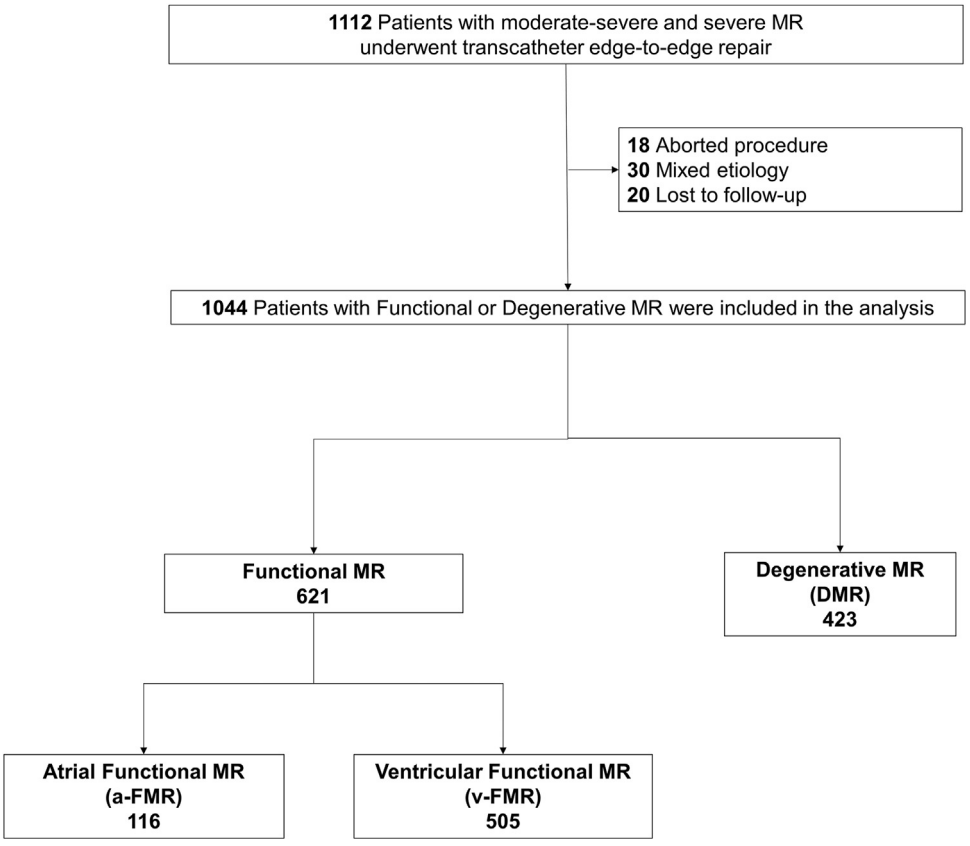
FMR was further classified depending on the alterations of the left ventricle or left atrium: FMR with moderate or severe LV remodeling (dysfunction or enlargement or both) was classified as FMR with predominant LV remodeling (v-FMR). FMR with no or mild LV remodeling but moderate or severe left atrial (LA) remodeling (dilatation) was classified as FMR with predominant atrial remodeling (a-FMR) (Figure 1). Detailed MR etiology was determined on the basis of cardiac imaging and the clinical context and diagnosis, particularly for FMR, such as the presence of clinically identified ischemic heart disease or cardiomyopathy.

Patients were selected for TEER after discussion by the multidisciplinary heart team.[9] All TEER procedures were conducted in accordance with local guidelines using standard techniques using the MitraClip device. This retrospective analysis of clinically acquired data was approved by the Institutional Review Boards, and the requirement to obtain written informed consent was waived because of the retrospective nature of the study. Baseline demographic and clinical data as well as echocardiographic measurements were collected from the hospital records and were analyzed retrospectively. In the present study, baseline clinical and echocardiographic characteristics, procedural details, and clinical outcomes after TEER were compared among patients with a-FMR, v-FMR, and DMR. For the purpose of this study, patients with mixed etiology were excluded from the analysis.

**ECHOCARDIOGRAPHIC ASSESSMENT.** Standard transesophageal and transthoracic echocardiographic examinations were performed and interpreted by experienced cardiologists according to the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.[11] From the parasternal long-axis view, LV dimensions were assessed. LV end-diastolic and end-systolic volumes were evaluated from the apical 2- and 4-chamber views, and the LV ejection fraction (LVEF) was calculated according to the Simpson biplane method, with normal function defined as LVEF assessed by transthoracic echocardiography of ≥54% for women and ≥52% for men. LV dilatation was evaluated by LV end-diastolic volumes on the basis of the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.[11]

Using the biplane method of disks, LA volume was measured at end-systole in the apical 2- and 4-chamber views and indexed to body surface area (LA volume index). Right ventricular (RV) diameter at the base and right atrial area were measured from the apical 4-chamber view. The severity of

**FIGURE 1** Study Flowchart




A total of 1,112 patients with moderate to severe and severe mitral regurgitation (MR) underwent transcatheter edge-to-edge mitral valve repair. After excluding patients who had aborted procedures or mixed etiology or were lost to follow-up, 1,044 patients were included in the analysis. Patients with functional MR were classified as having atrial functional mitral regurgitation (a-FMR) or ventricular functional mitral regurgitation (v-FMR) according to the predominant atrial or ventricular remodeling. DMR = degenerative mitral regurgitation.

MR and tricuspid regurgitation (TR) was graded according to a multiparametric approach including calculating the effective regurgitant orifice area (EROA), as recommended.[12-16] RV pressure was calculated from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation. Right atrial pressure was determined by the inspiratory collapse and diameter of the inferior vena cava. Systolic pulmonary arterial pressure was estimated as the sum of RV pressure and right atrial pressure, and tricuspid annular plane systolic excursion was measured.[11,17]

**OUTCOMES AND DATA COLLECTION.** The primary outcome of the present study was the composite endpoint of all-cause mortality and heart failure hospitalization at 2 years. Secondary outcomes included all-cause mortality at 2 years and residual MR on discharge transthoracic echocardiography. Follow-up was obtained by clinical visits and/or through telephone contacts at prespecified time points (1, 6, and 12 months and yearly thereafter). Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information.

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD and were compared using analysis of variance or the Kruskal-Wallis test as appropriate. Categorical variables are presented as percentages and were compared using the chi-square or Fisher exact test. Cumulative event rates were calculated using Kaplan-Meier survival analysis, and the log-rank test was used for comparison across

**TABLE 1 Baseline Characteristics**

| | Overall (N = 1,044) | a-FMR (n = 116) | v-FMR (n = 505) | DMR (n = 423) | *P* Value |
|---|---|---|---|---|---|
| Age, y | 76.3 ± 12.3 | 78.8 ± 9.7 | 72.1 ± 12.8 | 80.6 ± 10.5 | <0.001 |
| Female | 428 (41.0) | 65 (56.0) | 192 (38.0) | 171 (40.4) | 0.002 |
| Body surface area, $m^2$ | 1.82 ± 0.26 | 1.85 ± 0.27 | 1.84 ± 0.25 | 1.78 ± 0.28 | 0.002 |
| NYHA functional class III or IV | 960 (92.0) | 110 (94.8) | 480 (95.0) | 370 (87.5) | <0.001 |
| STS score, % | 8.6 ± 7.8 | 8.5 ± 6.9 | 9.3 ± 8.7 | 7.7 ± 6.8 | 0.006 |
| Atrial fibrillation | 570 (54.6) | 84 (72.4) | 265 (52.5) | 221 (52.2) | <0.001 |
| Hypertension | 859 (82.3) | 97 (83.6) | 426 (84.4) | 336 (79.4) | 0.14 |
| Diabetes mellitus | 267 (25.6) | 35 (30.2) | 169 (33.5) | 63 (14.9) | <0.001 |
| Hemoglobin, g/dL | 11.9 ± 2.0 | 11.8 ± 1.9 | 11.6 ± 2.1 | 12.3 ± 2.0 | <0.001 |
| BNP,[a] ng/L | 505.0 (246.0-1,192.3) | 357.0 (191.5-550.8) | 1,010.5 (425.3-2,119.8) | 313.0 (166.0-618.0) | <0.001 |
| Estimated GFR, mL/min/1.73 $m^2$ | 58.7 ± 28.4 | 59.4 ± 30.6 | 52.8 ± 28.8 | 65.4 ± 25.8 | <0.001 |
| Dialysis | 79 (7.6) | 6 (5.2) | 62 (12.3) | 11 (2.6) | <0.001 |
| Chronic lung disease | 76 (7.3) | 9 (7.8) | 35 (6.9) | 32 (7.6) | 0.90 |
| Peripheral vascular disease | 88 (8.4) | 11 (9.5) | 47 (9.3) | 30 (7.1) | 0.44 |
| Coronary artery disease | 451 (43.2) | 49 (42.2) | 278 (55.0) | 124 (29.3) | <0.001 |
| Prior percutaneous coronary intervention | 297 (28.4) | 24 (20.7) | 198 (39.2) | 75 (17.7) | <0.001 |
| Prior coronary artery bypass surgery | 242 (23.2) | 34 (29.3) | 145 (28.7) | 63 (14.9) | <0.001 |
| Prior myocardial infarction | 194 (18.6) | 18 (15.5) | 150 (29.7) | 26 (6.1) | <0.001 |
| Prior stroke | 71 (6.8) | 15 (12.9) | 39 (7.7) | 17 (4.0) | 0.002 |
| Prior pacemaker, ICD, or CRT | 355 (34.0) | 39 (33.6) | 256 (50.7) | 60 (14.2) | <0.001 |
| Prior ICD | 210 (20.1) | 5 (4.3) | 194 (38.4) | 11 (2.6) | <0.001 |

Values are mean ± SD or n (%). [a]BNP data were available in 782 patients (74.9%).

a-FMR = atrial functional mitral regurgitation; BNP = brain natriuretic peptide; CRT = cardiac resynchronization therapy; DMR = degenerative mitral regurgitation; GFR = glomerular filtration rate; ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; v-FMR = ventricular functional mitral regurgitation.

groups. The estimated HR with 95% CI was provided by Cox proportional hazards regression. Multivariable Cox regression analyses were performed with adjustment for the following variables: age, sex, dialysis, chronic lung disease, atrial fibrillation, pulmonary artery systolic pressure per increase of 10 mm Hg, severe TR, and residual MR moderate or greater. The proportional hazards assumption was confirmed by examination of log (−log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. All statistical analyses were performed using SPSS version 24.0 (IBM) and Stata version 14.2 (StataCorp). A 2-sided *P* value <0.05 was selected as the threshold of statistical significance.

## RESULTS

**PATIENT CHARACTERISTICS.** A total of 1,112 patients with moderate to severe or severe MR underwent TEER with the MitraClip at Cedars-Sinai Medical Center between March 2007 and April 2020. After 68 patients were excluded (18 patients with aborted procedures, 20 lost to follow-up, 30 with mixed MR etiology), 1,044 patients (116 with a-FMR, 505 with v-FMR, and 423 with DMR) were included in this study. The mean age of the study population was 76.3 years, 428 patients (41.0%) were women, and the Society of Thoracic Surgeons score was 8.6% (Table 1). Patients with v-FMR were younger (72.1 ± 12.8 years vs 78.8 ± 9.7 years vs 80.6 ± 10.5 years; $P < 0.001$) but had higher Society of Thoracic Surgeons scores (9.3% ± 8.7% vs 8.5% ± 6.9% vs 7.7% ± 6.8%; $P < 0.001$) compared with patients with a-FMR and DMR, respectively. Patients in the a-FMR group were more often women (56.0% vs 38.0% vs 40.4%; $P = 0.002$) and more often had chronic atrial fibrillation (72.4% vs 52.5% vs 52.2%; $P < 0.001$) compared with those with v-FMR and DMR, respectively. New York Heart Association functional class III and IV symptoms, diabetes mellitus, and coronary artery disease were more frequent in patients with a-FMR and v-FMR compared with those with DMR (Table 1).

**TABLE 2 Echocardiographic Characteristics**

| | Overall (N = 1,044) | a-FMR (n = 116) | v-FMR (n = 505) | DMR (n = 423) | *P* Value |
|---|---|---|---|---|---|
| LV end-diastolic diameter, mm | 54.7 ± 10.6 | 48.8 ± 7.5 | 60.1 ± 10.5 | 49.9 ± 8.0 | <0.001 |
| LV end-systolic diameter, mm | 41.3 ± 13.5 | 32.0 ± 6.7 | 50.8 ± 12.1 | 32.6 ± 7.7 | <0.001 |
| LV end-diastolic volume index, mL/m$^2$ | 68.6 ± 37.0 | 38.8 ± 11.9 | 87.7 ± 39.6 | 53.9 ± 24.0 | <0.001 |
| LV end-systolic volume index, mL/m$^2$ | 39.1 ± 32.7 | 14.8 ± 5.5 | 60.0 ± 35.1 | 20.8 ± 12.0 | <0.001 |
| LVEF, % | 47.4 ± 19.2 | 61.9 ± 6.3 | 31.9 ± 13.5 | 62.0 ± 11.1 | <0.001 |
| LA volume index, mL/m$^2$ | 61.2 ± 29.5 | 69.7 ± 39.6 | 60.1 ± 28.7 | 60.1 ± 26.6 | 0.004 |
| MR grade | | | | | |
| Moderate to severe | 291 (27.9) | 50 (43.1) | 157 (31.1) | 84 (19.9) | <0.001 |
| Severe | 753 (72.1) | 66 (56.9) | 34 8 (68.9) | 339 (80.1) | |
| EROA, cm$^2$ | 0.37 ± 0.24 | 0.30 ± 0.16 | 0.35 ± 0.20 | 0.42 ± 0.31 | <0.001 |
| Pulmonary artery systolic pressure, mm Hg | 47.0 ± 16.9 | 48.9 ± 16.7 | 47.1 ± 15.7 | 46.4 ± 18.4 | 0.36 |
| E velocity, cm/s | 119.5 ± 31.5 | 125.0 ± 26.9 | 112.5 ± 30.0 | 126.6 ± 32.5 | <0.001 |
| E/e′ ratio | 15.2 ± 7.0 | 14.0 ± 6.0 | 15.8 ± 7.6 | 14.8 ± 6.4 | 0.049 |
| RV end-diastolic diameter,[a] mm | 41.0 ± 8.0 | 40.2 ± 9.2 | 42.3 ± 8.3 | 39.6 ± 7.2 | <0.001 |
| Right atrial area,[a] mm$^2$ | 23.4 ± 8.4 | 25.1 ± 9.5 | 23.7 ± 8.4 | 22.6 ± 7.9 | 0.030 |
| Tricuspid annular plane systolic excursion, mm | 17.1 ± 4.9 | 15.9 ± 3.4 | 16.1 ± 4.5 | 18.9 ± 5.4 | <0.001 |
| TR grade | | | | | |
| Moderate or severe | 486 (46.6) | 63 (54.3) | 251 (49.7) | 172 (40.7) | 0.005 |
| Severe | 156 (14.9) | 25 (21.6) | 82 (16.2) | 49 (11.6) | 0.015 |

Values are mean ± SD or n (%). [a]RV end-diastolic diameter and right atrial area data were available in 811 (77.7%) and 826 (79.1%) patients, respectively.

EROA = effective regurgitant orifice area; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; RV = right ventricular; TR = tricuspid regurgitation; other abbreviations are as in Table 1.

**ECHOCARDIOGRAPHIC CHARACTERISTICS.** Baseline echocardiographic characteristics are summarized in Table 2. Patients with v-FMR had larger LV dimensions and volumes with lower LVEFs, whereas patients with a-FMR had significantly smaller LV dimensions and volumes and larger LA volume index. Patients with DMR more frequently had severe MR with larger EROAs compared with patients with FMR, whereas pulmonary artery pressure was similar among the 3 groups. RV end-diastolic diameter was larger in patients with v-FMR, whereas right atrial area was larger in patients with a-FMR. Although tricuspid annular plane systolic excursion was lower in patients with a-FMR and v-FMR, patients with a-FMR had more severe TR compared with those with v-FMR and DMR (moderate or severe TR, 54.3% vs 49.7% vs 40.7% [$P$ = 0.005]; severe TR, 21.6% vs 16.2% vs 11.6% [$P$ = 0.015]).

**PROCEDURAL AND ECHOCARDIOGRAPHIC OUTCOMES.** Procedural and echocardiographic outcomes are shown in Table 3. There were no significant differences among the 3 groups in conversion to open mitral valve surgery, fluoroscopy time, and procedure time. Fewer clips were used in the a-FMR group (1.5 ± 0.6 vs 1.6 ± 0.7 vs 1.8 ± 0.7; $P$ < 0.001). The incidence of residual MR more than moderate was not significantly different among the 3 groups (discharge, 5.2% vs 3.2% vs 2.6% [$P$ = 0.37]; 1 month, 3.0% vs 3.3% vs 4.0% [$P$ = 0.85]) (Figure 2). Echocardiographic parameters before and after TEER are shown in Figure 3. At 1 month, LV end-diastolic diameter, LVEF, and LA volume index were reduced in all subgroups. There were no significant differences among patients with a-FMR, v-FMR, and DMR in changes of LA volume index (−34.4 ± 29.3 mL/m$^2$ vs −27.1 ± 18.2 mL/m$^2$ vs −29.7 ± 22.3 mL/m$^2$; $P$ = 0.11) (Supplemental Figures 1 and 2).

**CLINICAL OUTCOMES.** Over a median follow-up duration of 540 days (IQR: 280-1,050 days), 321 patients died, and 401 patients reached the primary composite endpoint (all-cause mortality and heart failure hospitalization). Compared with patients with DMR, those with v-FMR and a-FMR had significantly higher 2-year event rates of the primary outcome (42.3% vs 31.5% vs 21.6%; overall log-rank $P$ < 0.001) and all-cause mortality (31.1% vs 26.8% vs 17.7%; overall log-rank $P$ < 0.001) (Central Illustration, Figure 4). The adjusted risk for primary outcome among patients with a-FMR was significantly higher than among patients with DMR (HR: 1.52; 95% CI: 1.08-2.13; $P$ = 0.017) and lower than among patients with v-FMR (HR: 0.69; 95% CI: 0.50-0.95; $P$ = 0.022).

**TABLE 3 Procedural and Echocardiographic Outcomes**

| | Overall (N = 1,044) | a-FMR (n = 116) | v-FMR (n = 505) | DMR (n = 423) | *P* Value |
|---|---|---|---|---|---|
| Procedural data | | | | | |
| Conversion to open mitral valve surgery | 1 (0.1) | 1 (0.9) | 0 (0) | 0 (0) | 0.11 |
| Fluoroscopy time, min | 23.1 ± 13.4 | 23.6 ± 16.2 | 23.3 ± 13.3 | 22.7 ± 12.6 | 0.74 |
| Procedure time, min | 120.5 ± 46.7 | 122.9 ± 50.7 | 118.0 ± 44.0 | 122.7 ± 48.5 | 0.34 |
| Number of clips | 1.7 ± 0.7 | 1.5 ± 0.6 | 1.8 ± 0.7 | 1.6 ± 0.7 | <0.001 |
| ≥2 | 591 (56.6) | 50 (43.1) | 310 (61.4) | 231 (54.6) | 0.001 |
| ≥3 | 111 (10.6) | 4 (3.4) | 66 (13.1) | 41 (9.7) | 0.007 |
| Echocardiographic findings at discharge | | | | | |
| LV end-diastolic diameter, mm | 52.8 ± 11.1 | 46.4 ± 7.1 | 59.1 ± 10.4 | 47.1 ± 8.4 | <0.001 |
| LV end-systolic diameter, mm | 41.4 ± 13.4 | 32.1 ± 6.7 | 50.5 ± 12.2 | 33.2 ± 8.1 | <0.001 |
| LVEF, % | 43.5 ± 18.3 | 57.3 ± 10.0 | 29.8 ± 13.6 | 55.8 ± 12.3 | <0.001 |
| LA volume index, mL/m$^2$ | 58.4 ± 30.9 | 60.6 ± 30.5 | 59.8 ± 32.9 | 55.9 ± 28.4 | 0.37 |
| Residual MR grade ≥3 | 33 (3.2) | 6 (5.2) | 16 (3.2) | 11 (2.6) | 0.37 |
| Echocardiographic findings at 1 mo | | | | | |
| LV end-diastolic diameter, mm | 52.6 ± 10.5 | 46.8 ± 7.5 | 58.7 ± 10.3 | 47.9 ± 7.8 | <0.001 |
| LV end-systolic diameter, mm | 40.7 ± 13.0 | 32.6 ± 7.4 | 50.3 ± 11.9 | 33.2 ± 7.9 | <0.001 |
| LVEF, % | 43.9 ± 18.3 | 55.7 ± 11.1 | 29.6 ± 14.2 | 55.4 ± 12.2 | <0.001 |
| LA volume index, mL/m$^2$ | 33.2 ± 17.5 | 40.1 ± 26.4 | 32.8 ± 13.4 | 32.1 ± 18.5 | 0.022 |
| Residual MR grade ≥3 | 25/701 (3.6) | 2/66 (3.0) | 11/337 (3.3) | 12/298 (4.0) | 0.85 |

Values are n (%), mean ± SD, or n/N (%).
Abbreviations as in Tables 1 and 2.

The adjusted risk for all-cause mortality among patients with a-FMR was significantly higher than among patients with DMR (HR: 1.49; 95% CI: 1.03-2.17; $P = 0.036$) but similar to patients with v-FMR (HR: 0.75; 95% CI: 0.53-1.08; $P = 0.12$).

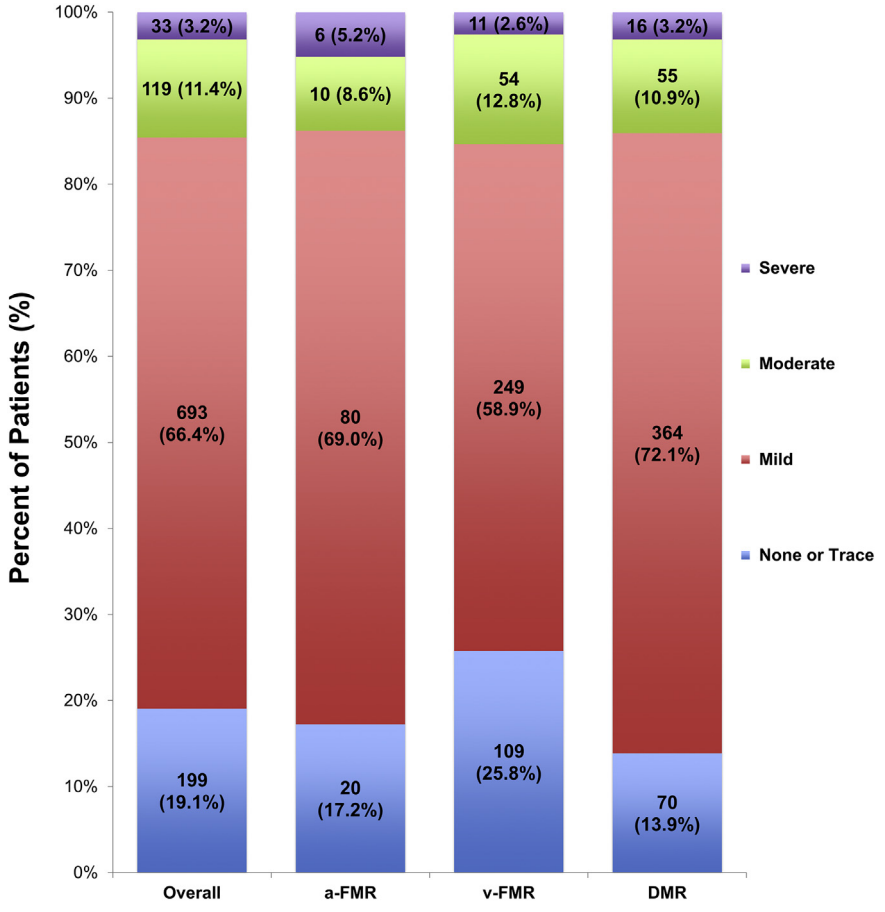
**IMPACT OF TR ON OUTCOMES.** Time-to-event curves of primary outcome and all-cause mortality according to severe TR for patients with a-FMR, v-FMR, and DMR are shown in **Figure 5** and in Supplemental Figure 1. Among all subgroups, severe TR was associated with significantly higher rates of primary outcome (a-FMR, 42.4% vs 28.5% [log-rank $P = 0.045$]; v-FMR, 57.1% vs 39.4% [log-rank $P = 0.004$]; DMR, 43.2% vs 18.7% [log-rank $P < 0.001$]) and all-cause mortality (a-FMR, 42.8% vs 22.2% [log-rank $P = 0.011$]; v-FMR, 42.9% vs 29.0% [log-rank $P = 0.019$]; DMR, 31.9% vs 15.8% [log-rank $P = 0.002$]). After multivariable adjustment, the impact of severe TR on primary outcome was consistently observed in the a-FMR (HR: 2.10; 95% CI: 1.07-4.12; $P = 0.032$), v-FMR (HR: 1.51; 95% CI: 1.09-2.09; $P = 0.013$), and DMR (HR: 1.98; 95% CI: 1.20-3.29; $P = 0.008$) subgroups (Supplemental Table).

## DISCUSSION

This is the first large study evaluating the clinical and echocardiographic characteristics and procedural and clinical outcomes following TEER according to MR etiology and cardiac remodeling. The major findings of this study are as follows: 1) the cohort of patients who underwent TEER consisted of predominantly those with classical v-FMR (48%), followed by DMR (41%), while a certain number of patients (11%) who had normal mitral valve structure and maintained normal LVEFs and LV chamber sizes were classified as having a-FMR; 2) these 3 subsets showed distinct different baseline clinical and echocardiographic characteristics: in particular, the a-FMR group had a higher rate of atrial fibrillation with dilated left and right atria and more severe TR despite normal LVEFs and LV sizes, whereas patients with v-FMR showed both LV and RV remodeling; and 3) the 2-year event rates of the primary outcome (all-cause mortality or heart failure hospitalization) and all-cause mortality were significantly different across the 3 groups, with the highest event rate in patients with v-FMR, followed by those with a-FMR.

The majority of patients in the present cohort had v-FMR and DMR. Patients with DMR showed preserved LVEFs but mild LV and LA enlargement, with larger EROAs and higher rates of severe MR. Because the indication for TEER for DMR includes anatomical suitability for TEER but also prohibitive or high risk for surgical mitral valve repair or replacement,[9] the DMR group in the current cohort was older, with more comorbidities compared with patients with DMR referred for surgery.[18,19] Importantly, clinical

**FIGURE 2** **Residual Mitral Regurgitation According to Etiology and LV Remodeling**

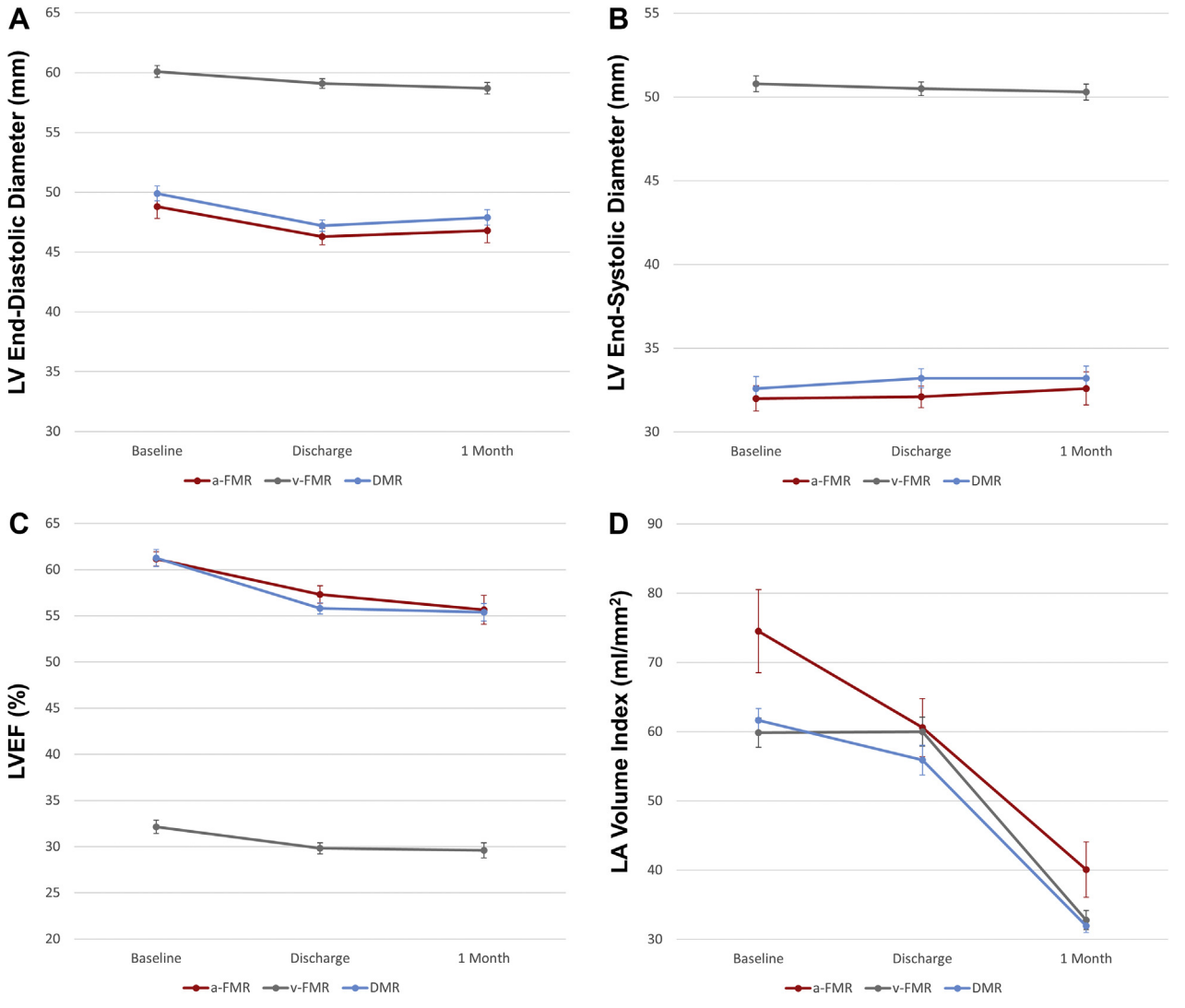



Incidence of residual MR in the entire cohort, as well as patients with a-FMR, v-FMR, and DMR. Abbreviations as in Figure 1.

outcomes after TEER in the present DMR group were comparable with those among patients in the EVEREST (Endovascular Valve Edge-to-Edge Repair) II trial (all-cause mortality at 1 year 18.5% vs 25.1%).[20] In addition, patients with v-FMR, defined as reduced LVEF with LV dilatation, had comparable 2-year rates of the primary outcome and all-cause mortality as those in the COAPT trial (42.3% vs 45.7% and 31.1% vs 29.1%, respectively).[7] Therefore, these 2 subsets (DMR and v-FMR) represent the traditional cohorts of patients with DMR and FMR who underwent TEER. It is noteworthy that our cohort included the distinct subset of patients with normal mitral valve structure and preserved LVEF without LV dilatation but LA enlargement (a-FMR), who were not categorized in either group (DMR and classical v-FMR). The prevalence of patients with a-FMR in this cohort (11%) was lower than that in the study from Olmsted County (27%),[4] which included predominantly patients with moderate MR regardless of mitral valve intervention.

The present study highlights that clinical outcomes after TEER differed significantly according to the etiology and mechanism of MR. Specifically, patients with v-FMR who showed LV and RV remodeling had the worst prognosis, whereas patients with a-FMR who had dilated left and right atria and more severe TR had surprisingly poor clinical outcomes after TEER. The event rate of primary outcomes in patients with a-FMR was significantly higher compared with that among patients with DMR despite similar LVEFs and more preserved LV size. Previous studies that evaluated the natural history of patients with a-FMR showed that their prognosis was as poor as that of patients with v-FMR.[4]

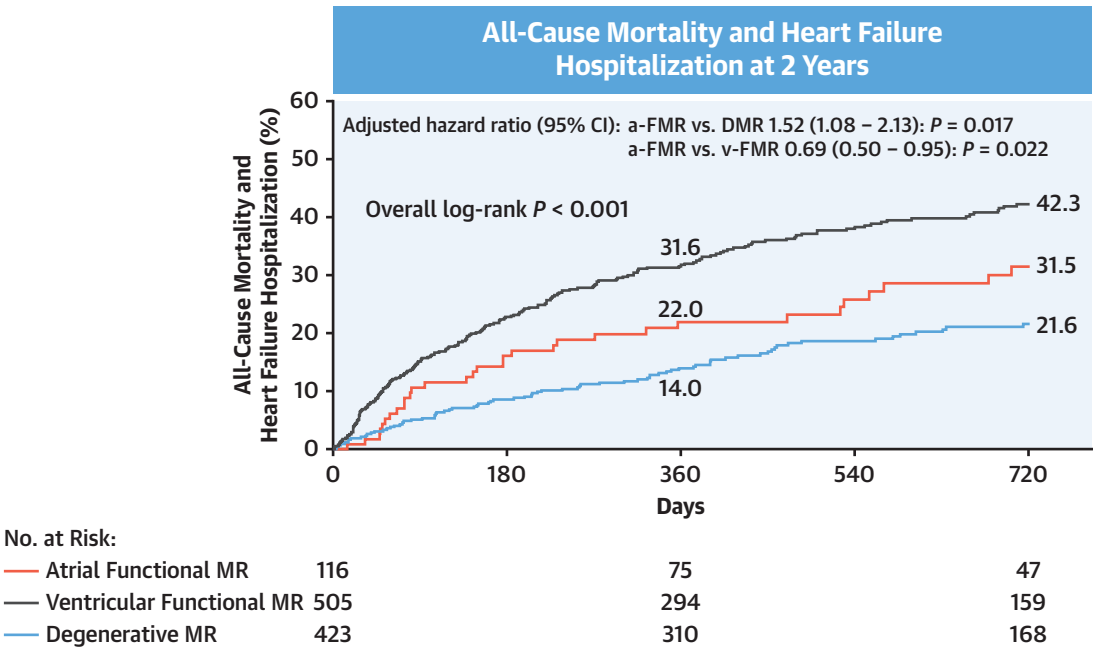
**FIGURE 3** **Echocardiographic Parameters Before and After Transcatheter Edge-to-Edge Repair**




Echocardiographic parameters at baseline, discharge and 1 month after transcatheter edge-to-edge repair are shown: **(A)** left ventricular (LV) end-diastolic diameter, **(B)** LV end-systolic diameter, **(C)** LV ejection fraction (LVEF), and **(D)** left atrial (LA) volume index. Abbreviations as in Figure 1.

Abnormal mitral valve structure is the primary cause of MR in patients with DMR, and thus a good response to MR reduction with TEER can be anticipated in this population. In contrast, among patients with v-FMR and those with a-FMR, MR is related to LV or LA remodeling, leading to mitral annular dilatation. Furthermore, higher rates of TR in patients with a-FMR and those with v-FMR, compared with patients with DMR, suggest advanced cardiac remodeling resulting in a limited response to TEER. In fact, severe TR was independently associated with clinical outcomes overall and in each subgroup after multivariable adjustment, with significant factors such as age, chronic lung disease, and residual MR. Previous randomized controlled clinical trials demonstrated the benefit of medical therapy, cardiac resynchronization therapy, and internal cardiac defibrillators in patients with reduced LVEFs.[21-27] As clearly shown in the COAPT trial, TEER was associated with a reduction in all-cause mortality or heart failure hospitalization in patients with v-FMR on top of these therapies. Indeed, TEER mitigated LV

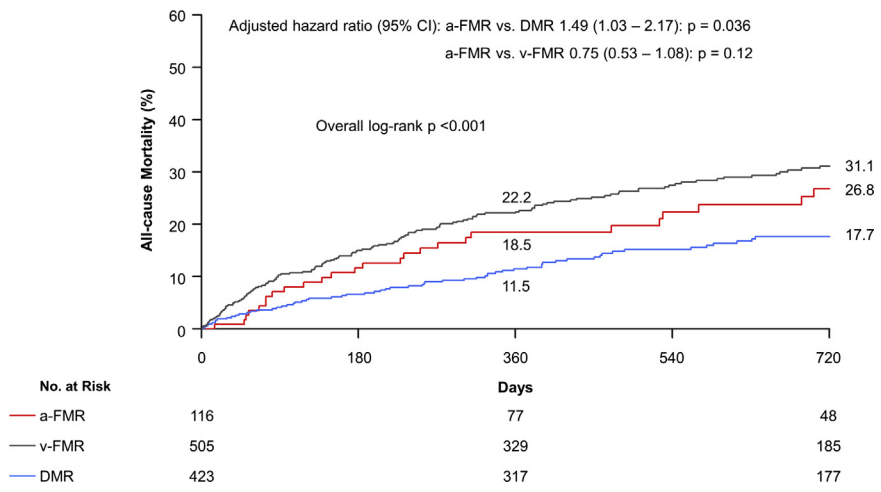
**CENTRAL ILLUSTRATION** **Time-to-Event Curves According to Mitral Regurgitation Etiology and Cardiac Remodeling**




**Yoon S-H, et al. J Am Coll Cardiol Intv. 2022;15(17):1711–1722.**

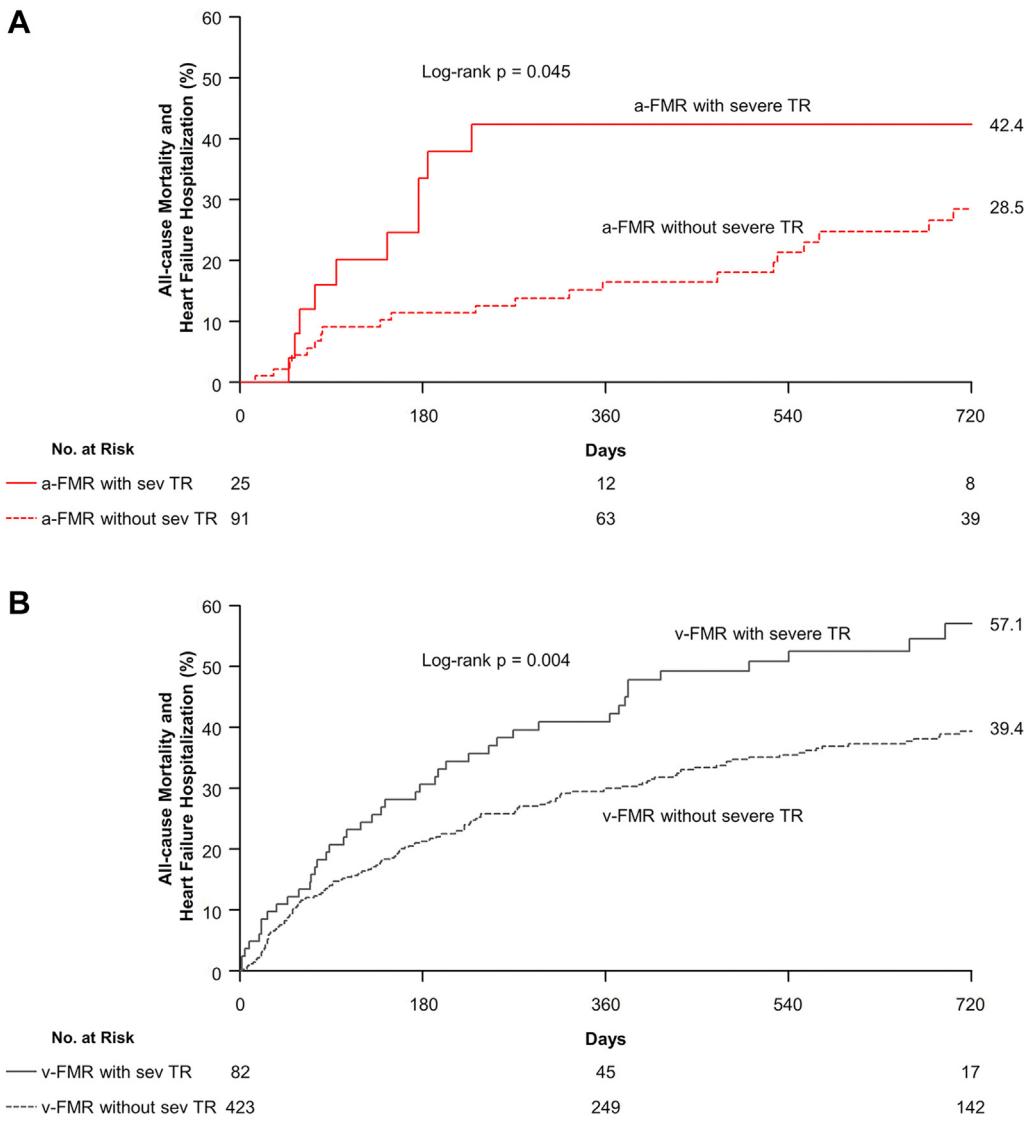
Time-to-event curves for the primary outcome (composite endpoint of all-cause mortality and heart failure hospitalization) between patients with atrial functional mitral regurgitation (FMR), ventricular FMR, and degenerative mitral regurgitation (DMR). Event rates were calculated using Kaplan-Meier analysis and were compared using the log-rank test.

**FIGURE 4** **All-Cause Mortality According to Mitral Regurgitation Etiology and Cardiac Remodeling**




Time-to-event curves for all-cause mortality among patients with a-FMR, v-FMR, and DMR. Event rates were calculated using Kaplan-Meier analysis and were compared using the log-rank test. Abbreviations as in Figure 1.

**FIGURE 5 Impact of Tricuspid Regurgitation on Primary Outcomes According to Mitral Regurgitation Etiology and Cardiac Remodeling**

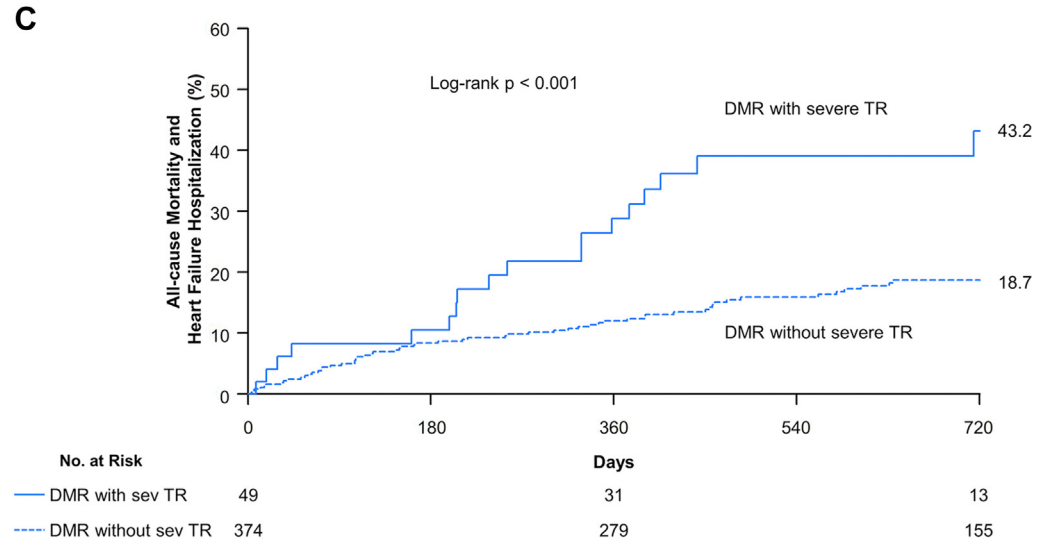



Time-to-event curves for the primary outcome (composite endpoint of all-cause mortality and heart failure hospitalization) in patients with or without severe tricuspid regurgitation (TR) with **(A)** a-FMR, **(B)** v-FMR, and **(C)** DMR. Event rates were calculated using Kaplan-Meier analysis and were compared using the log-rank test. Abbreviations as in Figure 1.

*Continued on the next page*

remodeling in patients with v-FMR compared with guideline-directed medical therapy alone.[8] The present study also showed that reduction of LA volume was observed after improvement of MR with TEER in patients with a-FMR, suggesting the hemodynamic benefit of TEER regardless of MR etiology and LV remodeling. As previous studies showed reductions in LA volume, MR severity, and LA function after successful cardioversion or ablation for atrial fibrillation,[28-31] early intervention for atrial fibrillation has the potential to improve the clinical outcomes of patients with a-FMR. Nonetheless, these studies are limited by the nature of an observational study and the sample size. Future studies are awaited to evaluate prognosis and treatment effect of transcatheter treatment in patients with a-FMR.

**FIGURE 5 Continued**




**STUDY LIMITATIONS.** This was a single-center study, and therefore, the findings need to be validated in future studies. Moreover, this was an observational study without a core laboratory analysis, which may limit generalized conclusions.

## CONCLUSIONS

TEER provided excellent procedural outcomes for patients with a-FMR, v-FMR, and DMR. However, patients with a-FMR and v-FMR had worse clinical outcomes compared with those with DMR.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Kar has received grants from Abbott, Boston Scientific, Edwards Lifesciences, and 4Tech; has been a consultant for Boston Scientific, Edwards Lifesciences, Medtronic, and 4Tech; and holds stock options in 4Tech. Dr Chakravarty has served as a speaker and consultant for Edwards Lifesciences, Boston Scientific, Medtronic, and Abbott. Dr Makkar has received grant support from Edwards Lifesciences; has served as a consultant for Abbott Vascular, Cordis, and Medtronic; and owns equity in Entourage Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**WHAT IS KNOWN?** Although the prevalence and prognosis of traditional v-FMR are well recognized, a-FMR is not uncommon and is associated with poor prognosis despite preserved LV systolic function.

**WHAT IS NEW?** TEER provided excellent procedural outcomes among patients with DMR, a-FMR, and v-FMR. However, both patients with a-FMR and those with v-FMR had worse 2-year outcomes compared with patients with DMR.

**WHAT IS NEXT?** Future studies are needed to evaluate prognosis and treatment effect of transcatheter treatment in patients with a-FMR.

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**KEY WORDS** **atrial functional mitral regurgitation, mitral regurgitation, percutaneous mitral valve repair, prognosis, transcatheter edge-to-edge repair**

**APPENDIX** **For supplemental figures and a supplemental table, please see the online version of this paper.**