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Global longitudinal strain for prediction of mortality in ST-segment elevation myocardial infarction and aortic stenosis patients: two sides of the same coin

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Abstract. – OBJECTIVE: Global longitudinal strain (GLS) predicts major adverse events in ST-segment elevation myocardial infarction (STEMI) and aortic stenosis (AS). Different cut-off values and different end-points have been proposed for prognostic stratification. We aimed to verify whether a single GLS cut-off value can be used to identify increased risk of all-cause death in STEMI and AS.

PATIENTS AND METHODS: One-hundred-seventeen successfully treated first STEMI (age 63.8±12.5 yrs, 70% men) and 64 AS (age 80.3±6.9 yrs, 44% men) patients, undergoing echocardiography before discharge and before AS treatment, respectively, were retrospectively analyzed. GLS was analyzed, together with pulmonary artery systolic pressure (PASP), Killip class and Genereux stage. End-point was all-cause death at 6-month follow-up.

RESULTS: All-cause death occurred in 4 (3.4%) STEMI and 5 (7.8%) AS patients (*p*=ns). AS patients who died had GLS similar to died STEMI patients (9.7±2.1 *vs.* 11.3±1.7, *p*=ns). GLS cut-off ≤12% predicted death with 89% sensitivity and 70% specificity (AUC 0.84, *p*=0.001): STEMI and AS patients with GLS ≤12% had worse survival than STEMI and AS patients with GLS >12% (log-rank *p*=0.001). At multivariate Cox regression analysis, lower GLS values independently predicted death (HR 0.667, 95% CI 0.451-0.986, *p*=0.042), and the prediction model was improved when GLS was added to old age, significant comorbidities, PASP and Killip/Genereux stage (χ^2 6.691 *vs.* 1.364, *p*=0.010).

CONCLUSIONS: Died patients with STEMI and AS show similar values of GLS. A unique cut-off value of GLS can reliably be used to stratify the risk of all-cause death at 6-month follow-up in both two clinical settings.

Key Words:
Global longitudinal strain, ST-segment elevation myocardial infarction, Aortic stenosis, All-cause death, Echocardiography.

Introduction

Non-invasive evaluation of left ventricular (LV) systolic function is one of the most pivotal measures in clinical cardiology, as it predicts outcome. In the last years, it has been widely established that global longitudinal strain (GLS) reflects intrinsic LV contractility better than LV ejection fraction (LVEF)[1] and is able to predict prognosis in different cardiovascular diseases (CVD)[2].

ST-segment elevation myocardial infarction (STEMI) and aortic stenosis (AS) are two important clinical settings in which GLS is currently considered a powerful prognostic indicator[3-6]. However, the cut-off of GLS proposed to predict major adverse events differs among previous studies, ranging from 10% to 15.8% in absolute values[7,8], with the variability possibly related to technical differences in GLS measurements among different echocardiographic vendors[9], but also to different clinical end-points

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used in different studies. Moreover, whether the cut-off of GLS to predict clinical events is different in patients with different heart diseases is hitherto unknown.

On the other hand, STEMI and AS seem to share a common tale intriguingly: indeed, in STEMI patients, although GLS improves over time[10], its value assessed early after revascularization and not at mid-term follow-up predicts prognosis[11]. Similarly, in AS patients, despite an overall improvement of GLS after aortic valve replacement (AVR)[12], only GLS values assessed before treatment are related to outcome[13], in addition to Genereux stage[8].

A unique prognostic cut-off value for GLS would, in fact, be desirable for risk stratification in different clinical settings, similar to what was established for LVEF (i.e., <40%)[14].

Thus, in this study, we aimed to investigate whether a unique GLS cut-off value may consistently predict prognosis in populations of patients with two different heart diseases, STEMI and AS.

Patients and Methods

Patient Populations

A consecutive series of patients with the first successfully treated STEMI and a consecutive series of patients with symptomatic severe AS, scheduled for aortic valve replacement (AVR), referred to Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, from February 2020 to May 2021, were retrospectively considered for enrollment.

STEMI was diagnosed based on the presence of typical chest pain lasting at least 20 minutes, associated with persistent ST-segment elevation (0.1 mV in 2 or more contiguous peripheral leads or 0.2 mV in 2 or more contiguous precordial leads) and elevation of cardiac troponin (at least one value above the 99th percentile of the upper reference limit)[15]. All patients were treated by primary or rescue percutaneous coronary intervention (PCI) of the culprit coronary artery within 12 hours of symptom onset, with subsequent completion of coronary revascularization by PCI in cases of multivessel coronary artery disease (CAD). In order to ensure that all studied patients were optimally treated, by avoiding potential bias in GLS measurements related to incomplete coronary revascularization, exclusion criteria included: (1) achievement of a thrombolysis in myocardial infarction (TIMI) flow grade ≤ 2 on culprit and non-culprit coronary arteries; (2) concomitant moderate/severe mitral and/or aortic valve disease; (3) previous percutaneous or surgical myocardial revascularization; (4) residual significant coronary artery stenosis that could not be revascularized.

Patients with AS were diagnosed as having symptomatic severe aortic stenosis (denoted by an aortic valve area <1 cm^2 or <0.6 cm^2/m^2 at echocardiography) and an expected survival >1 year[16]. All patients were treated by transcatheter aortic valve intervention (TAVI) or surgical aortic valve replacement (SAVR), based on a heart team decision. Patients with concomitant CAD, characterized by stenosis >70% in any proximal segment, underwent percutaneous or surgical revascularization in addition to AVR[16]. Patients with (1) a previous aortic valve surgery, (2) other concomitant valve repair/replacement, (3) acute infective endocarditis, or (4) predominantly aortic valve regurgitation at the time of enrollment were excluded.

Patient demographic and clinical data were gathered from electronic records of our hospital database (SI DHE Policlinico Gemelli, Rome, Italy, and Trackcare 2021.7 InterSystems Corporation, Cambridge, MA, USA). Data analyzed in this retrospective study were collected in two large registries carried out at our Center in patients with STEMI and patients with AS; both registries obtained approval from the Ethics Committee of Catholic University of the Sacred Heart (NCT02502747 and Prot. N.0014497/21, respectively). A written informed consent to be included in the registries and make available her/his data for any subsequent analysis was obtained from patients at the time of enrolment. Yet, oral informed consent for inclusion in this study was furtherly obtained from patients or relatives (in the case of dead patients) during follow-up telephone calls.

Echocardiography

All echocardiograms were performed using Philips CVX or Epiq ultrasound machines (Philips, Milan, Italy), equipped with a 3.5 MHz probe, prior to discharge in STEMI patients and prior to AVR in AS patients. All echocardiograms were performed, and images were stored by two experienced echocardiographers (L.M. for STEMI patients, E.R. for AS patients), whereas digitally stored images and clips were analyzed by another expert echocardiographer (G.D.), who was blinded to all clinical and

follow-up data. All of the echocardiographers had European certification of competency for transthoracic echocardiography, and no sonographer performed the exams. LV end-diastolic and end-systolic volumes and left atrial volume were indexed for body surface area (EDVi, ESVi and LAVi, respectively)[17]. LVEF were estimated using Simpson's biplane method[17], and a wall motion score index (WMSI) was obtained by visually assessing the LV contractility of each of the 16 myocardial segments of the LV, which were scored as 1 = normokinetic, 2 = hypokinetic, 3 = akinetic, or 4 = dyskinetic[17]. E-wave peak velocity from the mitral inflow profile and e' velocity from the septal and lateral mitral valve annuli were obtained by pulsed-wave Doppler and tissue Doppler, respectively, and averaged to derive the E/e' ratio. The pulmonary artery systolic pressure (PASP) was estimated as recommended[18]. Two-dimensional speckle-tracking echocardiography was used to measure GLS. Briefly, 4-chamber, 2-chamber, and 3-chamber views were acquired, automatically analyzed (using Tomtec software, Philips, Milan, Italy) as the magnitude of strain at the aortic valve closure, and averaged. Suboptimal images with inadequate tracking were excluded from the analysis. For practical purposes, GLS values were reported as absolute numbers throughout the text.

In order to determine the Genereux stage[19], additional data were collected in AS patients, including LV mass[17], mitral and tricuspid regurgitation severity[18], and tricuspid annular plane systolic excursion[18]. Finally, in order to check the effectiveness of AVR, mean aortic gradients were measured prior to and 24 hours after intervention[18].

Clinical Assessment and Risk Scores

Data about the number of diseased coronary arteries, the presence of chronic obstructive pulmonary disease (COPD), and other significant comorbidities, such as previous and current neoplasms, inflammatory or autoimmune diseases, and cerebrovascular events, were recorded, along with pharmacological therapy. The glomerular filtration rate (GFR) was calculated on admission in all patients by the Cockcroft-Gault formula[20].

As clinical risk scores, Killip class[21], instead of GRACE score[22] was determined at admission in STEMI patients, whereas Genereux classification[19] was used for AS patients.

Follow-Up and End-Point

The unique endpoint of the study was all-cause death at a follow-up of 6 months. The vital status of patients was ascertained by a cardiologist through telephone contact with the patients or their closest relatives.

Statistical Analysis

Statistical analysis was performed using the SPSS Statistics Version 20.0 (IBM Corp., Armonk, NY, USA) software for Windows. After checking for normal distribution, data were presented as mean ± standard deviation (SD) for continuous variables and as percentage for categorical variables and compared between groups by Student *t*-test or Chi-square test, respectively. A ROC curve analysis was made to identify the best cut-off value of GLS in the overall study population. To calculate cumulative survival rates, a Kaplan-Meier analysis was performed. To compare survival rates between the groups of STEMI and AS patients below and above the GLS cut-off value, the log-rank test was applied. Univariable Cox proportional hazard regression analyses were performed to assess the association of GLS and other relevant variables with all-cause mortality. Univariate predictors with $p \leq 0.10$ were included in multivariable Cox regression models. The hazard ratio (HR) and 95% confidence interval (CI) were obtained for all included variables. To assess the incremental prognostic value of GLS over the already known prognostic predictors, the changes in χ^2 of regression models after adding GLS were assessed. A two-sided p-value <0.05 was considered statistically significant throughout the study.

Results

General Characteristics

Overall, 226 STEMI and 80 AS patients were identified in the considered time period as potentially recruitable for the study. However, 109 patients in the STEMI population and 16 in the AS population did not fulfill the inclusion criteria and were, therefore, excluded (Figure 1). Thus, 117 STEMI and 64 AS patients formed the populations of this study. The general characteristics of the two study cohorts are summarized in Table I.

Among STEMI patients, 64 (55%) had an anterior and 53 (45%) a non-anterior infarction. The symptoms-to-balloon time for PCI was 6.4±5.3 hours and peak troponin 80.543±47.324 ng/L.

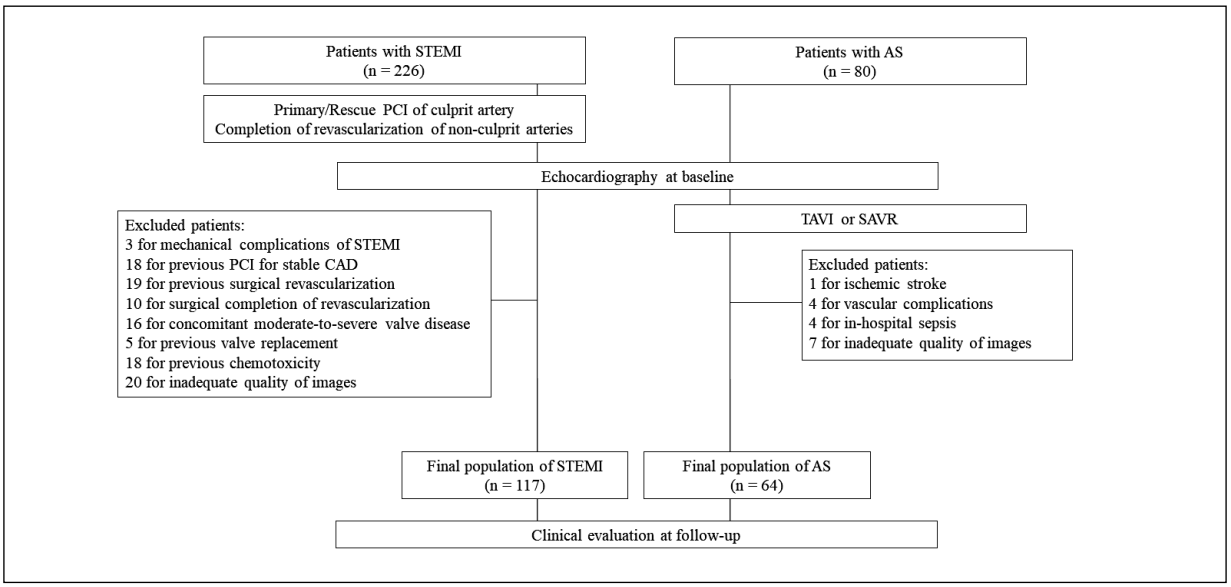

Figure 1. Flowchart of the study.

Among AS patients, 52 (81%) underwent TAVI and 12 (19%) underwent SAVR. The mean aortic gradient decreased from 50.3±10.9 mmHg before to 8.5±3.7 mmHg after AVR (p<0.001).

As compared to the STEMI population, patients with AS were older (p<0.001), more frequently female (p=0.001), and presented a higher prevalence of hypertension (p=0.001) and COPD (p=0.001), and a lower number of diseased coronary arteries (p<0.001) and a lower GFR (p<0.001); furthermore, at discharge, AS patients less frequently received beta-blockers (p<0.001), renin-angiotensin-aldosterone system inhibitors (p<0.001) and statins (p<0.001).

About echocardiographic findings, AS patients showed smaller EDVi (p=0.029) and ESVi (p<0.001), and a better LVEF (p<0.001) and WMSI (p<0.001), but worse GLS (p=0.010), LAVi (p<0.001), E/e' ratio (p<0.001) and PASP (p<0.001) compared to patients with STEMI.

Comparison between Survived and Died Patients

During the 6-month follow-up, 9 patients (5%) died in the total population of patients. Mortality did not differ significantly between STEMI and AS cohorts (3.4% *vs.* 7.8%, respectively, p=0.19) (Table I). In the STEMI population, age was older (p=0.022) and GLS values were lower (p=0.012) in died compared to survived patients, but there were no significant differences between the 2 groups in all the other clinical and echocardiographic data (Table I).

In the AS cohort, died patients also did not show significant differences compared to survived patients for most clinical data, except for a lower prevalence of hypertension (p=0.014), a tendency to a lower GFR (p=0.072) and a higher prevalence of Genereux stage 4 (p=0.07). Again, only GLS, among echocardiographic variables, showed lower values in died compared to survived AS patients (p=0.002), whereas neither the mean aortic gradient at baseline nor after AVR differed between the 2 groups (48.4±16.3 *vs.* 51.7±11.5 mmHg; p=0.55, and 11±3.6 *vs.* 8.1±3.9 mmHg; p=0.22, respectively).

When survived patients were compared between STEMI and AS groups, differences in clinical and echocardiographic data found in the overall cohorts were maintained (Table I). On the contrary, died STEMI patients were similar to died AS patients. Particularly, the GLS value of died patients was comparable between the two study cohorts (Table I, Figure 2).

GLS and Survival Analysis

By considering the two study cohorts together, a cut-off value of GLS ≤12% was found to predict all-cause death with 89% sensitivity and 70% specificity (AUC 0.84, p=0.001) (Figure 3).

Thus, based on such a cut-off, the two study cohorts were stratified into STEMI patients with

Table I. General characteristics of the study populations.

	STEMI				AS			
	Total (n = 117)	Survived (n = 113)	Died (n = 4)	p	Total (n = 64)	Survived (n = 59)	Died (n = 5)	p
Age, yrs, mean±SD	63.8±12.5	63.3±12.3	77.8±6	0.022	80.3±6.9*	80.4±6.9†	80.2±6.5	0.96
Male, n (%)	82 (70)	78 (69)	4 (100)	0.18	28 (44)*	25 (42)†	3 (60)	0.45
Hypertension, n (%)	66 (56)	64 (57)	2 (50)	0.74	52 (81)*	50 (85)†	2 (40)	0.014
Diabetes, n (%)	29 (25)	28 (25)	1 (25)	0.74	19 (30)	18 (30)	1 (20)	0.62
Dyslipidemia, n (%)	50 (43)	48 (42)	2 (50)	0.41	30 (47)	28 (47)	2 (40)	0.75
Smoking, n (%)	55 (47)	53 (47)	2 (50)	0.51	21 (33)	18 (30)†	3 (60)	0.18
Beta-Blockers, n (%)	117 (100)	113 (100)	4 (100)		36 (56)*	33 (56)	3 (60)	0.86
Antiplatelet/anticoagulant therapy, n (%)	117 (100)	113 (100)	4 (100)		64 (100)	59 (100)	5 (100)	
RAAS inibitors, n (%)	113 (96)	109 (96)	4 (100)	0.70	46 (72)*	43 (73)	3 (60)	0.54
Calcium-antagonist, n (%)	18 (15)	18 (16)	0	0.39	7 (11)	6 (10)	1 (20)	0.50
Statins, n (%)	115 (98)	111 (98)	4 (100)	0.79	34 (53)*	32 (54)	2 (40)	0.54
N. diseased coronary arteries, mean±SD	1.6±0.7	1.6±0.7	1.7±0.9	0.60	0.6±0.8*	0.6±0.8	0.8±0.8	0.62
COPD, n (%)	11 (9)	10 (9)	1 (24)	0.28	18 (28)*	16 (27)	2 (40)	0.54
Other significant comorbidities, yes/no, n (%)	42 (36)	39 (34)	3 (75)	0.10	26 (41)	23 (39)	3 (60)	0.36
GFR, ml/min, mean±SD	82.3±21.4	82.2±21.3	88±30.3	0.64	65±25.1*	66.8±25.4†	45.7±8.9§	0.072
Killip class				0.018				
I	80 (68)	79 (70)	1 (25)	0.06				
II	32 (27)	30 (26)	2 (50)	0.29				
III	3 (3)	2 (2)	1 (25)	0.006				
IV	2 (2)	2 (2)	0	0.77				
Genereux stage								0.37
0					3 (5)	3 (4)	0	0.65
1					10 (16)	10 (17)	0	0.32
2					31 (48)	29 (49)	2 (40)	0.70
3					17 (26)	15 (25)	2 (40)	0.46
4					3 (5)	2 (3)	1 (20)	0.07
EDVi, mL/m^2, mean±SD	52±12.4	52.1±12.1	49.6±21.7	0.70	47.7±12.8*	47.6±12.1†	48.7±21.5	0.85
ESVi, mL/m^2, mean±SD	26.4±10.1	26.5±10.2	22.5±8.3	0.44	20.6±10.6*	20.4±9.7†	22.5±19.6	0.68
LVEF, %, mean±SD	49.7±10.3	49.6±10.4	53.7±5	0.43	58.9±8.6*	59±7.7†	58.4±17.6	0.88
WMSI, mean±SD	1.6±0.4	1.6±0.4	1.5±0.5	0.58	1.1±0.3*	1.1±0.2†	1.3±0.7	0.11
GLS, %, mean±SD	14.9±4.6	15.1±4.6	11.3±1.7	0.012	13.3±3.1*	13.7±3.1†	9.7±2.1	0.002
E/e', mean±SD	10.6±4	10.7±4.1	9.8±2.2	0.67	15.3±5.9*	15.3±6.1†	14.8±3.8	0.86
LAVi, ml/m^2, mean±SD	32.3±9.7	32.2±9.4	34.2±17.1	0.68	48.6±15*	48.3±15†	52.4±16.8	0.56
PASP, mmHg, mean±SD	31.2±8.7	31.3±9.1	35±0	0.69	38.6±11*	37.8±10.9†	46±10.8	0.11

AS = aortic stenosis, EDVi = end-diastolic volume indexed for body surface area; ESVi = end-systolic volume indexed for body surface area; GFR = glomerular filtration rate; GLS = global longitudinal strain; LAVi = left atrial volume indexed for body surface area; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; SD = standard deviation; STEMI = ST-segment elevation myocardial infarction; WMSI = wall motion score index. *p<0.05 *vs*. total STEMI; †p<0.05 vs. Survived STEMI; §p<0.05 *vs*. Died STEMI.

GLS>12%, STEMI patients with GLS≤12%, and AS patients with GLS>12%, AS patients with GLS≤12%. Kaplan-Meier survival curves for all-cause death per cohort and GLS cut-off are depicted in Figure 4: an overall significant difference in survival rates was found among strata (log-rank p = 0.001), with most of the differences between patients with GLS≤12% and patients with GLS >12%.

Table II summarizes the results of Cox proportional hazard analyses for all-cause death: interestingly, on multivariate analysis, only GLS predicted all-cause death at 6-month follow-up (HR 0.667, 95% CI 0.451-0.986; p=0.042). Indeed, by adding GLS to a baseline model (Model 1) consisting of clinical characteristics associated with prognosis, a significant increase of χ^2 was found (6.691 *vs.* 1.364, p=0.001) (Figure 5).

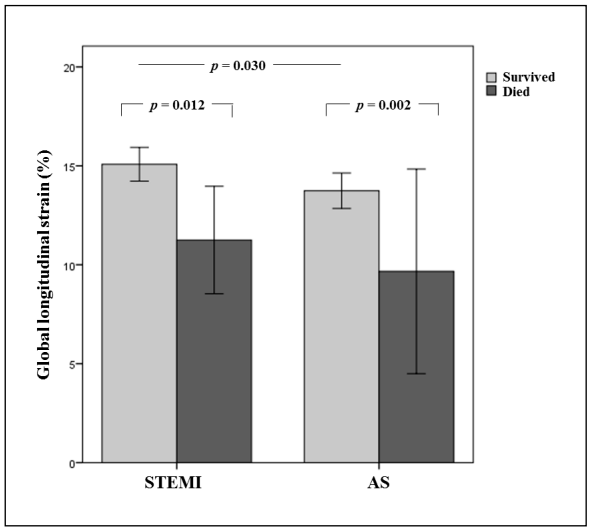

Figure 2. Differences in baseline GLS between survived and dead patients belonging to the two cohorts.

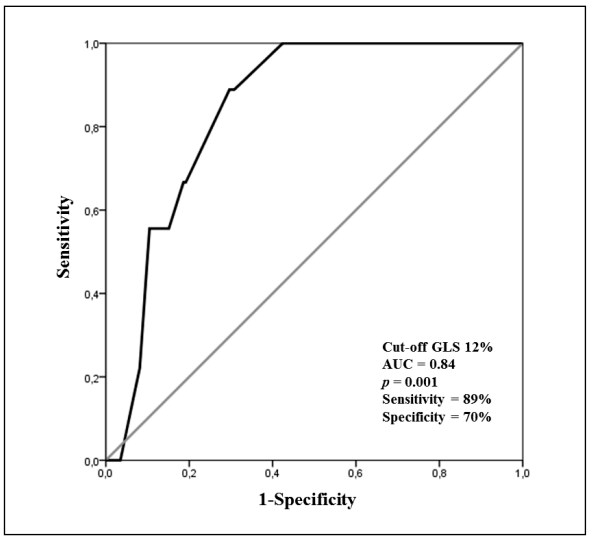

Figure 3. ROC curve analysis for a cut-off of baseline GLS predicting all-cause death at 6-month follow-up.

Discussion

To the best of our knowledge, this is the first study that aims to assess whether a unique cut-off value of GLS can be used as a predictor of prognosis in different clinical settings, such as STEMI and severe AS. Our results show that, despite different pathophysiology and successful treatments, patients with STEMI and those with severe AS who died within 6 months from discharge shared similar lower values of GLS at baseline, compared with surviving patients. Overall, a cut-off value of GLS ≤12% predicted all-cause death at follow-up independently of the

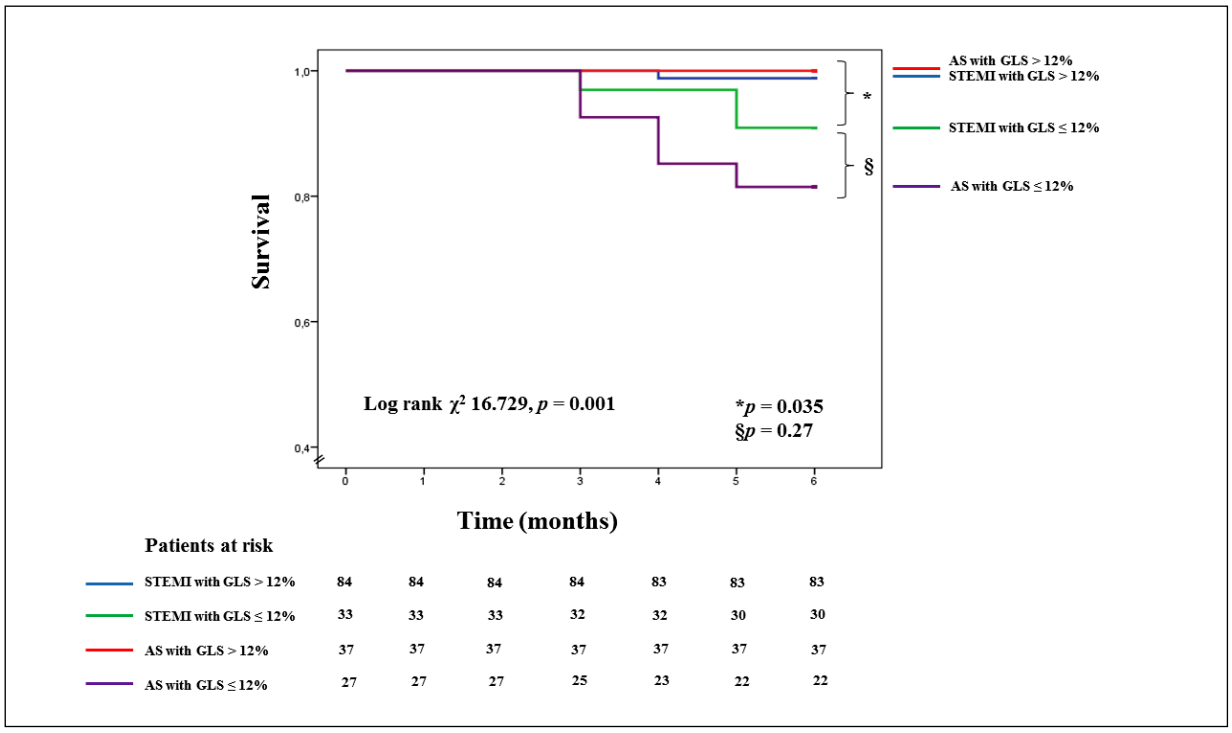

Figure 4. Kaplan-Meier curves for survival of patients stratified according to cohort and GLS cut-off.

Table II. Univariate and multivariate Cox regression analysis for prediction of all-cause death.

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age (per 1 year increase)	1.076 (1.002-1.156)	0.044	1.050 (0.917-1.203)	0.476
Male gender (yes/no)	2.251 (0.468-10.836)	0.312		
Hypertension (yes/no)	1.946 (0.487-7.781)	0.346		
Diabetes (yes/no)	0.898 (0.181-4.448)	0.895		
COPD (yes/no)	2.625 (0.656-10.495)	0.172		
Number of diseased coronary arteries (per 1 increase)	0.971 (0.451-2.091)	0.941		
Comorbidities (yes/no)	3.365 (0.841-13.454	0.086	3.955 (0.546-28.662)	0.174
GFR (per 1 ml/min increase)	0.973 (0.944-1.003)	0.081	0.968 (0.923-1.016)	0.193
LVEF (per 1% increase)	1.036 (0.964-1.113)	0.336		
PASP (per 1 mmHg increase)	1.068 (1.006-1.133)	0.030	1.072 (0.990-1.160)	0.089
Killip or Genereux stage (per 1 increase)	2.583 (1.355-4.924)	0.004	0.673 (0.156-2.908)	0.596
GLS (per 1% increase)	0.737 (0.605-0.897)	0.002	0.667 (0.451-0.986)	0.042

AS = aortic stenosis, EDVi = end-diastolic volume indexed for body surface area; ESVi = end-systolic volume indexed for body surface area; GFR = glomerular filtration rate; GLS = global longitudinal strain; LAVi = left atrial volume indexed for body surface area; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; SD = standard deviation; STEMI = ST-segment elevation myocardial infarction; WMSI = wall motion score index.

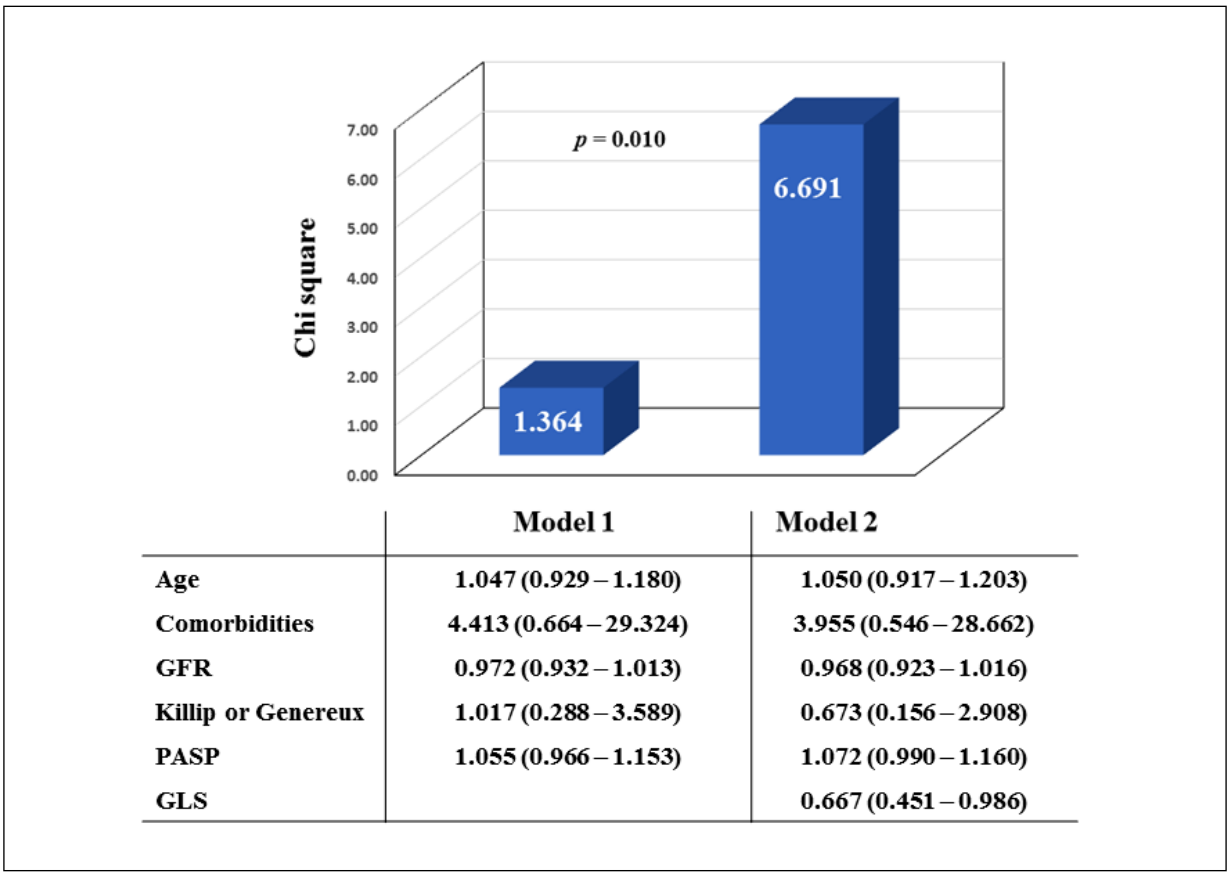

Figure 5. Incremental value of GLS on common prognostic parameters, for all-cause mortality. Data are presented as hazard ratios with corresponding 95% confidence intervals. GFR = glomerular filtration rate; GLS = global longitudinal strain; PASP = pulmonary artery systolic pressure.

cardiac disease, as well as of common clinical and echocardiographic parameters (Figure 6, Central Illustration). According to this finding, patients with STEMI or severe AS showing a GLS ≤12% might be considered at high risk despite optimal treatment and should therefore undergo a closer clinical follow-up, at least in the short-term after discharge.

Bases for a Common GLS Cut-off Value in STEMI and Severe AS

Although STEMI and AS present different clinical conditions with different pathophysiological mechanisms and implications, both determine various degrees of LV myocardial damage, including irreversible and structural myocardial fibrosis, that significantly affect survival[23,24]. In

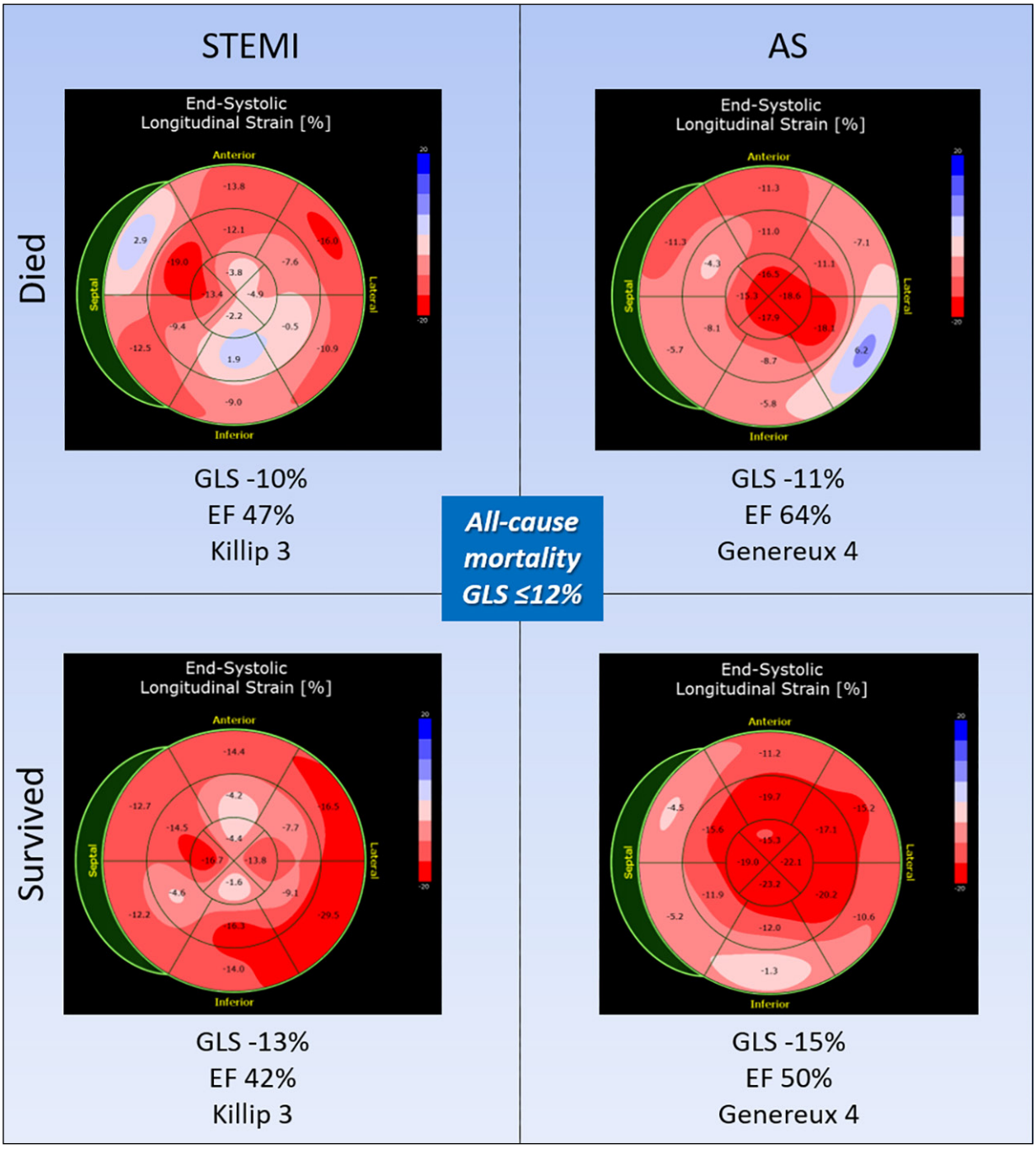

Figure 6. Central Illustration. Examples of survived and died STEMI and AS patients with corresponding GLS values.

the setting of STEMI, the ischemic wavefront progresses from the subendocardial to the subepicardial layer, and the final infarct size is considered one of the most important determinants of prognosis[25]. However, in addition to the replacement fibrosis within the infarct area, a more subtle interstitial fibrosis has been found in the remote myocardium of these patients, likely as a result of subclinical ischemia[26]. In severe AS, on the other hand, the development of myocardial hypertrophy in response to LV pressure overload progresses towards an adverse remodeling of the extracellular matrix, with the development of diffuse reactive interstitial fibrosis and, in advanced stages, gross nodular fibrosis[27,28]. Interestingly, similar to what occurs in the ischemic heart, a fibrosis gradient from the subendocardium to the subepicardium has been demonstrated in these patients[29], suggesting that myocardial ischemia, resulting from a supply-demand imbalance, is a contributing factor. Furthermore, similarly to myocardial infarction, replacement fibrosis in severe AS has been shown to be irreversible[30], as compared to diffuse fibrosis, which regresses following AVR[31].

Independent of the mechanisms, myocardial fibrosis results in alterations in myocardial mechanics. Although unable to measure myocardial fibrosis directly, GLS expresses the contractile function of longitudinal subendocardial myofibers and is able to differentiate between myocardial segments with active deformation and those with passive motion due to tethering[32]. In patients with STEMI, strain values predict infarct size, as they impair evolving from non-transmural to transmural infarctions[33,34]. Similarly, in AS, longitudinal strain decreases with increasing myocardial fibrosis[35]. According to such assumptions, the finding that the patients who died in the two groups of STEMI and severe AS shared similar values of GLS suggests that impaired GLS reflected increased myocardial fibrosis. This hypothesis is supported by the data by Hoffmann et al[36], who showed that a GLS ≤11.6%, a cut-off value very similar to ours, had a sensitivity of 65% and a specificity of 75% to predict significant focal myocardial fibrosis, as identified by a late gadolinium enhancement >10% of LV mass at cardiac MR. Moreover, in the study by Weidemann et al[35], all patients with severe AS who died early during follow-up had severe fibrosis. Finally, we cannot exclude that GLS values in our population could be, at least in part, load-dependent, as they are largely influenced by both preload and afterload changes[37]. However, in our died patients with frequent decompensated stages (i.e., Killip class and Genereux stage), reversal of adverse myocardial and LV remodeling seems less likely[27].

Prognostic Role of GLS in STEMI and AS

In patients with STEMI, GLS at discharge, but not GLS after 3 months, was significantly associated with a combined endpoint of death, reinfarctions, hospitalization for heart failure, angina, ventricular arrhythmia, new-onset atrial fibrillation, and stroke[11]. Our data are in accordance with these previous studies, showing that GLS assessed after revascularization predicted all-cause death and hospitalization for heart failure, even in patients with preserved LVEF, and independently of other clinical and echocardiographic parameters. Notably, the prognostic cut-off value of 12% of GLS emerging from our data is very similar to that reported in several previous studies, which ranged from 12.3% to 12.8%[38-40] in absolute values. Other authors, on the other hand, reported lower or higher cut-off levels, ranging from 9.27% to 14%[41-46]. Differences among studies, however, may depend on the variable time of assessment of GLS as well as differences in the variables included in the primary end-points of the studies.

In the setting of AS, it is widely appreciated that preoperative GLS is significantly associated with long-term postoperative major adverse events and cardiac mortality in patients with severe AS and preserved LVEF after AVR[13]. However, variability about GLS cut-offs between studies is even greater than that for STEMI. In asymptomatic severe AS with preserved LVEF, cut-offs of the GLS predicting outcome varied, indeed, from 14% to 18.2%[5-8,47]. Our data, however, are in accordance with those by Kusunose et al[48], who showed that GLS <12.1% was associated with a significant increase in mortality.

Limitations of the Study

Some limitations of our study should be acknowledged. First, we could only include a limited number of patients with few events, which precluded a separate analysis of the two populations included in the study. However, although our results need confirmation in larger studies, the similar GLS of deceased patients in the two groups suggests that the same prognostic cut-off could be applied to these two populations of patients.

Second, no data were collected on myocardial structure, in particular, on the extent of myocardial fibrosis. However, our purpose was not to correlate GLS with myocardial fibrosis but rather to assess whether lower GLS values had relevant prognostic implications, regardless of the mechanisms.

Finally, although cardiac magnetic resonance has emerged as a reference noninvasive method to assess myocardial fibrosis, strain analysis at echocardiography has low cost, greater availability, and rapid measurement offline after adequate image acquisition[32].

Conclusions

Our data show that a similar cut-off level of GLS predicts increased mortality in both patients with STEMI and those with severe AS, thus suggesting that a unique risk stratification cut-off level is possible to obtain and could be applied in clinical practice, independently of the clinical condition. Our data, however, needs to be confirmed in larger groups of patients as well as in different cardiac diseases.

Conflict of Interest

Dr. Aurigemma has been involved in advisory board activities by Abbott, Abiomed, Medtronic and Daiichi Sankyo. Dr. Burzotta received speaker's fees from Abiomed, Abbott, Medtronic, Terumo. Dr. Romagnoli and Prof. Trani have received speaker's fees by Medtronic, Abiomed, and St. Jude. The other authors disclose no conflicts of interest.

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Informed Consent

A written informed consent to be included in the registries and make available her/his data for any subsequent analysis was obtained from patients at the time of enrolment. Yet, oral informed consent for inclusion in this study was further obtained from patients or relatives (in case of dead patients) during follow-up telephone calls.

Ethics Approval

The protocol was conducted in accordance with the Helsinki Declaration and its latest amendments. Data analyzed in this retrospective study were collected in two large registries carried out at our Center in patients with STEMI and patients with AS; both registries obtained approval from the Ethics Committee of Catholic University of the Sacred Heart (NCT02502747 and Prot. N.0014497/21, respectively).

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Data Availability

E. Ravenna and G. Locorotondo designed the protocol, analyzed data and wrote the manuscript; L. Manfredonia collected data; G. Diana analyzed data; M. Filice collected data; F. Graziani, A.M. Leone, C. Aurigemma, E. Romagnoli, F. Burzotta, C. Trani, M. Massetti and A. Lombardo approved the manuscript, G.A. Lanza revised and finally approved the manuscript.

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