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ORIGINAL ARTICLE

Left Ventricular Global Longitudinal Strain Is Associated With Long-Term Outcomes in Moderate Aortic Stenosis

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BACKGROUND: Left ventricular global longitudinal strain (GLS) is associated with long-term outcomes of patients with severe aortic stenosis. However, its prognostic value in patients with moderate aortic stenosis remains unknown.

METHODS: Patients diagnosed with moderate aortic stenosis (1.0< aortic valve area ≤1.5 cm^2) and left ventricular ejection fraction ≥50% were identified. GLS was assessed by 2-dimensional strain imaging using speckle-tracking method. All-cause mortality was assessed according to the median GLS value.

RESULTS: Two hundred eighty-seven patients were included (median age 76 years; 47% male). Mean aortic valve area was 1.25 cm^2, left ventricular ejection fraction 62%, and median GLS −15.2%. During a median follow-up of 3.9 years, there were 103 deaths (36%). Mortality was higher in patients with GLS>−15.2% (hazard ratio 2.62 [95% CI 1.69–4.06]) compared with patients with GLS ≤−15.2% even after adjusting for confounders. Mortality rates at 1, 3, 5 years were 21%, 35%, 48%, respectively, in patients with GLS >−15.2%, and 6%, 15%, 19% in those with GLS ≤−15.2%. Even among those with left ventricular ejection fraction ≥60%, GLS discriminated higher-risk patients (*P*=0.0003). During follow-up, 106 (37%) patients underwent aortic valve replacement with median waiting-time of 2.4 years, and their survival was better than patients without aortic valve replacement. Among those patients undergoing aortic valve replacement, prognosis was still worse in patients with GLS >−15.2% (*P*=0.04). Mortality rates at 1, 3, 5 years were 2%, 10%, 20%, respectively, in patients with GLS >-15.2% and 2%, 5%, 6% in those with GLS ≤−15.2%.

CONCLUSIONS: Impaired GLS in moderate aortic stenosis patients is associated with higher mortality rates even among those undergoing aortic valve replacement.

Key Words: aortic valve ■ echocardiography ■ prognosis ■ transcatheter aortic valve replacement

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CLINICAL PERSPECTIVE

Left ventricular (LV) ejection fraction is a routine measure of LV systolic function and has played a critical role in the risk stratification of patients with aortic stenosis (AS). However, recent data have demonstrated that LV global longitudinal strain is a more sensitive marker for systolic dysfunction and provides incremental prognostic information in patients with severe AS when compared with LV ejection fraction. It has also been shown that clinical outcomes of the patients with moderate AS are poor. This underscores the importance of detecting even mild degrees of LV systolic dysfunction before AS becoming severe. This study demonstrates the potential utility of risk stratification using global longitudinal strain in patients with moderate AS. Even when AS was only moderate in severity, impaired global longitudinal strain values were associated with worse survival outcomes in patients with preserved LV ejection fraction, including those undergoing aortic valve replacement. Whether an earlier valvular intervention compared with frequent clinical surveillance using global longitudinal strain can improve the survival outcomes in patients with moderate, as well as severe AS, requires further investigations.

Aortic valve replacement (AVR) for severe aortic stenosis (AS) is recommended in symptomatic patients or in those with a left ventricular (LV) ejection fraction (LVEF) <50%.[1,2] LVEF is a widely used measure of LV systolic function and has played a critical role in the risk stratification of patients with AS.[3–5] Moreover, recent data have demonstrated that in patients with reduced LVEF and severe AS, decreased LVEF precedes the diagnosis of severe AS by several years.[5] This underscores the importance of detecting even mild degree of LV systolic dysfunction even before AS becomes severe.

In patients with moderate AS, decreased LVEF (<50%) has been shown to be associated with higher death or heart failure hospitalization rates.[6] Currently, the TAVR UNLOAD trial (Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure) is ongoing to investigate the survival benefit of transcatheter AVR in patients with moderate AS and LVEF <50%.[7] However, prognostic parameters in patients with moderate AS and preserved LVEF have not been well studied. It has been reported that global longitudinal strain (GLS) using 2-dimensional (2D) speckle-tracking system is reduced and associated with poor survival outcomes in patients with severe AS.[8–11] GLS is a more sensitive marker for systolic dysfunction than LVEF and can detect subtle myocardial dysfunction in AS patients.[12] We hypothesized that the subset of patients with moderate AS and preserved LVEF at high risk can be detected by LV GLS.

METHODS

We retrospectively identified consecutive patients with moderate AS diagnosed by echocardiography at the Mayo Clinic, Rochester, MN, from January 2012 to December 2012. Moderate AS was defined as aortic valve area (AVA) >1.0 and AVA ≤1.5 cm^2 with peak aortic transvalvular velocity <4 m/s or mean valve gradient <40 mm Hg. Subjects were excluded with any of the following criteria: previous valve surgery; active infective endocarditis; significant LV outflow tract obstruction (>3 m/s); more than moderate aortic or mitral valve regurgitation; chronic atrial fibrillation/flutter; and LV wall asynergy.[13] Patients with implanted pacemakers were also excluded from this study. *International Classification of Diseases, Ninth* and *Tenth* codes were used for identifying patients' demographics. Coronary artery disease (CAD) was defined based on these codes. Symptomatic status was abstracted from medical records and was defined as any of the three: syncope, dyspnea, or chest pain. All patients were followed until death or last contact, at which time they were censored. The timing of AVR was identified from medical records. Patients were stratified into 2 groups according to the median GLS, and all-cause mortality was compared. The Mayo Clinic Institutional Review Board approval was obtained for the current study (Institutional Review Board number 18-006393). Research authorizations were obtained from patients. Our data is available on request from the authors.

Echocardiography

Echo-Doppler data were obtained using commercially available ultrasonography systems. AVA was calculated by the continuity equation[14] and LVEF by the modified Simpson or the modified Quinones method.[13] LV mass index was calculated by the Devereux formula and indexed for body surface area. The degree of aortic and mitral regurgitation was classified according to the guidelines of the American Society of Echocardiography.[15] Calculation of relative wall thickness was done with the formula: (2×posterior wall thickness)/(LV end-diastolic diameter).[13] Diastolic function was assessed by mitral inflow velocity (early diastolic velocity and atrial velocity), early diastolic tissue velocity (e′) of the medial and the lateral mitral annulus, early transmitral diastolic velocity (E) to early diastolic mitral annular tissue velocity (E/e'), left atrium volume index, and tricuspid regurgitation velocity according to the guidelines.[16] Left atrium volume index was calculated using the area-length method by tracing in both the apical 2- and 4-chamber view.[13] Valvuloarterial impedance (Zva) was calculated as follows: (mean systolic aortic valve Doppler gradient+systolic blood pressure)÷stroke volume index.[17]

Strain Analysis With 2D Speckle-Tracking

Offline 2D strain imaging analysis was performed using speckle-tracking method from stored transthoracic echocardiography images (DICOM) using TomTec (TomTec Imaging

Systems GmbH, Unterschleissheim, Germany). Frame rates were at least 30 per second in all patients (median frame rate 30 [30, 30] frames/s). For assessing LV longitudinal strain using 2D-speckle tracking imaging, standard 2D grayscale images of the LV were acquired from conventional, apical 2-, 3-, and 4-chamber views. The peak strain of each segment was defined as the peak negative value on the strain curve as the time from the end-diastole to peak negative longitudinal strain to the end-systole in 16 LV segments. End-diastole and end-systole were defined as the largest and the smallest LV chamber volumes, respectively. GLS was calculated as the peak strain value from the averaged strain curve generated from 16 segments. Subjects were excluded from the analysis if there were >3 segments judged as unsatisfactory.

Intraobserver and Interobserver Variability for GLS

Twenty randomly selected images were reanalyzed for assessing the reproducibility of strain measurements. Interobserver reliability was assessed by a second operator who performed strain measurement in a random sample of 20 participants and was blinded to all clinical and imaging data.

Data Analysis

Continuous variables were summarized as a mean±SD or median (25th, 75th percentile) when data were non-normal. Categorical variables were presented as counts (%). A 2-tailed $P<0.05$ was considered statistically significant. Comparisons between groups were performed using 2-sample t test or χ^2 test for continuous and nominal variables, respectively, unless data were non-normal or the sample size small; in this case, the Wilcoxon rank-sum test and Fisher exact were applied instead.

Survival was estimated using a Kaplan-Meier curve, and the curves were compared using a log-rank test. Multivariable Cox proportional hazard model was applied to assess whether GLS independently predicted adverse survival outcome. Clinical and echocardiographic variables were selected based on clinical importance. The hazard ratios and 95% CI were reported. Penalized smoothing spline was applied to illustrate the association of GLS and the hazard ratio using univariate Cox proportional hazards method for assessing the tendency of the risk of overall mortality. Median of GLS value (−15.2%) was used as references for calculating hazard ratios.

Intraclass correlation coefficient was used for assessment of intraobserver and interobserver variability. Analyses were performed using JMP software, version 14.1.0 (SAS Institute, Cary, NC), R software, version 3.4.2 (The R Foundation, Vienna, Austria) and MedCalc statistical software, version 11.0 (MedCalc Software, Ostend, Belgium).

RESULTS

A total of 287 patients met our inclusion and exclusion criteria and were found to have satisfactory quality images for strain analysis. Patients' clinical characteristics are shown in Table 1. Median age was 76 years and 47% were male; 71% had hypertension, and 49% CAD. Echocardiographic parameters are shown in Table 2. Mean AVA was 1.26±0.14 cm², peak aortic

Table 1. Patient Characteristics: Patients With GLS≤−15.2% vs GLS>−15.2%

		GLS		
	Total (n=287)	≤−15.2% (n=146)	>−15.2% (n=141)	*P* Value
Age, y	76 (68–82)	74 (65–81)	78 (71–83)	0.005
Male sex, %	134 (47)	62 (42)	72 (51)	0.14
Heart rate, bpm	67.8±12.4	67.3±11.8	68.4±12.9	0.45
Body mass index, kg/m²	28.8±5.9	28.6±5.8	29.1±6.0	0.53
Body surface area, m²	1.88±0.24	1.86±0.23	1.89±0.26	0.31
Hypertension, %	202 (71)	103 (71)	99 (70)	0.95
Hyperlipidemia, %	197 (68)	101 (69)	96 (68)	0.84
Diabetes mellitus, %	95 (33)	42 (29)	53 (38)	0.11
Coronary artery disease, %	142 (49)	64 (44)	78 (55)	0.05
Myocardial infarction, %	43 (15)	15 (10)	28 (20)	0.02
Chronic obstructive pulmonary disease, %	48 (17)	20 (14)	28 (20)	0.16
Hemoglobin, g/dL	12.5±1.9	12.7±1.8	12.4±1.9	0.31
Creatinine, mg/dL	1.0 (0.8–1.3)	1.0 (0.8–1.2)	1.1 (0.9–1.4)	0.09
NT-proBNP, pg/dL	350 (99–2539)	182 (73–663)	816 (185–3508)	0.01
Aortic valve replacement, %	106 (37)	65 (45)	41 (29)	0.007
Any symptoms, %	115 (41)	49 (34)	66 (47)	0.02
Shortness of breath, %	79 (28)	33 (23)	46 (33)	0.06
Chest pain, %	29 (10)	10 (7)	19 (13)	0.06
Syncope, %	12 (4)	9 (6)	3 (2)	0.14

GLS indicates global longitudinal strain; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2. Echocardiographic Parameters: Patients With GLS≤−15.2% vs GLS>−15.2%

	Total (n=287)	GLS ≤−15.2% (n=146)	GLS >−15.2% (n=141)	*P* Value
GLS, %	−15.2±3.2	−17.6±1.9	−12.7±2.3	…
LVEF, %	62±6	63±5	61±6	0.0008
Aortic valve area, cm²	1.26±0.14	1.26±0.14	1.26±0.14	0.73
Indexed aortic valve area, cm²/m²	0.68±0.11	0.68±0.12	0.67±0.11	0.22
Peak aortic transvalvular velocity, m/s	3.20±0.50	3.27±0.49	3.13±0.49	0.02
Mean valve gradient, mm Hg	24.5±7.4	25.3±7.6	23.7±7.2	0.07
LV mass index, g/m²	101.1±25.9	97.2±22.1	105.1±28.9	0.01
Relative wall thickness	0.46±0.08	0.45±0.09	0.46±0.09	0.70
Cardiac output, L/min	6.21±1.14	6.27±1.13	6.15±1.15	0.36
Stroke volume index, mL/m²	50.7±8.2	52.3±7.7	49.0±8.5	0.0006
Average E/e′	13.8 (10.1–17.7)	13.9 (9.8–17.7)	13.6 (10.9–17.8)	0.67
Medial e′, m/s	0.06±0.02	0.06±0.02	0.05±0.02	0.0053
E, m/s	0.89±0.28	0.90±0.26	0.88±0.30	0.63
A, m/s	0.97±0.31	1.00±0.31	0.95±0.30	0.20
Deceleration time, ms	238.5±63.3	239.6±66.9	237.4±59.1	0.79
Left atrium volume index, mL/m²	38.7±12.6	38.2±12.5	39.3±12.8	0.47
Right ventricular systolic pressure, mm Hg	32 (28–39)	32 (28–39)	34 (28–41)	0.10
Valvuloarterial impedance (Zva), mmHg/mL/m²	3.14±0.63	3.01±0.57	3.28±0.66	0.0003

A indicates late diastolic velocity; E, early diastolic velocity; e′, early diastolic tissue velocity; GLS, global longitudinal strain; LV, left ventricular; and LVEF, LV ejection fraction.

transvalvular velocity 3.2±0.5 m/s, and mean valve gradient 24.5±7.4 mm Hg. Mean LVEF was 62±6 %.

Median value of GLS was −15.2 % (−17.1 to −13.8). There were 146 (51%) patients with GLS ≤−15.2% and 141 (49%) with GLS >−15.2%. Representative GLS images in apical 4-chamber view are shown in Figure 1. Patients with GLS >−15.2% were older, more symptomatic, had higher NT-proBNP levels, and more often had prior myocardial infarction (Table 1). In addition, patients with GLS >−15.2% less frequently underwent AVR (Table 1). They also had lower LVEF, lower peak aortic transvalvular velocity, lower stroke volume index, larger LV mass index, and higher valvuloarterial impedance (Table 2). Diastolic function parameters, such as average E/e′, left atrium volume index, and right ventricular systolic pressure, were similar between 2 groups (Table 2). However, mean medial e′ differed between 2 groups (P=0.0053), and smaller absolute value of GLS was significantly associated with lower medial e′ velocity (r=0.22, P<0.0001).

Survival Outcomes Based on GLS Levels

During a median follow-up of 3.9 (0.7–5.9) years, there were 103 deaths (35.9%). Mortality was significantly higher in patients with GLS >−15.2% compared with GLS ≤−15.2% (P<0.0001, Figure 2A). Mortality rate was 21% at 1 year, 35% at 3 years, and 48% at 5 years among patients with GLS >−15.2%. In those patients with GLS ≤−15.2%, mortality rate was 6% at 1 year, 15% at 3 years, and 19% at 5 years. GLS discriminated high-risk patients even among those with an LVEF ≥60% (n=188, P=0.0003, Figure 2B). In those with LVEF ≥60% and GLS >−15.2%, mortality rate was 20% at 1 year, 33% at 3 years, and 44% at 5 years. When GLS was ≤−15.2%, mortality rate was 7% at 1 year, 15% at 3 years, and 19% at 5 years. Regardless of the presence of CAD, mortality was higher in patients with GLS >−15.2% compared with GLS ≤−15.2% (Figure I in the Data Supplement). Of note, GLS was significantly different between patients with CAD versus those without CAD (−14.6±3.2% versus −15.6±3.18 %, respectively, P=0.01).

The multivariable Cox model is shown in Tables 3 and 4. GLS >−15.2% was independently associated with worse survival (hazard ratio 2.62 [95% CI, 1.69–4.06]) even after adjusting for age, sex, CAD, LVEF, mean valve gradient, and symptomatic status (Table 3). A second Cox model was built with GLS as a continuous variable (Table 4); higher GLS value was significantly associated with worse prognosis (hazard ratio 1.19 per 1% incremental [95% CI, 1.12–1.26]) after adjusting for confounders. The correlation between GLS and the risk of all-cause death is shown in Figure 3, with higher GLS values being associated with higher hazard ratios.

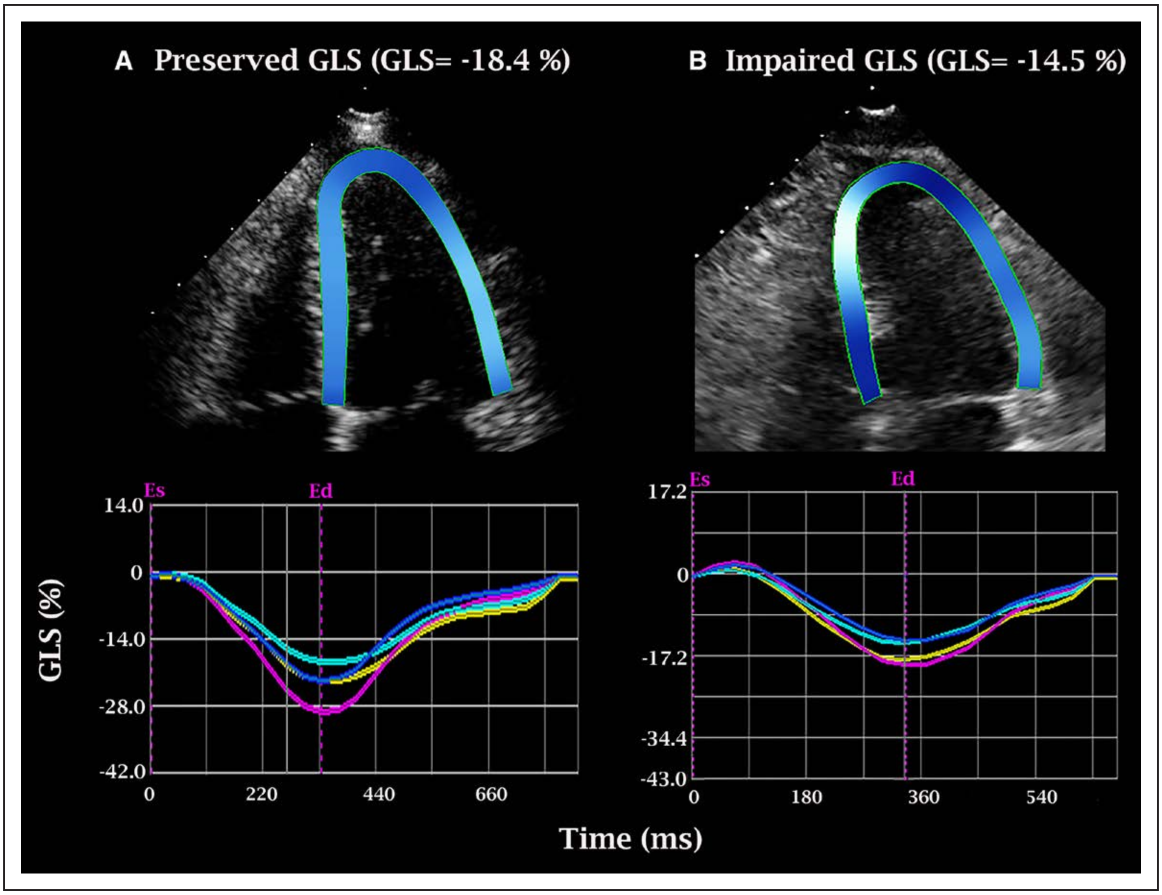

Figure 1. Representative global longitudinal strain (GLS) images in apical 4 chamber views.
Representative GLS images in apical 4-chamber views were shown; (**A**) normal GLS (−18.4%); a 62-year-old woman with moderate aortic stenosis (AS) and left ventricular ejection fraction (LVEF) is 69%; (**B**) impaired GLS (−14.5%); a 60-year-old woman with moderate AS and LVEF is 63%. Ed indicates end-diastole; and Es, end-systole.

Survival Outcomes for Patients With/ Without AVR

During follow-up, 106 (37%) patients underwent AVR. Seventy-five (70.8%) patients had AVA≤1 cm^2 at the time of AVR. Of these, 104 patients developed symptomatic severe AS (98.1%), and 2 patients were asymptomatic with severe AS requiring coronary artery bypass grafting surgery (1.9%). Median time from the diagnosis of moderate AS to AVR was 2.4 (1.3–3.8) years. For patients not undergoing AVR, mortality was significantly higher in patients with GLS >−15.2% compared to patients with GLS ≤−15.2% (*P*<0.0001, Figure 4A). Mortality rate was 28% at 1 year, 45% at 3 years, and

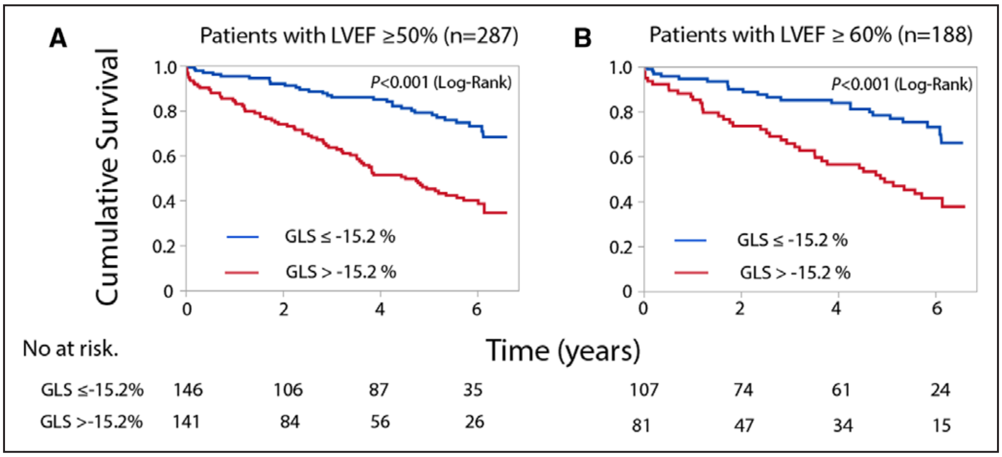

Figure 2. Survival outcomes for patients with moderate aortic stenosis.
A, All-cause of death was compared in patients with global longitudinal strain (GLS) ≤−15.2% to patients with GLS >−15.2% among those with left ventricular ejection fraction (LVEF) ≥50%. **B**, All-cause of death was compared in patients with GLS ≤−15.2% to patients with GLS >−15.2% among those with LVEF ≥60%.

Table 3. Cox Proportional Hazard Model–Multivariable Analysis: GLS as a Binary Variable

	Hazard Ratio (95% CI)	*P* Value
GLS>−15.2%	2.62 (1.69–4.06)	<0.0001
Age, y	1.03 (1.01–1.05)	0.0046
Male sex	0.73 (0.47–1.12)	0.15
Coronary artery disease	0.80 (0.54–1.20)	0.29
LVEF, %	0.97 (0.94–1.01)	0.14
Mean valve gradient, mm Hg	0.97 (0.94–1.00)	0.048
Symptoms	1.59 (1.06–2.36)	0.02

GLS indicates global longitudinal strain; and LVEF, left ventricular ejection fraction.

Table 4. Cox Proportional Hazard Model–Multivariable Analysis: GLS as a Continuous Variable

	Hazard Ratio (95% CI)	*P* Value
GLS, %	1.19 (1.12–1.26)	<0.0001
Age, y	1.03 (1.01–1.05)	0.0021
Male sex	0.75 (0.49–1.16)	0.19
Coronary artery disease	0.76 (0.51–1.14)	0.19
LVEF, %	0.97 (0.94–1.01)	0.18
Mean valve gradient, mm Hg	0.97 (0.94–1.00)	0.03
Symptoms	1.47 (0.99–2.20)	0.06

GLS indicates global longitudinal strain; and LVEF, left ventricular ejection fraction.

59% at 5 years among patients with GLS >−15.2%. Among patients with GLS ≤−15.2%, mortality rate was 10% at 1 year, 23% at 3 years, and 30% at 5 years. Similarly, among those undergoing AVR, mortality was higher in patients with GLS >−15.2% compared to patients with GLS≤−15.2% (*P*=0.04, Figure 4B). Mortality rate was 2% at 1 year, 10% at 3 years, and 20% at 5 years among patients with GLS >−15.2%. For patients with GLS ≤−15.2%, it was 2% at 1 year, 5% at 3 years, and 6% at 5 years.

Intraobserver and Interobserver

Intraclass correlation coefficient for intraobserver variability was 0.94 (95% CI, 0.91–0.97) and for interobserver variability 0.89 (95% CI, 0.85–0.93), indicating that reliability for GLS measurements was excellent.

DISCUSSION

Our results demonstrate that LV GLS is independently associated with survival outcomes among patients with moderate AS and preserved LVEF. In our cohort, reduced GLS was associated with poor survival outcomes even after AVR. GLS could potentially be one of the important parameters when considering earlier intervention for AS even when LVEF is preserved.

Epidemiology of Moderate AS

Moderate AS has been reported to be associated with decreased survival when compared with the normal population. Recently, Strange et al[18] reported that the 5-year mortality was 56% in total of 3315 patients with moderate AS. In a Veterans Affairs cohort, 63 deaths were observed in 104 individuals with moderate AS during the mean follow-up period of 1.8 years.[19] In a French population of patients with moderate AS and LVEF ≥50%, mortality rates were 13%, 28%, and 47% at 1, 3, and 6 years, respectively.[20] These observations demonstrate that the prognosis in patients with moderate AS is poor, even if LVEF is preserved.

Pathophysiology of Reduced GLS in Patients With Moderate AS

The incremental role of GLS for risk stratification of patients with moderate AS and preserved LVEF was demonstrated in this study. Reduced GLS has been shown to be associated with poor survival outcomes in patients with severe AS.[8–11] In patients with significant AS, LV hypertrophy occurs as a compensatory mechanism to keep wall stress normal but impairs coronary blood flow reserve, which initially occurs in the subendocardial layers.[21–26] Subsequently, fibrotic changes start subendocardially and ultimately affect LV longitudinal function.[27] Although this LV remodeling process has not been well documented in those with moderate AS, abnormal GLS is most likely associated with a combination of excessive increase in afterload related to AS[25,28] and associated comorbidities.[29–33]

Increased afterload could possibly be already overwhelming even when AS was only moderate among

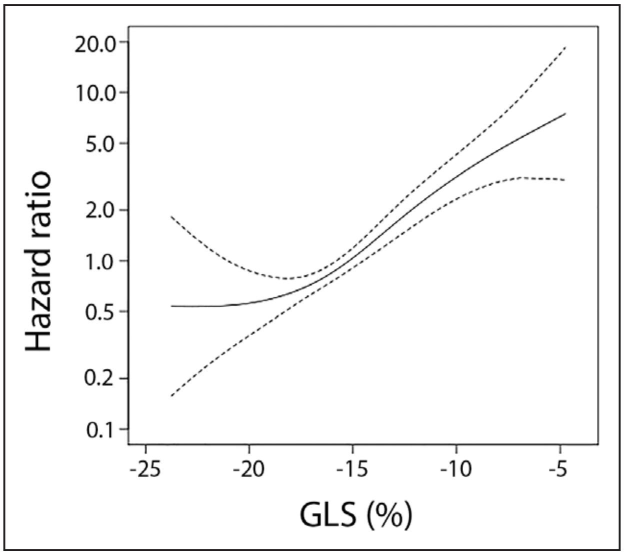

Figure 3. Association between global longitudinal strain (GLS) and the risk of overall mortality among patients with moderate aortic stenosis. Spline curve was illustrated for assessing the association of hazard ratio and GLS. GLS of −15.2% was a reference value. 95% CIs were shown.

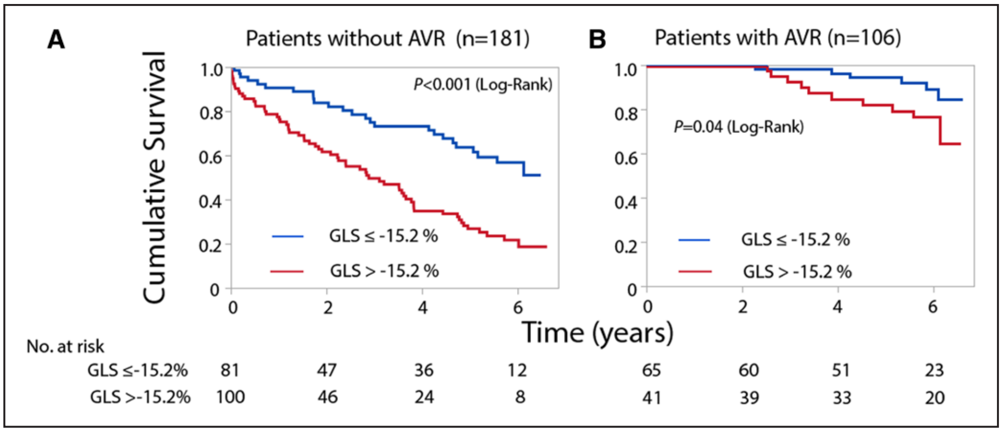

Figure 4. Survival outcomes for patients with/without aortic valve replacement (AVR).
The survival outcomes of patients without AVR (**A**) and with AVR (**B**) were shown. Patients were stratified into 2 groups based on global longitudinal strain (GLS) value of −15.2%.

patients with impaired GLS.[21,22] As shown in this study, patients with impaired GLS had larger LV mass index with concentric LV hypertrophy and lower e′ velocities compared with those with preserved GLS. It has been demonstrated that the LV wall thickness in AS was related to the anatomic characteristics of myocardial fibers, culminating in longitudinal systolic dysfunction.[34] Also, in a previous publication, some patients were found to have a decline of LVEF even before AS developing severe.[5] These findings may support our hypothesis for the excessive afterload in a subset of patients with moderate levels of aortic valve obstruction.

Comorbidities, such as CAD, hypertension, diabetes mellitus, obesity, or atherosclerosis, could also contribute to impaired GLS in moderate AS.[29–33] In addition, advanced age and CAD were also associated with GLS impairment, as previously reported.[35,36] The association with CAD might be of particular importance as CAD was present ≈50% of patients in our study, and CAD has been shown to be prevalent among patients with AS. However, it should be noted that GLS could discriminate high-risk patients regardless of CAD status (Tables 3 and 4, Figure I in the Data Supplement). Importantly, GLS can be also impaired in other cardiac disorders, such as hypertrophic cardiomyopathy and cardiac amyloidosis, and the presence of a concomitant myocardial disorder should be considered in those with AS and significantly reduced GLS.[37–41]

GLS Is an Independent Predictor of Survival Outcomes in Patients With Moderate AS

LVEF, the reference standard for assessment of global LV systolic function, was not able to predict survival among patients with moderate AS and preserved LVEF in our study. In contrast, GLS was significantly associated with survival even after adjusting for confounders. Although it was difficult to determine appropriate cutoff values for GLS associated with survival outcomes in this study, we successfully demonstrated that each incremental value of GLS was associated with worse survival outcomes in the multivariable model (Table 4) as well as Spline curve (Figure 3).

GLS and Survival Outcomes After AVR

In our study, GLS predicted survival outcomes in patients with moderate AS undergoing AVR, as well as patients without AVR. AVR is a well-established treatment for patients with severe AS. Based on the current management strategies, physicians usually follow patients until AS becomes severe and symptoms develop.[1,2] This is probably the reason for the median time interval from the time of diagnosis of moderate AS to AVR of 2.4 years in this study. It is quite revealing that 40% of patients with moderate AS were shown to be already symptomatic, and underlying comorbidities may contribute to symptom development. However, the symptoms in patients with AS are not specific, and it is often difficult to determine symptoms in these patients are truly cardiac in nature. It has been reported that impaired GLS is associated with symptomatic status, as well as myocardial damages defined by elevated high-sensitive troponin T level.[42] Preoperative GLS has been shown to be associated with myocardial fibrosis assessed by myocardial biopsy specimens obtained intraoperatively.[43] GLS could potentially provide incremental information when evaluating AS patients, especially when symptomatic status is difficult to be defined.

In patients with severe AS, it has been reported that patients with impaired GLS to have higher mortality rate than patients with normal GLS after AVR.[8,10,11] Development of LV fibrosis, the main pathophysiological mechanism involved in the reduction of GLS, might be more severely advanced in some cases and might thus be irreversible even after AVR.[25] AVR should be ideally performed before developing permanent LV fibrosis.[44] Therefore, risk stratification is extremely important even when AS is only moderate in severity. Furthermore, excellent reproducibility was shown in this study, and since the consistency among different ultrasound units has been already reported,[45] we propose that GLS should be evaluated in all patients with moderate AS to provide prognostic information.

Further studies will be necessary to answer whether earlier AVR compared with frequent clinical surveillance could improve the survival in patients with impaired GLS and moderate AS.

Study Limitations

Our study is a retrospective, single-center study, and patients with poor echocardiography image for GLS analysis were excluded. This could result in selection bias. We used the compressed DICOM images for GLS analysis; therefore, frame rate was decreased compared with the raw data analysis; thus, the GLS values were potentially lower than expected.

Conclusions

Among patients with moderate AS and preserved LVEF, mortality was significantly higher in patients with impaired GLS compared with patients with preserved GLS. Even after developing symptomatic severe AS requiring AVR, impaired GLS at the time of moderate AS was associated with poor survival outcomes. A randomized clinical trial is warranted to test whether those patients with moderate AS and impaired GLS benefit from an earlier intervention.

ARTICLE INFORMATION

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Disclosures

Dr Oh serves as a Director of the Echocardiography Core Lab at Mayo Clinic for Medtronic transcatheter aortic valve replacement trials and has a consulting agreement with Medtronic Inc for valve projects. The other authors report no conflicts.

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