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Background: Moderate aortic stenosis (AS) is associated with an increased risk for adverse events. Although reduced left ventricular (LV) global longitudinal strain (GLS) is associated with worse outcomes in patients with severe AS, its prognostic value in patients with moderate AS is unknown. The aim of this study was to investigate the prognostic implications of LV GLS in patients with moderate AS.

Methods: LV GLS was evaluated using speckle-tracking echocardiography in patients with moderate AS (aortic valve area 1.0-1.5 cm^2) and reported as absolute (i.e., positive) values. Patients were divided into three groups: LV ejection fraction (LVEF) < 50% (group 1), LVEF ≥ 50% but LV GLS < 16% (group 2), and LVEF ≥ 50% and LV GLS ≥ 16% (group 3). The LV GLS value of 16% was based on spline curve analysis. The primary end point was all-cause mortality.

Results: A total of 760 patients (mean age, 71 ± 12 years; 61% men) were analyzed. During a median follow-up period of 50 months (interquartile range, 26-94 months), 257 patients (34%) died. Patients with LVEF < 50% and LVEF ≥ 50% but LV GLS < 16% showed significantly higher mortality rates at 1-, 3-, and 5-year follow-up (82%, 71%, and 58%; and 92%, 77%, and 58%, respectively) compared with those with LVEF ≥ 50% and LV GLS ≥ 16% (96%, 91%, and 85%, respectively; $P < .001$). Long-term outcomes were not different between patients with LVEF < 50% and those with LVEF ≥ 50% but LV GLS < 16% ($P = .592$). LV GLS discriminated higher risk patients even among those with LVEF ≥ 60% ($P < .001$) or those who were asymptomatic ($P < .001$). On multivariable analysis, LVEF < 50% (hazard ratio, 2.384; 95% CI, 1.614-3.522; $P < .001$) and LVEF ≥ 50% but LV GLS < 16% (hazard ratio, 2.467; 95% CI, 1.802-3.378; $P < .001$) were independently associated with all-cause mortality.

Conclusions: In patients with moderate AS, reduced LV GLS is associated with an increased risk for all-cause mortality, even if LVEF is still preserved. (J Am Soc Echocardiogr 2022;35:791-800.)

Keywords: Moderate aortic stenosis, Left ventricular global longitudinal strain, Mortality, Aortic valve replacement

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Abbreviations
AS = Aortic stenosis
AVA = Aortic valve area
AVR = Aortic valve replacement
GLS = Global longitudinal strain
HR = Hazard ratio
LV = Left ventricular
LVEF = Left ventricular ejection fraction
NYHA = New York Heart Association

Recent data demonstrated poor long-term survival in patients with moderate aortic stenosis (AS), challenging traditional definitions of AS severity and timing of intervention in these patients.[1] Especially in patients with reduced left ventricular ejection fraction (LVEF; <50%), the presence of moderate AS seems to be associated with a marked incremental risk of mortality.[2,3] Left ventricular (LV) systolic dysfunction often coexists with moderate AS,[2,3] and the underlying AS itself may contribute to LV systolic dysfunction through afterload mismatch.[4] In addition, previous studies have demonstrated that a decline in LVEF already begins before AS becomes severe.[5] The TAVR UNLOAD trial (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure; NCT02661451) is therefore currently exploring the hypothesis that transcatheter aortic valve replacement (AVR) could improve outcomes in patients with moderate AS and reduced LVEF.[6] However, even patients with moderate AS and preserved LVEF (≥50%) have an increased risk for mortality,[7] and several studies using cardiac magnetic resonance imaging have demonstrated that LV structural and functional abnormalities are frequent despite preserved LVEF in patients with moderate and severe AS.[8-10] The LV remodeling response to AS pressure overload may indeed lead to the development of myocardial fibrosis (even when LVEF is still preserved), causing a progressive deterioration in LV diastolic function and eventually LV systolic performance, which are both associated with poor outcomes.[11-13] These observations underscore the need to identify echocardiographic parameters beyond LVEF to accurately detect the consequences of AS-related pressure overload on the LV myocardium. LV global longitudinal strain (GLS) permits quantification of active myocardial deformation in the longitudinal direction, which is a more robust marker of LV performance than LVEF.[14] Moreover, LV GLS relates to the extent of myocardial fibrosis in patients with severe AS[15] and is a strong prognostic marker in patients with severe AS.[16,17] Accordingly, LV GLS may be a more accurate marker than LVEF to detect subtle structural and functional changes in patients with moderate AS. However, the prognostic value of LV GLS has not been extensively explored in this patient population. Therefore, the aim of the present study was to evaluate the prognostic value of LV GLS in patients with moderate AS.

METHODS

Patient Population

Patients ≥18 years of age who presented between October 2001 and December 2019 with a first echocardiographic diagnosis of moderate AS at the Leiden University Medical Center were retrospectively identified. Moderate AS was defined as an aortic valve area (AVA) between 1.0 and 1.5 cm^2 with a peak aortic jet velocity < 4 m/sec and mean valve gradient < 40 mm Hg.[18] The definition of moderate AS on the basis of AVA was used to avoid the inclusion of patients with severe low-flow, low-gradient AS and is in line with previously published articles on moderate AS.[7,19] Patients with previous aortic valve surgery, congenital heart disease, infective endocarditis, heart transplantation, supra- or subvalvular AS, dynamic LV outflow tract obstruction, more than moderate aortic or mitral valve regurgitation, a paced rhythm at the time of echocardiography, and inadequate speckle-tracking analysis due to poor acoustic windows or insufficient data were excluded. All patients underwent complete clinical and echocardiographic evaluation at the time of first diagnosis of moderate AS. Patient information was prospectively collected from the departmental cardiology information system and retrospectively analyzed. Clinical data included demographic characteristics, cardiovascular risk factors, New York Heart Association (NYHA) functional class, and comorbidities. Patients were stratified into three groups according to LVEF and LV GLS (reported as absolute values): group 1, LVEF < 50%; group 2, LVEF ≥ 50% and LV GLS < 16%; and group 3, LVEF ≥ 50% and LV GLS ≥ 16%. The LV GLS value of 16% was identified as the optimal cutoff value, on the basis of spline curve analysis (i.e., where the predicted hazard ratio [HR] for all-cause mortality was ≥1; Figure 1). The institutional review board of the Leiden University Medical Center waived the need to obtain written informed consent because this study involved the retrospective analysis of clinically acquired data.

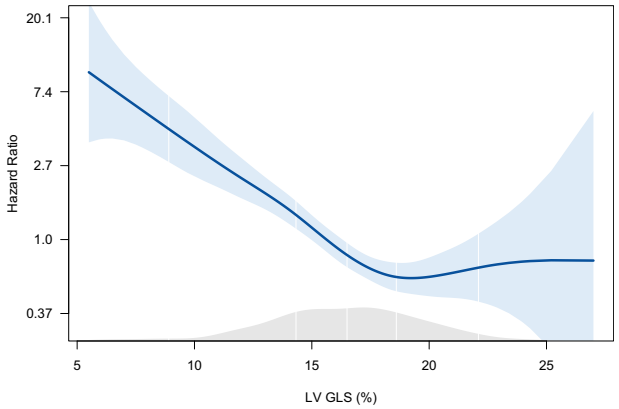


Figure 1 Association between LV GLS and the risk for all-cause mortality among patients with moderate AS and LVEF ≥ 50%.

Transthoracic Echocardiography

All echocardiographic examinations were performed by experienced echocardiographers using commercially available ultrasound systems (Vivid 7, E9 or E95; GE Vingmed Ultrasound, Horten, Norway). Data were digitally stored for offline analysis using commercially available software (EchoPAC versions 113 and 203; GE Medical Systems, Little Chalfont, United Kingdom), and images were retrospectively analyzed according to current guidelines.[20] In the parasternal long-axis view, LV dimensions were assessed and LV mass was calculated using the Devereux formula and indexed to body surface area.[20] LV end-diastolic and end-systolic volumes were measured in the apical two-chamber and four-chamber views and indexed to body surface area.[20] LVEF was calculated according to the Simpson biplane method.[20] Left atrial volumes were measured using the biplane method of disks and indexed to body surface area.[20] From the apical three- or five-chamber views, continuous-wave Doppler recordings were obtained to estimate peak aortic jet velocity.[21] Mean and peak transvalvular pressure gradients were calculated using the

HIGHLIGHTS

- Moderate AS is associated with an increased risk for mortality.
- LV GLS is independently associated with survival in moderate AS.
- LV GLS < 16% identifies patients with preserved LVEF who have worse outcomes.
- LV GLS remains associated with outcomes in asymptomatic patients with preserved LVEF.

Bernoulli equation.[21] AVA was calculated using the LV outflow tract diameter and velocity-time integrals of the aortic valve and LV outflow tract and indexed to body surface area.[21] The severity of tricuspid regurgitation was graded using a multiparametric approach, as recommended in current guidelines.[22,23] Pulsed-wave Doppler recordings of transmitral flow were used to obtain peak early (E) and late (A) diastolic velocities.[24] Using Doppler tissue imaging of the mitral annulus on the apical four-chamber view, e′ was measured at both the lateral and septal sides and averaged to calculate the E/e′ ratio.[24] Right ventricular systolic pressure was calculated from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation, adding right atrial pressure determined by the inspiratory collapse and

Table 1 Baseline clinical characteristics

Variable	Overall population (*N* = 760)	Group 1: LVEF < 50% (*n* = 145)	Group 2: LVEF ≥ 50%, LV GLS < 16% (*n* = 279)	Group 3: LVEF ≥ 50%, LV GLS ≥ 16% (*n* = 336)	*P*
Age, y	71.3 ± 11.8	72.9 ± 10.8	72.3 ± 10.6	69.9 ± 13.0*,†	.010
Sex, male	462 (60.8)	104 (71.7)	181 (64.9)	177 (52.7)*,†	<.001
Caucasian	715 (94.1)	138 (95.2)	259 (92.8)	318 (94.6)	.527
BMI, kg/m^2	26.9 ± 4.6	27.6 ± 4.6	27.3 ± 4.9	26.3 ± 4.3*,†	.004
BSA, m^2	1.91 ± 0.21	1.97 ± 0.22	1.93 ± 0.21	1.88 ± 0.19*,†	<.001
Systolic BP, mm Hg	140 ± 23	134 ± 21	142 ± 24*	140 ± 22*	.001
Diastolic BP, mm Hg	76 ± 13	75 ± 12	77 ± 13	76 ± 13	.113
Arterial hypertension	539 (71.4)	106 (73.6)	202 (72.7)	231 (69.4)	.540
Dyslipidemia	456 (60.6)	89 (61.8)	170 (61.6)	197 (59.2)	.782
DM	180 (23.8)	43 (29.9)	81 (29.1)	56 (16.8)*,†	<.001
Current smoker	92 (13.5)	16 (11.9)	36 (14.5)	40 (13.5)	.790
Obesity	161 (21.4)	40 (28.0)	67 (24.4)	54 (16.2)*,†	.005
CAD	314 (41.5)	83 (57.2)	115 (41.4)*	116 (34.7)*	<.001
Previous MI	154 (20.5)	54 (37.2)	51 (18.5)*	49 (14.7)*	<.001
Atrial fibrillation	194 (25.6)	49 (33.8)	81 (29.1)	64 (19.2)*,†	.001
Previous stroke	128 (16.9)	27 (18.6)	52 (18.7)	49 (14.7)	.344
COPD	93 (12.3)	20 (13.8)	39 (14.1)	34 (10.2)	.286
NYHA classes II–IV	309 (41.5)	79 (55.6)	123 (45.4)	107 (32.2)*,†	<.001
NYHA classes III and IV	122 (16.4)	36 (25.4)	45 (16.6)	41 (12.3)*	.002
Angina	95 (12.8)	18 (12.7)	39 (14.4)	38 (11.5)	.556
Syncope	15 (2.0)	4 (2.8)	4 (1.5)	7 (2.1)	.648
β-blocker	361 (48.1)	84 (58.3)	136 (49.3)	141 (42.6)*	.006
ACE inhibitor or ARB	421 (56.1)	85 (59.0)	148 (53.6)	188 (56.8)	.534
MRA	52 (7.0)	20 (14.1)	18 (6.6)	14 (4.2)	.001
Diuretic	289 (38.5)	77 (53.5)	103 (37.3)*	109 (32.9)*	<.001
CCB	217 (28.9)	24 (16.7)	86 (31.2)*	107 (32.3)*	.001
Statin	458 (61.0)	89 (61.8)	165 (59.8)	204 (61.6)	.875
Aspirin	316 (42.1)	60 (41.7)	117 (42.4)	139 (42.0)	.989
Oral anticoagulation	190 (25.3)	54 (37.5)	75 (27.2)	61 (18.4)*,†	<.001
eGFR, mL/min/1.73 m^2	72.5 ± 27.2	67.8 ± 27.1	71.2 ± 29.1	75.8 ± 25.2*	.012
Hemoglobin, g/dL	13.1 ± 1.9	13.1 ± 1.9	13.0 ± 1.9	13.2 ± 1.7	.474

Data are expressed as mean ± SD or number (percentage). Obesity was defined as BMI ≥ 30 kg/m^2.
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *BP*, blood pressure; *BSA*, body surface area; *CAD*, coronary artery disease; *CCB*, calcium channel blocker; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *eGFR*, estimated glomerular filtration rate; *MI*, myocardial infarction; *MRA*, mineralocorticoid receptor antagonist.
*P < .05 versus group 1.
†P < .05 versus group 2.

Table 2 Baseline echocardiographic characteristics

Variable	Overall population (*N* = 760)	Group 1: LVEF < 50% (*n* = 145)	Group 2: LVEF ≥ 50%, LV GLS < 16% (*n* = 279)	Group 3: LVEF ≥ 50%, LV GLS ≥ 16% (*n* = 336)	*P*
LV EDD, mm	48.7 ± 7.1	53.7 ± 8.2	48.5 ± 6.4*	46.6 ± 6.0*,†	<.001
LV ESV, mL	40 (29-55)	75 (54-102)	40 (30-51)*	34 (26-44)*,†	<.001
LV ESVi, mL/m^2	24 ± 14	42 ± 21	22 ± 8*	19 ± 7*,†	<.001
LV EDV, mL	99 (78-127)	130 (95-167)	99 (79-124)*	92 (75-114)*	<.001
LV EDVi, mL/m^2	55 ± 19	69 ± 28	53 ± 15*	51 ± 15*	<.001
LVEF, %	57.5 ± 10.9	39.7 ± 8.0	59.8 ± 6.1*	63.3 ± 5.9*,†	<.001
LV GLS, %	15.3 ± 3.9	10.8 ± 3.4	13.6 ± 2.1*	18.7 ± 1.9*,†	<.001
LVMI, g/m^2	112.9 ± 31.5	128.7 ± 38.6	116.0 ± 29.7*	103.5 ± 25.9*,†	<.001
LV remodeling patterns					<.001
Normal geometry	111 (16.0)	22 (16.9)	30 (11.5)	59 (19.6)†	<.05
Concentric remodeling	206 (29.8)	18 (13.8)	76 (29.1)*	112 (37.2)*	<.05
Concentric hypertrophy	226 (32.7)	34 (26.2)	101 (38.7)*	91 (30.2)†	<.05
Eccentric hypertrophy	149 (21.5)	56 (43.1)	54 (20.7)*	39 (13.0)*,†	<.05
LAVi, mL/m^2	34 (28-45)	41 (33-51)	34 (27-44)*	33 (27-41)*	<.001
E/e′ ratio	13.5 (9.7-17.9)	15.1 (11.5-20.7)	14.2 (10.5-18.9)*	12.0 (8.9-15.9)*,†	<.001
Bicuspid valve	82 (10.8)	15 (10.3)	20 (7.2)	47 (14.0)†	.025
AVA, cm	1.24 ± 0.14	1.24 ± 0.13	1.24 ± 0.14	1.25 ± 0.14	.573
AVAi, cm/m^2	0.66 ± 0.10	0.64 ± 0.09	0.65 ± 0.10	0.67 ± 0.09*,†	<.001
Peak aortic jet velocity, m/sec	3.1 ± 0.6	2.8 ± 0.5	3.1 ± 0.6*	3.2 ± 0.6*	.018
Aortic mean pressure gradient, mm Hg	23.4 ± 8.9	20.0 ± 8.2	24.1 ± 8.9*	24.2 ± 9.0*	<.001
Stroke volume index, mL/m^2	45 ± 11	38 ± 10	44 ± 10*	48 ± 11*,†	<.001
TAPSE, mm	22 ± 5	20 ± 5	22 ± 5*	23 ± 5*,†	<.001
PASP, mm Hg	30 (24-37)	32 (26-41)	30 (25-35)	29 (24-36)*	.006
Moderate or severe TR	107 (14.3)	23 (16.0)	43 (15.8)	41 (12.4)	.409

Data are expressed as mean ± SD, median (interquartile range), or number (percentage).
AVAi, AVA index; *EDD*, end-diastolic diameter; *EDV*, end-diastolic volume; *EDVi*, end-diastolic volume index; *ESV*, end-systolic volume; *ESVi*, end-systolic volume index; *LAVi*, left atrial volume index; *LVMI*, LV mass index; *PASP*, pulmonary artery systolic pressure; *TAPSE*, tricuspid annular plane systolic excursion; *TR*, tricuspid regurgitation.
*P < .05 versus group 1.
†P < .05 versus group 2.

diameter of the inferior vena cava.[20,25] For the evaluation of right ventricular systolic function, anatomical M-mode imaging was applied on the focused apical four-chamber view of the right ventricle to measure tricuspid annular plane systolic excursion.[25]

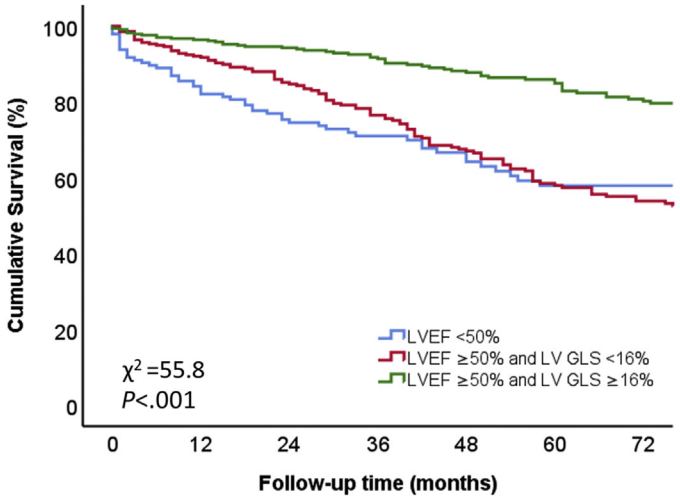
LV strain imaging analysis was performed using the speckle-tracking method from stored transthoracic echocardiographic images using EchoPAC. LV speckle-tracking analysis was performed from the apical views (two, three, and four chamber) at a frame rate > 40 frames/sec.[26] The region of interest was automatically created and manually adjusted to the myocardial thickness were necessary. LV GLS was then calculated by averaging the peak longitudinal strain values of the 17 segments, excluding segments that could not be traced correctly.[26] The values of LV GLS are reported as absolute (i.e., positive) values.

Clinical End Points

All patients were followed for the primary end point of all-cause mortality. Data on mortality were obtained from the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands), which is linked to the governmental death registry database. Indications for aortic valve surgery were based on contemporary guidelines.[18,27] Follow-up data were complete for all patients.

Statistical Analysis

Continuous data are presented as mean ± SD when normally distributed and as median (interquartile range) when not normally distributed. Categorical data are presented as frequencies and



Number at risk							
LVEF <50%	145	118	93	70	52	43	34
LVEF ≥50% and LV GLS <16%	279	254	203	167	131	102	89
LVEF ≥50% and LV GLS ≥16%	336	324	282	236	201	166	145

Figure 2 Kaplan-Meier curve for all-cause mortality. P = .592 for LVEF < 50% versus LVEF ≥ 50% and LV GLS < 16%; P < .001 for LVEF < 50% versus LVEF ≥ 50% and LV GLS ≥ 16%; P < .001 for LVEF ≥ 50% and LV GLS < 16% versus LVEF ≥ 50% and LV GLS ≥ 16%.

percentages. Continuous variables were compared using analysis of variance with Bonferroni post hoc analysis when normally distributed, whereas the Kruskal-Wallis test was used to compare continuous variables that did not adhere to a normal distribution. Categorical variables were compared using the Pearson χ^2 test. Changes in HR for all-cause mortality across the LV GLS values (as a continuous variable) in patients with preserved LVEF (≥50%) were investigated by fitting a spline curve. A value of 16% was identified on the basis of mortality excess (i.e., in which the predicted HR was ≥1). Event-free survival curves were generated using the Kaplan-Meier method, and differences among the three groups (group 1, LVEF < 50%; group 2, LVEF ≥ 50% and LV GLS < 16%; and group 3, LVEF ≥ 50% and LV GLS ≥ 16%) were analyzed using the log-rank test. Uni- and multivariable analyses of time to events were performed using Cox proportional-hazards models with LV GLS (as a continuous variable) as an independent variable. Next, uni- and multivariable analyses were also performed with the three groups (as a categorical variable) entered as an independent variable. The following covariables, considered to have a potential prognostic impact, were included: age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, NYHA functional class II to IV, LVEF, left atrial volume index, and AVA index. The occurrence of surgical or transcatheter AVR was entered as a time-dependent covariate. The proportional-hazards assumption was verified through the evaluation of Schoenfeld residuals. For both uni- and multivariable analyses, HRs with 95% CIs are presented. A two-sided P value < .05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows version 25.0 (IBM, Armonk, New York).

RESULTS

Patient Characteristics

A total of 760 patients met the inclusion criteria and had adequate echocardiographic image quality for strain analysis (Supplemental Figure 1). Baseline clinical characteristics of the overall population are shown in Table 1. The mean age was 71 ± 12 years, and 61% were men. More than half of the patients had arterial hypertension (71%) and dyslipidemia (61%), while diabetes mellitus was observed in almost one fourth of the patients (24%). Histories of coronary artery disease were seen in 314 patients (42%), of whom 154 (21%) had previous myocardial infarctions. Dyspnea, defined as NYHA functional class ≥ II was observed in 309 patients (42%). Echocardiographic parameters are shown in Table 2. Mean LVEF was 58 ± 11%, and 615 patients (81%) had LVEF ≥ 50%. Mean LV GLS was 15.3 ± 3.9%. Mean AVA was 1.24 ± 0.14 cm^2, mean AVA index was 0.66 ± 0.10 cm^2/m^2, mean aortic pressure gradient was 23 ± 9 mm Hg, and mean peak aortic jet velocity was 3.1 ± 0.5 m/sec.

Patients were subsequently divided into three groups: those with LVEF < 50%, those with LVEF ≥ 50% and LV GLS < 16%, and those with LVEF ≥ 50% and LV GLS ≥ 16%. A cutoff value of 16% for LV GLS to divide the patients with LVEF ≥ 50% into two groups was derived from a spline curve analysis (i.e., in which the predicted HR for all-cause mortality was ≥1; Figure 1). There were 145 patients (19%) with LVEF < 50%, 279 patients (37%) with LVEF ≥ 50% and LV GLS < 16%, and 336 patients (44%) with LVEF ≥ 50% and LV GLS ≥ 16%. Patients with LVEF < 50% were older, were more likely to be male, and had more obesity, more diabetes mellitus, more coronary artery disease and previous myocardial infarction,

Table 3 Uni -and multivariable Cox regression analyses to assess the association between LV GLS and all-cause mortality

Variable	All-cause mortality	
	HR (95% CI)	*P*
Univariable analysis		
LV GLS (continuous variable)	0.861 (0.835-0.887)	<.001
LVEF ≥ 50% and LV GLS ≥ 16%	Reference group	
LVEF ≥ 50% and LV GLS < 16%	2.641 (1.972-3.536)	<.001
LVEF < 50%	2.887 (2.043-4.078)	<.001
Multivariable analysis*		
LV GLS (continuous variable)†	0.847 (0.808-0.888)	<.001
LVEF ≥ 50% and LV GLS ≥ 16%	Reference group	
LVEF ≥ 50% and LV GLS < 16%	2.467 (1.802-3.378)	<.001
LVEF < 50%	2.384 (1.614-3.522)	<.001

*Adjusted for age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, NYHA functional classes II to IV, LVEF, left atrial volume index, AVA index, and AVR as a time-dependent covariate.

†LV GLS as a continuous variable and in dichotomous format (according to the three groups) were separately introduced in the multivariable model.

more atrial fibrillation, more impaired renal function, and more severe symptoms (according to NYHA functional class) compared with patients with LVEF ≥ 50% and LV GLS ≥ 16%. In addition, patients with LVEF < 50% also had more coronary artery disease and previous myocardial infarction and more often used diuretics compared with patients with LVEF ≥ 50% and LV GLS < 16%. Patients with coronary artery disease had lower LV GLS values than those without coronary artery disease (14.6% vs 15.8%, $P < .001$).

Regarding echocardiographic characteristics, patients with LVEF < 50% had larger LV volumes, lower LVEF and LV GLS, higher LV mass index, higher left atrial volume index, higher E/e′ ratio, and more pronounced right ventricular dysfunction compared with patients with LVEF ≥ 50% and LV GLS < 16%, as well as patients with LVEF ≥ 50% and LV GLS ≥ 16%.

Prognostic Impact of LV GLS in Moderate AS

During a median follow-up period of 50 months (interquartile range, 26-94 months), 257 patients (34%) died. The cumulative 1-, 3-, and 5-year survival rates were 92%, 82%, and 70%, respectively. Two hundred ninety patients (38%) underwent AVR at follow-up. Of these 290 patients who underwent AVR, 105 (36%) underwent transcatheter AVR and 185 (64%) underwent surgical AVR.

The Kaplan-Meier analysis showed significantly lower survival rates in patients with LVEF < 50% and patients with LVEF ≥ 50% but LV GLS < 16% compared with patients with LVEF ≥ 50% and LV GLS ≥ 16% ($P < .001$; Figure 2). Survival rates were 82% at 1 year, 71% at 3 years, and 58% at 5 years among patients with LVEF < 50%. In patients with LVEF ≥ 50% and LV GLS < 16%, survival rates were 92% at 1 year, 77% at 3 years, and 58% at 5 years. In patients with LVEF ≥ 50% and LV GLS ≥ 16%, survival rates were 96% at 1 year, 91% at 3 years, and 85% at 5 years. Long-term survival outcomes were not different between patients with LVEF < 50% and patients with LVEF ≥ 50% and LV GLS < 16% ($P = .592$). Interestingly, in the subgroup of patients with LVEF ≥ 50%, LV GLS identified high-risk patients even among those with LVEF ≥ 60% ($n = 371$, $P < .001$; Supplemental Figure 2). To further demonstrate the additional prognostic value of LV GLS over LVEF, another analysis was performed in which patients were first divided into three groups according to LVEF (i.e. <50%, 50%-60%, and ≥60%), showing that patients with LVEF 50% to 60% and those with LVEF < 50% had worse prognosis than patients with LVEF ≥ 60% ($P = .036$ and $P < .001$, respectively; Supplemental Figure 3A). Subsequently, patients in the upper two strata of LVEF were dichotomized according to LV GLS (<16% vs ≥ 16%), showing that the prognosis was determined mainly by lower values of LV GLS, regardless of LVEF (Supplemental Figure 3B).

The multivariable Cox model is shown in Table 3. On multivariable analysis, LV GLS as a continuous variable remained independently associated with all-cause mortality (HR, 0.847; 95% CI, 0.808-0.888; $P < .001$). When entering the three groups as a categorical variable, LVEF < 50% (HR, 2.384; 95% CI, 1.614-3.522; $P < .001$) and LVEF ≥ 50% and LV GLS < 16% (HR, 2.467; 95% CI, 1.802-3.378; $P < .001$) were independently associated with higher mortality. The results of the multivariable Cox regression analysis, showing the association between each individual variable and outcome, are provided in Supplemental Table 1.

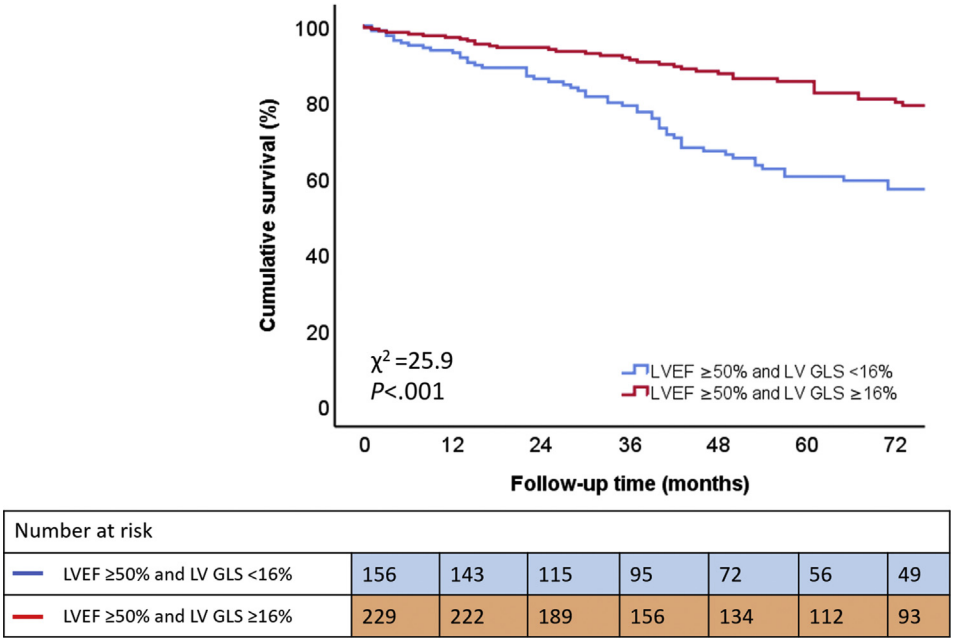
Supplemental Table 2 shows the results of the uni- and multivariable Cox regression analyses in the subgroup of patients with LVEF ≥ 60%.

Prognostic Impact of LV GLS in Asymptomatic Patients with Moderate AS

Of the 760 patients included in the study, 385 (51%) were asymptomatic (defined as being in NYHA functional class I, without angina pectoris or syncope) and had LVEF ≥ 50%. Baseline clinical characteristics of those patients are shown in Supplemental Table 3, while echocardiographic parameters are shown in Supplemental Table 4. The Kaplan-Meier analysis showed significantly lower survival rates in patients with LV GLS < 16% compared with those with LV GLS ≥ 16% ($P < .001$; Figure 3). Survival rates were 93% at 1 year, 79% at 3 years, and 60% at 5 years among patients with LV GLS < 16% ($n = 156$). In patients with LV GLS ≥ 16% ($n = 229$), survival rates were 97% at 1 year, 91% at 3 years, and 85% at 5 years. On multivariable analysis (Table 4), LV GLS as a continuous variable remained independently associated with all-cause mortality (HR, 0.855; 95% CI, 0.798-0.917; $P < .001$; Table 4). When entering LV GLS as a categorical variable, LV GLS < 16% was independently associated with all-cause mortality (HR, 2.658; 95% CI, 1.713-4.124; $P < .001$).

DISCUSSION

The main findings of the present study can be summarized as follows: (1) LV GLS is independently associated with survival in patients with moderate AS; (2) patients with moderate AS and reduced LVEF (<50%), as well as those with preserved LVEF (≥50%) but reduced



Number at risk							
LVEF ≥50% and LV GLS <16%	156	143	115	95	72	56	49
LVEF ≥50% and LV GLS ≥16%	229	222	189	156	134	112	93

Figure 3 Kaplan-Meier curve for all-cause mortality according to LV GLS in asymptomatic patients with LVEF ≥ 50%.

LV GLS (<16%), have significantly worse outcomes compared with patients with preserved LVEF (≥50%) and preserved LV GLS (≥16%); (3) long-term outcomes were not significantly different between patients with LVEF ≥ 50% but LV GLS < 16% and those with LVEF < 50%; and (4) the association between LV GLS and outcomes remains consistent in asymptomatic patients with moderate AS and preserved LVEF.

Pathophysiology of LV GLS in Moderate AS

AS severity often progresses slowly over a period of years, and compensatory mechanisms for the increase in pressure overload begin at an early stage of the disease process to reduce systolic wall stress and maintain LVEF. Chronic pressure overload with the formation of LV hypertrophy, however, can lead to a myocardial oxygen supply-demand mismatch,[28,29] resulting in subendocardial ischemia and fibrosis that first affects LV longitudinal function.[30,31] Previous studies have shown that a reduction in LV longitudinal function occurs simultaneously with AS progression, even in patients with moderate AS, providing evidence of impaired LV longitudinal strain despite normal LVEF in patients with significant AS.[32,33] In addition, Weidemann *et al.*[15] demonstrated that markers of LV systolic longitudinal function are associated with the severity of myocardial fibrosis in patients with significant AS. On the basis of these studies, the development of LV myocardial fibrosis seems to be one of the main pathophysiologic mechanisms to explain a reduction in LV systolic longitudinal function in patients with significant AS. Because cardiac structural changes occur in parallel with a progressive increase in AS severity, and LV fibrosis has been shown to be a strong predictor of outcomes in patients with severe AS,[8,15] assessing LV systolic longitudinal function at an earlier stage (i.e., before a critical amount of irreversible fibrosis has been formed) may provide strong prognostic information.

Prognostic Role of LV GLS in Moderate AS

Recent studies demonstrated that moderate AS is associated with a marked incremental risk for mortality in patients with heart failure and reduced LVEF.[2,3] In addition, Hayward *et al.*[34] showed that the major determinant of outcomes in 169 patients with moderate AS and reduced LVEF was the degree of LV systolic impairment assessed by LV GLS rather than LVEF.[34] However, even patients with moderate AS and preserved LVEF show an increased risk for adverse

Table 4 Uni -and multivariable Cox regression analyses to assess the association between LV GLS and all-cause mortality in asymptomatic patients with LVEF ≥ 50%

Variable	All-cause mortality	
	HR (95% CI)	*P*
Univariable analysis		
LV GLS (continuous variable)	0.845 (0.796-0.896)	<.001
LVEF ≥ 50% and LV GLS ≥ 16%	Reference	
LVEF ≥ 50% and LV GLS < 16%	2.549 (1.750-3.713)	<.001
Multivariable analysis*		
LV GLS (continuous variable)†	0.855 (0.798-0.917)	<.001
LVEF ≥ 50% and LV GLS ≥ 16%	Reference	
LVEF ≥ 50% and LV GLS < 16%	2.658 (1.713-4.124)	<.001

*Adjusted for age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, previous myocardial infarction, atrial fibrillation, estimated glomerular filtration rate, NYHA functional classes II to IV, LVEF, left atrial volume index, AVA index, and AVR as a time-dependent covariate.

†LV GLS as a continuous variable and in dichotomous format (according to the three groups) were separately introduced in the multivariable model.

events,[7] which may be partially explained by the presence of underlying LV myocardial fibrosis. LV GLS has the advantage over LVEF to unmask subclinical LV systolic dysfunction and identify structural and functional myocardial abnormalities at an earlier stage, enabling improved prediction of outcomes in patients with AS. LV GLS has indeed been shown to be a strong predictor of outcomes in patients with severe AS and preserved LVEF.[16,17,35] One of the main advantages of LV GLS assessment in patients with moderate AS may also be to risk-stratify patients with preserved LVEF, as it has already been shown that reduced LVEF is significantly associated with worse outcomes in these patients.[2,3] Recently, Zhu *et al.*[36] studied the prognostic value of LV GLS in a smaller cohort of patients with moderate AS and preserved LVEF and found that a cutoff value of 15.2% was associated with higher mortality rates, even among those undergoing AVR. Our data expand on these results by showing a strong, independent association between LV GLS and outcomes in a larger population of patients with moderate AS (760 vs 287 patients) and, importantly, show the incremental prognostic value of LV GLS over conventional parameters of LV systolic function (i.e., LVEF), even when adjusting for many more prognostically relevant comorbidities. Interestingly, the association between LV GLS and outcomes persisted in the subgroup of patients without any symptoms. In a large meta-analysis, including 1,067 asymptomatic patients with significant AS and preserved LVEF, Magne *et al.*[35] demonstrated that impaired LV GLS was associated with reduced survival. However, that study included patients with both moderate and severe AS, and most patients (82%) had severe AS. With recent results published from the AVATAR (Aortic Valve Replacement versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) study[37] and ongoing trials such as EARLY TAVR (Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; NCT03042104) and EVOLVED (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; NCT03094143), which are investigating whether asymptomatic patients with severe AS may benefit from early AVR, we are starting to understand that we should look not only at anatomic indices of AVA and pressure gradients but also at the consequences of pressure overload on LV performance. Whether early AVR may benefit patients with moderate AS and reduced LV GLS merits further investigation.

The present study also shows that long-term outcomes of patients with LVEF $\geq$ 50% but LV GLS $<$ 16% were not significantly different from patients with LVEF $<$ 50%. Studies have shown that a reduction in LV GLS occurs simultaneously with AS progression[32] and that LV longitudinal strain is associated with the extent of myocardial fibrosis on cardiac magnetic resonance imaging in patients with significant AS.[15] Myocardial fibrosis has been shown to have a strong association with outcomes in patients with severe AS.[38] Of interest, in a study by Dweck *et al.*,[8] including 143 patients with significant AS, 50% of patients with myocardial fibrosis on cardiac magnetic resonance imaging actually had moderate AS and, more than one half of the patients with myocardial fibrosis who died had moderate AS. The lack of cardiac magnetic resonance data in the present study disallows us to make any conclusions on the association between LV GLS and fibrosis, but the interesting interaction among LV GLS, myocardial fibrosis, and outcomes in moderate AS deserves further investigation.

It is important to mention that patients with moderate AS have a high prevalence of concomitant cardiovascular comorbidities. Therefore, abnormal LV GLS is most likely the result of not only an increase in valvular afterload but also the effects of the associated cardiovascular comorbidities on the LV myocardium (resulting in LV fibrosis formation). This demonstrates the complex but important interaction among LV myocardial function, valvular afterload, and arterial afterload. Although the degree to which each part of the ventricular-valvular-vascular axis plays a part in the reduction of LV longitudinal function remains an important challenge to clinicians, it might be of interest to target the valvular component in well-selected patients, thereby reducing LV afterload and improving LV longitudinal function.

Clinical Implications

Recent studies have shown that patients with moderate AS have a worse prognosis than initially assumed.[1,19] Risk stratification models incorporating LV GLS could therefore improve identification of patients with moderate AS who are at increased risk for adverse events and may benefit from more intensive follow-up. Even in patients with preserved LVEF, assessment of LV GLS could identify a subgroup of patients who have an increased risk for adverse events, and the present study showed that long-term outcomes in patients with moderate AS and preserved LVEF but reduced LV GLS were not different from those with reduced LVEF.

In addition, although current guidelines recommend serial echocardiography every 1 to 2 years for asymptomatic patients with moderate AS and preserved LVEF,[18] this study shows that the mortality rate in these patients is already 14% after 2 years when LV GLS falls below 16%. These observations underscore the potential value of LV GLS in risk-stratifying patients with moderate AS, even if they are still asymptomatic. Whether earlier AVR could improve survival in patients with impaired LV GLS and moderate AS requires prospective evaluation. The PROGRESS (A Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement) trial (NCT04889872) is currently recruiting patients to explore the hypothesis that transcatheter AVR could improve outcomes in patients with moderate AS.

Limitations

This study was limited by its retrospective, observational design. Patients with insufficient echocardiographic image quality for LV GLS analysis were excluded, which could result in selection bias. In addition, LV GLS is vendor dependent, and values cannot be compared directly across different echocardiographic platforms. Exercise testing aimed at confirming the asymptomatic status of patients was not systematically performed in all patients. Therefore, apparently asymptomatic patients who have abnormalities during exercise testing may have been included in the subanalysis of the present study. Brain natriuretic peptide was not available in all selected patients, which may also limit our conclusion. Doppler recordings were not systematically obtained from the right parasternal view. The present study population had a high prevalence of concomitant cardiovascular comorbidities, which could also have an impact on LV GLS. Furthermore, given the high prevalence of hypertension, measuring valvuloarterial impedance could have shown additional information, but the retrospective design precluded obtaining the necessary data for its calculation. Mortality was ascertained by review of hospital records linked to the governmental death registry database, and it was not possible to determine cardiac versus noncardiac causes of death.

CONCLUSION

In patients with moderate AS, LV GLS is associated with an increased risk for all-cause mortality. Assessment of LV GLS may therefore provide further risk stratification of patients with moderate AS and identify patients who would benefit from closer follow-up. Whether AVR could improve survival in patients with moderate AS and impaired LV GLS requires prospective evaluation.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2022.03.008.

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Supplemental Table S1 Multivariable Cox regression analysis showing the association between each individual variable and all-cause mortality

Variable	Multivariable analysis	
	HR (95% CI)	*P*
Age	1.046 (1.030-1.062)	<.001
Sex, male	1.160 (0.867-1.553)	.317
Arterial hypertension	1.011 (0.748-1.367)	.941
Diabetes mellitus	1.556 (1.160-2.086)	.003
Dyslipidemia	0.686 (0.519-0.909)	.009
Coronary artery disease	1.015 (0.740-1.392)	.927
Previous myocardial infarction	0.786 (0.543-1.138)	.203
Atrial fibrillation	0.888 (0.650-1.213)	.455
eGFR	0.989 (0.984-0.995)	<.001
NYHA functional class III or IV	0.861 (0.651-1.138)	.292
LVEF	1.015 (1.000-1.030)	.056
LA volume index	1.011 (1.002-1.020)	.019
AVA index	1.661 (0.349-7.913)	.524
AVR as time-dependent variable	0.971 (0.709-1.330)	.854
LV GLS (continuous variable)	0.847 (0.808-0.888)	<.001

LA, Left atrial.

Supplemental Table S2 Uni -and multivariable Cox regression analyses to assess the association between LV GLS and all-cause mortality in patients with LVEF ≥ 60%

Variable	All-cause mortality	
	HR (95% CI)	*P*
Univariable analysis		
LV GLS (continuous variable)	0.863 (0.811-0.918)	<.001
LV GLS ≥ 16%	Reference group	
LV GLS < 16%	2.209 (1.523-3.203)	<.001
Multivariable analysis*		
LV GLS (continuous variable)†	0.871 (0.818-0.927)	<.001
LV GLS ≥ 16%	Reference group	
LV GLS < 16%	2.301 (1.543-3.429)	<.001

*Adjusted for age, sex, diabetes mellitus, coronary artery disease, atrial fibrillation, estimated glomerular filtration rate, NYHA functional classes II to IV, left atrial volume index, AVA index, and AVR as a time-dependent covariable (to avoid overfitting of the model, arterial hypertension, dyslipidemia, previous myocardial infarction, and LVEF were not included in this multivariable Cox regression model).

†LV GLS as a continuous variable and in dichotomous format (according to the three groups) were separately introduced in the multivariable model.

Supplemental Table S3 Baseline clinical characteristics of the study population with asymptomatic, moderate AS, and LVEF ≥ 50%

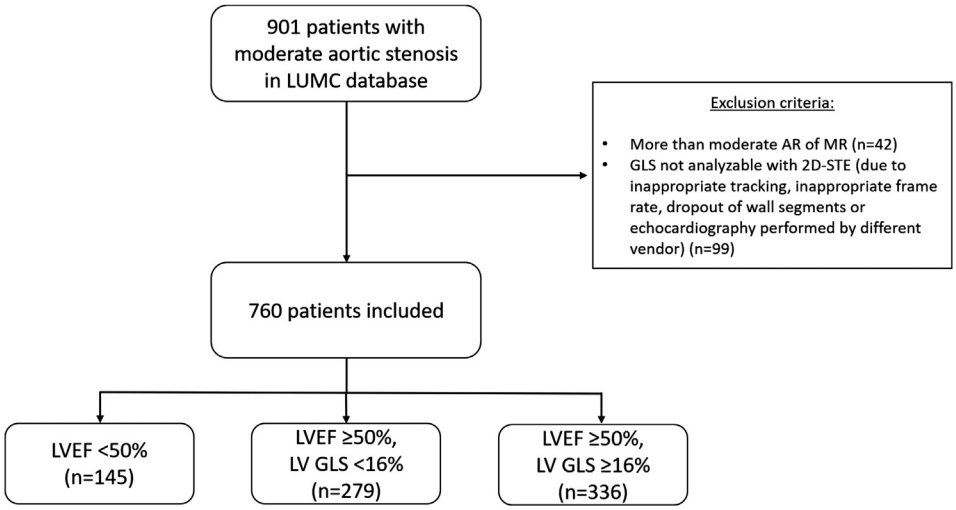
Variable	Overall population (*N* = 385)	LVEF ≥ 50%, LV GLS < 16% (*n* = 156)	LVEF ≥ 50%, LV GLS ≥ 16% (*n* = 229)	*P*
Age, y	70.2 ± 12.9	71.0 ± 11.2	69.7 ± 13.9	.314
Sex, male	231 (60.0)	105 (67.3)	126 (55.0)	.016
Caucasian	363 (94.3)	147 (94.2)	216 (94.3)	.969
BMI, kg/m^2	26.4 ± 4.4	27.1 ± 4.4	25.9 ± 4.3	.007
BSA, m^2	1.90 ± 0.21	1.93 ± 0.21	1.87 ± 0.20	.014
Arterial hypertension	259 (68.0)	107 (69.0)	152 (67.3)	.715
Dyslipidemia	220 (58.0)	93 (60.8)	127 (56.2)	.374
DM	82 (21.5)	46 (29.7)	36 (15.9)	.001
Current smoker	48 (14.4)	19 (14.0)	29 (14.6)	.984
Obesity	62 (16.3)	32 (20.8)	30 (13.2)	.051
CAD	128 (33.5)	59 (38.1)	69 (30.4)	.119
Previous MI	57 (15.1)	26 (17.1)	31 (13.7)	.367
Atrial fibrillation	73 (19.1)	37 (23.9)	36 (15.9)	.051
Previous stroke	61 (16.0)	28 (18.1)	33 (14.5)	.355
COPD	28 (7.3)	14 (9.0)	14 (6.2)	.291
β-blocker	161 (42.6)	68 (44.4)	93 (41.3)	.548
ACE inhibitor or ARB	200 (52.9)	78 (51.0)	122 (54.2)	.535
MRA	11 (2.9)	6 (4.0)	5 (2.2)	.321
Diuretic	117 (31.0)	52 (34.0)	65 (28.9)	.293
CCB	110 (29.1)	47 (30.7)	63 (28.0)	.568
Statin	214 (56.6)	85 (55.6)	129 (57.3)	.732
Aspirin	158 (41.8)	64 (41.8)	94 (41.8)	.992
Oral anticoagulation	66 (17.5)	33 (21.6)	33 (14.7)	.083
eGFR, mL/min/1.73 m^2	74.8 ± 25.0	73.3 ± 27.0	75.9 ± 23.5	.365
Hemoglobin, g/dL	13.4 ± 1.74	13.3 ± 1.71	13.4 ± 1.76	.756

Data are expressed as mean ± SD or number (percentage). Obesity was defined as BMI ≥ 30 kg/m^2.
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *BSA*, body surface area; *CAD*, coronary artery disease; *CCB*, calcium channel blocker; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *eGFR*, estimated glomerular filtration rate; *MI*, myocardial infarction; *MRA*, mineralocorticoid receptor antagonist.

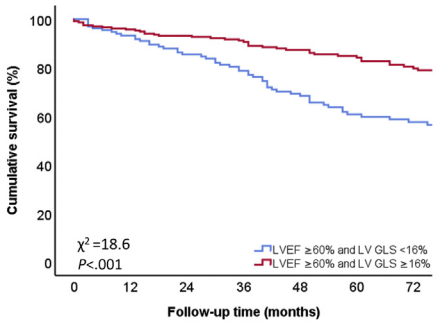
Supplemental Table S4 Baseline echocardiographic characteristics of the study population with asymptomatic, moderate AS, and LVEF ≥ 50%

Variable	Overall population (*N* = 385)	LVEF ≥ 50%, LV GLS < 16% (*n* = 156)	LVEF ≥ 50%, LV GLS ≥ 16% (*n* = 229)	*P*
LV EDD, mm	47.2 ± 6.1	48.3 ± 6.2	46.4 ± 5.9	.002
LV ESV, mL	36 (28-48)	41 (29-53)	34 (27-44)	<.001
LV ESVi, mL/m^2	20 ± 7	22 ± 8	19 ± 7	.001
LV EDV, mL	96 (76-118)	100 (79-125)	94 (74-115)	.060
LV EDVi, mL/m^2	52 ± 15	54 ± 15	51 ± 15	.136
LVEF, %	61.8 ± 5.8	60.0 ± 5.8	63.0 ± 5.5	<.001
LV GLS, %	16.6 ± 3.3	13.4 ± 2.1	18.7 ± 1.9	<.001
LVMI, g/m^2	107.0 ± 26.0	113.4 ± 26.8	102.4 ± 24.5	<.001
LAVi, mL/m^2	33 (27-41)	33 (27-42)	32 (27-40)	.443
E/e′ ratio	12.6 (9.3-16.7)	14.4 (10.7-19.4)	11.3 (8.8-14.9)	<.001
Bicuspid valve	49 (12.7)	15 (9.6)	34 (14.8)	.130
AVA, cm	1.25 ± 0.15	1.24 ± 0.15	1.26 ± 0.14	.157
AVAi, cm/m^2	0.67 ± 0.10	0.65 ± 0.09	0.68 ± 1.0	.002
Peak aortic jet velocity, m/sec	3.1 ± 2.1	3.0 ± 0.5	3.2 ± 2.7	.394
Aortic mean pressure gradient, mm Hg	23.1 ± 8.3	23.3 ± 8.5	23.0 ± 8.1	.749
Stroke volume index, mL/m^2	45.9 ± 11.0	43.6 ± 10.0	47.4 ± 11.4	.001
TAPSE, mm	23 ± 5	22 ± 5	23 ± 4	.032
PASP, mm Hg	29 (24-35)	29 (24-34)	29 (24-36)	.842
Moderate or severe TR	45 (11.9)	16 (10.5)	29 (12.9)	.474

Data are expressed as mean ± SD, median (interquartile range), or number (percentage).
AR, Aortic regurgitation; *EDD*, end-diastolic diameter; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *LAVi*, left atrium volume index; *LVMI*, LV mass index; *MR*, mitral regurgitation; *PASP*, pulmonary artery systolic pressure; *TAPSE*, tricuspid annular plane systolic excursion; *TR*, tricuspid regurgitation.



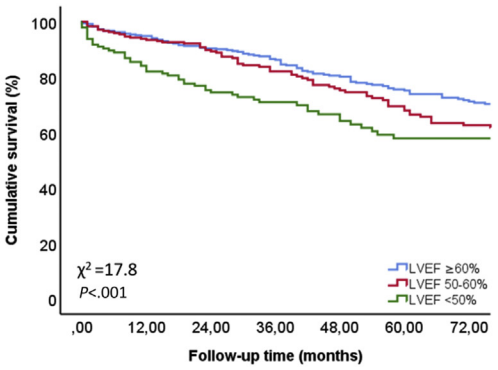
Supplemental Figure S1 Flowchart. *AR*, Aortic regurgitation; *LUMC*, Leiden University Medical Center; *MR*, mitral regurgitation; *STE*, speckle-tracking echocardiography.



Number at risk							
LVEF ≥60% and LV GLS <16%	135	125	104	93	75	59	51
LVEF ≥60% and LV GLS ≥16%	236	226	195	169	145	118	104

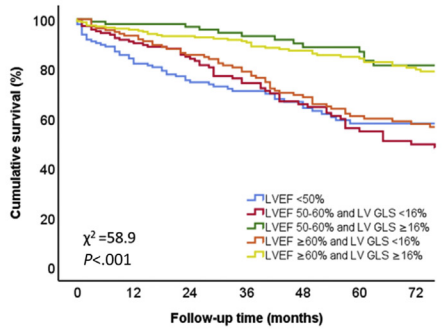
Supplemental Figure S2 Kaplan-Meier curve for all-cause mortality according to LV GLS in patients with LVEF ≥ 60%.

A



Number at risk							
LVEF ≥60%	371	351	299	262	220	177	155
LVEF 50-60%	244	227	186	141	112	91	79
LVEF <50%	145	118	93	70	52	43	34

B



Number at risk							
LVEF <50%	145	118	93	70	52	43	34
LVEF 50-60% and LV GLS <16%	144	129	99	74	56	43	38
LVEF 50-60% and LV GLS ≥16%	100	98	87	67	56	48	41
LVEF ≥60% and LV GLS <16%	136	126	105	93	75	59	51
LVEF ≥60% and LV GLS ≥16%	235	225	194	169	145	118	104

Supplemental Figure S3 Kaplan-Meier curve for all-cause mortality according to LVEF **(A)** and LVEF with further subcategorization according to LV GLS **(B)**.