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STRUCTURAL

Impact of Mitral Regurgitation Etiology on Mitral Surgery After Transcatheter Edge-to-Edge Repair

From the CUTTING-EDGE Registry

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ABSTRACT

BACKGROUND Although >150,000 mitral TEER procedures have been performed worldwide, the impact of MR etiology on MV surgery after TEER remains unknown.

OBJECTIVES The authors sought to compare outcomes of mitral valve (MV) surgery after failed transcatheter edge-to-edge repair (TEER) stratified by mitral regurgitation (MR) etiology.

METHODS Data from the CUTTING-EDGE registry were retrospectively analyzed. Surgeries were stratified by MR etiology: primary (PMR) and secondary (SMR). MVARC (Mitral Valve Academic Research Consortium) outcomes at 30 days and 1 year were evaluated. Median follow-up was 9.1 months (IQR: 1.1-25.8 months) after surgery.

RESULTS From July 2009 to July 2020, 330 patients underwent MV surgery after TEER, of which 47% had PMR and 53.0% had SMR. Mean age was 73.8 ± 10.1 years, median STS risk at initial TEER was 4.0% (IQR: 2.2%-7.3%). Compared with PMR, SMR had a higher EuroSCORE, more comorbidities, lower LVEF pre-TEER and presurgery (all $P < 0.05$). SMR patients had more aborted TEER (25.7% vs 16.3%; $P = 0.043$), more surgery for mitral stenosis after TEER (19.4% vs 9.0%; $P = 0.008$), and fewer MV repairs (4.0% vs 11.0%; $P = 0.019$). Thirty-day mortality was numerically higher in SMR (20.4% vs 12.7%; $P = 0.072$), with an observed-to-expected ratio of 3.6 (95% CI: 1.9-5.3) overall, 2.6 (95% CI: 1.2-4.0) in PMR, and 4.6 (95% CI: 2.6-6.6) in SMR. SMR had significantly higher 1-year mortality (38.3% vs 23.2%; $P = 0.019$). On Kaplan-Meier analysis, the actuarial estimates of cumulative survival were significantly lower in SMR at 1 and 3 years.

CONCLUSIONS The risk of MV surgery after TEER is nontrivial, with higher mortality after surgery, especially in SMR patients. These findings provide valuable data for further research to improve these outcomes.
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Mitral transcatheter edge-to-edge-repair (TEER) has emerged as an important treatment option for selected patients with primary and secondary severe mitral regurgitation (MR), with more than 150,000 MitraClip (Abbott Structural Heart) procedures performed worldwide.[1-3] Despite the excellent safety profile and improving efficacy, TEER failure may require mitral valve (MV) surgery, primarily due to recurrent or residual MR, or mitral stenosis. In our first report of the multicenter international CUTTING-EDGE registry, the primary indication for MV surgery post-TEER was recurrent MR.[4] Compared with MV repair/replacement of the native MV, MV surgery after failed TEER can be more challenging depending on MR etiology, mechanism of TEER failure, and degree of LV dysfunction. A better understanding of the mechanism of MR and subsequent TEER failure is critical to ensure optimal outcomes after MV intervention. However, the impact of MR etiology (primary vs secondary) on MV surgery after TEER has thus far not been evaluated. The present study sought to compare clinical and procedural outcomes of MV surgery after failed TEER stratified by MR etiology in the international CUTTING-EDGE registry.

METHODS

DATA SOURCE. The CUTTING-EDGE registry is a multicenter, international registry of patients who underwent MV surgery after TEER.[4] Patients who underwent MV surgery between July 2009 and July 2020 after TEER were included across 34 centers worldwide. Anonymized data were obtained from each institution's electronic health records and transmitted to a central site for data management and statistical analyses. Because all institutions contributed cases after obtaining local institutional review board approvals, the requirement to obtain patient consent was waived. Each institution adjudicated the 30-day and longer-term follow-ups of all subjects separately.

PATIENT SELECTION. We included all patients who underwent MV surgery after the index TEER procedure due to, but not limited to, the following conditions: residual or recurrent significant MR, significant mitral stenosis, leaflet injury, endocarditis, device detachment, and inability to place a device or device embolization. The scenarios of TEER failure leading to MV surgery were classified as follows: 1) aborted TEER (the TEER procedure was attempted but was unsuccessful, leading to MV surgery in the same or different hospital admission); 2) acute MV surgery (MV surgery after TEER was performed in the same index admission); and 3) delayed MV surgery (MV surgery after TEER was performed in a separate admission).

OUTCOMES OF INTEREST AND DEFINITIONS. Patients were stratified by MR etiology: primary disease (PMR) and secondary/mixed disease (SMR). MR related to degenerative/structural MV pathology was defined as PMR. SMR was defined as MR caused by global or regional left ventricular dysfunction and/or severe left atrial arrhythmias/dilation, with the MV structures normal or exhibiting only secondary late fibrosis and/or annular dilatation.

The primary outcomes included in-hospital, 30-day, and 1-year mortality rates after MV surgery.

ABBREVIATIONS AND ACRONYMS

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

MV = mitral valve

O/E = observed-to-expected

PMR = primary mitral regurgitation

SMR = secondary mitral regurgitation

TEER = transcatheter edge-to-edge repair

TR = tricuspid regurgitation

TV = tricuspid valve

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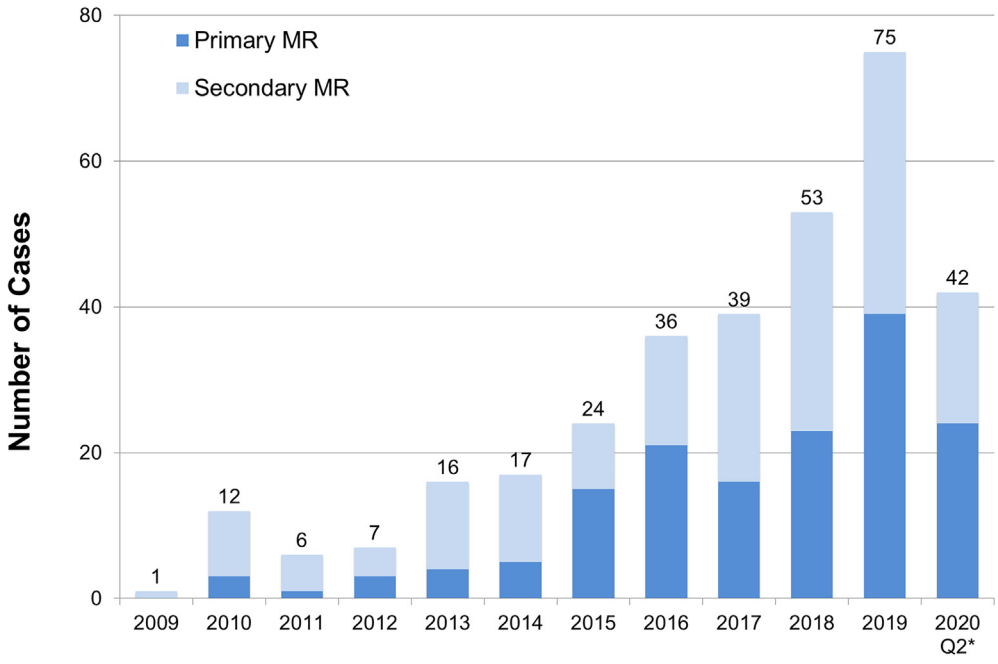
FIGURE 1 Temporal Trends in Annual MV Surgery After TEER Stratified by MR Etiology



Trends in the annual number of mitral valve (MV) surgery between 2009 and 2020 stratified by mitral regurgitation (MR) etiology among all patients in the CUTTING-EDGE registry. *Study period ended in second quarter (Q2) of 2020. TEER = transcatheter edge-to-edge repair.

The secondary outcomes were median interval from TEER to MV surgery, major in-hospital complications (new-onset atrial fibrillation, pacemaker implantation, stroke, vascular complication, major bleeding, or life-threatening bleeding), intensive care unit stay, hospital length of stay, as well as 30-day stroke and readmission rates. All clinical endpoints were reported according to MVARC (Mitral Valve Academic Research Consortium).[5,6] MVARC outcomes at 30 days and 1 year were compared between PMR and SMR.

The respective multidisciplinary heart teams determined the surgical indication and mechanism of TEER failure based on preoperative imaging and clinical presentation. The decision to perform MV repair vs replacement was at the discretion of the primary surgeon, keeping in mind the clinical condition of the patient, the mechanism of TEER failure, the surgeon's experience and preference, and the overall technical complexity of the procedure itself to achieve optimal outcomes.

The surgical risk was calculated for each patient using the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and the European System for Cardiac Operative Risk Evaluation (EuroSCORE II). Emergent MV surgery was defined as surgery performed during the same hospital admission within 6 hours of diagnosis; otherwise, the intervention was classified as urgent. The median interval from TEER to surgery was counted in months from the index TEER procedure date to the MV surgery date. Survival time was calculated in months from the date of MV surgery to the mortality date or date of the last follow-up if recorded as alive.

STATISTICAL ANALYSES. Baseline demographic, clinical, procedural, and echocardiographic characteristics were collected for all patients before the mitral TEER procedure and subsequent MV surgery and compared between PMR and SMR groups. Depending on the distribution of data, continuous variables are reported as mean ± SD or median (IQR), whereas categorical variables are reported as frequencies and proportions. The observed-to-expected (O/E) ratio of 30-day mortality was calculated as the ratio of the observed 30-day mortality to the median STS-PROM score at the time of MV surgery. Differences between the 3 pre-TEER MR groups were detected using the Student 2-sample *t*-test or Mann-Whitney *U* test for continuous variables, and chi-square or Fisher exact test for categorical variables.

Kaplan-Meier survival analysis was used to assess actuarial all-cause mortality separately for the overall paired cohort and stratified by type of MR (PMR vs SMR). Univariate Cox regression analysis was used to identify variables associated with 1-year mortality within the PMR and SMR cohorts. Because model building was limited by the relative number of mortality events, forward, stepwise, multivariable Cox regression models were developed. All variables with $P < 0.10$ from univariate analysis in addition to clinically relevant variables chosen a priori and deemed to influence the outcomes of interest were considered for the multivariable Cox regression analysis, and only those with $P < 0.05$ were included in the final model. A 2-sided $P < 0.05$ was considered statistically significant, and all statistical analyses were performed using SPSS version 24.0 (IBM).

RESULTS

BASELINE CLINICAL, PROCEDURAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS AT INDEX TEER. A total of 330 patients underwent MV surgery following TEER in the CUTTING-EDGE registry during the study period, of which 155 patients (47%) had PMR and 175 patients (53%) SMR. Temporal trends in annual MV surgery cases stratified by MR etiology are illustrated in Figure 1. The mean age at the time of index TEER procedure was 73.8 ± 10.1 years, and 42.7% were female (Table 1). Median STS risk score was 4.0% (IQR: 2.2%-7.3%), 48.0% were deemed high or extreme surgical risk by the local heart team, 26.4% had previous cardiac surgery, and 84.2% were in NYHA functional class III or IV. Compared with PMR, SMR patients had a higher EuroSCORE II (5.1% vs 3.8%; $P = 0.004$), more comorbidities including coronary artery disease (58.3% vs 42.6%; $P = 0.006$), diabetes mellitus (38.9% vs 23.9%; $P = 0.004$), atrial fibrillation (64.0% vs 52.3%; $P = 0.034$), chronic kidney disease (62.3% vs 41.3%; $P < 0.001$), and prior pacemaker/defibrillator implantation (38.9% vs 22.6%; $P = 0.002$).

SMR patients had shorter posterior leaflet length at the location of device (11.5 ± 2.9 mm vs 13.5 ± 3.8 mm; $P = 0.01$), and received the original MitraClip more frequently (63.7% vs 44.4%; $P = 0.001$), with fewer MitraClip NT (9.4% vs 22.9%; $P = 0.001$) (Supplemental Table S1). Compared with PMR, SMR patients had lower left ventricular ejection fraction (LVEF) (41.1% ± 13.8% vs 55.6% ± 10.6%; $P < 0.001$ pre-TEER; 42.5% ± 14.1% vs 53.7% ± 10%; $P < 0.001$ post-TEER) and larger mitral valve area (5.2 ± 2.1 cm^2 vs 4.3 ± 1.8 cm^2; $P = 0.039$ pre-TEER) (Supplemental Table S2). No differences were observed between the 2 groups in the severity of mitral and tricuspid regurgitation (TR), right ventricle dysfunction, and right ventricular systolic pressure.

TABLE 1 Baseline Clinical Characteristics at Index Mitral TEER

	Overall (N = 330)	PMR (n = 155)	SMR (n = 175)	*P* Value
Age, y	73.8 ± 10.1	74.3 ± 11.1	73.2 ± 9.2	0.33
Female	141 (42.7)	73 (47.1)	68 (38.9)	0.15
EuroSCORE II, %	4.7 (2.7-7.5)	3.8 (2.5-6.0)	5.1 (2.9-8.9)	0.004
STS-PROM at initial clip, %	4.0 (2.2-7.3)	4.1 (2.4-7.6)	3.9 (2.2-6.5)	0.27
Initial surgical risk for TMVr				0.21
Low	49 (17.6)	28 (19.6)	21 (13.2)	0.27
Intermediate	96 (34.4)	39 (27.3)	57 (35.8)	0.044
High	106 (38.0)	55 (38.5)	51 (32.1)	0.54
Extreme	28 (10.0)	15 (10.5)	13 (8.2)	0.69
Frailty	132 (47)	64 (47.8)	68 (46.3)	0.81
Coronary artery disease	168 (50.9)	66 (42.6)	102 (58.3)	0.006
Diabetes mellitus	105 (31.8)	37 (23.9)	68 (38.9)	0.004
Transient ischemic attack/stroke	28 (8.5)	15 (9.7)	13 (7.4)	0.55
Stroke	34 (10.3)	17 (11)	17 (9.7)	0.72
Cerebrovascular disease	28 (8.5)	11 (7.1)	17 (9.7)	0.43
Peripheral vascular disease	52 (15.8)	22 (14.2)	30 (17.1)	0.55
Chronic obstructive pulmonary disease	114 (34.5)	50 (32.3)	64 (36.6)	0.42
Atrial fibrillation	193 (58.5)	81 (52.3)	112 (64)	0.034
Chronic kidney disease	173 (52.4)	64 (41.3)	109 (62.3)	<0.001
Dialysis	14 (4.2)	4 (2.6)	10 (5.7)	0.18
Cirrhosis	18 (5.5)	9 (5.8)	9 (5.1)	0.81
Pulmonary hypertension	186 (56.4)	91 (58.7)	95 (54.3)	0.44
Prior pacemaker/ICD	80 (24.2)	22 (14.2)	58 (33.1)	<0.001
Hostile chest or chest deformity	16 (4.8)	9 (5.8)	7 (4)	0.46
Porcelain aorta	2 (0.7)	0 (0)	2 (1.3)	0.50
Prior cardiac surgery	87 (26.4)	39 (25.2)	48 (27.4)	0.71
Prior PCI	103 (31.2)	35 (22.6)	68 (38.9)	0.002
NYHA functional class				0.065
I	1 (0.3)	0 (0)	1 (0.6)	1.00
II	46 (15.5)	29 (20.9)	17 (10.8)	0.024
III	175 (58.9)	74 (53.2)	101 (63.9)	0.076
IV	75 (25.3)	36 (25.9)	39 (24.7)	0.89

Values are mean ± SD, n (%), or median (IQR).

ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PMR = primary mitral regurgitation; SMR = secondary mitral regurgitation; STS-PROM = Society of Thoracic Surgeons-Predicted Risk of Mortality; TEER = transcatheter edge-to-edge repair; TMVr = transcatheter mitral valve repair.

PROCEDURAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS DURING MV SURGERY. Preoperative echocardiography revealed moderate-severe and severe MR in 32.5% and 57.3% of the cases, respectively, whereas concomitant ≥moderate TR was present in 55.7%, and 22.0% had at least moderate right ventricular dysfunction (Table 2). Compared with PMR, SMR patients had a significantly lower LVEF (43.6% ± 13.7% vs 52.6% ± 11.0%; $P < 0.001$) and a higher mean MV

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TABLE 2 Preoperative Echocardiographic Characteristics at MV Surgery

	Overall (N = 330)	PMR (n = 155)	SMR (n = 175)	*P* Value
Imaging type				
TTE	163 (52.4)			
TEE	148 (47.6)	72 (48.3)	76 (46.9)	0.82
MR severity				0.88
None	2 (0.6)	1 (0.7)	1 (0.6)	
Mild	7 (2.2)	2 (1.3)	5 (3)	
Moderate	23 (7.3)	10 (6.7)	13 (7.9)	
Moderate to severe	102 (32.5)	49 (32.9)	53 (32.1)	
Severe	180 (57.3)	87 (58.4)	93 (56.4)	
TR severity				0.31
None	36 (11.7)	14 (9.5)	22 (13.6)	
Mild	101 (32.7)	49 (33.3)	52 (32.1)	
Moderate	94 (30.4)	42 (28.6)	52 (32.1)	
Moderate to severe	50 (16.2)	30 (20.4)	20 (12.3)	
Severe	28 (9.1)	12 (8.2)	16 (9.9)	
RV dysfunction severity				0.51
None	136 (52.5)	64 (51.6)	72 (53.3)	
Mild	66 (25.5)	31 (25)	35 (25.9)	
Moderate	39 (15.1)	22 (17.7)	17 (12.6)	
Moderate to severe	11 (4.2)	3 (2.4)	8 (5.9)	
Severe	7 (2.7)	4 (3.2)	3 (2.2)	
LVEF, %	47.9 ± 13.2	52.6 ± 11	43.6 ± 13.7	<0.001
MV MG, mm^2	5.4 ± 3.5	4.8 ± 2.9	5.9 ± 3.9	0.028
MVA, cm^2	2.8 ± 1.3	2.7 ± 1.2	2.9 ± 1.4	0.51
RVSP, mm Hg	48.8 ± 15.6	50.1 ± 15.7	47.4 ± 15.4	0.27
ASD presurgery				0.33
Closed	99 (32.1)	43 (29.1)	56 (35)	
Open	176 (57.1)	91 (61.5)	85 (53.1)	
Did not assess	33 (10.7)	14 (9.5)	19 (11.9)	

Values are n (%) or mean ± SD.

ASD = atrial septal defect; LVEF = left ventricular ejection fraction; MG = mean gradient; MR = mitral regurgitation; MV = mitral valve; MVA = mitral valve area; RV = right ventricle; RVSP = right ventricular systolic pressure; TEE = transesophageal echocardiogram; TEER = transcatheter edge-to-edge repair; TR = tricuspid regurgitation; TTE = transthoracic echocardiogram; other abbreviations as in Table 1.

gradient (5.9 ± 3.9 mm Hg vs 4.8 ± 2.9 mm Hg; $P = 0.028$).

The median time interval from the index TEER procedure to MV surgery was 3.5 months (IQR: 0.5-11.6 months) overall, with no significant differences between MR groups ($P = 0.74$) (Figure 2). Surgical indications included recurrent MR (33.6%), residual MR (28.8%), loss of leaflet insertion (25.2%), partial detachment (21.5%), mitral stenosis (14.5%), and clip embolization (2.1%), with no significant differences between the 2 groups, except for more MV surgery for mitral stenosis in SMR patients (19.4% vs 9.0%; $P = 0.008$) (Table 3). In terms of scenarios of TEER failure, 21.3% underwent MV surgery after an aborted TEER procedure, whereas 17.6% and 61.1% underwent MV surgery in the acute or delayed scenario, respectively. More aborted TEER cases were observed in SMR patients (25.7% SMR vs 16.2% PMR). During the same hospital admission, urgent or emergency surgery was required in 24.2% and 10.0% of patients, respectively, with no significant differences between MR groups.

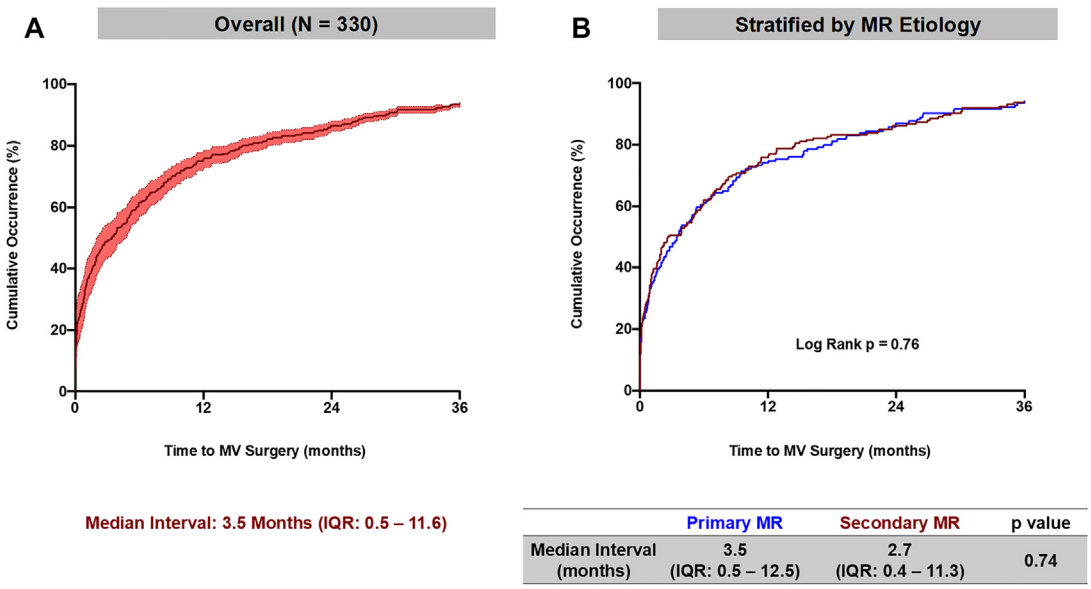
A majority of patients (92.7%) underwent MV replacement, whereas MV repair was performed in 7.3%. Compared with the PMR group, SMR patients had fewer MV repairs (4.0% vs 11.0%; $P = 0.019$). Concomitant tricuspid valve (TV) surgery was performed in 42.4% of patients, with no significant differences between MR groups ($P = 0.060$). The median cardiopulmonary bypass and cross-clamp times were 124 minutes (IQR: 100-156 minutes) and 79 minutes (IQR: 60-101 minutes), respectively, without differences between the 2 groups. Intraoperative echocardiographic characteristics are listed in Supplemental Table S3.

IN-HOSPITAL AND 30-DAY OUTCOMES AFTER MV SURGERY. The overall in-hospital and 30-day mortality was 15.2% and 16.7% respectively, with O/E ratio of 3.59 (95% CI: 1.89-5.28) and the vast majority (94.3%) of 30-day mortality occurring before discharge (Table 4). Compared with PMR, SMR patients trended higher 30-day mortality (20.4% vs 12.7%; $P = 0.072$), with higher O/E ratio (4.62 [95% CI: 2.64-6.59] vs 2.63 [95% CI: 1.22-4.04]). The 30-day readmission rate was 6.2%, with no significant differences between groups.

Median in-hospital (13 days [IQR: 8.3-21.8 days] in SMR vs 12 days [IQR: 8-18 days] in PMR; $P = 0.077$) and intensive care unit length of stay (67 vs 50 hours; $P = 0.97$) also did not differ between groups. There were no significant differences in postoperative complications between MR groups with the exception of more new-onset atrial fibrillation among PMR patients (18.1% vs 9.1%; $P = 0.023$). In-hospital major bleeding occurred in 15.8% of patients, and the stroke rate was 2.7%. Before discharge, no patients had significant residual MR, and 9 patients (3.6%) had significant residual TR (Supplemental Table S4).

MID-TERM OUTCOMES AFTER MV SURGERY AND ASSOCIATED PREDICTORS OF MORTALITY. One-year mortality after MV surgery was 31.3% overall, being significantly higher in the SMR group (38.3% vs 23.2%; $P = 0.019$). The overall median follow-up (including all mortality) was 17.8 months (IQR: 6.7-40.2 months) from the index TEER procedure and 9.1 months (IQR: 1.1-25.8 months) after MV surgery, with similar follow-up duration between groups. On Kaplan-Meier analysis, the actuarial estimates of cumulative survival after MV surgery were 75.9% at 1 year and 68.3% at 3 years overall (Figure 3A), with a significantly lower cumulative survival in SMR compared with PMR at 3 years (58.9%

FIGURE 2 Timing of MV Surgery After TEER



	Primary MR	Secondary MR	p value
Median Interval (months)	3.5 (IQR: 0.5 – 12.5)	2.7 (IQR: 0.4 – 11.3)	0.74

Cumulative probability plot with 95% CI showing timing of mitral valve surgery after index TEER procedure in the CUTTING-EDGE registry **(A)** and stratified by MR etiology **(B)**. The median interval from index TEER procedure to mitral valve surgery was 3.5 months (IQR: 0.5-11.6 months) overall, with no significant differences between MR groups ($P = 0.74$). Abbreviations as in Figure 1.

vs 79.6%; $P = 0.003$) (Figure 3B). Lower cumulative survival in SMR compared with PMR persisted despite risk-adjusted Cox regression analysis (adjusted HR for SMR: 2.3 [95% CI: 1.3-4.2]; $P = 0.006$), and landmark analysis at 30 days ($P = 0.002$) (Supplemental Figure S1). When further stratified by timing of MV surgery, SMR had lower cumulative survival after elective surgery (HR: 2.4 [95% CI: 1.2-4.6]; $P = 0.011$), but not after urgent/emergent surgery (HR: 1.6 [95% CI: 0.82-3.2]; $P = 0.17$) (Supplemental Figure S2).

Variables associated with 1-year mortality after MV surgery within PMR and SMR cohorts on univariate analysis are summarized in Supplemental Figure S3. On multivariable Cox regression, chronic kidney disease (HR: 3.16 [95% CI: 1.33-7.52]), preoperative MR severity (HR: 2.37 per grade [95% CI: 1.03-5.46 per grade]), and emergent surgery (HR: 2.93 [95% CI: 1.13-7.60]) were independent risk factors of 1-year mortality in the PMR cohort, whereas male sex (HR: 2.79 [95% CI: 1.11-7.02]), cirrhosis (HR: 7.26 [95% CI: 2.31-22.81]), pre-TEER TR severity (HR: 1.77 per grade [95% CI: 1.25-2.51 per grade]), and cardiopulmonary bypass time (HR: 1.57 per hour [95% CI: 1.14-2.16 per hour]) were independent risk factors of 1-year mortality in the SMR group (Figure 4).

DISCUSSION

This analysis from the CUTTING-EDGE registry examined the impact of initial MR etiology on MV surgery outcomes after a failed TEER procedure, and has several key findings (Central Illustration). First, compared with PMR, SMR patients exhibited a significantly higher 1-year mortality and a lower cumulative survival at 3 years after surgery, despite no differences in the scenario of TEER failure and timing of surgery. We can speculate that this was mainly due to the greater comorbidity burden in SMR patients with a subsequent higher surgical risk. Second, SMR patients presented more frequently with mitral stenosis as the mechanism of TEER failure, with higher mean gradients at the time of MV surgery. Third, SMR patients more often underwent MV replacement instead of repair. Finally, TR severity at the time of index TEER was an independent predictor of 1-year mortality in SMR patients. These findings are hypothesis generating and will provide further insights into the impact of MR etiology on TEER failure leading to MV surgery.

IMPACT OF MR ETIOLOGY ON CLINICAL OUTCOMES.

The 2 cohorts showed different demographic and

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TABLE 3 Procedural Characteristics at MV Surgery

	Overall (N = 330)	PMR (n = 155)	SMR (n = 175)	*P* Value
Scenario of TEER failure				0.095
Attempted TEER but failed due to MV injury leading to surgery, same or different hospital admission	70 (21.3)	25 (16.2)	45 (25.7)	
Acute TEER failure after implant leading to surgery, same admission	58 (17.6)	31 (20.1)	27 (15.4)	
Delayed TEER failure after implant leading to surgery, separate admission	201 (61.1)	98 (63.6)	103 (58.9)	
Mechanism of TEER failure				
Loss of leaflet insertion, SLDA	83 (25.2)	38 (24.5)	45 (25.7)	0.90
Partial detachment	71 (21.5)	31 (20)	40 (22.9)	0.59
Clip embolization	7 (2.1)	4 (2.6)	3 (1.7)	0.71
Mitral stenosis	48 (14.5)	14 (9)	34 (19.4)	0.008
Residual MR	95 (28.8)	46 (29.7)	49 (28)	0.81
Recurrent MR	111 (33.6)	59 (38.1)	52 (29.7)	0.13
Others	44 (13.3)	17 (11)	27 (15.4)	0.26
Timing of surgery				0.98
Elective	217 (65.8)	102 (65.8)	115 (65.7)	
Urgent, same hospital admission as initial diagnosis of needing surgery	80 (24.2)	37 (23.9)	43 (24.6)	
Emergent, within 6 h of diagnosis of needing surgery	33 (10)	16 (10.3)	17 (9.7)	
MV replacement or repair				0.019
Replacement	306 (92.7)	138 (89.0)	168 (96.0)	
Repair	24 (7.3)	17 (11)	7 (4)	
Concomitant TV repair or replacement				0.060
None	190 (57.6)	93 (60)	97 (55.4)	
Repair	134 (40.6)	62 (40)	72 (41.1)	
Replacement	6 (1.8)	0 (0)	6 (3.4)	
Surgical approach				0.38
Sternotomy	223 (67.8)	109 (70.8)	114 (65.1)	
Right thoracotomy	103 (31.3)	43 (27.9)	60 (34.3)	
Others	3 (0.9)	2 (1.3)	1 (0.6)	
Cannulation				0.51
Central	199 (60.3)	97 (62.6)	102 (58.3)	
Femoral	123 (37.3)	55 (35.5)	68 (38.9)	
Others	6 (1.8)	3 (1.9)	3 (1.7)	
CPB time, min	124 (100-156)	122 (95-154)	128 (103-157)	0.25
Cross clamp time, min	79 (61-101)	79 (62-103)	78 (60-101)	0.66
Use of IABP				0.12
No	296 (89.7)	143 (92.3)	153 (87.4)	
Pre-op	14 (4.2)	5 (3.2)	9 (5.1)	
Post-op	11 (3.3)	6 (3.9)	5 (2.9)	
Pre-op and post-op	9 (2.7)	1 (0.6)	8 (4.6)	

Values are n (%) or median (IQR).
CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; SLDA = single leaflet device attachment; other abbreviations as in Tables 1 and 2.

echocardiographic characteristics at the time of index TEER procedure. SMR patients had more comorbidities compared with PMR, as evidenced by the higher prevalence of coronary artery disease, diabetes, chronic kidney disease, and atrial fibrillation, with consequently higher surgical risk. This is not surprising because it is well recognized that patients with SMR have a greater comorbidity burden with cardiac and systemic implications, compared with those with degenerative disease.[7,8]

SMR patients also had lower LVEF before TEER and at the time of MV surgery. LV dysfunction has been shown to be a predictor of mortality after mitral TEER.[9] Likewise, MR severity has been linked to adverse prognosis in patients with reduced LVEF, highlighting the clinical and prognostic interdependence between SMR and LV dysfunction.[10] The adverse impact of baseline left ventricular dysfunction appears to persist even after MV surgery for failed TEER, as evidenced by significantly higher 1-year mortality in patients with SMR. LVEF at the time of MV surgery was also a univariate predictor of 1-year mortality in these patients. Thus, the poorer clinical outcomes observed in patients with SMR

TABLE 4 In-Hospital, 30-Day, and 1-Year Outcomes After MV Surgery

	Overall (N = 330)	PMR (n = 155)	SMR (n = 175)	*P* Value
In-hospital outcomes				
Ventilator, h	17 (9.0-48.0)	16 (8.0-39.0)	18.8 (9.8-88.3)	0.10
ICU LOS, h	60.0 (19.0-120.0)	67.0 (20.0-120.0)	50.0 (17.3-128.3)	0.97
Hospital LOS, d	12 (8-20)	12 (8-18)	13 (8.3-21.8)	0.077
New-onset atrial fibrillation	44 (13.3)	28 (18.1)	16 (9.1)	0.023
New pacemaker	31 (9.4)	15 (9.7)	16 (9.1)	1.00
Stroke	9 (2.7)	5 (3.2)	4 (2.3)	0.74
Vascular complication	14 (4.2)	5 (3.2)	9 (5.1)	0.43
Life-threatening bleed	29 (8.8)	17 (11)	12 (6.9)	0.24
Major bleed	52 (15.8)	23 (14.8)	29 (16.6)	0.76
Intraoperative mortality	3 (0.9)	2 (1.3)	1 (0.6)	0.60
In-hospital mortality	50 (15.2)	19 (12.3)	31 (17.7)	0.22
30-d Outcomes				
Mortality	53 (16.7)	19 (12.7)	34 (20.4)	0.072
Stroke	9 (2.9)	5 (3.3)	4 (2.4)	0.74
Readmission	16 (6.2)	7 (5.4)	9 (6.9)	0.80
Observed/expected ratio (95% CI)	3.59 (1.89-5.28)	2.63 (1.22-4.04)	4.62 (2.64-6.59)	
1-y Outcomes				
Mortality	67 (31.3)	23 (23.2)	44 (38.3)	0.019
Stroke	13 (6)	6 (5.9)	7 (6.1)	1.00
LVEF, %	46.2 ± 13.8	50.2 ± 11.7	40.2 ± 14.7	0.001
MG, mm Hg	4.1 ± 1.8	3.8 ± 1.4	4.4 ± 2.2	0.18
PG, mm Hg	8.9 ± 4.4	8.1 ± 4	9.9 ± 4.7	0.16
MVA, cm^2	2.9 ± 1.2	2.7 ± 1	3.2 ± 1.7	0.36
RVSP, mm Hg	35 ± 10.3	32.6 ± 8.8	39.9 ± 11.7	0.015
Cumulative survival at last follow-up	238 (74.6)	123 (82.6)	115 (67.6)	0.003

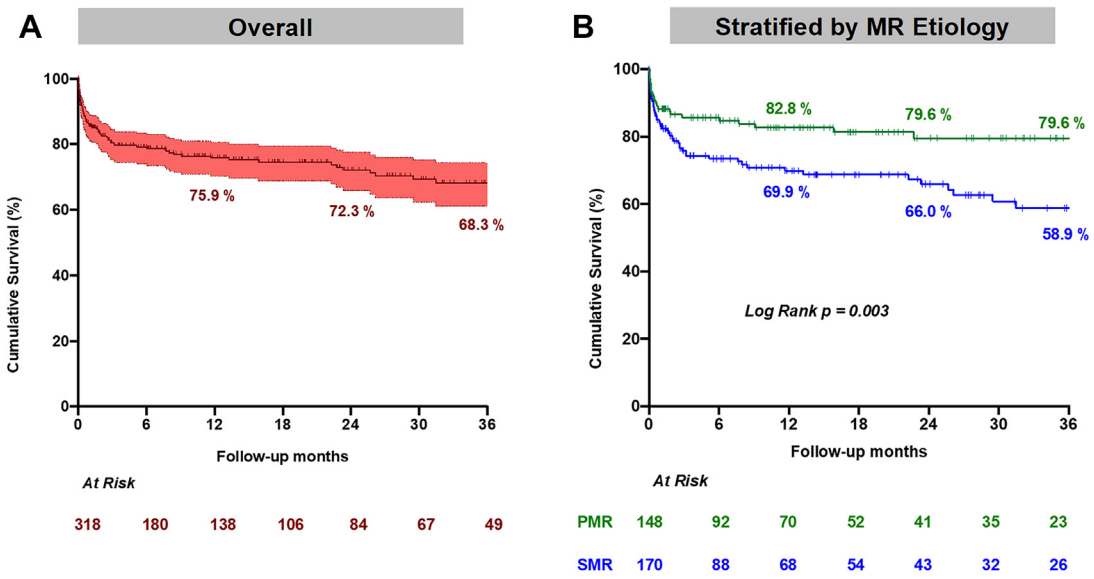
Values are median (IQR), n (%), or mean ± SD unless otherwise indicated.
LOS = length of stay; PG = peak gradient; other abbreviations as in Tables 1 and 2.

undergoing surgery for failed TEER might be related to differences in clinical phenotype, degree of LV dysfunction and comorbidity burden, with subsequently higher preoperative risk profile, rather than the technical success of the intervention itself.

MECHANISM OF TEER FAILURE LEADING TO MV SURGERY. SMR patients presented more frequently with mitral stenosis (19.4% vs 9.0%; $P = 0.008$) as the mechanism of TEER failure, with higher MV mean gradient at time of MV surgery (5.9 mm Hg vs 4.8 mm Hg; $P = 0.028$). The clinical impact of postprocedural mitral gradient after TEER is still a matter of debate, with studies showing conflicting results.[11] Yet, the incidence of mitral stenosis post-TEER is not negligible, ranging from 19% to 37% in contemporary studies.[12-16] Koell et al[15] recently reported that elevated mean gradient (≥5 mm Hg) was an independent predictor of adverse clinical and functional outcomes at 5-year follow-up in patients with PMR, but not SMR. However, 2 other studies in SMR patients found that an increased residual MV gradient was associated with worse outcomes, including higher all-cause mortality, left ventricular assist device implantation, and MV surgery.[13,17] Conversely, 2 studies, including the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, failed to show any association between elevated postprocedural mitral gradient and 2-year adverse events in either PMR or SMR cohorts.[14,16] Although the reasons for this conflicting evidence are unclear, several factors (heart rate, cardiac output, baseline MV area, left ventricular or left atrial systolic and diastolic function, number of clips) may influence mitral gradient and subsequent outcomes, irrespective of the underlying MR etiology.

The degree of residual MR has been shown to be a key determinant of clinical outcomes following surgical MV repair in patients with PMR [18] Similarly after TEER, residual MR ≥2+ has been shown to be associated with an increased risk of recurrent MR in both PMR and SMR patients, with increased mortality and heart failure rehospitalization.[19,20] In fact, in the U.S. Transcatheter Valve Therapy registry, ≤1+ MR was the only factor that mitigated 1-year mortality and rehospitalization after TEER.[3] In our study, nearly 70% of PMR and 60% of SMR patients underwent MV surgery due to residual or recurrent MR. Therefore, to avoid subsequent surgery due to significant MR post-

FIGURE 3 Kaplan-Meier Analysis for All-Cause Mortality After MV Surgery



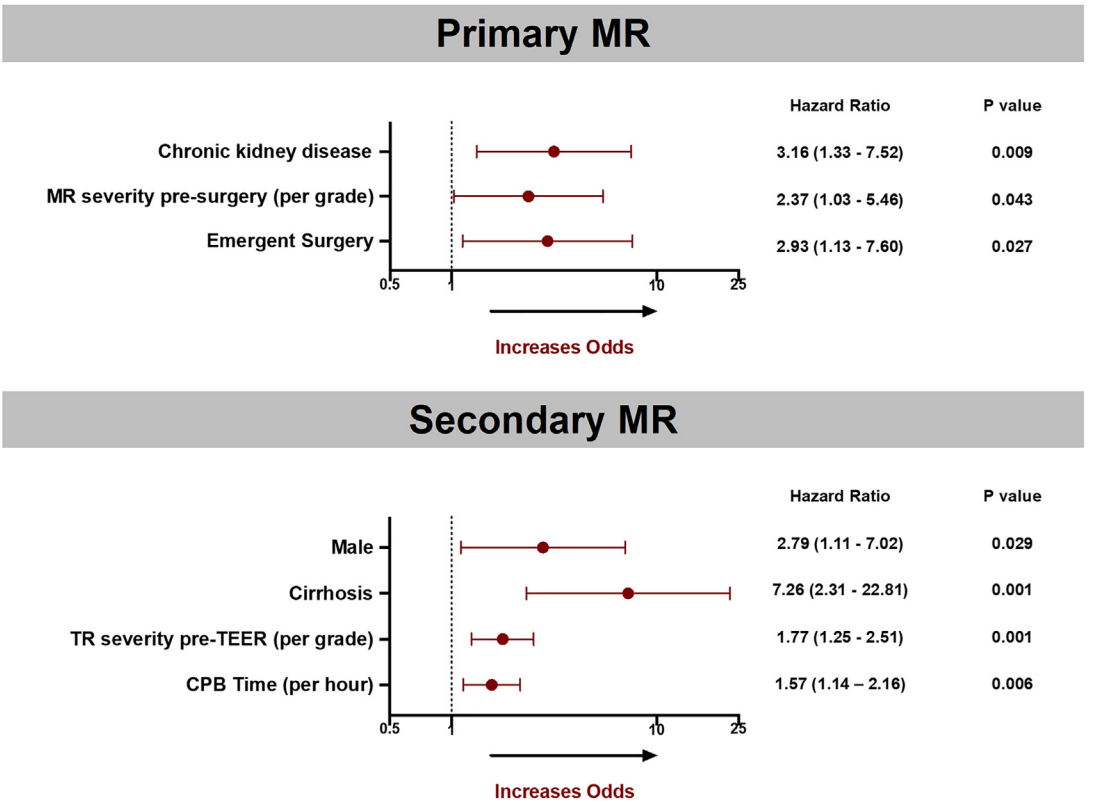
Cumulative survival with 95% CI after MV surgery preceded by TEER **(A)** and stratified by MR etiology **(B)**. Kaplan-Meier estimate of cumulative survival after MV surgery was 68.3% at 36 months **(A)**, with lower survival in secondary mitral regurgitation (SMR) compared with primary mitral regurgitation (PMR) (log rank $P = 0.003$) **(B)**. Abbreviations as in Figure 1.

TEER, the index TEER procedure should be optimized, aiming for residual MR ≤1+ while minimizing the risk of device-related mitral stenosis. This can be accomplished in 2 ways: 1) careful anatomical selection to avoid cases that would likely lead to a suboptimal result (unless the aim of TEER is for palliation); 2) improvement in TEER technology. The latter has been accomplished by the introduction of newer generation MitraClips to expand the anatomical suitability for TEER procedures. The EXPAND G4 post-approval study, evaluating the latest-generation MitraClip G4 system (Abbott Structural Heart), showed promising 30-day results across a wide range of MV anatomies, including those at risk of stenosis.[21] The EXPAND post-approval study, evaluating the third-generation MitraClip XTR/NTR system, showed sustained MR reduction with >90% ≤1+ MR at 1 year across a spectrum of SMR patients.[22] Improvements in technology, as well as consistency and reproducibility of technique, should optimize residual MR to ≤1+ in most TEER procedures and thereby reduce the need for subsequent MV surgery.

TYPE OF MV SURGERY IN PATIENTS WITH TEER FAILURE. Similar to earlier studies, the vast majority of patients with failed TEER underwent MV replacement. Only 7.3% of patients underwent MV repair surgery after TEER failure, with a significantly lower rate among patients with SMR compared with PMR (4.0% vs 11.0%; $P = 0.019$). Several technical factors might reduce the likelihood of MV repair in patients with SMR: 1) the lack of redundant tissue may limit the amount of leaflet left after device excision for a complex surgical repair; 2) the likelihood of repair decreases in mitral stenosis (the most common mechanism of TEER failure in patients with SMR) because device extraction is usually associated with extensive leaflet damage and excision; and 3) a complex mitral repair would have been necessary, with less predictable outcomes and prolonged cross-clamp and cardiopulmonary bypass times, increasing the risk of the operation. In this setting, a MV replacement would be more straightforward and predictable in a high-risk population with left (and right) ventricular dysfunction.

IMPACT OF CONCOMITANT TR. Moderate or greater TR at the time of mitral TEER has been associated with adverse short- and long-term outcomes.[3,23] In the COAPT trial, ≥2+ TR after TEER was identified as an independent predictor of mortality or heart failure hospitalization at 2 years.[24] In our study, despite no differences in TR severity either at index TEER or subsequent MV surgery between PMR and SMR groups, pre-TEER TR severity was found to be an

FIGURE 4 Forest Plot of Multivariable Predictors of All-Cause Mortality After MV Surgery



Forest plot showing multivariable predictors of 1-year mortality after mitral valve surgery for failed TEER stratified by MR etiology. CPB = cardiopulmonary bypass; TR = tricuspid regurgitation; other abbreviations as in Figure 1.

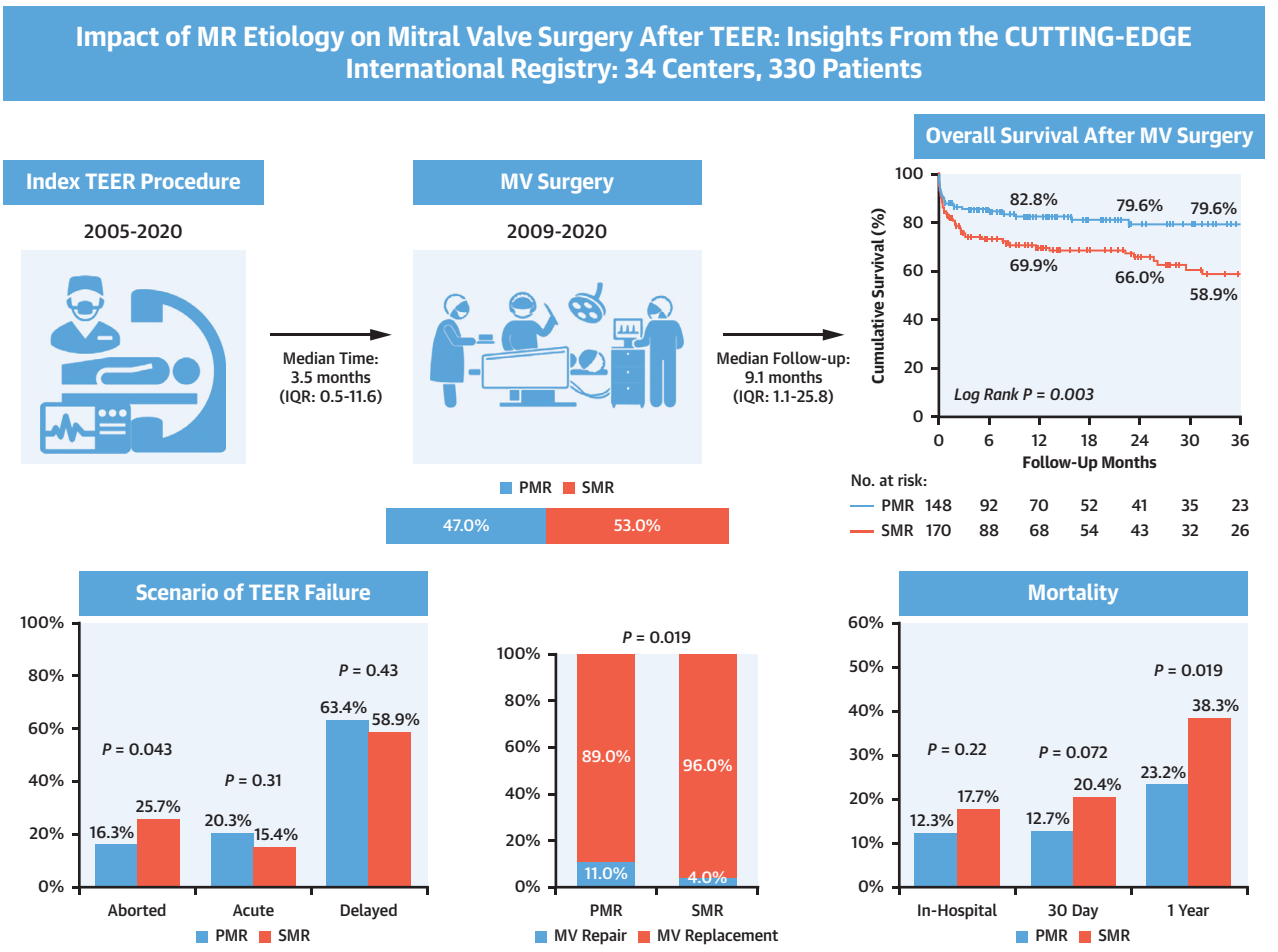
independent predictor of 1-year mortality after MV surgery in SMR patients, suggesting a greater impact of pre-TEER TR in the more vulnerable SMR cohort.

Furthermore, TR severity worsened from index TEER to subsequent MV surgery in both groups (≥2+ TR: 41.8% to 57.2% in PMR; 40.3% to 54.3% in SMR). In a recent analysis from our CUTTING-EDGE registry, we reported that despite ≥2+ TR being predictive of increased mortality after MV surgery, performing concomitant TV surgery after failed TEER did not increase 30-day and 1-year mortality.[25] These findings underscore the importance of more aggressively managing TR in patients at the time of index MV intervention.

Concomitant treatment of both mitral and tricuspid disease during left-sided valvular surgery is clearly recommended by current guidelines (Class I) and should be performed in patients with lower surgical risk.[1,2] Yet, due to comorbidities, patients with significant isolated TR are often ineligible for surgical intervention, especially those with prior cardiac surgery. Transcatheter treatment options have recently evolved to fill this therapeutic gap, and early data on concomitant or staged transcatheter MV and TV intervention suggest early mortality benefit of combined mitral and tricuspid TEER over isolated mitral TEER.[26] Hence, concomitant transcatheter repair of MR and TR might be an appropriate therapeutic choice in selected patients with significant TR, and randomized trials will likely shed light on this topic.

STUDY LIMITATIONS. Despite the strengths of this large global registry-based study, there are several limitations. First, the retrospective nature of this study had inherent biases, including time bias, as different TEER device generations were included with ~70% of the TEER failures comprising the older MitraClip classic and NT systems. Second, eligibility for the index TEER procedure and subsequent MV

CENTRAL ILLUSTRATION **Summary of the CUTTING-EDGE International Registry**



Zaid S, et al. J Am Coll Cardiol Intv. 2023;16(10):1176–1188.

From 2009 to 2020, 330 patients across 34 centers underwent mitral valve (MV) surgery for transcatheter edge-to-edge repair (TEER) failure, of which 47% had primary mitral regurgitation (PMR) and 53.0% had secondary mitral regurgitation (SMR). The median time to MV surgery was 3.5 months (IQR: 0.5-11.6 months), with a median follow-up of 9.1 months (IQR: 1.1-25.8 months) after MV surgery. Compared with PMR, SMR had more aborted TEER (25.7% vs 16.3%; $P = 0.043$) and fewer MV repairs (4.0% vs 11.0%; $P = 0.019$). Although in-hospital and 30-day mortality was similar between groups, SMR had significantly higher 1-year mortality (38.3% vs 23.2%; $P = 0.019$) and lower cumulative survival at 3 years (58.9% vs 79.6%; log rank $P = 0.003$), that persisted in the risk-adjusted Cox regression analysis (adjusted HR for SMR: 2.3 [95% CI: 1.3-4.2]; $P = 0.006$).

surgery was assessed independently by the respective heart teams at the local institutions, which might have introduced patient selection biases. We did not have data on the patient group that did not undergo or was declined MV surgery. This study was not designed to determine the true incidence of TEER failure requiring reintervention, and the volume of TEER procedures performed outside participating centers referred to our participating sites for reintervention were not captured. Third, there was no independent echocardiographic core laboratory to assess the echocardiographic parameters before and after the procedure. Fourth, although the granularity of the database was robust, we were unable to account for provider- or center-level variations in transcatheter and surgical techniques as well as the impact of procedural volume(either surgeon or hospital level) on outcomes. Finally, given the approval dates for TEER for PMR and SMR indications varied due to geographical differences, the associated selection bias in TEER failure requiring surgery could not be avoided.

CONCLUSIONS

In this report from the international CUTTING-EDGE registry, patients with SMR undergoing MV surgery for TEER failure had more operations for mitral stenosis, with fewer MV repair and worse prognosis compared with those with PMR. Our findings are hypothesis generating and will provide further insights into patients after TEER who may require MV surgery in the future.

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PERSPECTIVES

WHAT IS KNOWN? Although mitral TEER is widely performed in patients with severe primary and secondary MR, the impact of MR etiology on outcomes of MV surgery after failed TEER is not well understood.

WHAT IS NEW? SMR patients undergoing MV surgery for TEER failure had more operations for mitral stenosis, with fewer MV repair and a lower cumulative survival at 1 and 3-years after surgery.

WHAT IS NEXT? The potential risks associated with MV surgery after TEER may have implications on management of mitral regurgitation and TEER failure, particularly in patients with SMR. A systematic approach based on patient selection and risk stratification will be key to ensure optimal outcomes after MV intervention.

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KEY WORDS **mitral valve repair, mitral valve replacement, mitral valve surgery, transcatheter edge-to-edge repair**

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