Global longitudinal strain to determine optimal timing for surgery in primary mitral regurgitation: A systematic review

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Abstract

Background: Primary mitral regurgitation (PMR) results in adverse remodeling changes and left ventricular (LV) dysfunction. Assessing LV function has prognostic value in predicting morbidity and mortality. Indications for surgery include parameters such as LV ejection fraction (LVEF) and systolic dimensions. Current guidelines are limited in identifying patients at optimal time for surgery. Impaired postoperative LVEF indicates poor prognostic outcomes and subsequent heart failure. Global longitudinal strain (GLS) via speckle tracking echocardiography (STE) presents as a promising parameter to detect subclinical dysfunction in asymptomatic patients.

Methods: Following PRISMA guidelines, a literature search was conducted with Cochrane Library, PubMed, SCOPUS, and Web of Science. Key MeSH terms included “mitral regurgitation,” “mitral valve insufficiency,” “global longitudinal strain,” “deformation,” “LV-GLS,” and “GLS.” Inclusion criteria included (1) patients with severe PMR, (2) mixed population of symptomatic and asymptomatic patients, (3) standardized methods in assessing LV systolic function using 2D-STE, (4) valve repair or replacement surgery, and (5) patient outcomes measured after surgery. Search returned 234 papers, 12 of which met the inclusion criteria and were subsequently reviewed.

Results: Baseline GLS is an independent predictor of postoperative outcomes, ranging from ~17.9 to ~21.7% GLS. A significant negative correlation was observed between preoperative GLS and postoperative LVEF. Impaired baseline GLS was associated with higher mortality rates. Better long-term survival rates were seen in patients who underwent early surgery.

Conclusion: GLS shows sensitivity in predicting long-term postoperative outcomes. Further analysis is required to determine preoperative GLS threshold to identify asymptomatic patients at the optimal time for mitral valve surgery.

Keywords

echocardiography, global longitudinal strain, left ventricular function, primary mitral regurgitation
INTRODUCTION

Mitral regurgitation (MR) is defined as retrograde blood flow from the left ventricle (LV) through the mitral valve (MV) into the left atrium (LA). Primary MR (PMR), also known as organic, intrinsic, or degenerative MR, is due to organic or structural dysfunction of the MV. In the Euro Heart Survey, severe MR was the second most common valvular abnormality. With PMR disease progression, contractile function can be preserved, which can mask subclinical LV dysfunction. This may progress to adverse remodeling changes in the absence of clinical symptoms. These changes are often unmasked by changes in hemodynamic and loading conditions after surgical intervention, leading to heart failure (HF). Tribouilloy et al. observed a higher long-term survival with lower operative mortality in asymptomatic patients compared to patients with severe symptoms. The health burden of PMR necessitates identification of early subclinical LV dysfunction in asymptomatic patients, before irreversible remodeling changes occur. In doing so, clinicians can better define the optimal timing for surgery.

Surgery is recommended for asymptomatic patients with severe PMR and LV dysfunction (Table 1). LV dysfunction is defined as LV ejection fraction (LVEF) less than 60% and/or LV end-systolic diameter (LVESD) ≥ 45 mm. Surgery is also indicated for symptomatic patients with LVEF > 30%. In addition, surgery is recommended in patients with new-onset atrial fibrillation or pulmonary hypertension (systolic pulmonary arterial pressure [SPAP] > 50 mmHg). Recent work concluded that triggers for Class-I were associated with doubling of long-term death/HF risk. When triggers present, they necessitate rescue surgery and are not the triggers for preferred surgical timing. LVEF is a load-dependent measure of systolic function. Hemodynamic compensation in chronic volume overload, can preserve LVEF despite decline in myocardial contractile function. Therefore, LVEF is a relatively late marker in detecting myocardial dysfunction. In addition, echocardiographic measurements of LVEF have considerable intraobserver and interobserver variability. Therefore, there is a need for reproducible, accurate, and load-independent echocardiographic parameters that can detect early subclinical LV dysfunction in asymptomatic patients.

Cardiac contraction causes a change in myocardial length, described as deformation. Strain defines the intrinsic deformation by application of a force. Myocardial strain represents the percentage

### Table 1

**European Society of Cardiology (2017) guidelines**

<table>
<thead>
<tr>
<th>Class</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C</td>
<td>Mitral valve repair should be the preferred technique when the results are expected to be durable</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
<td>Surgery is indicated in symptomatic patient with LVEF &gt; 30%</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
<td>Surgery is indicated in asymptomatic patients with LV dysfunction (LVEF &lt; 60% and/or LVESD ≥ 45 mm)</td>
</tr>
<tr>
<td>IIa</td>
<td>B</td>
<td>Surgery should be considered in asymptomatic patients with preserved LV function (LVEF &gt; 60%) and AF secondary to MR or pulmonary hypertension (SPAP at rest &gt; 50 mmHg)</td>
</tr>
<tr>
<td>IIa</td>
<td>B</td>
<td>Surgery should be considered in asymptomatic patients with preserved LV function (LVEF &gt; 60%) and LVESD 40–44 mm when durable repair is likely, surgical risk is low, the repair is performed in a heart valve center, and at least one of the following findings is present: Flail leaflet Presence of significant LA dilatation in sinus rhythm (volume index ≥ 60 ml/m² BSA)</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>Mitral valve repair should be considered in symptomatic patients with severe LV dysfunction (LVEF &lt; 30% and/or LVESD &gt; 55 mm) refractory to medical therapy when the likelihood of successful repair is high and comorbidity low</td>
</tr>
<tr>
<td>IIb</td>
<td>C</td>
<td>Mitral valve replacement may be considered in symptomatic patients with severe LV dysfunction (LVEF &lt; 30% and/or LVESD &gt; 55 mm) refractory medical therapy when the likelihood of successful repair is low and comorbidity low</td>
</tr>
<tr>
<td>IIb</td>
<td>C</td>
<td>Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe PMR who fulfill the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the Heart Team, avoiding futility</td>
</tr>
</tbody>
</table>

Note: Table outlining recommendations of surgical intervention for chronic severe primary mitral regurgitation. Categorized by class of indication (I, IIa, and IIb) with corresponding level of evidence (LOE).

Abbreviations: AF, atrial fibrillation; BSA, body surface area; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure.
change in myocardial length from a relaxed to a contracted state, expressed as a negative percentage (Figure 1). Strain incorporates the study of different spatial components of myocardial contractility, including longitudinal, circumferential and radial strain, both globally and regionally (Figure 2A). Speckle tracking echocardiography (STE) is a novel imaging modality for the assessment of myocardial strain in determining LV global and regional function. It is commonly hypothesized that in many cardiac pathologies, the first change is the loss of function in endocardial and epicardial longitudinal fibers. This is compensated by augmenting circumferential fiber shortening in the mid-wall to preserve LV function. Global longitudinal strain (GLS) appears to be a strong predictor of long-term prognosis due to its potential to identify early LV dysfunction in patients with preserved LVEF (Figure 2B).

The study of GLS in PMR is a growing interest, indicating diagnostic and prognostic value. GLS by STE has a strong positive correlation with LVEF, especially in LV systolic impairment. Santoro et al. found that in severe MR, both LVEF and GLS are independently associated with LV and LA size, but only GLS is related to SPAP suggesting GLS to be a powerful predictor of cardiac damage. In addition, GLS offers an angle-independent assessment of myocardial deformation, with recent reports showing better reproducibility and reliability compared with LVEF. Farsalinos et al. demonstrated GLS to have the lowest degree of interobserver variation compared with other markers of ventricular function, including, LVEF and LVESD. GLS has been established in other cardiac fields, demonstrating prediction of 5 year all-cause mortality risk in patients with acute HF independently from LVEF. Guidelines for echocardiography acknowledge that strain and strain rate are reasonable markers for a quantitative assessment of myocardial function in asymptomatic patients with LVEF = 60%-65% or LVESD approximately 40 mm or 22 mm/m². However, GLS markers are not currently incorporated in clinical guidelines as indication for surgery. GLS shows promise in being a solution to the challenge that clinicians face in identifying asymptomatic patients with subclinical LV impairment as candidates for early MV surgery. The role of GLS in PMR will be discussed in this review.

2 | METHODS

A literature search was performed to organize relevant primary citations to answer the following research question: “Can GLS be used to determine optimal timing for surgery for asymptomatic patients with chronic severe PMR?”

In aid of answering this study question the following outcomes were set:
1) To establish a correlation between GLS and LVEF.
2) To assess whether preoperative GLS can detect and predict contractile impairment.

FIGURE 2 (A) Original schematic depicting physiology of global longitudinal strain (left ventricular (LV) longitudinal myocardial fibers arrangement in the epicardium and endocardium), circumferential strain (circumferentially arrayed fibers in the mid-wall) and radial strain. (B) Graphical display of the hypothesized changes that occur in global longitudinal strain (red), circumferential strain (yellow), and ejection fraction (blue) from early LV dysfunction to late LV dysfunction. Original illustration using ©BioRENDER 2020
3) To identify the association between GLS and postoperative outcomes.

A database search was conducted in May 2020, of the Cochrane Library, PubMed, SCOPUS, and Web of Science, as displayed in the PRISMA flowchart (Figure 3). The following keywords were searched: "mitral regurgitation," "mitral valve insufficiency," "global longitudinal strain," "deformation," "LV-GLS," "GLS." The generated publications had a filtered timescale from 2004 to 2020. This timeframe was determined due to the introduction of strain via STE in 2004.19 With the exclusion of duplicates, 234 studies were assessed via screening.

At the title/abstract screening stage, inclusion criteria included (1) primary research papers, (2) recruitment of patients with severe PMR, (3) mixed population of symptomatic and asymptomatic patients, (4) standardized methods in assessing LV function, and (5) assessment of LV systolic function using the 2D-STE. Studies were excluded if (1) publication date was before 2004, (2) patients with secondary MR or mixed MR, and (3) GLS measure were acquired using the Tissue Doppler imaging only.

Subsequently, 31 citations were retrieved and assessed for eligibility via a full-text screen. Studies were included if presented with (1) patient outcomes after MV surgery, (2) surgery included MV repair or replacement, and (3) credited and standardized statistical analysis of GLS. Studies without available full-text were removed. This generated 12 primary research papers to be included in the literature review. Informed consent and approval by the Institutional Review Board is not applicable. Data sharing not applicable to this article as no data sets were generated or analyzed during the study.

3 | RESULTS

The key findings from the 12 included primary studies are summarized in Table 2.20–31

3.1 | Correlation between GLS and LVEF

Mascle et al.23 concluded GLS to be a predictive factor of postoperative LV dysfunction, (odds ratio (OR) 4.2; [95% confidence interval (CI) 1.4–13], p = .009).23 Donal et al.22 concluded GLS at rest and during exercise correlated with postoperative LVEF. Donal et al.22 and Mascle et al.23 had similar study designs including postoperative outcome of LVEF < 50% at 6 ± 1 months follow-up. The preoperative measures were similar showing preserved mean LVEF, and impaired mean GLS. Both studies had consistent findings and concluded −18% GLS threshold can predict postoperative dysfunction.22,23

Interestingly, on linear regression analysis Donal et al.22 uniquely found that GLS during exercise and normalized for LVESD was the best predictor of postoperative LVEF. This group demonstrated this parameter to have additional prognostic value, beyond LVEF.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study population/design</th>
<th>ASx (%)</th>
<th>Follow-up</th>
<th>Outcome measured</th>
<th>Pre-op LVEF (%)</th>
<th>GLS (%)</th>
<th>Results GLS cut off (%)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancellotti et al.20</td>
<td>30</td>
<td>55</td>
<td>42/[90]</td>
<td>N/A</td>
<td>13 ± 8 months</td>
<td>LVEF &lt; 50%</td>
<td>67 ± 6 – 19 ± 3</td>
<td>Exercise-induced increase &lt; 1.9; $R^2 = .74$; $p = .001$</td>
</tr>
<tr>
<td>Florescu et al.21</td>
<td>28</td>
<td>64</td>
<td>100/[100]</td>
<td>100</td>
<td>14 days</td>
<td>↓ in LVEF &gt; 10%</td>
<td>63 ± 5 – 19 ± 4 – 18.0</td>
<td>$R^2 = .70$; $p &lt; .001$</td>
</tr>
<tr>
<td>Donal et al.22</td>
<td>77</td>
<td>67</td>
<td>100/[94]</td>
<td>N/A</td>
<td>6 ± 1 months</td>
<td>LVEF &lt; 50%</td>
<td>67 ± 12 – 18 ± 5 – 18.0</td>
<td>$R^2 = −0.42$; $p = .011$</td>
</tr>
<tr>
<td>Mascle et al.23</td>
<td>88</td>
<td>67</td>
<td>100/[82]</td>
<td>N/A</td>
<td>6 ± 1 months</td>
<td>LVEF &lt; 50%</td>
<td>66 ± 7 – 19 ± 4 – 18.0</td>
<td>OR = 4.20; CI 1.4–13; $p = .009$</td>
</tr>
<tr>
<td>Magne et al.24</td>
<td>135</td>
<td>56</td>
<td>32/[70]</td>
<td>100</td>
<td>23 ± 19 months</td>
<td>Cardiac event-free survival*</td>
<td>69 ± 6 – 20 ± 4 – 20.0</td>
<td>HR = 1.14; CI 1.04–1.26; $p = .007$</td>
</tr>
<tr>
<td>Witkowski et al.25</td>
<td>233</td>
<td>61</td>
<td>100/[100]</td>
<td>35</td>
<td>34 ± 20 months</td>
<td>LVEF &lt; 50%</td>
<td>66 ± 9 – 22 ± 4 – 19.9</td>
<td>OR = 23.16; CI 6.53–82.10; $p &lt; .001$</td>
</tr>
<tr>
<td>Pandis et al.26</td>
<td>130</td>
<td>65</td>
<td>100/[100]</td>
<td>N/A</td>
<td>4 ± 3 days</td>
<td>↓ in LVEF &gt; 10%</td>
<td>63 ± 11 – 20 ± 5 – 17.9</td>
<td>OR 0.81; CI 0.73–0.89; $p &lt; .0001$</td>
</tr>
<tr>
<td>Cho et al.27</td>
<td>43</td>
<td>58</td>
<td>100/[21]</td>
<td>100</td>
<td>3 months</td>
<td>↓ in LVEF/↑ in LVEDD</td>
<td>64 ± 6 – 18 ± 2 – 20.5</td>
<td>OR 2.44; CI 1.26–4.73; $p = .008$</td>
</tr>
<tr>
<td>Alashi et al.28</td>
<td>448</td>
<td>69</td>
<td>100/[92]</td>
<td>100</td>
<td>7.7 ± 2 years</td>
<td>Mortality</td>
<td>62 ± 3 – 21 ± 2 – 20.7</td>
<td>HR 1.17; CI 1.08–1.27; $p &lt; .001$</td>
</tr>
<tr>
<td>Mentias et al.29</td>
<td>737</td>
<td>68</td>
<td>65/[92]</td>
<td>100</td>
<td>8.3 ± 3 years</td>
<td>Mortality</td>
<td>62 ± 2 – 22 ± 2 – 21.7</td>
<td>HR 1.60; CI 1.47–1.73; $p &lt; .001$</td>
</tr>
<tr>
<td>Hiemstra et al.30</td>
<td>593</td>
<td>64</td>
<td>100/[98]</td>
<td>48</td>
<td>6.4 years</td>
<td>Mortality</td>
<td>65 ± 8 – 21 ± 4 – 20.6</td>
<td>HR 1.13; CI 1.06–1.21; $p &lt; .001$</td>
</tr>
<tr>
<td>Singh et al.31</td>
<td>31</td>
<td>23</td>
<td>100/[0]</td>
<td>0</td>
<td>7 days and 3 months</td>
<td>LVEF &lt; 50%</td>
<td>65 ± 10 – 16 ± 5</td>
<td>N/A N/A</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASx, asymptomatic; CI, 95% confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LVEF, left ventricular ejection fraction; MV, mitral valve; N, study sample size; OR, odds ratio.

*Percentage of patients in study that underwent MV surgery/[percentage of surgical cases that underwent MV repair.

+: Combined end-point of cardiac event free survival; freedom from cardiovascular-related death, MV surgery (indication from symptoms or left ventricular dysfunction) and heart failure hospitalization.
3.2 Detection and predictor of contractile impairment

Florescu et al. concluded the best prediction of postoperative decrease in LVEF >10% after MV repair was −18% GLS; sensitivity 83%, specificity 97%. This study highlights that LV deformation parameters including strain and strain rate can be altered in asymptomatic patients with preserved LV dimensions. Therefore, agrees that GLS is a sensitive parameter to detect early contractile impairment. Similarly, Pandis et al. retrospectively studied 130 patients and found that a higher baseline GLS of −17.9% predicted early postoperative reduction in LVEF > 10%.

Lancellotti et al. uniquely assessed GLS during exercise-echocardiography to determine whether patients with limited contractile reserve develop postoperative LV dysfunction. At baseline, patients without latent LV dysfunction had impaired GLS and limited contractile reserve during exercise compared to age-matched healthy controls. This highlights the ability of GLS to detect contractile impairment. An exercise-induced increase of 1.9% in GLS yielded high sensitivity (92.3%) and moderate specificity (70.6%) for predicting postoperative LV dysfunction. Changes in GLS at peak exercise were independently associated with postoperative reduction in LVEF (LVEF < 50%). Therefore, the group concluded that limited longitudinal contractile recruitment during exercise was predictive of postoperative LV dysfunction.

Cho et al. divided 43 asymptomatic patients with preserved LV systolic function into two groups at midterm follow-up (3 months) after surgery; (1) remodeling group (reduction in LVEF/increase in LV end-diastolic diameter [LVEDD]), (2) non-remodeling group. The group also examined the heterogenous GLS mechanics between myocardial walls. Remodeling group had lower baseline epicardial, mid-layer, and endocardial GLS compared with non-remodeling group. The most powerful predictor of postoperative remodeling in PMR with preserved preoperative contractile function was −20.5% mid-wall GLS (OR 2.44; [95% CI 1.26−4.73], p < .008).

Witkowski et al. assessed LV function at long-term follow-up (34 ± 20 months) after MV repair. Consistent with previous studies, GLS (19.9%) was an independent predictor of long-term LV dysfunction (OR 23.16; [95% CI 6.53-82.10], p < .001). When adjusted for other significant predictors using multivariate analysis, GLS remained the strongest independent predictor of long-term LV dysfunction, followed by LVESD ≥ 40 mm.

3.3 Associated clinical outcomes

Magne et al. identified the determinants and impact on outcome of brain natriuretic peptide (BNP) in asymptomatic patients. The group found that GLS was significantly impaired in patients with BNP > 40 pg/ml versus BNP < 40 pg/ml (−17.8% vs. −22.4%, respectively, p < .0001). The long-term (23 ± 19 months) postoperative outcome measured was cardiac event-free survival and reported that every 1% decrease in GLS was associated with 14% increased risk of a cardiac event. Multivariate analysis reported GLS as an independent predictor of cardiac event-free survival (hazard ratio (HR) 0.41; [95% CI 1.04−1.26], p = .007).

Alashi et al. studied 448 asymptomatic patients with severe PMR and preserved LVEF and observed all-cause mortality. During follow-up period (7.7 ± 2 years), mortality was 9%. Impaired GLS (−20.7%) was independently associated with higher long-term mortality, (HR 1.17; [95% CI 2.08−1.27], p < .001). Similarly, Mentias et al. concluded GLS value below the median (−21.7%) was associated with a higher mortality (HR 1.60; [95% CI 1.47−1.73], p < .001) despite patients being asymptomatic with preserved LV systolic function. Interestingly, Alashi et al. found that the combination of GLS and BNP appeared to be a synergistic outcome predictor and provided incremental prognostic utility.

Hiemstra et al. retrospectively studied 593 patients, majority of whom underwent MV repair. Multivariate regression analysis concluded that GLS was associated with all-cause mortality (HR 1.13; [95% CI 1.06−1.21], p < .001). Patients with impaired GLS showed a significant worse survival compared to preserved GLS. Cumulative survival for all-cause mortality was 94% at 5 years and 85% at 10 years for patients with preserved GLS (< −20.5%) and 81% and 60% for patients with impaired GLS (≥ −20.6%), respectively.

4 DISCUSSION

Impaired postoperative LVEF after surgery is associated with worse long-term prognosis and greater incidence of HF. However, in patients who do not meet Class I guidelines for surgery, there remains equipoise on whether an early surgery versus watchful waiting approach is superior. Hence, more sensitive and accurate imaging may provide more data on the optimum timing of surgery. The desired outcome of a successful surgery is a functional decrease in LV size and preserved LVEF, after surgery and at long-term follow-up. Many studies adopted the early MV surgery strategy, where recruited patients undergoing surgery had preserved mean LVEF (> 60%) and impaired GLS at baseline (Table 2). Of note, the research suggests other parameters in addition to GLS, including exercise-GLS, GLS normalized to LVESD and BNP, to have additional prognostic value. Further investigation with incorporating assessment of multiple parameters may provide better prognostic value in determining the optimal timing for surgery.

The reviewed studies have synonymously concluded GLS to be a predictor of postoperative LV dysfunction. However, the above studies derive to different GLS cut-off values to determine surgical outcomes; ranging from −17.9% to −21.7%. The lack of reproducibility is likely due to differing study and methodological designs. The follow-up periods varied between studies, from 4 ± 3 days to 8.3 ± 3 years. In addition, the postoperative outcomes were varied with some studies observing functional LV changes and others measuring mortality rates. As expected, the patient characteristics (i.e. gender, age, symptomatic status, proportion undergoing MV repair, and baseline LV measurements) vary between studies. Despite GLS showing promise as a reliable marker for detection of subclinical LV...
dysfunction in PMR, further investigation is required to determine a predictive GLS cut-off that demonstrates both reproducibility and efficacy.

### 4.1 GLS as a clinical tool

The literature agrees there is a significant correlation between GLS and LVEF. Impaired preoperative GLS was negatively correlated with postoperative LVEF. LVEF has long been considered a robust parameter of LV systolic function and a predictor of late survival. The established correlation between these two parameters translates that GLS can be a reliable clinical tool to determine LV systolic function and have similar prognostic utility as LVEF.

A key strength in Pandis et al.'s and Florescu et al.'s studies was that postoperative outcome were set as change in LVEF rather than an absolute LVEF value. The latter isolates measurements from an individual patient's baseline. This carries the risk of grouping patients with a low follow-up LVEF as having a worse postoperative outcome than those with higher follow-up LVEF, but with a greater reduction from baseline. Therefore, change in LVEF (e.g., reduction > 10%) yields a better correlation between a patient’s baseline GLS with postoperative outcomes. Future prospective studies assessing GLS mechanics should adopt similar experimental methods when assessing relative changes in pre- and post-operative GLS.

Presently, the Class I recommendation for surgery for patients with PMR requires LV dysfunction to be present. The issue that lies is that current preoperative methods that assess LV impairment later corresponds with poor postoperative outcomes. The literature conclusively highlights GLS has sensitivity to detect subclinical LV impairment, despite patients being asymptomatic with preserved LVEF. In addition, an association was seen between baseline GLS and postoperative outcomes, where impaired GLS was associated with higher mortality rates and increased risk of cardiac events. Importantly, reproducible findings between studies were seen at short-, mid- and long-term follow-up. This demonstrates the maintained sensitivity of GLS to predict LV dysfunction at multiple postoperative stages. Therefore, GLS can be used as a marker to identify asymptomatic patients undergoing early LV systolic impairment and risk stratify them based on likelihood of developing postoperative dysfunction.

Cho et al.'s study is praised for its novelty in discriminating GLS mechanics between myocardial layers. Previous work by Manaka et al. demonstrated that systolic impairment may originate at the endocardium and extend to the epicardium. Cho et al. concluded that mid-wall layer GLS has optimal predictive value; where preoperative mid-wall GLS was correlated with postoperative LVEF and LVEDD. Therefore, differentiation of strain by multi-layer STE, particularly mid-wall GLS may possess specific prognostic value in detecting early LV systolic dysfunction and warrants further clinical investigation.

In addition, Lancellotti et al.'s exploration of GLS using exercise-echocardiography opened an innovative avenue of clinical research. Exercise-echocardiography is a useful tool to evaluate symptoms in patients with mild PMR. In addition, exercise-GLS can determine functional capacity and assess haemodynamic changes in stable and/or asymptomatic patients, thus having incremental prognostic value.

### 4.2 Limitations of GLS

Despite the plethora of literature agreeing the clinical efficacy of GLS in PMR, there are limitations of this imaging modality. Its use is largely limited by inconsistent algorithms used by different echocardiographic vendors. GE Vivid, Philips, and Toshiba showed little inter-vendor agreement on GLS measurements. However, a multi-industry joint initiative in 2015 has significantly reduced inter-vendor variability. Furthermore, inter-vendor reproducibility for strain analysis has shown to be higher than traditional echocardiographic parameters, including LVEF and peak Doppler velocities. Although many of the included studies used similar vendors, (e.g. GE Vivid) and processing software, (e.g. EchoPAC), majority of the echocardiographic data collected was before 2015. Therefore, inter-vendor variability is likely bias.

In addition, the accuracy of GLS calculated is largely dependent on standardized image acquisition and quality. Guidelines stipulate that when regional tracking is suboptimal in more than two myocardial segments in a single view, the calculation of GLS should be avoided. Furthermore, the entire LV myocardium must be discernible on the gray-scaled images, which can pose a particular challenge in the setting of severe LV dilatation. Judgment of suboptimal image acquisition is subjective and may be prone to operator-related errors.

The clinical application of 2D strain imaging to quantify GLS in pathological states requires the definition of a normal range. Reported normal ranges largely vary across studies. Technical factors, patient related factors (age, ethnicity, and gender) and hemodynamic factors (heart rate and blood pressure) may constitute potential influences in determining GLS. Majority of studies have defined their own normal ranges using a relatively small sample size of a limited age range. To identify patients with subclinical LV dysfunction that are suitable for MV surgery, that is, impaired GLS, a normal range must be defined.

### 4.3 Determining optimal timing for MV surgery

Findings from the reviewed studies conclude that GLS is a sensitive marker to detect subclinical LV dysfunction in asymptomatic patients with chronic severe PMR with additional prognostic value in determining postoperative outcomes. However, there is lack of a standardized baseline threshold value to stipulate when surgery is indicated within this cohort of patients. This poses a challenge in determining the optimal time for surgical intervention. Nonetheless, GLS shows promise in being the parameter of choice to identify...
patients at the preferred time. Serial measurements can assess relative changes in GLS from baseline and may aid risk stratification particularly during the preoperative active surveillance stage. This has been adopted in other cardiac fields. In cardio-oncology, a relative reduction in GLS more than 15% from baseline can define chemotherapy-related cardiac dysfunction. Further prospective clinical studies are required where a relative change in GLS, demonstrating LV dysfunction, may be suggestive of early MV surgery, and subsequently correspond with better postoperative outcomes.

5 | CONCLUSION

PMR is a prevalent valvular abnormality that poses a great health burden with disease progression. With a global transition to incorporate preventative measures, detection of early subclinical LV dysfunction has sparked great interest. Assessment of deformation characteristics, namely GLS via STE, has been a focus in determining a preoperative predictive parameter of early systolic impairment in asymptomatic patients. Studies have demonstrated GLS to be able to detect early LV impairment and a preoperative GLS cut-off value that is predictive of postoperative outcomes, ranging from −17.9 to −21.7%. In addition, a correlation between preoperative GLS in patients without latent dysfunction and postoperative LVEF and association of GLS with clinical outcomes has been observed. However, gaps in the field remain. Most studies were retrospective in design. In addition, there is lack of consensus of a baseline GLS cut-off value. Furthermore, inter-vendor variability makes standardized GLS application challenging. This highlights the need for prospective studies to investigate GLS in severe chronic PMR. Further analysis such as assessing serial changes in baseline GLS during active surveillance stage may better identify patients with subclinical LV dysfunction at the optimal time for MV repair, consequently resulting in better postoperative outcomes.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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REFERENCES


