Rev Esp Cardiol. 2024;77(8):621–631

Original article

Preprocedural transthoracic echocardiography for predicting outcomes of transcatheter edge-to-edge repair for chronic primary mitral regurgitation

Alon Shechter,[a,b,c,*] Vivek Patel,[a] Danon Kaewkes,[a,d] Mirae Lee,[a,e] Gloria J. Hong,[f] Ofir Koren,[a,g] Tarun Chakravarty,[a] Keita Koseki,[a,h] Takashi Nagasaka,[a,i] Sabah Skaf,[a] Moody Makar,[a] Raj R. Makkar,[a] and Robert J. Siegel[a,j,*]

[a] *Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, United States*
[b] *Department of Cardiology, Rabin Medical Center, Petach Tikva, Israel*
[c] *Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[d] *Department of Medicine, Faculty of Medicine, Khon Kaen University, Thailand*
[e] *Division of Cardiology, Department of Medicine, Samsung Changwon Hospital, Changwon, Republic of Korea*
[f] *Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, United States*
[g] *Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel*
[h] *Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan*
[i] *Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, Maebashi, Japan*
[j] *David Geffen School of Medicine, University of California Los Angeles, Los Angeles, United States*

Article history:
Received 21 September 2023
Accepted 4 December 2023
Available online 22 December 2023

Keywords:
Mitral regurgitation
Mitral transcatheter edge-to-edge repair
Transcatheter mitral valve repair
MitraClip
Transthoracic echocardiography

ABSTRACT

Introduction and objectives: Limited data exist on the prognostic usefulness of transthoracic echocardiography preceding MitraClip for chronic primary mitral regurgitation (MR). We evaluated the predictive ability of transthoracic echocardiography in this setting.

Methods: A total of 410 patients (median age, 83 years, 60.7% males) were included in the study. The primary outcome was the 1-year composite of all-cause mortality or heart failure hospitalization. Secondary endpoints encompassed individual elements of the primary outcome, the persistence of significant functional impairment or above-moderate MR at 1 year, and above-mild MR at 1-month.

Results: The only parameter associated with the risk of the primary outcome was a ventricular end systolic diameter index of $\geq$ 2.1 cm/m^2, corresponding to the cohort's 4th quartile (HR, 2.44; 95%CI, 1.09-4.68; P = .022). Concurrently, higher left atrial volume index (LAVi) and a mid-diastolic medial-lateral mitral annular diameter (MAD) equal to or above the cohort's median of 32.2 mm were linked to a higher probability of death and heart failure hospitalization, respectively. LAVi of $\geq$ 60 mL/m^2, above-mild mitral annular calcification, and above-moderate tricuspid regurgitation conferred higher odds of functional class III-IV or above-moderate MR persistence. All variables except LAVi and MAD, as well as indexed mid-diastolic medial-lateral MAD of $\geq$ 20.2 mm/m^2 and mitral effective regurgitant orifice area of $\geq$ 0.40 cm^2, were associated with greater-than-mild MR at 1 month.

Conclusions: Preprocedural increased indexed left heart dimensions, mainly left ventricular end-systolic diameter index, MAD, mitral annular calcification, mitral effective regurgitant orifice area, and tricuspid regurgitation mark a less favorable course post-MitraClip for chronic primary MR.

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2024.02.016

* Corresponding authors.
E-mail addresses: alonshechter@gmail.com (A. Shechter), Robert.Siegel@cshs.org (R.J. Siegel).
@ShechterAlon

https://doi.org/10.1016/j.rec.2023.12.001
1885-5857/

Ecocardiografía transtorácica previa al procedimiento para predecir los resultados de la reparación percutánea de borde a borde en la insuficiencia mitral primaria crónica

Palabras clave:
Insuficiencia mitral
Reparación mitral percutánea de borde a borde
Reparación percutánea de la válvula mitral
MitraClip
Ecocardiografía transtorácica
Pronóstico

RESUMEN

Introducción y objetivos: Hay pocos datos sobre la utilidad pronóstica de la ecocardiografía transtorácica antes de una MitraClip para la insuficiencia mitral (IM) primaria crónica. El objetivo del estudio es evaluar su capacidad predictiva en este contexto.

Métodos: Se incluyó a un total de 410 pacientes (media de edad, 83 años; el 60,7% varones). El objetivo primario fue el combinado de mortalidad por cualquier causa y las hospitalizaciones por insuficiencia cardiaca a 1 año. Los objetivos secundarios fueron los elementos individuales del objetivo primario, la persistencia de incapacidad funcional significativa o IM superior a moderada a 1 año y la IM superior a leve a 1 mes.

Resultados: Un diámetro telesistólico indexado del ventrículo izquierdo $\geq$ 2,1 cm/m^2, correspondiente al cuarto cuartil de la cohorte, fue el único parámetro asociado con el objetivo primario del estudio (HR = 2,44; IC95%, 1,09-4,68; p = 0,022). Asimismo un mayor volumen de la aurícula izquierda indexado (VAIi) y un diámetro del anillo mitral medial-lateral (MAD) medido en mesodiástole mayor o igual que la mediana de la cohorte de 32,2 mm se relacionaron con mayores probabilidades de muerte y hospitalización por IC respectivamente. Un VAIi $\geq$ 60 ml/m^2, una calcificación del anillo mitral mayor que leve y una insuficiencia tricuspídea mayor que moderada confirieron mayores probabilidades de estar en clase funcional III-IV o de persistencia de la IM en grado mayor que moderado. Todas las variables, excepto el VALi y la MAD, y un MAD $\geq$ 20,2 mm/m^2 y un área del orificio regurgitante efectivo mitral $\geq$ 0,40 cm^2 se asociaron con una IM mayor que leve al cabo de 1 mes.

Conclusiones: El aumento de las dimensiones indexadas del hemicardio izquierdo antes del procedimiento, principalmente el diámetro telesistólico indexado del ventrículo izquierdo, el diámetro y la calcificación del anillo mitral, el área del orificio regurgitante efectivo mitral y la insuficiencia tricuspídea, marca una evolución menos favorable tras el implante de MitraClip en la IM primaria crónica.

Abbreviations

LAVi: left atrial volume index
LVESDi: left ventricular end-systolic diameter index
MAD: mitral annular diameter
M-L: medial-lateral
PMR: primary mitral regurgitation
TEER: transcatheter edge-to-edge repair

INTRODUCTION

Transcatheter edge-to-edge repair (TEER) is a well-established treatment for chronic primary mitral regurgitation (PMR).[1] While associated with excellent short-term structural results, the procedure is challenged by less than optimal clinical outcomes, which could theoretically be optimized by improved patient selection. A readily available, noninvasive, and highly standardized imaging modality, transthoracic echocardiography (TTE) plays a key role in screening mitral TEER candidates and may prove useful for risk stratification purposes as well. To date, however, the prognostic value of preprocedural TTE in the setting of TEER for chronic PMR has not been substantiated.

Previous studies exploring the utility of imaging studies in the triage of patients considered for TEER have either focused on transesophageal echocardiographic (TEE) parameters,[2] evaluated only a few TTE variables simultaneously, incorporated clinical characteristics in the analyses,[3] and/or been performed in functional[4–9] or heterogenous MR[10–15] cohorts. Similarly, imaging factors included in current outcome prediction models for mitral TEER have not been validated exclusively in the chronic PMR population.[16–19] To address this knowledge gap, we assessed the prognostic significance of common TTE parameters obtained prior to TEER for chronic PMR, using the data of a large, real-world registry.

METHODS

Data availability

The data used in this article will be shared upon reasonable request to the corresponding authors.

Study population and outcomes

Our study represents a retrospective analysis of the Cedars-Sinai database of consecutive TEER procedures performed between January 1, 2013 and January 1, 2021 in adult patients for moderate-to-severe or greater MR accompanied by myocardial dysfunction and/or symptoms despite maximally tolerated medical therapy. Each intervention was undertaken following a Heart Team discussion, which considered overall patient status as judged

clinically, standardized/formal surgical risk and operability, published scientific evidence, and patient preferences.

The inclusion criteria for the study were as follows: *a)* a diagnosis of chronic PMR, based on a morphologically abnormal valve apparatus as assessed during the intraprocedural TEE; *b)* the performance of an isolated, first-ever TEER; and *c)* the availability of a viewable preprocedural TTE.

The primary outcome was the composite of all-cause mortality or heart failure (HF) hospitalization during the first postprocedural year. Secondary endpoints included individual components of the primary outcome, as well as the persistence of significant functional impairment at 1 year, indicated by a New York Heart Association (NYHA) class III-IV, or above-moderate MR. A greater-than-mild MR at 1 month was also examined.

The study conformed to the Declaration of Helsinki and was approved by the Cedars-Sinai Institutional Review Board, which waived the need for informed consent.

Procedural aspects

MitraClip (Abbott Vascular Inc, United States) was the sole system employed in the registry. All procedures were performed under general anesthesia and used a trans-septal approach and femoral venous access. TEE, fluoroscopy, and right heart catheterization were used for guidance and monitoring. Technical success was defined as actual device deployment not accompanied by surgical intervention or major complications within the first 24 hours.[20]

Echocardiographic assessment

Echocardiograms were performed and interpreted by experienced sonographers and level III-trained echocardiologists, following accepted guidelines.[21–23] The ultrasound system used was EPIQ (Philips, United States). Postprocessing used PICOM365 (SciImage, United States), QLAB 12.0 (Philips, United States), and TomTec Arena (TomTec Imaging Systems, Germany) for 2-dimensional (2D), 3-dimensional (3D), and speckle-tracking measurements, respectively.

All parameters were evaluated by multiple, focused, and zoomed views. For each continuous structural variable, a body surface area-indexed value was calculated. Regarding hemodynamic variables, either the highest or averaged values were considered based on rhythm regularity. To ensure reliability and consistency, all baseline continuous parameters were assessed by 2 study members (A. Shechter and M. Lee), who were blinded to patient history. In addition, selected mitral and left ventricular (LV) parameters were compared with those obtained by intraprocedural TEE and preprocedural cardiac computed tomography (CCT) exams, respectively. The latter were performed in patients simultaneously considered for valve replacement.

Mitral valve (MV)-related echocardiographic parameters included regurgitation severity, transmitral mean pressure gradient (TMPG), peak E wave velocity, presence and extent of mitral annular calcification (MAC), leaflet calcification, mitral annular diameter (MAD), and leaflet tethering/restriction. MR severity was evaluated by integration of qualitative and quantitative measures and graded as 0 (up-to-minimal), 1 (mild/mild-to-moderate), 2 (moderate), 3 (moderate-to-severe), or 4 (severe). The peak E wave velocity and TMPG were inferred from pulsed-wave (PW) or continuous-wave (CW) mitral inflow tracings, respectively. MAC was assessed semiqualitatively and described as above-mild when involving more the one-third of the annular circumference on the parasternal short axis view[24] or protruding into the LV on apical views. Leaflet immobility was quantified based on leaflet closing angles on the parasternal long axis (PLAX) view. Anterior-posterior (AP) and medial-lateral (M-L) MAD lengths were measured at mid- and end-diastole in the PLAX and apical 4-chamber views, respectively.

Non-MV-related variables consisted of chamber function and dimensions, concomitant valvulopathies, pulmonary arterial systolic pressure (PASP), and LV global longitudinal strain (LVGLS). Left ventricular ejection fraction (LVEF) and left heart chamber volumes were calculated using the Simpson biplane method of disks, whereas global right ventricular (RV) function was assessed qualitatively. LV mass index was computed using the American Society of Echocardiography formula. Tricuspid annular plane systolic excursion (TAPSE) corresponded to the vertical displacement of the lateral tricuspid annular edge according to M-mode tracing in the apical 4-chamber view. Tricuspid regurgitation (TR) was quantified in a similar fashion to MR. PASP was calculated by combining the maximal CW-derived TR pressure gradient with the estimated right atrial pressure; the latter was dictated by inferior vena cava diameter and collapsibility as revealed in the subcostal views. LVGLS was calculated semiautomatically following manual adjustments of cardiac cycle and tracing borders as needed, by averaging endocardial strain measurements in the apical windows.

Intraprocedural pulmonary venous flow pattern (PVFP) improvement and normalization required any increase or the emergence of a value of ≥ 1, respectively, in the peak systolic/diastolic velocity ratio on any PV by PW interrogation.

Data collection

Patient assessment was carried out at baseline, hospital discharge, and at 1 month and 1 year postprocedure. Data were extracted from an electronic medical chart, which was updated in real-time by medical providers and state authorities.

Statistical analysis

Variables are reported as frequencies and percentages or medians [interquartile ranges]. Selected continuous variables were assessed for correlation and change over time using the Pearson *r* coefficient and Wilcoxon test, respectively. Interobserver reliability regarding continuous TTE parameters was evaluated by the intraclass correlation coefficient (ICC).

To identify associations with outcomes, Cox and binary logistic regression multivariable analyses were performed that incorporated baseline TTE parameters with perceived or previously proven[3,17] prognostic significance and a P value of $< .1$ in univariable models. Continuous variables were assessed both as such and as dichotomous, using the medians and 1st/4th quartiles of the cohort, as well as guideline-cited thresholds for intervention.[25,26] Both LVGLS-inclusive/exclusive models were constructed.

The cumulative incidence of the primary outcome and its separate components as a function of TTE parameters identified by the regression models was further analyzed by the log-rank test and was graphically displayed using the Kaplan-Meier method.

To address potential confounders encountered by the "echo-only" regression models, "comprehensive" models were constructed for the primary outcome and its elements. In addition to preprocedural TTE parameters, these included baseline clinical parameters and procedural features showing differing frequencies among patients with and without TTE findings associated with the risk of the primary outcome (all as determined by the Pearson chi-

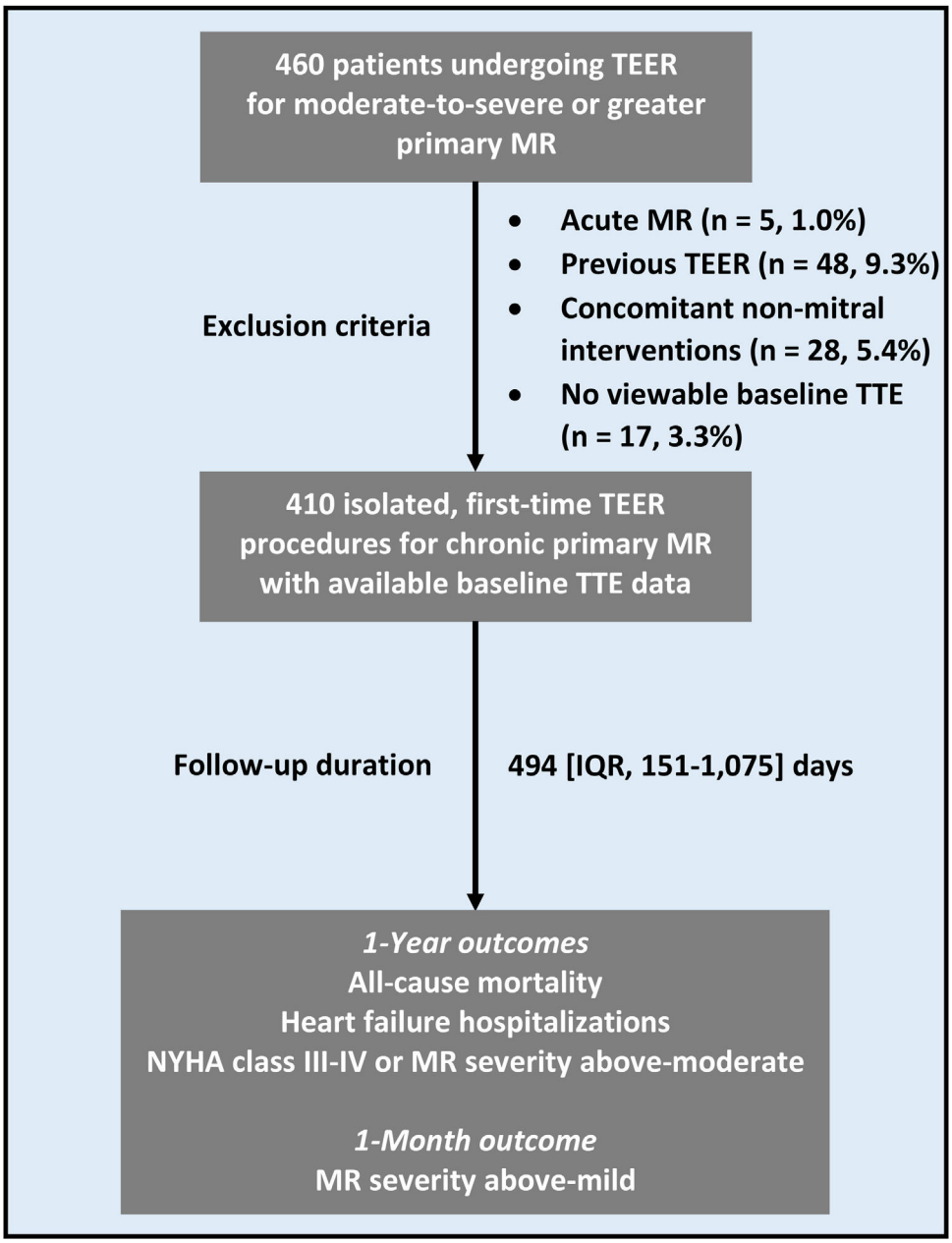


Figure 1. Study flow chart. IQR, interquartile range; MR, mitral regurgitation; NYHA, New York Heart Association; TEER, transcatheter edge-to-edge repair; TTE, transthoracic echocardiogram.

square, Fisher exact, or Mann-Whitney *U* tests), as well as the year of TEER performance, device generation, and data availability regarding 1-month MR grade.

Cases with missing values were censored from the relevant calculations. Statistical significance was defined as a 2-sided *P* value of $< .05$. All analyses were performed using SPSS 24 (IBM Corporation, United States).

RESULTS

Baseline characteristics of the study population

A total of 410 patients were included in the analysis and followed up for a median of 494 [151-1075] days (figure 1). These patients were characterized by a median age of 83 [76-88] years, a predominance of male sex (n = 249, 60.7%), and a high burden of comorbidities, mostly hypertension (table 1). HF was highly symptomatic, as shown by NYHA class III-IV in 377 (91.9%) patients. Reflecting this profile, interventional risk was medium-to-high.

Baseline TTE, performed 25 [IQR, 8-54] days prior to the procedure, demonstrated severe MR in most of the patients (n = 349, 85.5%) (table 2). Overall, MR was attributed to degenerative disease in 403 (98.3%) patients, annular/leaflet calcification in 6 (1.5%), and a combination of the 2 in 1 (0.2%). Almost half of the patients (n = 195, 47.6%) had an LVEF of $\leq$ 60% or an LV end-systolic diameter (LVESD) of $\geq$ 4.0 cm. A similar proportion exhibited a left atrial volume index (LAVi) of $\geq$ 60 mL/m^2, and a little more than a third had MAC and a PASP of $>$ 50 mmHg. The median LVGLS was −15.9 [−18.9-(−12.3)]%.

Table 1
Baseline clinical characteristics

	Total cohort (n = 410)
Demographic details	
Age	
Median, y	83 (76-88)
≥75 y	318 (77.6)
Male sex	249 (60.7)
Body surface area (Mosteller formula), m^2	1.77 [1.59-2.00]
Comorbidities	
Obesity, body mass index ≥ 30 kg/m^2	53 (12.9)
Diabetes mellitus	77 (18.9)
Hypertension	332 (81.2)
Smoking	12 (2.9)
Chronic obstructive pulmonary disease	50 (12.2)
Anemia	238 (58.0)
Stage ≥ III chronic kidney disease	309 (76.3)
Previous MI, PCI, or CABG	120 (29.3)
Prior stroke or transient ischemic attack	52 (12.7)
Peripheral arterial disease	35 (8.6)
Atrial fibrillation/flutter	220 (53.7)
Heart failure features	
New York Heart Association class	
II	33 (8.0)
III	176 (42.9)
IV	201 (49.0)
KCCQ12 score, points	42.2 [20.8-66.2]
6-minute walk test distance, m	244 [150-335]
Serum B-type natriuretic peptide, pg/mL	328 [175-639]
Procedural risk	
STS score for mitral valve repair	5.2 [2.9-8.0]
Mitral regurgitation international database score	9 (8-10)
MitraScore	3 (2-4)
Treatment	
Medications	
Beta-blockers	250 (61.0)
Renin angiotensin system inhibitors	186 (45.4)
Mineralocorticoid receptor antagonists	44 (10.7)
Loop diuretics	283 (69.0)
Antiarrhythmics	68 (16.6)
Antiplatelets	231 (56.3)
Oral anticoagulants	182 (44.)
Cardiac implantable electronic device	
Total	69 (16.8)
Any defibrillator device	17 (4.1)
Any pacemaker device	62 (15.1)

CABG, coronary artery bypass grafting; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.
Data are presented as No. (%) or median [interquartile range].

Importantly, the interobserver reliability was good for all continuous parameters (ICC > 0.87, $P < .001$). In addition, mid-diastolic MAD correlated with its end-diastolic counterpart, TEE parallel, and TEE 3D MV area (Pearson $r \geq 0.72$, $P < .001$). CCT, undertaken in 79 (19.3%) individuals within 0 [IQR, 0-8] days of the preprocedural TTE, revealed higher indexed LV volumes that nevertheless correlated with the echocardiographic observations (Pearson $r \geq 0.77$, $P < .001$).

Table 2
Baseline echocardiographic data

	Total cohort (n = 410)
Mitral valve	
Preprocedural transthoracic echocardiography	
Mitral regurgitation severity	
Moderate-to-severe	59 (14.5)
Severe	349 (85.5)
Mitral effective regurgitant orifice area by PISA, cm^2	0.40 [0.28-0.52]
Mitral regurgitant volume by PISA, mL	55.3 [41.9-77.2]
Transmitral mean pressure gradient, mmHg	3 (2-4)
wave peak velocity, cm/sec	126 [105-149]
Mitral annular calcification	
Any	149 (36.3)
Above-mild	53 (12.9)
Mitral leaflet calcification	109 (27.4)
Mitral annular diameter at mid-diastole	
Anterior-posterior, mm	28.9 [25.4-32.7]
Index, mm/m^2	16.0 [14.1-18.6]
Medial-lateral, mm	32.2 [28.7-36.0]
Index, mm/m^2	17.8 [15.6-20.2]
Mitral annular diameter at end-diastole, mm	
Anterior-posterior	26.9 [21.4-30.9]
Medial-lateral	29.2 [24.8-33.1]
Mitral leaflet tethering/restriction	22 (5.4)
Anterior leaflet closing angle, degrees	37 [35-42]
Posterior leaflet closing angle, degrees	46 [45-53]
Intraprocedural transesophageal echocardiography	
Mitral leaflet prolapse and/or flail	
Any	403 (98.3)
Anterior	10 (2.4)
Posterior	306 (74.6)
Bileaflet	87 (21.2)
Maximal prolapse height, mm	6.0 [5.0-8.0]
Medial-lateral mitral annular diameter at mid-diastole, mm	33.7 [29.5-38.5]
Index, mm/m^2	19.0 [16.0-22.0]
Mitral valve area by 3-dimensional planimetry, cm^2	5.5 [4.3-6.8]
Left heart	
Left ventricular ejection fraction	
Median, %	63 [56-68]
≤ 60%	180 [43.9]
< 20%	2 (0.5)
Left ventricular end-systolic diameter	
Median, cm	3.2 [2.8-3.8]
≥ 4.0cm	80 (19.5)
Index, cm/m^2	1.8 [1.5-2.1]
Left ventricular ejection fraction ≤ 60% or Left ventricular end-systolic diameter ≥ 4.0 cm	195 (47.6)
Left ventricular end-diastolic diameter	
Median, cm	5.0 [4.5-5.5]
Index, cm/m^2	2.8 [2.5-3.1]
Left ventricular end-systolic volume	
Median, mL	33.0 [22.8-48.3]
Index, mL/m^2	18.5 [13.1-25.8]
Left ventricular end-diastolic volume, mL	
Median, mL	92.0 [65.0-120.0]
Index, mL/m^2	50.7 [38.4-64.7]

Table 2 *(Continued)*
Baseline echocardiographic data

	Total cohort (n = 410)
Left ventricular mass index, ASE formula, g/m²	117.2 [92.5-140.9]
Left atrial volume index	
Median, mL/m²	60.0 [44.0-76.0]
≥ 60, mL/m²	193 (47.1)
Moderate of greater aortic stenosis/regurgitation	32 (7.8)
Right heart	
Right ventricular dysfunction	
Any	100 (27.1)
Moderate/severe	39 (10.6)
Basal right ventricular diameter at end-diastole, cm	4.0 [3.5-4.4]
Above-moderate tricuspid regurgitation	76 (18.6)
Right ventricular-pulmonary arterial coupling	
TAPSE, mm	18 (15-22)
PASP	
Median, mmHg	43 (33-57)
> 50 mmHg	159 (38.8)
> 70 mmHg	41 (10.0)
TAPSE/PASP, mm/mmHg	0.41 [0.29-0.61]
Speckle-tracking	
Left ventricular global longitudinal strain, %	−15.9 [−18.9-(−12.3)]

ASE, American Society of Echocardiography; PASP, pulmonary arterial systolic pressure; PISA, proximal isovelocity surface area; TAPSE, tricuspid annular plane systolic excursion
Data are presented as No. (%) or median [interquartile range].

Procedural details and results

Most procedures employed 1 to 2 first/second-generation devices and targeted the A2P2 segment (table 1 of the supplementary data). Almost all (n = 401, 97.8%) were completed successfully, allowing for next-day discharge in most patients.

Immediately following clip deployment, MR regressed to mild-or-less in 317 (77.3%) patients and PVFP improved in 300 (85.5%). Later in the first postprocedural year, both LVEF, left heart dimensions, and PASP significantly decreased (table 2 of the supplementary data).

Outcomes

By 1 year, 61 (14.9%) patients had experienced the primary outcome of all-cause mortality (n = 35, 8.5%) or HF hospitalizations (n = 37, 9.0%). Of the 375 patients who survived to the first postprocedural year, 217 (57.9%) remained under active surveillance at Cedars-Sinai and had available data relating to functional status or residual MR (functional status, n = 204/375, 54.4%; residual MR, n = 184/375, 49.1%). Among the latter, 40 (18.4%) were found to be in NYHA class III-IV (n = 24/204, 11.8%) or to demonstrate above-moderate MR (n = 19/184, 10.3%) at 1 year. One-month MR grade, which as a continuous variable directly correlated with its 1-year counterpart (Pearson $r = 0.75$, $P < .001$), was above-mild in 115 (36.6%) of the 314 individuals with viewable echocardiograms, the latter comprising 77.5% (n = 314/405) of patients remaining alive at 1 month.

Baseline echocardiographic parameters associated with the outcomes

After multivariable analysis, an LVESD index (LVESDi) of ≥ 2.1 cm/m², corresponding to the 4th quartile of the cohort, emerged as the only preprocedural TTE parameter that was associated with the risk of the primary outcome, more than doubling its risk (hazard ratio [HR], 2.44; 95% confidence interval [95%CI], 1.09-4.68; $P = .022$) (table 3 of the supplementary data and table 3). An LVESDi of ≥ 2.1 cm/m² also conferred a higher probability of all-cause mortality (HR, 2.17, 95%CI, 1.28-4.88; $P = .020$) and HF hospitalizations (HR, 3.27; 95%CI, 1.38-5.75; $P = .007$) in separate analyses (tables 4 and 5 of the supplementary data), and was associated with higher rates and cumulative incidences of all above-mentioned outcomes (figure 2, table 6 of the supplementary data, and figure 1 of the supplementary data). Of note, the univariate link between increased LVESD and the cumulative incidence of the primary outcome was observed regardless of baseline LVEF and LVESD intervention cutoffs (figures 2 and 3 of the supplementary data).

Table 3
Multivariable echocardiography-only cox proportional hazard model for the composite outcome of all-cause mortality or heart failure hospitalization at 1 year

	Speckle-tracking not included		Speckle-tracking included	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Mitral valve-related baseline echocardiographic parameters				
Mitral effective regurgitant orifice area by PISA, continuous	4.56 (0.54-8.46)	.165	2.42 (0.25-12.73)	.443
Mitral annular calcification	1.37 (0.57-3.28)	.479	1.71 (0.64-4.58)	.287
Medial-lateral mitral annular diameter ≥ 32.2 mm	1.83 (0.73-4.59)	.196	2.94 (1.00-5.64)	.051
Nonmitral valve-related baseline echocardiographic parameters				
Left ventricular ejection fraction ≤ 56%	1.57 (0.67-3.72)	.302	1.79 (0.63-5.09)	.275
Left ventricular end-systolic diameter index ≥ 2.1 cm/m²*	2.25 (1.09-4.60)	.025	2.44 (1.09-4.68)	.022
Left ventricular end-diastolic diameter, continuous	1.25 (0.75-2.07)	.393	1.12 (0.65-1.92)	.693
Tricuspid annular plane systolic excursion > 18 mm	1.93 (0.79-4.71)	.147	2.24 (0.75-6.64)	.148
Speckle-tracking				
Left ventricular global longitudinal strain less negative than −12.3%	NA	NA	1.10 (0.38-3.25)	.857

95%CI, 95% confidence interval; HR, hazard ratio; NA, not applicable; PISA, proximal isovelocity surface area.
* Left end-systolic volume and left ventricular end-systolic volume index all significantly correlated with left ventricular end-systolic diameter index of ≥ 2.1 cm/m² (Pearson $r = 0.41$ and 0.50, respectively, all $P < .001$) and were therefore not included in the multivariable analysis.

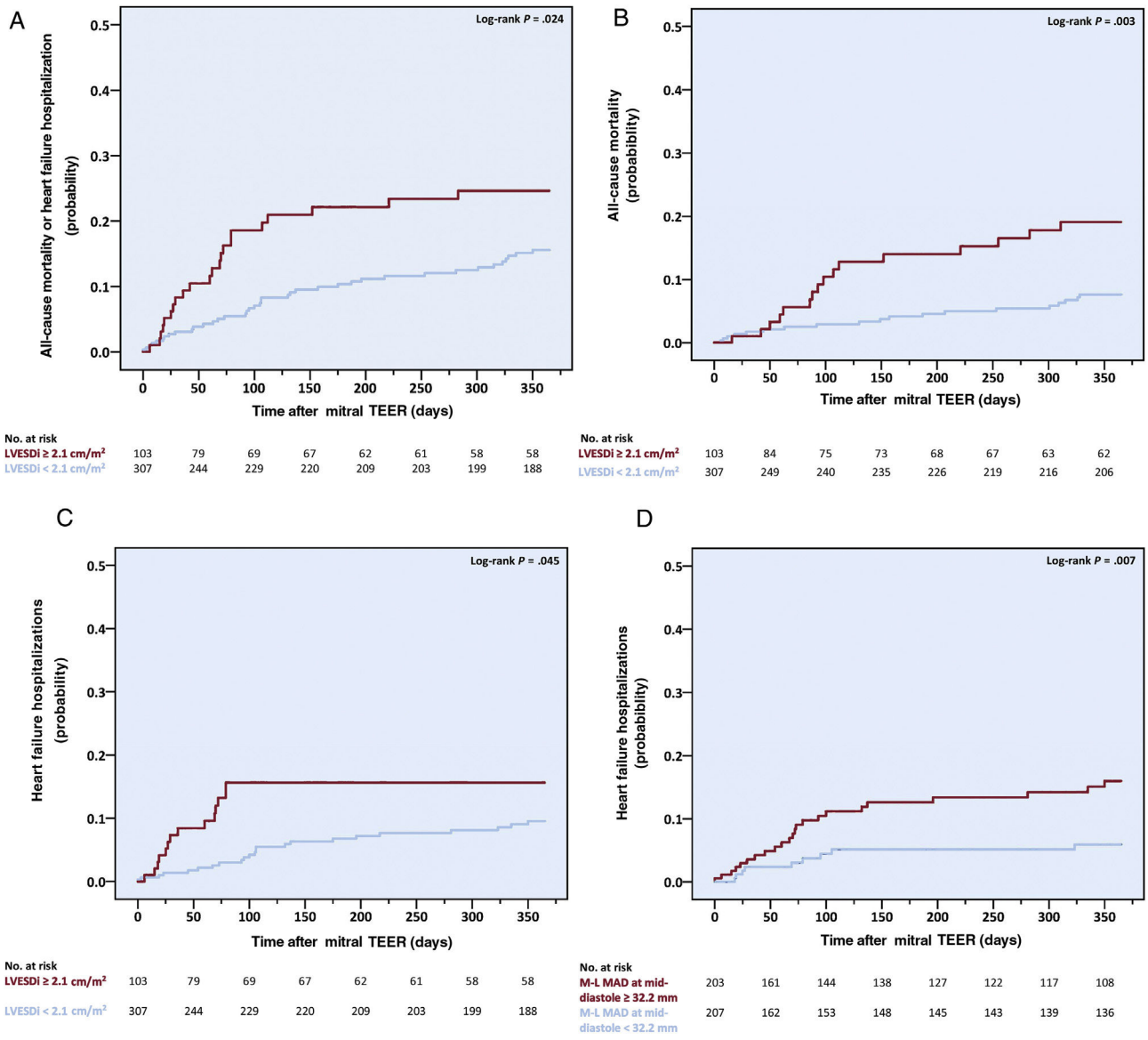


Figure 2. All-cause mortality and heart failure hospitalization. Increased baseline LVESDi was associated with a higher 1-year cumulative incidence of the composite of all-cause mortality or heart failure hospitalization (A) and of its separate components (B,C). Increased mid-diastolic M-L MAD was associated with earlier heart failure hospitalization (D). LVESDi, left ventricular end-systolic diameter index; M-L, medial-lateral; MAD, mitral annular diameter; TEER, transcatheter edge-to-edge repair.

Apart from LVESD, an increased LAVi (as a continuous variable) at baseline was also associated with a higher risk of all-cause mortality (HR, 1.02; 95%CI, 1.01-1.04; $P = .012$), and a mid-diastolic M-L MAD of $\geq$ 32.2 mm, - with a higher risk (HR, 4.29; 95%CI, 1.55-6.90; $P = .005$) and earlier occurrence of HF readmissions. An above-mild MAC, while leading only to a trend toward a higher HF hospitalization risk, was nevertheless linked to excess HF hospitalizations (n = 9/53, 17.0% vs n = 28/357, 7.8%, $P = 0.040$), most of which (n = 6/9) were attributed to noncardiac causes.

Regarding functional status and residual MR, an LAVi of $\geq$ 60 mL/m^2, an above-mild MAC, and an above-moderate TR prior to TEER were associated with a higher odds of NYHA class III-IV or above-moderate MR persistence at 1-year postprocedure, and patients exhibiting a higher number of such characteristics had higher rates of the combined outcome (table 7 of the supplementary data and figure 3). All TTE parameters associated with the 1-year endpoints, except LAVi and M-L MAD, as well as an indexed mid-diastolic M-L MAD of $\geq$ 20.2 mm/m^2 and a mitral effective regurgitant orifice area (EROA) of $\geq$ 0.40 cm^2, conferred a higher risk of greater-than-mild MR at 1 month (table 8 of the supplementary data). Of note, patients with above-mild MR at 1 month experienced a steeper intraprocedural rise in the TMPG (2 [IQR, 1-3] vs 1 [IQR, 0-2] mmHg, $P = .028$), were treated by fewer clips (1 [IQR, 0-1] vs 2 [IQR, 1-2]; $P = .437$), and were marginally more likely to exhibit above-mild MR immediately after clip deployment (n = 12/24, 50% vs n = 30/91, 33.0%, $P = .123$) if they had above-mild (compared with up-to-mild) MAC at baseline.

Lastly, exploratory regression models that integrated baseline clinical variables and procedural aspects whose frequencies differed between the low and high LVESDi groups, year of intervention, device generation, and data availability largely reproduced the

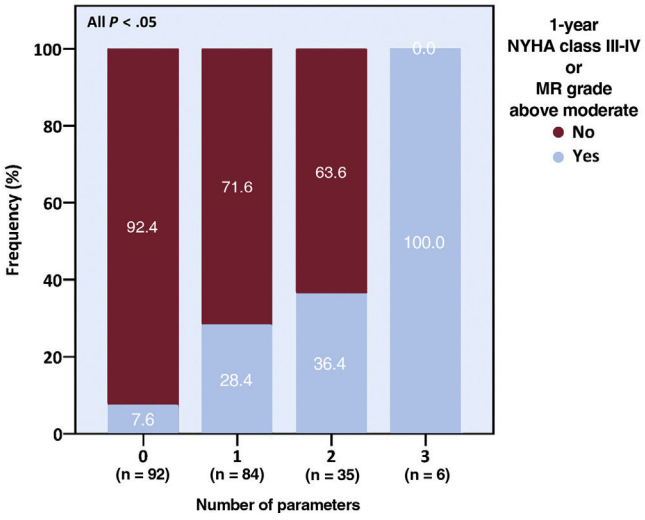


Figure 3. Functional status and grade of mitral regurgitation. A higher baseline parameter burden was associated with increased rates of significant functional impairment or MR at 1 year. The parameters were left atrial volume index of ≥ 60 mL/m^2, above-mild mitral annular calcification, and greater-than-moderate tricuspid regurgitation. MR, mitral regurgitation; NYHA, New York Heart Association.

results of the TTE-only based analyses (tables 9-15 of the supplementary data). Additionally, they suggested a possible association between an increased mid-diastolic M-L MAD and both the primary outcome and all-cause mortality.

DISCUSSION

Our study evaluated the prognostic significance of TTE findings prior to TEER for chronic primary MR. Aiming for simplicity and applicability, we analyzed well-standardized, widely-accepted parameters that can be readily used in daily clinical practice. Regarding MAD, the mid-diastolic rather than the end-diastolic value was considered because of a clearer delineation of the annular edges at maximal valve opening.

The main findings of this study were as follows (figure 4): *a)* an LVESDi of ≥ 2.1 cm/m^2 was associated with higher rate, cumulative incidence and risk of the primary outcome of all-cause mortality or HF hospitalization at 1 year and of each of its components; *b)* a higher LAVi (as a continuous variable) and a mid-diastolic M-L MAD of ≥ 32.2 mm conferred an increased risk of all-cause mortality and HF hospitalizations, respectively; *c)* an LAVi of ≥ 60 mL/m^2, an above-mild MAC, and an above-moderate TR were associated with higher odds of NYHA class III-IV or ≥ moderate-to-severe MR persistence at 1 year; *d)* all the above-mentioned TTE parameters except LAVi and M-L MAD, as well as an indexed mid-diastolic M-L MAD of ≥ 20.2 mm/m^2 and a mitral EROA of ≥ 0.40 cm^2, were associated with an elevated odds of exhibiting above-mild MR at 1 month; and *e)* other structural, functional, and hemodynamic parameters, including LVGLS, were not predictive of any of the examined outcomes.

Highlighting baseline TTE-derived measures of left cardiac chambers and MAD, along with MAC and TR, as potential markers of postinterventional clinical outcomes, our results could have been driven by the extent of the underlying disease and/or accompanying comorbidities associated with these parameters, as well as their impact on procedural success. As shown, patients with

Prognostically meaningful transthoracic echocardiographic parameters obtained prior to transcatheter edge-to-edge repair for chronic primary mitral regurgitation

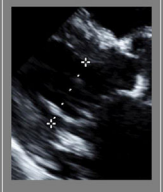
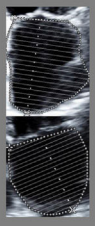
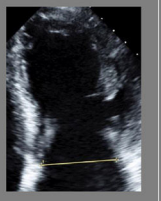
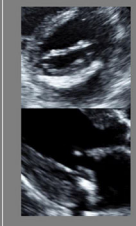
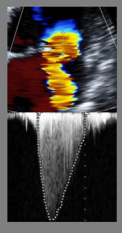
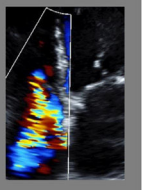
		Study cohort 410 patients undergoing an isolated, first-ever TEER for chronic symptomatic primary MR of moderate-to-severe or greater degree and who have a viewable baseline TTE					
							
		LVESDi ≥ 2.1 cm/m^2	Increased LAVi	Increased M-L MAD at mid-diastole	Above-mild MAC	EROA ≥ 0.40 cm^2	Above-moderate TR
1-Year	All-cause mortality or HF hospitalizations	HR 2.44 95%CI 1.09-4.68 *P* = .022					
	All-cause mortality	HR 2.17 95%CI 1.28-4.88 *P* = .020	Continuous: HR 1.02 95%CI 1.01-1.04 *P* = .012				
	HF hospitalizations	HR 3.27 95%CI 1.38-5.75 *P* = .007		≥ 32.2 mm: HR 4.29 95%CI 1.55-6.90 *P* = .005			
	NYHA class III-IV or above-moderate MR		≥60 mL/m^2: OR 2.40 95%CI 1.45-6.07 *P* = .016		OR 3.40 95%CI 1.13-8.61 *P* = .039		OR 3.00 95%CI 1.27-9.50 *P* = .013
1-Month	Above-mild MR	OR 1.67 95%CI 1.17-3.56 *P* =.028		≥20.2 mm/m^2: OR 2.66 95%CI 1.21-5.86 *P* =.015	OR 2.93 95%CI 1.06-6.12 *P* =.039	OR 2.90 95%CI 1.40-6.01 *P* =.004	OR 4.49 95%CI 1.52-8.29 *P* =.007

Figure 4. Central illustration. Among 410 patients undergoing mitral TEER for chronic symptomatic primary MR, preprocedural TTE findings of increased indexed left heart chambers dimensions—most importantly LVESDi—as well as mid-diastolic M-L MAD, MAC, TR extent, and mitral EROA were associated with adverse outcomes. Cutoff values represent the medians (LAVi, M-L MAD, and EROA) or 4th quartiles (LVESDi, M-L MAD index) of the cohort. Empty cells denote the absence of prognostic significance.

95%CI, 95% confidence interval; EROA, effective regurgitant orifice area; HF, heart failure; HR, hazard ratio; LAVi, left atrial volume index; LVESDi, left ventricular end-systolic diameter index; M-L, medial-lateral; MAC, mitral annular calcification; MAD, mitral annular diameter; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram.

vs without an LVESDi of ≥ 2.1 cm/m^2 displayed a higher serum B-type natriuretic peptide level, more pronounced biventricular dysfunction, and an increased LV mass index, all of which is consistent with a more advanced myocardial remodeling process that may impair the therapeutic ability of TEER in the setting of intrinsic MR.[27] Accordingly, patients with an LVESDi of ≥ 2.1 cm/m^2 required more clips per procedure and showed greater residual MR at 1-month and worse outcomes at 1 year. As possible manifestations of a transition toward a myopathic disorder less amenable to an isolated valvular intervention,[28,29] higher LAVi and MAD were also linked to a less favorable course. As for significant MAC and TR, their association with adverse events may have been mediated by a greater burden of comorbidities,[30] direct hazard,[31,32] and suboptimal technical results, the latter being exemplified by the association between an above-mild MAC and an exaggerated TMPG increase, fewer deployed clips per patient, and greater residual MR.

Our study has 2 practical implications. The first is that LVESDi is more effective than LVESD in the preprocedural risk stratification of patients undergoing TEER for chronic PMR. As stressed, LVESDi correlated with procedural results and clinical events, whereas LVESD did not. Increased LVESDi may represent an earlier stage of cardiac deterioration complicating volume overload states, which may not be fully appreciated by the non-indexed, heart size variability indifferent LVESD. Indeed, most (n = 62/80, 77.5%) of the patients with a high LVESD also had a high LVESDi, whereas only a few patients (n = 41/330, 12.4%) within the low LVESD subgroup exhibited elevated LVESDi. Nevertheless, the association between LVESDi and the primary outcome was independent of LVESD. In addition to its better sensitivity, LVESDi may provide a more accurate estimate of cardiac remodeling in patients with lower body surface area, and specifically women, who may theoretically display normal LVESD despite advanced MR. This apparent predictive advantage of an indexed measure of dimension resembles the one observed in the aorta[33] and may be attested, both conceptually and for the exact cutoff value, by future prospective studies.

The second implication arising from our work is that most echocardiographic parameters suggested by current practice guidelines and risk stratification tools as indications, contraindications, or outcome predictors for chronic PMR interventions may have limited ability to predict the clinical course following an isolated, first-time TEER performed exclusively for chronic symptomatic PMR. This could be due to the different populations studied and analytical approaches used. In this regard, LVEF of ≤ 60% and LVESD of ≥ 4.0 cm, both of which indicate LV dysfunction justifying invasive treatment according to the guidelines, have been analyzed in asymptomatic individuals scheduled for either conservative[34] or surgical management.[35] Our patients, on the other hand, were all symptomatic, percutaneous candidates. Similarly, various indices and cutoff values of LV function[17] and dimensions,[7,11,14] as well as PASP[18] and LVGLS,[36] previously shown to predict outcomes after mitral TEER, have been examined in functional or heterogenous MR cohorts, some of which were exposed to concomitant nonmitral interventions able to influence subsequent outcomes independently. Furthermore, the prognostic usefulness of these parameters was based on mixed imaging/clinical models potentially prone to bias. By contrast, our analyses specifically included chronic PMR patients who underwent a stand-alone TEER and comprehensively focused on TTE variables.

We believe that our study could assist clinicians in the preprocedural risk stratification and postprocedural monitoring strategy used in mitral TEER for chronic PMR. Specifically, timing the intervention and tailoring the follow-up based on the presence of prognostically meaningful echocardiographic characteristics at baseline may improve outcomes and reduce futility, eventually enhancing resource utilization. Given the observational approach and paucity of data on symptom duration in the current study, implementing its findings in real-world practice may best await validation by further, prospective explorations targeting case selection and surveillance.

Limitations

First, the single-center, retrospective design of the study and its lack of central adjudication may hamper the generalizability of results. However, our sample was relatively large, resembled a recently published American nationwide registry,[37] and was assessed by experienced echocardiologists blinded to patient files, all of which potentially improved validity. Second, the lack of follow-up data on functional status and MR grade, as well as the low absolute number of outcome events, negatively impacted statistical power, making some analyses, and particularly those that included non-TTE variables, exploratory. Nevertheless, data availability was comparable to that of previous real-world registries[12,13] and was similarly distributed in the various subgroups, somewhat limiting the probability of bias. In addition, the lack of follow-up data did not affect the regression models, suggesting that it did not influence the results. Furthermore, the better-documented 1-month MR grade, which has previously been associated with longer-term outcomes[38] and is currently used to determine procedural success,[20] correlated well with its 1-year counterpart and was associated with most of the prognostically meaningful TTE observations, thus supporting the latter's significance. Third, our study focused on 2D TTE measurements while disregarding 3D parameters,[39] as the latter could be analyzed only in a fraction of patients (n = 80, 19.5%). Notwithstanding possible inaccuracies in measurement, reliability and consistency were acceptable, as indicated by good interobserver/modality agreement. Further reinforcing validity were the multivariable analyses, which are among the most comprehensive to date. Fourth, baseline medical therapy was somewhat suboptimal, precluding the extrapolation of our findings to medically optimized populations. However, this represented patient tolerance and was consistent with the real-world setting of the study.[40] Last, our observations may be less applicable to patients treated with the newest-generation devices and delivery systems or to rheumatic MR cases, as these were either underrepresented or not included in the study.

CONCLUSIONS

Preprocedural TTE findings of enlarged MAD, significant MAC and TR, elevated mitral EROA and, most importantly, increased indexed left heart chamber size, mainly LVESDi, are associated with a less favorable course following TEER for chronic PMR. Pending prospective validation, incorporating these variables in the clinical decision pathways preceding and following the procedure may prove beneficial.

FUNDING

None declared.

ETHICAL CONSIDERATIONS

The study conformed to the Declaration of Helsinki and was approved by the Cedars-Sinai Institutional Review Board, which waived the need for informed consent. We confirm that possible

sex/gender biases were taken into account in the preparation of this article.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

The study did not involve the use of artificial intelligence.

AUTHORS' CONTRIBUTIONS

A. Shechter conceptualized the project, gathered data, performed analyses, and written the first draft of the manuscript. All coauthors have participated in the revision of the text.

WHAT IS KNOWN ABOUT THE TOPIC?

Preprocedural TTE is widely used to screen mitral TEER candidates. Its prognostic usefulness in the setting of chronic primary MR is not well-established.

WHAT DOES THIS STUDY ADD?

In our single-center analysis of 410 patients, increased indexed left chamber size, EROA, MAD, and the extent of MAC and TR at baseline were associated with a less favorable course following the procedure. Of these, LVESDi $\geq$ 2.1 cm/m^2 was the only parameter to independently confer a higher risk of the composite of death or HF hospitalization at 1 year. In contrast, biventricular function, nonindexed heart dimensions, and PA pressure—all of which play a central role in current practice guidelines and risk models—were not predictive of outcomes.

CONFLICTS OF INTEREST

R.R. Makkar received grant support from Edwards Lifesciences Corporation, is a consultant for Abbott Vascular, Cordis, and Medtronic, and holds equity in Entourage Medical. T. Chakravarty is a consultant, proctor, and speaker for Edwards Lifesciences and Medtronic, a consultant for Abbott Lifesciences, and is a consultant and speaker for Boston Scientific. A. Schechter was granted a general research scholarship by the California Chapter of the American College of Cardiology through the Save a Heart Foundation. The remaining authors have no conflicts of interest to disclose.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2023.12.001

REFERENCES

1. Feldman T, Foster E, Glower DD, et al. EVEREST II Investigators. *Percutaneous Repair or Surgery for Mitral Regurgitation N Engl J Med.* 2011;364:1395–1406.
2. Mauri L, Garg P, Massaro JM, et al. The EVEREST II Trial: Design and Rationale for a Randomized Study of the Evalve MitraClip System Compared with Mitral Valve Surgery for Mitral Regurgitation. *Am Heart J.* 2010;160:23–29.
3. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ. EVEREST II Investigators. *Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II J Am Coll Cardiol.* 2015;66:2844–2854.
4. Kaneko H, Neuss M, Weissenborn J, Butter C. Prognostic Significance of Right Ventricular Dysfunction in Patients with Functional Mitral Regurgitation Undergoing MitraClip. *Am J Cardiol.* 2016;118:1717–1722.
5. Cimino S, Maestrini V, Cantisani D, et al. 2D/3D Echocardiographic Determinants of Left Ventricular Reverse Remodelling after MitraClip Implantation. *Eur Heart J Cardiovasc Imaging.* 2019;2:558–564.
6. Keßler M, Seeger J, Muche R, Wöhrle J, Rottbauer W, Markovic S. Predictors of Rehospitalization after Percutaneous Edge-to-Edge Mitral Valve Repair by MitraClip Implantation. *Eur J Heart Fail.* 2019;21:182–192.
7. Debonnaire P, Heyning CMV, Haddad ME, et al. Left Ventricular End-Systolic Dimension and Outcome in Patients with Heart Failure Undergoing Percutaneous MitraClip Valve Repair for Secondary Mitral Regurgitation. *Am J Cardiol.* 2020;126:56–65.
8. Hahn RT, Asch F, Weissman NJ, et al. Impact of Tricuspid Regurgitation on Clinical Outcomes: The COAPT Trial. *J Am Coll Cardiol.* 2020;76:1305–1314.
9. Scotti A, Munafò A, Adamo M, et al. MiZüBr Registry. Transcatheter Edge-to-Edge Repair in COAPT-Ineligible Patients: Incidence and Predictors of 2-Year Good Outcome. *Can J Cardiol.* 2022;38:320–329.
10. Toggweiler S, Zuber M, Sürder D, et al. Two-Year Outcomes after Percutaneous Mitral Valve Repair with the MitraClip System: Durability of the Procedure and Predictors of Outcome. *Open Heart.* 2014;1:e000056.
11. Capodanno D, Adamo M, Barbanti M, et al. *GRASP-IT Investigators Predictors of Clinical Outcomes after Edge-to-Edge Percutaneous Mitral Valve Repair Am Heart J.* 2015;170:187–195.
12. Puls M, Lubos E, Boekstegers P, et al. One-Year Outcomes and Predictors of Mortality after MitraClip Therapy in Contemporary Clinical Practice: Results from the German Transcatheter Mitral Valve Interventions Registry. *Eur Heart J.* 2016;37:703–712.
13. Kalbacher D, Schäfer U, Bardeleben VRS, et al. Long-Term Outcome, Survival and Predictors of Mortality after MitraClip Therapy: Results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry. *Int J Cardiol.* 2019;277:35–41.
14. Polimeni A, Albanese M, Salerno N, et al. Predictors of Outcomes in Patients with Mitral Reurgitation Undergoing Percutaneous Valve Repair. *Sci Rep.* 2020;10:17144.
15. Shechter A, Vaturi M, Kaewkes D, et al. Prognostic Value of Baseline Tricuspid Annular Plane Systolic Excursion-to-Pulmonary Artery Systolic Pressure Ratio in Mitral Transcatheter Edge-to-Edge Repair. *J Am Soc Echocardiogr.* 2023;36:391–401.
16. Kavsur R, Spieker M, Iliadis C, et al. of the Heart Failure Network Rhineland. Mitral Regurgitation International Database (MIDA) Score Predicts Outcome in Patients with Heart Failure Undergoing Transcatheter Edge-to-Edge Mitral Valve Repair. *J Am Heart Assoc.* 2021;10:e019548.
17. Raposeiras-Roubin S, Adamo M, Freixa X, et al. A Score to Assess Mortality After Percutaneous Mitral Valve Repair. *J Am Coll Cardiol.* 2022;79:562–573.
18. Shah N, Madhavan MV, Gray WA, et al. Prediction of Death or HF Hospitalization in Patients with Severe FMR: The COAPT Risk Score. *J Am Coll Cardiol Intv.* 2022;15:1893–1905.
19. Scotti A, Latib A, Rubbio AP, et al. MiZüBr and GIOTTO Investigators. Derivation and Validation of a Clinical Risk Score for COAPT-Ineligible Patients Who Underwent Transcatheter Edge-to-Edge Repair. *Am J Cardiol.* 2023;186:100–108.
20. Stone GW, Adams DH, Abraham WT, et al. Mitral Valve Academic Research Consortium (MVARC). Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document from the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol.* 2015;66:308–321.
21. Zoghbi WA, Adams D, Bonow RO, et al.Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017;30:303–371.
22. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE Recommendations for the Use of Echocardiography in New Transcatheter Interventions for Valvular Heart Disease. *J Am Soc Echocardiogr.* 2011;24:937–965.
23. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39.
24. Barasch E, Gottdiener JS, Larsen EK, Chaves PH, Newman AB, Manolio TA. Clinical Significance of Calcification of the Fibrous Skeleton of the Heart and Aortosclerosis in Community Dwelling Elderly. The Cardiovascular Health Study (CHS). *Am Heart J.* 2006;151:39–47.
25. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2021;143:e72–e227.
26. Vahanian A, Beyersdorf F, Praz F, et al. ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. *Eur Heart J.* 2022;43:561–632.
27. Gaasch WH, Meyer TE. Left Ventricular Response to Mitral Regurgitation: Implications for Management. *Circulation.* 2008;118:2298–2303.
28. Messika-Zeitoun D, Bellamy M, Avierinos JF, et al. Left Atrial Remodelling in Mitral Regurgitation – Methodologic Approach, Physiological Determinants, and Outcome Implications: A Prospective Quantitative Doppler-Echocardiographic and Electron Beam-Computed Tomographic Study. *Eur Heart J.* 2007;28:1773–1781.
29. Kreidel F, Zaid S, Tamm AR, et al. Impact of Mitral Annular Dilation on Edge-to-Edge Therapy with MitraClip-XTR. *Circ Cardiovasc Interv.* 2021;14:e010447.
30. Fox CS, Vasan RS, Parise H, et al. Framingham Heart Study. Mitral Annular Calcification Predicts Cardiovascular Morbidity and Mortality: the Framingham Heart Study. *Circulation.* 2003;107:1492–1496.

31. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical Outcome of Isolated Tricuspid Regurgitation. *J Am Coll Cardiol Img.* 2014;7:1185–1194.
32. Brunner S, Wolfrum M, Moccetti F, et al. The Relevance of Tricuspid Regurgitation in Patients Undergoing Percutaneous Treatment of Mitral Regurgitation. *Catheter Cardiovasc Interv.* 2022;99:1848–1856.
33. Yang LT, Michelena HI, Scott CG, et al. Outcomes in Chronic Hemodynamically Significant Aortic Regurgitation and Limitations of Current Guidelines. *J Am Coll Cardiol.* 2019;73:1741–1752.
34. Rosenhek R, Rader F, Klaar U, et al. Outcome of Watchful Waiting in Asymptomatic Severe Mitral Regurgitation. *Circulation.* 2006;113:2238–2244.
35. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic Prediction of Survival after Surgical Correction of Organic Mitral Regurgitation. *Circulation.* 1994;90:830–837.
36. Medvedofsky D, Milhorini Pio S, Weissman NJ, et al. COAPT Investigators. Left Ventricular Global Longitudinal Strain as a Predictor of Outcomes in Patients with Heart Failure with Secondary Mitral Regurgitation: The COAPT Trial. *J Am Soc Echocardiogr.* 2021;34:955–965.
37. Makkar RR, Chikwe J, Chakravarty T, et al. Transcatheter Mitral Valve Repair for Degenerative Mitral Regurgitation. *JAMA.* 2023;329:1778–1788.
38. Bedogni F, Popolo Rubbio A, Grasso C, et al. Italian Society of Interventional Cardiology (GIse) registry Of Transcatheter treatment of mitral valve regurgitaTiOn (GIOTTO): Impact of Valve Disease Aetiology and Residual Mitral Regurgitation after MitraClip Implantation. *Eur J Heart Fail.* 2021;23:1364–1376.
39. Kassar M, Praz F, Hunziker L, et al. Anatomical and technical predictors of three-dimensional mitral valve area reduction after transcatheter edge-to-edge repair. *J Am Soc Echocardiogr.* 2022;35:96–104.
40. Desai RJ, Patorno E, Vaduganathan M, et al. Effectiveness of Angiotensin-Neprilysin Inhibitor Treatment versus Renin-Angiotensin System Blockade in Older Adults with Heart Failure in Clinical Care. *Heart.* 2021;107:1407–1416.