Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis

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Aims
To assess the capacity of global longitudinal strain (GLS) in patients with aortic stenosis (AS) to (i) detect the subclinical left ventricular (LV) dysfunction [LV ejection fraction (LVEF) ≥50% patients]; (ii) predict all-cause mortality and major adverse cardiac events (MACE) (all patients), and (iii) provide incremental prognostic information over current risk markers.

Methods and results
Patients with AS (n = 146) and age-matched controls (n = 12) underwent baseline echocardiography to assess AS severity, conventional LV parameters and GLS via speckle tracking echocardiography. Baseline demographics, symptom severity class and comorbidities were recorded. Outcomes were identified via hospital record review and subject/physician interview. The mean age was 75 ± 11, 62% were male. The baseline aortic valve (AV) area was 1.0 ± 0.4 cm² and LVEF was 59 ± 11%. In patients with a normal LVEF (n = 122), the baseline GLS was controls 21 ± 2%, mild AS 18 ± 3%, moderate AS 17 ± 3% and severe AS 15 ± 3% (P,0.001). GLS correlated with the LV mass index, LVEF, AS severity, and symptom class (P,0.05). During a median follow-up of 2.1 (inter-quartile range: 1.8–2.4) years, there were 20 deaths and 101 MACE. Unadjusted hazard ratios (HRs) for GLS (per %) were all-cause mortality (HR: 1.42, P,0.001) and MACE (HR: 1.09, P,0.001). After adjustment for clinical and echocardiographic variables, GLS remained a strong independent predictor of all-cause mortality (HR: 1.38, P,<0.001).

Conclusions
GLS detects subclinical dysfunction and has incremental prognostic value over traditional risk markers including haemodynamic severity, symptom class, and LVEF in patients with AS. Incorporation of GLS into risk models may improve the identification of the optimal timing for AV replacement.

Keywords
Aortic stenosis • Echocardiography • Myocardial function • Outcomes

Introduction
The assessment of symptomatic status and left ventricular (LV) function are key components in the risk stratification of patients with aortic stenosis (AS). Symptomatic AS is associated with an approximate mortality rate of 25% per annum in untreated patients.1,2 Timely intervention with aortic valve (AV) replacement (AVR) is associated with a small but usually acceptable mortality risk and survivors of AVR enjoy life expectancy similar to age-matched controls.3 The increasing age and clinical complexity of patients presenting with AS make symptom diagnosis challenging and often unreliable.4,5 Current guidelines identify LV ejection fraction (LVEF) as an objective marker of elevated cardiac risk.2,6 However, when compared with patients undergoing AVR with a normal LVEF, patients with an impaired LVEF have increased operative mortality,7,8 inferior long-term prognosis7 and in up to 50% of cases do not recover a normal LV function following AVR, suggesting that an impaired LVEF is an advanced stage of...

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dysfunction associated with permanent myocardial damage.\textsuperscript{8–10} Objective markers are required to assist risk stratification of patients with AS and to identify high-risk patients before LVEF declines.

Speckle tracking echocardiography (STE) is a new, validated technique which enables highly reproducible, angle-independent assessment of regional and global LV systolic function in longitudinal, circumferential and radial planes.\textsuperscript{11–13} Longitudinal strain, which is predominantly governed by the subendocardial layer, is most sensitive in the presence of myocardial disease.\textsuperscript{13} To date, published data utilizing STE for the assessment of longitudinal strain has concentrated on the detection of subclinical LV dysfunction in patients with severe AS\textsuperscript{14–16} and LV functional recovery post-AVR.\textsuperscript{17,18} In patients with AS, the prognostic capacity of longitudinal strain, in particular whether longitudinal strain can predict all-cause mortality remains uncertain.

The aims of this prospective cohort study were as follows:

(i) To assess the capacity of global longitudinal strain (GLS) to detect the subclinical LV dysfunction in patients with AS and preserved LVEF (patients with LVEF \( \geq 50\% \) only).

(ii) To assess the capacity of GLS to predict adverse outcomes of all-cause mortality (primary endpoint) and major adverse cardiac events (MACE) (secondary endpoint) in patients with AS (all patients).

(iii) To assess whether GLS provides incremental prognostic value over current risk markers including the mean AV gradient, symptomatic status and LVEF in patients with AS (all patients).

\textbf{Methods}

\textbf{Study population}

Consecutive patients with mild, moderate and severe AS over 18 years of age were recruited from the cardiology clinic of an Australian tertiary university teaching hospital between June 2008 and May 2010. Patients with an additional valve lesion greater than moderate severity were excluded. Outcome data analysis was performed on the total study population (\( n = 146 \)). For assessment of the subclinical LV dysfunction (aim 1), only patients with an LVEF \( \geq 50\% \) were included (\( n = 122 \); Figure 1). The control group (\( n = 12 \)) were age matched and had no history of cardiovascular disease. This study complies with the Declaration of Helsinki. The study protocol was approved by the institutional ethics board at Austin Health, Melbourne and all patients gave informed consent.

\textbf{Baseline data collection}

At baseline, demographics, comorbidities and symptomatic status were recorded and transthoracic echocardiography (TTE) performed. Comorbidity assessment incorporated the age-adjusted Charlson comorbidity index (age-CCI),\textsuperscript{19} a validated risk index for the prediction of mortality in chronic disease. Coronary angiography was performed on all patients under consideration for AVR and in patients with clinical symptoms suggestive of myocardial ischaemia. Coronary artery disease was defined as a stenosis \( \geq 50\% \).

The presence and severity of AS-related symptoms (angina, syncope and dyspnoea) were recorded with a composite symptom severity score incorporating the Canadian Cardiovascular Society angina scale and New York Heart Association class: I, no symptoms; II, symptoms with moderate exertion; III, symptoms with mild exertion and IV, symptoms at rest.

\textbf{Echocardiography}

TTE was performed using commercially available ultrasound systems (GE Vivid 7, 2.5 MHz transducer) in the left lateral decubitus position by experienced sonographers. Measurements and recordings were obtained according to the American Society of Echocardiography (ASE) guidelines.\textsuperscript{20,21} The LV mass index (LVMi) was defined using the ASE formula. LVEF was defined by Simpson’s biplane method. The ratio of early mitral inflow (E) to early mitral annular velocity (e’) at the septal annulus using tissue Doppler imaging was calculated to assess the diastolic function.\textsuperscript{72} Pulsed-wave and continuous-wave Doppler ultrasound was used to record velocities through the LV outflow tract (LVOT) and AV, respectively. The AV was examined from multiple windows including apical, suprasternal and right parasternal to obtain the peak AV velocity and the mean AV gradient. The AV area (AVA) was calculated using the continuity equation.\textsuperscript{23} AS severity was classified according to current American Heart Association/American College of Cardiology guidelines\textsuperscript{2} as mild (AVA of \( > 1.5 \text{ cm}^2 \) or the mean AV gradient of \( < 25\text{ mmHg} \)), moderate (AVA of \( 1.0–1.5 \text{ cm}^2 \) or mean AV gradient of \( 25–40\text{ mmHg} \)), or severe AS (AVA of \( < 1.0 \text{ cm}^2 \) or mean AV gradient of \( > 40\text{ mmHg} \)).

\textbf{Speckle tracking echocardiography: global longitudinal strain}

For optimal image acquisition, a narrow image sector was chosen to enable frame rates between 55 and 90 frames per second. Three consecutive cardiac cycles in the apical two-, three- and four-chamber views were acquired for offline analysis (EchoPac, GE Vingmed, version 6.1.0). GLS was defined as the average peak systolic strain across 18 myocardial segments, 6 from each of the three standard apical views. End systole was determined from the LV outflow Doppler flow profile. The endocardium was manually traced in each view and the region of interest width adjusted to include the entire myocardium. Myocardial motion was tracked by automated software and only segments with adequate tracking were accepted for further analysis. Subject data were accepted for analysis when at least 12 of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Study population flow chart.}
\end{figure}
Global longitudinal strain and subclinical dysfunction in patients with aortic stenosis

One-hundred and twenty patients with AS and LVEF ≥ 50% were included in the analysis for the subclinical dysfunction (mild AS, 26%; moderate AS, 21%; and severe AS 53%). The mean GLS results were control −21.2 ± 2.4%, mild AS −17.9 ± 2.6%, moderate AS −16.8 ± 2.9%, severe AS −15.0 ± 3.1% (ANOVA P < 0.001; Figure 2). The subclinical LV dysfunction, defined as a GLS > 2 SD below the mean of the age-matched control population, was present in 17, 40, and 69% of patients with mild, moderate, and severe AS, respectively (P < 0.001). GLS was significantly associated with the mean AV gradient (r = 0.41, P < 0.001), AVA (r = −0.33, P < 0.001), LVEF (r = −0.37, P < 0.001), LVMI (r = 0.32, P = 0.001), log E/e′ (r = 0.26, P = 0.008), and composite symptom class (I −17.1 ± 2.6%, II −15.0 ± 3.1%, III −14.2 ± 0.9).

Table I Baseline patient characteristics according to final outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Alive</th>
<th>Dead</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>146</td>
<td>126</td>
<td>20</td>
<td>0.004</td>
</tr>
<tr>
<td>Age (years)</td>
<td>75 ± 11</td>
<td>74 ± 10</td>
<td>81 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>91 (62)</td>
<td>79 (63)</td>
<td>12 (60)</td>
<td>0.82</td>
</tr>
<tr>
<td>Age-CCI</td>
<td>6 ± 3</td>
<td>6 ± 2</td>
<td>9 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>116 (79)</td>
<td>102 (81)</td>
<td>14 (70)</td>
<td>0.26</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>58 (40)</td>
<td>43 (34)</td>
<td>15 (75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>49 (34)</td>
<td>34 (27)</td>
<td>15 (75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38 (26)</td>
<td>29 (23)</td>
<td>9 (45)</td>
<td>0.04</td>
</tr>
<tr>
<td>Symptom severity class</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>86 (59)</td>
<td>78 (62)</td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>41 (28)</td>
<td>38 (30)</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>15 (10)</td>
<td>10 (8)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean aortic valve gradient (mmHg)</td>
<td>40 ± 20</td>
<td>39 ± 19</td>
<td>44 ± 23</td>
<td>0.28</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>0.8 ± 0.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>59 ± 11</td>
<td>60 ± 10</td>
<td>49 ± 15</td>
<td>0.01</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>120 ± 38</td>
<td>117 ± 35</td>
<td>139 ± 50</td>
<td>0.08</td>
</tr>
<tr>
<td>E/e′ &lt; 15 (septal)</td>
<td>77 (53)</td>
<td>63 (50)</td>
<td>14 (70)</td>
<td>0.004</td>
</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>−15 ± 4</td>
<td>−16 ± 3</td>
<td>−10 ± 4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD or n (%) unless stated. Age-CCI, age-adjusted Charlson comorbidity index.

Global longitudinal strain and aortic stenosis

Follow-up

Patients were followed yearly with repeat TTE and clinical assessment. At each visit, symptomatic status and comorbidities were recorded. Outcomes were determined via interview of the patient or managing physician and hospital record review. MACE was defined as death or hospitalization due to cardiac causes and included cardiac mortality, non-fatal myocardial infarction, congestive cardiac failure, arrhythmia, cerebrovascular accident, AVR (surgical and percutaneous) and other AS-related admission such as syncope, aortic valvuloplasty or angina. For MACE analysis, patient data were censored at the first MACE episode. Outcomes were assessed by two independent adjudicators blinded to the echocardiographic data.

Statistical analysis

Analysis was performed using the Predictive Analytics Software Statistics 18 (SPSS, Inc., Chicago, IL, USA). Continuous data are reported as the mean ± standard deviation (SD) and comparison between groups utilized the independent samples t-test or ANOVA for parametric variables with Bonferroni statistics to correct for multiple comparisons. Categorical variables are presented as numbers (%) and compared by χ² analysis. Pearson’s correlation statistic assessed correlations with GLS. Data with non-normal distributions were log transformed prior to analysis. Multivariate Cox proportional hazards analysis with forward stepwise selection was performed using significant variables (P < 0.05) from univariate analysis to identify independent predictors of all-cause mortality. Two multivariate models were examined: Model 1 incorporating the age-CCI and Model 2 incorporating age and individual comorbidities. Receiver-operating characteristic (ROC) curve analysis determined the GLS value with the best combination of sensitivity and specificity for all-cause mortality. Kaplan–Meier curves were constructed to depict survival between the groups. The log-rank test was used to compare survival curves. Two-tailed P values of < 0.05 were considered statistically significant.

Results

One-hundred and forty-six patients were enrolled in the study and no patient was lost to follow-up. Baseline characteristics of patients are detailed in Table 1. Baseline AS severity was mild (22%), moderate (25%), and severe (53%). Over a median follow-up of 2.1 (inter-quartile range: 1.8–2.4) years, there were 20 deaths and 101 patients recorded a MACE. GLS was measurable in 135 of 146 studies (feasibility 92%); baseline characteristics of excluded patients were similar to the analysed cohort. The mean GLS analysis time was 5 min per subject.

18 myocardial segments were tracked successfully. GLS is a negative parameter and less negative values represent lesser degrees of contraction. For outcomes analysis, GLS was classified into two groups: satisfactory GLS ≤ −15% and low GLS > −15%. A GLS cut-off of −15% has previously been shown to predict an abnormal response to exercise in asymptomatic AS. Managing physicians were blinded to the GLS results. Reproducibility of GLS measurement, expressed as the coefficient of variation, has been previously published by our group as 3.5 and 6.3% for intra-observer and inter-observer variation, respectively.24
3.1%, and IV $-9.2 \pm 2.0\%$, $P < 0.001$). GLS was also significantly lower in patients with a history of congestive cardiac failure (GLS $14.2 \pm 3.2\%$ versus 16.8 $\pm 2.9\%$, $P < 0.001$). GLS was not associated with coronary artery disease ($P = 0.29$) or diabetes mellitus ($P = 0.09$).

**All-cause mortality**

Twenty deaths were recorded during the follow-up period. The cause of death was confirmed as cardiac in 11 cases [congestive cardiac failure ($n = 4$), sudden cardiac death ($n = 3$), acute coronary syndrome ($n = 2$) and AVR-related mortality ($n = 2$)], non-cardiac in 3 patients and was uncertain in 6 patients. The baseline GLS was significantly lower in patients who died during follow-up (dead $10 \pm 4\%$; alive $16 \pm 3\%$, $P < 0.001$). Patients who received guideline-indicated AVR ($n = 70$) during the study had lower mortality (7%) than patients with severe AS managed conservatively (47%; $P < 0.001$). The baseline GLS was associated with mortality following AVR ($n = 5$; dead $9 \pm 4\%$; alive $15.5 \pm 3\%$, $P < 0.001$).

**Predictors of all-cause mortality**

On univariate analysis, GLS was a strong predictor of all-cause mortality (unadjusted hazard ratio (HR): 1.42 (per %), 95% confidence interval (CI): 1.27–1.59, $P < 0.001$) (Figure 3) and all but one death occurred in patients with a low GLS ($> -15\%$) at baseline. The remaining patient had severe pulmonary hypertension. Other univariate predictors of all-cause mortality were age, age-CCI, coronary artery disease, congestive cardiac failure, symptom severity class, LVMI, LVEF, AVA, and E/e’ (Table 2).

Multivariate analysis demonstrated the baseline GLS to be a strong independent predictor of all-cause mortality after adjustment for important clinical and echocardiographic variables with a 28–38% increase in the relative risk of all-cause mortality per

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**Figure 2** Box plot demonstrating the relationship between global longitudinal strain and aortic stenosis severity in patients with preserved left ventricular ejection fraction (≥50%). Global longitudinal strain was measurable in 114/122 patients with AS (95%). *P < 0.01, †P < 0.001. AS, aortic stenosis.

**Figure 3** Kaplan–Meier plot illustrating the overall survival of patients with aortic stenosis. Patients are stratified into satisfactory (GLS $\leq -15\%$) and low (GLS > $-15\%$) global longitudinal strain groups (log rank $P < 0.001$). GLS, global longitudinal strain.

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**Table 2** Predictors of all-cause mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate predictors</td>
<td>1.10</td>
<td>1.03–1.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.88</td>
<td>0.36–2.15</td>
<td>0.78</td>
</tr>
<tr>
<td>Symptom severity class</td>
<td>2.61</td>
<td>1.67–4.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-adjusted Charlson comorbidity index</td>
<td>1.57</td>
<td>1.30–1.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5.12</td>
<td>1.82–13.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>6.76</td>
<td>2.45–18.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.60</td>
<td>1.08–6.27</td>
<td>0.03</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.57</td>
<td>0.22–1.49</td>
<td>0.25</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>0.94</td>
<td>0.91–0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean aortic valve gradient (mmHg)</td>
<td>1.01</td>
<td>0.99–1.04</td>
<td>0.23</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.17</td>
<td>0.03–0.78</td>
<td>0.02</td>
</tr>
<tr>
<td>E/e’ &gt; 15 (septal)</td>
<td>10.7</td>
<td>1.41–81.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>1.42</td>
<td>1.27–1.59</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariate predictors (Model 1)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global longitudinal strain (%)</td>
<td>1.28</td>
<td>1.09–1.49</td>
</tr>
<tr>
<td>Symptom severity class</td>
<td>1.68</td>
<td>1.10–2.57</td>
</tr>
<tr>
<td>Age-adjusted Charlson comorbidity index</td>
<td>1.27</td>
<td>1.02–1.58</td>
</tr>
</tbody>
</table>

Multivariate predictors (Model 2)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global longitudinal strain (%)</td>
<td>1.38</td>
<td>1.20–1.60</td>
</tr>
<tr>
<td>Symptom severity class</td>
<td>2.36</td>
<td>1.47–3.79</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>3.66</td>
<td>1.12–12.0</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval. Model 1 included the age-adjusted Charlson comorbidity index ($\chi^2 = 68.6, P < 0.001$). Model 2 included age and individual comorbidities ($\chi^2 = 519, P < 0.001$).
1% decrease in the magnitude of GLS (Table 2). Additional independent prognostic markers of all-cause mortality were symptom severity class and the age-CCI (Model 1); and symptom severity class and congestive cardiac failure (Model 2). Baseline AS severity parameters, LVMI, LVEF, diastolic function and age did not predict all-cause mortality on multivariate analysis.

Additional independent prognostic markers of all-cause mortality were symptom severity class and the age-CCI (Model 1); and symptom severity class and congestive cardiac failure (Model 2). Baseline AS severity parameters, LVMI, LVEF, diastolic function and age did not predict all-cause mortality on multivariate analysis.

Figure 4A–C demonstrates the incremental prognostic value of GLS over current risk markers. In each graph, all-cause mortality is primarily determined by a low GLS rather than the mean AV gradient, symptomatic status or LVEF, respectively. Notably GLS assessment may assist in the detection of high-risk individuals with low-gradient AS (Figure 4A) or asymptomatic AS (Figure 4B). Furthermore, the adverse prognosis of the ‘low GLS, LVEF ≥50%’ group (Figure 4C) supports an association between the subclinical LV dysfunction and mortality risk. Using ROC curve analysis for all-cause mortality, area-under-curve (AUC) values were GLS (0.90, P < 0.001), LVEF (0.71, P = 0.002), AVA (0.66, P = 0.02), and mean AV gradient (0.57, P = 0.33; Figure 5). A GLS threshold of −15% had a sensitivity of 94% and a specificity of 68% for detecting all-cause mortality (HR: 30.5, 95% CI: 4.1–229.0, P = 0.001). A GLS threshold of −12.8% produced the best combination of sensitivity (83%) and specificity (87%) for all-cause mortality.

### Major adverse cardiac events

One-hundred and one patients (69%) recorded an MACE during the follow-up period. The proportion of MACE according to initial AS severity was severe (72%), moderate (25%) and mild (3%). The causes of first MACE were AVR (57%), non-fatal myocardial infarction (10%), cardiac death (6%), congestive cardiac failure (6%), arrhythmia (6%), cerebrovascular accident (2%) and other AS-related admission (13%). MACE was strongly dependent on the baseline GLS (per %; HR: 1.09, 95% CI: 1.04–1.15, P < 0.001). One-year MACE-free survival in patients with a low GLS was only 25% compared with 58% in patients with satisfactory GLS (P < 0.001; Figure 6). The HR for MACE with low GLS was 2.46 (95% CI: 1.62–3.74, P < 0.001).

### Discussion

To the authors’ knowledge, this is the first prospective study to demonstrate the independent prognostic capacity of GLS for all-cause mortality in patients with AS. Furthermore, we highlight the incremental value of GLS over existing guideline-validated risk markers, symptoms, LVEF and haemodynamic severity. GLS is a simple, rapid and reproducible parameter for the assessment of risk in patients with AS and incorporation of GLS into risk stratification models may enable better identification of the optimal timing for AVR.

### Global longitudinal strain and subclinical dysfunction in aortic stenosis

This study documents a high prevalence of subclinical LV dysfunction in patients with moderate and severe AS, suggesting traditional risk models which concentrate on AV gradients, AVA and impairment of LVEF are insensitive to early maladaptive processes within the LV myocardium. The subclinical LV dysfunction has been described in patients with mild to moderate AS,16,17,25 but this is the first study to identify an association between the subclinical dysfunction (defined by GLS) and increased all-cause mortality in patients with AS. In addition, we found significant associations between GLS and measures of AS severity, LVMI, LV function (LVEF and E/e′), and clinical status (symptom class, congestive cardiac failure).

### Prognostic markers in aortic stenosis

In our study, a GLS threshold of −15% identified patients with a 30-fold risk of all-cause mortality. The association between GLS and all-cause mortality was independent of existing risk stratification variables including age, gender, symptoms, cardiac and non-cardiac comorbidities, mean AV gradient, AVA, and LVEF. A low GLS (>−15%) was associated with MACE-free survival of just 25% at 1 year, indicating a possible threshold for early operation in patients with uncertain or absent symptoms. In addition, GLS...
assessment identified a high-risk cohort with low-gradient AS. Finally, there was an association between low GLS and post-AVR mortality.

The majority of studies evaluating longitudinal strain in patients with AS, has used older tissue Doppler imaging technology. Advantages of STE for strain measurement over tissue Doppler techniques include angle-independence, ease, and reproducibility of both regional and global assessments. To date, published data utilizing STE for assessment of longitudinal strain has concentrated on the detection of subclinical LV dysfunction, LV functional recovery post-AVR, and prediction of composite cardiac endpoints. Lafitte et al. studied patients with severe, asymptomatic AS and LVEF >55% (n = 60, follow-up 12 months) and demonstrated an association between basal longitudinal strain (average six basal segments) and the composite endpoint of cardiac hospitalization, AVR or cardiovascular death. Lancellotti et al. studied asymptomatic patients with moderate to severe AS (n = 163, follow-up 20 ± 19 months) and found GLS ≥ −15.9% was a significant predictor of symptom development, AVR or death. Lancellotti et al. defined GLS as the average of 12 segments from apical two- and four-chamber views: a less rigorous assessment than the 18 segment model employed in our study.

The development of symptoms and LV systolic dysfunction (LVEF <50%) are poor prognostic factors in severe AS. However, the increasing age and medical complexity of patients can make accurate assessment of symptomatic status difficult. Furthermore, improvements in surgical techniques and the advent of percutaneous valve implantation techniques have shifted the emphasis towards identifying high-risk asymptomatic patients before LVEF declines. Potential objective prognostic markers include LVMI, myocardial fibrosis and myocardial strain. LVMI is an independent predictor of symptom development in asymptomatic AS. Histopathological and cardiac magnetic resonance studies have confirmed the presence of fibrosis within the hypertrophied LV myocardium of patients with severe AS. Furthermore, the amount of myocardial fibrosis predicts LV functional recovery and all-cause mortality late after AVR. These findings emphasize the need to move beyond current AVR guidelines and identify markers of early LV dysfunction.

GLS is associated with LVMI and is influenced by myocyte contraction, surrounding the tissue composition (myocardial fibrosis) and pressure–volume characteristics of the LV. Therefore, GLS represents an ideal marker of LV myocardial dysfunction in patients with AS. GLS is predominantly governed by the sub-endocardial layer; therefore it is the most sensitive strain parameter in the presence of myocardial disease. The middle and subepicardial myocardial layers are concerned with circumferential and twist mechanics and help determine LVEF, however are less susceptible to damage from chronic pressure overload in AS. Therefore, abnormalities in GLS characteristically detect early myocardial dysfunction whilst a reduced LVEF reflects a more transmural disease process.

Study limitations

As a consequence of sample size and follow-up duration, the number of all-cause mortality events was low, therefore further studies of larger cohorts with longer follow-up duration are required to confirm our findings and identify the best GLS threshold for prediction of adverse outcomes. Secondly, STE is dependent upon adequate image quality and frame rates, but feasibility (92%) and reproducibility in our study was high.
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Conclusions
Abnormal GLS, reflecting the LV systolic dysfunction, is a common finding in patients with moderate and severe AS and frequently precedes symptoms and a reduction in LVEF. The measurement of GLS is rapid, highly reproducible and in patients with AS, GLS is a strong predictor of adverse cardiac events, including all-cause mortality and provides incremental prognostic value over guideline-validated risk markers, such as haemodynamic severity, symptoms and LVEF. The incorporation of GLS into risk models may improve the identification of the optimal timing for AVR.

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