Global longitudinal strain and long-term outcome in patients presenting to the emergency department with suspected acute coronary syndrome

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Abstract

Aims: We have previously shown that 2-dimentional strain is not a useful tool for ruling out acute coronary syndrome (ACS) in the emergency department (ED). The aim of the present study was to determine whether in patients with suspected ACS, global longitudinal strain (GLS), measured in the ED using 2-dimensional strain imaging, can predict long-term outcome. Methods: Long-term (median 7.7 years [IQR 6.7-8.2]) major adverse cardiac events (MACE; cardiac death, ACS, revascularization, hospitalization for heart failure or atrial fibrillation) and all-cause mortality data was available in 525/605 patients (87%) enrolled in the Two-Dimensional Strain for Diagnosing Chest Pain in the Emergency Room (2DSPER) study. The study prospectively enrolled patients presenting to the ED with chest pain and suspected ACS but without a diagnostic ECG or elevated troponin. GLS was computed using echocardiograms performed within 24 hours of chest pain. MACE of patients with worse GLS (> median GLS) was compared to patients with better GLS (? median GLS). Results: Median GLS was -18.7%. MACE occurred in 47/261 (18%) of patients with worse GLS as compared with 45/264 (17%) with better GLS, adjusted HR 0.87 (95% CI 0.57-1.33, P=0.57). There was no significant difference in all-cause mortality or individual end-points between groups. GLS did not predict MACE even in patients with optimal 2-dimensional image quality (n=164, adjusted HR=1.51, 95% CI 0.76-3.0). Conclusions: GLS did not predict long-term outcome in patients presenting to the ED with chest pain and suspected ACS, supporting our findings in the 2DSPER study.

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Running head: Outcome of suspected ACS by GLS

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Abstract

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Methods: Long-term (median 7.7 years [IQR 6.7-8.2]) major adverse cardiac events (MACE; cardiac death, ACS, revascularization, hospitalization for heart failure or atrial fibrillation) and all-cause mortality data was available in 525/605 patients (87%) enrolled in the Two-Dimensional Strain for Diagnosing Chest Pain in the Emergency Room (2DSPER) study. The study prospectively enrolled patients presenting to the ED with chest pain and suspected ACS but without a diagnostic ECG or elevated troponin. GLS was computed using echocardiograms performed within 24 hours of chest pain. MACE of patients with worse GLS (> median GLS) was compared to patients with better GLS ([?] median GLS).

Results: Median GLS was -18.7%. MACE occurred in 47/261 (18%) of patients with worse GLS as compared with 45/264 (17%) with better GLS, adjusted HR 0.87 (95% CI 0.57-1.33, P =0.57). There was no significant difference in all-cause mortality or individual end-points between groups. GLS did not predict MACE even in patients with optimal 2-dimensional image quality (n=164, adjusted HR=1.51, 95% CI 0.76-3.0).

Conclusions: GLS did not predict long-term outcome in patients presenting to the ED with chest pain and suspected ACS, supporting our findings in the 2DSPER study.

Clinical Trial Registration— URL:http://.clinicaltrials.gov. Unique identifier: NCT01163019.

Key Words: Global longitudinal strain, speckle tracking echocardiography, major adverse cardiac events, long-term outcome, acute coronary syndrome

Left ventricular (LV) systolic function, routinely assessed by echocardiography, is an important predictor of patient outcome.[1] Left ventricular ejection fraction (LVEF), commonly used to assess LV systolic function, is operator dependent, has significant interobserver variability, and does not necessarily represent myocardial contractility.[2,3] Two-dimensional longitudinal strain (2DLS) using speckle tracking imaging echocardiography can be analyzed using an automated, reproducible tool for the assessment of global and segmental LV

function.[4–6] Global longitudinal strain (GLS), calculated from 18 LV segments, has been shown to correlate well with pressure-volume loop-derived contractility indices.[2]GLS has been shown to be an independent predictor of outcome, better than LVEF, in patients with heart failure, myocardial infarction and valvular heart disease.[7–11]

Despite the fact that the use of GLS is recommended by current guidelines, the recently published SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) study, a prospective multicenter randomized trial, failed to meet its primary endpoint, preventing a significant reduction in LVEF at 1 year using a GLS-guided strategy.[12–14] These results emphasize the need for large prospective studies to evaluate the utility of GLS in routine clinical practice.

The 2-Dimensional Strain Echocardiography for Diagnosing Chest Pain in the Emergency Room (2DSPER) study was a multicenter, prospective, blinded study designed to assess the utility of 2DLS in the assessment of low to moderate risk patients presenting to the emergency department (ED) with suspected acute coronary syndrome (ACS).[15]In that study 2DLS was not found to be a useful tool for ruling out ACS in the ED, despite the fact that several small studies had reported that 2DLS can accurately detect coronary artery disease (CAD) and identify patients with ACS.[16–21] This discrepancy could be partly explained by the fact that unlike the other studies, in which most patients without ACS had normal 2DLS, in 2DSPER many patients without ACS had abnormal 2DLS. The prognostic significance of abnormal 2DLS in these patients is unclear, and to the best of our knowledge, there are no studies that assessed the utility of 2DLS for the prediction of outcome in patients presenting to the ED with chest pain.

The aim of the present study was to determine whether GLS can predict long-term outcome in patients presenting to the ED with suspected ACS.

Methods

Study population

The 2DSPER was a prospective multicenter blinded study conducted by the Israeli Echo Research Group.[15] Patients over the age of 45 who presented to the ED with chest pain and suspected ACS were enrolled from 11 Israeli medical centers participating in the study between September 2010 and February 2014. Patients were excluded if they had [?]1mm ST segment deviation, elevated initial troponin, previous myocardial infarction or coronary bypass surgery, other than normal sinus rhythm, complete left bundle brunch block, moderate or severe valvular heart disease or cardiomyopathy.

Patients were diagnosed as having ACS based on the clinical presentation and evidence of myocardial ischemia on stress ECG, stress echocardiography or scintigraphy and/or in the presence of a culprit lesion ([?]70 stenosis in a major coronary artery) on coronary computed tomography angiography (CCTA) or invasive coronary angiography.

The study was approved by the local institutional review board of each participating center and all patients signed an informed consent form.

Echocardiography

Transthoracic echocardiography was performed using commercially available General Electric systems (VIVID Q, S6 or Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). Apical long axis, 4-chamber and 2-chamber views were digitally recorded at a frame rate of >40 fps for offline 2DLS analysis. Standard echocardiographic findings, but not 2DLS findings, were available to the attending physician.

An echo study was performed within 24h of the patients' last chest pain episode. Patients with suboptimal 2D echo image quality, defined as [?]2 technically suboptimal segments from apical views, were excluded from the study. All echocardiograms were analyzed in a core lab (Lady Davis Carmel Medical Center) by a single experienced sonographer (IA) blinded to all clinical data. Of the 700 patients initially enrolled in

the 2DSPER study 48 (6.9%) did not meet the 2D echo image quality criteria and were withdrawn from the study after the initial core lab analysis. The final cohort included 605 patients who had complete clinical and echocardiographic data, including adequate 2DLS analysis. In all 605 patients included, tracking in all LV segments was feasible according to the 2DLS analysis software.

All 605 echocardiograms included in the final 2DSPER study cohort were reviewed by a second experienced sonographer (MG) blinded to all clinical and 2DLS data. Studies with the best image quality, defined as optimal visualization of all left ventricular segments throughout the cardiac cycle in all 3 apical views, were classified by the blinded sonographer as high quality, and the rest as low quality.[22]

All echocardiograms were analyzed using a dedicated 2DLS software (EchoPAC SW version 113.0.3; GE Vingmed Ultrasound AS). For each patient GLS was computed by averaging all 18 segments. Reproducibility of GLS measurements in the 2DSPER study has been previously reported.[15]

Long-term follow-up

Long-term follow-up was available in 6 of the 11 centers participated in the 2DSPER study. Data on major adverse cardiac events (MACE, defined as cardiac death, ACS, revascularization, hospitalization for heart failure or atrial fibrillation) and all-cause mortality was collected using electronic patient records between October 2018 and May 2020. We defined cardiac death as death resulting from an acute myocardial infarction, sudden cardiac death or heart failure, or death due to a cardiac procedure.[23]

Statistical analysis

Continuous variables are presented as mean±SD or medians and interquartile range, and categorical variables as numbers and percentages. Patients were divided into worse GLS group (GLS>median) and better GLS group (GLS[?]median). Characteristics of worse and better GLS groups were compared using the Student's t -test or the Mann Whitney test as appropriate for continuous variables and χ^2 or Fisher's exact test for categorical data. Survival curves for MACE were constructed using the Kaplan–Meier method and compared between GLS groups using the log-rank test. Patients were followed from the date of discharge till the first occurrence of MACE, non-cardiac death or end of follow-up, whichever came first. Cox proportional hazard regression models were used to calculate hazards ratios (HR) and corresponding 95% confidence intervals (CI) for MACE, it's individual components and all-cause mortality, and to assess the univariate and the multivariate predictors of MACE. Models were adjusted for relevant demographic, clinical and echocardiographic variables. Differences were considered statistically significant at the 2-sided P <0.05. Statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM, New York, NY).

Results

Study population

Long-term follow up was available in 525 patients (87% of the 605 patients included in the final analysis of 2DSPER, 99% of the 529 patients from the 6 centers with available long-term follow-up). A histogram of GLS values derived from the baseline echocardiogram in the 525 patients with available long-term follow-up is presented in Figure 1. Median GLS was -18.7%. Patients were divided into "better GLS" group (GLS [?] -18.7%, n=264) and "worse GLS" group (GLS > -18.7%, n=261). GLS was abnormal (> -17% according to current guidelines) in 120/525 patients (23%).[24]Patient characteristics are summarized in Table 1. Patients with worse GLS were more likely to be men. There was no difference in coronary risk factors, except for smoking which was more prevalent in patients with worse GLS. Patients with worse GLS had a higher body mass index, and higher creatinine and hemoglobin levels. There was no difference in medical treatment between groups

Echocardiographic findings are summarized in Table 2. Patients with worse GLS were: less likely to have high 2D image quality, more likely to have lower LVEF and wall motion abnormality and more likely to have

thicker LV walls. Although they had more impaired early LV relaxation, there was no difference in their E/e' ratio.

Data from initial ED visit and hospitalization is presented in Table 3. Patients with worse GLS were more likely to be admitted to the hospital and undergo invasive coronary angiography, and less likely to undergo coronary computed tomography angiography. They were more likely to be diagnosed with ACS, mostly unstable angina pectoris, and undergo revascularization.

Long term outcome

Median follow-up was 7.7 years (IQR 6.7-8.2 years). There was no difference in long-term all-cause mortality between groups (Table 4). Long-term MACE occurred in 92 patients (17.5%). Cardiac death was very low in both groups, and there was no significant difference in long-term MACE or in the individual end-points between groups (Table 4, Figure 2). ACS or revascularization accounted for 68/92 (74%) of MACE. Hospitalization for heart failure was rare even in the group of patients with worse GLS. We repeated the analysis with a GLS cutoff value of -17%, the cutoff value for abnormal GLS.[24] There was no significant difference in long-term MACE between patients with normal vs. abnormal GLS (log-rank P =0.64).

To determine whether suboptimal 2D image quality was the cause of our findings, we repeated the same analysis in the 164 patients with optimal 2D image quality (better GLS: n= 97, worse GLS: n=67). Long-term MACE tended to be higher in the worse GLS group (HR=1.85, 95%CI 0.94-3.63,P =0.07(, but there was no statistically significant difference in MACE after adjustment for history of CAD, hypertension and ACS at presentation (HR=1.51, 95% CI 0.76-3.0, P =0.24).

Independent predictors of long-term MACE were male gender, hypertension, history of CAD and ACS at presentation (Table 5). Thus, a worse GLS did not predict long-term outcome.

Discussion

Our data clearly show that in patients presenting to the ED with chest pain and suspected ACS, GLS does not predict long term outcome, namely cardiac death, ACS, revascularization, hospitalization for heart failure or atrial fibrillation. The results were the same whether we defined worse GLS as GLS > -18.7% (median GLS) or GLS > -17% (abnormal GLS according to guidelines), or when we analyzed only patients with optimal 2D echo image quality. To the best of our knowledge, this is the first study to report the effect of GLS on long-term outcome in patients with suspected ACS. We have previously reported a significantly higher 6-month MACE in patients with ACS as compared to patients in which ACS was excluded (5.8% vs. 0.6%,P =0.0002).[15] The fact that 6-month MACE was extremely rare in 2DSPER in patients in whom ACS was excluded, suggests that the likelihood of missing significant CAD in these patients was very low.

GLS has been shown to be a good predictor of outcome, better than LVEF, in patients with heart failure, myocardial infarction and severe valvular disease.[7–11,25] In a meta-analysis of 16 published articles which included 5721 patients, Kalam et al concluded that GLS predicts all-cause mortality and MACE (cardiac death, hospitalization for heart failure and malignant arrhythmia).[10] Most of the patients included in the meta-analysis had myocardial infarction, heart failure or severe valvular or myocardial disease. In contrast to our study population, these patients were sicker, had a wider range of GLS values and included more patients with abnormal GLS values, thus explaining the discrepancy between the other studies and ours. Even in patients with heart failure and preserved LVEF, mean GLS was worse and standard deviation wider, as compared to our group of patients with worse GLS (-15.2 $\pm$ 4.6% in the study of Park et al, compared to -16.7$\pm$1.5% in our study).[9] Most of our patients had good LV function. In 2DSPER, patients without ACS had worse GLS as compared to control groups in previous studies reporting high diagnostic accuracy of 2DLS.[17,19] Worse GLS, however, was not associated with poor outcome in our study.

In addition, most patients with ACS included in 2DSPER had unstable angina pectoris and one vessel disease, and good outcome is expected in such patients. In sicker patients with myocardial enzyme leak and

severe CAD, 2DLS is unnecessary for the diagnosis of ACS.[26]

Although 2DLS and GLS are accurate, reproducible and automated measures of LV contraction, they are dependent on 2D echo image quality and loading conditions which limit their accuracy, similar to LVEF.[4,27,28] Another measure of LV strain, global circumferential strain, has been shown to be a better predictor of outcome when compared to GLS.[25] In 2DSPER we used a new 2DLS parameter, the peak systolic strain value identifying the worst 20% LV segments (PSS20%), since this parameter was reported to outperform GLS in diagnosing ACS, because of its ability to identify minor wall motion abnormalities.[17] Unfortunately, in the 2DSPER study PSS20% was not superior to GLS in diagnosing ACS.[15] Similar to most other studies assessing the utility of LV strain in predicting outcome, we used GLS, since GLS is a simple and robust diagnostic tool, readily available in most commercial echo machines.

In our study, independent predictors of long-term MACE were history of CAD, ACS diagnosis, male gender and hypertension, but not GLS. Only 14% of our study population had ACS, and recurrent ACS or revascularization accounted for the majority of long-term events included in MACE, not heart failure or cardiac death. In a study from Poland of 2731 patients with unstable angina pectoris, the predictors of death or coronary events during 3 years follow-up were age, kidney disease, hypertension, diabetes, previous stroke and previous percutaneous coronary interventions.[29] In another study of 230 patients discharged from the ED with a diagnosis of chest pain of undetermined origin, 4.4% had MACE during 12 months of follow-up, and the predictors of MACE were abnormal ECG, diabetes, or preexisting CAD.[30] As expected, in our study similar to the other studies, markers of CAD at baseline predicted late coronary events. GLS, contrary to previous reports, not only failed to accurately identify ACS in the ED, but failed to predict future cardiac events as well, thus extending our findings from the 2DSPER multicenter study, of a limited value for GLS in low-risk patients presenting to the ED with suspected ACS.

Limitations

Long-term follow-up in our study was incomplete (87% of the patients included in 2DSPER had long-term follow-up). Long-term follow-up, however, was available in 99% of the patients included in the 6 centers participating in the currents study, thus minimizing selection bias. Given the unequivocal nature of our results (Figure 2), it is highly unlikely that complete follow-up would significantly alter our findings. GLS is dependent on 2D image quality.[22,27] In 2DPSER mid-range systems, frequently utilized in the ED, were used. We do not know whether using high-end machines would have significantly improved GLS accuracy and its predictive power. However, only patients with adequate 2D image quality were included in 2DSPER, hence making our findings relevant to everyday practice. Furthermore, GLS did not predict outcome even in the subgroup of patients with optimal 2D echo image quality.

Conclusions

GLS did not predict long-term outcome in patients presenting to the ED with chest pain and suspected ACS with neither a diagnostic ECG or elevated cardiac enzymes. These data support our findings in the original 2DSPER multicenter study, and together with the SUCCOUR study, emphasize the need for large prospective trials to evaluate the clinical utility of GLS. We conclude that 2DLS is not a useful tool for the diagnosis of ACS and for predicting outcome in low to intermediate risk patients presenting to the ED with chest pain and suspected ACS.

Conflict of interest: NLC, DSB, SS, MJ, ML and AS report non-financial support from GE Healthcare, Haifa, Israel, during the conduct of the study.

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Figure Legends

Figure 1: Histogram of baseline GLS values in study population (n=525)

Figure 2: Kaplan–Meier curves showing long-term MACE by GLS groups

Log-rank P =0.57. Worse GLS: GLS> -18.7% (median GLS). Better GLS: GLS< -18.7%.

Table 1: Patient Characteristics

Variable	**Better GLS**	**Worse GLS**	P Value
	(n = 264)	*(n = 261)*	
Age (y)	58.7±8.3 [57.3]	57.4±8.5 [56.0]	0.07
Male gender	167 (63.3%)	210 (80.5%)	**<0.0001**
Height (cm)	169.8±10.0 [170.0]	171.5±8.2 [172.0]	**0.033**
Weight (kg)	80.0 ±15.0 [79.0]	84.7±15.5 [83.0]	**0.001**
BMI (kg/m^2)	27.7±4.5 [27.3]	28.7±4.7 [28.3]	**0.01**
Known CAD	20 (7.6%)	28 (10.7%)	0.21
Previous PCI	17 (6.4%)	26 (10.0%)	0.14
TIMI score*	1.64±1.20 [1.0]	1.82±1.10 [2.0]	0.06
Risk factors			
Hypertension	118 (44.7%)	127 (48.7%)	0.36
Diabetes	59 (22.3%)	72 (27.6%)	0.17
Hyperlipidemia	147 (55.7.0%)	149 (57.0%)	0.75
FH of CAD	94 (35.6%)	89 (34.0%)	0.72
Current smoker	80 (30.3%)	106 (40.6%)	**0.014**
Medications at enrolment			
Aspirin	110 (41.7%)	108 (41.4%)	0.97
Beta blockers	47 (17.8%)	49 (18.8%)	0.77
Nitrates	6 (2.3%)	3 (1.1%)	0.32
ACE-I	47 (17.8%)	59 (22.6%)	0.17
ARB	25 (9.3%)	18 (6.9%)	0.28
CCB	35 (13.3%)	28 (10.7%)	0.37
Laboratory results			
Creatinine (mg%)	0.85±0.18 [0.83]	0.90±0.20 [0.89]	**0.004**
Hb (g%)	13.9±1.3 [14.0]	14.3±1.4 [14.3]	**0.009**
Troponin T (ng/L)+	15.32±64.0 [7.0]	34.8±142.8 [4.0]	0.73

*Unstable angina/non-ST elevation myocardial infarction TIMI score[31]

+Highest troponin during initial emergency department admission

ACE-I= angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, BMI=body mass index, CAD=coronary artery disease, CCB=calcium channel blocker, FH=family history, Hb=hemoglobin, PCI=percutaneous coronary intervention

Table 2: Echocardiographic findings

Variable	**Better GLS**	**Worse GLS**	*P* Value	*P* Value
	(n = 264)	*(n = 261)*		
High 2D image quality	97 (36.7%)	67 (25.7%)	**0.006**	**0.006**
Heart rate (beats/min)*	66.7±11.9 [66.0]	68.5±11.1 [67.0]	0.07	0.07
BP systolic (mmHg)*+	129.0±18.2 [129.0]	131.4±18.7 [130.0]	0.36	0.36
BP diastolic (mmHg)*+	77.2±9.3 [78.0]	79.8±12.9 [80.0]	**0.01**	**0.01**
LVEF (%)	62.0±3.6 [60.0]	59.5±5.2 [60.0]	**<0.0001**	**<0.0001**
WMA	9 (3.4%)	42 (16.1%)	**<0.0001**	**<0.0001**
LVEDD (cm)	4.5±0.43 [4.5]	4.6±0.48 [4.5]	0.05	0.05
LVESD (cm)	2.80±0.43 [2.80]	2.96±0.55 [3.0]	**0.006**	**0.006**
IVS (cm)	1.00±0.15 [1.0]	1.05±0.17 [1.0]	**<0.0001**	
PW (cm)	0.93±0.13 [0.9]	0.97±0.15 [1.0]	**0.001**	
LA (cm)	3.56±0.47 [3.6]	3.50±0.46 [3.5]	0.85	
PASP (mmHg) ++	25.65±7.2 [25.0]	24.4±6.2 [23.5]	0.1	
E (cm/sec)	70.8±15.0 [70.0]	65.8±15.1 [64.0]	**<0.0001**	
A (cm/sec)	69.9±17.6 [68.0]	67.4±17.5 [66.0]	0.1	
E/A	1.06±0.30 [0.99]	1.04±0.50 [0.95]	0.07	0.07
DecT (msec)	209.0±48.7 [205.0]	225.1±53.4 [208.0]	0.14	0.14
e' septal (cm/sec)	8.07±2.08 [8.0]	7.5±2.0 [7.0]	**0.001**	**0.001**
e' lateral (cm/sec)	10.3±2.7 [10.0]	9.3±2.8 [9.0]	**<0.0001**	**<0.0001**
e' mean (cm/sec)	9.1±2.4 [9.0]	8.2±2.3 [8.5]	**<0.0001**	**<0.0001**
E/e' mean	8.1±2.6 [7.6]	8.4±3.2 [7.6]	0.28	
GLS	-20.8±1.6 [-20.5]	-16.7±1.5 [-17.0]	**<0.0001**	

Numbers in brackets represent medians

*At the time of echocardiography

+18 missing (3.4%)

++230 unavailable (43.8%)

BP=blood pressure, DecT=E-wave deceleration time, IVS=interventricular septum, LA=left atrium, LVEDD=left ventricular end-diastolic diameter, LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic diameter, PASP=pulmonary artery systolic pressure, PW=posterior wall, WMA=wall motion abnormality

Table 3: Initial workup, coronary anatomy, revascularization and final diagnosis

Variable	**Better GLS**	**Worse GLS**	*P* Value
	(n = 264)	*(n = 261)*	
Hospital admission	163 (61.7%)	212 (81.2%)	**<0.0001**
CCTA n (%)	33 (12.5%)	17 (6.5%)	**0.02**

Variable	**Better GLS**	**Worse GLS**	*P* Value
Calcium score	190.5±288.3 [42.0]	112.9±225.4 [9.0]	0.76
Coronary angiography n (%)	45 (17.0%)	74 (28.4%)	**0.002**
1 vessel disease	19/45 (42.2%)	27/74 (36.5%)	0.34
Severe CAD*	2/45 (4.4%)	6/74 (8.1%)	0.70
Culprit lesion identified+	24/72 (33.3%)	43/87(49.4%)	**0.041**
No culprit lesion identified	48/72 (66.7%)	44/87 (50.6%)	
Revascularization	22 (8.3%)	38 (14.6%)	**0.025**
PCI	22/22 (100%)	35/38 (92.0%)	0.29
CABG	0/22 (0%)	3/38 (7.9%)	0.18
ACS	26 (9.8%)	47 (18.0%)	**0.007**
Unstable angina	23/26 (88.5%)	40/47 (85.1%)	0.65
NSTEMI	3/26 (11.5%)	5/47 (10.6%)	
STEMI++	0/26 (0%)	2/47 (4.3%)	

*Three vessel or left main or proximal left anterior descending CAD

+Diameter stenosis [?]70% on CCTA or coronary angiography

++During observation

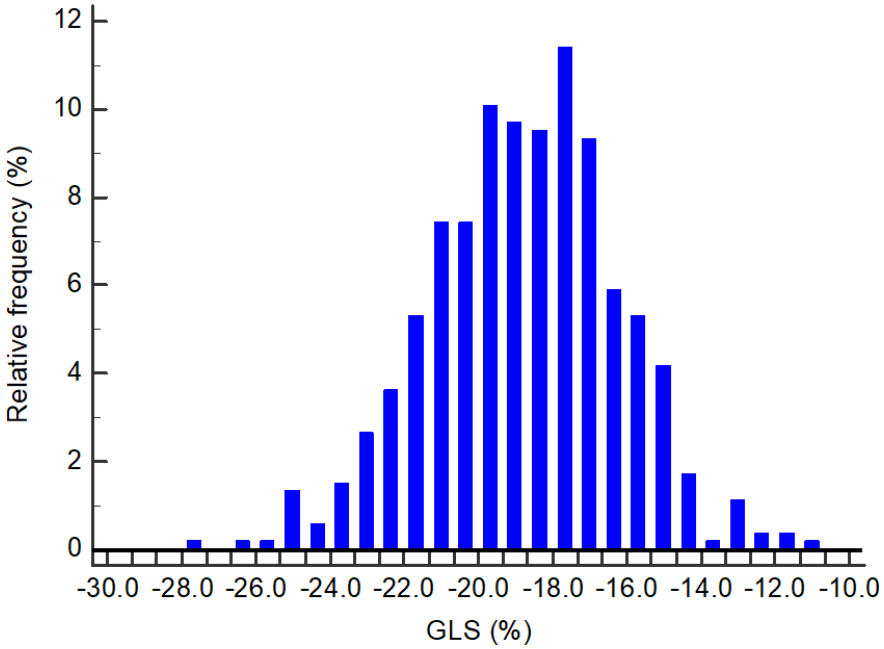
ACS=acute coronary syndrome, CABG=coronary artery bypass grafting, CAD=coronary artery disease, CCTA=coronary computed tomography angiography, NSTEMI=non-ST elevation myocardial infarction, PCI=percutaneous coronary intervention, STEMI=ST-elevation myocardial infarction

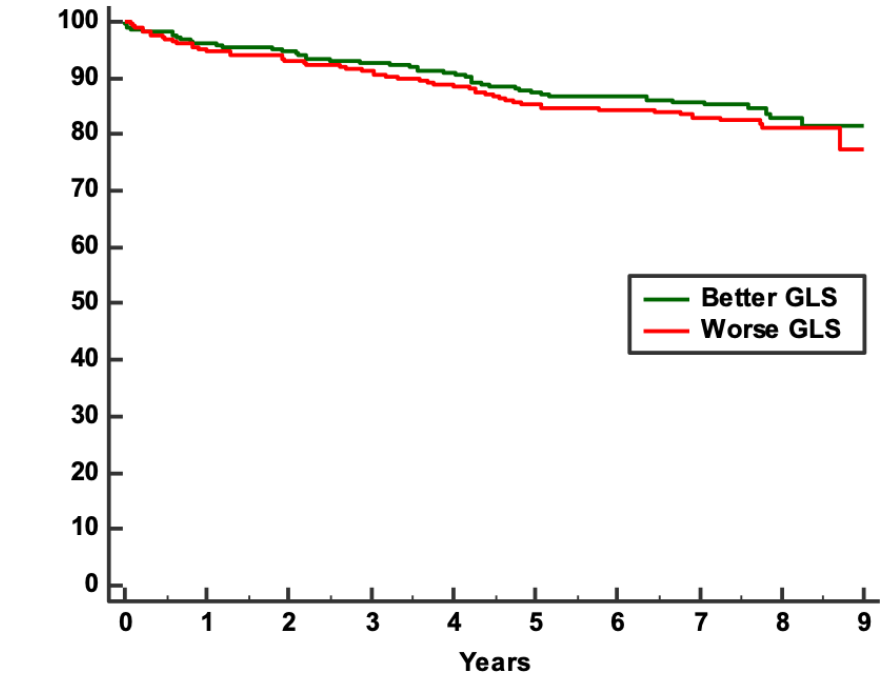
Table 4: Long-term outcome

Variable	**Better GLS** (n=264)	**Worse GLS** (n=261)	**Unadjusted HR** (95% CI)	*P* Value	**Adjusted HR** (95% CI)	*P* Value
All-cause mortality	16 (6.1%)	12 (4.6%)	0.77 (0.37-1.63)	0.50	0.74 (0.34-1.61)	0.45
MACE	45 (17.0%)	47 (18.0%)	1.13 (0.75-1.70)	0.57	0.87 (0.57-1.33)	0.51
Cardiac death	1 (0.4%)	2 (0.8%)	2.06 (0.18-22.68)	0.56	-	-
ACS	20 (7.6%)	23 (8.8%)	1.24 (0.68-2.26)	0.48	0.86 (0.47-1.47)	0.64
Revascularization	27 (10.2%)	28 (10.7%)	1.12 (0.66-1.90)	0.68	0.83 (0.47-1.47)	0.53
Hospitalization for HF	5 (1.9%)	3 (1.1%)	0.63 (0.15-2.62)	0.52	0.54 (0.13-2.40)	0.41
Atrial fibrillation	13 (4.9%)	8 (3.1%)	0.63 (0.26-1.51)	0.29	0.69 (0.28-1.70)	0.42

Adjusted HR for cardiac death could not be calculated due to small numbers.

ACS=acute coronary syndrome, HF=heart failure, HR=hazard ratio, MACE=major adverse cardiac events (cardiac death, ACS, revascularization, hospitalization for heart failure or atrial fibrillation)





Number at risk

Group: Better GLS									
264	**253**	**247**	**242**	**236**	**226**	**221**	**195**	**108**	**29**
Group: Worse GLS									
261	**246**	**238**	**233**	**226**	**215**	**206**	**174**	**79**	**13**