Prognostic Importance of Left Ventricular Global Longitudinal Strain in Patients with Severe Aortic Stenosis and Preserved Ejection Fraction

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Background: Impaired left ventricular (LV) speckle-tracking-derived global longitudinal strain (GLS) magnitude (GLS worse than 14.7%) has been associated with poor outcome in patients with severe aortic stenosis (AS) and preserved LV ejection fraction (EF).

Objectives: To test the hypothesis that GLS magnitude ≤ 15% obtained with vendor-independent speckle-tracking strain software may be able to identify patients with severe AS who are at higher risk of death, despite preserved LVEF and no or mild symptoms.

Methods: GLS was retrospectively obtained in 332 patients with severe AS (aortic valve area indexed [AVAi] < 0.6 cm^2/m^2), no or mild symptoms, and LVEF ≥ 50%. Absolute values of GLS were collected. Survival analyses were carried out to study the impact of GLS magnitude on all-cause mortality.

Results: During a median follow-up period of 42 (37-46) months, 105 patients died. On multivariate analysis, and after adjustment of known clinical and/or echocardiographic predictors of outcome and aortic valve replacement as a time-dependent covariate, GLS magnitude ≤ 15% was independently associated with mortality during follow-up (all $P < .01$). Adding GLS magnitude ≤ 15% (adjusted hazard ratio = 1.99 [1.17-3.38], $P = .011$) to a multivariate model including clinical and echocardiographic variables of prognostic importance (aortic valve replacement, aortic valve area, LV stroke volume index < 30 mL/m^2, and LVEF<60%) improved the predictive performance with improved global model fit, reclassification, and better discrimination. After propensity score matching ($n = 196$), increased risk of mortality persisted among patients with GLS magnitude ≤ 15% compared with those with GLS > 15% (hazard ratio = 2.10; 95% confidence interval, 1.20-3.68; $P = .009$).

Conclusions: In this series of patients with severe AS, no or mild symptoms, and LVEF ≥ 50%, GLS obtained with vendor-independent speckle-tracking strain software was an effective tool to identify patients with a poor outcome. Detection of myocardial dysfunction by identifying GLS magnitude < 15% in patients with severe AS, no or mild symptoms, and LVEF ≥ 50%, can aid in risk assessment. (J Am Soc Echocardiogr 2020;33:1454-64.)

Keywords: Aortic stenosis, Surgery, Speckle-tracking, Echocardiography, Outcome

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Thellier and Altes contributed equally to this work.

Conflicts of Interest: None.

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Abbreviations

AS = Aortic stenosis

ASE = American Society of Echocardiography

AVA = Aortic valve area

AVAi = Aortic valve area indexed

AVR = Aortic valve replacement

BSA = Body surface area

CI = Confidence interval

CAD = Coronary artery disease

EACVI = European Association of Cardiovascular Imaging

EF = Ejection fraction

GLS = Global longitudinal strain

HR = Hazard ratio

ICC = Intraclass correlation coefficient

IDI = Integrated discrimination improvement

LAV = Left atrial volume

LAVi = Left atrial volume indexed

LV = Left ventricular, ventricle

LVEF = Left ventricular ejection fraction

LVH = Left ventricular hypertrophy

NRI = Net reclassification improvement

RAP = Right atrial pressure

RV = Right ventricular

SMD = Standardized mean difference

sPAP = Systolic pulmonary artery pressure

SV = Stroke volume

SVi = Stroke volume indexed

Calcific aortic stenosis (AS) is the most prevalent valvular heart disease in developed countries.[1] The sole effective treatment for patients with severe symptomatic AS remains surgical or transcatheter aortic valve replacement (AVR). American and European guidelines alike indicate that left ventricle (LV) dysfunction, defined by left ventricular (LV) ejection fraction (LVEF) < 50%, is a class I indication for AVR, even in asymptomatic patients.[2,3] As early as the 1970s, Dumesnil *et al.*[4] reported work on echocardiography showing that M-mode tracings can reveal depressed LV longitudinal systolic shortening despite normal LVEF in AS patients compared with controls.[4] One way to assess LV longitudinal shortening is to calculate LV global longitudinal strain (GLS) using speckle-tracking echocardiography.[5] In a recent participant data meta-analysis, Magne *et al.*[6] elegantly demonstrated by pooling 10 studies that impaired GLS (defined as GLS < 14.7%) was associated with a 2.5-fold increased risk of mortality. Recently, a 15% cutoff value has been suggested, which is easier to remember and thus might allow a wider acceptance.[7,8] However, significant intervendor variability with significant differences in GLS values obtained with equipment from different vendors, and also between earlier or later (upgraded) versions of the same software, may limit the generalization of GLS use in clinical practice.[9-12]

Hence, the present study was designed to test the hypothesis that an absolute value of GLS ≤ 15% obtained with vendor-independent speckle-tracking strain software may be able to identify patients with severe AS who are at higher risk of death, despite preserved LVEF and no or only mild symptoms.

METHODS

Study Population

Consecutive patients ages ≥ 18 years with a diagnosis of severe AS (defined as aortic valve area [AVA] ≤ 1 cm^2 and/or AVA normalized to body surface area [BSA] ≤ 0.6 cm/m^2), preserved LVEF ≥ 50%, and no or minimal AS-related symptoms who attended the echocardiography laboratory of the Groupement des Hôpitaux de l'Institut Catholique de Lille, Lille Catholic University, from 2011 to 2018 were eligible for inclusion in the present study. Exclusion criteria were (1) moderate or greater aortic and/or mitral and/or tricuspid regurgitation; (2) past or current symptoms of New York Heart Association class III-IV heart failure; (3) angina or syncope; (4) prosthetic valve or supra- or subvalvular AS, congenital heart disease, or dynamic LV outflow tract obstruction; (5) mitral stenosis; and (6) patient refusal to participate in the study. The study population comprised 332 patients who were followed for the duration of the study (2011-18). The present study is a retrospective analysis of a prospective registry.

Clinical and demographic data were collected at baseline. The Charlson comorbidity index, a summation of the patient's individual comorbidities, was calculated.[13] The Charlson comorbidity index includes history of myocardial infarction, congestive heart failure, peripheral artery disease, cerebrovascular disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate or severe renal disease, solid tumor, leukemia, and lymphoma. Coronary artery disease (CAD) was defined by documented history of acute coronary syndromes, confirmation by coronary angiography (reduction of normal diameter ≥ 50% in the left main coronary artery and ≥70% in the right coronary artery, left anterior descending coronary artery, left anterior descending coronary artery, or circumflex coronary artery), or history of coronary revascularization. Symptoms were ascertained by each patient's personal cardiologist. Follow-up information was obtained retrospectively.

The study was approved by an independent ethics committee and was conducted in accordance with institutional policies, national legal requirements, and the revised Declaration of Helsinki. Given the retrospective nature of the analysis, informed consent was waived. All patients agreed to participate in the study when contacted for follow-up.

Echocardiography

All patients underwent a comprehensive Doppler echocardiography study, using commercially available ultrasound systems (General Electric Vivid E9, Vivid E95, Vivid 7, General Electric HealthCare, Horten, Norway; Philips IE 33 and Epiq 7, Philips, Andover, MA) by experienced echocardiographers. Aortic flow was recorded using continuous-wave Doppler, by imaging and nonimaging transducers, systematically in several acoustic windows (apical five-chamber, right parasternal, suprasternal, epigastric).[14] The highest aortic velocity was used to calculate aortic time-velocity integral and mean pressure gradient. As recommended by current guidelines, wall (high-pass) filters were set at a high level and gain was decreased to optimize identification of the velocity curve from the spectrogram envelope. The LV stroke volume (LV SV) was calculated by multiplying the LV outflow tract area by the LV outflow tract time-velocity integral obtained by pulsed Doppler in the apical

HIGHLIGHTS

- GLS is often impaired despite preservation of LVEF in severe AS and no or mild symptoms.
- GLS < 15% is associated with an increased risk of mortality during follow-up in this population.
- GLS provides added prognostic information over echocardiographic predictors in AS.
- Detection of myocardial dysfunction by GLS < 15% can aid in risk assessment.

five-chamber view. The LV outflow tract diameter was measured in zoomed parasternal long-axis views in early systole at the level of aortic cusp insertion (inner-to-inner edge). The AVA was calculated using the continuity equation, and AVA and LV SV were indexed to BSA. Left ventricular hypertrophy (LVH) was defined as LV mass index > 95 g/m^2 in women and 115 g/m^2 in men according to the American Society of Echocardiography (ASE) formula.[15] Elevated filling pressure was defined by E/e′ > 14.[7] Left atrial volume (LAV) was calculated using the Simpson biplane method and indexed to BSA (LAVi). The transtricuspid pressure gradient was recorded from any view with continuous-wave Doppler imaging and was used to determine the peak systolic pulmonary artery pressure (sPAP) using the modified Bernoulli equation (sPAP = 4Vmax^2 + RAP), where V is the peak tricuspid regurgitation velocity and RAP is the right atrial pressure. The RAP was assumed to be 3, 8, or 15 mm Hg based on the diameter of the inferior vena cava and importance of inspiratory collapse during a brief sniff, as recommended by current European Association of Cardiovascular Imaging (EACVI)/ASE guidelines.[15] Moderate or greater right ventricular (RV) dysfunction was determined by a multiparameter approach including semiquantitative assessment by visual examination and quantitative assessment using tricuspid annular systolic velocity (S′ <9.5 cm/sec) and/or tricuspid annular plane systolic excursion <17 mm.[7] Echocardiographic measurements were performed according to current EACVI/ASE guidelines.[15] When patients were in sinus rhythm, three cardiac cycles were averaged for all measures. For patients in atrial fibrillation, five cardiac cycles were averaged. Echocardiograms were stored in Digital Imaging and Communications in Medicine format without compression (full frame format) in EchoPAC/Image Vault (General Electric HealthCare) and Intellispace Cardiovascular (Philips) to allow subsequent offline analysis.

The GLS analysis was performed using vendor-independent two-dimensional speckle-tracking imaging software (Image Arena, 2D Cardiac Performance Analysis v. 2.30, TomTec Imaging Systems, Unterschleissheim, Germany) after transfer of echocardiograms in Digital Imaging and Communications in Medicine format from GE Echopac and Philips Intellispace CardioVascular to TomTec Image Arena. All GLS measurements were retrospectively performed for research purposes by an investigator (N.T.) blinded to the patient's clinical status and outcome. The GLS was measured following semiautomatic tracing of the endocardial border in the three apical views (apical four-, three-, and two-chamber views). The videoloops were acquired with a minimal frame rate of 50 frames per second. After frame-by-frame analysis during one cardiac cycle of the LV endocardial speckle-tracking, the software provides 16-segment regional segmentation curves (six basal segments, six middle segments, four apical segments). Global longitudinal strain was defined as the average value of maximum deformation of each of the 16 segments during the systole before aortic valve closure (Figure 1). Tracking adequacy was checked visually, followed by manual adjustment of the endocardial border if considered suboptimal. Intra- and interobserver variability of each GLS measurement was tested on a randomly selected set of 20 echocardiograms from the study population.

Clinical Decision and Follow-Up

After the initial medical management, treatment was conservative or surgical, as deemed appropriate by the patient's personal physician.

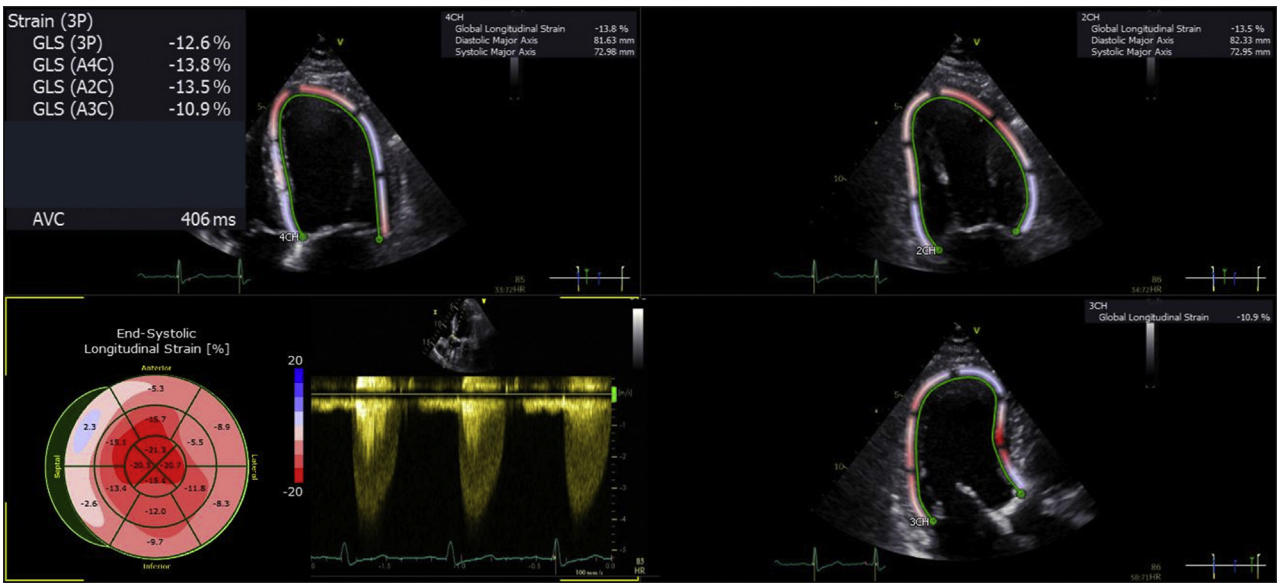

Figure 1 GLS obtained in a patient with severe asymptomatic AS. Longitudinal strain values were obtained in the three apical views and represented on a parametric display (bull's-eye). GLS is depressed in this patient (12.6%) despite preserved LVEF at 55%. *AVC*, aortic valve closure.

The majority of patients were followed clinically and echocardiographically in our institution's outpatient clinic. Others were followed in public hospitals or private practices by referring cardiologists working in coordination with our tertiary center. Follow-up information was obtained retrospectively. Events were ascertained by direct patient interview and physical examination and/or via repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. The outcome variable of the study was all-cause mortality. Clinical decisions regarding medical management and referral for surgery were made by the heart team with the approval of the patient's cardiologist in accordance with current practice guidelines.

Statistical Analysis

Continuous variables are expressed as median (25th-75th percentile) or mean ± SD, and categorical variables are expressed as absolute numbers and percentages. To simplify interpretation of the results as well as the discussion, GLS values, although negative, are reported as absolute values. The study population was divided according to GLS > or ≤15%. The Pearson χ^2 statistic or Fisher's exact test was used to examine associations between the two groups and baseline categorical variables. Individual differences were compared using Mann-Whitney *U* tests (with Bonferroni correction for multiple comparisons). The intraclass correlation coefficient (ICC) was used to express variability. The ICC estimates and their 95% confidence interval (CI) were calculated based on a single rater/measurement, absolute-agreement, two-way fixed-effects model.

Event rates ± standard errors of the overall population and of two groups were estimated according to the Kaplan-Meier method and compared using two-sided log-rank tests. Univariate and multivariate analyses of time to events were performed using Cox proportional hazards models. We did not use model-building techniques. For each model, we retained covariates that we considered would potentially have a prognostic impact on an epidemiologic basis to increase the external validity of the analyses. The effect of AVR on mortality was considered in all models and analyzed as a time-dependent covariate.[16] We thus tested the following models: model 1 including clinical factors (age, sex, body mass index, Charlson comorbidity index [not including age], CAD, hypertension, atrial fibrillation); model 2 including classical echocardiographic factors of prognostic importance previously included in an extra-aortic cardiac disorder staging[7] (AVA, LVH, LAVi > 34 mL/m^2, sPAP ≥ 60 mm Hg, grade II diastolic dysfunction, RV dysfunction ≥ moderate, LVEF < 60%, LV SV indexed [SVi] < 30 mL/m^2); and model 3 including clinical and selected echocardiographic factors previously known to be strongly associated with outcome in AS (that is AVA, LV SVi < 30 mL/m^2, and LVEF<60%) to avoid overfitting of this final model.

The proportional hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. Overall performance of the multivariate models was assessed using the likelihood ratio test and the Bayesian information criterion. The increased discriminative value of GLS was investigated by estimating the Harrell *C* statistic for models with and without GLS. To enable comparison between *C* statistics, a total of 999 bootstrap samples of the patients in our study population were generated using the library (boot) in R, and the difference in Harrell *C* statistics between the models with and without GLS was computed for each of the 999 samples. We hence obtained the 95% bootstrap CIs of the 999 estimates, for which the lower and upper bounds were the 2.5th and 97.5th percentiles of the resampling distribution, respectively. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were determined to further describe the added utility of GLS when added to the multivariate model. The IDI measures the new model's ability to improve integrated sensitivity without compromising integrated specificity. The NRI measures the appropriateness of patient reclassification on the basis of the probability of death at selected time points. Both NRI and IDI were computed at 48 months using the R package survIDINRI. We conducted subgroup analyses (for GLS > and ≤15%) to determine the homogeneity of the GLS-mortality association. First, we estimated the effect of GLS on mortality in each subgroup using a Cox univariate model and then formally tested for first-order interactions, entering interaction terms separately for each subgroup. Estimates of sensitivity, specificity, and positive and negative predictive values for the GLS 15% and 14.7% cutoff values were computed from time-dependent receiver operating curves using the timeROC package in R. Sensitivity analysis was also conducted to compare the occurrence of mortality during follow-up between patients with GLS ≤ 15% and >15% matched by age, sex, atrial fibrillation, Charlson comorbidity index, AVA, LV SVi, LVEF, and occurrence of mild-to-moderate RV dysfunction using a 5-to-1 digit-matching propensity score greedy algorithm (MatchIT package in R). The nearest-neighbor matching method was used. Standardized mean differences (SMDs) before and after matching were estimated to assess the quality of the propensity score matching procedure. Absolute SMDs < 0.2 were considered an indicator of adequate balance and thus sufficient bias reduction. The quality of the matching was visually assessed by the distribution of propensity scores (jitter plot of the distance measure, QQplots, and histograms of propensity score density for observations before and after matching). A significance level of 0.05 was assumed for all tests. All *P* values are the results of two-tailed tests. Data were analyzed with SPSS version 25.0 (IBM, Armonk, NY), R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), and MedCalc version 12.5.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Baseline Characteristics

The study population consisted of 332 patients with a median age of 79 (interquartile range, 71, 85 years), with 196 being women (59%, Table 1). The clinical and echocardiographic characteristics of the study population are depicted in Table 1. Mean GLS was 13.8% ± 4.1% (median 14.2% interquartile range, 16.7%, 11.0%). Global longitudinal strain reproducibility was excellent, with intraobserver ICC = 0.95 (0.86-0.98) and interobserver ICC = 0.93 (0.83-0.97).

GLS at Baseline and Risk for Death during Follow-Up

During a median follow-up period of 42 months (interquartile range 37-46 months), there were 123 AVRs and 105 deaths. In patients who underwent AVR, aortic bioprostheses were used in 71% of cases (*n* = 87), percutaneous valves in 24% (*n* = 30), and mechanical valves in 5% (*n* = 6). Among patients who underwent surgical AVR, 25 (20%) had at least one associated coronary artery bypass graft at the time of surgery.

Table 1 Demographic, clinical, and echocardiographic parameters according to GLS > and ≤ 15%

Variable	All (*N* = 332)	GLS > 15 (*n* = 140)	GLS ≤ 15 (*n* = 192)	Overall *P* value
Demographic and clinical characteristics				
Age, years	79 [71;85]	76 [66;82]	82 [74;88]	<.001
Women	196 (59)	79 (56)	117 (61)	<.001
BSA, m^2	1.84 [1.70;1.98]	1.84 [1.70;1.98]	1.84 [1.68;1.97]	.647
BMI, kg/m^2	27.1 [23.9;31.3]	26.7 [23.9;31.0]	27.1 [23.9;31.3]	.606
SBP, mm Hg	140 [123;150]	140 [130;150]	135 [123;146]	.068
Hypertension	235 (71)	98 (70.0)	137 (71.4)	.884
Diabetes mellitus	118 (36)	45 (32.1)	73 (38.0)	.323
CAD	77 (23)	35 (25.0)	42 (21.9)	.593
Atrial fibrillation	97 (29)	21 (15)	76 (40)	<.001
Charlson comorbidity index	2 [1;3]	1 [0;2]	2 [1;3]	<.001
New York Heart Association functional class I	194 (58)	90 (64)	104 (54)	.065
Echocardiographic parameters				
Aortic valve				
AVA, cm^2	0.85 [0.70;1.00]	0.89 [0.76;1.03]	0.82 [0.67;0.96]	.002
AVAi, cm^2/m^2	0.47 [0.39;0.55]	0.49 [0.42;0.56]	0.45 [0.37;0.54]	.003
Peak aortic jet velocity, m/sec	3.80 [3.14;4.29]	3.88 [3.21;4.29]	3.73 [3.10;4.28]	.617
Mean pressure gradient, mm Hg	35 [24;45]	35 [24;46]	35 [23;45]	.827
Other parameters				
LV EDD, mm	45 [41;49]	46 [42;50]	44 [40;49]	.041
LV SVi, mL/m^2	39 [32;44]	41 [36;47]	36 [30;42]	<.001
LVEF, %	61 [57;66]	63 [59;66]	60 [55;65]	.001
GLS, %	14.1 [11.0;16.7]	17.20 [16.00;18.75]	11.60 [9.10;13.53]	by design
LV Mi, g/m^2	108 [90;129]	102 [88.8;120]	112 [90.0;135]	.057
LAVi, mL/m^2	42 [31;53]	38 [30;49]	44 [33;57]	.016
E/e' ratio > 14	107 (32)	35 (25)	72 (40)	.007
sPAP, mm Hg (*n* = 204)	35 [30;43]	33 [28;40]	36 [31;45]	.002
RV dysfunction ≥ moderate	46 (14)	6 (4)	40 (21)	<.001

BMI, Body mass index; *EDD*, end-diastolic diameter; *Mi*, mass indexed to body surface area; *SBP*, systolic blood pressure.
Continuous variables are presented as median [25th;75th percentile]. Categorical variables are presented as absolute *n* (%).

Relationship between GLS ≤ 15% and Mortality

At time-dependent receiver operating curve analysis, GLS ≤ 15% exhibited 77% ± 5% sensitivity and 64% ± 5% specificity for 48-month mortality prediction, leading to a positive predictive value of 56% ± 5% and a negative predictive value of 83% ± 4%. A 14.7% cutoff value as previously proposed by Magne *et al.*[6] yielded very similar results, with a slightly lower sensitivity at 75% ± 5% and a slightly higher specificity at 66% ± 5%, leading to a positive predictive value of 57% ± 5% and a negative predictive value of 82% ± 4%. One hundred ninety-two patients (58%) had a GLS ≤ 15%, and 140 (42%) patients had a GLS > 15%. The clinical and echocardiographic characteristics of the study population according to GLS ≤ and >15% are depicted in Table 1.

As shown in Table 1, patients with GLS ≤ 15% were older, more frequently were women, more frequently had atrial fibrillation, and had more comorbidities as indicated by a higher Charlson's comorbidity index. Aortic stenosis was more severe in these patients as indicated by a lower AVA but similar transaortic gradients and velocities. Left ventricular EF was slightly lower in these patients as was LV SVi. Right ventricular dysfunction was more frequently found in patients with GLS ≤ 15%. Lastly, sPAP was higher in patients with GLS ≤ 15% compared with patients with GLS > 15%.

The 48-month estimate of overall mortality was significantly higher in patients with GLS ≤ 15% compared with those with GLS > 15% (52% ± 5% vs 19% ± 4%, log-rank $P < .0001$; Figure 2). In contrast, GLS ≤ 15% was not associated with an increased occurrence of AVR during follow-up ($P = .48$). After adjustment for clinical covariates of prognostic importance including age, sex, Charlson comorbidity index, CAD, hypertension, atrial fibrillation, body mass index, and AVR as a time-dependent covariate, GLS ≤ 15% remained significantly associated with an increased risk of mortality: adjusted hazard ratio (HR) = 2.07 (95% CI, 1.23-3.49, $P = .006$; Figure 3A). After adjustment for classical echocardiographic parameters of prognostic importance (AVA, LVH, LAVi ≥ 34 mL/m^2, sPAP > 60 mm Hg, E/e' > 14, RV dysfunction, LVEF < 60%, and LV SVi < 30 mL/m^2) and AVR as a time-dependent covariate, GLS ≤ 15% remained significantly associated with an increased risk of mortality: adjusted HR = 2.63 (1.53–4.50; $P < .001$; Figure 3B). After adjustment for

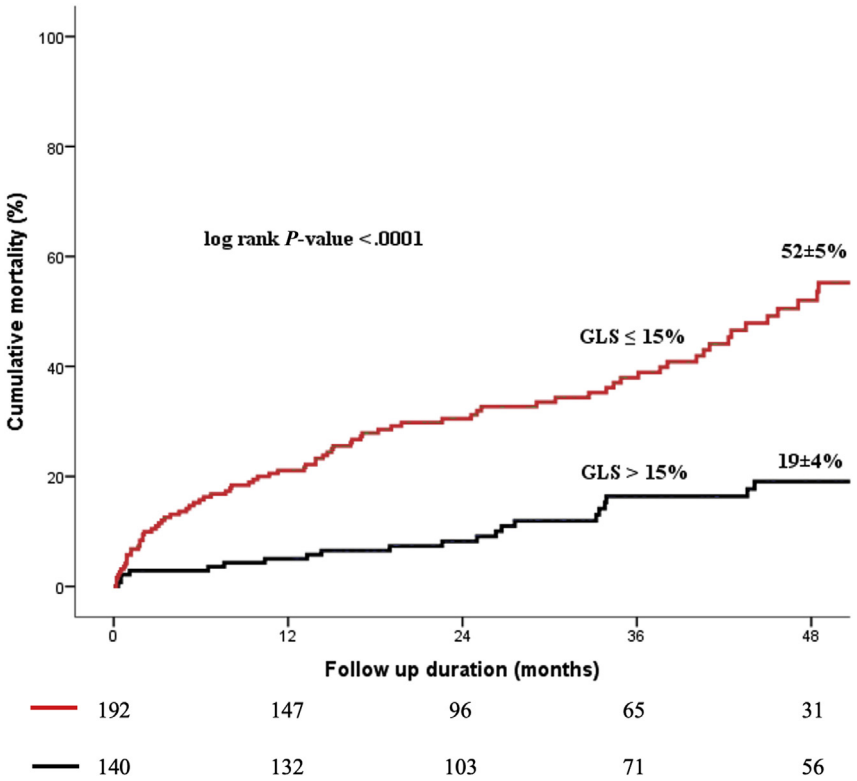

Figure 2 Kaplan-Meier 48-month estimates of overall mortality according to GLS ≤ 15% or GLS > 15%.

clinical parameters, AVA, LV SVi < 30 mL/m^2, LVEF < 60%, and AVR as a time-dependent covariate, GLS ≤ 15% remained significantly associated with an increased risk of mortality: adjusted HR = 1.99 (1.17–3.38; P = .011; Figure 3C). Adding GLS ≤ 15% to this multivariate model resulted in a significant improvement in the model fit, as indicated by a lower Bayesian information criterion (Table 2), and better model discrimination, as indicated by higher C statistics. At 48 months, adding GLS ≤ 15% to the multivariate model resulted in improvements in reclassification indices (Table 2). Using GLS and LVEF as continuous variables in this multivariate model did not alter the relationship between GLS and mortality (adjusted HR per percentage of absolute decrease in GLS 1.06 [1.0, 1.11]; P = .046). The association of GLS ≤ 15% and mortality risk was consistent in all subgroups of patients with severe AS and no or mild symptoms (Figure 4).

Impact of GLS on Mortality in the Propensity-Matched Cohort

The baseline characteristics of covariates used for propensity matching before and after matching are shown in Table 3. Between-group balance was obtained for all matched covariates. Ninety-eight patients with GLS ≤ 15% were matched to 98 patients with GLS > 15%. The 48-month estimate of overall mortality remained significantly higher in patients with GLS ≤ 15% compared with those with GLS > 15% (45% ± 7% vs 23% ± 5%, log-rank P = .008; Figure 5), with a two-fold increased risk of mortality compared with those with GLS > 15%: HR = 2.10 (1.20-3.68, P = .009).

DISCUSSION

The present study clearly indicates that (1) GLS is frequently impaired despite preservation of LVEF in patients with severe AS and no or mild symptoms, (2) vendor-independent software-measured GLS is associated with a considerable increased risk of mortality during follow-up in this population, (3) GLS provides additional prognostic information over clinical and classical echocardiographic predictors of poor outcome in AS.

LV Dysfunction in AS

Left ventricular systolic dysfunction with LVEF < 50% occurs late in the course of AS, as LVEF may be maintained despite reduced myocardial contractility and potentially irreversible alterations in myocardial function owing to myocardial fibrosis by the use of preload reserve leading to diastolic dysfunction[17] or changes in LV geometry including LV concentric hypertrophy and remodeling.[18,19] Cramariuc *et al.*[20] previously demonstrated that a higher degree of LVH and concentric remodeling is associated with decreased LV longitudinal deformation assessed by two-dimensional speckle-tracking in patients with AS.[20,21] In addition, impairment of LV longitudinal shortening or strain correlates with the presence of symptoms in patients with AS, is associated with LV myocardial fibrosis by cardiac magnetic resonance imaging, and predicts elicited symptoms during exercise testing in the subset of asymptomatic patients who are able to exercise.[22-26] Hence, the assessment of LV GLS may be helpful to identify patients with severe AS who present significant

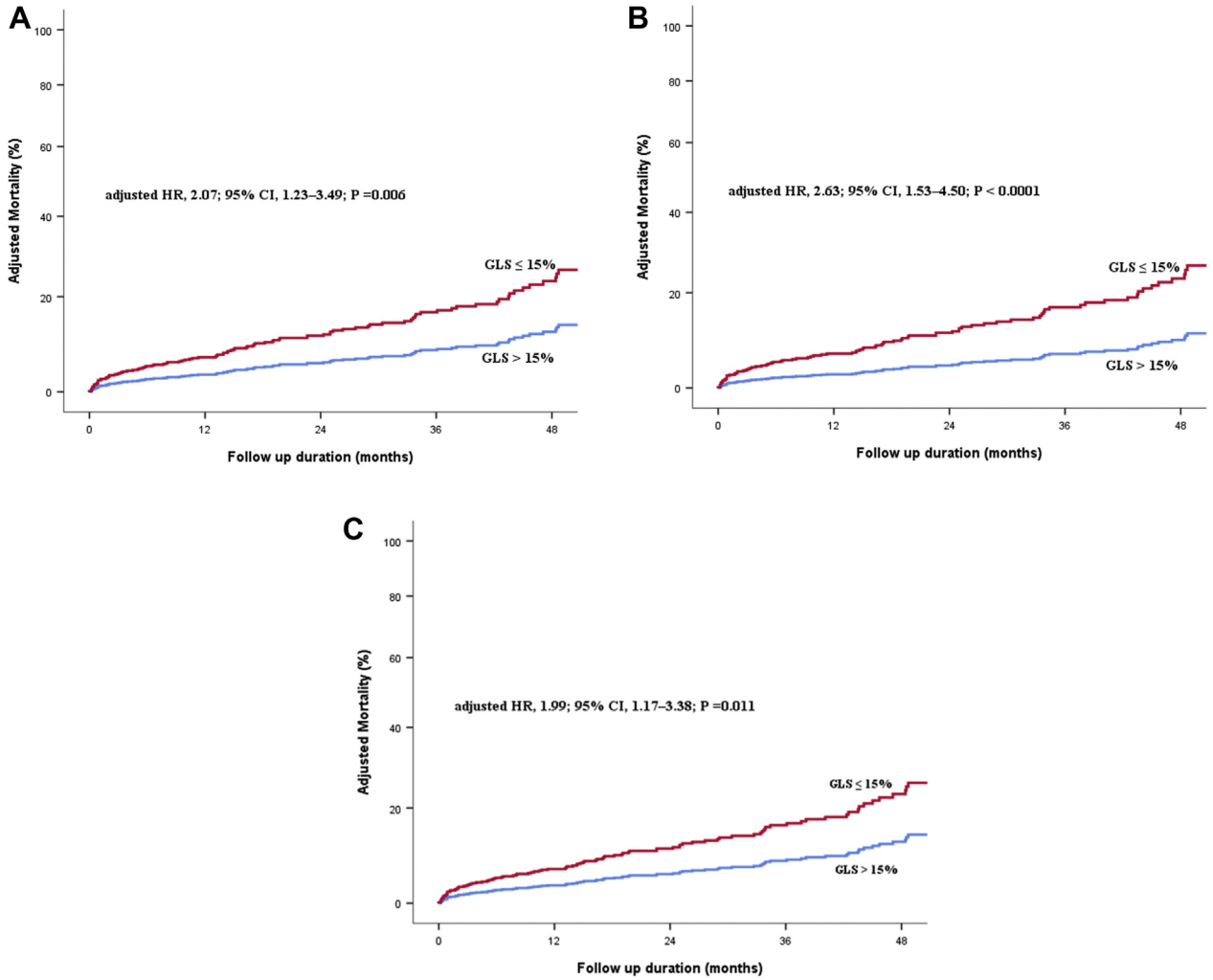

Figure 3 **(A)** Cumulative hazard of overall mortality according to GLS ≤ 15% or GLS > 15%, adjusted for age, sex, Charlson comorbidity index, CAD, hypertension, atrial fibrillation, body mass index, and AVR as a time-dependent covariate. **(B)** Cumulative hazard of overall mortality according to GLS ≤ 15% or GLS > 15%, adjusted for echocardiographic parameters including AVA, LVH, LAV index ≥ 34 mL/m^2, sPAP > 60 mm Hg, E/e' > 14, RV dysfunction, LVEF < 60%, and LV SVi < 30 mL/m^2 with AVR as a time-dependent covariate. **(C)** Cumulative hazard of overall mortality according to GLS ≤ 15% or GLS > 15%, adjusted for age, sex, Charlson comorbidity index, CAD, hypertension, atrial fibrillation, body mass index, AVA, LVEF < 60%, and LV SVi < 30 mL/m^2 with AVR as a time-dependent covariate.

Table 2 Cox multivariate models: predictive value, discrimination, and reclassification of the multivariate models with and without GLS on overall mortality

Overall mortality	Multivariate model without GLS	Multivariate model with GLS	*P* value (model with vs model without GLS)
Adjusted HR (95% CI)		1.99 (1.17-3.38)	.011
BIC	1045.436	1044.682	
Harrell *C* statistic	0.824	0.832	
C statistic difference (95% CI)		(0.0002-0.0252)	
IDI	Reference	0.021 (0.002-0.061)	.020
NRI	Reference	0.333 (0.032-0.476)	.033

BIC, Bayesian information criterion.

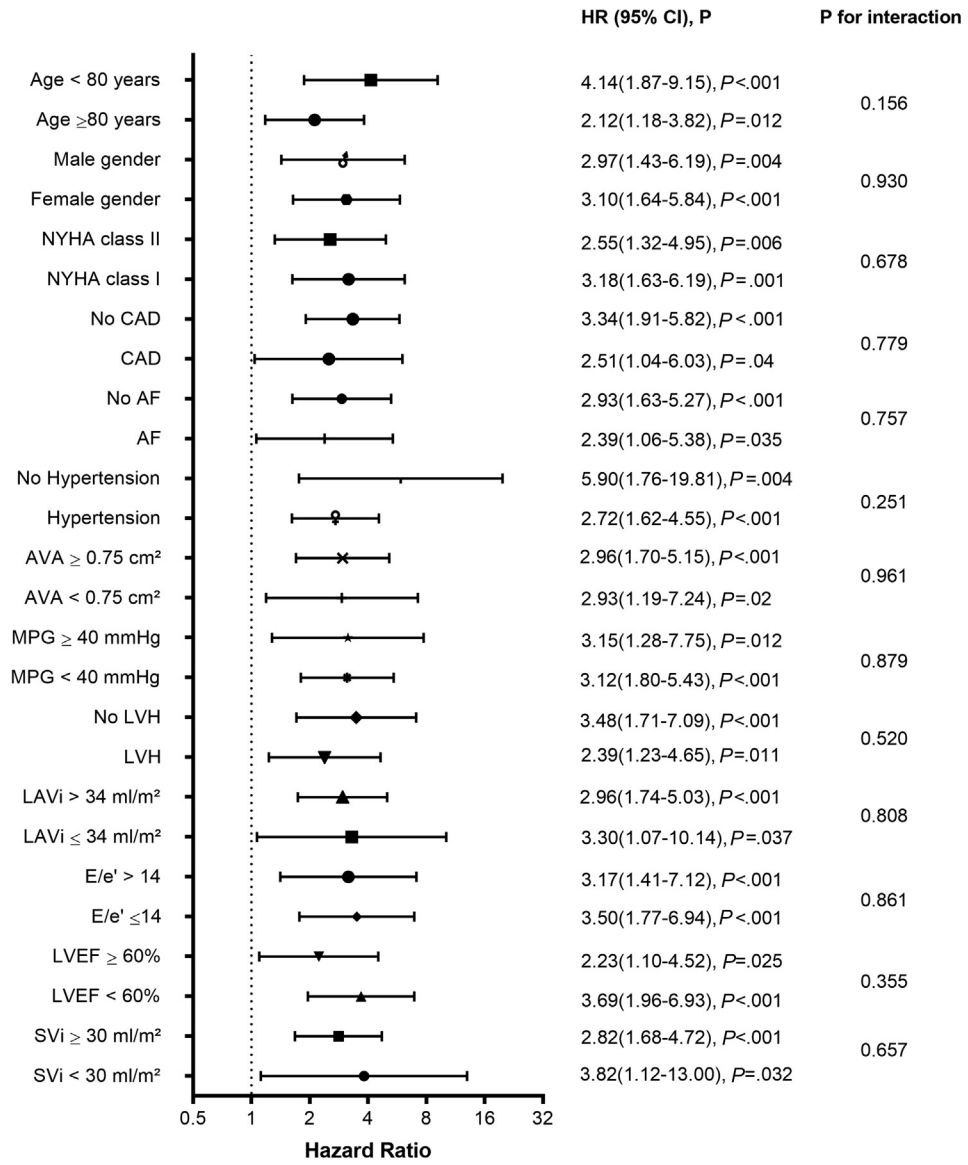

Figure 4 HR and 95% CI for risk of overall mortality associated with GLS ≤ 15% or GLS > 15% in subgroups of patients with severe AS, preserved LVEF, and no or minimal symptoms. *MPG*, Mean pressure gradient; *NYHA*, New York Heart Association.

myocardial damage and who are at higher risk, despite preserved LVEF and no or only mild symptoms.

Prognostic Impact of LV GLS in Asymptomatic AS

In a recent participant data meta-analysis, Magne *et al.*[6] observed a 2.5-fold increased risk of mortality in patients with impaired GLS (defined as GLS < 14.7%) compared with those with preserved GLS. It is, however, noteworthy that mortality was the primary endpoint in only three of these studies. In addition, the vast majority of the studies included in this meta-analysis involved a single-vendor speckle-tracking strain software (General Electric). Hence, the use of GLS from other vendors would potentially result in different cutoff values, which may lead to confusion. Moreover, in most of these studies, the majority of patients had symptomatic AS.[27-29] In addition, the context of retrospective data pooling with limited statistical adjustment (age, sex, AVAi, LVEF) necessarily involved incomplete control of confounding factors. Nevertheless, the present study confirms the findings of this meta-analysis by showing that a decrease in GLS below 15% (a cutoff value close to 14.7%) is associated with a twofold increased risk of mortality in patients without severe symptoms related to AS. Global longitudinal strain provides additional prognostic information over clinical but also echocardiographic parameters. We demonstrated here that GLS ≤ 15% provides independent prognostic information over these classical echocardiographic indices. The prognostic impact of GLS ≤ 15% was consistent in all subgroups of patients including those with LVEF ≥ 60% and those in a low-flow state despite having preserved LVEF. Therefore, the present study demonstrates the importance of assessing LV longitudinal function as part of the multiparametric prognostic workup of patients with severe asymptomatic or mildly symptomatic AS. Importantly, the negative predictive value of GLS > 15% was high in the present report, thereby suggesting that these patients may be conservatively followed until

Table 3 Baseline characteristics according to GLS > and ≤ 15% before and after propensity score matching

Covariates	Entire cohort			Matched cohort		
	GLS > 15 (*n* = 140)	GLS ≤ 15 (*n* = 192)	SMD	GLS > 15 (*n* = 98)	GLS ≤ 15 (*n* = 98)	SMD
Age, years	73 ± 13	80 ± 13	0.650	75 ± 10	77 ± 11	0.137
Women	79 (56)	117 (61)	0.092	55 (56)	53 (54)	0.041
Atrial fibrillation	21 (15)	76 (40)	0.574	17 (17)	19 (19)	0.053
Charlson comorbidity index	1.5 ± 1.7	2.2 ± 2	0.390	1.8 ± 1.8	1.8 ± 1.6	0.006
AVA, cm^2	0.88 ± 0.19	0.81 ± 0.21	0.356	0.88 ± 0.20	0.87 ± 0.19	0.052
LV SVi, mL/m^2	42 ± 9	36 ± 8	0.661	40 ± 8	39 ± 8	0.082
LVEF, %	63 ± 6	61 ± 7	0.322	62 ± 6	61 ± 7	0.128
RV dysfunction ≥ moderate	6 (4)	40 (21)	0.516	5 (5)	5 (5)	<0.001

SMDs are reported for the entire cohort and for the matched cohort. SMDs < 0.2 after matching were considered as indicators of adequate balance and thus sufficient bias reduction. Continuous variables are presented as mean ± SD. Categorical variables are presented as absolute *n* (%).

symptoms or LV dysfunction develop in the absence of other factors of poor outcome.

Speckle-Tracking Longitudinal Strain Assessment in AS

Clinicians have hesitated to accept GLS in clinical practice because of the differences observed in longitudinal strain values obtained with speckle-tracking software products released by various manufacturers.[30,31] Changes in vendor and reader can be expected to influence GLS values by up to 5%.[32] Although the ASE and the EACVI have set up an expert group, combining researchers and industry members, to achieve a consensus document detailing speckle-tracking measurements,[33,34] previous reports highlighted that software upgrades made after this consensus were responsible for significant changes in GLS values that exceeded the interobserver variability of the measurement.[10,12] As a consequence, most studies in the setting of asymptomatic AS have been performed with one single

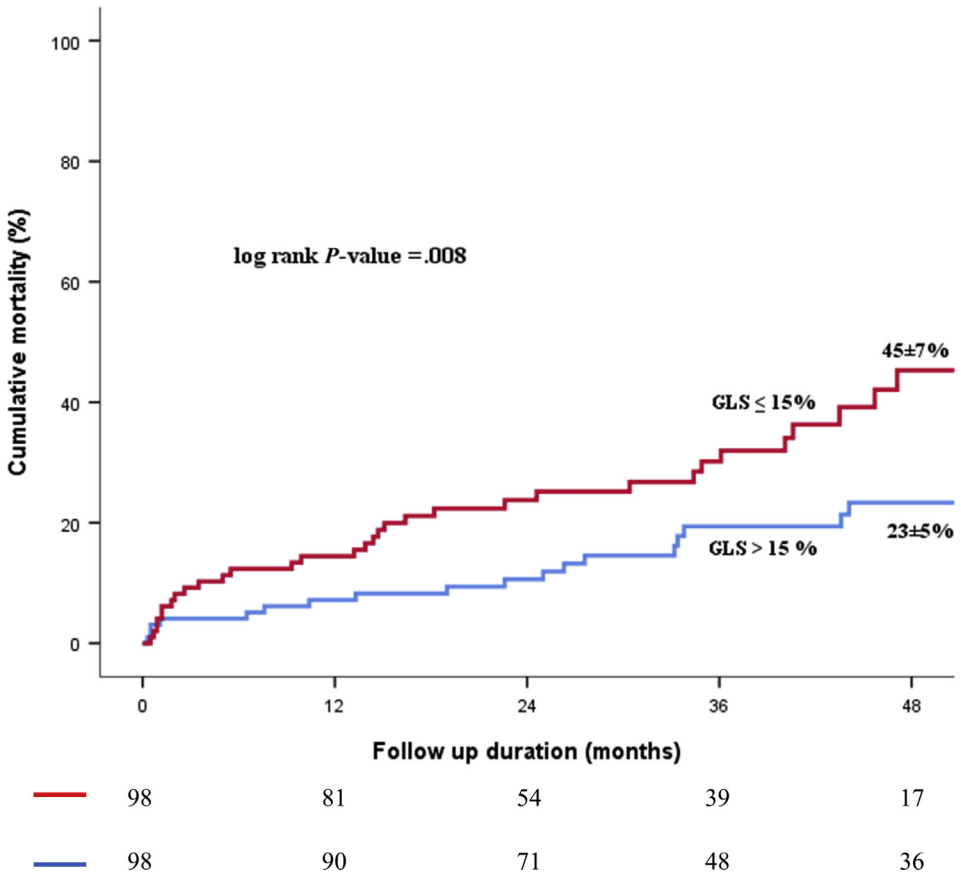

Figure 5 Kaplan-Meier 48-month estimates of overall mortality according to the different GLS subgroups in the propensity-matched cohort.

vendor (General Electric). Nagata *et al.*[35] used the same vendor-independent software as in the present study in a similar population. The present study confirms Nagata *et al.*'s finding by showing that this vendor-independent speckle-tracking strain software enabled us to calculate GLS values with a unique cutoff level regardless of the manufacturer of the echocardiography equipment. This type of methodology could be expected to favor more widespread acceptance of GLS measurements in routine daily practice. However, it should be acknowledged that identifying specific cutoff points remains an issue if upgrades to this software influence GLS values as previously reported with vendor-specific software products.[12] In addition, Nagata *et al.*[12] previously reported in normal subjects that intervendor agreement of GLS values using vendor-independent speckle-tracking software was only modest, with nonnegligible limits of agreement. Nevertheless, the intervendor agreement of GLS using vendor-independent speckle-tracking software cannot be assessed in the present study, as patients did not undergo scanning with both GE and Philips systems.

Limitations

This study was conducted in a single high-volume center with a dedicated heart valve unit. Further multicenter studies are needed to confirm these findings. The use of all-cause mortality as an endpoint may represent a limitation compared with the use of cause-specific mortality. However, all-cause mortality remains an unbiased endpoint. Whereas echocardiograms were prospectively collected, speckle-tracking strain analysis and follow-up data were obtained retrospectively; hence, our study presents inherent limitations of this type of analysis. Cardiac magnetic resonance imaging was not available in the vast majority of the study population. Hence, we cannot provide data on LV myocardial fibrosis. This study used an observational design, which implies that the baseline variables in the two groups determined on the basis of the GLS value (≤15% vs >15%) may have been imbalanced. However, the final results remained unchanged after Cox multivariate analyses and propensity score matching performed to control the impact of these differences on mortality. Very recently, Levy-Neuman *et al.*[36] observed that reduced exercise basal LS was associated with future cardiovascular events in patients with moderate to severe asymptomatic AS. However, LS was not obtained during exercise in our study population. Lastly, a limitation of the study is that one cannot assess whether the intervention (AVR) at various levels of reduced GLS can reverse the rates of adverse outcomes.

CONCLUSION

In this series of patients with severe AS, no or mild symptoms, and LVEF ≥ 50%, GLS obtained with vendor-independent speckle-tracking strain software was an effective tool to identify patients with a poor outcome. Detection of myocardial dysfunction by identifying GLS ≤15% in patients with severe AS, no or mild symptoms, and LVEF ≥ 50% can aid in risk assessment. Further larger prospective multicentric studies are needed to confirm the present findings.

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