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Global longitudinal strain in chronic asymptomatic aortic regurgitation: systematic review

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Abstract

Chronic aortic regurgitation (AR) patients typically remain asymptomatic for a long time. Left ventricular mechanics, namely global longitudinal strain (GLS), has been associated with outcomes in AR patients. The authors conducted a systematic review to summarize and appraise GLS impact on mortality, the need for aortic valve replacement (AVR) and disease progression in AR patients. A literature search was performed using these key terms 'aortic regurgitation' and 'longitudinal strain' looking at all randomized and nonrandomized studies conducted on chronic aortic regurgitation. The search yielded six observational studies published from 2011 and 2018 with a total of 1571 patients with moderate to severe chronic AR. Only two studies included all-cause mortality as their endpoint. The other studies looked at the association between GLS with AVR and disease progression. The mean follow-up period was 4.2 years. We noted a great variability of clinical, methodological and/or statistical origin. Thus, meta-analytic portion of our study was limited. Despite a relevant heterogeneity, an impaired GLS was associated with adverse cardiac outcomes. Left ventricular GLS may offer incremental value in risk stratification and decision-making.

Key Words

- aortic regurgitation
- global longitudinal strain
- outcomes
- aortic valve replacement

Background

Chronic aortic regurgitation (AR) patients typically remain asymptomatic for a long time. In asymptomatic chronic severe AR, current European Society of Cardiology guidelines recommend as a Class I indication (Level of Evidence: B) to perform aortic valve replacement (AVR) when the left ventricular ejection fraction (LVEF) is <50%. AVR is a Class IIa indication (Level of Evidence: B) when severe left ventricular dilatation (left ventricle (LV) diastolic diameter >70 mm or LV systolic diameter >50 mm) develops in patients with a LVEF >50% (1). AVR is, therefore, the cornerstone to halt LV dysfunction. Patients with AR and reduced LVEF have higher mortality and heart failure risk (2). Changes in systolic function identify patients likely to develop symptoms and require AVR (3). Even 6–7 years after AVR, there is residually increased interstitial fibrosis that is associated with mortality (4, 5).

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Global longitudinal strain (GLS) assessed with 2D speckle-tracking echocardiography (2D-STE), can be used to identify subclinical LV dysfunction in these patients (6, 7). Although there is no randomized study yet to indicate that surgery is better than conservative therapy in patients with chronic asymptomatic AR (8), it has been shown that even above-average values of GLS confer a poor prognosis (8, 9, 10).

This state-of-art systematic review assesses and critically summarizes studies to date on the impact of GLS on outcomes in patients with chronic moderate to severe AR.

Methods

Data sources and searches

Literature search was performed by one of the authors using the databases of MEDLINE, EMBASE, and the Cochrane Library, using the key terms 'aortic regurgitation' and 'longitudinal strain' from inception to November 2019. No language restrictions were selected. The bibliographies of all eligible studies were also screened for relevant reports. The selection of the papers to be included followed a three-step methodology: (1) reading of the title, (2) reading of the abstract, and (3) reading of the full text. In stages (1) and (2), efforts were made to aim to be more inclusive than exclusive. The full text of each pre-selected study was examined to verify the completeness of all inclusion criteria. Two of the authors assessed the eligibility of studies and disagreements were solved between the two authors. One author extracted the relevant data from eligible studies, which was then checked by another author.

Inclusion criteria

Studies were selected if they met the following criteria: (1) adult population (>18 years old), (2) asymptomatic or mild symptoms, (3) on conservative management, (4) patients with at least moderate chronic AR, (5) analyzed GLS with 2D-STE, and (6) evaluated symptom development, change in LV function, need for AVR, and/or all-cause mortality. The following exclusion criteria were used: case reports, case series and conference abstracts.

Outcomes

The main outcome of interest was all-cause mortality. Also, need for AVR and disease progression (symptoms and/or change in LV function) were analyzed.

Risk of bias assessment

A modified version of the Newcastle-Ottawa Quality Assessment Scale of cohort studies was used to assess the quality of included papers. Briefly, the scale appraises methodological quality in three domains: selection, comparability, and outcome. Studies score points for each subset domain and they are classified as high risk (1–3 points), intermediate risk (4–5 points), or low risk (6–9 points) of bias. Papers were included irrespective of the quality assessment score.

Data collection and statistical analysis

Review authors were not blinded to author, institution, journal, or results of a study for its assessment. For each paper, the following data were extracted: first author, publication year, country of origin, vendor used for echocardiography, reliability data, population studied, length of follow-up, LVEF and GLS. Hazard ratio (HR) and/or odds ratio (OR) were extracted directly from the studies along with 95% confidence intervals or *P* values. If these were not reported, other data, such as mean and standard deviation, for GLS in each group were recorded. Categorical data are expressed as a percentage and continuous variables as means ± standard deviation or medians with interquartile range. Wherever reported, we collected the results of the receiver operator curve (ROC) analysis as area under the curve (AUC), sensitivity and specificity and the estimated cutoff. Also, C-statistic and net reclassification indexes are reported where available. The data were then computerized in a dedicated database. A qualitative analysis of published data was performed, which is absolutely crucial when looking at observational studies. To avoid variability in reporting and interpretation, we used GLS percentages as negative values, regardless of whether absolute or negative integer were reported in the original study. In our report, a more negative value GLS is referred to a as *better* and a value closer to zero (less negative) is referred to *worse*.

Results

Search results

A total of 305 eligible titles were identified and screened (Fig. 1). Abstracts of 40 papers were judged for relevance. Upon reading the full texts, six papers were retained for analysis. All of the studies were observational and published between 2011 and 2018 (9, 10, 11, 12, 13, 14).

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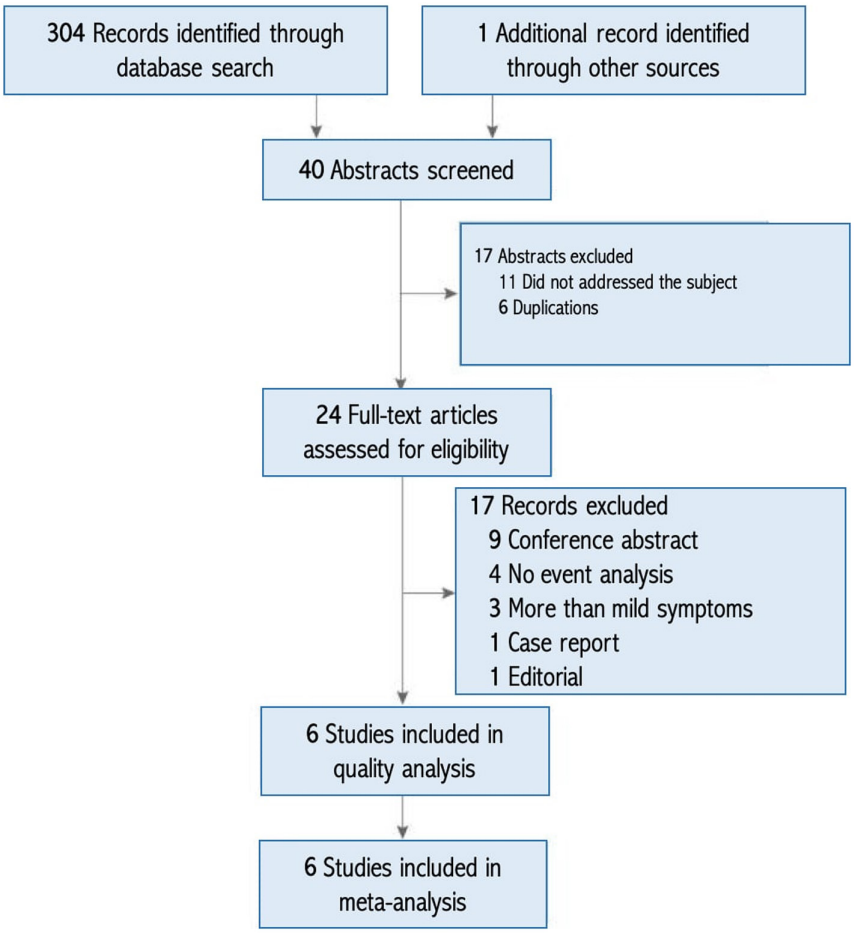

Figure 1
Flow chart of studies selection.

In this report, we first describe studies' characteristics, and then we elaborate on the outcomes.

Description of included literature

Baseline characteristics of the studies are listed in Table 1. Half of them were prospective (10, 12, 13) and the others were retrospective (9, 11, 14). The search yielded no randomized controlled trial. Most studies were small, although one recruited 1063 patients (9). Worth to underline that four studies (11, 12, 13, 14) had sample sizes with less than 100 patients. Two papers were based on samples from the United States (9, 10), and one paper came from each of the following countries: the Netherlands (11), Denmark (12), Lithuania (13), and Korea (14).

The search identified 1571 subjects from six studies. The definition of chronic AR varied among the authors. Four studies included only patients with chronic AR who were asymptomatic and with preserved LVEF (≥50%) (9, 10, 11, 13). One paper (12) included patients with at least moderate AR, but 6% had a NYHA≥II and mean LVEF was 58.2 ± 5.1%. In another sample (14), some patients had mild left ventricle dysfunction. Length of follow-up varied among studies from 1.6 ± 0.6 to 6.8 ± 3.0 years. Patients were middle-aged (48 ± 16 to 57 ± 13 years) and ≥ 50% were male. The prevalence of a bicuspid aortic valve varied from 36 to 60% (9, 10, 11, 13). LVEF was assessed by biplano Simpson's method in all studies (9, 10, 11, 12, 13, 14). The mean LVEF ranged from 47.9 ± 12.1 to 61 ± 5%. Left ventricular end-systolic diameter varied from 34 ± 7 to 39 ± 5 mm (9, 10, 11, 13). The mean GLS ranged from 14.7 ± 4.5 to 19.5 ± 0.2%. Only one study (9) reported the Society of Thoracic Surgeons score, with a mean of 4.4 ± 5.0%. Studies mostly reported outcomes during conservative management, such as the time-to-AVR/disease progression. Reports on mortality analyzed the entire sample, including those who previously underwent AVR (9, 14). The ultrasound equipment varied between papers (Table 2), but most used equipment was from one vendor. LV peak systolic GLS measurements were obtained from images recorded in the apical four-chamber, two-chamber, and three-chamber views (9, 10, 11, 12, 13). In one study, only apical four-chamber views were used due to poor image quality (14). Two

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Table 1 Description of the studies included in the systematic review.

Author, Year	Inclusion criteria	Exclusion criteria	Hardware Software Procedure	Follow-up period	Primary outcome	Secondary outcome
Alashi, 2018 (9)	≥III chronic AR, LVEF ≥50% and iLVESD <2.5 cm/m^2	Other ≥ moderate valvular disease, hypertrophic cardiomyopathy, congenital disease, previous cardiac surgery, symptoms, CAD, technical issues	Philips Medical Systems; Siemens Medical Solutions; General Electric Velocity Vector Imaging (Syngo VVI, Siemens) 2D-STE	Mean of 6.8 ± 3.0 years	All-cause mortality	Need of AVR
Ewe, 2015 (11)	NR	Acute AR, LVEF ≤50%, ≥ mild valvular disease, CAD, previous cardiac surgery, technical issues	General Electric (Vivid-7 and E9) EchoPAC version 110.0.0, GE-Vingmed 2D-STE	Mean of 4.2 ± 3.2 years	Need of AVR	
Kusunose, 2014 (10)	Moderate-to-severe AR, LVEF >50%, LVEDD ≤70 mm, LVESD ≤50 mm, iLVESD ≤25 mm/m^2	NR	General Electric (Vivid 7 or Vivid 9); Philips (Sonos 5500 or iE33) Velocity Vector Imaging (Syngo VVI, Siemens) 2D-STE	Mean of 2.5 ± 1.8 years	Need of AVR	
Olsen, 2011 (12)	Moderate-to-severe chronic AR	Previous cardiac surgery, other valvular disease, CAD, compromised LV function of known other reason than AR, atrial fibrillation.	General Electric (Vivid 7 and Vivid 7 Dimension) EchoPAC PC version 6.1.1 (GE-Vingmed) 2D-STE	Mean of 1.6 ± 0.6 years	Development of symptoms or deterioration of LV size or function	
Park, 2015 (14)	Moderate-to-severe chronic AR	Other valvular heart disease, congenital heart disease, previous cardiac surgery	General Electric (Vivid 7) EchoPAC PC (GE-Vingmed) 2D-STE	5.3 years	All-cause mortality	Need of AVR
Verseckaite, 2018 (13)	Moderate-to-severe chronic AR	Ovalve disease, symptoms or a history of CAD, LV wall motion abnormalities, atrial fibrillation, and left bundle branch block	General Electric (Vivid 7) EchoPAC PC version 112 (GE-Vingmed) 2D-STE	Mean of 4.7 ± 2.6 years	Deterioration of the LVEF (≤50%)	

NR, not reported.

studies provided information on inter observer and/or intraobserver reproducibility, with intraclass correlation coefficients above 0.80 (9, 10). Quality appraisal of the included studies is reported in Table 3.

Outcomes

Outcomes of the included papers are shown in Table 2. Only two studies reported all-cause mortality (9, 14). Although mortality was an endpoint for one other study, during follow-up period no death occurred (10). The others analyzed either the need for AVR or disease progression (symptoms and/or change in LV function). A total of 2593 patient-entries and a total of 985 events (death, AVR and/or disease progression) were analyzed. The meta-analytic portion of our study was limited by significant heterogeneity observed across studies that could not be explained by subgroup analyses or metaregressions. While attempting to meta-analyze the data, the I^2 statistic, varied between 0.51 and 0.65. Also, the number of studies

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Table 2 Results of studies number of events, mean LVEF and GLS and cardiac outcomes.

Author, year	Sample discrimination	Patients (no.)		Age (mean ± s.d.)		LVEF (mean ± s.d.)		GLS (mean ± s.d.)		Hazard ratio/odds ratio	Outcome
		Event	No Event	Event	No Event	Event	No Event	Event	No Event		
Alashi, 2017 (9)	All sample[a]	146	917	NR	NR	NR	NR	NR	NR	HR = 1.08 (1.03–1.18)	Death
Alashi, 2017 (9)	On conservative	671	392	53 ± 16	54 ± 14	57 ± 4	57 ± 4	19.5 ± 2.0	19.5 ± 2.0	NR	AVR
Ewe, 2015 (11)	On conservative	26	23	55 ± 16	42 ± 15	61 ± 5	62 ± 5	15.7 ± 2.0	17.6 ± 2.7	HR = 1.20 (1.01–1.44)	AVR
Olsen, 2011 (12)	On conservative	8	27	NR	NR	57.6 ± 3.6	58.7 ± 5.4	16.3 ± 3.3	19.0 ± 2.6	NR	AVR or symptoms
Olsen, 2011 (12)	AVR vs conservative	29	35	57 ± 13	56 ± 14	50.3 ± 10.9	58.2 ± 5.1	14.0 ± 4.2	18.3 ± 2.9	NR	AVR
Park, 2015 (14)	All sample*	16	44	68.8 ± 12.3	50.7 ± 16.9	42.9 ± 13.4	49.8 ± 11.2	12.1 ± 3.7	15.7 ± 4.3	HR = 1.3 (1.01–1.71)	Death
Park, 2015 (14)	AVR vs conservative	38	22	51.8 ± 14.7	61.9 ± 20.8	49.2 ± 11.71	45.7 ± 12.7	14.6 ± 4.7	14.8 ± 4.1	NR	AVR
Verseckaite, 2018 (13)	On conservative	12	28	54 ± 13	42 ± 15	55 ± 3	59 ± 4	16.9 ± 2.5	20.1 ± 1.6	OR = 2.58 (1.02–6.57)	Symptoms
Kusunose, 2014 (10)	On conservative	50	109	NR	NR	NR	NR	NR	NR	HR = 1.64 (1.19–2.26)	AVR

[a]Including those submitted to AVR.
NR, not reported.

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Table 3 Quality assessment of the included papers based on Newcastle–Ottawa Quality Assessment Scale – Cohort Studies.

	Alashi, 2017 (9)	Ewe, 2015 (11)	Kusunose, 2014 (10)	Olsen, 2011 (12)	Park, 2015 (14)	Verseckaite, 2018 (13)
Selection category						
Representativeness of the cohort		*	*			*
Assessment of exposure reliability	*		*			
Completeness of collection of potential confounders	*	*	*	*	*	*
Demonstration that the outcome of interest not present at start of study (and/or sensitively analysis)		*	*	*		*
Outcome category						
Assessment of outcome	*	*	*	*	*	*
Was follow-up long enough for outcomes to occur	*	*	*		*	*
Adequacy of follow up of cohorts	*	*	*	*	*	*
Total	4	6	7	4	4	6

examining the primary endpoint was insufficient. Even though we tried to conduct the meta-analysis with extreme rigor, the results of highly heterogeneous studies may be less interpretable and useful.

GLS and all-cause mortality

One study (9) recruited the majority of the patients (1063 patients against 60 patients (14)). In Alashi *et al.* study (9) more than half of the cohort underwent AVR at a median of 42 days (3–122 days) from the baseline echocardiogram. Park *et al.* (14) reported that 13.2% of patients submitted to AVR did not have a proper surgical indication, while 81.8% were under conservative management despite having criteria for surgery. The most common causes of deferred surgery were patient's refusal and withholding of physicians due to old age or poor condition.

Of the 1123 patients included, 151 were dead (13.4%). The incidence of all-cause mortality varied from 14% to 27% during a mean maximum follow-up of 6.8 ± 3.0 years (9, 14). The mean follow-up duration was longer in AVR group than the conservative treatment group (71 ± 30 months vs 40 ± 29 months, $P < 0.001$ (14)). Adjusted HR for mortality risk varied between 1.11 and 1.3 (9, 14). Addition of GLS to a clinical model provided incremental prognostic value. An increased C-statistic from 0.61 to 0.77 and an improved reclassification (continuous net reclassification improvement 0.24–0.23) were reported (9). Kaplan–Meier survival analysis showed a higher survival in patients with a better GLS. The estimated cutpoints for GLS varied from −12.5 to −19.5%. These different thresholds were chosen based on either ROC curve analysis (14) or the median value (9), respectively. The −12.5% cutoff was associated with an AUC of 0.74, a sensitivity of 69% and a specificity of 79% (14). Using quadratic spline, patients with a GLS better than approximately -19% had an excellent 5-year survival. Worth to underline is that the risk of death continuously increased when GLS worsened to <−19% and that patients with no surgery and a worse GLS worse had a higher long-term mortality. AVR seemed to blunt the impact of a worsening GLS on the risk of 5-year death (9). In contrast, in one study (14), GLS was more predictive of all-cause death in the AVR than in the conservative group (AUC 0.89 vs 0.68). Thus, despite a significant variation of cutoff values as well as on statistical analysis, there was a consistent finding of a worse strain being associated with increased all-cause mortality.

Need for AVR and disease progression

All the six studies examined the association between GLS with AVR and/or disease progression (9, 10, 11, 12, 13, 14). Most of the studies reported on the need of AVR (9, 10, 11, 14) and two on disease progression, either symptom development (12) or left ventricular dysfunction (LVEF < 50% (13)). A total of 1,606 patient-entries and 834 events were analyzed. The other half of the patients (48.1%) remained free of symptoms. The reported incidence of this endpoint, however, varied greatly from 9 to 63% (9, 10, 11, 12, 13, 14). Noteworthy to underscore that some patients underwent AVR for indications other than symptoms or LV dysfunction (9), were on conservative management despite an appropriate surgical indication or received AVR without a proper indication (14).

Globally, a worse GLS was evident in patients who later required AVR and/or developed symptoms. Adjusted HR varied from 1.20 to 2.58 (95% CI 1.01–6.57). Mean GLS for patients that needed AVR and/or disease progression varied

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between −16 ± 3.3 and −19.5 ± 2%, in contrast to those who remained free of AVR and symptoms (−17.6 ± 2.7 to −20.9 ± 2.2%). Only three studies examined the threshold value for GLS to predict AVR and/or disease progression. These different cutoffs were determined by ROC curve analysis. The optimal cutpoint varied between −17.4 and −19.3%. AUC's varied between 0.70 and 0.89 with sensitivity ranging from 77 to 88% and specificity from 57 to 84% (11, 12, 13). A GLS cutpoint of −19.3% had the highest sensitivity to predict AVR with a negative predictive value of 100%. A GLS worse than −15.1% had the highest positive predicted value (75%). Under these assumptions, patients with a better GLS than −19.3% would be free from AVR and/or disease progression and three out four patients with a worse GLS than −15.1% will require AVR (11).

Discussion

In our systematic review on chronic aortic regurgitation, we note significant heterogeneity. First, to mention is the variability in the clinical profile of the included patients. Second, most of the studies had a small sample size with the exception of one large study. Indeed, when the sample size is small, the confidence intervals are wide due to imprecision, which will often cause the pooled estimate to cross the null hypothesis. Third, different methodologies and the use of different vendors to analyze GLS. Last, the variable follow-up duration and variable definition of endpoints were present. This degree of heterogeneity poses interpretive challenges and make it impossible to conduct a meta-analysis. We present our results in the format of a systematic review. Despite all the shortcomings, we noted that in the majority of the studies, a worse GLS was associated with increased cardiac events. Chronic AR is an insidious disease with a clinically silent phase of variable duration followed by a relatively rapid decline. Echocardiographic deformation imaging may help to halt adverse cardiac outcomes in those with preserved LVEF and no symptoms. Based on our review, it might be reasonable to proceed to early AVR when GLS is worse than −19% (Fig. 2, central illustration).

Myocardial strain and LV systolic function

Strain has been used to gain a greater understanding of the pathophysiology of cardiac conditions (15). Currently, GLS is accepted as the parameter of myocardial deformation that is more reproducible and less susceptible to technical factors (16), and, therefore, the most accurate and sensitive parameter of early LV dysfunction (17). It has been proposed as a prognostic marker in patients with preserved ejection fraction (EF) (18) as it has emerged as a more sensitive index of LV systolic performance than EF itself (19). Nevertheless, both EF and strain are loading-dependent parameters (20). Reduced deformation despite preserved EF can be explained through geometric factors, and these confounders hamper the use of EF as an index of LV systolic function (21). GLS relation to myocardial fibrosis has been studied and it is documented that 70% of segments with late gadolinium enhancement have a GLS reduction (22). Also, wall stress is associated with myocardial strain (23).

Myocardial strain and valvular heart disease

Strain is being used to assess the effects of valvular disease on myocardial function (15). LVEF sensitivity for the detection of myocardial dysfunction is lower than previously stated and EF changes occur late, when cardiac damage is often irreversible. GLS was tested for the assessment of all valvular diseases and it has been associated with disease progression, the occurrence of heart failure, and impaired outcomes after surgery (17). In aortic stenosis patients with preserved EF, an impaired GLS was a predictor of reduced survival (24). In severe mitral regurgitation, GLS appeared to be a better predictor of cardiac events and mortality, regardless of LV dysfunction (25). In asymptomatic primary mitral regurgitation, the risk of death progressively increased as GLS worsened to ≥−21% (26). In moderate to severe aortic stenosis, a GLS ≥-12.1% was associated with poor survival (10). According to our review, GLS threshold for AR varied from −18 to −19% (9, 10, 11, 12, 13), although one study reported a value of −12.5% (14). This valvular heart disease GLS variability for asymptomatic patients could probably be explained by preload and afterload differences, and also mirrors LVEF variability. After 4.9 years of follow-up of 748 AR patients managed either medically or surgically, AVR was associated with better survival: baseline symptoms were the hallmark of mortality, even after AVR (27). These results suggest that it seems reasonable to make an early referral of asymptomatic AR patients without waiting for symptoms to develop or LV enlargement and/or dysfunction. Popovic et al. (8) argue the need for multimodal imaging follow-up of these patients in order to develop a risk profile and determine the best timing for AVR referral. Our review suggests that GLS enables early detection of subtle LV dysfunction in patients with chronic moderate to severe AR, making it a 'rule in' tool to trigger additional studies or to guide the timing of surgery.

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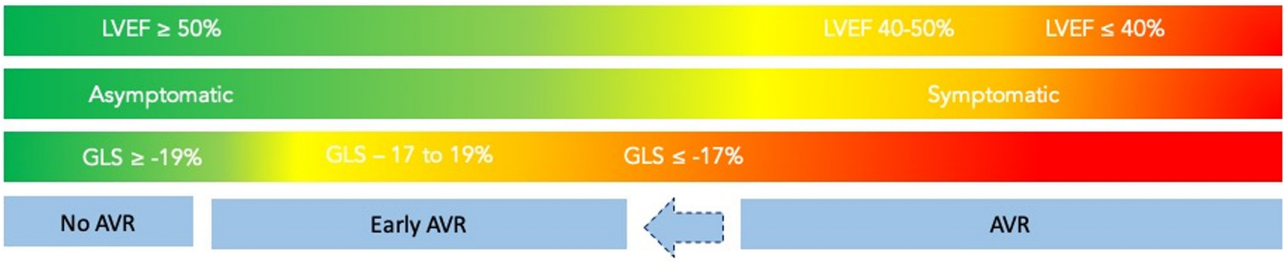
First Author [Ref]	n	Follow-up, years (mean±SD)	LVEF (%, mean±SD)	Software	GLS (%, mean±SD)	GLS cutpoint (%)
Time-to-AVR and/or disease progression*						
Ewe [11]	AVR: 26 No AVR: 23	4.2±3.2	AVR: 61±5 No AVR: 62±5	EchoPAC	AVR: 15.7±2.0 No AVR: 17.6±2.7	- 17.4
Olsen [12]	AVR/symptoms: 8 No AVR/symptoms: 27	1.6±0.6	AVR/symptoms: 50.3±10.9 No AVR/symptoms: 58.2±5.1	EchoPAC	AVR/symptoms: 16.3±3.3 No AVR/symptoms: 19±2.6	- 18
Verseckaite [13]	Symptoms: 12 No symptoms: 28	4.7±2.6	Symptoms: 55±3 No symptoms: 59±4	EchoPAC	Symptoms: 16.9±2.5 No symptoms: 20.1±1.6	- 18.5
Time-to-death						
Alashi [9]	Death: 146 No death: 917	6.8±3.0	Death: NR No death: NR	VVI	Death: NR No death: NR	- 19.5
Park [14]	Death: 16 No death: 44	5.3	Death:42.9±13.4 No death: 49.8±11.2	EchoPAC	Death: 12.1±3.7 No death: 15.7±4.3	- 12.5

* Only studies that reported a GLS threshold are reported.
AVR = aortic valve replacement; GLS = global longitudinal strain; LVEF = left ventricle ejection fraction.



Aortic regurgitation is characterized by a long asymptomatic phase, lasting several decades, during which left ventricular functional changes develops progressively. LVEF remains normal until late in the course of the disease. Impaired GLS performed well in the prediction of need of AVR and disease progression, with the best cutoff values ranging from -17 to -19%.

Figure 2
Central illustration: left ventricular GLS to predict outcomes in chronic aortic regurgitation.

Study limitations

Our primary endpoint was all-cause mortality because it is an objective assessment. However, most of the studies did not report mortality but, instead, the need for AVR and disease progression. Information on potential confounders was limited and inconsistent, and the small number of studies made impossible the use of metaregression to explore sources of heterogeneity between studies. Some authors argue that it is through the heterogeneity of studies in meta-analyses that the performance and variability of a test can be appreciated in different patient groups and sources of variation can be identified (28). Despite being reported that the variations in 2D-STE of GLS may be more subtle than are often portrayed (29), different vendor-specific hardware and software may introduce systematic differences among studies. Thus, we assumed that the reduced number of studies, the degree of clinical, methodological and statistical heterogeneity precluded the meta-analytic process. Our study is, therefore, a more comprehensive and analytical review of literature on the prognostic value of GLS in chronic AR. Notwithstanding, our systematic report made it possible to bring together relevant data on this topic and will help outline future studies.

Conclusion

The evidence indicates that GLS is useful in AR, with values worse than −17 to −19% being associated with poor cardiac outcomes. Larger prospective studies are needed to further define the role of GLS and better identify associated thresholds. A randomized controlled trial to test whether the identification of an imaging biomarker vs watchful waiting, in asymptomatic patients, would trigger earlier aortic valve replacement and translate in better outcomes is warranted.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
All authors have contributed to the manuscript. Rogério Teixeira and Diana de Campos have designed, elaborated the review and have written the

paper. Carolina Saleiro, Ana Botelho and Lino Gonçalves provided critical reviews of the data and of the manuscript.

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