Review

Global longitudinal strain in stress test of asymptomatic severe aortic stenosis: a focused meta-analysis

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Abstract

Objectives: In asymptomatic severe aortic stenosis (AS) with preserved ejection fraction, subclinical myocardial dysfunction often precedes symptoms by years. Left ventricular ejection fraction (LVEF) is not a determining factor of this early impairment. Global longitudinal strain (GLS) can detect subtle impairment earlier, but its behaviour during exercise stress testing in this context has not been thoroughly assessed. We examined whether GLS at rest and during exercise can distinguish patients with abnormal stress test responses from those with normal responses, and whether exercise-derived strain adds information beyond resting measurements.

Methods: The researchers conducted a comprehensive review of studies published up to August 21, 2025, using databases including PubMed, Scopus, and Web of Science. They included studies reporting Global Longitudinal Strain (GLS) in asymptomatic patients with severe aortic stenosis (AS) who had a left ventricular ejection fraction (LVEF) of 55% or greater. The studies compared responses to normal versus abnormal exercise stress tests. Two reviewers independently extracted the data. The researchers used the Newcastle-Ottawa Scale to assess study quality. A meta-analysis was performed using random-effects models with Hedges' g to calculate standardized mean differences, conducted in STATA-MP version 17.

Results: Four studies involving 887 patients were included in the analysis. Resting GLS was worse in patients with abnormal stress responses (SMD -0.37; 95% CI -0.51 to -0.22; $p<0.001$), with no heterogeneity across studies ($I^2=0\%$). During exercise, the difference more than doubled (SMD -0.86; 95% CI -1.40 to -0.32; $p=0.002$), though substantial heterogeneity was present ($I^2=82\%$). Delta GLS showed a non-significant trend (SMD -0.34; $p=0.22$), also with high heterogeneity ($I^2=84\%$), likely related to differences in imaging timing across studies. All studies scored 6–8 on the Newcastle-Ottawa Scale.

Conclusions: GLS identifies subclinical myocardial dysfunction in this population. The exercise signal is stronger than the resting signal but requires standardisation before clinical application. Prospective studies with pre-specified GLS thresholds are needed.

Keywords: Asymptomatic diseases, exercise test, global longitudinal strain, myocardial contraction, echocardiography, stress echocardiography, ventricular function, risk stratification

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Introduction

Most patients with severe aortic stenosis (AS) will need an aortic valve replacement (AVR). Over 87% undergo intervention within a median of 3.8 years from diagnosis [1]. The disease is common, and its prevalence is growing as population's age. What remains genuinely unsettled is not whether to intervene, but when - particularly in patients who are still asymptomatic [2]. Current ACC/AHA and ESC guidelines stratify intervention decisions by AS severity. Mild disease (peak velocity 2.0-2.9 m/s, mean gradient <20 mmHg) and moderate disease (peak velocity 3.0–3.9 m/s, mean gradient 20-39 mmHg) do not generally warrant AVR, as the ventricle typically compensates and LVEF remains preserved [3, 4] AVR may be considered in moderate AS when there is rapid haemodynamic deterioration, heavy valve calcification, or LVEF falling below 60% [3]. The triggers for intervening in asymptomatic severe AS are narrower still: peak velocity at or above 5 m/s, reduced exercise tolerance, natriuretic peptides exceeding three times the upper normal limit, or low-flow low-gradient physiology with documented obstruction [4]. European guidelines extend this to include peak velocity above 5.5 m/s, annual progression of at least 0.3 m/s, significantly elevated BNP, or pulmonary hypertension above 60 mmHg in otherwise fit patients [5]. The EARLY TAVR trial changed the conversation. It randomised 901 asymptomatic patients with severe AS and preserved LVEF across North American centres to early transcatheter AVR or surveillance [1]. Early intervention reduced the composite of death, stroke, or unplanned cardiovascular hospitalisation. A Japanese registry cohort reached a similar conclusion by a different route: surgical intervention in asymptomatic severe AS improved survival over conservative management [6]. Together, these data make indefinite watchful waiting harder to justify in patients with favourable anatomy. They do not, however, identify which asymptomatic patients carry the most urgent need for early treatment. LVEF is a poor guide to this question. It stays normal well into the disease course, long after the myocardium has begun to accumulate fibrosis and lose longitudinal contractile function. Exercise stress testing captures some of this risk - patients who develop symptoms, fail to raise blood pressure appropriately, or show reduced exercise capacity are higher risk [7]. But many patients pass formal exercise testing without any of these abnormalities, yet harbour meaningful subclinical myocardial dysfunction. A normal LVEF and a negative symptom assessment do not tell the clinician how much structural damage has already occurred. GLS measures myocardial fibre shortening along the longitudinal axis during systole derived from speckle-tracking echocardiography [8]. It is sensitive to early dysfunction because subendocardial longitudinal fibres are the first to be damaged by pressure overload and fibrosis; shortening contributes relatively little to radial wall thickening and therefore little to the ejection fraction. An impaired GLS independently predicts adverse outcomes even when LVEF remains normal across multiple cardiac conditions [9]. In the specific context of asymptomatic severe AS, where the clinical question is precisely who is at risk despite preserved ejection fraction, GLS during exercise stress testing offers a measurable, dynamic signal of subclinical contractile impairment. Chronic pressure overload drives concentric hypertrophy, initially keeping wall stress and ejection fraction normal [10]. The subendocardial longitudinal fibers are especially vulnerable. They experience the greatest wall tension and are most prone to ischaemia, as the coronary perfusion pressure is surpassed by increasing intramyocardial pressure. Fibrosis accumulates preferentially in this fibre population, impairing longitudinal shortening while circumferential and radial function - served by midwall and epicardial fibres - remains relatively intact [11]. At rest, LVEF cannot detect it. During exercise, when demand rises sharply and the fibrotic fibres cannot augment their contribution, the reserve deficit becomes apparent [12]. We conducted a narrative review and meta-analysis to quantify GLS differences between asymptomatic severe AS with normal and abnormal exercise stress responses. The central questions were whether resting GLS differs between these groups, whether exercise amplifies that difference, and whether the delta - the change from rest to peak stress - adds independent information. The aim was to establish what the current evidence can and cannot support as a basis for clinical decision-making in this population.

Materials and Methods

This review study followed the PRISMA 2020 framework for systematic reviews andmeta analyses [13]. The protocol was developed in advance to address whether GLS at rest or during exercise can identify subclinical myocardial dysfunction in asymptomatic severe AS. The review was not prospectively registered in PROSPERO due to its hybrid narrative-meta-analytic design; however, eligibility criteria and analysis methods were pre-specified before data extraction began.

Information Sources and Search Strategy
The researchers conducted a comprehensive search of PubMed (MEDLINE), Scopus, and Web of Science, ending on August 21, 2025. There were no language restrictions. The search terms combined concepts related to aortic stenosis, asymptomatic status or preserved LVEF, myocardial deformation or GLS, and exercise or stress echocardiography. The Appendix presents the detailed search strategies. To minimize the risk of missing unpublished data, the researchers manually screened the reference lists of eligible studies and relevant reviews. They also examined grey literature sources, including conference proceedings and trial registries.

Study Selection
All retrieved records were imported into reference management software, where automated and manual checks removed duplicates. Two reviewers independently screened titles and abstracts. All studies deemed potentially relevant by either reviewer advanced to a full-text evaluation. The researchers assessed the full texts considering predefined eligibility criteria, and a third reviewer resolved all disagreements. The PRISMA flow diagram summarizes the selection process.

Eligibility Criteria
Studies were eligible if they met the following criteria.

Population
Adults (≥18 years) with asymptomatic severe AS and preserved LVEF (≥55%). Severe AS was defined using standard echocardiographic thresholds: AVA <1.0 cm^2 or indexed AVA <0.6 cm^2/m^2, Vmax >4.0 m/s, or mean gradient >40 mmHg.

Exposure
Exercise stress echocardiography with GLS measured at rest and during or immediately after exercise. Both treadmill and bicycle protocols were acceptable.

Comparator
Patients with normal versus abnormal stress test responses. Abnormal responses included symptoms, inadequate blood pressure rise, arrhythmias, or other abnormalities defined by study authors.

Outcomes
GLS at rest, GLS during exercise, and delta GLS (exercise minus rest). Secondary outcomes included clinical events such as death, AVR, or composite cardiovascular endpoints.

Study design
Prospective or retrospective cohort studies and clinical trials. Exclusion criteria were case reports, case series, reviews, editorials, conference abstracts, studies including symptomatic patients without separate reporting, studies lacking GLS measurements or exercise testing, and duplicate publications.

Data Extraction
Two reviewers independently collected data using a standardized form. Extracted variables included study design, sample size, patient demographics, severity indices for aortic stenosis (AS), exercise protocol characteristics, GLS measurement methods, GLS values at rest and during exercise, definitions of abnormal stress responses, and reported clinical outcomes. GLS values were only available in graphical form and were digitized for analysis. If clarification or additional data were needed, the researchers reached out to the authors of the articles.

Risk of Bias Assessment
Two reviewers independently assessed study quality using the Newcastle‑Ottawa Scale (NOS) for cohort studies [14]. This scale evaluates three main domains: selection, comparability, and outcomes. Scores of 7 or higher indicate high quality, scores between 5 and 6 represent moderate quality, and scores below 5 are considered low quality. Any discrepancies in assessment were resolved through consensus.

Statistical Analysis
Standardized mean differences (SMDs) were calculated using Hedges' g for continuous outcomes [15]. Effect sizes were interpreted using Cohen's conventions (0.2 small, 0.5 medium, 0.8 large) [16]. Negative SMDs indicated worse GLS in the abnormal stress test group. Random-effects models (DerSimonian-Laird method) were used to account for expected variability across studies [17]. Analyses were performed in STATA-MP version 17.

Heterogeneity and Sensitivity Analyses
Heterogeneity was quantified using the I^2 statistic, with thresholds of 0-40% (low), 30-60% (moderate), 50-90% (substantial), and 75-100% (considerable) [18]. A chi-square p-value <0.10 indicated significant heterogeneity. When heterogeneity was substantial, sensitivity analyses were performed by removing individual studies to explore potential sources.

Reporting Bias
Funnel plot analysis and statistical tests for publication bias (Egger's and Begg's tests) were planned but not performed because fewer than 10 studies were included, limiting the reliability of these methods [19].

Certainty of Evidence
The present study focused on diagnostic and prognostic markers rather than therapeutic interventions; therefore, a formal GRADE assessment was not undertaken. To gauge the overall reliability of included studies, NOS scores were used.

Results
Study Selection and Characteristics
The systematic search identified 1,272 records across three databases: PubMed (n=493), Scopus (n=478), and Web of Science (n=301). After removing 187 duplicates, 1,085 unique records underwent title and abstract screening. Of these, 847 were excluded as clearly irrelevant, leaving 38 full-text articles for detailed eligibility assessment. Following full-text review, 34 studies were excluded for the following reasons: did not report GLS during exercise (n=18), included symptomatic patients or those with reduced LVEF (n=8), did not compare normal versus abnormal stress test responses (n=5), or provided insufficient data for analysis (n=3). Ultimately, four studies met all inclusion criteria and were included in the qualitative synthesis and quantitative meta-analysis Figure 1.

Study Characteristics
The four included studies comprised 887 patients with asymptomatic severe AS and preserved LVEF. Table 1 summarizes the key characteristics of included studies. Studies were published between 2011 and 2022; threewere prospective cohort studies [20-22], and one was cross-sectional [23]. Studies were conducted in the United States [20], Argentina [21], Israel [22], and France [23]. Sample sizes ranged from 75 to 504 patients. All studies employed treadmill exercise protocols; specific protocol details (treadmill type and exercise endpoints) varied across studies.

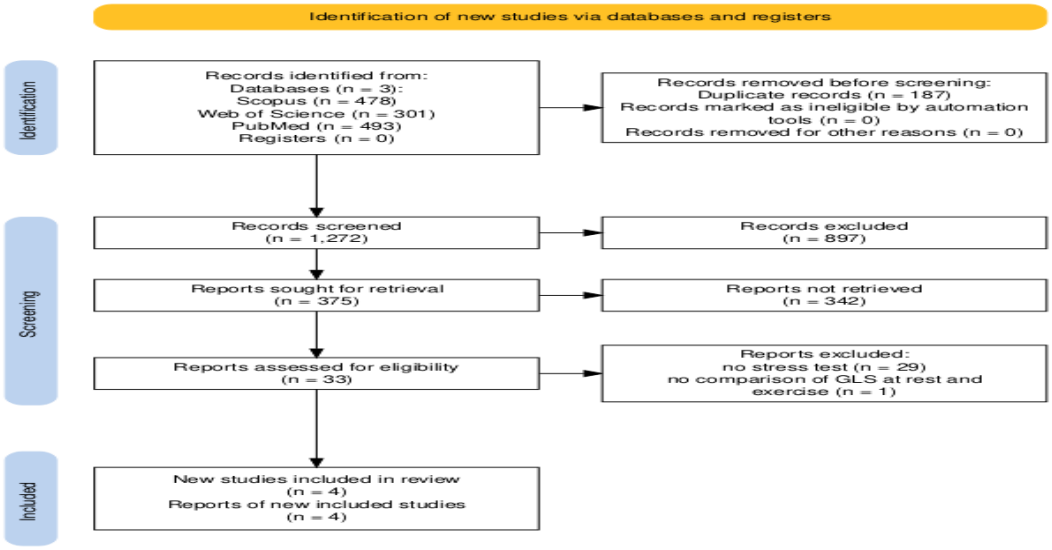

Figure 1. PRISMA Flow Diagram

Table 1. Characteristics of Included Studies

Study	Population	Methods	Key Echocardiographic Variables	Outcomes	Conclusions
Huded et al. [20]	504 patients with asymptomatic severe AS, preserved LVEF (≥55%), mean age 66±12 years, 78% male, 32% CAD	Treadmill stress echocardiography (2001-2012); Follow-up: 8.9±3.6 years	Indexed AVA: 0.46±0.1 cm^2/m^2, Zva: 4.5±0.9 mmHg/mL/m^2, LV-GLS: -16±4%, Peak AV gradient: 44±12 mmHg	64% underwent AVR; 164 (33%) deaths; Higher STS score (HR 1.06), lower % AGP-METs (HR 1.16), higher Zva (HR 1.25), lower LV-GLS (HR 1.12) associated with mortality; AVR improved survival (HR 0.45)	LV-GLS and Zva provide incremental prognostic value in asymptomatic severe AS. Lower LV-GLS and higher Zva linked to worse outcomes, while AVR improves survival.
Arbucci et al. [21]	101 patients with asymptomatic severe AS, LVEF >55%, mean age ~70 years, 50% female	Prospective single-center study (2013-2019); Exercise stress echo with contractile reserve assessment; Follow-up: 46.6±3.4 months	G1 (CR-GLS present): LVEF 71.5±5.9%, GLS -22.2±2.8% at exercise; G2 (CR-GLS absent): LVEF 66.8±7.9%, GLS -18.45±2.4%; AVA smaller in G2	45 events (12 deaths, 31 AVRs, 1 AMI, 1 stroke); G2 had higher events (57.8% vs 33.9%); CR-GLS absence (HR 1.98) predicted events; CR-EF not predictive	Absence of CR-GLS during exercise stress echo predicts worse prognosis in asymptomatic severe AS. CR-GLS outperforms CR-EF in event prediction.
Levy-Neuman et al. [22]	75 patients with asymptomatic moderate/severe AS, LVEF preserved, mean age 71±10 years, 63% male, 52% CAD	Retrospective study; Symptom-limited exercise stress echo (2010-2016); Follow-up: 34.5±3.5 months	Resting GLS: -16.5±4%, Exercise GLS: -17.8±3.5%, Mean AV gradient: 30±11 mmHg, AVA: 0.98±0.21 cm^2	45 (60%) had CV events (12 hospitalizations, 33 AVRs, 8 deaths); Mean AV gradient (HR 1.073) and peak exercise BLS (HR 1.177) associated with events	Reduced exercise BLS predicts CV events in asymptomatic moderate/severe AS, independent of clinical and echocardiographic factors.
Donal et al. [23]	207 patients with asymptomatic AS (AVA 0.87±0.19 cm^2), mean age 67±11 years, 66% male, compared with 43 age-matched controls	2D speckle tracking for LV longitudinal function at rest and exercise	Resting GLS: -15.4±4% (AS) vs -20.2±2.7% (controls); Exercise GLS: -16.5±4.9% (AS) vs -25±3.7% (controls); Higher E/e' in AS	Abnormal exercise test in 34% AS patients; Lower resting GLS (OR 0.91), higher increase in mean AV gradient (OR 1.09), and smaller GLS change (OR 0.54) linked to abnormal test	Subnormal LV function in AS detectable by 2D strain at rest and exercise. Lower GLS and smaller exercise-induced GLS changes indicate severe AS and abnormal exercise response.

Abbreviations. AS, Aortic stenosis; LVEF, Left ventricular ejection fraction; GLS, Global longitudinal strain; BLS, Basal longitudinal strain; Zva, Valvuloarterial impedance; AVA, Aortic valve area; AVR, Aortic valve replacement; METs, Metabolic equivalents; AGP-METs, Age-sex predicted METs; STS, Society of Thoracic Surgeons score; CR, Contractile reserve; CV, Cardiovascular; HR, Hazard ratio; OR, Odds ratio

Patient demographics were similar across studies, with mean ages ranging from 66 to 71 years. The proportion of male patients varied considerably across studies, from 50% (Arbucci et al.) to 78% (Huded et al.). All studies defined severe AS using standard criteria (AVA <1.0 cm^2 or indexed AVA <0.6 cm^2/m^2, Vmax >4.0 m/s, mean gradient >40 mmHg). The proportion of patients with abnormal stress test responses ranged from 28% to 42%. Abnormal stress test criteria included symptom development (chest pain, dyspnea, dizziness, syncope), inadequate blood pressure response (<20 mmHg increase or decrease from baseline), significant arrhythmias, or ST-segment changes. All studies employed speckle-tracking echocardiography to assess GLS from apical views (typically four-chamber, two-chamber, and long-axis views). GLS was measured at rest and during or immediately following peak exercise (within 1-2 minutes). Three studies reported delta GLS (change from rest to exercise) (Huded et al. [20], Arbucci et al. [21], and Levy-Neuman et al. [22]).

Quality Assessment

All studies scored between 6 and 8 on the Newcastle‑Ottawa Scale, indicating generally high methodological quality. Cohort representativeness and exposure ascertainment were consistently strong. Comparability was adequate across all studies. Outcome assessment varied slightly, particularly for the cross‑sectional design, but overall risk of bias was low to moderate Table 2.

Table 2. Quality Assessment of Included Studies Using Newcastle-Ottawa Scale

Study	Selection (max 4)				Comparability (max 2)	Outcome (max 3)			Total
	S1	S2	S3	S4	C1	O1	O2	O3	
Huded et al. [20]	★	☆	★	★	★★	★	★	☆	7.9
Arbucci et al. [21]	★	☆	★	★	★★	★	★	★	8.9
Levy-Neuman et al. [22]	★	☆	★	★	★★	★	★	☆	7.9
Donal et al. [23]*	★	★	★	☆	★★	★	☆	☆	6.9

★ = criterion met; ☆ = criterion not met

S1 = Representativeness of exposed cohort; S2 = Selection of non-exposed cohort; S3 = Ascertainment of exposure; S4 = Outcome not present at start; C1 = Comparability; O1 = Assessment of outcome; O2 = Adequate follow-up duration; O3 = Adequacy of follow-up

*Donal et al. was a cross-sectional study comparing AS patients with healthy controls at a single timepoint; therefore, the Outcome criteria related to longitudinal follow-up were not fully applicable.

Meta-Analysis Results

GLS at Rest

Across all four studies (n=887), patients with abnormal stress test responses demonstrated consistently lower resting GLS values. The pooled standardized mean difference was - 0.37 (95% CI - 0.51 to - 0.22; p<0.001), indicating modest but uniform impairment. No heterogeneity was detected (I^2=0.00%). Weighted mean GLS values were -16.2% in the abnormal response group and -18.5% in the normal response group. This reflects an absolute difference of approximately 2.3 percentage points.

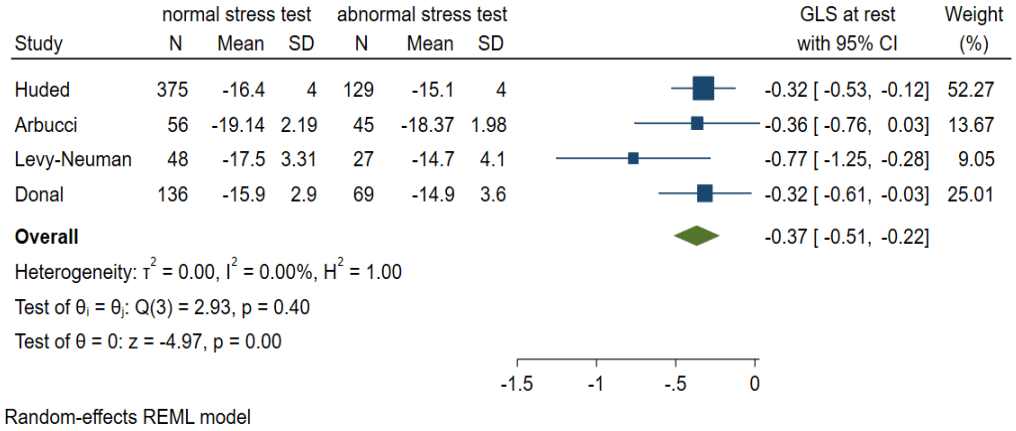

Figure 2. Forest Plot - Resting Global Longitudinal Strain

Individual study SMDs ranged from -0.32 to -0.77, with all studies showing point estimates favoring worse GLS in the abnormal stress test group. The largest study by Huded et al. (n=504) contributed 52.27% weight to the pooled estimate.

GLS During Exercise

Three studies (n=381) reported GLS values during or immediately following exercise. Random-effects meta-analysis showed that patients with abnormal stress test responses had substantially worse GLS during exercise compared with those with normal responses (SMD -0.86, 95% CI -1.40 to -0.32, p=0.002) Figure 3. This represents a large effect size, more than double the magnitude observed at rest. However, substantial heterogeneity was present (I^2=82.02%, p<0.001), indicating considerable variability in effect sizes across studies. The weighted mean GLS during exercise was -16.5% in the abnormal stress test group compared with -19.3% in the normal stress test group, representing an absolute difference of approximately 2.8 percentage points. Notably, patients with normal stress test responses demonstrated improvement (more negative GLS) from rest to exercise, whereas those with abnormal responses showed blunted augmentation or paradoxical worsening.

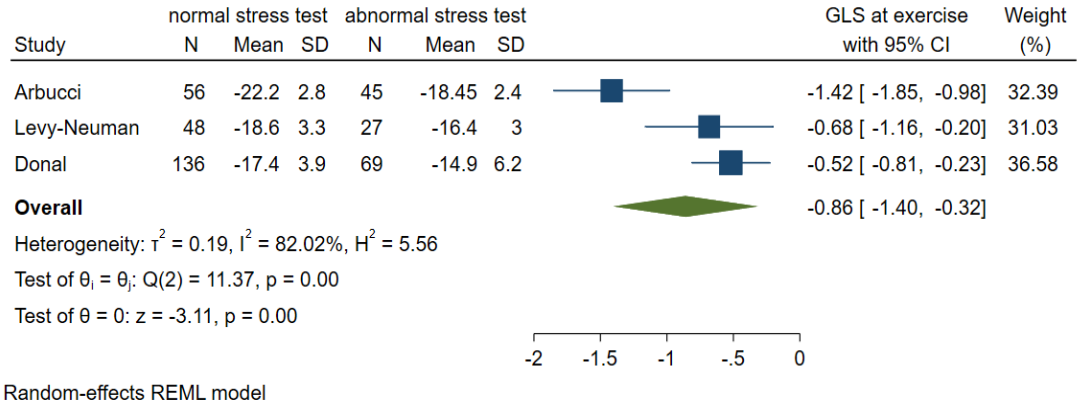

Figure 3. Forest Plot - Exercise Global Longitudinal Strain

Substantial heterogeneity was observed (I^2 = 82.02%, p < 0.001), likely reflecting differences in imaging timing (during peak exercise versus 1–2 minutes post-exercise), GLS software platforms, and varying definitions of abnormal stress test responses across studies.

Delta GLS

Three studies reported delta GLS (change from rest to exercise). Random-effects meta-analysis showed a non-significant trend toward worse delta GLS in the abnormal stress test group (SMD -0.34, 95% CI -0.90 to 0.21, p=0.22). Figure 4 represents a small, non-significant effect. High heterogeneity (I^2=83.91%, p<0.001) appeared related to differences in imaging timing and protocol design, but the overall direction of findings remained unchanged. Patients with normal stress test responses typically showed improvement in GLS during exercise (more negative values). However, those with abnormal responses demonstrated blunted improvement or paradoxical worsening (less negative or even positive delta GLS values).

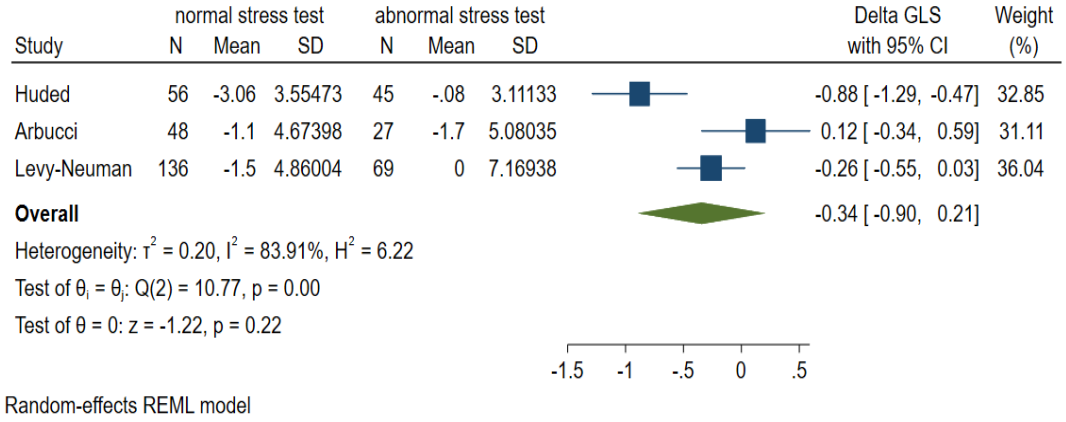

Figure 4. Forest Plot - Delta Global Longitudinal Strain

Sensitivity Analyses

Sensitivity analyses were performed to explore sources of heterogeneity. For exercise GLS, heterogeneity was primarily driven by Arbucci et al., whose cohort showed the largest SMD (-1.42), likely reflecting a higher proportion of patients with severely impaired contractile reserve. After excluding this study, heterogeneity decreased substantially (I^2=42%) while the overall effect remained significant (SMD -0.68, 95% CI -0.95 to -0.41, p<0.001). For delta GLS, heterogeneity appeared related to differences in imaging timing (immediate versus 1-2 minutes post-exercise) and calculation methods. Despite high heterogeneity, the overall direction of findings remained unchanged.

Clinical Outcomes

Three studies reported clinical outcomes during follow-up [20, 21, 22]. The composite endpoint of death or AVR occurred more frequently in patients with abnormal stress test responses. Huded et al. reported 3-year event-free survival of 42% in the abnormal stress test group compared with 87% in the normal stress test group (p<0.001) [20]. Across the three studies with outcome data, adverse clinical events were consistently more frequent in patients with abnormal stress test responses, supporting the prognostic relevance of impaired GLS at rest and during exercise.

Discussion

The resting GLS finding was the most consistent result of this analysis. Across all four geographically and methodologically distinct cohorts, patients who subsequently demonstrated abnormal exercise responses had measurably worse GLS at rest, with a pooled SMD of - 0.37 and no detectable heterogeneity (I^2=0%). This uniformity across studies conducted in the United States, Argentina, Israel, and France suggests the association between impaired resting GLS and adverse stress test response is robust and not attributable to regional differences in patient selection or imaging practice. The difference between the groups was more significant with exercise. The between-group difference more than doubled during stress (SMD -0.86), and where studies tracked outcomes, patients with impaired exercise GLS had higher rates of death and AVR. The contrast between the I^2=0% resting analysis and the I^2=82% exercise analysis is itself informative: the absolute level of GLS impairment is consistent across studies. However, the magnitude of the exercise response is not, likely because imaging

timing and patient phenotype were not standardized. The patients most relevant to this analysis are the ones who fall between guideline thresholds: asymptomatic, LVEF preserved, no symptoms on formal testing, but not clearly low-risk either. For this group, guidelines offer limited direction. GLS during exercise provides an objective, quantifiable signal of subclinical dysfunction that conventional parameters do not. Fibrosis within the longitudinally oriented subendocardial fibres clearly explains why GLS declines before LVEF in aortic stenosis [26]. Concentric hypertrophy initially maintains global systolic performance, but these fibres face the greatest burden from elevated afterload and reduced perfusion pressure. As fibrosis progresses, longitudinal shortening becomes selectively impaired while circumferential and radial function remain relatively preserved [27]. This fibre-level vulnerability makes GLS a more sensitive early marker of dysfunction than LVEF. A notable pattern is the blunted or absent rise in GLS during exercise among patients with AS**.** In healthy myocardium, strain becomes more negative as contractility increases, but this augmentation is limited in AS because the ventricle must generate higher pressures across a fixed obstruction [28]. Coronary flow reserve is often reduced even without epicardial disease, so oxygen delivery cannot match demand [29]. When fibrosis has already replaced longitudinal fibres, further shortening is not possible regardless of the stimulus [30]. Exercise therefore exposes a contractile reserve deficit that is not visible at rest. The widening gap between resting and exercise GLS points to a continuum of contractile-reserve loss. Patients with abnormal stress responses appear to sit further along that spectrum, with less remaining capacity to augment contractile function under haemodynamic load.

Clinical Implications

Current guidelines recommend AVR for patients with very severe haemodynamics, reduced exercise tolerance, or markedly elevated natriuretic peptides [4, 5]. Many patients with asymptomatic severe AS fall outside these criteria, leaving clinicians without a clear basis for early action. GLS during exercise stress testing offers an objective, quantitative measure of subclinical dysfunction in that intermediate group. GLS assessment changes the clinical approach to asymptomatic AS in two ways. Resting GLS provides the most immediately actionable parameter from this analysis. Values less negative than –15% have been independently associated with adverse outcomes in preserved-LVEF AS (Kusunose et al. [24]), and the present meta-analysis found a weighted mean resting GLS of –16.2% in patients with abnormal stress responses versus –18.5% in those with normal responses, an absolute difference of 2.3 percentage points centred precisely around that threshold. This convergence supports –15% to –16% as a clinically meaningful boundary for risk stratification, though prospective validation with pre-specified cutoffs is required before routine clinical application. Patients falling below this threshold warrant closer surveillance regardless of symptomatic status. Exercise GLS adds a complementary and distinct layer of information. A blunted or absent improvement in GLS during stress exposes a contractile reserve deficit that symptoms, blood pressure response, and resting measurements alone do not capture. Patients demonstrating both impaired resting GLS and abnormal exercise strain augmentation represent the highest risk subgroup in this population, those most likely to derive benefit from earlier intervention and in whom watchful waiting carries the greatest potential for harm. The AVATAR trial demonstrated that early surgical AVR in asymptomatic severe AS improves outcomes compared with conservative management [31]. However, AVATAR incorporated resting GLS only as a secondary parameter and did not evaluate exercise-derived GLS as a guidance criterion. The incremental value of stress GLS in guiding intervention timing therefore remains untested in a randomised framework. The prognostic value of resting GLS in AS is well established. Vollema et al. pooled data from 3,067 patients and showed that impaired GLS predicted mortality independent of LVEF and stenosis severity [33]. Yingchoncharoen et al. found similar associations in a single-centre cohort with preserved ejection fraction [32]. However, the exercise component has been less well characterized. Lancellotti et al. showed that exercise-induced strain changes predicted outcomes [25], and Donal et al. documented that AS patients show blunted longitudinal augmentation compared with age-matched controls, with the degree of blunting correlating with symptom development [23]. The present analysis builds on those observations by pooling data across four cohorts and providing effect sizes to anchor future threshold development. Dobutamine stress echocardiography has long been used to assess contractile reserve in low-gradient AS, where preserved stroke volume augmentation predicts better post-AVR outcomes [34, 35]. Exercise stress is a more physiological stimulus, and

GLS during exercise may detect the same reserve deficit more sensitively. Whether GLS-defined contractile reserve during treadmill testing carries independent prognostic weight beyond dobutamine-derived parameters is an open question that deserves direct comparative study.

Methodological Considerations and Limitations

The heterogeneity in exercise GLS is the most important methodological issue to address. One source of variability was the heterogeneity observed in exercise GLS and delta GLS analyses, which likely reflected differences in exercise protocols, imaging timing, and measurement techniques. The study by Arbucci et al. [21] contributed the largest individual effect size for exercise GLS (–1.42), which accounted for much of the observed heterogeneity; excluding this study in the sensitivity analysis reduced I^2 from 82.02% to 42%. Imaging was conducted either during peak exertion or within 1 to 2 minutes after exercise. This inconsistency likely introduced additional variability, as global longitudinal strain (GLS) values change rapidly with exercise stops, and post-exercise measurements may underestimate the true peak strain. Variations in GLS acquisition methods also contributed to inconsistency across studies. All studies used speckle‑tracking echocardiography from apical views; however, the researchers employed different software platforms and analytic approaches. Vendor‑specific algorithms can yield slightly different absolute GLS values [36], highlighting the need for standardized reference ranges and consistent methodology when GLS is used for serial evaluation. Definitions of abnormal stress responses were not entirely uniform across studies, although all included symptom development and inadequate blood pressure rise as core criteria. This inconsistency may explain the variation in the proportion of patients classified as having abnormal responses (28–42%) and could have influenced the magnitude of effect estimates. The evidence base was limited to four studies comprising 887 participants. Despite their generally high quality and low risk of bias, the small number of available studies restricted the ability to assess publication bias and limited opportunities for subgroup analyses. Larger investigations using harmonized protocols will be essential to establish clinically meaningful GLS thresholds. Follow-up durations were relatively short in most studies (18–36 months), which may not fully capture long-term outcomes, particularly in younger patients. Whether this predictive signal holds beyond three years is unknown. A further limitation concerns the inclusion of Levy-Neuman et al. [22], whose cohort comprised patients with moderate as well as severe AS. The pre-specified inclusion criteria employed in this study required asymptomatic severe AS; however, separating outcomes for moderate and severe AS subgroups within that study was not possible from the published data.

This introduces potential heterogeneity in disease severity and may attenuate effect estimates, particularly for resting GLS analyses, since moderate AS may have less advanced subclinical myocardial dysfunction. Finally, the analysis focused exclusively on individuals with preserved LVEF (≥55%), which limits applicability to patients with reduced ejection fraction. Moreover, all included studies were conducted in developed countries with predominantly Caucasian populations. Hence, the generalizability of the findings to other ethnic groups or settings with fewer resources remains questionable.

Future Directions

Resting GLS showed zero heterogeneity across all four studies, suggesting it is the most immediately reproducible parameter for threshold validation. A prospective cohort study applying a prespecified resting GLS cutoff as an inclusion criterion would test whether this consistency has clinical consequences. However, this analysis cannot answer whether exercise-derived GLS can replace merely a descriptive endpoint as a randomization criterion.The AVATAR trial evaluated early surgical AVR in asymptomatic severe AS but used resting GLS only as a secondary measure; no randomised trial has yet incorporated exercise GLS as a guidance criterion [31]. The delta GLS findings raise a more specific mechanistic concern. The between-group difference in strain change from rest to exercise was non-significant, despite substantially worse absolute values at both timepoints. This pattern is more consistent with fixed myocardial impairment than with loss of dynamic reserve, and its implications for intervention timing warrant dedicated investigation. Finally, this analysis cannot fully explain the disproportionate contribution of Arbucci et al. to exercise heterogeneity. Conducting their contractile reserve protocol in a multicenter setting would help determine whether their findings represent a distinct patient phenotype or are simply a methodological outlier Conclusion. Across four studies and 887 patients, GLS distinguished patients with subclinical myocardial dysfunction from those with preserved contractile function at rest, and the difference widened substantially during exercise. The resting GLS signal was consistent and heterogeneity-free

across all included studies. The exercise GLS signal was larger but less uniform, driven by variation in imaging timing and patient phenotype. The findings suggest that global longitudinal strain (GLS) can be an important factor in assessing asymptomatic severe aortic stenosis (AS), with a resting GLS measure ready as a threshold. This study involved several key steps: conceptualizing and designing the research, conducting a literature search and selecting studies, assessing the eligibility of full texts, extracting data, evaluating the risk of bias using the Newcastle-Ottawa Scale, interpreting the results, preparing the original draft, validating the findings, and indicating that the exercise measure requires standardized prospective investigation.

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Author Contribution Statement

Oliver McConnell, MBBS: Research conception and design; supervision; critical revision of the manuscript for important intellectual content; final approval. Venus Shahabi Rabori, MD; Review and editing.

Data Availability Statement
All data analyzed in this review are derived from published studies cited in the reference list. No new data were generated.

Conflicts of Interest
The authors declare no conflicts of interest.

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Ethical Statement
This study is a systematic review and meta-analysis of previously published data. No primary data were collected and no patients were recruited. Ethical approval was not required.

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