Global longitudinal strain and outcome after endoscopic mitral valve repair

Martin Kotrc, Jozef Bartunek, Jan Benes, Monika Beles, Marc Vanderheyden, Filip Casselman, Tomas Ondrus, Yujing Mo, Frank Van Praet and Martin Penicka

1 Cardiovascular Center, Aalst, Belgium; 2 Department of Cardiology, Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic; and 3 Department of Cardiovascular and Thoracic Surgery, OLV Clinic, Aalst, Belgium

Abstract

Aims Identification of heart failure (HF) patients with secondary mitral regurgitation (SMR) that benefit from mitral valve (MV) repair remains challenging. We have focused on the role of left ventricular global longitudinal strain (LV-GLS) and reservoir left atrial longitudinal strain (LASr) for the prediction of long-term survival and reverse remodelling in patients with SMR undergoing endoscopic MV repair.

Methods and results The study population consisted of 110 patients (age 67 ± 11 years, 66% men) with symptomatic SMR undergoing isolated MV repair using a minimally invasive surgical approach. Speckle tracking-derived LV-GLS and LASr were assessed in apical views using vendor-independent software. Over a median of 7.7 years (IQRs 2.9–11.2), 64 patients (58%) died. Significant reverse LV (↓ LVEESVI >10 mL/m²), LA (↓ LAVI >10 mL/m²) remodelling or both were observed in 43 (39%), 37 (34%) and 19 (17%) patients, respectively. LV-GLS (HR 0.68, 95% CI 0.58–0.79, P < 0.001) and LASr (HR 0.93, 95% CI 0.88–0.97, P < 0.01) but not LV ejection fraction (LVEF) and LA volume index (LAVi) emerged as independent predictors of all-cause mortality in Cox regression analysis. LV-GLS was the only independent predictor of LV reverse remodelling (OR 1.24, 95% CI 1.05–1.43, P < 0.001) whereas LAVi and LASr were both independent predictors of LA reverse remodelling (both P < 0.05). In patients with atrial fibrillation at baseline, only LASr was an independent predictor (P < 0.05) of LA reverse remodelling.

Conclusions In patients with SMR undergoing endoscopic MV repair, LV-GLS and LASr are independently associated with long-term survival and reverse remodelling and may be helpful in selecting SMR patients who may benefit from this procedure.

Keywords Secondary mitral regurgitation; Survival; Strain; Reverse remodelling; Endoscopic mitral valve repair

Introduction

Minimally invasive mitral valve (MV) repair is associated with improved prognosis in selected patients with HF and secondary mitral regurgitation (SMR). However, selecting individuals who might benefit from MV intervention remains challenging. In the randomized COAPT trial, transcatheter MV repair using MitraClip was associated with significant reduction of all-cause mortality compared with guideline-directed medical therapy. Yet, despite the overall survival benefit, patients assigned to the MitraClip arm exhibited high mortality as well as left ventricular (LV) and atrial (LA) adverse remodelling. Therefore, identifying parameters that may predict long-term survival and reverse remodelling following minimally invasive MV repair in SMR patients is of utmost importance.

LVEF and LAVI are routinely used parameters for assessing LV and LA function. However, several studies suggest that these indices may not be appropriate to identify individuals that may benefit from MV repair. In patients with SMR, LV global longitudinal strain (LV-GLS) measured by speckle tracking echocardiography, unlike LVEF, has been
demonstrated to be independently associated with increased risk of all-cause mortality. Decreased LASr is the earliest marker of LA dysfunction. LASr has been recently shown to be independently associated with all-cause mortality in patients with significant secondary MR and its incremental prognostic value over LA volume and left ventricular global longitudinal strain has been demonstrated. However, the long-term outcome implications of LV-GLS and LASr in patients with SMR undergoing minimally invasive MV repair remain inconclusive. Therefore, the aim of the present study was to assess the contribution of LV-GLS and LASr in predicting long-term survival and reverse remodelling in symptomatic patients with SMR undergoing endoscopic MV repair.

Methods

Patients

Using a retrospective review of prospectively collected data, we identified 110 consecutive patients (n = 110, age 67 ± 11 years, 66% men) with symptomatic SMR that had undergone isolated MV repair using video-assisted minimally invasive surgical approach between 2006 and 2012. An undersized rigid or semi-rigid annuloplasty ring was used in all patients, concomitant tricuspid valve (TV) annuloplasty and/or the MAZE procedure was performed whenever considered appropriate by the surgeon.

Patients were found eligible if they had [1] LVEF < 45%; [2] significant SMR (grade 3–4/4) present in at least 2 separate assessments; [3] acceptable quality baseline echocardiography with a sufficient frame rate allowing LV and LA strain analysis. Acute coronary syndrome or myocardial revascularization within previous 6 months, moderate/severe concomitant aortic valve stenosis or regurgitation, mitral regurgitation of degenerative, rheumatic or infective aetiology or limited life-expectancy were considered as exclusions. The study protocol was performed in accordance with the ethics committees of our institutions. The need for consent to participate in the research study was waived in view of its observational and anonymous nature.

Echocardiography

Baseline echocardiography was performed within 4 weeks prior to MV surgery; last available echocardiogram (performed at least 6 months post-surgery) was used for follow-up analysis. All echocardiographic data were stored digitally in the hospital information system and analysed using TomTec (TomTec Imaging Systems GmbH, Unterschleissheim, Germany) by an experienced reader blinded to clinical outcomes. Assessment of LV dimensions, volumes and ejection fractions (biplane Simpson method) and LAVI was performed according to current recommendations. SMR was defined as restrictive systolic leaflet motion in accordance with current recommendations. Significant SMR was defined as grade 3/4 or 4/4. Although quantitative assessment of SMR severity was not consistently available in this retrospective study, only patients with significant SMR (grades 3/4 and 4/4) at two different occasions were selected for the study. All patients were symptomatic despite diuretics. The SMR was also clinically considered severe enough to indicate MV intervention. LV-GLS and LASr were assessed using the speckle tracking technique. Briefly, endocardial borders were drawn manually in apical views and automatically tracked using software. Tracking was manually adjusted in suboptimal cases. LV-GLS and LASr were calculated as the average of the segmental values in apical views. In patients with AFib, cycles with the most similar RR intervals were used for LV and LA strain analysis. The left atrial reservoir strain (LASr) was defined as the first peak positive deflection and represented the LA reservoir function. The LARS was calculated as the mean longitudinal strain in 2 apical views (4 and 2 chambers) using R-R gating as the zero-reference point. Intra- and inter-observer variability was assessed in 20 randomly selected patients. The intra-class correlation coefficient for intra- and inter-observer variability was 0.93 (95% CI, 0.88–0.98) and 0.88 (95% CI, 0.83–0.93), respectively, for LV-GLS, and 0.91 (95% CI, 0.85–0.96) and 0.87 (95% CI, 0.81–0.93), respectively, for LASr.

Left ventricle and left atrium reverse remodelling

LV and LA reverse remodelling was defined as decrease of LVEFVSI and LAVI by at least 10 mL/m². This cut-off represents 14–17% change from baseline values in our study, which we have considered clinically relevant. These cut-offs are in agreement with previously published studies. LV reverse remodelling was defined as an improvement in either LVEDVI or LVEF of >12–15% in multiple other studies. An improvement in LA end-systolic volume >15% has been used as a definition of LA reverse remodelling as well. Further, the selected cut-offs (10 mL/m²) are also large enough to avoid incidental noise associated with intraobserver or day-to-day variability of assessment.

Follow-up

Follow-up data were obtained using hospital and ambulatory records or electronic files of patients (75% of patients). Survival status of remaining 25% of patients was obtained at the end of follow-up from national population registry; at the same time the survival status of remaining 75% of
patients with known vital status was compared with data in national population registry obtaining the same data in all patients.

Statistical analysis

Data are expressed as the mean ± SD. Receiver-operating characteristic curves were constructed to assess the area under the curve for LV-GLS and LASr when predicting 5 year mortality and LV/LA reverse remodelling. Logistic regression was used to identify baseline predictors of AF recurrence, reverse LV (decrease in LVEDVI <10 mL/m²) and LA remodelling (decrease in LAVI <10 mL/m²). Cox proportional hazard model was used to identify independent predictors of all-cause mortality. Clinically relevant parameters were included in the univariable analysis. All significant predictors in the univariable analysis were included in the multivariable analysis. For avoidance of overfitting, the general rule of thumb of 10 clinical events per covariate included in the model was fulfilled. For all tests, values of \( P < 0.05 \) were considered significant. For statistical analysis, R 3.6.2. was used.

Results

Patients

A total of 110 patients with significant SMR were enrolled; 46% had ischaemic aetiology of HF, the remaining 54% had dilated cardiomyopathy. The majority of patients were severely symptomatic men with significant LV and LA remodelling. A total of 72 patients (65%) had AF (23/21% paroxysmal AF, 49/44% long-standing persistent). All patients

| Table 1 Baseline and perioperative characteristics |
|-----------------------------------------------|
| Clinical data | |
| Age, years | 67 ± 11 | 61 ± 12 | 72 ± 9 | <0.001 |
| Male sex, n (%) | 73 (66) | 33 (72) | 40 (63) | 0.411 |
| Ischaemic aetiology, n (%) | 51 (46) | 16 (34) | 35 (55) | 0.053 |
| Diabetes, n (%) | 22 (20) | 6 (13) | 16 (25) | 0.151 |
| MDRD, mL/min/1.73 m² | 62 ± 23 | 73 ± 17 | 54 ± 23 | <0.001 |
| COPD, n (%) | 11 (10) | 2 (4) | 9 (14) | 0.116 |
| Stroke, n (%) | 17 (15) | 4 (9) | 13 (20) | 0.180 |
| NYHA III/IV, n (%) | 74 (67) | 25 (52) | 50 (78) | 0.007 |
| Atrial fibrillation, n (%) | 72 (65) | 25 (54) | 47 (73) | 0.044 |
| Therapy | |
| Beta-blockers, n (%) | 78 (71) | 33 (72) | 45 (70) | 1.00 |
| ACE inhibitors/ARB, n (%) | 76 (69) | 31 (67) | 45 (70) | 0.84 |
| MRA, n (%) | 67 (61) | 25 (54) | 42 (66) | 0.24 |
| CRT, n (%) | 110 (100) | 46 (100) | 64 (100) | 1.00 |
| Implantable defibrillator, n (%) | 16 (15) | 7 (15) | 9 (14) | 1.00 |
| Echocardiography | |
| Heart rate, min | 81 ± 18 | 83 ± 19 | 80 ± 17 | 0.47 |
| Systolic blood pressure, mmHg | 125 ± 25 | 125 ± 25 | 125 ± 26 | 0.905 |
| LV end-diastolic diameter, mm | 61 ± 10 | 61 ± 10 | 61 ± 9 | 0.700 |
| LV end-systolic diameter, mm | 51 ± 10 | 51 ± 11 | 51 ± 10 | 0.781 |
| LVEDVI, mL/m² | 100 ± 36 | 101 ± 35 | 100 ± 37 | 0.882 |
| LVESVI, mL/m² | 69 ± 28 | 69 ± 29 | 69 ± 28 | 0.946 |
| LV ejection fraction, % | 53 ± 8 | 33 ± 8 | 33 ± 8 | 0.604 |
| LV GLS, % | -6.8 ± 2.7 | -8.9 ± 2.4 | -5.4 ± 1.8 | <0.001 |
| LA diameter, mm | 48 ± 6 | 48 ± 7 | 48 ± 9 | 0.859 |
| LAVI, mL/m² | 60 ± 20 | 56 ± 18 | 63 ± 23 | 0.152 |
| Reservoir LAS, % | 19.3 ± 8.9 | 23.4 ± 10.7 | 16.9 ± 6.6 | 0.001 |
| Systolic PAP, mmHg | 36 ± 12 | 33 ± 13 | 38 ± 11 | 0.073 |
| Perioperative data | |
| STS score, % | 4.9 ± 7.4 | 1.6 ± 1.9 | 7.4 ± 8.9 | <0.001 |
| Clamp, min | 85 ± 29 | 88 ± 31 | 83 ± 28 | 0.488 |
| MAZE, n (%) | 36 (33) | 17 (27) | 19 (30) | 0.537 |
| TV annuloplasty, n (%) | 44 (40) | 16 (35) | 28 (44) | 0.431 |
| Procedure-related mortality | |
| Operative mortality, n (%) | 1 (1) | NA | 1 (2) | NA |
| In-hospital mortality, n (%) | 8 (7) | NA | 8 (13) | NA |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; LA, left atrial; LAS, LA longitudinal strain; LAVI, LA volume index; LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVESVI, LV end-systolic volume index; LV GLS, LV global longitudinal strain; MDRD, Modification of Diet in Renal Disease; MRA, mineralocorticoid receptor antagonist; PAP, pulmonary artery pressure; TV, tricuspid valve.
Table 2  Long-term outcomes

| All patients (N = 110) | Survivors (N = 46) | Non-survivors (N = 64) | P |
|------------------------|-------------------|------------------------|---|
| **All-cause mortality**|                   |                        |   |
| 1-year mortality, n (%)| 13 (12)           | NA                     |   |
| 5-year mortality, n (%)| 43 (39)           | NA                     |   |
| Total mortality, n (%)  | 64 (58)           | 64 (100)               |   |
| Heart failure hospitalizations, n (%) | 30 (27) | 9 (20) | 21 (33) | 0.136 |
| NYHA III, IV, n (%)    | 74 (67)           | 24 (52)                | 50 (78) | 0.007 |
| Follow-up              | 17 (67)**         | 2 (5)*                 | 15 (34)** | <0.001 |
| **Atrial fibrillation, n (%)** | 72 (65) | 25 (54) | 47 (73) | 0.044 |
| Baseline               |                   |                        |    |
| Follow-up              |                   |                        |    |
| Redo mitral valve surgery, n (%) | 4 (5)  | 0 | 4 (9) | 0.116 |
| LVEDVI, mL/m²           | 100 ± 36          | 101 ± 35               | 100 ± 37 | 0.882 |
| Follow-up (n = 84)     | 96 ± 44           | 86 ± 33*               | 109 ± 56 | 0.048 |
| LVESVI, mL/m²           | 69 ± 28           | 69 ± 29                | 69 ± 28 | 0.882 |
| Follow-up (n = 84)     | 65 ± 28           | 51 ± 28*               | 79 ± 55 | 0.023 |
| ↓ LVESVI >10 mL/m²     | 33 (39%)          | 46 (55%)               | 18 (21%) | 0.007 |
| LV ejection fraction, %| 33 ± 8            | 33 ± 8                 | 33 ± 8 | 0.604 |
| Baseline               |                   |                        |    |
| Follow-up (n = 84)     |                   |                        |    |
| LAVI, mL/m²            | 60 ± 20           | 56 ± 18                | 63 ± 23 | 0.152 |
| Follow-up (n = 84)     | 54 ± 18*          | 49 ± 16*               | 59 ± 18 | 0.020 |
| ↓ LAVI >10 mL/m²       | 29 (34%)          | 34 (40%)               | 24 (28%) | 0.551 |
| Systolic PAP, mmHg     | 36 ± 12           | 33 ± 13                | 38 ± 11 | 0.073 |
| Baseline               |                   |                        |    |
| Follow-up (n = 84)     |                   |                        |    |
| CI, confidence interval; HR, hazard ratio.

*P < 0.05.
**P < 0.01.
***P < 0.001 versus baseline.

Table 3  Predictors of all-cause mortality in all patients (total mortality) and in individuals successfully discharged from hospital

| Total mortality | Total mortality | Mortality in discharged patients |
|-----------------|-----------------|----------------------------------|
| HR (95% CI)     | P value         | HR (95% CI)                      | P value |
| Age             | 1.07 (1.04–1.10)| <0.001                           | 0.78    | 1.00 (0.97–1.06) | 0.59 |
| Male sex        | 0.76 (0.45–1.26)| 0.26                             |        | 1.00 (0.97–1.01) | 0.58 |
| Ischaemic aetiology | 1.70 (1.04–2.80)| 0.036                           | 1.62 (0.92–2.86) | 0.12 | 1.51 (0.79–2.92) | 0.22 |
| MDRD            | 0.97 (0.96–0.98)| <0.001                           | 0.99 (0.98–1.01) | 0.40 | 1.00 (0.98–1.01) | 0.58 |
| Diabetes        | 1.57 (0.88–2.70)| 0.12                             |        | 2.09 (1.01–4.36) | 0.049 |
| NYHA III/IV     | 2.27 (1.25–4.13)| 0.007                            | 2.09 (1.04–4.19) | 0.038 | 2.09 (1.01–4.36) | 0.049 |
| Atrial fibrillation | 1.80 (1.03–3.14)| 0.039                           | 1.24 (0.48–3.21) | 0.66 | 1.15 (0.42–3.11) | 0.79 |
| LVEDVI          | 1.00 (0.99–1.01)| 0.675                            |        | 2.09 (1.01–4.36) | 0.049 |
| LVESVI          | 1.00 (0.99–1.01)| 0.929                            |        | 2.09 (1.01–4.36) | 0.049 |
| LV ejection fraction | 0.99 (0.96–1.02)| 0.46                             |        | 2.09 (1.01–4.36) | 0.049 |
| LV GLS          | 0.67 (0.59–0.76)| <0.001                           | 0.68 (0.58–0.79) | <0.001 | 0.68 (0.58–0.80) | <0.001 |
| LAVI            | 1.01 (0.99–1.02)| 0.28                             |        | 2.09 (1.01–4.36) | 0.049 |
| Reservoir LAS   | 0.93 (0.89–0.97)| <0.001                           | 0.93 (0.88–0.97) | 0.001 | 0.94 (0.89–0.98) | 0.007 |
| RVEDD basal     | 1.00 (0.97–1.04)| 0.60                             |        | 2.09 (1.01–4.36) | 0.049 |
| RVEDD mid       | 1.00 (0.96–1.05)| 0.93                             |        | 2.09 (1.01–4.36) | 0.049 |
| TAPSE           | 0.96 (0.89–1.03)| 0.29                             |        | 2.09 (1.01–4.36) | 0.049 |
| FAC             | 0.98 (0.95–1.01)| 0.07                             |        | 2.09 (1.01–4.36) | 0.049 |

CI, confidence interval; HR, hazard ratio.

Multivariable analysis was performed with all parameters that were identified as significant predictors in univariable analysis (i.e. age, aetiology of LV dysfunction, MDRD, NYHA, history of atrial fibrillation, LV-GLS and LASr). Items in bold are statistically relevant findings (P < 0.05).
underwent restrictive MV repair, concomitant MAZE was performed in 33% and TV annuloplasty in 40% of patients. None of the patients underwent concomitant myocardial revascularization. Acute periprocedural reduction of SMR to < grade 2+4 was achieved in all patients. Operative and in-hospital mortality was 1% and 7%, respectively. The median hospital stay length was 12 days (IQR 9–23 days). Patients’ characteristics is in Table 1.

**Baseline characteristics and follow-up**

After a median follow-up of 7.7 years (IQR 2.9–11.2 years), a total of 46 patients (42%) were still alive (survivors) whereas 64 patients (58%) had died from any cause (non-survivors). Compared with non-survivors, long-term survivors were younger, had better renal function, lower NYHA functional class, lower prevalence of AF and more preserved LV-GLS and LASr at baseline (all P < 0.05) (Table 1). On the contrary, no differences were found in heart failure medication or device therapy, LVEF or LAVI (Table 2).

Time between baseline and follow-up clinical and echocardiographic assessment was significantly shorter in non-survivors (median 2.7 IQR 1.4–4.8, vs. 4.1 IQR 1.5–5.4 years, P = 0.015). NYHA functional class significantly improved in both groups (Table 2). The majority of patients (87%) had either no or mild SMR at follow-up. Four patients (3.6%) developed severe recurrent SMR, necessitating redo MV surgery. Survivors exhibited a significant reduction in LV and LA volume and an increase in LV ejection fraction (all P < 0.05), with no favourable changes observed in non-survivors (Table 2).

![Figure 1](image-url) **Figure 1** Spline and Kaplan–Meier curves for all-cause mortality according to LV-GLS (A,B) and LASr (C,D). Prediction of all-cause mortality across a range of LV-GLS (A) and LASr (C) using the spline curve. The shadow area represents a 95% confidence interval. Time to all-cause mortality according to LV-GLS (B) ≥ −7% (red) and < −7 (black). Time to all-cause mortality according to LASr (D) ≥ 16% (red) and <16 (black).
Predictors of all-cause mortality

Univariable Cox proportional hazard analysis was performed including clinically relevant parameters (Table 3). Age, aetiology of LV dysfunction, MDRD, NYHA, history of atrial fibrillation, LV-GLS, and LASr were found to be significant predictors of all-cause mortality ($P < 0.05$, Table 3). These variables were included into multivariable model that identified only NYHA class, LV-GLS and LASr as significant independent predictors of all-cause mortality (Table 3).

Based on spline curve analysis, the optimal cut-off value of LV-GLS for predicting all-cause mortality was $< -7\%$. A total of 52 out of 60 patients (87\%) with LV-GLS $< -7\%$ died, compared with 12 out of 50 individuals (24\%) with more preserved LV-GLS (Figure 1). LV-GLS showed the largest area under the curve when predicting 5 year mortality, with a sensitivity of 87\% (95\% CI 74–96\%) and a specificity of 73\% (95\% CI 61–84\%) (Figure 2). In contrast, LASr, LAVI, and LVEF displayed smaller area under the curve values.

Left ventricle reverse remodelling

A significantly higher percentage of survivors exhibited LV reverse remodelling (↓ LVESVI $> 10$ mL/m$^2$) compared with non-survivors (55\% vs. 21\%, $P < 0.01$) (Figure 3). Based on multivariable regression analysis, LV-GLS emerged as the only independent predictor of LV reverse remodelling (OR 1.24, 95\% CI 1.05–1.43, $P < 0.001$) (Supporting Information, Table S1). The optimal cut-off value of LV-GLS ($\geq -8.2\%$) for predicting LV reverse remodelling was higher than that ($\geq -7\%$) for predicting long-term survival (Figure 3). Despite similar values at baseline, patients with more preserved LV-GLS showed significantly smaller LV volume and higher

**Figure 2** ROC curve analysis showing the accuracy of LV-GLS (red solid), LVEF (red dotted), LASr (black solid) and LAVI (black dotted) for predicting 5 year mortality (abbreviations in text).

**Figure 3** ROC curve analysis showing the accuracy of LV-GLS (red solid) and LVEF (red dotted) for predicting LV reverse remodelling (abbreviations in text).

**Figure 4** LV volume and LVEF in patients with more preserved (blue bars) versus lower (yellow bars) LV-GLS at baseline and follow-up. Patients with more preserved LV-GLS at baseline showed significant LV reverse remodelling at follow-up. In contrast, in patients with more impaired LV-GLS at baseline, LV deteriorated during follow-up.

**Predictors of all-cause mortality**

Univariable Cox proportional hazard analysis was performed including clinically relevant parameters (Table 3).Age, aetiology of LV dysfunction, MDRD, NYHA, history of atrial fibrilation, LV-GLS, and LASr were found to be significant predictors of all-cause mortality ($P < 0.05$, Table 3). These variables were included into multivariable model that identified only NYHA class, LV-GLS and LASr as significant independent predictors of all-cause mortality (Table 3).

Based on spline curve analysis, the optimal cut-off value of LV-GLS for predicting all-cause mortality was $< -7\%$. A total of 52 out of 60 patients (87\%) with LV-GLS $< -7\%$ died, compared with 12 out of 50 individuals (24\%) with more preserved LV-GLS (Figure 1). LV-GLS showed the largest area under the curve when predicting 5 year mortality, with a sensitivity of 87\% (95\% CI 74–96\%) and a specificity of 73\% (95\% CI 61–84\%) (Figure 2). In contrast, LASr, LAVI, and LVEF displayed smaller area under the curve values.

**Left ventricle reverse remodelling**

A significantly higher percentage of survivors exhibited LV reverse remodelling (↓ LVESVI $> 10$ mL/m$^2$) compared with non-survivors (55\% vs. 21\%, $P < 0.01$) (Figure 3). Based on multivariable regression analysis, LV-GLS emerged as the only independent predictor of LV reverse remodelling (OR 1.24, 95\% CI 1.05–1.43, $P < 0.001$) (Supporting Information, Table S1). The optimal cut-off value of LV-GLS ($\geq -8.2\%$) for predicting LV reverse remodelling was higher than that ($\geq -7\%$) for predicting long-term survival (Figure 3). Despite similar values at baseline, patients with more preserved LV-GLS showed significantly smaller LV volume and higher
LVEF at follow-up (all $P < 0.01$) compared with those with lower LV-GS (Figure 4).

**Left atrium reverse remodelling and atrial fibrillation recurrence**

Prevalence of LA reverse remodelling ($\downarrow$ LAVI > 10 mL/m$^2$) or AF at follow-up was similar between survivors and non-survivors (NS). LAVI ($P = 0.009$) and LASr ($P = 0.039$) were the only independent predictors of LA reverse remodelling in all patients (Supporting Information, Table S2), only LASr in those with baseline AF ($P = 0.030$).

**Discussion**

The present study shows that in HF patients with significant SMR undergoing endoscopic MV repair, LV-GS (but not LVEF) is the strongest predictor of long-term survival and the only predictor of LV reverse remodelling. In addition, LASr is also independently associated with long-term survival and LA reverse remodelling, unlike LAVI. Taken together, these data suggest that longitudinal strain, as opposed to routinely used LVEF or LAVI, more accurately reflects the haemodynamic consequences of SMR and its impact upon LV and LA function.

SMR is highly prevalent and portends poor prognoses.\textsuperscript{22,23} Whereas some observational as well as randomized studies have reported improved survival associated with MV intervention, others have detected no benefits.\textsuperscript{2,3,5,24} Notably, Wu et al. observed no survival benefit in patients undergoing isolated open-chest MV repair compared with conservative management.\textsuperscript{24} In contrast, a propensity-matched analysis reported improved outcomes following minimally invasive MV repair using videothoracoscopy.\textsuperscript{1} This suggests that, in severely ill patients, less invasive procedures such as endoscopic or transcatheter MV repair may be more suitable than standard open-chest surgery. Recently, two randomized trials (MITRA-FR and COAPT) utilizing transcatheter MV repair with MitraClip demonstrated controversial effects on all-cause mortality.\textsuperscript{2,5} Like in patients with advanced LV remodelling, the independent prognostic significance of SMR reduces as the severity of LV dysfunction increases.\textsuperscript{22,23} Therefore, the more advanced LV disease in the MITRA-FR trial may have partly resulted in the lack of survival benefit.\textsuperscript{5,6,10} These observations suggest that, in the patient population with SMR, routinely used LVEF may underestimate the degree of LV disease and, consequently, may not be the optimal method when selecting appropriate candidates for MV intervention.

**Global longitudinal strain of left ventricle in secondary mitral regurgitation**

In patients with heart failure and reduced LVEF, LV-GS has shown incremental prognostic value in addition to LVEF irrespective of SMR severity.\textsuperscript{10,25,26} In a recent study involving 650 patients with SMR, Namazi et al. demonstrated that, unlike LVEF, impaired LV-GS was independently associated with increased risk of all-cause mortality.\textsuperscript{10} The current study extends these findings, revealing LV-GS to be the strongest independent predictor of long-term survival and the only independent predictor of LV reverse remodelling in patients with SMR undergoing endoscopic MV repair. Interestingly, very similar cut-off ($-8.65\%$) for LV-reverse remodelling was recently reported in a group of HF patients undergoing MitraClip implantation.\textsuperscript{27}

In contrast, and in agreement with the Namazi study, neither LV volume nor LVEF were associated with outcomes. These results suggest that, in patients with SMR and reduced LV function, LV-GS may be a more accurate marker of LV structural and functional impairment than LVEF.\textsuperscript{28}

**Strain of left atrium in secondary mitral regurgitation**

Chronic mitral regurgitation is associated with LA remodelling. Speckle tracking-derived LASr has been shown to be a sensitive marker of LA structural and functional impairment.\textsuperscript{9,11} In degenerative mitral regurgitation, LASr has been shown to correlate with the degree of mitral regurgitation and predict LA reverse remodelling.\textsuperscript{29–31} In SMR, data on LASr as outcome parameters are scarce. Moreover, in SMR versus degenerative MR, the relationship between LASr and outcomes may be hampered by concomitant LV systolic dysfunction and high prevalence of AF. Öztürk et al. demonstrated three-dimensional LASr, unlike LAVI, to be independently associated with mortality based on a 12-month follow-up following MitraClip implantation.\textsuperscript{32} It must be noted, however, that the short follow-up and low number of endpoints ($n = 7$) were major limitations of the same study.\textsuperscript{32} In our study, which involved a longer follow-up period and a higher number of endpoints ($n = 64$), LASr emerged as an independent predictor of all-cause mortality and LA reverse remodelling. In contrast, and similar to the findings of the Öztürk study, LAVI was not associated with mortality. This suggests that, in LA volume overload, LASr may be a more useful method of predicting outcomes than LAVI. Debate continues as to whether LASr can provide incremental information beyond LV-GS. In patients with different LV disorders, LV end-diastolic pressure, LV end-systolic volume index and LV-GS have been shown to be independently associated with LASr.\textsuperscript{33,34} In the present study, despite moderate correlations ($r = -0.35, P = 0.001$ not shown)
between both parameters, LASr showed a significant association with all-cause mortality independently of LV-GLS. This indicates that, in patients with SMR, assessment of LA function may provide incremental information beyond LV systolic function.

**Study limitations**

Quantitative assessment of SMR severity was not consistently available in this study. Our strain analysis revealed importantvendor dependency and thus the cut-off values of LV-GLS and LASr should be interpreted with caution. However, in the present study, vendor-independent software was used to minimize this limitation.

**Conclusions**

We demonstrate that, in patients with SMR and impaired LV ejection fraction undergoing endoscopic MV repair, more preserved LV-GLS and LASr are independently associated with long-term survival and reverse remodelling. In contrast, routinely used LVEF and LAVI were not found to predict survival.

We therefore speculate that both LV GLS as well as LASr may be helpful when selecting SMR patients who stand to most benefit from MV intervention.

**Conflict of interest**

The authors have no conflicts of interest to declare.

**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1:** Predictors of LV reverse remodelling.

**Table S2:** Predictors of LA reverse remodelling.

**References**

1. Penicka M, Kotrc M, Ondrus T, Mo Y, Casselman F, Vanderheyden M, van Camp G, van Praet F, Bartunek J. Minimally invasive mitral valve annuloplasty confers a long-term survival benefit compared with state-of-the-art treatment in heart failure with functional mitral regurgitation. *Int J Cardiol*. 2017; 244: 235–241.

2. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock JI, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Shulman RN, Goliasch G. A unifying conceptual framework for distinguishing proportionate and disproportionate functional mitral regurgitation. *J Am Coll Cardiol*. 2018; 73: 2307–2318.

3. Giannini C, D’Ascenzo F, Fiorelli F, Spontoni P, Swoans MJ, Velazquez EJ, Armeni P, Adamo M, De Carlo M, Petronio AS. A meta-analysis of Mitraclip combined with medical therapy vs medical therapy alone for treatment of mitral regurgitation in heart failure patients. *ESC Heart Failure*. 2018; 5: 1150–1158.

4. Bartko PE, Arfsten H, Heitzinger G, Pavo N, Toma A, Strunk G, Hengstenberg C, Hülsmann M, Goliash G. A unifying concept for the quantitative assessment of secondary mitral regurgitation. *J Am Coll Cardiol*. 2019; 73: 2506–2517.

5. Obadia JF, Messika-Zeitoun D, Leurent G, Jung B, Bonnet G, Piriou N, LeFèvre T, Piot C, Rouleau F, Carrière D, Nejjar M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux I, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Bouteïe F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Meuwton N. Percutaneous repair or medical treatment for secondary mitral regurgitation. *J Am Coll Cardiol*. 2018; 72: 2297–2306.

6. Packer M, Grayburn PA. New evidence supporting a novel conceptual framework for distinguishing proportionate and disproportionate functional mitral regurgitation. *JAMA Cardiol*. 2020; 5: 469–475.

7. Gyoten T, Schenk S, Rochor K, Herwig V, Harnath A, Grimmig O, Just S, Fritzsche D, Messroghli D. Outcome comparison of mitral valve surgery and MitraClip therapy in patients with severely reduced left ventricular dysfunction. *ESC Heart Fail*. 2020; 7: 1781–1790.

8. Asch FM, Grayburn PA, Siegel RJ, Kar S, Lim DS, Zoroff JG, Mishell JM, Whisenant B, Mack MJ, Lindenfeld J, Abraham WT, Stone GW, Weissman NJ, COAPT Investigators. Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT trial. *J Am Coll Cardiol*. 2019; 74: 2969–2979.

9. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, Ballo P. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2011; 24: 898–908.

10. Namazi F, van der Bijl P, Hirasawa K, Kamperidis V, van Wijngaarden SE, Mertens B, Leon MB, Hahn RT, Stone GW, Narula J, Ajmone Marsan N, Delgado V, Bax JJ. Prognostic value of left ventricular global longitudinal strain in patients with secondary mitral regurgitation. *J Am Coll Cardiol*. 2020; 75: 750–758.

11. Yoshida Y, Nakanishi K, Daimon M, Ishiwata J, Sawada N, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, di Tullio MR, Homma S, Komuro I. Alteration of cardiac performance and serum B-type natriuretic peptide level in healthy aging. *J Am Coll Cardiol*. 2019; 74: 1789–1800.

12. Stassen J, Namazi F, van der Bijl P, van Wijngaarden SE, Kamperidis V, Marsan NA, Delgado V, Bax JJ. Left atrial reservoir function and outcomes in secondary mitral regurgitation. *J Am Soc
13. Casselman FP, Van Slycke S, Wellsen F, De Geest R, Dегrieck I, Van Praet F, Vermeulen Y, Vanermen H. Mitral valve surgery can now routinely be performed endoscopically. Circulation. 2003; 108: II48–II54.

14. Jeannart H, Casselman F, Beelen R, Wellsen F, Bakir I, Van Praet F, Cammu G, Degrieck V, Vermeulen Y, Vanermen H. Modified maze during endoscopic mitral valve surgery: the OLV clinic experience. Ann Thorac Surg. 2006; 82: 1765–1769.

15. Lang RM, Badano LP, Mor-Avi V, Afifalo J, Armstrong A, Emande L, Flachskampf FA, Foster E, Geldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Psikal NA, Rosca M, Cameli M, Sade D, Bönner F, Horn P, Kelm M, De Geest R, Degrieck I, Vanpraet F, Vermeulen Y, Vanermen H, Voigt JU, Industry representatives, Sengupta PP, Lancellotti P, Thomas JD, Marwick T, Mertens L, Popescu BA, Edvardsen T, Lancellotti P, Muraru D, Picard MH, FA, Foster E, Goldstein SA, Kuznetsova T, D, Bönner F, Horn P, Kelm M, De Geest R, Degrieck I, Vanpraet F, Vermeulen Y, Vanermen H, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16: 233–270.

16. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard D, Chono T, Mumm B, Houle H, Voigt JU. Recommendations for echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013; 14: 611–644.

17. Badano LP, Colias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, D’Hooge J, Donal E, Fraser AG, Marwick T, Mertens I, Popescu BA, Sengupta PP, Lancellotti P, Thomas JD, Voigt JU, Industry representatives, Prater D, Chono T, Mumon B, Houle H, Healthinners S, Hansen G, Abe Y, Pedri S, Reviewers: this document was reviewed by members of the 2016–2018 EACVI Scientific Documents Committee, Delgado V, Gimelli A, Cosyns B, Gerber B, Flachskampf F, Haagaa K, Calderisi M, Cardim N, Kaufmann P, Masci PG, Marsan NA, Rosca M, Cameli M, Sade LE. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018; 19: 591–600.

18. Spieker M, Marpert J, Afzal S, Scheiber D, Bönner F, Horn P, Kelm M, Westenfeld R. Extent and determinants of left ventricular reverse remodeling in patients with secondary mitral regurgitation undergoing MitraClip implantation. Int J Cardiol Heart Vasc. 2021; 34: 100840.

19. Bulluck H, Carberry J, Carrick D, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay M, Mahrous A, Ford I, Oldroyd KG, Berry C. Redefining adverse and reverse left ventricular remodeling by cardiovascular magnetic resonance following ST-segment-elevation myocardial infarction and their implications on long-term prognosis. Circ Cardiovasc Imaging. 2020; 13: e009937.

20. St John Sutton M, Linde C, Gold MR, Lancellotti P, Zhang Y, McElroy H, Hooge J, Donal E, Fraser AG, Abraham WT, Ghio S, Cerkvenik J, Daubert JC, REVERSE Study Group. Left ventricular architecture, long-term reverse remodeling, and clinical outcome in mild heart failure with cardiac resynchronization: results from the REVERSE trial. JACC Heart Fail. 2017; 5: 169–178.

21. Sun Y, Song S, Zhang Y, Mo W, Zhang X, Wang N, Xia Y, Tse G, Liu Y. Effect of angiogenic receptor neprilysin inhibitors on left atrial remodeling and prognosis in heart failure. ESC Heart Fail. 2022; 9: 667–675.

22. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol. 2015; 65: 1231–1248.

23. Bartko PE, Hulsmann M, Hung J, Pavo N, Levine RA, Pibarat P, Vahanian A, Stone GW, Goliasch G. Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction. Eur Heart J. 2020; 41: 2799–2810.

24. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005; 45: 381–387.

25. Bertini M, Ng AC, Antoni ML, Nucifora G, Ewe SH, Auger D, Marsan NA, Schalij MJ, Bax JJ, Delgado V. Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy. Circ Cardiovasc Imaging. 2012; 5: 383–391.

26. Sengelov M, Jorgensen PG, Jensen JS, Bruun NE, Olsen FJ, Fritz-Hansen T, Nochioha K, Biering-Sorensen T. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. JACC Cardiovasc Imaging. 2015; 8: 1351–1359.

27. Papadopoulos K, Ikonomidis I, Chrissoheris M, Chalapas A, Kourkouveli P, Parissis J, Spargias K. MitraClip and left ventricular reverse remodelling: a strain imaging study. ESC Heart Fail. 2020; 7: 1409–1418.

28. Kamperidis V, Marsan NA, Delgado V, Bax JJ. Left ventricular systolic function assessment in secondary mitral regurgitation: left ventricular ejection fraction vs. speckle tracking global longitudinal strain. Eur J Heart J. 2016; 37: 811–816.

29. Cameli M, Lisi M, Giacomini E, Caputo M, Navarri R, Malandino A, Bello P, Agricola E, Mondillo S. Chronic mitral regurgitation: left atrial deformation analysis by two-dimensional speckle tracking echocardiography. Echocardiography. 2011; 28: 327–334.

30. Candan O, Ozdemir N, Aung SM, Hatipoglu S, Karabay CY, Guler A, Gencen C, Dogan C, Omayeenc O, Bakal RB. Atrial longitudinal strain parameters predict left atrial reverse remodeling after mitral valve surgery: a speckle tracking echocardiography study. Int J Cardiovasc Imaging. 2014; 30: 1049–1056.

31. Inciardi RM, Rossi A, Barghini G, Benfari G, Maffeis C, Greco C, Drago A, Guazz M, Ribichini FL, Cicoira M. Mitral regurgitation, left atrial structural and functional remodelling and the effect on pulmonary haemodynamics. Eur J Heart Fail. 2020; 22: 499–506.

32. Ozturk C, Fusell T, Sinning JM, Werner N, Nickenig G, Hammerstingl C, Schueler R. Alterations in left atrial structure and function in chronic heart failure patients with functional mitral regurgitation after MitraClip. Catheter Cardiovasc Interv. 2020; 96: 676–684.

33. Sarvari SI, Haugaa KH, Stokke TM, Ansari HZ, Leren IS, Heggom F, Smiseth OA, Edvardsen T. Strain echocardiographic assessment of left atrial function predicts recurrence of atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2016; 17: 660–667.

34. Wakami K, Ohite N, Asada K, Fukuta H, Goto T, Mukai S, Narita H, Kimura G. Correlation between left ventricular end-diastolic pressure and peak left atrial wall strain during left ventricular systole. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2009; 22: 847–851.