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Incremental value of left ventricular global longitudinal strain in moderate aortic stenosis and reduced left ventricular ejection fraction☆

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ABSTRACT

Background: Moderate aortic stenosis (AS) often coexists with left ventricular (LV) systolic dysfunction and may affect survival through afterload mismatch. Because outcomes are ultimately driven by the condition of the LV, accurate assessment of LV performance is crucial to improve risk stratification. This study investigated the prognostic value of LV global longitudinal strain (GLS) in patients with moderate AS and reduced LV systolic dysfunction.

Methods: Patients with moderate AS (aortic valve area 1.0–1.5 cm^2) and reduced LV ejection fraction (EF) (<50%) were identified. LVGLS was evaluated with speckle-tracking echocardiography. Patients were divided into 2 groups according to an LVGLS value of 11%, based on spline curve analysis. The primary endpoint was all-cause mortality.

Results: A total of 166 patients (mean age 73 ± 11 years, 71% male) were included. The cumulative 1- and 5-year mortality rates were higher in patients with LVGLS <11% (25% and 60%) versus LVGLS ≥11% (10% and 27%) ($p < 0.001$). On multivariable analysis, LVGLS as a continuous variable (HR 0.753; 95% CI 0.673–0.843; $p < 0.001$) and as a categorical variable (<11%) (HR 3.028; 95% CI 1.623–5.648; $p < 0.001$) were independently associated with outcomes, whereas LVEF was not. LVGLS provided additional prognostic information in patients with/without coronary artery disease and with mildly versus severely reduced LVEF. In addition, LVGLS had incremental prognostic value over established risk factors, including LVEF.

Conclusion: The combination of moderate AS and reduced LV systolic dysfunction is associated with a high mortality risk. LVGLS, but not LVEF, is independently associated with mortality and provides incremental prognostic value over established risk factors in patients with moderate AS and reduced LVEF.

1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease, affecting 2–4% of patients older than 65 years [1]. Recent studies have demonstrated that moderate AS is not as benign as previously assumed, with reported outcomes almost as unfavorable as in severe AS [2,3]. Moderate AS often coexists with left ventricular (LV) systolic dysfunction and patients with both moderate AS and reduced LV ejection fraction (EF) exhibit particularly poor outcomes [4,5]. Indeed, moderate AS may further reduce LV systolic dysfunction through afterload mismatch, thereby compromising outcomes. An accurate assessment of LV systolic function therefore seems essential to better risk-stratify patients with moderate AS and reduced LVEF. In addition, although patients with moderate AS and reduced LVEF represent a heterogeneous population, previous papers have treated these patients as a homogeneous population and identification of variables that improve risk stratification in patients with moderate AS and reduced LVEF have not been evaluated. An improved risk stratification of these patients is important, especially

Abbreviations list: AS, aortic stenosis; AVR, aortic valve replacement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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with ongoing trials investigating the potential benefits of transcatheter aortic valve replacement (AVR) in patients with moderate AS and reduced LVEF [6]. Although LV systolic function is most commonly measured with LVEF, LV global longitudinal strain (GLS) has shown to be impaired at an earlier stage in patients with AS [7] and has shown incremental prognostic value over LVEF in patients with severe AS, as well as in patients with heart failure and reduced LVEF [8,9]. The prognostic value of LV GLS in patients with moderate AS and concomitant reduced LVEF, as well as its incremental prognostic value over LVEF, has not been previously investigated. Therefore, the aim of the current study was to evaluate the prognostic value of LV GLS in patients with moderate AS and reduced LVEF.

2. Methods

2.1. Patient population

Patients ≥18 years who presented between 2001 and 2019 with a first diagnosis of moderate AS in the presence of LV systolic dysfunction at the Leiden University Medical Center, Leiden, The Netherlands, were retrospectively identified. Moderate AS was defined as an aortic valve area between 1.0 and 1.5 cm^2 with a peak aortic jet velocity < 4 m/s and mean valve gradient <40 mmHg [10]. Consequently, no patients with severe low-flow, low-gradient AS were included and the definition is in line with previous published articles on moderate AS [11,12]. LV systolic dysfunction was defined as LVEF <50% [13]. Patients with congenital heart disease, heart transplantation, supra -or subvalvular AS, dynamic LV outflow tract obstruction, infectious endocarditis, previous aortic valve surgery, a paced rhythm at the time of echocardiography or inadequate image quality for speckle tracking strain 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. Patient information was collected from the departmental cardiology information system and was retrospectively analyzed. Clinical data included demographic characteristics, cardiovascular risk factors, comorbidities and heart failure medication. Patients were divided into two groups according to LV GLS. An LV GLS value of 11% was chosen, based on spline curve analysis (Fig. 1). The study complies with the Declaration of Helsinki and was approved by the institutional review board. Due to the retrospective design of the study, the medical ethical committee waived the need for written informed consent.

2.2. Transthoracic echocardiography

Echocardiographic examinations were acquired by experienced echocardiographers using commercially available ultrasound systems (Vivid-7, E9 or E95, General Electric Vingmed, Horten, Norway). Images were digitally stored for offline analysis using commercially available software (EchoPac version 113 and 203; GE Medical Systems, Horten, Norway) and retrospectively analyzed according to current guidelines [14]. LV dimensions were assessed in the parasternal long-axis view and LV mass was calculated using the Devereux's formula [14]. LV end-diastolic and end-systolic volumes were measured in the apical 2-chamber and 4-chamber views, and LVEF was calculated according to the Simpson's biplane method [14]. Left atrial volumes were measured by the biplane method of disks [14]. Continuous wave Doppler recordings were obtained to estimate the peak aortic jet velocity from the apical 3- or 5-chamber views and the parasternal right view, if feasible [15]. Mean and peak transvalvular pressure gradients were calculated using the Bernoulli Eq. [15]. Aortic valve area was calculated using the continuity Eq. [15]. Pulsed wave-Doppler recordings of the transmitral flow were used to obtain peak early (E) and late (A) diastolic velocities [16]. Using tissue Doppler imaging of the mitral annulus on the apical 4-chamber view, the e' was measured at both the lateral and septal side, and averaged to calculate the E/e' ratio [16]. The right ventricular

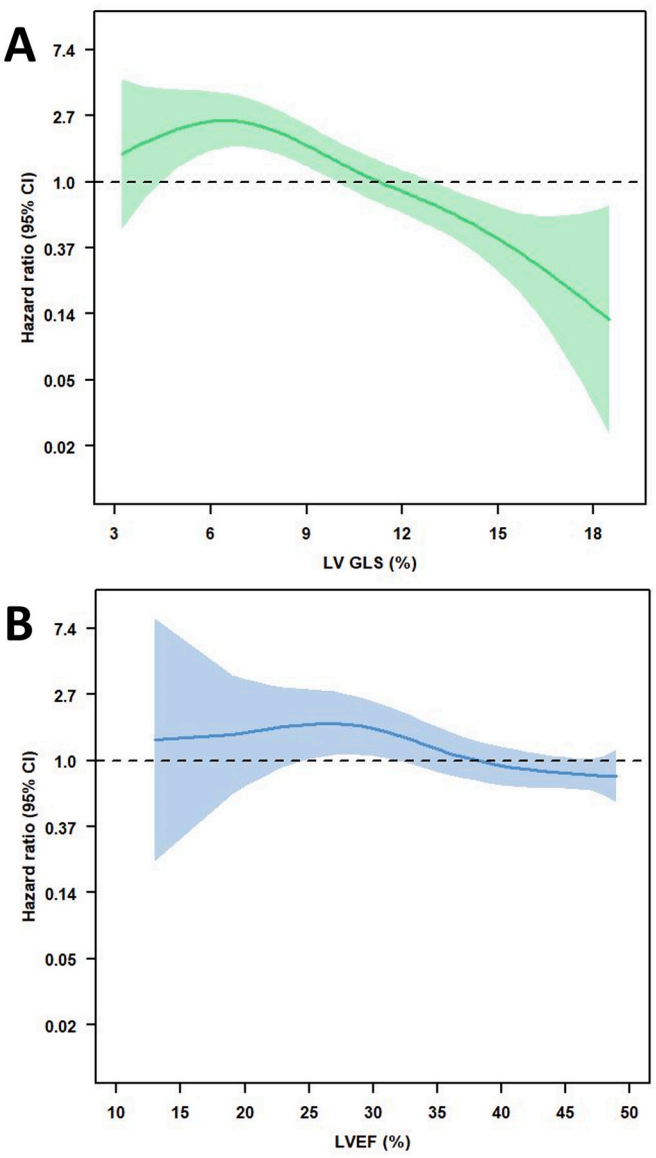

Fig. 1. Spline curves for all-cause mortality.
The first spline curve demonstrates the hazard ratio for all-cause mortality at follow-up according to LV GLS (green line) with 95% confidence intervals (shaded green area) (A). The second spline curve demonstrates the hazard ratio for all-cause mortality at follow-up according to LVEF (blue line) with 95% confidence intervals (shaded blue area) (B).
LVEF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

systolic pressure was calculated from the peak velocity of the tricuspid regurgitant jet, adding the right atrial pressure (determined by the inspiratory collapse and diameter of the inferior vena cava) [14,17]. Tricuspid annular plane systolic excursion was measured with the anatomical M-mode applied on the focused apical 4-chamber view of the right ventricle [17]. LV speckle tracking strain analysis was performed on the apical views (2-, 3-, and 4-chamber) at a frame rate > 40fps, using EchoPac (GE Medical Systems, Horten, Norway) [18]. The region of interest was automatically created and manually adjusted to the myocardial thickness. LV GLS was then calculated by averaging the peak longitudinal strain values of the 17 segments, excluding segments that could not be traced correctly [18]. The values of LV GLS are reported as positive values.

2.3. Clinical endpoints

All patients were followed-up for the primary endpoint 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 [10].

2.4. Statistical analysis

Continuous data are presented as mean ± standard deviation when normally distributed and as median (interquartile range) when not normally distributed. Categorical data are presented as absolute numbers and percentages. Continuous variables were compared using the independent sample Student *t*-test when normally distributed whereas the Mann-Whitney *U* test was used to compare continuous variables that did not adhere to a normal distribution. Categorical variables were compared using the Pearson chi-square test. Changes in hazard ratio (HR) for all-cause mortality across the LV GLS values (as a continuous variable) were investigated by fitting a spline curve. A value of 11% was identified, based on mortality excess (i.e. where the predicted HR was ≥1). Linear regression analysis was performed to identify variables that were significantly associated with LV GLS. Event-free survival curves were generated using the Kaplan-Meier method and differences between groups were analyzed using the log-rank test. Uni- and multivariable analyses of time to events were performed using Cox proportional hazard models with LV GLS introduced as a categorical and a continuous variable. The occurrence of surgical or transcatheter AVR was entered as a time-dependent covariate. For both uni- and multivariable analyses, HRs with 95% confidence intervals (CI) were presented. The proportional hazards assumption was verified through the evaluation of Schoenfeld residuals. To inspect for multicollinearity, the Pearson correlation coefficient was calculated between continuous variables, assuming no significant multicollinearity when the correlation coefficient was <50%. In addition, the Variation Inflation Factor was calculated, assuming no significant multicollinearity when this value was <5. A 2-sided *p* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows, version 25.0 (IBM, Armonk, New York).

3. Results

3.1. Patient characteristics

A total of 166 patients (mean age 73 ± 11 years, 71% male) were included. Baseline clinical and echocardiographic characteristics of the overall population are shown in Table 1. A history of coronary artery disease was seen in 93 (56%) patients, of whom 60 (36%) had a previous myocardial infarction. Atrial fibrillation was present in 61 (37%) patients. Patients with an LV GLS <11% were more likely to have coronary artery disease and atrial fibrillation, had more impaired renal function, and received more diuretics and mineralocorticoid receptor antagonists, compared to patients with an LV GLS ≥11%.

Mean aortic valve area was 1.23 ± 0.13 cm^2, mean pressure gradient 20 ± 8 mmHg and peak aortic jet velocity 2.8 m/s. The median LVEF was 42 (35–47)%, mean LV GLS 11.0 ± 3.5% and mean stroke volume index 38 ± 10 ml/m^2. Patients with an LV GLS <11% had higher LV and left atrial volumes, higher LV mass index, lower LVEF and stroke volume index, more impaired right ventricular systolic dysfunction and higher pulmonary artery pressures. Aortic valve area and pressure gradients were not different between both groups.

3.2. Prognostic value of left ventricular global longitudinal strain

During a median follow-up of 34 (18–67) months, 73 (44%) patients

Table 1
Baseline clinical characteristics and echocardiographic variables.

	Overall population	LV GLS < 11%	LV GLS ≥ 11%	p value
	(*n* = 166)	(*n* = 89)	(*n* = 77)	
Age, years	73 (±11)	73 (±10)	73 (±12)	0.990
Male sex (%)	118 (71%)	67 (75%)	51 (66%)	0.200
BMI, kg/m^2	27.5 (±4.6)	27.4 (±4.5)	27.6 (±4.6)	0.824
BSA, m^2	1.96 (±0.22)	1.98 (±0.23)	1.92 (±0.20)	0.075
Arterial hypertension (%)	122 (74%)	64 (72%)	58 (76%)	0.520
Dyslipidemia (%)	102 (62%)	57 (64%)	45 (59%)	0.524
DM (%)	47 (29%)	28 (32%)	19 (25%)	0.359
Current smoker (%)	19 (13%)	9 (11%)	10 (14%)	0.539
Obesity (%)	43 (26%)	21 (24%)	22 (29%)	0.460
CAD (%)	93 (56%)	62 (70%)	31 (40%)	<0.001
Previous myocardial infarction (%)	60 (36%)	38 (43%)	22 (29%)	0.059
Atrial fibrillation (%)	61 (37%)	39 (44%)	22 (29%)	0.042
Previous stroke (%)	30 (18%)	15 (17%)	15 (20%)	0.661
COPD (%)	22 (13%)	10 (11%)	12 (16%)	0.410
NYHA class III-IV (%)	39 (24%)	23 (26%)	16 (22%)	0.503
Angina (%)	18 (11%)	11 (13%)	7 (9%)	0.504
Syncope (%)	4 (3%)	3 (3%)	1 (1%)	0.387
Beta-blocker (%)	98 (59%)	54 (61%)	44 (58%)	0.717
ACEi or ARB (%)	100 (61%)	56 (63%)	44 (58%)	0.510
MRA (%)	24 (15%)	19 (22%)	5 (7%)	0.007
Diuretic (%)	89 (54%)	58 (65%)	31 (41%)	0.002
Statin (%)	102 (62%)	59 (66%)	43 (57%)	0.201
Aspirin (%)	68 (41%)	41 (46%)	27 (36%)	0.170
Oral anticoagulation (%)	65 (39%)	38 (43%)	27 (36%)	0.347
eGFR, mL/min/1.73m^2	68 (±28)	63 (±26)	74 (±28)	0.015
Hemoglobin, g/dl	13.0 (±1.9)	12.9 (±1.8)	13.2 (±2.0)	0.295
LV ESV, ml	73 (52–100)	91 (69–113)	61 (42–76)	<0.001
LV ESVi, ml/m^2	36 (29–51)	45 (35–56)	30 (21–40)	<0.001
LV EDV, ml	129 (95–163)	144 (115–177)	115 (82–141)	<0.001
LV EDVi, ml/m^2	65 (50–81)	72 (60–86)	58 (41–72)	<0.001
LVEF, %	42 (35–47)	38 (30–42)	45 (42–48)	<0.001
LV GLS, %	11.0 (±3.5)	8.3 (±1.8)	14.1 (±2.0)	<0.001
LVMI, g/m^2	128 (±38)	138 (±38)	116 (±34)	<0.001
LAVi, ml/m^2	41 (33–52)	45 (36–57)	37 (29–46)	<0.001
E/e'	15 (12–21)	16 (12–24)	15 (11–18)	0.057
Bicuspid valve, %	17 (10%)	6 (7%)	11 (14%)	0.110
AVA, cm	1.23 (±0.13)	1.25 (±0.14)	1.22 (±0.12)	0.155
AVAi, cm/m^2	0.64 (±0.09)	0.64 (±0.10)	0.64 (±0.08)	0.923
Peak aortic jet velocity, m/s	2.8 (±0.55)	2.7 (±0.55)	2.9 (±0.55)	0.100
Aortic mean pressure gradient, mmHg	20 (±8)	19 (±8)	21 (±9)	0.195
Stroke volume index, ml/m^2	38 (±10)	36 (±10)	41 (±9)	0.004
TAPSE, mm	20 (±5)	19 (±5)	21 (±5)	0.014
PASP, mmHg	33 (26–41)	36 (27–48)	31 (25–37)	0.006

Values are presented as mean ± SD, median (IQR) or n (%).
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AVA = aortic valve area; AVAi = aortic valve area index; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; EDV = end-diastolic volume; EDVi = end-diastolic volume index; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESV = end-systolic volume; ESVi = end-systolic volume index; GLS = global longitudinal strain; LAVi = left atrium volume index; LV = left ventricular; MI = mass index; MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.
Obesity was defined as BMI ≥ 30 kg/m^2.

died. The cumulative 1-, 3- and 5-year survival rates were 82%, 68% and 55%, respectively. Sixty-eight (41%) patients underwent AVR at follow-up (transcatheter AVR: 31 (19%); surgical AVR: 37 (22%)). The clinical and echocardiographic characteristics of the patients who underwent AVR are shown in Table S1. Survival rates were significantly lower in patients with LV GLS <11% when compared to patients with LV GLS ≥11%. ($p < 0.001$) (Fig. 2). Survival rates were 75% at 1 year, 55% at 3 years and 40% at 5 years among patients with LV GLS <11%, whereas survival rates were 90% at 1 year, 84% at 3 years and 73% at 5 years among patients with LV GLS ≥11%. The Kaplan-Meier curves according to LV GLS in patients with versus without coronary artery disease are shown in Fig. S1, whereas the Kaplan-Meier curves according to LV GLS in patients with mildly reduced (41–49%) versus reduced LVEF (≤40%) [13] are shown in Fig. S2. Both figures show the incremental value of LV GLS to identify high risk patients.

The uni -and multivariable Cox regression analyses are shown in Table 2. On univariable analysis, LV GLS as a continuous variable (HR 0.841; 95% CI 0.785–0.902; $p < 0.001$) and as a categorical variable (HR 2.871; 95% CI 1.733–4.756; $p < 0.001$) were both significantly associated with outcomes. On univariable analysis, LVEF as a continuous variable was also significantly associated with outcomes (HR 0.972; 95% CI 0.946–0.998; $p = 0.034$) (Table S1). On multivariable analysis, both LV GLS as a continuous variable (HR 0.753; 95% CI 0.673–0.843; $p < 0.001$) as well as a categorical variable (HR 3.028; 95% CI 1.623–5.648; p < 0.001) remained independently associated with outcomes, after adjusting for age, sex, coronary artery disease, atrial fibrillation, LVEF and AVR as a time dependent covariable. In a sensitivity analysis, these findings were confirmed using a second, third and fourth multivariable model (Table 2). In contrast, LVEF was not independently associated with outcomes on any of these multivariable models (Table S2). The hazard ratio for each covariable is provided in Table S3. Fig. 1 also demonstrates that there was a more or less linear relationship between LV GLS and the HR of mortality, whereas no clear relationship was shown between LVEF and the HR of mortality.

Linear regression analysis was performed to identify variables that were associated with LV GLS. According to this analysis, coronary artery disease (ß -0.276; 95% CI -2.952 to −0.889; $p < 0.001$), atrial fibrillation (ß -0.156; 95% CI -2.210 to −0.027; $p = 0.045$), estimated glomerular filtration rate (β 0.207; 95% CI 0.006 to 0.047; $p = 0.011$), peak aortic jet velocity (β 0.159; 95% CI 0.037 to 0.1.944; $p = 0.042$) and aortic mean pressure gradient (ß 0.125; 95% CI 0.007 to 0.0045; $p = 0.031$) were significantly associated with LV GLS. On multivariable analysis however, only CAD remained independently associated with LV GLS (ß -0.210; 95% CI -2.677 to −0.325; $p = 0.013$) (Table S4).

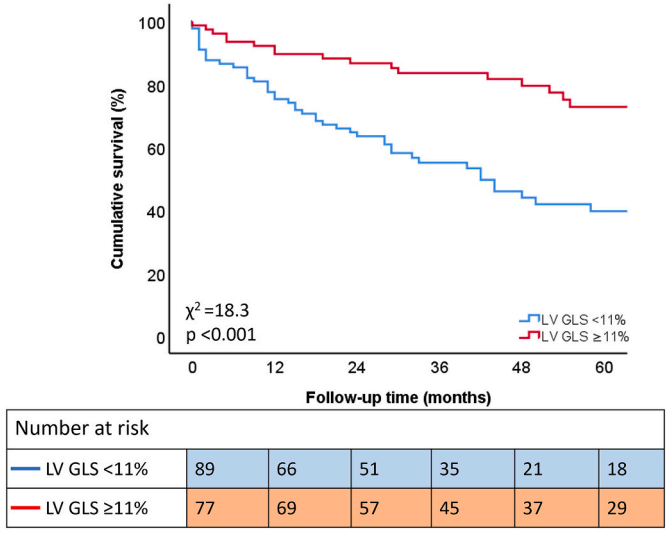

Fig. 2. Kaplan Meier curve for all-cause mortality.
LV GLS = left ventricular global longitudinal strain.

Table 2
Uni -and multivariable Cox regression analysis.

	All-cause mortality	
	HR (95% CI)	*p*-value
	Univariable analysis	
LV GLS, % (continuous variable)	0.841 (0.785–0.902)	<0.001
LV GLS ≥11%	*Reference group*	
LV GLS <11%	2.871 (1.733–4.756)	<0.001
	Multivariable analysis*	
LV GLS, % (continuous variable)	0.753 (0.673–0.843)	<0.001
LV GLS ≥ 11%	*Reference group*	
LV GLS < 11%	3.028 (1.623–5.648)	<0.001
	Multivariable analysis**	
LV GLS, % (continuous variable)	0.833 (0.767–0.905)	<0.001
LV GLS ≥ 11%	*Reference group*	
LV GLS < 11%	2.705 (1.509–4.848)	0.001
	Multivariable analysis***	
LV GLS, % (continuous variable)	0.754 (0.677–0.839)	<0.001
LV GLS ≥ 11%	*Reference group*	
LV GLS < 11%	3.520 (1.951–6.351)	<0.001
	Multivariable analysis****	
LV GLS, % (continuous variable)	0.797 (0.708–0.897)	<0.001
LV GLS ≥ 11%	*Reference group*	
LV GLS < 11%	2.755 (1.448–5.241)	0.002

* Adjusted for age, sex, coronary artery disease, atrial fibrillation, left ventricular ejection fraction and aortic valve replacement as a time dependent covariable.
** Adjusted for age, previous myocardial infarction, estimated glomerular filtration rate, left atrial volume index, aortic valve area index and aortic valve replacement as a time dependent covariable.
*** Adjusted for age, arterial hypertension, diabetes mellitus, New York Heart Association functional class III-IV, left ventricular ejection fraction and aortic valve replacement as a time dependent covariable.
**** Adjusted for age, left ventricular end-systolic volume, left ventricular mass index, tricuspid annular plane systolic excursion, pulmonary artery systolic pressure and and aortic valve replacement as a time dependent covariable.

3.3. Incremental prognostic value of LV GLS

To determine the incremental prognostic value of LV GLS in addition to currently used clinical and echocardiographic parameters, a likelihood ratio test was performed. The addition of LVEF to the baseline model showed no significant increase in the chi-square value ($p = 0.321$). In contrast, the addition of LV GLS to the baseline model and LVEF showed a significant increase in the chi-square value (chi-square difference 12.8, $p < 0.001$), demonstrating the incremental prognostic value of LV GLS over LVEF in patients with moderate AS and reduced LVEF (Fig. S3).

4. Discussion

The main findings of the current study, which included patients with moderate AS and reduced LVEF, can be summarized as follows: 1) the combination of moderate AS and reduced LVEF is associated with very high mortality rates; 2) LV GLS is independently associated with survival; and 3) LV GLS has incremental prognostic value over LVEF.

4.1. Outcomes of patients with moderate AS and reduced LVEF

Recent observational studies have shown that moderate AS is associated with an increased risk of adverse events [2,3]. In particular, patients with moderate AS and reduced LVEF seem to have very poor outcomes [4,5]. In 305 patients with moderate AS (aortic valve area 1.0–1.5 cm^2) and LV systolic dysfunction (LVEF <50%), van Gils and colleagues showed that the rate of all-cause death or heart failure hospitalization was 48% and the mortality rate 36%, at 4 years follow-up

[5]. These results are in line with the observations in the current study, which showed 3 -and 5-year mortality rates of 32% and 45%, respectively.

Moderate AS and LV systolic dysfunction often coexist, and the AS itself may contribute to a reduced LVEF through afterload mismatch. The importance of looking at both the vascular and valvular afterload in patients with moderate AS was highlighted by Briand et al., who showed that the valvulo-arterial impedance in patients with moderate AS and decreased arterial compliance was similar to patients with severe AS and a normal arterial compliance [19]. Because arterial stiffness is often increased in patients with heart failure and reduced LVEF but may be difficult to treat with guideline-directed medical therapy (especially in the elderly), treatment of the increased valvular afterload by AVR becomes an attractive strategy. The final purpose is to reduce the total afterload imposed on the LV, thereby improving LV performance. As such, a sensitive and accurate assessment of LV performance is essential to better risk-stratify patients with moderate AS and to evaluate the potential effects of AVR on LV performance.

4.2. LV GLS in moderate AS and reduced LVEF

Quantifying LV systolic function is vital to risk stratify patients with heart failure and reduced LV performance [13]. In contrast to LVEF, which only represents a volumetric change, LV GLS permits the quantification of active myocardial deformation and is a more robust marker of LV performance than LVEF [20]. In addition, LV GLS has shown a good correlation with the extent of myocardial fibrosis in patients with heart failure (both on histology and cardiac magnetic resonance imaging) [21,22]. In a large study, including 1065 patients with heart failure and reduced LVEF, Sengelov et al. showed that LV GLS was an independent predictor of mortality and a superior prognostic marker compared to other echocardiographic parameters, including LVEF [9].

AS progression is accompanied by compensatory LV remodeling. However, especially in patients with pre-existing LV systolic dysfunction, an afterload mismatch occurs, resulting in an increased wall stress and a further reduction in LV performance [23]. An increased wall stress reduces subendocardial perfusion and increases myocardial oxygen consumption, thereby accelerating the formation of replacement fibrosis, which is often already present in patients with heart failure and reduced LVEF [24,25]. LV GLS has shown to correlate well with the extent of myocardial fibrosis in patients with severe AS [26]. In addition, LV GLS has shown to be a strong prognostic marker in patients with severe AS and a wide range of LVEF [8,27], as well as in patients with moderate AS and preserved LVEF [28]. The prognostic value of LV GLS in patients with moderate AS and concomitant LV systolic dysfunction however, has not been previously investigated.

The results of the current study show a strong, independent association between LV GLS and mortality in patients with moderate AS and reduced LVEF. Interestingly, LVEF was not independently associated with outcomes. In addition, the spline curves show that the relationship between LV GLS and mortality was more or less linear, whereas no relationship could be found between LVEF and mortality. Finally, LV GLS provided incremental prognostic value over established risk factors, whereas this was not the case for LVEF.

4.3. Clinical implications

AVR is currently indicated for patients with severe AS and LV systolic dysfunction, but not for moderate AS [10]. Nonetheless, patients with moderate AS and impaired LVEF have a dismal prognosis [4,5] and this could potentially be explained by the observation that patients with LV systolic dysfunction are more vulnerable to an increased valvular afterload. Although the potential benefit of AVR in patients with moderate AS and reduced LVEF remains unknown, patient-prosthesis mismatch after AVR (which often corresponds to moderate AS) has been associated with worse outcomes in patients with reduced LVEF [29]. In addition, a study of the Duke Echocardiography Database reported a mortality benefit with AVR in patients with moderate AS and reduced LVEF [30]. Accurate assessment of LV systolic function seems crucial to improve risk stratification of patients with moderate AS and reduced LVEF, to select patients who may potentially benefit from AVR and to evaluate the LV response after treatment. In this regard, the current study shows that LV GLS provides superior information over LVEF. In patients with a very low LV GLS (i.e. <11%), the first step should be to optimize heart failure therapy and to identify all comorbidities (e.g. coronary artery disease, diabetes mellitus, arterial hypertension, …) that have an impact on LV GLS as well. Future studies are needed to investigate whether AVR could further benefit patients who are well treated for their comorbidities but still have a very low LV GLS. The potential benefit of afterload reduction with early transcatheter AVR in patients with moderate AS and LV systolic dysfunction is currently being evaluated in the Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure (TAVR UNLOAD) trial [6].

4.4. Limitations

The present study was a single center, retrospective study. LV GLS is vendor-dependent and values cannot be compared directly across different echo platforms. Due to the retrospective design, calculation of the valvulo-arterial impedance was not feasible. The definition of moderate AS based on AVA was chosen to avoid inclusion of patients with low-flow, low-gradient severe AS. However, some patients with mild AS may have been included, as dobutamine stress echocardiography is not routinely performed to differentiate between true moderate and pseudo-moderate low-flow low-gradient AS. Data on AS progression were not available. Sub-analyses on cardiovascular an non-cardiovascular mortality were not performed. Future studies are needed to investigate whether the non-invasive assessment of myocardial work by pressure-strain loops can provided incremental value in patients with moderate AS and reduced LVEF.

5. Conclusion

In patients with moderate AS and reduced LVEF, LV GLS is independently associated with all-cause mortality and provides incremental prognostic value over established risk factors, whereas this was not the case for LVEF.

Disclosures

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Data availability statement

Data are available upon reasonable request.

Author statement

Jan Stassen: conceptualization, acquisition, analysis, interpretation of data, writing - original draft; visualization; Gurpreet K Singh:

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.11.035.

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