

# Identification of Subclinical Myocardial Dysfunction and Association with Survival after Transcatheter Mitral Valve Repair



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**Background:** Transcatheter mitral valve repair (TMVr) using edge-to-edge mitral valve clip is effective for patients with mitral regurgitation (MR) and high or prohibitive surgical risk. Global longitudinal strain (GLS) allows evaluation of subclinical myocardial dysfunction, but its incremental clinical utility into risk stratification, beyond traditional clinical parameters, is unknown in patients treated with TMVr. We sought to evaluate the association of baseline GLS with 1-year all-cause mortality in patients treated with TMVr using edge-to-edge mitral valve clip.

**Methods:** We analyzed 155 patients who underwent transcatheter edge-to-edge mitral valve clip implantation (mean age,  $83 \pm 7$  years; 48% were women; mean left ventricular ejection fraction,  $56\% \pm 10\%$ , Society of Thoracic Surgeons Predicted Risk of Mortality score for repair,  $6.62\% \pm 5.22\%$ ). Baseline left ventricular GLS was obtained by two-dimensional speckle-tracking echocardiography, averaging 18 segments from three apical views. Receiver operating characteristic analyses were used to assess the GLS cut point associated with all-cause mortality. Multivariable models with Cox regression tested its relationship after adjustment for baseline comorbidities.

**Results:** During a median follow-up of 316 days, all-cause deaths occurred in 30 patients at a median of 156 days after TMVr. The area under the curve of preoperative GLS associated with the outcome was 0.60, with a cutoff point of  $-14.5\%$ . Baseline GLS  $> -14.5\%$  was associated with 1-year mortality (hazard ratio = 2.50; 95% CI, 1.20-5.21;  $P = .02$ ) before and after adjustment for baseline characteristics. After accounting for baseline characteristics, patients with GLS  $> -14.5\%$  had worse 1-year mortality than those with GLS  $\leq -14.5\%$  ( $\chi^2 P < .001$ ). In nested Cox proportional hazards models, the addition of baseline GLS to Society of Thoracic Surgeons Predicted Risk of Mortality score, left ventricular ejection fraction, and the etiology of MR significantly increased the model  $\chi^2$  value ( $\chi^2 = 12.32$ ).

**Conclusions:** Baseline GLS is independently associated with 1-year all-cause mortality in patients who undergo TMVr, and its assessment improves risk stratification in these patients. (J Am Soc Echocardiogr 2020;33:1474-80.)

**Keywords:** All-cause mortality, Global longitudinal strain, Mitral regurgitation, Transcatheter edge-to-edge mitral valve clip, Transcatheter mitral valve repair

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Mitral regurgitation (MR) is one of the most common valve diseases in developed countries,<sup>1</sup> and its prevalence is expected to increase with an aging population.<sup>2</sup> Severe MR is associated with increased morbidity and mortality without mitral valve (MV) intervention.<sup>3,4</sup> Transcatheter MV repair (TMVr) with edge-to-edge MV clip is an effective treatment of patients with severe symptomatic MR who have high or prohibitive surgical risk.<sup>5</sup> However, there is heterogeneity in the clinical response to transcatheter edge-to-edge MV clip procedure despite achieving adequate MR reduction with a reported 25% mortality at 1-year in the ACC/AHA Transcatheter Valve Therapy registry.<sup>6</sup> Current guidelines emphasize evaluation of symptoms and assessment of left ventricular ejection fraction (LVEF) and left ventricular end-systolic diameter (LVESD)<sup>7,8</sup> as triggers for MV intervention. However, subclinical myocardial dysfunction assessed by global longitudinal strain (GLS) might be present in patients with severe MR, despite normal LVEF and LVESD, and may be associated with poor prognosis.<sup>9</sup>

Abbreviations
<b>DMR</b> = Degenerative mitral regurgitation
<b>FMR</b> = Functional mitral regurgitation
<b>GLS</b> = Global longitudinal strain
<b>LV</b> = Left ventricular
<b>LVEF</b> = Left ventricular ejection fraction
<b>LVEDD</b> = Left ventricular end-systolic diameter
<b>MR</b> = Mitral regurgitation
<b>MV</b> = Mitral valve
<b>STS-PROM</b> = Society of Thoracic Surgeons Predicted Risk of Mortality
<b>TMVr</b> = Transcatheter mitral valve repair
<b>TTE</b> = Transthoracic echocardiography

Speckle-tracking echocardiography-derived GLS has been shown to be a noninvasive imaging technique that can detect the subclinical myocardial dysfunction beyond LVEF.<sup>10,11</sup> While preoperative GLS was shown to be associated with poor outcomes in patients with severe degenerative MR (DMR) who underwent surgical MV replacement or repair,<sup>9,12</sup> its clinical utility is unknown in patients treated with TMVr with edge-to-edge MV clip, which is currently approved for the treatment of patients with DMR and high surgical risk. Growing worldwide experience with TMVr<sup>13,14</sup> will continue the drive for improving outcomes and identification of predictors beyond standard clinical parameters. Therefore, we sought to evaluate the association of baseline GLS with 1-year all-cause mortality after TMVr with

edge-to-edge MV clip in patients with severe MR, beyond LVEF and other traditional clinical risk factors.

## METHODS

### Study Design

We conducted a retrospective cohort analysis of consecutive patients with MR who underwent TMVr with edge-to-edge MV clip (MitraClip, Abbott Vascular, Menlo Park, CA) at Minneapolis Heart Institute, Abbott Northwestern Hospital (Minneapolis, MN), from September 1, 2012, through May 31, 2018. This study was approved by the Allina Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All study patients provided informed consent for use of their medical record for research purposes, in accordance with Minnesota statutes. Patients who had acute procedural failure, a repeat transcatheter edge-to-edge MV clip procedure, off-label use such as hypertrophic obstructive cardiomyopathy, or previous mitral surgery were excluded. These latter exclusions were chosen as the fundamental relationship between cardiac structure or function, as assessed by GLS, and clinical outcomes are relatively less certain. We also excluded patients with no available baseline transthoracic echocardiography (TTE) study or with inadequate echocardiographic image quality for GLS analysis defined by more than one out of three apical long-axis views where more than two contiguous segments had poor tracking despite manual correction.

### Transthoracic Echocardiogram

A comprehensive TTE was performed before TMVr in accordance with societal guidelines using several echocardiographic systems (Philips iE33 and CX-50, Philips Medical Systems, Andover, MA).<sup>15</sup> Mitral regurgitation was quantified by an integrated approach including valve morphology and measurement of the effective

regurgitant orifice and the regurgitated volume using the proximal isovelocity surface area method. Severe MR was confirmed on the basis of an effective regurgitant orifice area  $\geq 0.40$  cm<sup>2</sup> and regurgitant volume  $\geq 60$  mL/beat by using the proximal isovelocity surface area method.

### Strain Analysis

Strain analysis was performed offline using commercially available software (2D Cardiac Performance Analysis version 4.3.2.5; TomTec, Munich, Germany) as described elsewhere.<sup>16</sup> The 18-segment model (six segments per view) was used for GLS analysis by averaging the three apical long-axis views (two, three, and four chamber). For patients in atrial fibrillation, we used the single index beat method, which has been validated for GLS evaluation in these patients.<sup>17</sup> In short, it establishes that if the R-R interval ratio of the two preceding beats equals 1, then the third beat can be used as the representation of average left ventricular (LV) contractility. Therefore, in these patients, we chose the index cardiac cycle just after two cardiac cycles of similar length and/or with a maximal R-R interval difference of  $< 60$  msec. All GLS measurements were conducted by M.F. and digitally stored and later analyzed completely blinded for all clinical and survival data.

### Statistical Analysis

The primary endpoint of the study was 1-year all-cause death after TMVr with edge-to-edge MV clip. The electronic medical record was reviewed in its entirety for patient demographics, symptom status, comorbidities, and clinical outcomes. Occurrence of death was confirmed through review of the electronic medical records and confirmed by examination of Minnesota Department of Health records.

Categorical variables are presented as frequency (percentage) and were compared using the  $\chi^2$  test. In the case of selected variables in which a single cell had fewer than five patients, Fisher's exact test was used. Continuous variables are presented as mean  $\pm$  SD and compared using Student's *t* test or Mann-Whitney-Wilcoxon test as appropriate. A random sample of 15 patients from the study cohort was chosen to determine intraobserver and interobserver variability of GLS measurements using intraclass correlation (ICC). The interobserver variability of GLS was assessed between M.F. and H.N. Receiver operating characteristic analysis was performed to evaluate a cutoff value of baseline GLS associated with all-cause mortality. Survival after TMVr within each group is displayed using Kaplan-Meier curves. Univariable and multivariable Cox regression analyses were performed to evaluate the association between baseline GLS and the instantaneous risk of 1-year all-cause mortality. A series of nested models with the separate addition of GLS to Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score were undertaken. The incremental value of GLS was assessed comparing the model  $\chi^2$  at each step. A two-sided  $P < .05$  was considered statistically significant. All statistical analyses were performed using SPSS version 25 (IBM, Armonk, NY) and GraphPad Prism Version 7.0 (GraphPad Software, San Diego, CA).

## RESULTS

A total of 267 patients received TMVr with edge-to-edge MV clip at our institution during the study period. Study workflow is shown in Figure 1. Reasons for exclusion were (1) TMVr procedure failure ( $n = 19$ ); (2) repeat TMVr procedure ( $n = 24$ ); (3) hypertrophic

**HIGHLIGHTS**

- Mortality in high-risk severe MR patients treated with MitraClip was associated with baseline GLS values.
- Reduced GLS at baseline was associated with 1-year all-cause mortality.
- Results may improve current risk stratification in patients considered for MitraClip therapy.

obstructive cardiomyopathy ( $n = 8$ ); (4) previous mitral surgery ( $n = 6$ ); (5) TTE performed at outside hospital without available images ( $n = 44$ ); and (6) available TTE images but inadequate for GLS analysis ( $n = 11$ ). Among patients who met the clinical criteria for the study, baseline GLS was assessable in 93.4%. The final study cohort included 155 patients (137 [88.4%] had DMR and 18 [11.6%] functional MR [FMR]). The primary endpoint (1-year all-cause death) occurred in 30 patients at a median of 156 days (interquartile range, 37-265 days) from TMVr procedure.

Intraclass correlation was assessed by measuring GLS in all three apical views in 15 random patients (total of 45 measurements). Both intraobserver (ICC = 0.98) and interobserver (ICC = 0.95) reliability for TTE-derived GLS measurements were high, indicating excellent reproducibility of the GLS measurements.

**Baseline Patient Characteristics**

Baseline clinical and imaging characteristics of all patients according to their association with the primary outcome are shown in [Tables 1 and 2](#). The mean age was  $82.6 \pm 6.7$  years, 48% were women, the mean STS-PROM score for repair was  $6.62\% \pm 5.22\%$ , and 88% had DMR. The mean LVEF was  $56.5\% \pm 10.4\%$ , and the mean GLS was  $-16.9\% \pm 3.9\%$ . Patients with the primary outcome had significantly higher prevalence of hypertension, higher STS-PROM score, and lower GLS. There was no significant difference in the mean LVEF and LVESD between patients with the primary outcome and those without. Baseline clinical and imaging characteristics comparing patients with DMR and those with FMR are available in [Supplemental Table 1](#).

**Association of Baseline GLS with Outcome**

A cutoff value of baseline GLS associated with all-cause mortality was identified with a receiver operating characteristic curve analysis. The

area under the curve of preoperative GLS was 0.60 (95% CI, 0.49-0.71) with a best cutoff point of  $-14.5\%$  ([Supplemental Figure 1](#)).

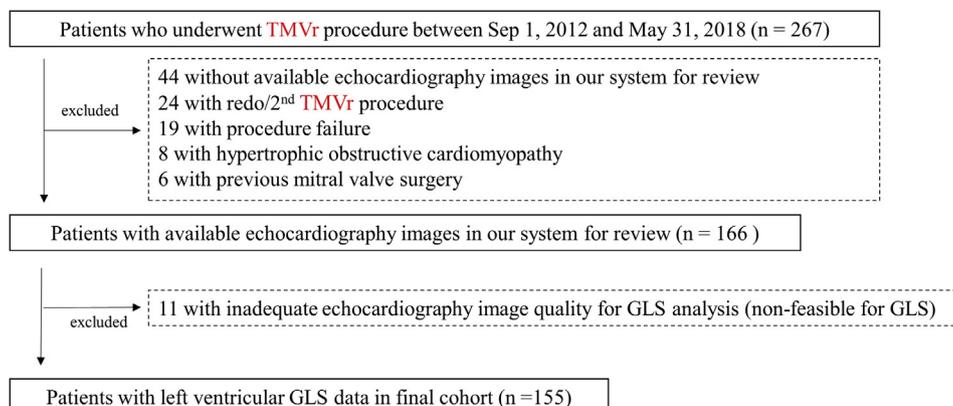
During a median follow-up of 316 days after TMVr with edge-to-edge MV clip (interquartile range, 62-642 days), 1-year all-cause deaths occurred in 30 patients (cumulative event rate 19.4%). Of the 155 patients in this study, 105 (67.7%) had impaired LVEF ( $\leq 60\%$ ) on baseline echocardiography. There was a trend toward higher mortality in patients with impaired LVEF than in those with normal LVEF (21% vs 16%,  $P = .19$ ), which did not reach statistical significance ([Supplemental Figure 2](#)). Patients with  $\text{GLS} > -14.5\%$  had significantly higher 1-year mortality than those with  $\text{GLS} \leq -14.5\%$  ( $\chi^2 = 6.36$ ,  $P = .012$ , [Figure 2](#)). [Figure 3](#) shows the box plot distribution of baseline GLS according to the primary endpoint and the MR etiology.

In the univariable Cox regression analysis, STS-PROM score ( $> 8\%$ ) and  $\text{GLS} > -14.5\%$  were independently associated with all-cause mortality ([Table 3](#)). Five different multivariate models were created with consideration of the possibility of variable overfitting ([Table 4](#)). A  $\text{GLS} > -14.5\%$  remained independently associated with all-cause mortality after adjusting for STS-PROM score, etiology of MR, reduced LVEF, dilatation of LVESD, significant tricuspid regurgitation, atrial fibrillation, and pulmonary artery systolic pressure. [Figure 4A](#) demonstrates the adjusted survival curves after accounting for STS-PROM score and reduced LVEF ( $\leq 60\%$ ). Increased 1-year mortality in those patients with  $\text{GLS} > -14.5\%$  remained unchanged.

This study included six procedure-related deaths within 20 days after TMVr with edge-to-edge MV clip. Even when excluding these six patients, the patients with  $\text{GLS} > -14.5\%$  still had significantly higher 1-year mortality than those with  $\text{GLS} \leq -14.5\%$  ( $\chi^2 = 4.53$ ,  $P = .033$ ), and baseline  $\text{GLS} > -14.5\%$  was independently associated with increased 1-year mortality after adjustment for STS-PROM score ( $> 8\%$ ) and reduced LVEF ( $\leq 60\%$ ; hazard ratio = 2.46; 95% CI, 1.02-5.93;  $P = .045$ ).

**Incremental Prognostic Value of Baseline GLS**

The incremental prognostic value of GLS was assessed using nested Cox proportional hazards models by adding this variable to STS-PROM score and LVEF. While adding reduced LVEF ( $\leq 60\%$ ) to high STS-PROM score ( $> 8\%$ ) did not provide incremental value,  $\text{GLS} > -14.5\%$  exhibited incremental value for the risk of 1-year all-cause mortality with a significant increase in the model  $\chi^2$  value ([Figure 4B](#)).



**Figure 1** Study flowchart. A total of 267 patients with severe MR who underwent TMVr with edge-to-edge MV clip at our institution during the study period. A total of 112 patients were excluded, leaving 155 patients who have GLS data included in the final analysis.

**Table 1** Baseline clinical characteristics

Baseline characteristics	All patients (N = 155)	Patients with endpoint (n = 30)	Patients without endpoint (n = 125)	P value
Age, years	82.6 ± 6.7	83.1 ± 4.9	82.5 ± 7.0	.64
Sex, female	75 (48.4)	10 (33.3)	65 (52.0)	.07
Body mass index, kg/m <sup>2</sup>	26.1 ± 5.2	25.3 ± 4.1	26.3 ± 5.4	.34
Diabetes	33 (21.3)	8 (26.7)	25 (20.0)	.42
Hypertension	118 (76.1)	27 (90.0)	91 (72.8)	.047
Atrial fibrillation	104 (67.1)	16 (53.3)	88 (70.4)	.07
COPD	44 (28.4)	10 (33.3)	34 (27.2)	.50
Coronary artery disease	76 (49.0)	17 (56.7)	59 (47.2)	.35
Previous CABG	37 (23.9)	8 (26.7)	29 (23.2)	.69
Previous MI	20 (12.9)	5 (16.7)	15 (12.0)	.49
Permanent pacemaker	29 (18.7)	5 (16.7)	24 (19.2)	.75
NYHA functional class III or IV	145 (93.5)	30 (100.0)	115 (92.0)	.24
STS-PROM score for repair, %	6.62 ± 5.22	9.22 ± 8.39	5.99 ± 3.91	.048
STS-PROM score for repair >8%	40 (25.8)	12 (40.0)	28 (22.4)	.048

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NYHA, New York Heart Association. Values are shown as n (%), mean ± SD.

## DISCUSSION

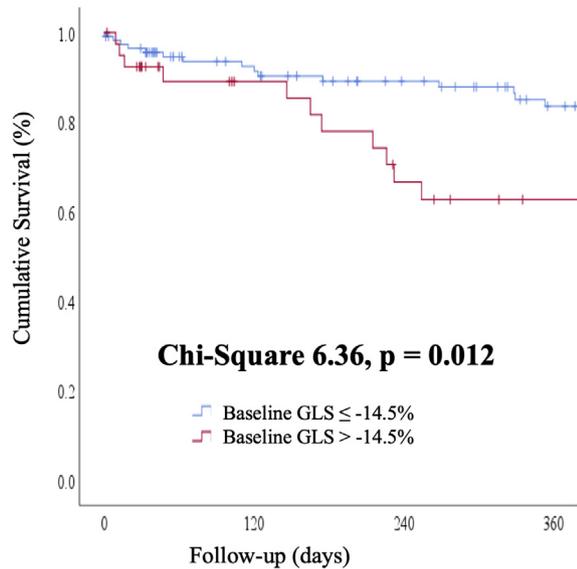
In this study, we evaluated the association of baseline GLS with 1-year all-cause mortality using a cohort of patients with symptomatic severe

MR treated with transcatheter edge-to-edge MV clip. Our study has two key findings. First, patients with baseline GLS > -14.5% had higher all-cause mortality post-TMVR than those with GLS ≤ -14.5%. Second, baseline GLS was independently associated with

**Table 2** Baseline echocardiographic characteristics

Echocardiographic parameter	All patients (N = 155)	Patients with endpoint (n = 30)	Patients without endpoint (n = 125)	P value
Etiology of MR				.11
DMR	137 (88.4)	24 (80.0)	113 (90.4)	
FMR	18 (11.6)	6 (20.0)	12 (9.6)	
Effective regurgitant orifice area, cm <sup>2</sup>	0.47 ± 0.30	0.55 ± 0.37	0.45 ± 0.28	.19
Regurgitant volume, mL	72.2 ± 42.3	78.2 ± 47.7	70.6 ± 40.9	.47
LV end-diastolic diameter, mm	49.2 ± 8.1	50.4 ± 8.4	48.9 ± 8.0	.34
LVESD, mm	33.8 ± 9.4	35.6 ± 10.2	33.4 ± 9.2	.25
LV ejection fraction, %	56.5 ± 10.4	53.0 ± 12.1	57.3 ± 9.7	.08
Left atrium volume index, mL/m <sup>2</sup>	67.8 ± 28.0	60.9 ± 20.6	69.8 ± 29.6	.09
PASP, mm Hg	51.2 ± 15.3	53.9 ± 15.4	50.5 ± 15.3	.33
Moderate to severe tricuspid regurgitation	74 (47.7)	18 (60)	56 (44.8)	.13
Moderate to severe aortic regurgitation	9 (5.8)	2 (6.7)	7 (5.6)	.82
Moderate to severe aortic stenosis	18 (11.6)	3 (10.0)	15 (12.0)	.12
GLS, %	-16.9 ± 3.9	-15.5 ± 4.2	-17.2 ± 3.7	.027

PASP, pulmonary artery systolic pressure. Values are shown as n (%), mean ± SD.



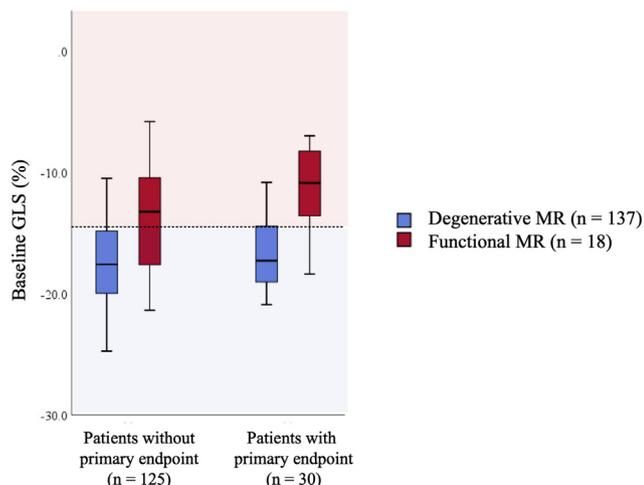
GLS ≤ -14.5%	115	85	71	56
GLS > -14.5	40	24	17	12

**Figure 2** All-cause mortality after TMVr by baseline GLS. Unadjusted Kaplan-Meier survival curve: patients with GLS > -14.5% had higher mortality than those with GLS ≤ -14.5%.

1-year all-cause mortality and exhibited incremental value for the risk of all-cause death over other clinical and echocardiographic characteristics including LVEF. Our study results may have implications for optimal patient selection and risk stratification.

**Role of GLS Evaluation in Patients with MR Undergoing Surgical Intervention**

Although the current indications for MV intervention in severe MR patients mainly rely on the presence of symptoms, reduction of LVEF, and/or dilatation of LVESD,<sup>7,8</sup> these parameters might be insufficient. Mentias *et al.*<sup>18</sup> using a cohort of 733 asymptomatic patients with moderate to severe DMR and preserved LVEF showed that a



**Figure 3** Distribution of baseline GLS according to 1-year outcome and MR etiology.

**Table 3** Univariable Cox regression analysis for all-cause mortality

Parameters	Hazard ratio (95% CI)	P value
<b>Clinical parameters</b>		
Age, years	1.02 (0.97-1.08)	.45
Sex, female	0.51 (0.24-1.09)	.08
Diabetes	1.13 (0.50-2.55)	.77
Hypertension	2.76 (0.84-9.12)	.10
Atrial fibrillation	0.62 (0.30-1.28)	.20
Coronary artery disease	1.38 (0.67-2.86)	.38
eGFR, mL/minute/1.73 m <sup>2</sup>	0.95 (0.93-0.98)	<.01
Frailty	1.58 (0.76-3.29)	.22
NYHA functional class III or IV	0.21 (0.01-3.40)	.27
STS-PROM score for repair >8%	2.12 (1.02-4.41)	.040
FMR	2.35 (0.96-5.79)	.06
<b>Echocardiographic parameters</b>		
Effective regurgitant orifice area, cm <sup>2</sup>	2.69 (0.83-8.75)	.10
Regurgitant volume, mL	1.00 (0.99-1.01)	.42
LVESD ≥ 40 mm	1.73 (0.78-3.81)	.18
LVEF ≤ 60%	1.72 (0.76-3.87)	.19
Left atrium volume index, mL/m <sup>2</sup>	0.99 (0.98-1.01)	.32
PASP, mm Hg	1.01 (0.99-1.04)	.38
Moderate to severe tricuspid regurgitation	1.96 (0.94-4.09)	.07
GLS > -14.5%	2.50 (1.20-5.21)	.015

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure.

preoperative GLS < -21.7% was independently associated with mortality with median follow-up of 8.3 years.

Left ventricular ejection fraction and LVESD can remain preserved until the end stage of MR due to LV hyperkinesis in compensation for volume overload of the left ventricle. Speckle-tracking echocardiography-derived GLS can detect subclinical myocardial dysfunction and provides incremental prognostic value in a variety of clinical settings beyond LVEF.<sup>10,11</sup> Left ventricular ejection fraction describes a relative change of stroke volume, whereas GLS describes the longitudinal deformation and shortening of the myocardium through the cardiac cycle.

For patients undergoing surgical intervention, Kim *et al.*,<sup>12</sup> in a study of 506 patients with severe DMR who underwent surgical repair or replacement, showed that preoperative GLS was associated with all-cause mortality and provided incremental prognostic information beyond conventional risk factors including LVEF. Witkowski *et al.*<sup>19</sup> reported that baseline GLS > -19.9% predicted 1-year postoperative LVEF < 50% in 233 patients with moderate to severe DMR who underwent surgical mitral repair. Of note, patients currently

**Table 4** Multivariable models of risk factors associated with all-cause mortality

Variables	Hazard ratio (95% CI)	P value
<b>Multivariate model 1</b>		
STS-PROM score >8%	2.33 (1.11-4.87)	.025
FMR	1.70 (0.64-4.53)	.29
GLS > -14.5%	2.42 (1.08-5.40)	.031
<b>Multivariate model 2</b>		
STS-PROM score >8%	2.37 (1.13-4.95)	.022
Reduced LVEF ≤60%	1.37 (0.59-3.21)	.47
GLS > -14.5%	2.54 (1.17-5.54)	.019
<b>Multivariate model 3</b>		
STS-PROM score >8%	2.35 (1.12-4.92)	.024
Frailty	1.81 (0.86-3.81)	.12
GLS > -14.5%	3.11 (1.46-6.63)	.003
<b>Multivariate model 4</b>		
STS-PROM score >8%	1.34 (0.58-3.13)	.49
eGFR	0.96 (0.93-0.99)	.007
GLS > -14.5%	2.48 (1.17-5.24)	.018

eGFR, estimated glomerular filtration rate; PASP, pulmonary artery systolic pressure.

undergoing TMVr are older and have higher prevalence of comorbidities and clinical risk than those treated with surgical MV intervention.<sup>3</sup> Therefore, these previous results do not necessarily apply to the patients undergoing TMVr.

**Prognostic Value of GLS in TMVr with Edge-to-Edge MV Clip**

Our study is first to demonstrate that mortality risk associated with impaired GLS appears to be independent of and incremental to other

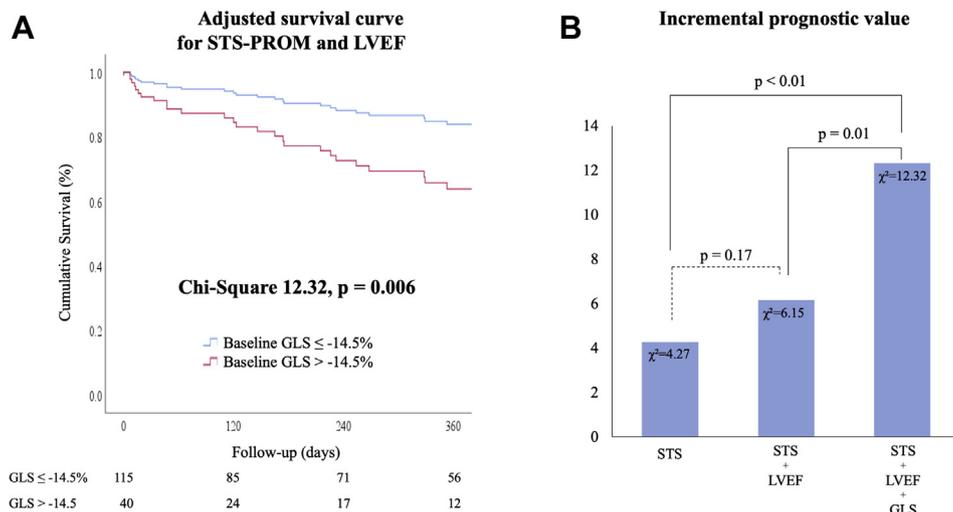
clinical and echocardiographic characteristics especially above STS-PROM score, LVEF, and etiology of MR in a cohort of patients treated with TMVr with edge-to-edge MV clip.

Little data are available on the role of preoperative GLS evaluation for outcomes in patients treated with TMVr using edge-to-edge MV clip. Citro *et al.*<sup>20</sup> using a smaller cohort of 41 symptomatic patients with moderate to severe FMR treated with TMVr showed that baseline GLS ≥ -9.25% was associated with lack of reverse LV remodeling defined as >10% reduction in LV end-systolic volumes at 6 months' follow-up. Given the small number of events, they were not able to establish an independent association with clinical outcomes. We build on their findings by showing, in a cohort of symptomatic severe MR patients treated with transcatheter edge-to-edge MV clip, that baseline GLS was capable of providing independent and incremental risk stratification. The differences in GLS cutoff values between their study and ours could well be due to the differences in the study populations, etiology of MR, and chosen endpoints. While in our studied population, patients had predominantly DMR (88%) with preserved LVEF (56.5% ± 10%), Citro *et al.*<sup>20</sup> included only patients with secondary MR with mean LVEF of 34% ± 5%. Further prospective studies are needed to define the role of baseline GLS assessment in the risk stratification of patients being considered for TMVr.

Global longitudinal strain has emerged as an important tool to quantify the degree of subclinical myocardial dysfunction seen in patients with severe MR but not captured by traditional echocardiographic parameters. Patients currently undergoing TMVr have higher prevalence of comorbidities and clinical risk than those treated with surgical MV intervention.<sup>3</sup> Although identification of abnormal GLS should not preclude performance of transcatheter edge-to-edge MV clip procedure, its baseline assessment provides the opportunity to identify patients who might benefit from a closer follow-up after the intervention.

**Limitations**

First, this was a single-center, retrospective study evaluating predominantly primary DMR patients. We acknowledge that the number of



**Figure 4** Prognostic impact of baseline GLS. **(A)** Adjusted survival curves: the worse mortality in patients with GLS > -14.5% remained unchanged after adjustment for STS-PROM score and reduced LVEF (≤60%). **(B)** While adding reduced LVEF (≤60%) to high STS-PROM score (>8%) did not provide incremental value, GLS > -14.5% exhibited incremental value for the risk of 1-year all-cause mortality above high STS-PROM score and LVEF.

patients with secondary FMR is too small to be evaluated independently and that further larger studies including these patients are needed to confirm and expand our findings. The discriminatory capability of GLS, in isolation, is modest in this cohort with mixed primary and secondary MR, and other comorbidities could be also associated with the outcomes in these patients. However, we showed incremental value of reduced GLS above FMR, STS-PROM score, and frailty on mortality using multivariable Cox regression analysis and nested models. Second, cause of death was not available for all patients, limiting the causal relationship analysis. Third, although we have only analyzed at this time the prognostic role of baseline GLS, it is possible that interval GLS changes might be equally associated with the outcomes. However, the follow-up post-TMVR data on GLS changes and reverse remodeling are not currently available at the time of this analysis. Fourth, longer follow-up was not available at the time of this analysis, limiting the association of baseline GLS with long-term outcomes. Fifth, other important parameters such as brain natriuretic peptides levels and 6-minute walk distance were not consistently assessed in this cohort but are potentially associated with their outcomes. Finally, we acknowledge that we did not perform an external validation of the proposed cutoff value of GLS of  $-14.5\%$ . Our findings would require validation in other groups before the routine implementation of this new parameter.

## CONCLUSION

In patients with symptomatic severe MR treated with TMVR with edge-to-edge MV clip, preprocedure GLS  $> -14.5\%$  was independently associated with 1-year mortality. Assessment of baseline GLS provides independent and incremental prognostic value above multiple clinical and echocardiographic characteristics and improves risk stratification in these patients.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.echo.2020.07.003>.

## REFERENCES

- Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005-11.
- Coffey S, Cairns BJ, Jung B. The modern epidemiology of heart valve disease. *Heart* 2016;102:75-85.
- Niikura H, Gossel M, Kshetry V, Olson S, Sun B, Askew J, et al. Causes and clinical outcomes of patients who are ineligible for transcatheter mitral valve replacement. *JACC Cardiovasc Interv* 2019;12:196-204.
- Goel SS, Bajaj N, Aggarwal B, Gupta S, Poddar KL, Ige M, et al. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol* 2014;63:185-6.
- Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011;364:1395-406.
- Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR Jr, Stebbins A, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT Registry Report. *J Am Coll Cardiol* 2017;70:2315-27.
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739-91.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation* 2014;129:e521-643.
- Hiemstra YL, Tomsic A, van Wijngaarden SE, Palmen M, Klautz RJM, Bax JJ, et al. Prognostic value of global longitudinal strain and etiology after surgery for primary mitral regurgitation. *JACC Cardiovasc Imaging* 2020;13:577-85.
- Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging* 2018;11:260-74.
- Collier P, Phelan D, Klein A. A test in context: myocardial strain measured by speckle-tracking echocardiography. *J Am Coll Cardiol* 2017;69:1043-56.
- Kim HM, Cho G-Y, Hwang I-C, Choi H-M, Park J-B, Yoon YE, et al. Myocardial strain in prediction of outcomes after surgery for severe mitral regurgitation. *JACC Cardiovasc Imaging* 2018;11:1235-44.
- Sorajja P, Mack M, Vemulapalli S, Holmes DR Jr, Stebbins A, Kar S, et al. Initial experience with commercial transcatheter mitral valve repair in the United States. *J Am Coll Cardiol* 2016;67:1129-40.
- Maisano F, Franzen O, Baldus S, Schafer U, Hausleiter J, Butter C, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, non-randomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol* 2013;62:1052-61.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, 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.e14.
- Fukui M, Xu J, Abdelkarim I, Sharbaugh MS, Thoma FW, Althouse AD, et al. Global longitudinal strain assessment by computed tomography in severe aortic stenosis patients: feasibility using feature tracking analysis. *J Cardiovasc Comput Tomogr* 2019;13:157-62.
- Lee CS, Lin TH, Hsu PC, Chu CY, Lee WH, Su HM, et al. Measuring left ventricular peak longitudinal systolic strain from a single beat in atrial fibrillation: validation of the index beat method. *J Am Soc Echocardiogr* 2012;25:945-52.
- Mentias A, Naji P, Gillinov AM, Rodriguez LL, Reed G, Mihaljevic T, et al. Strain echocardiography and functional capacity in asymptomatic primary mitral regurgitation with preserved ejection fraction. *J Am Coll Cardiol* 2016;68:1974-86.
- Witkowski TG, Thomas JD, Debonnaire PJ, Delgado V, Hoke U, Ewe SH, et al. Global longitudinal strain predicts left ventricular dysfunction after mitral valve repair. *Eur Heart J Cardiovasc Imaging* 2013;14:69-76.
- Citro R, Baldi C, Lancellotti P, Silverio A, Provenza G, Bellino M, et al. Global longitudinal strain predicts outcome after MitraClip implantation for secondary mitral regurgitation. *J Cardiovasc Med* 2017;18:669-78.