Prognostic value of left ventricular global longitudinal strain in patients with severe aortic stenosis for Transcatheter Aortic Valve Implantation-related morbidity and mortality: a systematic review and meta-analysis

Brief title: LV-GLS predicts post-TAVI outcomes

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Twitter: Meta-analysis by @NielsStens and colleagues highlighted that preprocedural LV-GLS was associated w/ post-TAVI all-cause mortality and MACE. Addition of LV-GLS to current-guideline based assessment of LVEF may improve AS risk stratification. #CardioTwitter #JACCIMG #TAVR

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STRUCTURED ABSTRACT

OBJECTIVES: The aim of this systematic review and meta-analysis was to evaluate the prognostic value of preprocedural left ventricular global longitudinal strain (LV-GLS) for post-Transcatheter Aortic Valve Implantation (TAVI)-related morbidity and mortality.

BACKGROUND: Traditional echocardiographic parameters, including left ventricular (LV) ejection fraction (LVEF), demonstrate limited prognostic value for post-TAVI outcomes. Several studies have reported conflicting results regarding the potential role of LV global longitudinal strain (LV-GLS) in this setting, which in part may relate to studies being underpowered and/or using various methodological approaches.

METHODS: A systematic search was conducted in PubMed, Embase and Web of Science from January 2001 to April 2022. We included all studies on patients with severe aortic stenosis who underwent TAVI, and in which the association between preprocedural 2D-speckle-tracking-derived LV-GLS and clinical outcomes was investigated. An inversely-weighted random effects meta-analysis was adopted to investigate the association between LV-GLS vs primary (i.e. all-cause mortality) and secondary (i.e. major cardiovascular events [MACE]) post-TAVI outcomes.

RESULTS: Of the 1,130 identified records, 12 were eligible, all of which had a low-to-moderate risk of bias (Newcastle-Ottawa scale). On average, 2,049 patients demonstrated preserved LVEF (52.6±5.0%), but impaired LV-GLS (-13.6±1.6%). Patients with a lower LV-GLS had a higher all-cause mortality (pooled hazard ratio (HR) 2.01 [95% confidence interval (CI): 1.59, 2.55]) and MACE (pooled odds ratio (OR) 1.26 [95%CI: 1.08, 1.47]) risk compared to patients with higher LV-GLS. In addition, each 1% decrease of LV-GLS was associated with an increased mortality (HR 1.06 [95%CI: 1.04, 1.08]) and MACE risk (OR 1.08 [95%CI: 1.01, 1.15]).

CONCLUSIONS: Preprocedural LV-GLS was significantly associated with post-TAVI morbidity and mortality. This suggests a potential clinically important role of pre-TAVI evaluation of LV-GLS for risk stratification of patients with severe aortic stenosis. Registration number: CRD42021289626.

KEYWORDS: Aortic stenosis, Echocardiography, Morbidity, Mortality, Strain, Transcatheter Aortic Valve Replacement

CONDENSED ABSTRACT

Traditional echocardiographic parameters, including left ventricular (LV) ejection fraction, demonstrate limited prognostic value for post-Transcatheter Aortic Valve Implantation (TAVI) outcomes. The current meta-analysis evaluates the prognostic value of preprocedural LV global longitudinal strain (LV-GLS) for post-TAVI mortality and major cardiovascular events (MACE). Our results highlight that preprocedural LV-GLS was significantly associated with post-TAVI mortality and MACE. This suggests a potentially clinically important role of pre-TAVI evaluation of LV-GLS for risk stratification of patients with severe aortic stenosis.

ABBREVIATIONS LIST

AS = aortic stenosis

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

LV = left ventricle

LVEF = left ventricular ejection fraction

LV-GLS = left ventricular global longitudinal strain

MACE = major cardiovascular events

NYHA = New York Heart Association functional class

OR = odds ratio

SD = standard deviation

TAVI = Transcatheter aortic valve implantation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become the method of choice to treat symptomatic, severe aortic stenosis (AS) in older patients with intermediate and high surgical risk [1, 2]. The indication for aortic valve replacement is based on symptomatology and systolic dysfunction of the left ventricle (LV), reflected by an ejection fraction (EF) of <50% [1, 2]. Interpretation of AS symptoms in older patients remains challenging [3], posing a strong emphasis on early detection of LV systolic dysfunction to facilitate timely replacement of the native calcified aortic valve. The concentric remodeling of the LV, induced by the persistent increase in afterload due to AS, can mask decrements in LVEF until very late in the AS disease process [4]. Consequently, LVEF has limited value for risk stratification within the older population with AS.

In the past years, several studies have demonstrated that myocardial deformation assessment via 2D-speckle tracking represents a reliable method to evaluate clinical and subclinical systolic dysfunction [5-7]. LV global longitudinal strain (LV-GLS) may indicate subtle changes in LV mechanics already present during early stages of AS, even when LVEF is preserved [4]. Previous studies have examined whether impaired LV-GLS is associated with post-TAVI outcomes, both in symptomatic and asymptomatic patients with AS [8,9]. Similarly, studies have explored the relation between preprocedural LV-GLS and post-TAVI outcomes. However, studies have reported conflicting results, which in part may relate to studies being underpowered and/or using various methodological approaches. Pooling of these studies may provide better insight into the potential prognostic value of preprocedural LV-GLS for post-TAVI morbidity and mortality.

Therefore, we systematically reviewed the current literature and performed a comprehensive meta-analysis to evaluate the prognostic value of LV-GLS for post-TAVI outcomes. We hypothesize that preprocedural LV-GLS predicts post-TAVI related morbidity and mortality in patients with severe AS. Identifying patients at high risk for developing clinical outcomes after TAVI allows for timely recognition, intervention and intensified follow-up.

METHODS

This meta-analysis was reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses checklist [10]. The protocol of this meta-analysis is registered within the PROSPERO system (CRD42021289626).

Information sources and search strategy

A systematic literature search was performed in three bibliographic databases, including PubMed, Embase (Ovid), and Web of Science, from January 2001 to April 2022. The search strategy included a combination of the following terms: strain, speckle tracking, TAVI, mortality, and cardiovascular events. **Supplemental Table 1** highlights the search strategy that was used within the selected bibliographic databases. Reference lists of relevant articles were thoroughly screened for additional studies.

Eligibility criteria

To be eligible for inclusion in this systematic review and meta-analysis, manuscripts had to: 1) include patients with AS that underwent TAVI; 2) quantify the LV-GLS using 2D-speckle tracking before TAVI; 3) investigate the association between preprocedural LV-GLS versus primary (i.e. all-cause mortality) and secondary (i.e. major adverse cardiovascular events [MACE, i.e. incident rehospitalization, stroke, heart failure, myocardial infarction, revascularization or death]) postprocedural outcomes; 4) define follow-up time as the interval between pre-TAVI and the end of follow-up (determined by either occurrence of an event or the duration of the study); 5) be written in English and be published in a peer-reviewed journal; and 6) be performed in adults. Studies addressing bicuspid valves were excluded. In addition, reviews, case studies and conference abstracts were excluded, but no further restrictions regarding study design were applied.

Data selection and extraction

Study selection was performed by two independent researchers (NS, OvI). All titles and abstracts of the retrieved articles were screened for the inclusion and exclusion criteria. Subsequently, full-texts of the

relevant manuscripts were retrieved and reviewed. The results from both researchers were compared and discussed until consensus was reached. In case of continued disagreement a third researcher was consulted (DT). After consensus was reached, the included studies were then summarized within a pre-formatted data sheet, where report (i.e. author and year), study (i.e. sample characteristics, criteria used for AS), patient (i.e. disease and surgical risk status, presence of comorbidities, measures of cardiac function), survival (i.e. outcome measure, number of events, follow-up duration, prognostic value of LV-GLS) and measurement (i.e. echo and analysis software vendor) characteristics were described. Authors were contacted whenever insufficient data were reported. When multiple manuscripts from the same research group were included with overlapping time ranges, authors were asked to send data from unique patients only, to prevent patients from appearing twice in the meta-analysis.

Risk of bias assessment

The risk of bias of included studies was independently rated by two researchers (NS, OvI) using the Newcastle-Ottawa Scale [11]. Results were discussed until consensus was reached, where a third researcher (DT) was consulted in case of continued disagreement. Included studies were rated on three different domains, including the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome. The quality score ranges from 0 to 9 points, where 1-3, 4-6 and 7-9 points are reflecting a high, intermediate and low risk of bias respectively.

Syntheses of results

Unadjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI) were extracted from included studies that included all-cause mortality as their outcome measure, whilst unadjusted odds ratios (OR) and corresponding 95% CI were extracted from studies that included MACE as their outcome measure. Transformation of HRs and ORs using the natural logarithm was performed to allow accurate estimation of the 95% confidence interval for the pooled estimate. An inverse variance-weighted random-effects model was subsequently used to pool per % LV-GLS decrease hazard ratios for all-cause mortality following the DerSimonian and Laird approach [12]. In an individual analysis, we explored trends when LV-GLS was presented on a dichotomous scale (i.e. impaired vs preserved LV-

GLS) for all-cause mortality and MACE separately. The median LV-GLS was used as a cutoff to dichotomize LV-GLS if between -12 and -15%. If this criterion was not satisfied, authors were contacted to share the hazard ratio / odds ratio corresponding to a LV-GLS of -13.5%. To evaluate heterogeneity present within the included studies, we used the I^2 test, with >50% indicating significant heterogeneity. Inverted funnel plots were used to exploratively evaluate the presence of publication bias. Analyses were performed in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using the *meta*-package (version 5.1-1) [13], where a two-tailed p-value of 0.05 was used to claim statistical significance. Data is presented as mean ± standard deviation (SD), median with interquartile range (IQR), or frequency and proportion, as appropriate.

RESULTS

Search results

In total, 1,130 studies were identified after applying the specified search string in PubMed, Embase and Web of Science. Screening of the titles and abstracts in respect to the inclusion and exclusion criteria, combined with the removal of duplicates, resulted in the exclusion of 1,075 articles. Subsequent assessment of the full text of the remaining 55 articles resulted in further exclusion of 38 articles, leaving 17 relevant studies. To overcome methodological constraints in pooling of the data, authors were contacted to provide data on LV-GLS vs primary (all-cause mortality) and secondary (i.e. MACE) outcomes. Authors of nine publications provided unpublished data [14-22]. Five studies originally met the requirements for inclusion, but were excluded due to incomplete data reporting [23-26] or covering the same cohort [27] as another included study [15]. Taken together, this resulted in the inclusion of twelve studies in the meta-analysis of which nine evaluated the association of preprocedural LV-GLS with all-cause mortality (n=1,750) [14-16, 19-22, 28, 29] and five with MACE (n=498) [17, 18, 19, 22, 30] respectively. **Figure 1** visualizes the sequential steps performed above.

Population characteristics

Preprocedural characteristics of the included studies are depicted in **Table 1**. The analytical cohort of the twelve included studies comprised 2,049 unique patients (49.8% women) with AS who underwent TAVI. Mean age was 81.1±1.4 years and NYHA class ≥III was reported in 66.0%. Mean aortic valve area was 0.70±0.04 cm^2 with a mean transaortic pressure gradient of 43.6±4.9 mmHg. Comorbidities were frequent (prevalence hypertension 77.7%, diabetes 27.1%, coronary artery disease 54.6%). On average, patients demonstrated preserved LVEF (mean 52.6±5.0%) but impaired LV-GLS (mean -13.6±1.6%). In terms of risk of bias, five studies had an intermediate risk of bias (Newcastle-Ottawa Scale: 6) and the remaining studies showed a low risk of bias (Newcastle-Ottawa Scale ≥7, **Supplemental Table 2**).

LV-GLS vs clinical outcomes

During a median follow-up of 24.7 months (IQR 22.5, 32.9), overall all-cause mortality was 25.5% (n=447). Patients with a lower preprocedural LV-GLS had a higher risk of all-cause mortality compared to patients with a higher LV-GLS (pooled HR 2.01 [95% CI: 1.59, 2.55], p <0.001, I^2= 0% [95% CI: 0%, 68%], p = 0.74; **Figure 2A**). Each 1% lower LV-GLS (i.e., towards 0%) was associated with an increased mortality risk after TAVI (pooled HR 1.06 [95% CI: 1.04, 1.08], p <0.001, I^2=0% [95% CI: 0%, 65%], p=0.79; **Figure 2B**).

In addition, during a median follow-up of 16.8 months (IQR 13.6, 36,7), MACE occurred in 117 patients (23.5%). Patients with a lower preprocedural LV-GLS had a higher odds of MACE compared to patients with a higher LV-GLS (pooled OR 1.26 [95% CI: 1.08, 1.47], p=0.003, I^2=0% [95% CI: 0%, 79%], p=0.67; **Figure 3A**). In addition, each 1% decrease in LV-GLS was associated with an increased odds of MACE after TAVI (pooled OR 1.08 [95% CI: 1.01, 1.15], p=0.022, I^2= 0% [95% CI: 0%, 85%], p=0.67; **Figure 3B**).

Explorative assessment of publication bias for the association between preprocedural LV-GLS (on a continuous and dichotomous scale) and all-cause mortality via inverted funnel plots showed a symmetrical pattern, suggesting no publication bias (**Supplemental Figure 1**).

DISCUSSION

The aim of this meta-analysis was to evaluate the prognostic value of LV-GLS for post-TAVI morbidity and mortality in patients with severe, symptomatic AS undergoing TAVI. First, despite different cut-off values when LV-GLS was modelled on a dichotomous scale, those with a lower preprocedural LV-GLS demonstrated a significantly higher post-TAVI risk for all-cause mortality (101% increased risk) and MACE (1.26 times higher odds) compared to individuals with a higher LV-GLS. In addition, we found that every percentage point decline in LV-GLS was associated with an increased risk for post-TAVI all-cause mortality (6% higher risk) and MACE (1.08 times higher odds). Taken together, our meta-analysis demonstrates that LV-GLS significantly predicts post-TAVI outcomes (**Central Illustration)**, which suggests an important role for the preprocedural evaluation of LV-GLS for risk stratification of patients with severe symptomatic AS for clinical outcomes post-TAVI.

Assessment of systolic dysfunction has been considered the mainstay of risk stratification in patients with AS. Current guidelines advocate the presence of an impaired LVEF as a gatekeeper for aortic valve replacement [1, 2]. However, the recovery of LV function after TAVI varies widely and more sensitive methodologies to detect subclinical LV dysfunction are warranted. Speckle-tracking has emerged as a relevant method to quantify sub-clinical and clinical systolic dysfunction. Unfortunately, studies that used LV-GLS as a prognostic factor for events post-TAVI were often limited by a small sample size, causing the majority of studies to conclude that LV-GLS has no significant prognostic value. The ability to pool data from 2,049 individuals within our meta-analysis effectively overcomes this limitation. Indeed, in our meta-analysis we found preprocedural LV-GLS to significantly predict post-TAVI all-cause mortality in patients with severe, symptomatic AS.

Compared to all-cause mortality, the association between preprocedural LV-GLS and post-TAVI cardiovascular morbidity has been less extensively described in literature. The pooling of the four included studies reinforces both the limitation of relatively small sample sizes, but also the potential benefit of meta-analyses to provide better insight into these areas. Our meta-analysis showed that preprocedural LV-GLS is also significantly related to post-TAVI morbidity. It should be noted that an odds ratio is dependent on the number of events and the sample size [31], which may explain the observation that the pooled effect is largely determined by two individual studies. Nevertheless, reports have highlighted that the preprocedural LV-GLS correlated with the improvement in NYHA functional class [32] and complication rate directly following TAVI [33]. To further support our observations, previous work using computed tomography angiography reinforced that a lower LV-GLS is related to a higher risk of all-cause mortality and heart failure hospitalizations [34]. Whilst it remains premature to make definitive conclusions, the presented evidence, paired with recent reports, suggest that LV-GLS also has potential to predict post-TAVI morbidity. This warrants future studies to elaborate on the association between preprocedural LV-GLS and post-TAVI morbidity.

The observation that LV-GLS has predictive capacity for mortality and potentially morbidity in patients undergoing TAVI raises the question about the potential underlying physiological mechanism. In essence, AS transcends the definition of an isolated valvular disease with its considerable implications for cardiac function and structure. Compensatory left ventricular hypertrophy develops in response to the persistent pressure overload induced by the stenotic aortic valve, as an attempt to compensate and normalize left ventricular wall stress and systolic function. Since the subendocardial myocytes are susceptible to reductions in coronary blood flow [35], the accompanied myocardial ischemia mainly affects longitudinally-oriented muscle fibers. If pressure overload persists, irreversible myocardial fibrosis and a reduction in myocardial (longitudinal) function may occur. This may explain that global LV afterload, left ventricular mass and replacement fibrosis are independently associated with LV-GLS in patients with AS [36, 37]. In addition, transthyretin cardiac amyloidosis is often co-existing in patients with AS [38].

In patients with cardiac amyloidosis, the degree of deposed myocardial amyloid fibrils strongly correlated with longitudinal strain in all segments in a 17-segment model [39]. Also others found that LV-GLS is more impaired in AS patients with concurrent transthyretin cardiac amyloidosis compared to those with isolated AS [40]. These processes may contribute to the ability of LV-GLS to predict post-TAVI all-cause mortality.

Although our meta-analysis revealed that a dichotomous cut-off has prognostic value, substantial variation in using cut-off values was present between these studies. This raises questions on its applicability, but also what would represent the optimal LV-GLS cut-off for prognosis of post-TAVI outcomes in patients with severe symptomatic AS. Variation in cut-offs was minimized by setting a range of LV-GLS for the dichotomous analysis (i.e., between -12 and -15%). Since no clear trend was observed in a change in HRs in relation to the increase in cut-off values (**Figure 2**), it seems unlikely that the variation in cut-offs explained the large inter-study variability that we observed when LV-GLS was modelled on a dichotomous scale. Alternatively, differences in the patient's risk profile may play an important role in this large inter-study variability. Although all studies included patients with severe, symptomatic AS, differences in comorbidity prevalence (i.e. hypertension, diabetes, coronary artery disease) and/or disease status (i.e. mean transvalvular gradient, NYHA functional class) may affect the association between LV-GLS and post-TAVI mortality. In addition, data regarding the degree of myocardial fibrosis and cardiac amyloidosis were not present, even though these entities are frequently encountered in patients with AS [38, 40, 41].

Study limitations

Some limitations should be considered. First, in asymptomatic patients with more than moderate AS, the association between % decline LV-GLS and mortality appears to follow a non-linear shape [8]. The exact shape of the dose-response curve between preprocedural LV-GLS and post-TAVI all-cause mortality remains to be clarified [28, 34]. In other words, each additional decrease in % LV-GLS would be

highly informative upon demonstration of a linear pattern in symptomatic patients that undergo TAVI. Insufficient data were available to elaborate on the shape of the dose-response curve. Another limitation is that the majority of the included studies were retrospective cohort studies, whilst all studies reported univariate hazard ratios. This highlights that residual confounding may be present, which could affect the pooled estimates in either direction [42].

Conclusions

This meta-analysis showed that preprocedural LV-GLS as measured by 2D-speckle tracking is a significant predictor for TAVI-related mortality in patients with severe, symptomatic AS, irrespective of how LV-GLS was modelled. Even though LVEF is commonly used in patients with AS for risk prediction and adopted as a gatekeeper for aortic valve replacement, LVEF seems to remain preserved until late in the AS disease process due to compensatory mechanisms in cardiac structure. Indeed, LVEF seems largely preserved in severe, symptomatic AS patients from the studies we included in our meta-analysis. In contrast to LVEF, alterations in LV-GLS seem to occur early in the disease process of AS, potentially even preceding changes in LVEF. Addition of evaluation of LV-GLS to current guideline-based assessment of LVEF may provide clinicians with better risk stratification for patients undergoing TAVI.

CLINICAL PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this meta-analysis of twelve studies including 2,049 patients with severe, symptomatic aortic stenosis, we demonstrate that preprocedural LV-GLS significantly predicts post-TAVI outcomes. This suggests an important role for the evaluation of LV-GLS for risk stratification of patients with severe symptomatic AS for clinical outcomes post-TAVI.

TRANSLATIONAL OUTLOOK: Alterations in LV-GLS seem to occur early in the disease process of AS, potentially even preceding changes in LVEF. Addition of evaluation of LV-GLS to current

guideline-based assessment of LVEF may therefore provide clinicians with improved risk stratification, allowing for timely recognition, intervention and intensified follow-up.

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Not applicable.

DATA AVAILABILITY STATEMENT

The analyzed dataset underlying this manuscript will be shared on reasonable request to the corresponding author.

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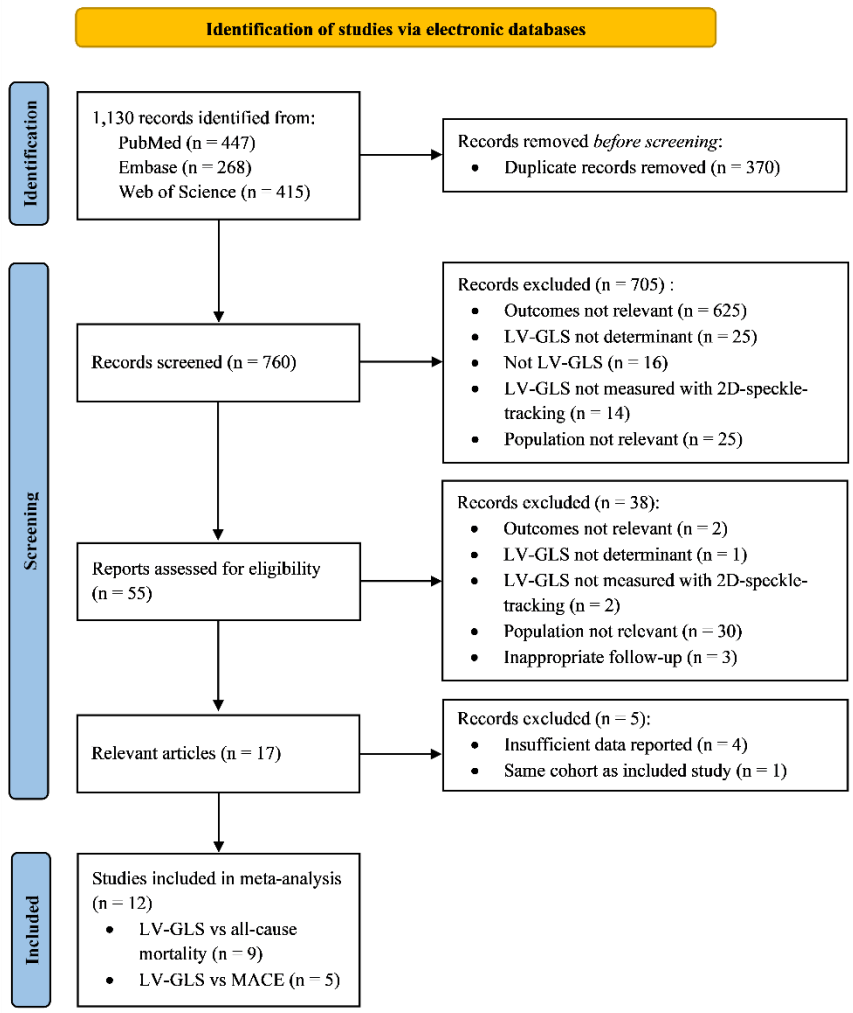
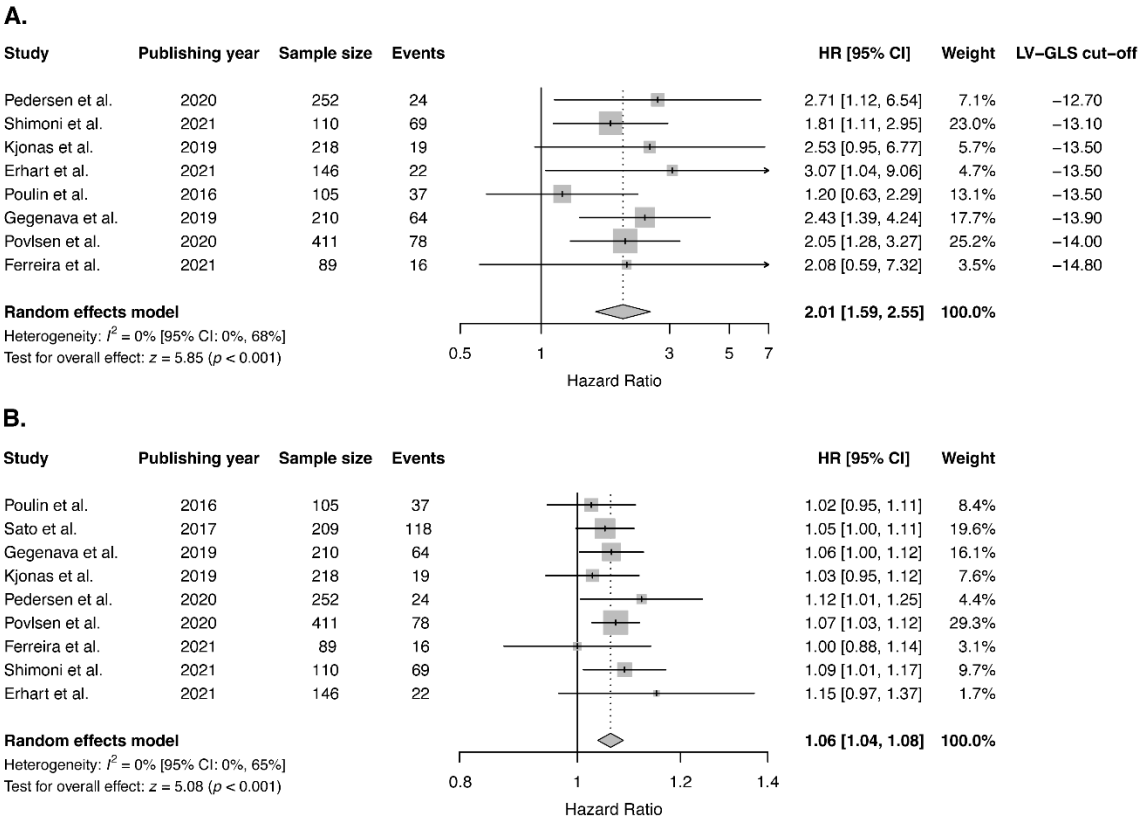
FIGURE TITLES AND LEGENDS

Figure 1. Flowchart of study screening process.



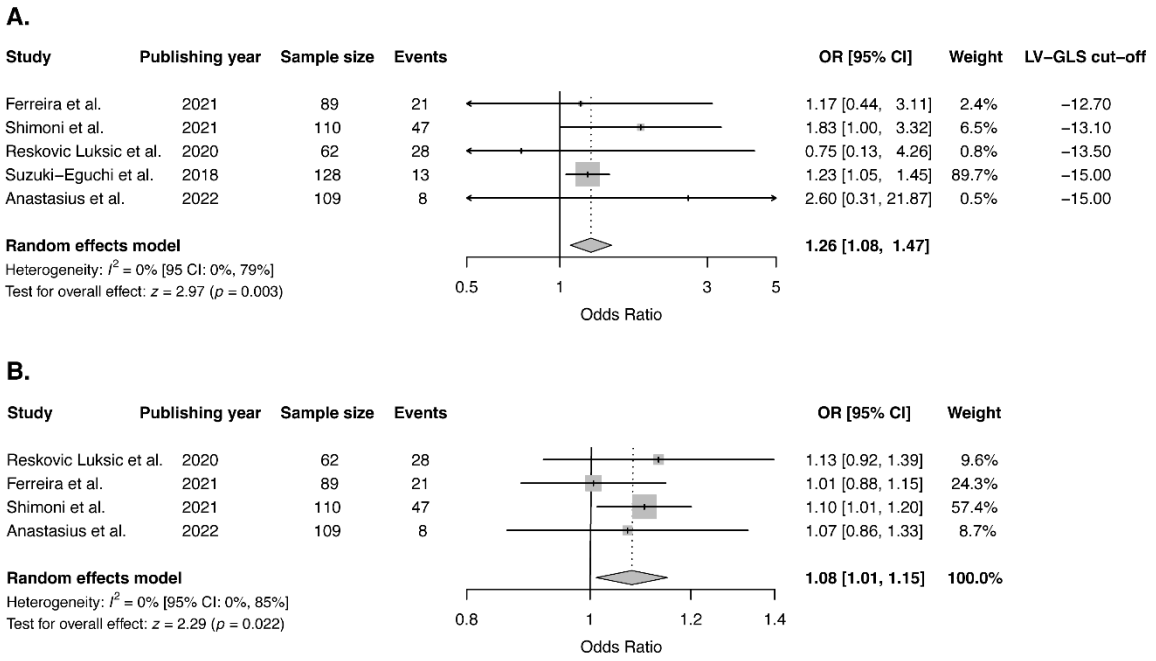
The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) flow diagram highlights the number of records identified, included and excluded, and the reasons for exclusions, through the different phases of the systematic review and meta-analysis. *LV-GLS* left ventricular global longitudinal strain, *MACE* major adverse cardiovascular events, *TAVI* transcatheter aortic valve implantation.

Figure 2. Forest plot for the association between LV-GLS and all-cause mortality.



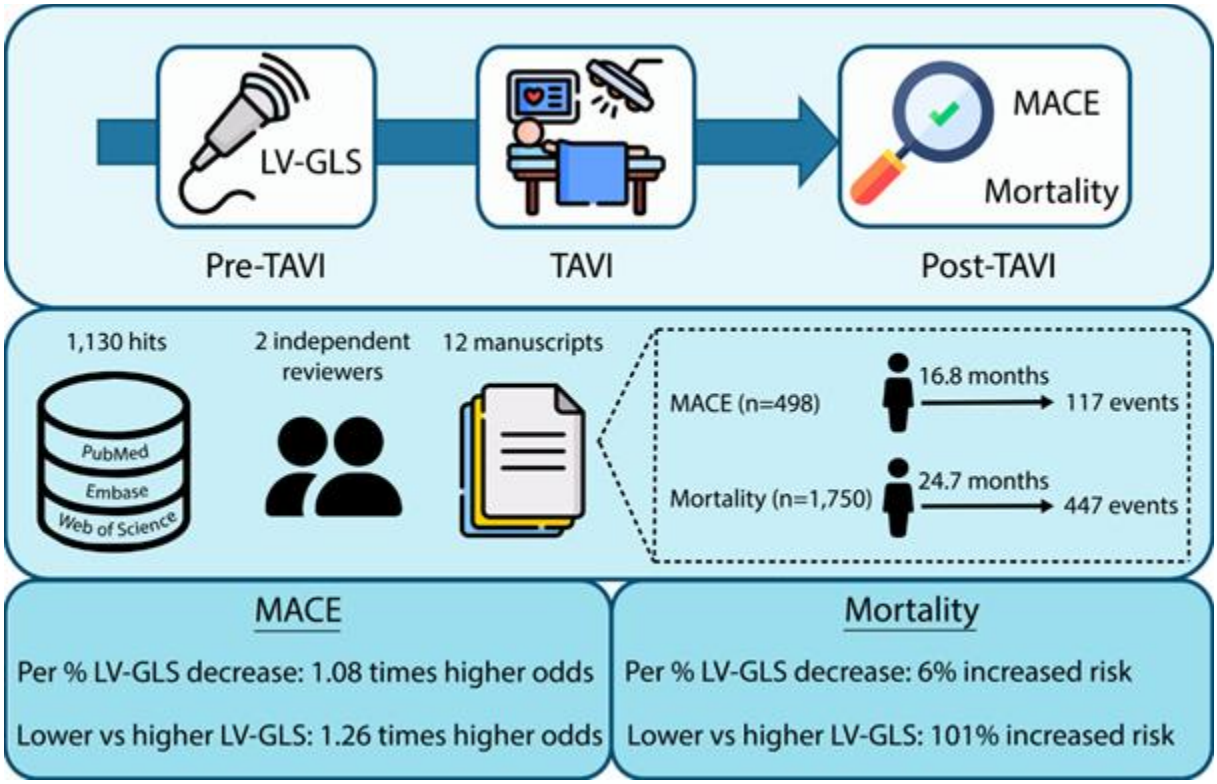
LV-GLS on a dichotomous (**A**) and continuous (**B**) scale versus all-cause mortality. Sato et al. did not present data regarding the association between LV-GLS (on a dichotomous scale) and all-cause mortality, so this study was removed from section A. Weights are obtained via the random effects analysis.

Figure 3. Forest plot for the association between LV-GLS and MACE.



LV-GLS on a dichotomous (**A**) and continuous (**B**) scale versus MACE. Suzuki-Eguchi et al. did not present data regarding the association between LV-GLS (on a continuous scale) and MACE, so this study was removed from section B. Weights are obtained via the random effects analysis.

Central Illustration. Preprocedural LV-GLS predicts post-TAVI mortality and MACE.



LV-GLS left ventricular global longitudinal strain, *MACE* major adverse cardiovascular events, *TAVI* transcatheter aortic valve implantation.

599 **TABLES**

600 **Table 1. Population characteristics of the included studies**

Study	Design	Outcome	N	Sex (% women)	Age (years)	AVA (cm2)	Mean Transaortic gradient (mmHg)	NYHA class ≥ III (%)	HTN (%)	DM (%)	CAD (%)	LVEF (%)	LV-GLS (%)	Follow-up (months)
Erhart et al.	Retrospective cohort	All-cause mortality	146	49	81.8 [7.2]	0.79 [0.25]	37.5 [16.3]	41	80	25	53	56.0 [15.5]	-17.0 [4.1]	24.3 [5.7]
Gegenava et al.	Retrospective cohort	All-cause mortality	210	50	80 ± 7	0.7 ± 0.2	41 ± 18	57	76	26	60	46 ± 10	-14 ± 4	31 [31]
Kjønas et al.	Prospective cohort	All-cause mortality	218	45	81.5 ± 6.8	NR	NR	NR	68	28	67	49 ± 12	-11 ± 4	33 ± 8
Pedersen et al.	Retrospective cohort	All-cause mortality	252	51	79.3 ± 6.7	0.67 ± 0.16	43 ± 17	51	74	24	38	51 ± 11.2	-12.7 ± 3.7	19 [10]
Poulin et al.	Retrospective cohort	All-cause mortality	105	42	82.1 ± 7.8	0.68 ± 0.17	49 ± 15	88	82	29	66	53.8 ± 11.8	-12.6 ± 3.9	38.5 [19.5]
Povlsen et al.	Prospective cohort	All-cause mortality	411	46	80.1 ± 7.1	0.7 ± 0.3	39 ± 16	78	73	18	NR	50 ± 13	-14.0 ± 5.2	25.1 [19.4]
Sato et al.	Retrospective cohort	All-cause mortality	209	42	81 ± 10	NR	47 ± 15	94	84	41	84	50 ± 14	-12.0 ± 3.7	44.2 [28.0]
Shimoni et al.	Retrospective cohort	All-cause mortality Hospitalization / cardiac death	110	62	83 [6]	0.73 ± 0.16	45 ± 12	14	90	36	38	55 ± 8.7	-13.4 ± 3.4	57 [35]
Anastasius et al.	Prospective	HF hospitalization and death	109	51	81 ± 7.3	0.7 [0.2]	42.9 ± 13.2	82	96	34	41	62 [13]	-15 [3.4]	14.1 [14.0]
Ferreira et al.	Retrospective cohort	All-cause mortality MACE: all-cause mortality, stroke	89	56	82.1 ± 5.9	0.6 ± 0.2	57.0 ± 16.8	72	87	28	52	56.7 ± 10.0	-13.0 ± 3.8	13.4 [25.8]

		and HF hospitalization												
Reskovic Luksic et al.	Retrospective cohort	MACE: mortality and HF hospitalizations	62	63	84.5 ± 6.6	0.77 ± 0.21	46.8 ± 17.3	61	71	26	44	64.5 ± 8.0	-16.7 ± 2.4	42.0 ± 22.8
Suzuki-Eguchi et al.	Retrospective cohort	MACE: mortality and HF/stroke hospitalization	128	66	83.7 ± 4.2	0.65 ± 0.18	50 ± 18	NR	73	27	34	62 ± 13	-15 ± 4.4	19.4 [NR]

Data are presented as mean ± SD, median [IQR], number or percentage as appropriate. Pedersen et al. and Povlsen et al. showed overlap in patients, so Pedersen et al. represents solely the unique patients of this cohort. Shimoni et al. provided data regarding an extended cohort. Kjønås et al. provided data regarding an extended follow-up.

AVA aortic valve area, *CAD* coronary artery disease, *DM* diabetes, *LV-GLS* global longitudinal strain, *HF* heart failure, *HTN* hypertension, *IQR* interquartile range, *LVEF* left ventricular ejection fraction, *MACE* major cardiovascular events, *NOS* Newcastle-Ottawa Scale, *NR* not reported, *NYHA* New York Heart Association functional classification, *SD* standard deviation.