

ORIGINAL RESEARCH

CORONARY, PERIPHERAL, AND STRUCTURAL INTERVENTIONS

Impact of Residual Transmitral Mean Pressure Gradient on Outcomes After Mitral Transcatheter Edge-to-Edge Repair



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ABSTRACT

BACKGROUND There is conflicting evidence regarding the effect of residual transmitral mean pressure gradient (TMPG) after mitral transcatheter edge-to-edge repair (M-TEER). Different TMPG cutoffs have been employed in prior studies with varying results.

OBJECTIVES The purpose of this study was to examine the association between residual TMPG and M-TEER outcomes.

METHODS Consecutive patients undergoing M-TEER at our institution between 2014 and 2022 were included and divided based on quartiles of pre-discharge TMPG. Outcomes were assessed using Kaplan-Meier analysis and Cox proportional hazard models. We performed subgroup analyses according to mitral regurgitation (MR) mechanism. The primary outcome was all-cause mortality or heart failure hospitalization.

RESULTS We included 283 patients (age 76.7 ± 10.8 years, 42.8% women, 78.4% Caucasian, and baseline TMPG 2.4 ± 1.3 mm Hg). Higher baseline TMPG was a predictor of increased TMPG after M-TEER (coefficient 0.60 [95% CI: 0.40-0.70]; $P < 0.001$). In comparison with pre-discharge TMPG quartiles 1 to 3, those in quartile 4 (7.0 ± 1.1 mm Hg) had an increased risk of 3-year all-cause mortality or heart failure hospitalization (adjHR: 1.53 [95% CI: 1.03-2.26]; $P = 0.034$), as well as all-cause mortality alone (adjusted HR [adjHR]: 1.68 [95% CI: 1.09-2.60]; $P = 0.020$). Among patients with primary MR, similar findings were seen for the composite endpoint (adjHR: 2.08 [95% CI: 1.15-3.77]; $P = 0.016$), and all-cause mortality (adjHR: 2.70 [95% CI: 1.40-5.19]; $P = 0.003$). However, this association did not reach statistical significance in secondary MR.

CONCLUSIONS In this single-center study, higher residual TMPG after M-TEER was associated with worse outcomes at intermediate- to long-term follow-up. The effect was mainly driven by increased mortality especially in patients with primary MR. Operators should strive to lower residual TMPG before the conclusion of the procedure.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****adjHR** = adjusted HRs**MR** = mitral regurgitation**M-TEER** = mitral transcatheter
edge-to-edge repair**TEE** = transesophageal
echocardiogram**TMPG** = transmitral mean
pressure gradient**TTE** = transthoracic
echocardiogram

Mitral transcatheter edge-to-edge repair (M-TEER) has become a safe and effective option for management of patients with primary mitral regurgitation (MR) at high to prohibitive surgical risk, and those with secondary MR who remain symptomatic despite optimal guideline-directed medical therapy.^{1,2} The guidelines recommend careful assessment of several parameters after M-TEER including mitral valve area, residual transmitral mean pressure gradient (TMPG), peak velocity, and Doppler velocity index to evaluate for functional failure of the implanted device.³ There is conflicting evidence regarding the impact of residual TMPG on outcomes after M-TEER which may also vary based on the mechanism of MR, including primary versus secondary.³ Furthermore, there is no consensus regarding what TMPG cutoff predicts poor outcomes with studies reporting different cutoffs including 4.4 mm Hg, 5 mm Hg, or quartiles.⁴⁻⁷ Given this uncertainty in relationship between residual TMPG cutoff and outcome, we sought to assess outcomes of M-TEER based on quartiles of TMPG obtained prior to discharge. Additionally, we evaluated the relationship between TMPG and outcomes stratified by mechanism, primary, and secondary MR.

METHODS

PATIENT SELECTION AND DATA COLLECTION. We included all consecutive patients with moderate-to-severe or severe MR who underwent successful M-TEER using the MitraClip device (Abbott Vascular) at Houston Methodist Hospital between March 2014 and March 2022. Candidates with symptomatic primary MR at increased surgical risk or secondary MR on guideline-directed medical therapy were selected for the procedure if they had suitable anatomy for M-TEER after careful evaluation by a multidisciplinary heart team. We excluded patients who had aborted M-TEER procedures (N = 19), and those with missing data on TMPG at discharge (N = 3).

The study was conducted with proper ethical oversight and was approved by the Institutional Review Board at Houston Methodist Hospital. Informed consent was waived given the retrospective nature of the study. Baseline characteristics, procedural details, and outcomes were extracted from our prospectively collected institutional registry. Missing data were collected by review of the electronic medical records. All supporting data are available within the manuscript and online supplementary files.

ECHOCARDIOGRAPHIC ASSESSMENT. All included patients in this study underwent intraprocedural guidance using transesophageal echocardiograms (TEEs). Baseline and pre-discharge transthoracic echocardiograms (TTEs) were performed by experienced sonographers and interpreted by level-3 echocardiographers. The severity of MR was graded according to the American Society of Echocardiography guidelines including mild, moderate, moderate-to-severe, and severe.⁸ MR was classified according to mechanism into: 1) primary or degenerative MR if the primary pathology was related to the valve leaflet or chordae; 2) secondary or functional MR if the mechanism of the regurgitation was related to left ventricular dysfunction, or mitral annulus dilation including secondary to atrial fibrillation; or 3) mixed MR if both mechanisms were observed. Postprocedural TTEs obtained prior to hospital discharge were used to calculate mean TMPG using continuous Doppler waveform tracing of the mitral diastolic inflow as described in the guidelines.⁹ In patients with atrial fibrillation, the average measurement over 3 to 5 consecutive beats was reported.

STUDY OUTCOMES. The study outcomes included a composite endpoint of all-cause mortality or heart failure hospitalization, as well as its individual endpoints at 3 years of follow-up. Additionally, we performed subgroup analyses based on the mechanism of MR including primary and secondary after excluding patients with mixed etiology. We conducted a secondary analysis to compare outcomes according to different hemodynamic profiles of residual TMPG and MR after M-TEER. We divided the study cohort to 4 groups including TMPG quartiles 1 to 3 with less than moderate MR ($\leq 1+$), TMPG quartiles 1 to 3 with moderate or greater MR ($\geq 2+$), TMPG quartile 4 with MR $\leq 1+$, and lastly those with TMPG quartile 4 and MR $\geq 2+$.

STATISTICAL ANALYSIS. Patients were stratified based on quartiles of TMPG on pre-discharge TTE. Categorical variables were described as counts and proportions and compared using chi-square test. Continuous variables were expressed as mean \pm SD and compared by analysis of variance test, or as median (IQR) and compared using the Kruskal-Wallis test. A multivariable linear regression model was performed to identify the predictors of elevated TMPG after M-TEER. Variables with *P* value < 0.20 in the univariable analysis were considered eligible to be entered into the multivariable model. The unadjusted and adjusted coefficients and 95% CIs were reported.

Next, we performed survival analysis to compare time to endpoints using the log-rank test and Kaplan-Meier curves were constructed. To adjust for between-group differences including quartiles 1 to 3 versus quartile 4, we performed Cox proportional hazards regression analysis. Similarly, variables with P value <0.20 in the univariable analysis were considered eligible to be entered into the multivariable model. These variables included: 1) age, atrial fibrillation/flutter, baseline hemoglobin, baseline creatinine, left ventricular ejection fraction, baseline tricuspid regurgitation, and residual MR at discharge in the overall cohort; 2) sex, race, atrial fibrillation/flutter, baseline hemoglobin, baseline creatinine, left ventricular ejection fraction, and baseline mitral valve area in patients with primary MR; and 3) age, baseline hemoglobin, baseline tricuspid regurgitation, mitral annular calcification severity, and baseline mitral valve area in those with secondary MR (Supplemental Tables 1 to 3). The associations were expressed as HRs with respective 95% CI. Adjusted survival curves were performed for graphical representation of these comparisons. A 2-tailed P value of 0.05 was used for significance testing. Statistical analysis was conducted using SPSS, version 26.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

BASELINE CHARACTERISTICS. We included 283 patients who met the study inclusion criteria. Overall, the mean age was 76.7 ± 10.8 years, 42.8% were women, 78.4% were Caucasians, and the mean Society of Thoracic Surgeons risk score for mitral valve repair was $5.4\% \pm 5.6\%$. Patients with TMPG in the fourth quartile had higher baseline TMPG 3.2 ± 1.5 mm Hg with lower mitral valve area 4.9 ± 1.4 cm² in comparison with lower quartiles (Table 1). The median follow-up time was 23.6 months (IQR: 11.3-40.5).

PROCEDURAL CHARACTERISTICS. There was no statistically significant difference in the number of clips used or residual MR across the groups (Table 2). Among patients with quartiles 1 through 4, the mean final intraprocedural TMPG was 2.3 ± 1.1 mm Hg, 2.9 ± 1.1 mm Hg, 3.6 ± 1.2 mm Hg, and 4.6 ± 1.4 mm Hg, respectively. Residual TMPG on pre-discharge TTE was higher than during the procedure across the quartiles, as follows: 1.9 ± 0.5 mm Hg, 3.2 ± 0.3 mm Hg, 4.3 ± 0.4 mm Hg, and 7.0 ± 1.1 mm Hg, respectively (Figure 1). Among patients in the fourth quartile, the mean TMPG was 6.6 ± 2.7 mm Hg at 30 days ($N = 216$), and 5.5 ± 2.5 mm Hg at 1 year ($N = 141$).

PREDICTORS OF TMPG AFTER M-TEER. We found that the number of deployed clips, baseline TMPG, younger age, female sex, body mass index, prior surgical ring, mitral annular calcification, and smaller valve area were associated with higher residual TMPG after multivariable adjustment. The use of wider or longer clips did not predict elevated TMPG (Table 3).

PRIMARY AND SECONDARY ENDPOINTS. Patients with higher residual TMPG in the fourth quartile had an increased risk of the composite endpoint of all-cause mortality or heart failure hospitalization at 3 years after M-TEER in comparison with those with TMPG quartiles 1 to 3 (adjusted HR [adjHR]: 1.53; 95% CI: 1.03-2.26; $P = 0.034$) (Central Illustration). Similarly, the risk of individual secondary endpoint of all-cause mortality was also higher with TMPG quartile 4 (adjHR: 1.68; 95% CI: 1.09-2.60; $P = 0.020$), but there was no difference in the risk of heart failure hospitalization (adjHR: 1.55; 95% CI: 0.83-2.91; $P = 0.169$) (Figure 2). Next, we performed a subgroup analysis of outcomes according to the mechanism of MR. Among patients with primary MR, similar findings were seen with higher risk of all-cause mortality or heart failure hospitalization (adjHR: 2.08; 95% CI: 1.15-3.77; $P = 0.016$), and all-cause mortality (adjHR: 2.70; 95% CI: 1.40-5.19; $P = 0.003$) in patients with quartile 4 versus quartiles 1 to 3 (Figure 3A). On the other hand, the association between elevated TMPG and outcomes did not reach statistical significance in patients with secondary MR (Figure 3B).

Finally, patients with the worst hemodynamic profile including TMPG quartile 4 and moderate or greater residual MR had an increased risk of all-cause mortality or heart failure hospitalization in comparison with those with TMPG quartiles 1 to 3 who had less than moderate MR (adjHR: 5.44; 95% CI: 2.39-12.39; $P < 0.001$). Similar findings were noted in patients with primary MR, but there were no significant differences in patients with secondary MR (Supplemental Figure 1).

DISCUSSION

In this single-center experience, we examined the association between residual TMPG after M-TEER at discharge and outcomes. The main study findings are as follows: patients with higher TMPG in the fourth quartile were found to have an increased risk of the composite endpoint of all-cause mortality or heart failure hospitalization, as well as the individual endpoint of all-cause mortality at 3 years after M-TEER. Similar observations were seen in patients with primary MR, however, the association between increased residual TMPG and outcomes did not reach

TABLE 1 Baseline Demographic, Clinical, and Echocardiographic Characteristics According to Quartiles of Residual Post-TEER TMPG at Discharge

	Overall (N = 283)	Quartile 1 (n = 65)	Quartile 2 (n = 67)	Quartile 3 (n = 84)	Quartile 4 (n = 67)	P Value	
						Overall	Q4 vs Q1-3
Demographics and clinical characteristics							
Age (y)	76.7 ± 10.8	79.6 ± 10.1	77.1 ± 10.7	76.6 ± 10.8	76.7 ± 10.8	0.023	0.010
Women (%)	121 (42.8%)	22 (33.8%)	22 (32.8%)	42 (50.0%)	35 (52.2%)	0.028	0.073
Caucasian (%)	222 (78.4%)	40 (75.4%)	55 (82.1%)	67 (79.8%)	51 (76.1%)	0.756	0.596
BMI (kg/m ²)	26.2 ± 6.0	24.3 ± 4.7	25.7 ± 5.3	26.8 ± 6.1	27.6 ± 7.1	0.010	0.023
STS risk MV repair	5.4 ± 5.6	5.1 ± 4.1	5.5 ± 4.6	4.9 ± 4.5	5.9 ± 7.6	0.683	0.427
STS risk MV replacement	7.4 ± 6.6	6.9 ± 4.8	7.4 ± 5.9	6.7 ± 5.1	8.4 ± 9.9	0.512	0.288
Prior surgical ring (%)	25 (8.8%)	2 (3.1%)	2 (3.0%)	12 (14.3%)	9 (13.4%)	0.016	0.129
Hypertension (%)	198 (70.0%)	46 (70.8%)	48 (71.6%)	58 (69.0%)	46 (68.7%)	0.978	0.789
Diabetes (%)	75 (26.5%)	12 (18.5%)	13 (19.4%)	26 (31.0%)	24 (35.8%)	0.052	0.048
Coronary artery disease (%)	104 (36.7%)	28 (43.1%)	23 (34.3%)	28 (33.3%)	25 (37.3%)	0.633	0.913
Prior PCI (%)	51 (18.1%)	17 (26.6%)	13 (19.4%)	10 (11.9%)	11 (16.4%)	0.140	0.596
Prior CABG (%)	61 (21.6%)	13 (20.0%)	11 (16.4%)	21 (25.0%)	16 (23.9%)	0.584	0.204
Prior myocardial infarction (%)	67 (23.7%)	20 (30.8%)	16 (23.9%)	19 (22.6%)	12 (17.9%)	0.377	0.685
Prior stroke (%)	37 (13.1%)	7 (10.8%)	11 (16.4%)	8 (9.5%)	11 (16.4%)	0.466	0.353
Atrial fibrillation/flutter (%)	165 (58.3%)	37 (59.9%)	48 (71.6%)	51 (60.7%)	29 (43.3%)	0.010	0.004
Prior pacemaker or ICD (%)	83 (29.3%)	16 (24.6%)	21 (31.1%)	23 (27.4%)	23 (34.3%)	0.617	0.304
Dialysis (%)	20 (7.1%)	4 (6.2%)	4 (6.0%)	4 (4.8%)	8 (11.9%)	0.347	0.075
Serum hemoglobin (g/dL)	11.5 ± 2.2	12.3 ± 2.0	11.4 ± 2.4	11.4 ± 1.8	11.0 ± 2.3	0.006	0.009
Serum creatinine (mg/dL)	1.2 (1.0-1.7)	1.1 (0.9-1.5)	1.3 (1.0-1.7)	1.2 (1.0-1.8)	1.2 (1.0-1.9)	0.430	0.971
Prior 2-week NYHA functional class (%)						0.628	0.236
I	8 (2.9%)	2 (3.2%)	1 (1.6%)	1 (1.2%)	4 (6.1%)		
II	49 (17.7%)	10 (15.9%)	12 (18.8%)	17 (20.2%)	10 (15.2%)		
III	183 (66.1%)	41 (65.1%)	42 (65.6%)	59 (70.2%)	41 (62.1%)		
IV	37 (13.4%)	10 (15.9%)	9 (14.1%)	7 (8.3%)	11 (16.7%)		
Echocardiographic characteristics							
Etiology of MR (%)						0.421	0.300
Primary	157 (55.5%)	42 (64.6%)	33 (49.3%)	50 (59.5%)	32 (47.8%)		
Secondary	111 (39.2%)	20 (30.8%)	31 (46.3%)	30 (35.7%)	30 (44.8%)		
Mixed	15 (5.3%)	3 (4.6%)	3 (4.5%)	4 (4.8%)	5 (7.5%)		
Baseline MR severity (%)						0.264	0.780
Moderate-to-severe	54 (19.1%)	14 (21.5%)	17 (25.4%)	11 (13.1%)	12 (17.9%)		
Severe	229 (80.9%)	51 (78.5%)	50 (74.6%)	73 (86.9%)	55 (82.1%)		
Baseline TMPG (mm Hg)	2.4 ± 1.3	1.7 ± 0.7	2.1 ± 1.0	2.5 ± 1.2	3.2 ± 1.5	<0.001	<0.001
Baseline mitral valve area, cm ²	5.3 ± 1.6	5.7 ± 1.5	5.4 ± 1.6	5.2 ± 1.6	4.9 ± 1.4	0.014	0.013
MAC (%)						0.032	0.007
None	199 (70.3%)	53 (81.5%)	47 (70.1%)	58 (69.0%)	41 (61.2%)		
Mild	53 (18.7%)	11 (16.9%)	15 (22.4%)	16 (19.0%)	11 (16.4%)		
Moderate	18 (6.4%)	1 (1.5%)	2 (3.0%)	7 (8.3%)	8 (11.9%)		
Severe	13 (4.6%)	0 (0.0%)	3 (4.5%)	3 (3.6%)	7 (10.4%)		
LVEF (%)	51.4 ± 14.7	52.0 ± 14.0	51.0 ± 15.1	51.9 ± 14.6	50.5 ± 15.0	0.917	0.582
LA volume index (mL/m ²)	63.3 ± 26.6	66.1 ± 28.6	65.2 ± 28.5	62.1 ± 23.4	61.2 ± 26.6	0.670	0.411
LVEDVi (mL/m ²)	87.8 ± 36.8	95.5 ± 45.8	88.5 ± 31.3	85.5 ± 28.1	83.9 ± 44.5	0.718	0.542
LVESVi (mL/m ²)	45.2 ± 28.2	46.7 ± 27.8	49.5 ± 31.6	41.0 ± 22.0	46.7 ± 33.8	0.708	0.823
PA systolic pressure (mm Hg)	52.8 ± 17.7	50.4 ± 16.8	47.6 ± 15.5	55.9 ± 17.4	56.2 ± 19.5	0.019	0.101
Tricuspid regurgitation severity (%)						0.277	0.364
None/trace	69 (24.4%)	12 (18.5%)	12 (17.9%)	25 (29.8%)	20 (29.9%)		
Mild	105 (37.1%)	29 (44.6%)	31 (46.3%)	26 (31.0%)	19 (28.4%)		
Moderate	80 (28.3%)	15 (23.1%)	18 (26.9%)	26 (31.0%)	21 (31.3%)		
Severe	29 (10.2%)	9 (13.8%)	6 (9.0%)	7 (8.3%)	7 (10.4%)		

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

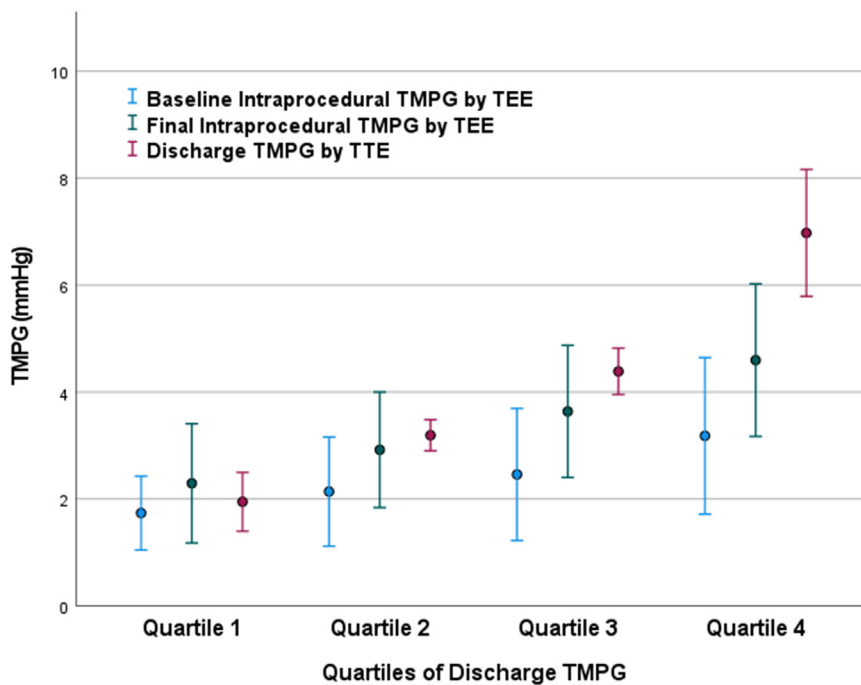
BMI = body mass index; CABG = coronary artery bypass graft; ICD = intracardiac cardioverter defibrillator; LA = left atrium; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; MAC = mitral annular calcification; MR = mitral regurgitation; MV = mitral valve; PA = pulmonary artery; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TEER = transcatheter edge-to-edge repair; TMPG = transmitral pressure gradient.

TABLE 2 Procedural Characteristics and Outcomes According to Quartiles of Residual Post-TEER TMPG at Discharge

	Overall (N = 283)	Quartile 1 (n = 65)	Quartile 2 (n = 67)	Quartile 3 (n = 84)	Quartile 4 (n = 67)	P Value	
						Overall	Q4 vs Q1-3
Number of clips (%)						0.721	0.402
1	149 (52.7%)	35 (53.8%)	38 (56.7%)	45 (53.6%)	31 (46.3%)		
2	119 (42.0%)	28 (43.1%)	27 (40.3%)	33 (39.3%)	31 (46.3%)		
≥3	15 (5.3%)	2 (3.1%)	2 (3.0%)	6 (7.1%)	5 (7.5%)		
Final intraprocedural TMPG (mm Hg)	3.4 ± 1.5	2.3 ± 1.1	2.9 ± 1.1	3.6 ± 1.2	4.6 ± 1.4	<0.001	<0.001
Discharge TMPG (mm Hg)	4.1 ± 1.9	1.9 ± 0.5	3.2 ± 0.3	4.3 ± 0.4	7.0 ± 1.1	<0.001	<0.001
30-day TMPG (mm Hg) (N = 216)	4.5 ± 2.3	3.1 ± 1.7	3.5 ± 1.2	4.6 ± 1.8	6.6 ± 2.7	<0.001	<0.001
1-year TMPG (mm Hg) (N = 141)	4.3 ± 2.2	3.8 ± 2.3	3.6 ± 1.7	4.4 ± 2.1	5.5 ± 2.5	<0.001	0.002
Residual MR at discharge (%)						0.637	0.430
None/trace	52 (18.4%)	11 (16.9%)	11 (16.4%)	19 (22.6%)	11 (16.4%)		
Mild	182 (64.3%)	41 (63.1%)	48 (71.6%)	48 (57.1%)	45 (67.2%)		
Moderate	40 (14.1%)	11 (16.9%)	6 (9.0%)	15 (17.9%)	8 (11.9%)		
Moderate-to-severe	6 (2.1%)	1 (1.5%)	2 (3.0%)	2 (2.4%)	1 (1.5%)		
Severe	3 (1.1%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	2 (3.0%)		
Residual moderate or less MR at discharge (%)	274 (96.8%)	63 (96.9%)	65 (97.0%)	82 (97.6%)	64 (95.5%)	0.908	0.488
30-day moderate or less MR (%) (N = 255)	235 (92.5%)	55 (93.2%)	56 (94.9%)	70 (90.9%)	54 (91.5%)	0.824	0.740
1-year moderate or less MR (%) (N = 145)	167 (92.3%)	36 (87.8%)	40 (93.0%)	54 (93.1%)	37 (94.9%)	0.658	0.491

Values are n (%) or mean ± SD.
 Abbreviations as in Table 1.

FIGURE 1 Comparison of Baseline, Final Intraprocedural, Discharge, and 30-Day TMPG Among Patients With Different Quartiles of TMPG at Discharge



The error bars represent 1 SD around the mean. TMPG = transmitral mean pressure gradient; TTE = transthoracic echocardiogram.

TABLE 3 Linear Regression Analysis for Predictors of Elevated TMPG After Mitral TEER

	Univariable		Multivariable	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Age, per 10-y increase	-0.33 (-0.53, -0.12)	0.002	-0.32 (-0.46, -0.08)	0.005
Female	0.65 (0.19-1.10)	0.005	0.65 (0.28-1.10)	0.001
White race	-0.10 (-0.64, 0.46)	0.748	-	-
Body mass index	0.06 (0.02-0.09)	0.003	0.04 (0.01-0.07)	0.015
Atrial fibrillation/flutter	-0.67 (-1.14, -0.24)	0.003	-0.19 (-0.67, 0.12)	0.175
Prior surgical ring	1.06 (0.27-1.85)	0.008	1.00 (0.30-1.67)	0.005
Secondary MR	0.32 (-0.21-0.72)	0.277	-	-
MAC severity, per grade	0.51 (0.25-0.79)	<0.001	0.41 (0.16-0.65)	<0.001
Baseline LVEF	-0.01 (-0.02, 0.01)	0.610	-	-
Baseline TR severity, per grade	-0.06 (-0.32, 0.16)	0.512	-	-
Baseline mitral valve area, per cm ²	-0.23 (-0.37, -0.09)	0.002	-0.22 (-0.33, -0.06)	0.005
Baseline intraprocedural TMPG, per mm Hg	0.69 (0.49-0.82)	<0.001	0.60 (0.40-0.70)	<0.001
Number of deployed clips	0.38 (0.02-0.76)	0.039	0.77 (0.47-1.13)	<0.001
Wider clips	0.01 (-0.49, 0.50)	0.988	-	-
Longer clips	-0.20 (-0.66, 0.26)	0.392	-	-

Variables with $P < 0.20$ in the univariable analysis were considered eligible to be entered into the multivariable model. Variables with $P < 0.05$ in the multivariable analysis were considered significant predictors of elevated TMPG after mitral TEER.

LA = left atrial; TR = tricuspid regurgitation; other abbreviations as in Table 1.

statistical significance among patients with secondary MR. Additionally, patients who had a combination of elevated TMPG in the highest quartile and moderate or greater MR had poor outcomes. Finally, an elevated baseline TMPG correlated with increased TMPG after M-TEER.

The American Society of Echocardiography guidelines use different mean TMPG cutoffs to

define abnormal prosthetic valve function including ≥ 5 mm Hg for regurgitant valves and >10 mm Hg for stenotic valves.¹⁰ The Mitral Valve Academic Research Consortium adopted a cutoff of 5 mm Hg as a criterion for stenosis of implanted mitral devices.¹¹ However, this cutoff of 5 mm Hg may be too low and its applicability may vary based on several factors including the type of procedure, the etiology of mitral valve

FIGURE 2 Comparison of Primary Composite Outcome and Secondary Individual Endpoints After M-TEER According to Quartiles of TMPG

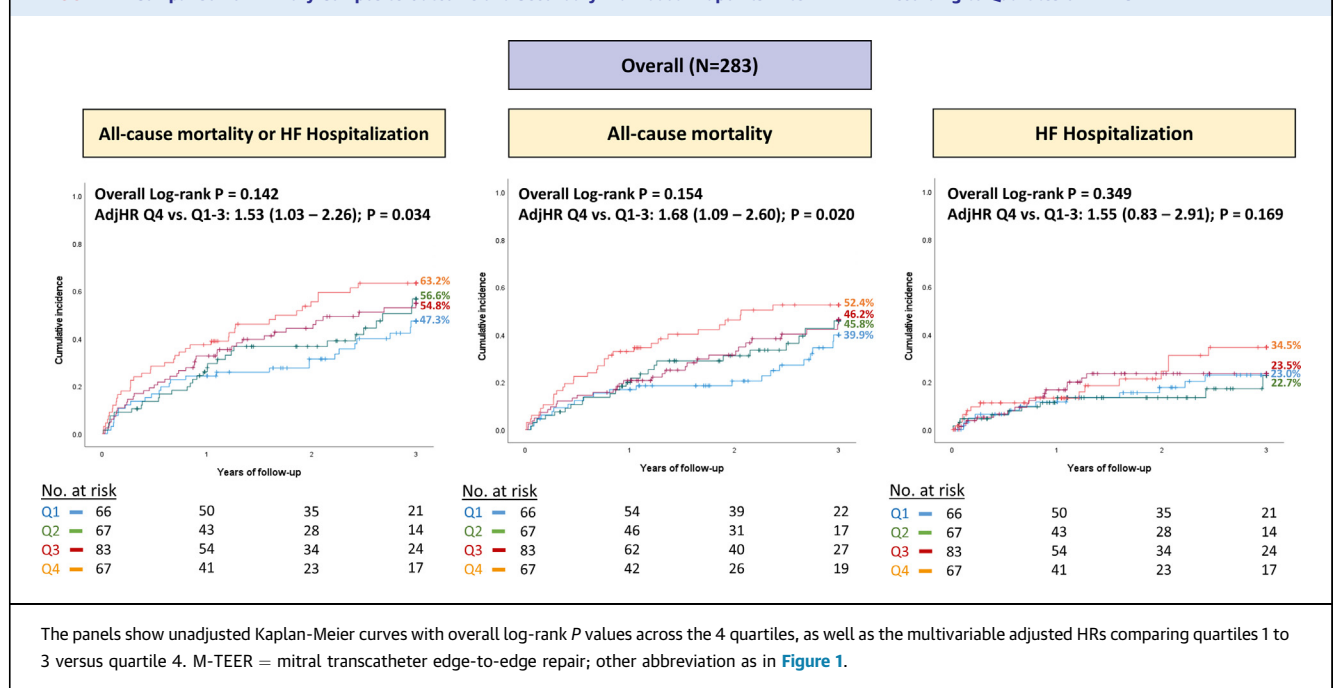
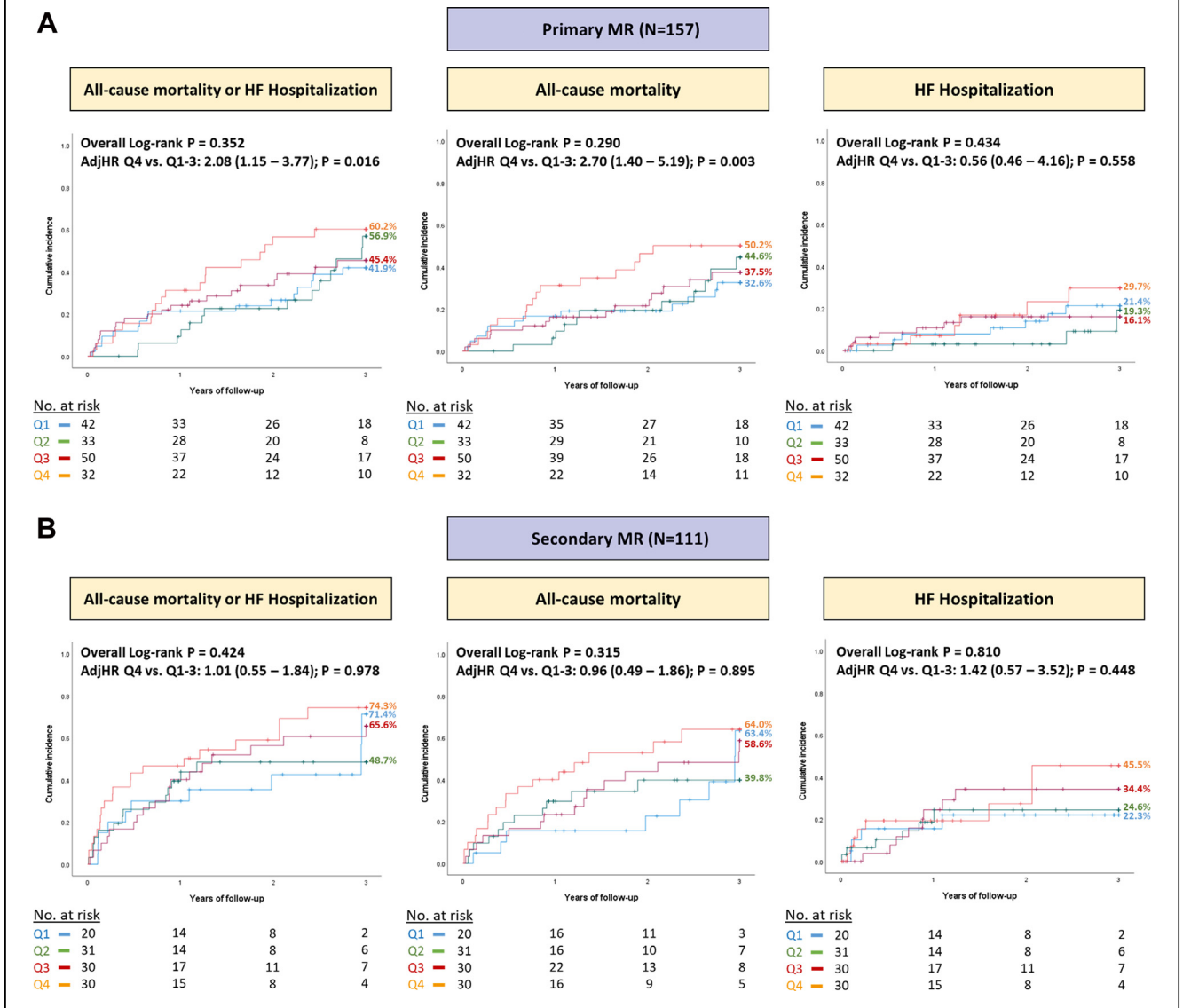


FIGURE 3 Comparison of Outcomes After M-TEER According to the Mechanism of MR, Including Primary MR and Secondary MR

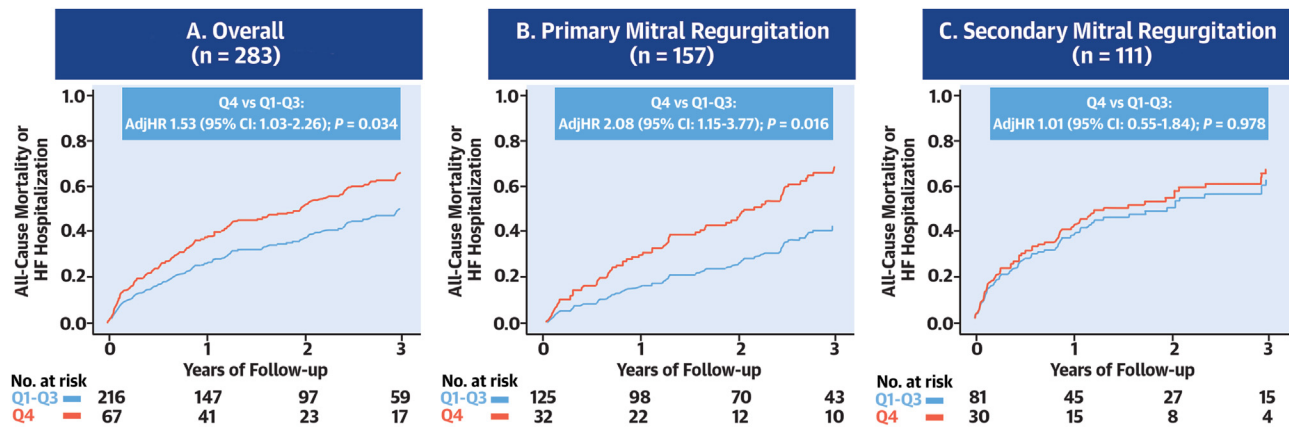


Patients with mixed etiology of mitral regurgitation were excluded from this analysis (N = 15). (A and B) Show unadjusted Kaplan-Meier curves with overall log-rank P values across the 4 quartiles, as well as the multivariable adjusted HRs comparing quartiles 1 to 3 versus quartile 4. MR = mitral regurgitation; other abbreviation as in Figure 2.

dysfunction, and hemodynamic parameters.³ Currently, there is no definitive consensus regarding the use of a specific TMPG cutoff in patients undergoing M-TEER for prognostication since prior publications have presented conflicting results based on different cutoffs.

Baseline TMPG and small mitral valve area have been shown to predict elevated residual TMPG after M-TEER.^{3,12} Other studies showed that patients with elevated pre- and post-TEER TMPG were more likely to be women, with a higher prevalence of mitral

annular calcification, and a higher number of deployed mitral clips.^{5,13,14} In the present analysis, all these factors were important predictors of elevated TMPG after M-TEER, in addition to younger age, body mass index, and prior surgical ring. Multimodality imaging may play a role in identifying patients at risk of developing post-TEER mitral stenosis. Certain preprocedural parameters identified by multidetector computed tomography may be associated with high TMPG after M-TEER including smaller mitral annulus area, mitral annulus diameters, and mitral valve

CENTRAL ILLUSTRATION Association Between Predischarge TMPG in Quartiles 1 to 4 and Outcomes After M-TEER

- Pre-discharge TMPG in the fourth quartile (Q4; highest gradient) was associated with higher rates of all-cause mortality or heart failure hospitalization at 3 years after M-TEER when compared with TMPG in quartiles 1-3 (lower gradients).
- Similar findings were observed in patients with primary mitral regurgitation.
- The association between elevated TMPG and outcomes did not reach statistical significance in patients with secondary mitral regurgitation.

Sammour YM, et al. *JACC Adv.* 2024;3(10):101227.

Impact of transmitral mean pressure gradient (TMPG) on the primary composite outcome of all-cause mortality or heart failure hospitalization at 3 years after M-TEER in (A) all patients; (B) primary mitral regurgitation; and (C) secondary mitral regurgitation. Patients with mixed etiology were excluded from the subgroup analyses shown in (B and C) (N = 15). The panels show adjusted survival analyses stratified by quartiles 1 to 3 versus quartile 4. The variables used for multivariable adjustment are shown in [Supplemental Tables 1 to 3](#). M-TEER = mitral transcatheter edge-to-edge repair.

orifice area.¹⁵ Another study showed that mitral annulus area and leaflet area measured by 3-dimensional TEE were stronger predictors of elevated TMPG after M-TEER than baseline TMPG or mitral valve orifice area in patients with secondary MR.¹⁶ Efforts should be made to identify patients at risk of elevated TMPG after M-TEER and try to mitigate that risk by selecting the appropriate candidates for the procedure, deploying fewer clips if applicable, and consider transcatheter mitral valve replacement if anatomically suitable in those at high risk for developing significant mitral stenosis after M-TEER.

Furthermore, we demonstrate that there are differences between final intraprocedural TMPG by TEE, and predischarge TMPG by TTE, which are likely attributed to being under anesthesia, and having lower heart rate during the procedure.^{17,18} Interestingly, the differences between intraoperative and discharge TMPG became more apparent upon progression from quartile 1 to quartile 4. This trend may

be explained by the observation that patients in the higher quartiles exhibited elevated body mass index, a greater degree of mitral annular calcification, and smaller valve area. These factors, which may influence left atrial compliance, could potentially lead to more noticeable differences between intraprocedural and postprocedural TMPG when loading conditions change after the procedure.

Elevated TMPG has been linked with worse outcomes after M-TEER, but the evidence has not been consistent, and it may vary according to the mechanism of MR, which may not only entail primary versus secondary but also the underlying etiologies for each disease process.³ In primary MR, the left ventricular function and compliance are often normal, and higher TMPG after M-TEER may be more indicative of smaller valve area or residual MR.³ Several studies reported an association between postprocedural TMPG and outcomes in patients with primary MR, however different cutoffs were used to

define an elevated gradient. In an analysis of 104 patients with primary MR, a TMPG >4.4 mm Hg was associated with worse outcomes at 2 years.⁴ Another analysis of 265 patients showed that a TMPG ≥ 5 mm Hg was associated with death or heart failure rehospitalization at 5 years.⁵ On the other hand, there was another study that showed no association between increased TMPG and all-cause mortality or heart failure hospitalization at 2 years in 419 patients with primary MR. However, that study analyzed patients according to TMPG quartiles, and those in the fourth quartile had higher heart rates, greater residual MR, and less comorbidities. Also, the primary outcomes were separated at 2 years and a longer follow-up may have been needed to reach significance.⁶ Our study showed that patients with primary MR and higher TMPG in the fourth quartile had higher risk of the composite outcome of all-cause mortality or heart failure hospitalization, which was mainly related to increased mortality, but there were no differences in heart failure hospitalization after multivariable adjustment.

Furthermore, a recent study from the TVT (Transcatheter Valve Therapy) registry involving 19,088 patients with primary MR compared outcomes based on procedural success defined as achieving moderate or less residual MR, with TMPG of <10 mm Hg. This was associated with significantly lower mortality rates compared with unsuccessful procedures. Patients who had both TMPG ≤ 5 mm Hg and mild or less MR had the lowest rates of mortality and heart failure hospitalization.¹⁹ In our cohort, we found a similar observation where patients with higher TMPG in the fourth quartile who also had moderate or greater residual MR after the procedure had an increased risk of adverse events in comparison with those with TMPG quartiles 1 to 3 and less than moderate MR. It is worth mentioning that the number of our patients in the worst hemodynamic profile group was very small.

With regard to secondary MR, patients have diminished left ventricular function and compliance, along with elevated diastolic pressures which may result in a lower TMPG after M-TEER. Therefore, interpreting differences according to TMPG in the setting of secondary MR may be more complex and prone to variability.³ Several studies reported no association between postprocedural TMPG and outcomes in secondary MR using different cutoffs. A post hoc study of 250 patients with secondary MR from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial by Halaby and colleagues stratified TMPG according to quartiles, similar to the present analysis, and

similarly they showed no association with all-cause mortality or heart failure hospitalization at 2 years.⁷ Two other analyses of 151 and 445 patients with secondary MR showed similar findings of no relationship between TMPG >4.4 mm Hg and >5 mm Hg, respectively, and outcomes at intermediate to long-term follow-up.^{4,5} One possible explanation for these findings could be that the benefits obtained with reduction of functional MR may outweigh the negative effect of mild to moderate mitral stenosis after M-TEER.⁵ On the contrary, a multicenter registry from Italy analyzed 570 patients with secondary MR and found that postprocedural TMPG ≥ 4 mm Hg was an independent predictor of adverse events at 2 years.²⁰ Another single-center study of 268 patients with secondary MR from Germany suggested that TMPG >4.4 mm Hg by echocardiography or >5 mm Hg invasively predicted worse outcomes at 2 years.²¹ It is possible that in our study, a larger number of patients and longer follow-up may have been necessary to show a difference with higher TMPG in secondary MR.

Based on the current available evidence, Hahn and Hausleiter emphasized on the importance of mitral stenosis assessment after M-TEER in their editorial. This can be achieved by reporting preprocedural and postprocedural TMPG with respective heart rate, and by measuring the mitral valve area using 3-dimensional planimetry. They also recommended to aim for TMPG <5 mm Hg, along with mild or less residual MR and mitral valve area >2 cm² especially in patients with primary MR.³ However, obtaining accurate mitral valve area measurements after M-TEER may be challenging, as the valve anatomy may be distorted or thickened, with multiple orifices due to the presence of the clip. Future studies with larger numbers of patients are required to identify the TMPG cutoff associated with worse outcomes after M-TEER. A better understanding of this cutoff may help in selecting appropriate candidates for the procedure, optimize the procedure, and again, considering transcatheter mitral valve replacement for those at highest risk for developing mitral stenosis.

STUDY LIMITATIONS. Our findings should be interpreted within the context of certain limitations including being single-center, retrospective, and observational with a relatively small number of patients especially in the subgroups analyses according to the mechanism of MR. Additionally, the echocardiograms were not reviewed by an external core laboratory given the retrospective nature of the study, however, all echocardiograms were exclusively interpreted by experienced level-3

echocardiographers at our center. Furthermore, our study included different generations of the MitraClip device which may create bias. Other commercially available devices were not used at our institution and outcomes may differ with them given the differences in design. Due to the small number of patients with secondary MR, our ability to detect statistically significant differences among the groups was limited. As a result, our conclusion that higher postclip TMPG are not associated with outcomes in this population may be affected. It is also possible we may have missed some hospitalizations for heart failure in patients who presented to outside hospitals. Finally, external validation of our findings with larger prospective studies is important.

CONCLUSIONS

Elevated mitral valve gradient after M-TEER was associated with higher all-cause mortality or heart failure hospitalizations at intermediate follow-up. This effect was mainly seen among patients with primary MR and was mainly related to increased mortality. Future studies may be needed to better understand the relationship between TMPG and outcomes after M-TEER and identify an optimal cutoff that operators should try to stay under at the conclusion of the procedure.

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Dr Atkins is a consultant for WL Gore & Associates. Dr Reardon is a consultant for Medtronic, Boston Scientific, Abbott, and WL Gore &

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our study builds up on the available literature and shows that patients with higher predischARGE TMPG in the fourth quartile had worse outcomes at 3 years after M-TEER. Upon stratifying patients according to the mechanism of MR, this association persisted in patients with primary MR, but did not reach statistical significance among those with secondary MR.

TRANSLATIONAL OUTLOOK: When planning future studies, it is important to understand the effect of residual TMPG on outcomes according to the mechanism of MR and identify an optimal TMPG cutoff to target during the procedure.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.