ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2024) **25**, 1164–1176
https://doi.org/10.1093/ehjci/jeae083

**ORIGINAL PAPER**

# Prognostic value of left ventricular global longitudinal strain in transcatheter edge-to-edge repair for chronic primary mitral regurgitation

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*Received 26 January 2024; revised 28 February 2024; accepted 8 March 2024; online publish-ahead-of-print 26 March 2024*

**Aims** Left ventricular global longitudinal strain (LVGLS) is a known outcome predictor in transcatheter edge-to-edge repair (TEER) for functional mitral regurgitation (MR). We aimed to assess its prognostic yield in the setting of TEER for chronic primary MR.

**Methods and results** We conducted a single-centre, retrospective analysis of 323 consecutive patients undergoing isolated, first-time procedures. Stratified by baseline LVGLS quartiles (≤−19%, −18.9% to −16%, −15.9% to −12%, >−12%), the cohort was evaluated for the primary composite outcome of all-cause mortality or heart failure hospitalizations, as well as secondary endpoints consisting of mitral reinterventions and the persistence of significant residual MR and/or functional disability—all along the first year after intervention. Subjects with worse (i.e. less negative) LVGLS exhibited higher comorbidity, more advanced HF, and elevated procedural risk. Post-TEER, those belonging to the worst LVGLS quartile group sustained increased mortality (16.9% vs. 6.3%, Log-Rank $P = 0.005$, HR 1.75, 95% CI 1.08–4.74, $P = 0.041$) and, when affected by LV dysfunction/dilatation, more primary outcome events (21.1% vs. 11.5%, Log-Rank $P = 0.037$, HR 1.68, 95% CI 1.02–5.46, $P = 0.047$). No association was demonstrated between baseline LVGLS and other endpoints. Upon exploratory analysis, 1-month post-procedural LVGLS directly correlated with and was worse than its baseline counterpart by 1.6%, and a more impaired 1-month value—but not the presence/extent of deterioration—conferred heightened risk for the primary outcome.

**Conclusion** TEER for chronic primary MR is feasible, safe, and efficacious irrespective of baseline LVGLS. Yet, worse baseline LVGLS forecasts a less favourable post-procedural course, presumably reflecting a higher-risk patient profile.

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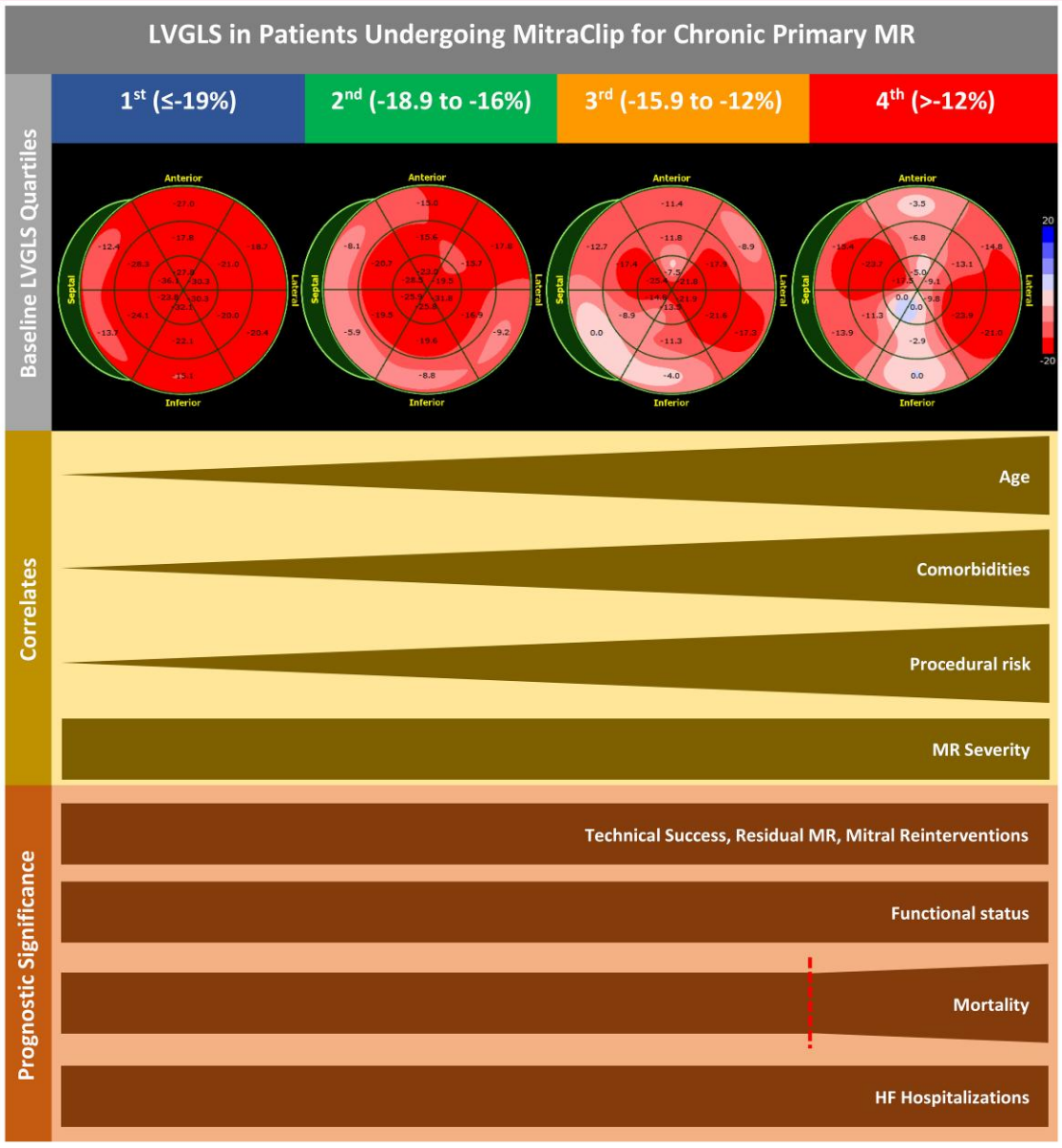
## Graphical Abstract




**Keywords** mitral regurgitation • mitral transcatheter edge-to-edge repair • transcatheter mitral valve repair • MitraClip • global longitudinal strain

# Introduction

Transcatheter edge-to-edge repair (TEER) has revolutionized the treatment of significant mitral regurgitation (MR) accompanied by symptoms or cardiac deterioration, enabling individuals at high surgical risk to benefit from a direct corrective intervention. Paralleling this therapeutic breakthrough, myocardial strain imaging has been introduced that holds the potential to enhance risk stratification by facilitating a more sensitive, reproducible assessment of myocardial function.[1] While extensively validated in the setting of functional MR,[2–4] the prognostic utility of two-dimensional (2D) left ventricular global longitudinal strain (LVGLS) is less well established in patients undergoing TEER for primary MR (PMR).[5] To address this knowledge gap, relevant to a constantly growing number of individuals worldwide, we examined the post-mitral TEER trajectory of a large, contemporary sample as a function of baseline LVGLS. Furthermore, we evaluated the change in LVGLS from baseline to 1 month following the procedure and assessed its relation to the post-interventional course as well.

# Methods

## Study population and outcomes

Our study represents a retrospective analysis of the Cedars-Sinai registry of consecutive mitral TEER procedures performed between 1 January 2013

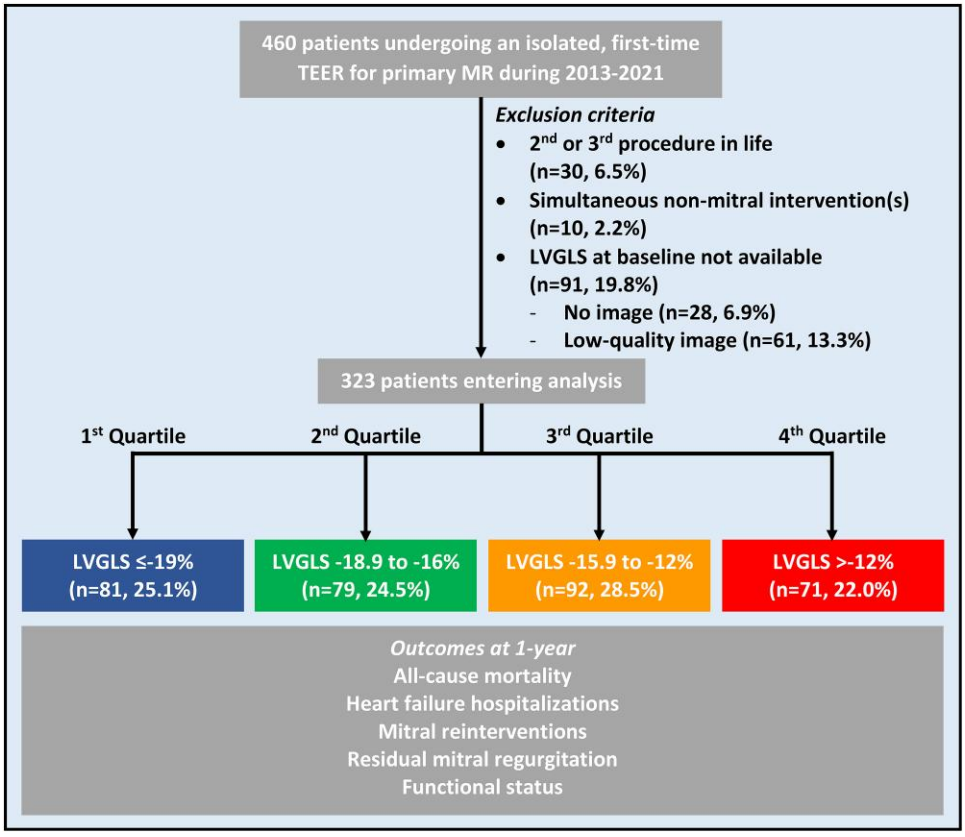



**Figure 1** Study flow chart. IQR, interquartile range; LVGLS, left ventricular global longitudinal strain; MR, mitral regurgitation; TEER, transcatheter edge-to-edge repair.

and 1 January 2021 on adult patients for moderate-to-severe or greater MR leading to symptoms or myocardial remodelling. All interventions were decided upon by a dedicated Heart Team and after weighing patient preferences and best scientific evidence at the time.

Inclusion criteria for the study consisted of: (i) a diagnosis of chronic PMR, defined by abnormal valve morphology on the intraprocedural transoesophageal echocardiogram (TEE); (ii) the performance of an isolated, first-ever procedure; and (iii) availability of pre-procedural transthoracic echocardiographic (TTE) images of sufficient quality for LVGLS measurements.

The primary outcome was the composite of all-cause mortality or heart failure (HF) hospitalizations during the first post-procedural year. Secondary outcomes consisted of individual elements of the primary outcome, as well as mitral reinterventions and the persistence of significant (i.e. moderate-to-severe or greater) residual MR and/or functional disability [i.e. New York Heart Association (NYHA) class III–IV].

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

## Procedural aspects

All procedures employed the MitraClip™ system (Abbott Vascular Inc., Santa Clara, CA); were performed under general anaesthesia; and utilized a trans-septal approach and a femoral venous access. TEE, fluoroscopy, and right heart catheterization served for guidance and monitoring. Technical success was defined by actual device deployment not followed by surgical intervention or major complications within the first 24 h.[6]

## Echocardiographic assessment

Echocardiograms were performed by experienced sonographers and level III-trained echocardiologists and interpreted by two study members (A.S. and G.J.H.) blinded to patient history, all in accordance with societal guidelines.[7–9] The ultrasound system used was EPIQ (Philips, Andover, MA). Post-test processing utilized PICOM365 (Scilmage, Los Altos, CA), QLAB 12.0 (Philips, Andover, MA), and TomTec Arena (TomTec Imaging Systems, Unterschleissheim, Germany) for 2D, three-dimensional (3D), and speckle-tracking measurements, respectively.

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). Left ventricular ejection fraction (LVEF) and left heart chambers volumes were calculated using the Simpson's biplane method of disks. Right ventricular (RV) function was evaluated qualitatively using an eyeball assessment of global contraction in the standard (mainly RV focused) views and by virtue of the tricuspid annular plane systolic excursion (TAPSE) and TAPSE to pulmonary arterial systolic pressure ratio. LVGLS was calculated semi-automatically at peak systole by averaging software-generated endocardial strain measurements in the two-, three-, and four-chamber apical windows. For this purpose, 50.0 [interquartile range (IQR), 47.3–52.5] Hz frame-rate images were analysed, one for each view, with manual adjustments of the cardiac cycle and left ventricular (LV) endocardial borders as needed. Analysed images underwent an initial quality check by the software algorithm and were ultimately selected if containing <2 segments with poorly-defined endocardial borders per reader's judgement.

Intraprocedural pulmonary venous flow pattern improvement and normalization required any rise or the emergence of a value of ≥1, respectively, in the peak systolic/diastolic velocity ratio on any pulmonary vein.

**Table 1 Baseline clinical characteristics**

| | Total cohort ($n = 323$) | 1st quartile LVGLS ≤ −19% ($n = 81$) | 2nd quartile LVGLS −18.9 to −16% ($n = 79$) | 3rd quartile LVGLS −15.9 to −12% ($n = 92$) | 4th quartile LVGLS > −12% ($n = 71$) | Pooled *P*-value |
|---|---|---|---|---|---|---|
| *Demographic details* | | | | | | |
| Age | | | | | | |
| Median (years) | 83 (76–88) | 83 (73–87) | 82 (74–87) | 86 (79–89) | 84 (78–89) | 0.059 |
| ≥75 years | 255 (78.9) | 55 (67.9) | 59 (74.7) | 80 (87.0)[a] | 61 (85.9) | **0.006** |
| Sex male | 201 (62.2) | 48 (59.3) | 41 (51.9) | 63 (68.5) | 49 (69.0) | 0.078 |
| Non-White race | 39 (12.1) | 12 (14.8) | 7 (8.9) | 14 (15.2) | 6 (8.5) | 0.380 |
| *Comorbidities* | | | | | | |
| Body surface area, Mosteller formula ($m^2$) | 1.8 (1.6–2.0) | 1.8 (1.6–1.9) | 1.7 (1.5–2.0)[b,c] | 1.8 (1.7–2.1)[a] | 1.9 (1.7–2.1)[a] | **0.004** |
| Diabetes mellitus | 55 (17.2) | 5 (5.2) | 13 (16.5) | 19 (20.9)[a] | 18 (26.1)[a] | **0.009** |
| Hypertension | 261 (81.1) | 57 (70.4) | 64 (81.0) | 80 (87.9)[a] | 60 (84.5) | **0.025** |
| Chronic obstructive pulmonary disease | 43 (13.3) | 13 (16.0) | 11 (13.9) | 11 (12.0) | 8 (11.3) | 0.812 |
| Anaemia | 181 (56.0) | 44 (54.3) | 49 (62.0) | 52 (56.5) | 36 (50.7) | 0.557 |
| Stage ≥ III chronic kidney disease | 242 (75.9) | 59 (72.8) | 65 (82.3) | 72 (79.1) | 46 (67.6) | 0.157 |
| Previous myocardial infarction, PCI, or CABG | 94 (29.1) | 16 (19.8) | 21 (26.6) | 30 (32.6) | 27 (38.0) | 0.073 |
| Prior stroke or transient ischaemic attack | 38 (11.8) | 11 (13.6) | 7 (8.9) | 13 (14.1) | 7 (9.9) | 0.650 |
| Peripheral arterial disease | 28 (8.7) | 6 (7.5) | 7 (8.9) | 8 (8.7) | 7 (9.9) | 0.966 |
| Atrial fibrillation/flutter | 174 (53.9) | 27 (33.3)[b] | 39 (49.4)[a,b] | 53 (57.6)[a,b] | 55 (77.5)[a] | **<0.001** |
| *Heart failure features* | | | | | | |
| New York Heart Association class | | | | | | 0.320 |
| II | 25 (7.7) | 6 (7.4) | 6 (7.6) | 9 (9.8) | 4 (5.6) | |
| III | 130 (40.2) | 24 (29.6) | 36 (45.6) | 37 (40.2) | 33 (46.5) | |
| IV | 168 (52.0) | 51 (63.0) | 37 (46.8) | 46 (50.0) | 34 (47.9) | |
| KCCQ12 score (points) | 41.67 (20.83–65.50) | 61.72 (29.17–72.27) | 39.58 (20.83–63.54) | 41.93 (22.40–60.29)[a] | 32.29 (16.67–58.85)[a] | **0.012** |
| 6-Min walk test distance (m) | 244 (151–335) | 266 (173–414) | 274 (151–335) | 213 (171–304) | 213 (122–335) | 0.182 |
| Serum B-type natriuretic peptide level (pg/mL) | 321 (163–641) | 229 (136–459) | 341 (146–685)[b] | 317 (195–636)[a,b] | 459 (278–847)[a] | **<0.001** |
| *Procedural risk* | | | | | | |
| Society of Thoracic Surgeons score for mitral valve repair (points) | 5.0 (2.8–8.1) | 4.2 (2.5–6.2) | 4.9 (2.6–9.3) | 6.4 (3.1–9.6)[a] | 5.7 (3.0–8.3)[a] | **0.026** |
| Mitral Regurgitation International Database score (points) | 9 (7–10) | 8 (7–9) | 8 (7–9)[b] | 9 (8–10)[a,b] | 10 (9–11)[a] | **<0.001** |
| MitraScore (points) | 3 (2–4) | 3 (2–4) | 3 (2–4) | 3 (3–4) | 3 (2–4) | 0.102 |
| *Treatment* | | | | | | |
| Medications | | | | | | |
| Beta blockers | 147 (45.5) | 46 (56.8) | 38 (48.1)[b] | 59 (64.1) | 54 (76.1) | **0.004** |

*Continued*

**Table 1 Continued**

| | Total cohort ($n = 323$) | 1st quartile LVGLS ≤ −19% ($n = 81$) | 2nd quartile LVGLS −18.9 to −16% ($n = 79$) | 3rd quartile LVGLS −15.9 to −12% ($n = 92$) | 4th quartile LVGLS > −12% ($n = 71$) | Pooled *P*-value |
|---|---|---|---|---|---|---|
| Renin angiotensin system inhibitors | 147 (45.5) | 38 (46.9) | 33 (41.8) | 40 (43.5) | 36 (50.7) | 0.697 |
| Mineralocorticoid receptor antagonists | 31 (9.6) | 7 (8.6) | 5 (6.3) | 7 (7.6) | 12 (16.9) | 0.120 |
| Loop diuretics | 219 (67.8) | 52 (64.2) | 47 (59.5) | 66 (71.7) | 54 (76.1) | 0.119 |
| Cardiac implantable electronic device | | | | | | |
| Total | 53 (16.4) | 4 (4.9)[b] | 8 (10.1)[b] | 20 (21.7)[a] | 21 (29.6)[a] | **<0.001** |
| Pacemaker | 37 (11.5) | 3 (3.7) | 5 (6.3) | 16 (17.4)[a] | 13 (18.3)[a] | **0.004** |
| Implantable cardioverter defibrillator | 3 (0.9) | 0 (0.0) | 0 (0.0) | 2 (2.2) | 1 (1.4) | 0.358 |
| Cardiac resynchronization therapy | 4 (1.2) | 0 (0.0) | 1 (1.3) | 1 (1.1) | 2 (2.8) | 0.479 |
| Cardiac resynchronization therapy-defibrillator | 9 (2.8) | 1 (1.2) | 2 (2.5) | 1 (1.1) | 5 (7.0) | 0.091 |
| Haemodialysis | 7 (2.2) | 0 (0.0) | 5 (6.3) | 1 (1.1) | 1 (1.4) | 0.903 |

Data are presented as number (percentage) or median (interquartile range). Figures in bold denote statistical significance.
CABG, coronary artery bypass grafting; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVGLS, left ventricular global longitudinal strain; PCI, percutaneous coronary intervention.
[a]$P < 0.05$ vs. LVGLS ≤ −19%.
[b]$P < 0.05$ vs. LVGLS > −12%.
[c]$P < 0.05$ vs. LVGLS −15.9 to −12%.

## Data collection

Per institutional protocol, patients were assessed at baseline, hospital discharge, and 1-month and 1-year post-procedure. Data were retrospectively extracted from an electronic medical chart, which was updated in real-time by regional medical providers and state authorities.

## Statistical analysis

The study cohort was first analysed in its entirety. Additional, exploratory survival analyses concerning the primary outcome were undertaken based on the presence of pre-procedural LV dysfunction or dilatation [i.e. LVEF of ≤60% or LV end-systolic diameter (LVESD) of ≥4.0 cm] and in a subgroup of patients with measurable 1-month LVGLS.

At all stages, variables were reported as frequencies and percentages or medians and IQR, and compared using the Pearson's $\chi^2$, Fisher's exact, or Kruskal–Wallis tests, with the Bonferroni correction to control for type 1 errors. Temporal changes in the same parameters were assessed by the McNemar or Wilcoxon signed rank tests. Selected continuous variables were tested for correlation using the Pearson's *r* coefficient. Intra- and inter-observer reliability in LVGLS assessment were ascertained by the intraclass correlation coefficient, which proved high (>0.80, $P < 0.001$).

The evolving probabilities of experiencing clinical events as a function of LVGLS at baseline and at 1 month were illustrated using the Kaplan–Meier method, whereas cumulative events' incidences were compared by the Log-Rank test. Associations between LVGLS and outcomes were examined by multivariable analyses that incorporated parameters of perceived or previously proven[10] prognostic significance that also demonstrated a *P*-value of <0.1 on univariable analyses. Within the various models, continuous variables—LVGLS included—were assessed both as such and as dichotomous, using the cohort's quartiles/medians and/or accepted thresholds for intervention.[11,12] Either Cox or binary logistic regression methods were employed, as appropriate. Lastly, and in light of the absolute number of observations, additional conservative analyses were undertaken that included only the MitraScore and LVGLS.

Cases with missing values were censored from the relevant calculations. A two-sided *P*-value of <0.05 defined statistical significance. All analyses were performed using SPSS 24 (IBM Corporation, Armonk, NY).

# Results

## Baseline characteristics of the study population

Three hundred and twenty-three patients met inclusion criteria and were followed for 460 (IQR, 129–1021) days (*Figure 1*). Baseline TTE, performed 26 (IQR, 8–51) days prior to TEER, demonstrated rounded LVGLS quartile ranges as follows: 1st quartile ($n = 81$, 25.1%), −19% and below; 2nd quartile ($n = 79$, 24.5%), −18.9 to −16%; 3rd quartile ($n = 92$, 28.5%), −15.9 to −12%; and 4th and worst quartile ($n = 71$, 22.0%), above −12%.

Overall, the study cohort was elderly with a median age of 83 (IQR, 76–88) years and predominately male ($n = 201$, 62.2%) (*Table 1*). Major variations in pre-procedural clinical characteristics were apparent across the four LVGLS groups, translating to a higher age, a greater burden of comorbidities, more advanced HF indices, and an increased interventional risk within the worse (i.e. less negative) ones. Likewise, the use of cardiac implantable electronic devices rose as the LVGLS was more impaired.

**Table 2** **Baseline echocardiographic data**

| | Total cohort ($n = 323$) | 1st quartile LVGLS ≤ −19% ($n = 81$) | 2nd quartile LVGLS −18.9 to −16% ($n = 79$) | 3rd quartile LVGLS −15.9 to −12% ($n = 92$) | 4th quartile LVGLS > −12% ($n = 71$) | Pooled *P*-value |
|---|---|---|---|---|---|---|
| Exam time prior to procedure (days) | 26 (8–51) | 27 (11–50) | 24 (6–54) | 30 (9–55) | 23 (8–50) | 0.493 |
| *Mitral valve parameters* | | | | | | |
| Severe mitral regurgitation | 279 (86.9) | 74 (92.5) | 69 (87.3) | 77 (84.6) | 59 (83.1) | 0.316 |
| Effective regurgitant orifice area by PISA | | | | | | |
| Median ($cm^2$) | 0.40 (0.29–0.53) | 0.47 (0.35–0.62) | 0.44 (0.30–0.61)[a] | 0.39 (0.27–0.47)[b] | 0.37 (0.26–0.50)[b] | **0.001** |
| ≥0.40 $cm^2$ | 148 (53.0) | 46 (67.5) | 42 (56.8) | 33 (43.4)[b] | 27 (44.3)[b] | **0.012** |
| Regurgitant volume by PISA (mL) | 55.8 (42.8–77.3) | 70.4 (51.0–91.7) | 57.8 (44.4–82.6)[a] | 52.8 (39.7–74.8)[b] | 47.7 (35.6–63.3)[b] | **<0.001** |
| Transmitral mean pressure gradient | | | | | | |
| Median (mmHg) | 3 (2–4) | 3 (2–4) | 3 (2–4) | 3 (2–4) | 3 (2–4) | 0.894 |
| ≥5 mmHg | 53 (16.5) | 14 (17.7) | 12 (15.2) | 18 (19.6) | 9 (12.7) | 0.668 |
| Mitral valve prolapse/flail | | | | | | |
| Any | 311 (96.3) | 80 (98.8) | 76 (96.2) | 89 (96.7) | 66 (93.0) | 0.302 |
| Bileaflet prolapse | 48 (14.9) | 11 (13.6) | 13 (16.5) | 13 (14.1) | 11 (15.5) | 0.955 |
| Flail | 191 (59.1) | 49 (60.5) | 49 (62.0) | 58 (63.0) | 35 (49.3) | 0.138 |
| Mitral annular calcification | | | | | | |
| Any | 105 (32.5) | 21 (25.9) | 29 (36.7) | 35 (38.0) | 20 (28.2) | 0.248 |
| Moderate and above | 48 (14.9) | 9 (11.1) | 13 (16.5) | 17 (18.5) | 9 (12.7) | 0.517 |
| Rheumatic changes | 1 (0.3) | 1 (1.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.392 |
| *Left heart parameters* | | | | | | |
| Left ventricular ejection fraction | | | | | | |
| Median (%) | 63 (55–68) | 65 (60–71) | 65 (61–70)[a,c] | 59 (54–66)[a,b] | 51 (38–64)[b] | **<0.001** |
| ≤60% | 143 (44.3) | 23 (28.4) | 19 (24.1) | 54 (58.7)[b] | 47 (66.2)[b] | **<0.001** |
| <50% | 45 (13.9) | 0 (0.0) | 1 (1.3) | 11 (12.0)[a,b] | 33 (46.5)[b] | **<0.001** |
| Left ventricular end-diastolic diameter (cm) | 5.0 (4.5–5.5) | 5.0 (4.7–5.5) | 4.9 (4.4–5.3) | 5.0 (4.5–5.5) | 5.1 (4.4–5.8) | 0.501 |
| Left ventricular end-systolic diameter (cm) | | | | | | |
| Median (cm) | 3.2 (2.8–3.8) | 3.1 (2.8–3.5) | 3.1 (2.5–3.5)[a,c] | 3.3 (2.9–3.9)[b] | 3.5 (2.9–4.4)[b] | **<0.001** |
| ≥4.0 cm | 61 (18.9) | 6 (7.4) | 7 (8.9)[b] | 22 (23.9)[b] | 26 (36.6)[b] | **<0.001** |
| Left ventricular ejection fraction ≤60% or left ventricular end-systolic diameter ≥4.0 cm | 153 (47.4) | 26 (32.1) | 20 (25.3)[a] | 59 (64.1)[b] | 48 (67.6)[b] | **<0.001** |
| Left ventricular mass index, ASE formula ($g/m^2$) | 118.4 (93.2–141.3) | 113.5 (91.0–135.9) | 114.9 (90.5–135.7) | 126.9 (96.6–144.2) | 119.8 (96.3–149.4) | 0.100 |
| Left atrial volume index | | | | | | |
| Median ($mL/m^2$) | 60.0 (44.2–75.5) | 56.0 (43.0–72.5) | 58.0 (39.8–73.0) | 58.0 (44.9–73.2) | 68.4 (54.0–84.5) | 0.059 |
| ≥60 $mL/m^2$ | 153 (49.4) | 32 (41.0) | 35 (46.1) | 40 (46.0) | 46 (66.7)[b] | **0.011** |

*Continued*

**Table 2 Continued**

| | Total cohort ($n = 323$) | 1st quartile LVGLS ≤ −19% ($n = 81$) | 2nd quartile LVGLS −18.9 to −16% ($n = 79$) | 3rd quartile LVGLS −15.9 to −12% ($n = 92$) | 4th quartile LVGLS > −12% ($n = 71$) | Pooled *P*-value |
|---|---|---|---|---|---|---|
| Moderate and above aortic stenosis/regurgitation | 32 (9.9) | 7 (8.6) | 12 (15.2) | 8 (8.7) | 5 (7.0) | 0.331 |
| *Right heart parameters* | | | | | | |
| Qualitative global right ventricular dysfunction | 72 (24.6) | 9 (12.5)[a] | 15 (20.5)[a] | 19 (22.9)[a] | 29 (44.6) | **<0.001** |
| Right ventricular end-diastolic basal diameter (cm) | | | | | | |
| Median (cm) | 3.9 (3.5–4.4) | 3.8 (3.4–4.3) | 4.1 (3.5–4.6) | 3.9 (3.3–4.4) | 4.0 (3.6–4.4) | 0.058 |
| ≥4.2 cm | 108 (34.1) | 22 (27.5) | 32 (40.5) | 29 (33.0) | 25 (35.7) | 0.372 |
| Moderate-to-severe and above tricuspid regurgitation | 51 (15.8) | 12 (14.8) | 18 (22.8) | 10 (10.9) | 11 (15.5) | 0.200 |
| Tricuspid annular plane systolic excursion (TAPSE) | | | | | | |
| Median (mm) | 18 (15–22) | 21 (18–26) | 19 (16–22)[a,b] | 17 (15–21)[a,b] | 16 (12–18)[b] | **<0.001** |
| <17 mm | 81 (36.0) | 10 (17.5) | 18 (31.0) | 28 (42.4)[b] | 25 (56.8)[b] | **<0.001** |
| Pulmonary arterial systolic pressure (PASP) | | | | | | |
| Median (mmHg) | 43 (33–57) | 40 (31–55) | 48 (35–62) | 43 (33–58) | 45 (32–56) | 0.402 |
| >50 mmHg | 127 (39.3) | 33 (40.7) | 35 (44.3) | 33 (35.9) | 26 (36.6) | 0.667 |
| TAPSE/PASP (mm/mmHg) | 0.41 (0.30–0.60) | 0.51 (0.37–0.80) | 0.41 (0.29–0.58)[a,b] | 0.44 (0.30–0.60)[a,b] | 0.34 (0.23–0.44)[b] | **0.001** |
| *Speckle tracking* | | | | | | |
| Global longitudinal strain (%) | −15.9 (−19.0 to −12.4) | −20.8 (−22.4 to −20.0) | −17.5 (−18.5 to −16.9)[a,b,c] | −14.1 (−15.0 to −12.9)[a,b] | −10.2 (−11.2 to −8.6)[b] | **<0.001** |

Data are presented as number (percentage) or median (interquartile range). Figures in bold denote statistical significance.
ASE, American Society of Echocardiography; LVGLS, left ventricular global longitudinal strain; PISA, proximal isovelocity surface area.
[a]$P < 0.05$ vs. LVGLS > −12%.
[b]$P < 0.05$ vs. LVGLS ≤ −19%.
[c]$P < 0.05$ vs. LVGLS −15.9 to −12%.

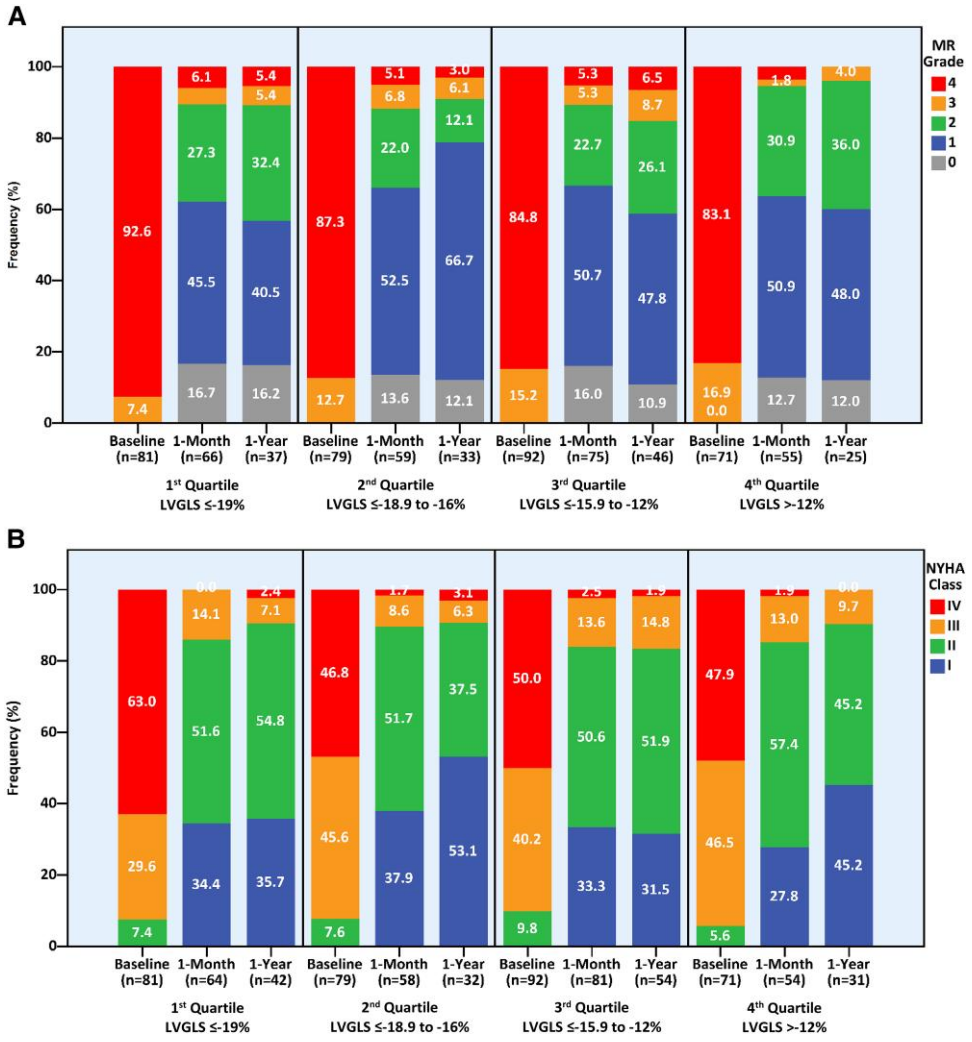



**Figure 2** Mitral regurgitation grade and functional status at baseline and during the first post-procedural year. (*A*) Mitral regurgitation grade, (*B*) functional status. LVGLS, left ventricular global longitudinal strain; MR, mitral regurgitation; NYHA, New York Heart Association.

Regarding echocardiographic parameters, most patients ($n = 279$, 86.9%) presented to TEER with severe MR due to prolapse/flail, the proportion of which was comparable in the various study groups (*Table 2*). Biventricular function and left heart dimensions were generally more abnormal among subjects with worse LVGLS.

## Procedural details and post-procedural results

All patients underwent similarly successful procedures and exhibited a comparable periprocedural course irrespective of LVGLS allocation (see Supplementary data online, *Table S1*). Yet, a significant drop in invasively measured mean pulmonary arterial pressure was only observed in those of the 1st (i.e. most negative) LVGLS quartile group.

Resembling the immediate post-procedural phase, the 1-month and 1-year follow-up appointments revealed similarly significant improvement from baseline in MR severity and NYHA functional class across all LVGLS groups (see Supplementary data online, *Tables S2* and *S3* and *Figure 2*). Concurrently, 1-month left heart function and dimensions remained more deranged among patients with worse LVGLS.

## Primary outcome

By 1-year post-procedure, 44 (13.6%) patients sustained the primary outcome, a composite of all-cause deaths ($n = 28$. 8.7%) or HF hospitalizations ($n = 24$, 7.4%) (see Supplementary data online, *Table S3*). Subjects within the worst (i.e. above −12%) LVGLS group also suffered the highest cumulative incidence of this composite event (*Figure 3*), and the worst LVGLS quartile range conferred a higher risk for it (HR 1.68, 95% CI 1.02–5.46, $P = 0.047$) (*Table 3* and Supplementary data online, *Table S4*).

Upon an exploratory subgroup analysis, a significant association between an extremely impaired (i.e. less negative than −12%) LVGLS at baseline and the primary outcome was only evident in patients exhibiting abnormal LVEF or LVESD prior to the procedure ($n = 153$, 47.3%) (Log-Rank $P = 0.015$, HR 1.18, 95% CI 1.01–1.37, $P = 0.032$) (*Figure 3* and Supplementary data online, *Table S5*). Further, patients with both conditions ($n = 48$, 14.9%) experienced a higher cumulative incidence of the primary outcome compared with those with either or none (see Supplementary data online, *Figure S1*). This is in spite of abnormal LVEF/LVESD not demonstrating any association with the primary outcome by itself.

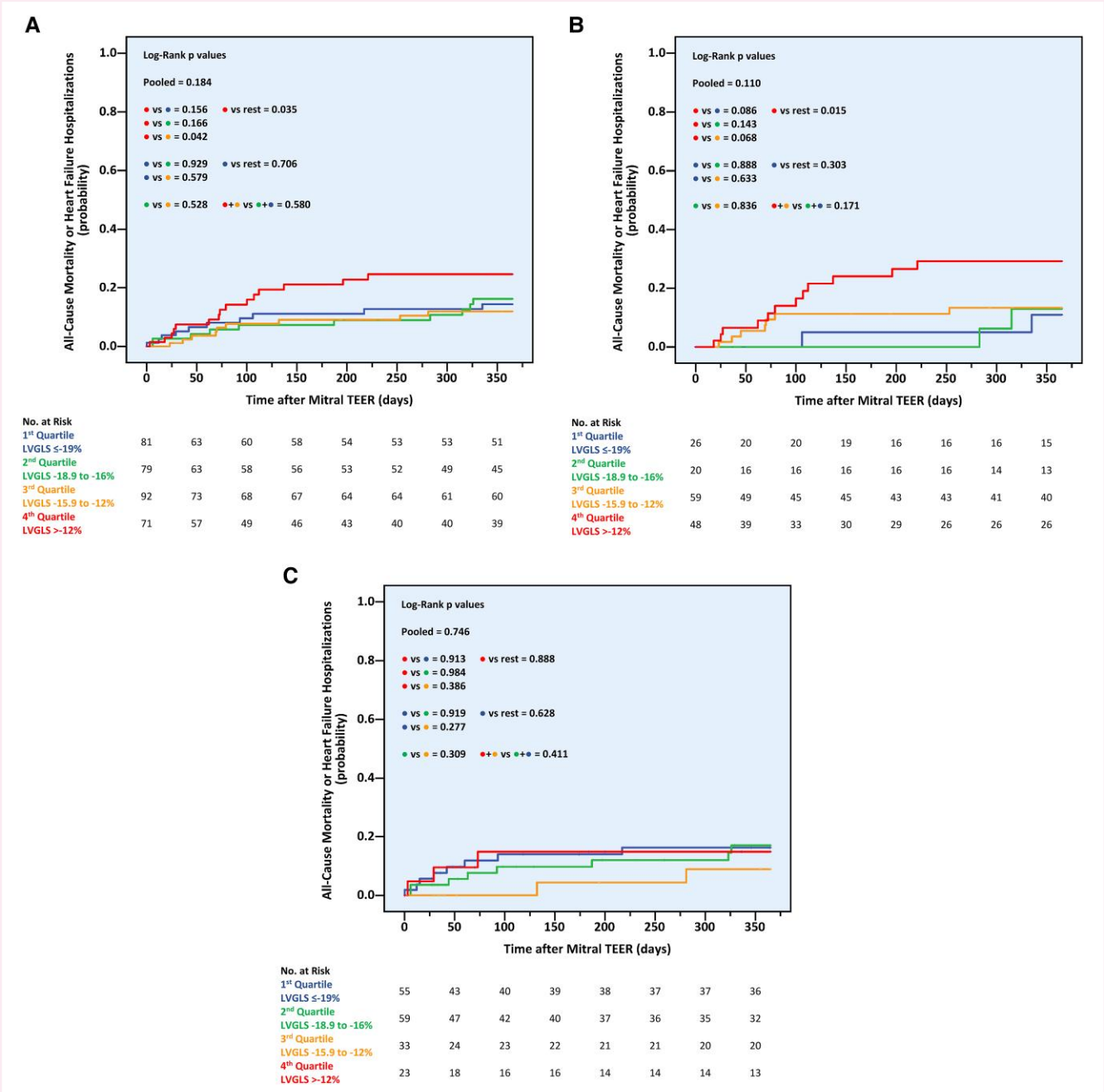



**Figure 3** One-year cumulative incidence of the primary outcome (*A*) total cohort, (*B*) patients with left ventricular dysfunction or dilatation, (*C*) patients without left ventricular dysfunction or dilatation. LVGLS, left ventricular global longitudinal strain; TEER, transcatheter edge-to-edge repair.

## Secondary outcomes

Overall mortality was observed more frequently and at an earlier stage following TEER within the worst LVGLS quartile group (see Supplementary data online, *Table S3* and *Figure 4*). In contrast, mitral reinterventions, reported in a total of 24 (7.4%) cases, tended to be performed at a more distant timeframe among patients harbouring the worst vs. best (i.e. −19% or lower) LVGLS (274 ± 141 vs. 251 ± 149 days, Log-Rank $P = 0.055$). No differences were noted in the rates or cumulative incidences of other outcomes across the LVGLS quartiles and median groups. Accordingly, freedom from significant residual MR and/or functional incapacitation was observed in a great majority of patients remaining alive and in active surveillance at Cedars-Sinai regardless of pre-procedural LVGLS, reaching 77.0% ($n = 104/135$) and 88.1% ($n = 141/159$) in the total cohort, respectively.

As for outcomes' risks, only that of mortality was associated with baseline LVGLS, being higher in patients with the worst quartile values (HR 1.75, 95% CI 1.08–4.74, $P = 0.041$) (*Table 3* and Supplementary data online, *Tables S6–S8*).

## One-month LVGLS

Of the 144 (45.3%) patients with analysable echocardiograms at 1-month post-procedure, 92 (63.9%) experienced a net worsening

**Table 3 Risk for one-year outcomes**

| | Risk associated with less negative LVGLS | | Risk associated with LVGLS > −19% | | Risk associated with LVGLS > −16% | | Risk associated with LVGLS > −12% | |
|---|---|---|---|---|---|---|---|---|
| | HR/OR (95% CI)[a] | *P*-value | HR/OR (95% CI)[a] | *P*-value | HR/OR (95% CI)[a] | *P*-value | HR/OR (95% CI)[a] | *P*-value |
| *Primary outcome* | | | | | | | | |
| All-cause mortality or heart failure hospitalizations | 1.09 (0.94–1.28)[b] | 0.248 | 1.15 (0.57–2.32) | 0.707 | 1.18 (0.65–2.14) | 0.581 | 1.68 (1.02–5.46)[b] | **0.047** |
| *Secondary outcomes* | | | | | | | | |
| All-cause mortality | 1.03 (0.91–1.17)[b] | 0.667 | 1.11 (0.30–4.16[b] | 0.877 | 1.30 (0.61–2.74) | 0.495 | 1.75 (1.08–4.74)[b] | **0.041** |
| Heart failure hospitalizations | 1.02 (0.91–1.14)[b] | 0.740 | 1.32 (0.57–3.04) | 0.514 | 1.57 (0.71–3.47) | 0.261 | 1.65 (0.72–3.79) | 0.239 |
| Mitral reinterventions | 0.95 (0.83–1.08)[b] | 0.416 | 0.54 (0.24–1.24) | 0.146 | 0.88 (0.30–2.58)[b] | 0.820 | 0.32 (0.08–1.37) | 0.125 |
| All-cause mortality, heart failure hospitalizations, or mitral reinterventions | 1.03 (0.97–1.09) | 0.397 | 0.93 (0.53–1.64) | 0.802 | 0.89 (0.54–1.47) | 0.649 | 1.38 (0.79–2.40) | 0.263 |
| Significant residual mitral regurgitation | 1.01 (0.89–1.15)[c] | 0.890 | 0.98 (0.29–3.28) | 0.968 | 1.14 (0.39–3.34) | 0.807 | 0.30 (0.04–2.42) | 0.261 |
| Functional disability | 1.06 (0.94–1.19)[d] | 0.346 | 1.40 (0.44–4.48) | 0.573 | 1.57 (0.59–4.23) | 0.369 | 0.75 (0.20–2.75) | 0.665 |
| Significant residual mitral regurgitation or functional disability | 1.07 (0.97–1.18) | 0.204 | 1.69 (0.63–4.53) | 0.298 | 1.71 (0.75–3.88) | 0.199 | 0.66 (0.21–2.12) | 0.488 |

CI, confidence interval; HR, hazard ratio; LVGLS, left ventricular global longitudinal strain; OR, odds ratio. Figures in bold denote statistical significance.
[a]Per univariable analysis unless specified otherwise.
[b]Per multivariable analysis.
[c]Moderate-to-severe and above mitral regurgitation.
[d]New York Heart Association class III or IV.

(i.e. increase) in the LVGLS compared with baseline, by an absolute 1.6 (IQR, −0.8–3.9) % and a relative 8.9 (IQR, −5.5–25.2) % (see Supplementary data online, *Table S3*). While the 1-month value directly correlated with its baseline counterpart, the difference between the two inversely correlated with the pre-procedural one (Pearson's $r =$ 0.54 and −0.61, respectively, all $P < 0.001$). Consequently, patients with less negative baseline LVGLS exhibited similarly less negative 1-month LVGLS, but at the same time numerically fewer patients within the worse baseline LVGLS quartile groups experienced worsening in the LVGLS at 1 month.

According to exploratory survival analysis, 1-month LVGLS less negative than the subgroup's rounded median of −15% was associated with higher cumulative incidence and risk of the primary outcome (unadjusted HR 6.07, 95% CI 1.37–8.66, $P = 0.018$) (see Supplementary data online, *Figure S2*). However, no prognostic significance was demonstrated for the quantitative/qualitative change in LVGLS. Lastly, and per multivariable model, 1-month LVGLS less negative than −15% was not associated with baseline LVGLS but rather with increased mitral effective regurgitant orifice area and reduced RV-pulmonary arterial coupling (see Supplementary data online, *Table S9*).

# Discussion

Our study explored the correlates and prognostic significance of LVGLS, as assessed by 2D TTE, in real-world patients undergoing TEER for chronic PMR. Analysing a single-centre registry of 323 isolated, first-time procedures, we found that: (i) less negative pre-procedural LVGLS marked a sicker patient profile, characterized by greater burden of comorbidities, more pronounced HF and biventricular dysfunction, and higher interventional risk; (ii) notwithstanding differences in presentation, overall procedural aspects were comparable across the various baseline LVGLS quartile groups and technical success rates were similarly high irrespective of baseline LVGLS, leading to a significant and sustained improvement in MR severity and functional capacity compared with baseline in most cases; (iii) an LVGLS of above −12% at baseline, corresponding to the cohort's 4th and worst quartile, was associated with increased cumulative incidence and risk of the primary composite outcome of all-cause mortality or HF hospitalizations at 1 year, a finding that was accounted for by death events and confined to patients with abnormal LVEF/LVESD; (iv) upon exploratory analysis, one-month LVGLS directly correlated with and was generally worse compared with baseline LVGLS, whereas the degree of LVGLS deterioration was less pronounced in patients with a more impaired baseline LVGLS; and (v) a worse LVGLS at 1 month, but not the presence or extent of LVGLS worsening from baseline to 1 month, was associated with a higher cumulative incidence of the primary outcome.

To date, literature on speckle tracking analysis in the setting of mitral TEER has mainly focused on functional MR cohorts. In a 565-patient sub-analysis of the COAPT,[2] worse baseline LVGLS values were accompanied by more advanced echocardiographic and biochemical indices of LV dysfunction, and excess mortality or HF hospitalizations were noted within the worst (vs. best) LVGLS tertile group during the 10–24-month period post-intervention. Noteworthy, LVGLS as a continuous variable was not independently associated with the risk for the combined endpoint. Another 380-case study from our institution[3] found that a baseline LVGLS of above −7% was associated with

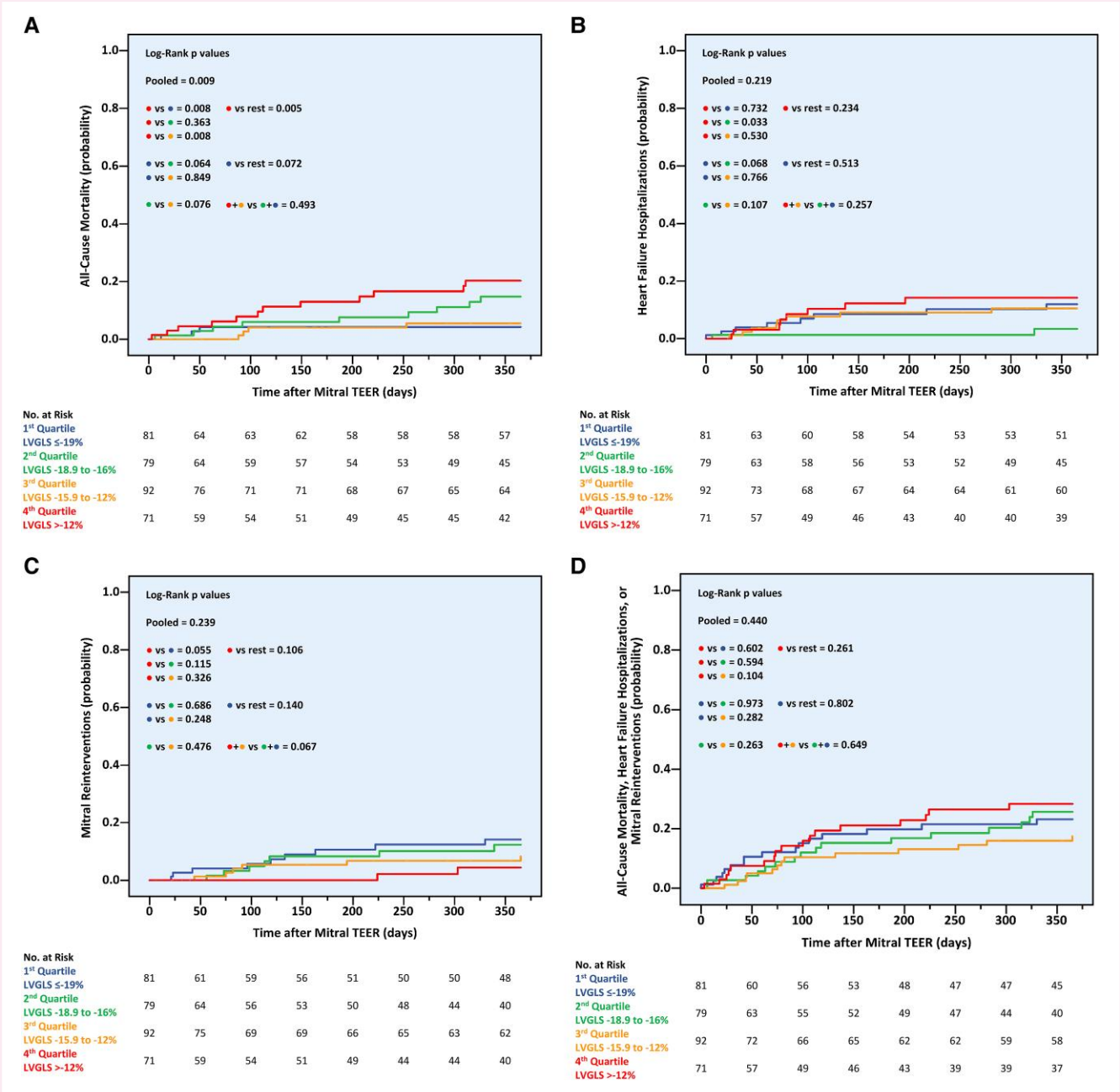



**Figure 4** One-year cumulative incidence of secondary outcomes. (*A*) All-cause mortality. (*B*) Heart failure hospitalizations. (*C*) Mitral reinterventions. (*D*) All-cause mortality, heart failure hospitalizations, or mitral reinterventions. LVGLS, left ventricular global longitudinal strain; TEER, transcatheter edge-to-edge repair.

more deranged pre-procedural LV function and dimensions and conferred increased risk of deaths or HF hospitalizations along the first 2 post-procedural years. Like the COAPT sub-study, a male predominance was most evident in the worse LVGLS group, however overall patient profile was comparable. Procedural features and technical success, too, were not related to baseline LVGLS. The most recent study prior to ours,[4] which employed 172 patients with reduced LVEF, almost all with functional ($n = 123$) or mixed-aetiology ($n = 42$) MR, largely reproduced the results of the earlier works and further revealed worse LV metrics and 1-year cardiovascular mortality incidence and risk in those with baseline LVGLS of >−8.4% and LVEF of <30%. No significant differences in baseline clinical characteristics were observed across the various LVGLS-LVEF groups. Regarding post-procedural LVGLS, several smaller explorations (22–65 patients), again all in functional MR samples, have demonstrated either no change,[13] improvement,[14] or a mixed trend[15] in LVGLS from baseline to 6 months. In the only study thus far[5] to report on predominately primary MR patients ($n = 137/155$, 88.4%), baseline LVGLS less negative than −14.5% was associated with higher rate, cumulative incidence, and risk of all-cause mortality at 1-year post-TEER overall, offering incremental predictive value to LVEF and the combination of LVEF and the Society of Thoracic

Surgeons risk score. Notably, median follow-up duration was less than an actual 1 year and the multivariable models incorporated three covariates at a time. The current analysis, representing the first large-scale study dedicated to LVGLS in TEER patients with PMR only, suggested speckle tracking imaging as clinically and prognostically important in these cases as well, as outlined below.

Three main 'take-home' messages may be offered based on our study. The first is that TEER for chronic PMR appears to be equally feasible, safe, and efficacious among patients with diverse baseline LVGLS ranges, including those with the worst, or least negative, one. Consequently, baseline LVGLS may not play a substantial role in forecasting procedural complexity and success in this subset of patients. Other than reflecting operator experience and infrastructure capabilities of a high-volume centre, the comparable procedural aspects and results observed in the various LVGLS groups in our registry may also be explained by similarities in baseline valvular substrate and related HF symptomology. Alternatively, it could be that mitral TEER is inherently advantageous across all LVGLS values and irrespective of MR aetiology, a notion that may be tested by future, more heterogenous studies.

The second message arising from our study is that in patients undergoing TEER for chronic PMR, baseline LVGLS may nevertheless serve as an indicator of general morbidity and expected post-procedural clinical course, thus aiding in risk stratification and case selection. Although not independently associated with the odds of above-moderate MR and/or NYHA class III–IV persistence at 1 year, nor with the risk for 1-year HF hospitalizations and mitral reinterventions, a worse LVGLS range at baseline did imply higher burden of comorbidities and ventricular dysfunction pre-procedurally and was linked with reduced survival during the first post-interventional year. Interestingly, it was only in those patients with pre-existent LV dysfunction/dilatation that baseline LVGLS assumed a prognostic role—despite the latter not possessing any independent predictive ability on their own. Apart from highlighting the incremental value of speckle tracking over traditional 2D imaging, this finding underscores the importance of integrating both for the purpose of outcome prediction. In view of the study's retrospective nature as well as small absolute sample size, low number of events, and lack of data on specific causes of death, we were not able to verify causality and specifically determine whether LVGLS merely served as a risk marker or also actively participated in the generation of outcomes. These matters may be best addressed by a larger, prospective research.

On a final note, our study suggested that LVGLS prior to TEER for chronic PMR could be used for estimating the short-term LVGLS response to the intervention, and that LVGLS at 1-month post-procedure may be prognostically meaningful as is the baseline one. As mentioned, the worse the pre-TEER LVGLS, the worse the 1-month LVGLS, and the less pronounced deterioration in LVGLS from baseline to 1 month. This was consistent with LVGLS being a surrogate of loading conditions and with mitral TEER inflicting a general unloading effect (and consequent reduction in LV contractile force).[16] As for prognostication, a worse post-interventional LVGLS was associated with earlier, more frequent composite events, presumably reflecting lasting associations with the pre-procedural state. The reason underlying the lack of association between the change in LVGLS from baseline to 1 month and the primary outcome could originate in reduced statistical power. This may explain the discrepancy between the results of the current study and those of our recent report showing a more favourable course in the presence (vs. absence) of LVEF reduction at 1 month following TEER for PMR.[16]

## Limitations

First, the study's single-centre, retrospective design, along with small sample of selected subjects treated in a high-skilled facility, may hamper generalizability of results. However, our cohort was among the largest to date in relative terms, resembled a nationwide registry,[17] and was blindly assessed by experienced readers. Further enhancing validity were the study's focus on isolated, first-time procedures and its reliance on comprehensive regression models. Secondly, the low number of events as well as missing data may have interfered with interpretation of results, making some of the analyses—and particularly those that pertain to the 1-month LVGLS—exploratory. Yet, data non-availability corresponded to that of previous real-world registries; was similar across the different groups; encompassed only echocardiographic findings and functional status (as opposed to clinical events that were documented in all patients regardless of follow-up location); and was not associated with outcomes—thus limiting the possibility of bias. Thirdly, the assessment of LVGLS relied on 2D TTE, which is patient-, operator-, and machine-dependent. However, our approach demonstrated good intra- and inter-observer reliability; reflected common practice; is readily applicable; and could allow for future comparative studies. Fourthly, and again expressing the real-world nature of the study, medical treatment was suboptimal, making it difficult to extrapolate findings to medically optimized cohorts. Lastly, our results may not apply to rheumatic MR cases as these were under-represented in the study.

## Conclusion

Based on the Cedars-Sinai experience, TEER for chronic PMR was equally feasible, safe, and efficacious in all pre-procedural LVGLS settings, leading to a comparable, significant improvement in MR grade and functional capacity. Nevertheless, post-procedural survival was less favourable among patients exhibiting the worst baseline LVGLS values, presumably reflecting their more advanced disease state and higher-risk profile. Larger, prospective, and preferentially multi-centre studies are needed to validate and better characterize the emerging prognostic significance of LVGLS in this population.

# Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

## Acknowledgements

The study was supported in part by the California Chapter of the American College of Cardiology through the Save a Heart Foundation.

**Conflict of interest:** R.R.M. received grant support from Edwards Lifesciences Corporation, is a consultant for Abbott Vascular, Cordis, and Medtronic, and holds equity in Entourage Medical. T.C. is a consultant, proctor, and speaker for Edwards Lifesciences and Medtronic, is a consultant for Abbott Lifesciences, and is a consultant and speaker for Boston Scientific. Other authors have no conflicts of interest to disclose.

## Data availability

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

# Author contribution

A.S. has conceptualized the project, performed statistical analysis, and written the first draft of the manuscript. G.J.H. has taken part in data collection and assisted in writing the first draft of the manuscript. R.J.S. has supervised the project. All co-authors have participated in revision of the text.

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