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ORIGINAL PAPER

Implications of myocardial strain in primary mitral regurgitation—a cardiovascular magnetic resonance study

Simone Romano [1†], Danai Kitkungvan[2,3†], Duc T. Nguyen[4], Carlos El-Tallawi[2], Edward A. Graviss[4], Afshin Farzaneh-Far[5‡], and Dipan J. Shah [2*‡]

[1]Department of Medicine, Section of Internal Medicine C, University of Verona, Verona, Italy; [2]Houston Methodist DeBakey Heart and Vascular Center, Houston Methodist Hospital, Houston, TX, USA; [3]Division of Cardiovascular Medicine, Department of Internal Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA; [4]Department of Pathology and Genomic Medicine, Houston Methodist Hospital Research Institute, Houston, TX, USA; and [5]Division of Cardiology, Department of Medicine, Duke University, Durham, NC, USA

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Aims

Chronic primary mitral regurgitation (MR) results in progressive left ventricular (LV) remodelling. Abnormal myocardial deformation (strain) can be present despite preserved ejection fraction (EF). Cardiovascular magnetic resonance (CMR) feature-tracking techniques allow assessment of global longitudinal strain (GLS) from routine cine images. The aim of this study is to evaluate the prognostic value of CMR feature tracking–derived GLS in patients with primary MR.

Methods and results

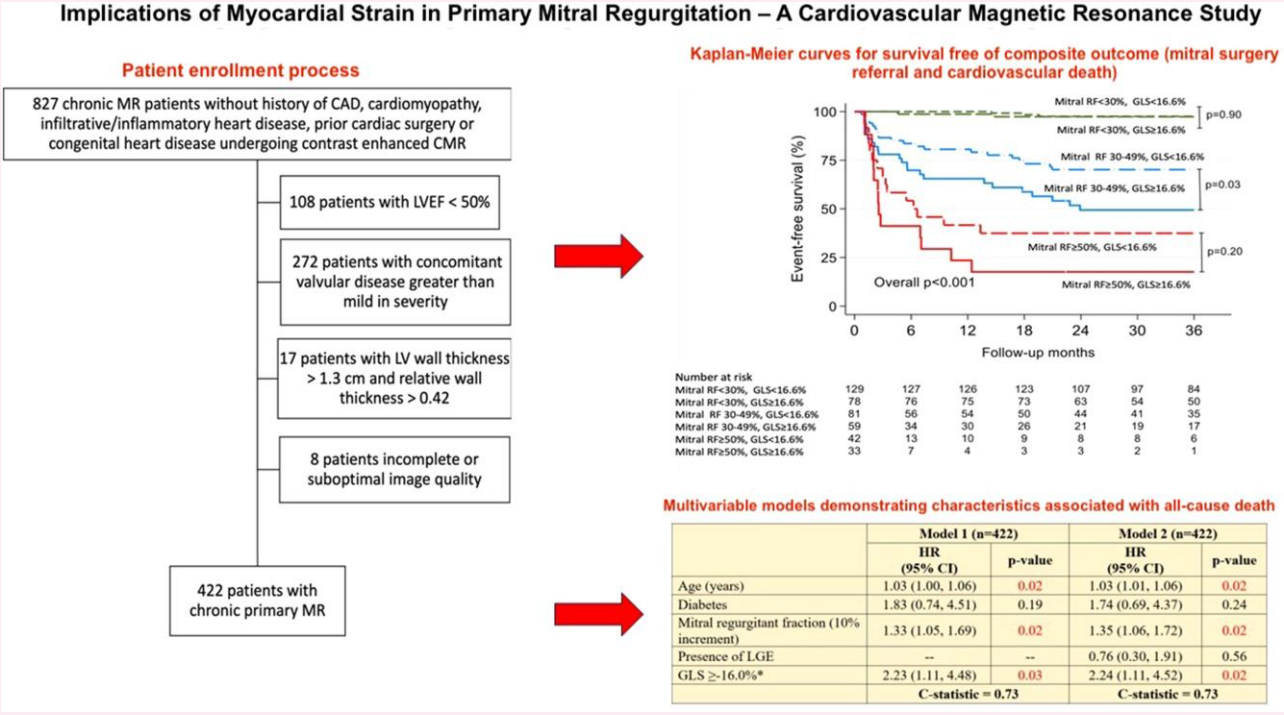
Consecutive patients undergoing CMR for chronic MR from January 2012 to June 2018 were enrolled. Patients with LVEF <50% were excluded. The composite primary outcome aiming to detect decompensation related to MR comprised (i) referral for mitral surgery owing to symptoms or LV systolic dysfunction or (ii) cardiovascular death. The secondary outcome was all-cause death. A total of 422 patients were followed for a median of 2.7 years, and the primary endpoint was met in 93 patients (34 patients reported symptoms at baseline). At multivariable analysis, GLS≥ −16.6% was associated with primary outcome [hazard ratio (HR) 1.90, $P = 0.01$]. In moderate MR cohort, patients with GLS≥ −16.6% had worse event-free survival, whereas there was no significant difference in mild or severe MR groups. GLS≥ −16.0% remained associated with all-cause death after adjusting for other covariates including the MR severity (HR 2.24, $P = 0.02$).

Conclusion

In patients with primary MR with preserved systolic function, GLS was associated with our composite outcomes and all-cause death. GLS may serve as a marker of cardiac dysfunction in the patients with primary MR with preserved systolic function allowing identification of patients likely to decompensate during observation.

* Corresponding author. E-mail: djshah@houstonmethodist.org
† These authors are co-first authors.
‡ These authors are co-senior authors.

Graphical Abstract



	Model 1 (n=422)		Model 2 (n=422)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	1.03 (1.00, 1.06)	0.02	1.03 (1.01, 1.06)	0.02
Diabetes	1.83 (0.74, 4.51)	0.19	1.74 (0.69, 4.37)	0.24
Mitral regurgitant fraction (10% increment)	1.33 (1.05, 1.69)	0.02	1.35 (1.06, 1.72)	0.02
Presence of LGE	--	--	0.76 (0.30, 1.91)	0.56
GLS ≥-16.0%*	2.23 (1.11, 4.48)	0.03	2.24 (1.11, 4.52)	0.02
	C-statistic = 0.73		C-statistic = 0.73	

Keywords mitral regurgitation • cardiovascular magnetic resonance imaging • left ventricular function • global longitudinal strain • feature tracking

Introduction

Primary mitral regurgitation (MR) is caused by a structural abnormality of the mitral valve.[1] It is the most common valvular disease in the USA, with a prevalence increasing with advanced age and the second most common valvular disease requiring intervention, only superseded by aortic stenosis.[2,3] Chronic MR results in progressive remodelling of the left ventricle, manifesting initially as volume overload with preserved contractile function. Favourable loading conditions in MR increase left ventricular (LV) ejection fraction (EF) but do not affect the extent of myocardial shortening.[4] Thus, LVEF should be considered a late marker of LV dysfunction and a 'normal' LVEF may mask subclinical LV dysfunction. The significance of this conundrum is acknowledged in the recently published ACC/AHA Guidelines on valvular heart disease which highlight the need for studies examining the role of earlier markers of myocardial dysfunction to define the optimal timing of intervention.[4]

Direct assessment of myocardial fibre deformation with global longitudinal strain (GLS) imaging has shown promise in providing diagnostic and prognostic information that is incremental to LVEF.[5] GLS has been recognized as a sensitive marker of LV dysfunction, regardless of LV function.[6] While GLS is also load-dependent, it evaluates the myocardial longitudinal deformation and is more sensitive in identifying myocardial dysfunction. The recent development of cardiovascular magnetic resonance (CMR) feature-tracking technology shows promises in allowing measurement of longitudinal strain using routine cine images in the clinical setting without specialized pulse sequences.[7] The underlying principle is based on the recognition of 'patterns of features' or 'irregularities' in the image that are tracked and followed in successive frames.[7] Importantly, this approach can be applied to routine cine CMR acquisitions, thus avoiding the need for dedicated pulse sequences, which are required for other specialized CMR strain techniques. GLS has been shown to provide prognostic value in several clinical conditions.[8–12] However, the data on prognostic value of GLS in primary MR are scarce and limited to GLS derived from echocardiographic technique.[13–15] Therefore, the aim of the present study is to evaluate the prognostic role of CMR feature tracking–derived GLS in primary MR population with preserved systolic function.

Methods

Study population

Consecutive patients undergoing contrast-enhanced CMR for assessment of chronic MR at the Houston Methodist Hospital (Houston, TX, USA) from January 2012 to June 2018 were enrolled into the DEBAKEY CMR Registry (NCT04281823), a prospective longitudinal registry designed to assess the utility of CMR in various disease states. We excluded patients with the following confounding causes of myocardial structural abnormality by clinical history as reported by the patients or available medical records: (i) coronary artery disease, (ii) cardiomyopathy, (iii) infiltrative/inflammatory heart disease (e.g. amyloidosis, sarcoidosis or myocarditis), (iv) prior cardiac surgery, or (v) congenital heart disease. Additionally, patients with the following findings on CMR were excluded: (i) LVEF < 50%; (ii) coexisting valvular disease that was greater than mild in severity (except for tricuspid regurgitation that is secondary to MR; all primary tricuspid regurgitations related to structural leaflet abnormalities such as endocarditis or carcinoid heart disease were excluded); or (iii) greater than mild concentric LV hypertrophy (LV wall thickness >1.3 cm and relative wall thickness >0.42). By their inherent nature, the aforementioned criteria also excluded patients with secondary MR, thus leaving only patients with primary MR in the study cohort. The patient

enrolment process is summarized in *Figure 1*. The likely aetiology of primary MR was deduced using all available medical history and diagnostic testing, including CMR findings. Mitral valve prolapse was defined as >2-mm displacement of any mitral valve scallops into the left atrium, as indicated on a three-chamber view.[16,17] The study was approved by the institutional review board at the Houston Methodist Research Institute, and the patients gave written informed consent (IRB number: Pro00001568).

CMR imaging protocol

CMR images were acquired using either 1.5-T or 3.0-T clinical scanners (Siemens Avanto, Aera, or Verio; Siemens, Erlangen, Germany) with phased-array coil systems. A standard examination consisted of a cine CMR for anatomic and functional assessment in a short-axis stack and two-, three-, and four-chamber views using a steady-state free-precession sequence Additionally, to evaluate mechanism of MR, a high-resolution stack of small field-of-view cine CMR of the mitral valve was performed 'en-face' along with sequential three-chamber views to cover all mitral scallops. Flow across the aortic valve was ascertained using phase-contrast imaging. Standard late gadolinium enhancement (LGE) CMR identified replacement fibrosis using a magnitude and phase-sensitive segmented inversion recovery sequence ~10 min after intravenous gadolinium contrast administration (gadopentetate dimeglumine or gadoterate meglumine, at a constant dose of 0.15 mmol/kg). Short- and long-axis LGE images (two-, three-, and four-chamber) were acquired in identical orientations to the cine images. An electrocardiographically gated modified Look-Locker inversion recovery sequence (MOLLI) with motion correction was performed at a mid-LV short-axis level in a matching position for pre- and post-contrast administration (~15 min). The pre-contrast MOLLI acquisition was performed using a 5(3)3 sampling scheme, and the post-contrast acquisition used a 4(1)3(1)2 sampling scheme.

CMR image analysis

The LV and right ventricular (RV) volumes were measured by planimetry of the endocardial borders, on a stack of short-axis cine images covering both ventricles from base to apex. Papillary muscles and trabeculae were excluded from the LV cavity (i.e. included in LV mass). LV end-diastolic volume, LV end-systolic volume, RV end-diastolic volume, and RV end-systolic volume were calculated by summation of these images. Mitral regurgitant volume was calculated as the difference between LV stroke volume and aortic-forward stroke volume. Mitral regurgitant fraction was calculated as follows: mitral regurgitant volume/(LV stroke volume—aortic regurgitant volume).[18] The presence and extent of replacement fibrosis, as demonstrated by LGE, was assessed in all LV segments according to the ACC/AHA 17-myocardial-segment model by a consensus of two readers who were blinded to clinical history and other imaging information. LGE was only considered present if it was identified on two contiguous or orthogonal slices and seen on both magnitude and phase-sensitive image reconstruction. A semi-quantitative method was used to calculate the burden of replacement fibrosis as a percentage of the left ventricle. The extent of LGE involvement in each 17-LV segment was scored as 0 for no LGE detected, 1 for 1–25%, 2 for 26–50%, 3 for 51–75%, and 4 for 76–100%. The total per cent LV scar volume was calculated from the summed score divided by 68 (maximum score) assuming that each sub-segment equally represented 1/68th of the total LV myocardial volume.[19] For extracellular volume (ECV) analysis, quantitative parametric images of myocardial T1 were generated with manual contouring to define a region of interest in the mid-LV septum at the same location for pre- and post-contrast. We excluded areas where LGE or artefacts were present in the septum; for this situation, the region of interest was placed in either the anteroseptum or inferoseptum where no LGE or artefact was evident. ECV was calculated using the following validated formula: $ECV = [(\Delta R1 \text{ myocardium})/(\Delta R1 \text{ blood pool}) \times (1 - \text{Hct})]$, where Hct refers to the haematocrit recorded on a venous blood sample obtained at the time of CMR and $\Delta R1 = 1/T1$ post-contrast $- 1/T1$ pre-contrast.

CMR strain analysis

Feature-tracking analysis for assessment of GLS was performed in a core lab after the database of clinical, imaging, and follow-up events was locked. The analysis was performed by a single physician (SR) who was blinded to all other study data. GLS was calculated by averaging the values obtained in the apical two- to three- and four-chamber views (18 segments) using

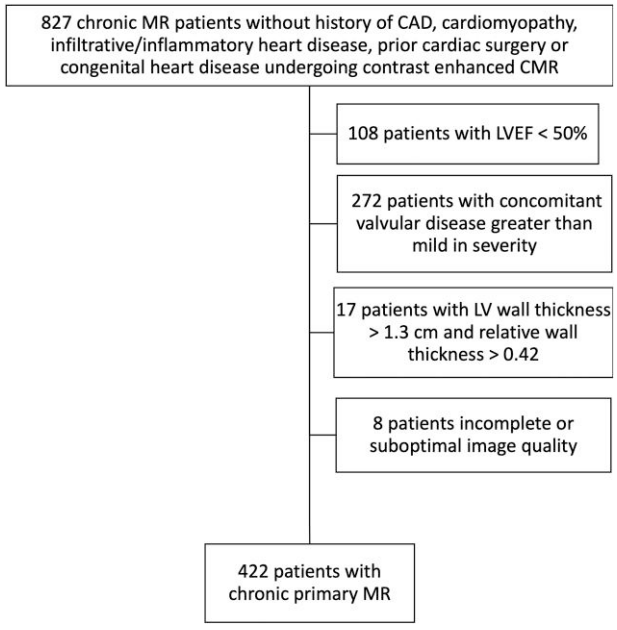


Figure 1 A diagram depicting patient selection process.

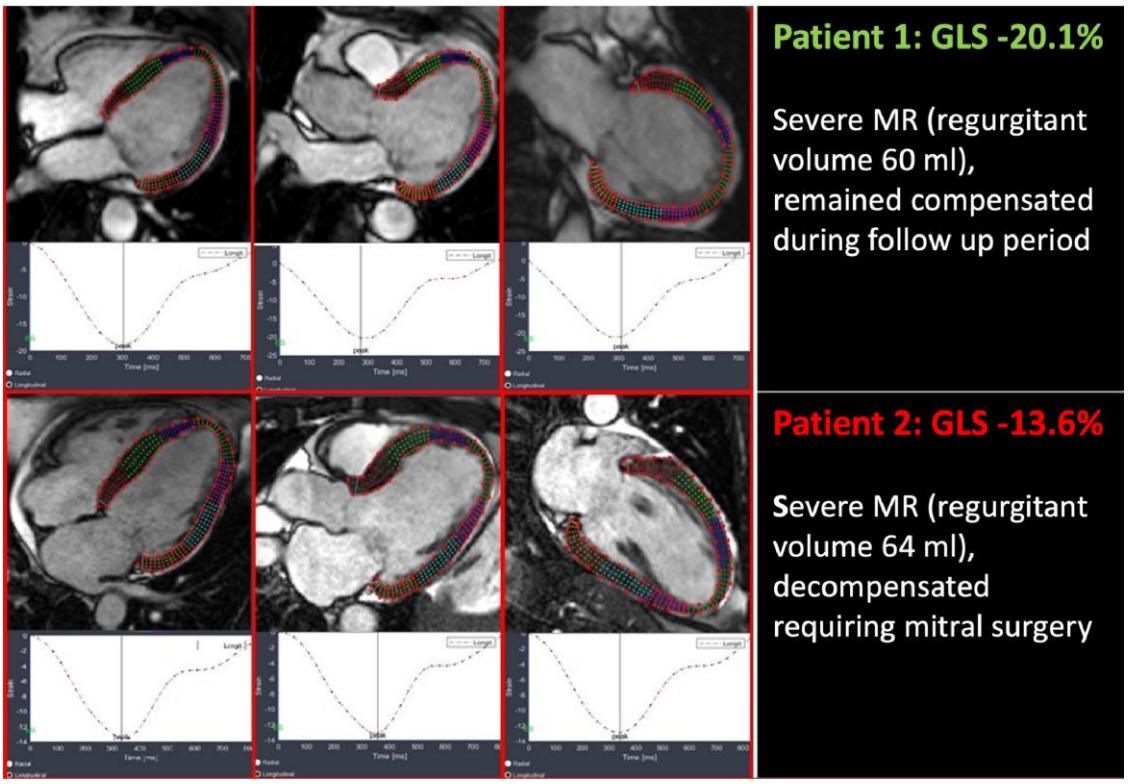


Figure 2 An example of GLS in patients with severe MR. The top panel demonstrates patients with severe MR with preserved GLS that remained compensated during follow-up period, whereas the bottom panel demonstrates patients on with worse GLS, despite relatively similar regurgitant volume, decompensated requiring mitral surgery.

the Qstrain package (Medis Medical Imaging Systems, Leiden, The Netherlands). LV endocardial borders were automatically traced at the end of the diastole; subsequently, the software tracked the endocardial layer throughout the cardiac cycle. When necessary, the operator manually adjusted the endocardial border (*Figure 2*). Measurement of GLS required ~15 min of analysis time per case. GLS measurements showed good reproducibility. The Bland–Altman analysis of inter-observer repeatability showed a bias of 0.16% (95% limits of agreement: −2.08 to 2.40%), whereas the Bland–Altman analysis of intra-observer repeatability showed a bias of −0.07% (95% limits of agreement: −1.59 to 1.45%).[6]

Symptoms related to MR and study outcomes

Self-reported symptoms of dyspnoea on exertion or declining exercise tolerance were obtained from patient interviews at the time of CMR examination. To confirm the clinical significance, as these symptoms can be non-specific, we only considered that they were related to MR if the patients were subsequently referred for mitral surgery owing to their symptoms, or the patient experienced cardiovascular death within 90 days after CMR.

All patients regardless of symptoms related to MR at the time of CMR were followed longitudinally for clinical events. Our composite primary outcome aiming to detect decompensation related to MR included (i) referral for mitral surgery owing to symptomatic MR or progressive LV systolic dysfunction or (ii) cardiovascular death that occurred prior to mitral surgery. We excluded patients who underwent mitral valve surgery within 30 days after CMR to avoid potential bias of a predesignated CMR scan 'en-route' to surgery. The decisions for mitral valve surgical referral were made by the treating physicians who were blinded to GLS data. The secondary outcome was all-cause death. Follow-up data were collected from review of electronic medical record, structured telephone interviews with the patients, relatives, and/or their healthcare providers, and the National Death Index. For ascertainment of cardiovascular-related death, in patients whose cause of death was equivocal, the patient data were presented to an adjudication committee consisting of two board-certified cardiologists blinded to imaging data for further determination. The last round of follow-up data collection was performed in January 2020.

Statistical analysis

The patient characteristics were reported as frequencies and proportions for categorical variables and as median and inter-quartile range for continuous variables. The optimal cut-points of GLS in discriminating primary and secondary outcome were determined by the receiver-operating characteristic curve analysis with a Youden index.[20] Cox regression modelling was conducted to determine the characteristics associated with a higher risk of composite events and all-cause death. Variable selection for the models was conducted on the basis of established clinically important variables that known from prior studies and clinical judgement (*a priori* selection) and the Stata's Lasso method with the cross-validation selection option.[21] To avoid over fitting, some variables which were significant in the univariate analysis, but insignificant in multivariable modelling, were not selected in the final model if their exclusion did not affect the diagnostic performance of the final model. The discrimination power of predictive models was assessed using the *C*-statistic. The model's good calibration was determined by a non-significant Hosmer–Lemeshow's goodness-of-fit test. Event-free survival for the composite primary outcome was depicted by the Kaplan–Meier curves. Differences between subgroups of mitral regurgitant fraction and

GLS were compared by the log-rank test. All analyses were performed on Stata version 17 (StataCorp LLC, College Station, TX, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Following the clinical history screening process, a total of 827 patients with chronic MR were enrolled. After excluding patients with imaging findings that could represent secondary MR or confounding aetiologies for myocardial structural abnormalities, 422 patients remained and comprised the primary MR study cohort (*Figure 1*). Data on the prevalence of replacement fibrosis and ECV of the patient in the current cohort were reported in our prior studies.[22,23] Imaging was performed with 1.5- and 3-T scanners in 147 patients (35%) and 275 patients (65%), respectively. Baseline characteristics and CMR data are summarized in *Table 1* and Supplementary data online, *Table S1*. Of the total cohort, 47.9% were men with a median age of 61.8 years (inter-quartile 51.7, 70.7 years). Mitral valve prolapse was the most common aetiology of primary MR (228 patients, 54.0%; posterior mitral leaflet prolapse in 133 patients, 31.5%) followed by mitral calcification and/or thickening resulting in restriction or malcoaptation of leaflets (91 patients, 21.6%), rheumatic MR (15 patients, 3.6%), prior infective endocarditis (7 patients, 1.7%), suspected radiation related or connective tissue disease (3 patients, 0.7%), and indeterminate in 78 patients (18.5%). There was a spectrum of MR severity with a median regurgitant volume of 29.0 mL (inter-quartile 13.0 mL, 52.0 mL) and regurgitant fraction of 30% (inter-quartile 16.0%, 45%). LGE was found in 90 patients (21.3%) with LGE burden of 1.9% ± 0.9% of the left ventricle. The median ECV was 25.8% (inter-quartile 24.2%, 28.1%). The optimal threshold of GLS for identifying the primary composite outcome (referral for mitral surgery or cardiovascular death) and secondary outcome (all-cause death) was −16.6% (area under the curve 0.54, sensitivity 0.46, specificity 0.61) and −16.0% (area under the curve 0.60, sensitivity 0.50, specificity 0.70), respectively (see Supplementary data online, *Figure S1*).

Table 1 Baseline characteristics

	Total (*n* = 422)
Clinical variables	
Age (years)	61.8 (51.5, 70.7)
Male gender	202 (47.9)
Body surface area (m^2)	1.9 (1.7, 2.1)
History of heart failure	52 (12.3)
Diabetes	33 (7.8)
Hyperlipidaemia	170 (40.3)
Hypertension	224 (53.1)
Current smoking	21 (5.0)
Systolic blood pressure (mmHg)	130.0 (120.0, 141.0)
Diastolic blood pressure (mmHg)	75.0 (67.0, 83.0)
Atrial fibrillation	44 (10.4)
Mitral valve prolapse	228 (54)
CMR measures	
Left atrial volume index (mL/m^2)	61.2 (46.1, 83.8)
LV ejection fraction (%)	65.1 (60.1, 71.0)
LV EDV index (mL/m^2)	86.6 (69.3, 105.5)
LV ESV index (mL/m^2)	29.9 (21.8, 38.9)
LV mass index (g/m^2)	63.3 (53.4, 78.0)
RV ejection fraction (%)	55.0 (50.0, 60.4)
RV EDV index (mL/m^2)	77.0 (63.5, 93.5)
RV ESV index (mL/m^2)	34.3 (26.5, 45.0)
Mitral regurgitant volume (ml)	29.0 (13.0, 52.0)
Mitral regurgitant fraction (%)	30.0 (16.0, 45.0)
Mitral regurgitant fraction <30%	207 (49)
Mitral regurgitant fraction 30–50%	140 (33)
Mitral regurgitant fraction ≥50%	75 (18)
Presence of LGE	90 (21.3)
Extracellular volume (%)	25.8 (24.2, 28.1)
Global longitudinal strain (%)	−17.2 (−19.0, −15.2)

Values are in number (%) for categorical variables or median (inter-quartile range) for continuous variables.
EDV, end-diastolic volume; ESV, end-systolic volume.
Baseline characteristics stratified by GLS are provided in Supplementary data online, *Table S1*.

Symptoms and clinical events related to MR

Our criteria for symptomatic MR at the time of CMR procedure were met in 89 patients. Of them, 88 were referred for mitral surgery and 1 experienced cardiovascular death within 90 days of CMR. The average mitral regurgitant volume and fraction in the symptomatic MR group were 68.8 ± 27.0 mL and 51.1 ± 8.8%, respectively. The prevalence of symptomatic MR patients was highest in the worst GLS tertile (*Figure 3*).

During the follow-up period [a median follow-up time 2.7 years (inter-quartile 0.5, 4.6 years)], the primary outcome was met in 93 patients (22.0%). Of note, 34 out of 93 patients met our definition of symptomatic MR at the time of CMR. Among 93 patients with primary outcome, 89 patients were referred for mitral valve surgery and 4 suffered cardiovascular death. In the group of 89 patients referred for mitral surgery, 72 patients (80.9%) developed symptoms that led to referral, whereas 17 patients (19.1%) underwent MV surgery owing to progressive LV systolic dysfunction. Of all 89 patients referred for mitral surgery, 81 patients underwent mitral repairs, 5 underwent mitral replacement, and 3 were referred for procedure but declined. The median time to composite clinical events was 5.6 months (inter-quartile 2.0, 18.0 months). Male gender, the severity of MR, presence of mitral valve prolapse, ECV, and GLS were found to be associated with a composite of referral for mitral surgery and cardiovascular death on multivariable analysis (*Table 2* and Supplementary data online, *Table S2*). Furthermore, adding ECV and GLS to traditional parameters (MR severity and LV volume) provided incremental value as demonstrated in *Figure 4*. Of note, the left atrial volume index and RVEF were not included in the final model to avoid overfitting and collinearity, and their exclusion did not impact diagnostic performance. In our cohort of patients (all of whom had preserved systolic function), the presence of LGE and LVEF was not significantly associated with the primary composite outcome. Kaplan–Meier curves for event-free survival from mitral surgery referral and cardiovascular death, stratified by severity of MR and GLS of −16.6% as a threshold, are demonstrated in *Figure 5*. Patients with mild MR demonstrated favourable event-free survival irrespective of GLS. In patients with moderate MR, those with GLS ≥ −16.6% demonstrated worse event-free survival, whereas in patients with severe MR, using GLS for stratification did not demonstrate statistically significant difference.

All-cause death was found in 32 patients during the follow-up period. Multivariable Cox regression models analysing factors associated with all-cause death in primary MR patients are given in *Table 3* (univariate analysis in Supplementary data online, *Table S3*). Worsening

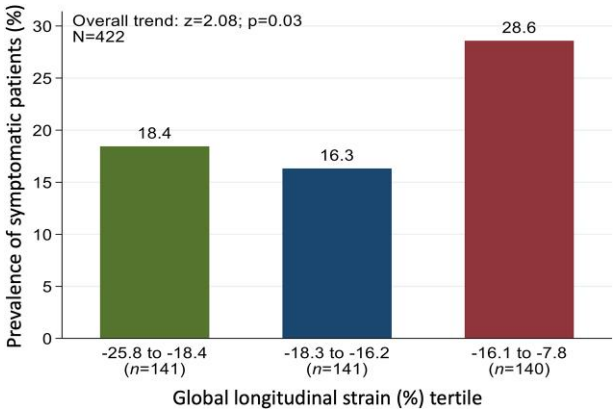


Figure 3 A prevalence of symptomatic MR at the time of CMR stratified by tertile of GLS.

Table 2 Multivariable model demonstrating characteristics associated with composite of mitral surgery referral owing to symptomatic MR or progressive LV systolic dysfunction and cardiovascular death

	HR (95% CI)	*P*-value
Age (years)	1.01 (0.99, 1.02)	0.55
Male gender	2.04 (1.24, 3.34)	0.01
Systolic blood pressure (mmHg)	1.01 (1.00, 1.02)	0.12
LV EDV index (per 20 mL/m2)	1.22 (0.98, 1.50)	0.07
LV mass index (per 20 g/m2)	0.73 (0.54, 1.00)	0.051
Mitral regurgitant fraction (10% increment)	2.23 (1.77, 2.79)	<0.001
Presence of mitral valve prolapse	1.91 (1.05, 3.46)	0.03
Presence of LGE	0.76 (0.47, 1.22)	0.26
Extracellular volume fraction (per 5%)	2.08 (1.30, 3.31)	0.002
GLS ≥ −16.6%[a]	1.90 (1.22, 2.97)	0.01
	C-statistic = 0.89	

EDV, end-diastolic volume.
[a]GLS of −16.6% was identified as an optimal cut-point for this analysis by a Youden index (sensitivity 0.46, specificity 0.61, and area under the curve 0.54).
Univariable analysis is provided in Supplementary data online, *Table S2*.

GLS (using GLS ≥ −16.0% as a threshold) remained independently associated with all-cause death after adjusting for other covariates including the severity of MR.

Discussion

Our study is the first investigation to demonstrate the prognostic relevance of CMR-assessed longitudinal function in patients with chronic primary MR with preserved EF.

Our data show that CMR feature-tracking GLS is independently associated with composite adverse outcomes and all-cause mortality in patients with chronic primary MR with preserved systolic function. In addition, GLS provides incremental predictive value over traditional parameters.

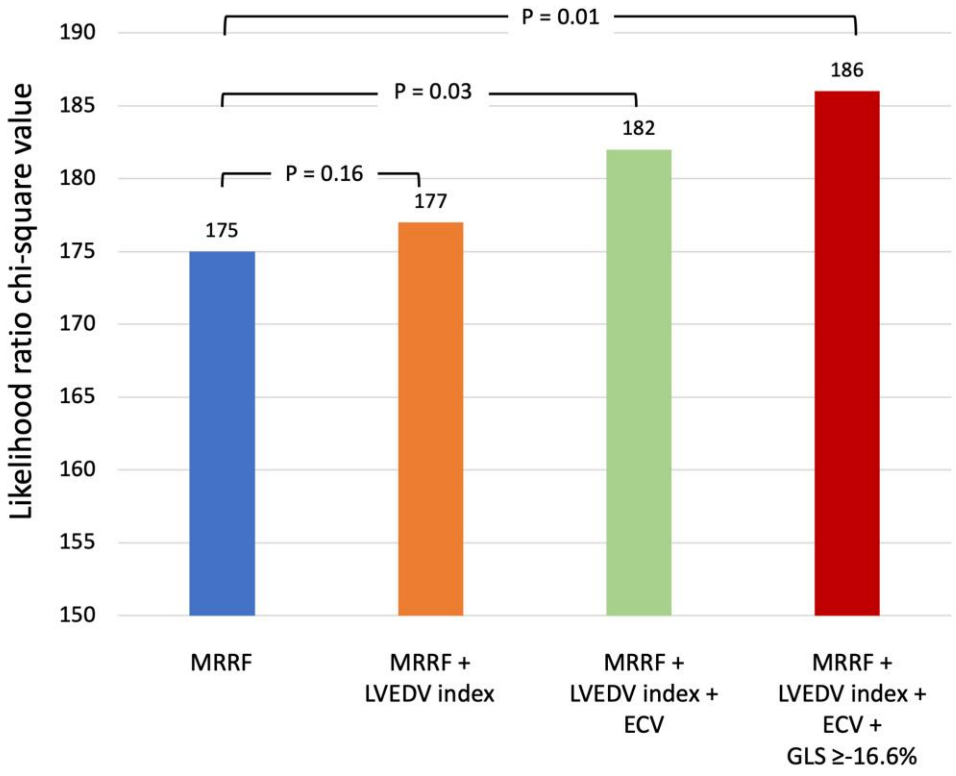
Knowledge gaps in patients with valvular heart disease

Several knowledge gaps in patients with valvular heart disease exist. The optimal timing of a valvular intervention remains unknown in patients with asymptomatic severe valvular disease or symptomatic moderate valvular disease. In patients with MR, a meta-analysis suggests that a strategy of early surgery may improve survival and increase the likelihood of mitral valve repair compared with watchful waiting strategy.[24] However, it is unlikely that all patients will be candidates for earlier intervention; thus, identification of the subgroup most likely to benefit would be essential for optimal patient management. Newer approaches such as early markers of cardiac dysfunction using advanced imaging or circulating blood markers to identify high-risk patients are needed. Despite LVEF being the conventional echocardiographic parameter to estimate LV function, its impairment may be evident at a later stage in the disease process. Moreover, it does not take into consideration the direction of the blood flow and the intrinsic contractile properties of the myocardium. For these reasons, whereas LVEF provides a global measure of LV function, it fails to give an accurate estimate of the real LV inotropic status and ability to distinguish the longitudinal and circumferential functions.

GLS in MR

Likely because of their subendocardial location, the myocardial fibres are highly sensitive to disturbance by various noxious stimuli.[25] In an experimental model, a rapid reduction in mitral annular motion has been demonstrated after ischaemia induction.[26] Manaka *et al.*[27] demonstrated that myocardial systolic impairment may occur on the endocardial side and extends to the epicardium. Longitudinal function plays a fundamental role in cardiac systole by reducing the longitudinal LV size as the mitral annulus is pulled towards the apex; in fact, it has been demonstrated that longitudinal motion can mobilize as much as 60% of stroke volume.[28]

The geometrical change that occurs owing to MR can directly impair the longitudinal fibres and may have an impact on LV longitudinal function regardless of myocardial contractility. The myocardial fibre geometry of the left ventricle changes gradually from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium.[29] Additionally, during the remodelling phase of MR, the LV geometry becomes more globular following the LV dilatation. Therefore, the alignment of the muscle fibres becomes more transverse, preserving the myocardial contractility but impairing the longitudinal contraction. Kim *et al.*[30] demonstrated that speckle-tracking



Multivariable model for composite outcome (decompensation and cardiovascular death)		
	HR (95% CI)	p-value
Mitral regurgitant fraction (MRRF)	1.08 (1.06, 1.11)	<0.001
Left ventricular end diastolic volume index (LVEDV index)	1.01 (1.00, 1.02)	0.09
Extracellular volume (ECV)	1.10 (1.01, 1.20)	0.03
Global longitudinal strain (GLS) ≥-16.6%	1.54 (1.01, 2.35)	0.04

Figure 4 Incremental value of ECV and GLS in predicting composite outcome (mitral surgery referral and cardiovascular death).

longitudinal strain becomes depressed earlier than the LVEF in MR cohort. In patients with MR, a proportion of the regurgitant volume is emptied into the left atrium before the aortic valve opens.[31] In addition, the lower wall stress during early and late systole and the reduced afterload result in an increased total LV stroke volume.[32] These two mechanisms can further mask an existing LV dysfunction that LVEF cannot detect but may potentially be uncovered by assessment of longitudinal function.

The results of our study compliment previous echocardiography-derived GLS investigations in primary MR. Mentias *et al.*[33] showed that resting and exercise LV-GLS provided incremental prognostic utility in asymptomatic patients with primary MR and preserved systolic function. They also demonstrated that abnormal resting LV-GLS was associated with higher mortality in this patient population.[33] In addition, Kim *et al.*[34] have shown that in patients with severe primary MR, GLS is an independent predictor of all-cause mortality after surgery in comparison with conventional parameters. A recent systematic review evaluating the role of echocardiography-derived GLS in severe primary MR after mitral repair or replacement concluded that impaired baseline GLS was associated with higher mortality rates.[35] In patients with secondary MR, Namazi *et al.*[36] showed that impaired GLS was independently associated with an increased risk of all-cause mortality, whereas LVEF was not. In addition, Kamperidis *et al.*[37] concluded that in patients with severe secondary MR, speckle-tracking GLS identified more deterioration in LV systolic function than LVEF.

Limitations

Valvular patients are frequently referred to CMR as a second-line test, and as such, a referral bias might have affected the prevalence of disease, comorbidities, and rate of adverse clinical events in the patients in this study. Symptoms related to MR reporting by the patients were subjective and objective measurement of symptoms such as exercise stress testing was not systematically performed in our study. However, the addition of other criteria, including surgical referral, although it has its own limitation, should minimize and allow us to include patients with clinically relevant MR-related symptoms for further analysis. Additional information from echocardiogram, despite beyond the scope of current study, would be of value; however, as a referral centre, the echocardiograms for many of our patients were performed in the referring cardiologist's office, not available to us, and the reports frequently did not include a complete quantification of MR. For these reasons, our study did not compare GLS by echocardiogram with GLS by CMR, but the future studies that assess this will be important to

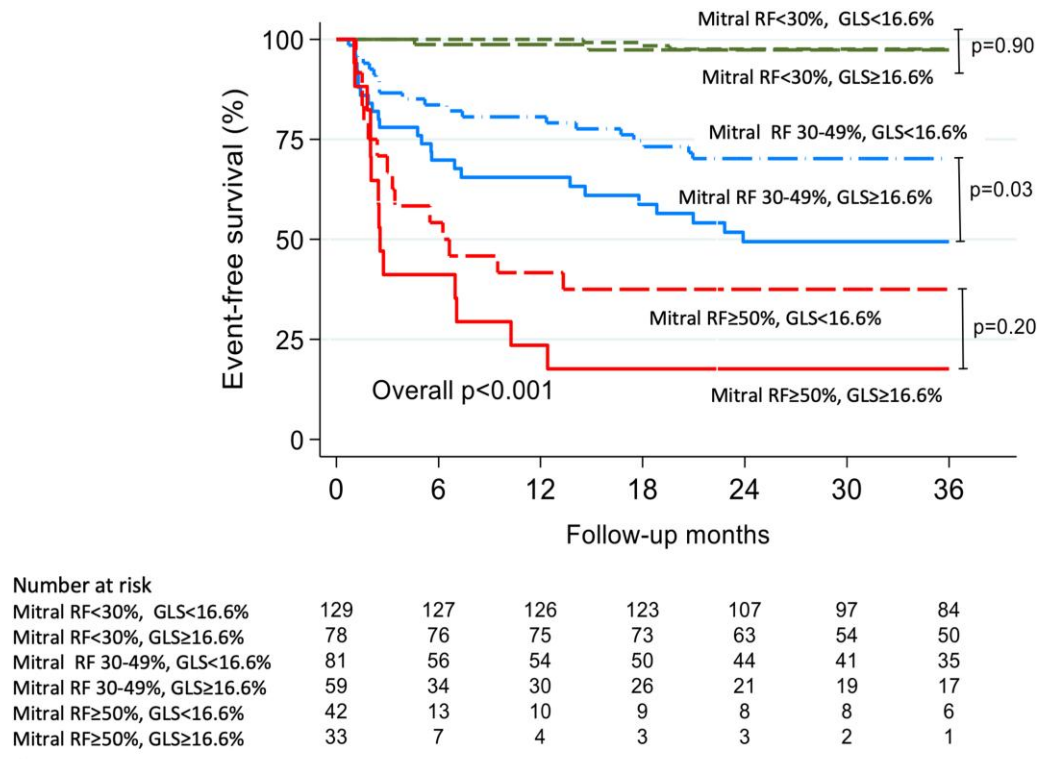


Figure 5 Kaplan–Meier curves for survival free of composite outcome (mitral surgery referral and cardiovascular death).

Table 3 Multivariable models demonstrating characteristics associated with all-cause death in patients with primary MR

	Model 1 ($n = 422$)		Model 2 ($n = 422$)	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age (years)	1.03 (1.00, 1.06)	0.02	1.03 (1.01, 1.06)	0.02
Diabetes	1.83 (0.74, 4.51)	0.19	1.74 (0.69, 4.37)	0.24
Mitral regurgitant fraction (10% increment)	1.33 (1.05, 1.69)	0.02	1.35 (1.06, 1.72)	0.02
Presence of LGE	–	–	0.76 (0.30, 1.91)	0.56
GLS ≥ −16.0%[a]	2.23 (1.11, 4.48)	0.03	2.24 (1.11, 4.52)	0.02
	C-statistic = 0.73		*C*-statistic = 0.73	

[a]GLS of −16.0% was identified as an optimal cut-point for this analysis by a Youden index (sensitivity 0.50, specificity 0.70 and area under the curve 0.60).
Univariable analysis is provided in Supplementary data online, *Table S3*.

perform. Despite stringent study design, we acknowledged that it may not be possible to entirely exclude certain secondary MR such as atrial function MR or functional MR in dilated cardiomyopathy with mild systolic dysfunction given that there were some overlap features with our primary MR cohorts and transoesophageal echocardiogram was not performed in all patients to determine aetiology of MR. However, these specific populations should comprise a small fraction of our study given that among 78 patients with indeterminate MR aetiology, there are four patients with LVEF between 50 and 60% and LV end-diastolic volume index >100 mL/m^2 and 7 patients with severely enlarged left atrium (LA volume index >72 mL/m^2). MR severity is known and found to be a strong predictor of adverse outcome in our patients with primary MR. When the patients were stratified by a severity of MR (*Figure 5*), a statistical significance for association of GLS and our composite outcome only achieved in moderate but not severe MR group despite similar magnitude of the difference between those with a GLS above or below −16.6%. The lack of a statistically significance for the severe MR group is likely related to a smaller number of subjects in severe MR group, and the use of GLS in this population requires further investigation and should not be disregarded. The prognostic and clinical implication of GLS in patients with primary MR needs to be confirmed in future studies that should emphasize on answering the questions whether (i) earlier intervention in patients with MR with impaired GLS will successfully improve long-term outcomes, (ii) there is

inter-vendor variability in GLS measurements, and (iii) the numerical thresholds of GLS may trigger earlier mitral intervention.

Conclusion

In patients with primary MR with preserved systolic function, GLS was associated with our composite outcomes of mitral surgery referral owing to symptoms or LV systolic dysfunction and cardiovascular death. Additionally, GLS is independently associated with all-cause mortality in this population. Our findings suggest that GLS may represent a marker of cardiac dysfunction in patients with primary MR with preserved systolic function allowing for the identification of patients likely to decompensate during observation.

Supplementary data

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

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Conflict of interest: None

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Apostolidou E, Maslow AD, Poppas A. Primary mitral valve regurgitation: update and review. *Glob Cardiol Sci Pract* 2017;**2017**:e201703.
2. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet* 2009;**373**:1382–94.
3. Lung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW *et al.* A prospective survey of patients with valvular heart disease in Europe: the euro heart survey on valvular heart disease. *Eur Heart J* 2003;**24**:1231–43.
4. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F *et al.* 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;**143**:e35–71.
5. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart* 2014;**100**:1673–80.
6. 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**(2 Pt 1):260–74.
7. Pedrizzetti G, Claus P, Kilner PJ, Nagel E. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. *J Cardiovasc Magn Reson* 2016;**18**:51.
8. Romano S, Mansour IN, Kansal M, Gheith H, Dowdy Z, Dickens CA *et al.* Left ventricular global longitudinal strain predicts heart failure readmission in acute decompensated heart failure. *Cardiovasc Ultrasound* 2017;**15**:6.
9. Romano S, Judd RM, Kim RJ, Kim HW, Klem I, Heitner JF *et al.* Feature-Tracking global longitudinal strain predicts death in a multicenter population of patients with ischemic and nonischemic dilated cardiomyopathy incremental to ejection fraction and late gadolinium enhancement. *JACC Cardiovasc Imaging* 2018;**11**:1419–29.
10. Romano S, Judd RM, Kim RJ, Kim HW, Klem I, Heitner J *et al.* Association of feature-tracking cardiac magnetic resonance imaging left ventricular global longitudinal strain with all-cause mortality in patients with reduced left ventricular ejection fraction. *Circulation* 2017;**135**:2313–5.
11. Romano S, Judd RM, Kim RJ, Heitner JF, Shah DJ, Shenoy C *et al.* Feature-Tracking global longitudinal strain predicts mortality in patients with preserved ejection fraction: a multicenter study. *JACC Cardiovasc Imaging* 2020;**13**:940–7.
12. Romano S, Judd RM, Kim RJ, Kim HW, Heitner JF, Shah DJ *et al.* Prognostic implications of mitral annular plane systolic excursion in patients with hypertension and a clinical indication for cardiac magnetic resonance imaging: a multicenter study. *JACC Cardiovasc Imaging* 2019;**12**:1769–79.
13. 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**(2 Pt 2):577–85.
14. Medvedofsky D, Pio M, Weissman S, Namazi NJ, Delgado F, Grayburn V *et al.* Left ventricular global longitudinal strain as a predictor of outcomes in patients with heart failure with secondary mitral regurgitation: the COAPT trial. *J Am Soc Echocardiogr* 2021;**34**:955–65.
15. Bijvoet GP, Teske AJ, Chamuleau SAJ, Hart EA, Jansen R, Schaap J. Global longitudinal strain to predict left ventricular dysfunction in asymptomatic patients with severe mitral valve regurgitation: literature review. *Neth Heart J* 2020;**28**:63–72.
16. Levine RA, Stathogiannis E, Newell JB, Harrigan P, Weyman AE. Reconsideration of echocardiographic standards for mitral valve prolapse: lack of association between leaflet displacement isolated to the apical four chamber view and independent echocardiographic evidence of abnormality. *J Am Coll Cardiol* 1988;**11**:1010–9.
17. Han Y, Peters DC, Salton CJ, Bzymek D, Nezafat R, Goddu B *et al.* Cardiovascular magnetic resonance characterization of mitral valve prolapse. *JACC Cardiovasc Imaging* 2008;**1**:294–303.
18. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA *et al.* Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–71.
19. Klem I, Heiberg E, Van Assche L, Parker MA, Kim HW, Grizzard JD *et al.* Sources of variability in quantification of cardiovascular magnetic resonance infarct size—reproducibility among three core laboratories. *J Cardiovasc Magn Reson* 2017;**19**:62.
20. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;**3**:32–5.
21. Hastie T, Tibshirani R, Wainwright M. *Statistical Learning with Sparsity: the Lasso and Generalizations*. Boca Raton, FL: CRC Press; 2015.
22. Kitkungvan D, Nabi F, Kim RJ, Bonow RO, Khan MA, Xu J *et al.* Myocardial fibrosis in patients with primary mitral regurgitation with and without prolapse. *J Am Coll Cardiol* 2018;**72**:823–34.
23. Kitkungvan D, Yang EY, Tallawi E, Nagueh KC, Nabi SF, Khan F *et al.* Extracellular volume in primary mitral regurgitation. *JACC Cardiovasc Imaging* 2021;**14**:1146–60.
24. Goldstone AB, Patrick WL, Cohen JE, Aribeana CN, Popat R, Woo YJ. Early surgical intervention or watchful waiting for the management of asymptomatic mitral regurgitation: a systematic review and meta-analysis. *Ann Cardiothorac Surg* 2015;**4**:220–9.
25. Sanderson JE. Left and right ventricular long-axis function and prognosis. *Heart* 2008;**94**:262–3.
26. Henein MY, Gibson DG. Long axis function in disease: editorial. *Heart* 1999;**81**:229–31.
27. Manaka M, Tanaka N, Takei Y, Kurohane S, Takazawa K, Yamashina A. Assessment of regional myocardial systolic function in hypertensive left ventricular hypertrophy using harmonic myocardial strain imaging]. *J Cardiol* 2005;**45**:53–60.
28. Henein MY. Normal long axis function. *Heart* 1999;**81**:111–3.
29. Sengupta PP, Korinek J, Belohlavek M, Narula J, Vannan MA, Jahangir A *et al.* Left ventricular structure and function: basic science for cardiac imaging. *J Am Coll Cardiol* 2006;**48**:1988–2001.
30. Kim MS, Kim YJ, Kim HK, Han JY, Chun HG, Kim HC *et al.* Evaluation of left ventricular short- and long-axis function in severe mitral regurgitation using 2-dimensional strain echocardiography. *Am Heart J* 2009;**157**:345–51.
31. Eckberg DL, Gault JH, Bouchard RL, Karliner JS, Ross J. Mechanics of left ventricular contraction in chronic severe mitral regurgitation. *Circulation* 1973;**47**:1252–9.
32. Ross J. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy. *J Am Coll Cardiol* 1985;**5**:811–26.
33. 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.
34. 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. *J Am Coll Cardiol Img* 2018;**11**:1235–44.
35. Modaragamage Dona AC Afoke J Punjabi PP Kanaganayagam GS. Global longitudinal strain to determine optimal timing for surgery in primary mitral regurgitation: a systematic review. *J Card Surg*. 2021;**36**:2458–66.
36. Namazi F, van der Bijl P, Hirasawa K, Kamperidis V, van Wijngaarden SE, Mertens B *et al.* Prognostic value of left ventricular global longitudinal strain in patients with secondary mitral regurgitation. *J Am Coll Cardiol* 2020;**75**:750–8.
37. 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 Heart J* 2016;**37**:811–6.