The predictive value of global longitudinal strain on clinical outcome in patients with ST-segment elevation myocardial infarction and preserved systolic function

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Background: Left ventricular ejection fraction (LVEF) is fundamental for risk stratification after ST-segment elevation myocardial infarction (STEMI). However, it lacks discrimination power within normal range. Novel echocardiographic deformation parameters may be of benefit for those with post-MI preserved LVEF.

Objectives: We hypothesized that semiautomated calculation of baseline global longitudinal strain (GLS) can identify high-risk group among patients with LVEF ≥ 50% following STEMI.

Methods: During the period from January to July 2017, 110 patients with successful reperfusion of STEMI and LVEF ≥ 50% were prospectively included. Within 48 hours, patients underwent a baseline GLS study with follow-up study at 30 days. The endpoint was a composite of cardiovascular mortality, rehospitalization for heart failure, and urgent revascularization.

Results: Mean GLS value changed from −16 ± 4% at baseline to −12 ± 4% at 30-day follow-up (P < .001). At 30 days, cardiovascular mortality was reported in 4.5%, 11.8% were rehospitalized due to heart failure, and 5.4% underwent urgent revascularization. ROC curve analysis showed that a cutoff baseline GLS value >−12.65% predicted 30-day MACEs with a sensitivity and specificity of 77.8% and 83.7%, respectively (AUC 0.784, 95% CI 0.646–0.921, P < .001). An adjusted multivariate logistic regression analysis revealed that baseline GLS value >−12.65% to be the only significant independent predictor for occurrence of MACEs (OR 19.54, 95% CI 6.3–61.1, P < .001).

Conclusion: Early GLS calculation predicts 30-day outcome in patients with preserved LVEF following reperfusion of STEMI.

KEYWORDS
2D echocardiography, myocardial infarction, myocardial strain

1 INTRODUCTION

Increasing number of patients experience only modest reduction (if any) of their left ventricular (LV) systolic function as assessed by LV ejection fraction (LVEF) at the time of hospital discharge after ST-segment elevation myocardial infarction (STEMI), thanks to emergent pharmacological or mechanical reperfusion together with modern antithrombotic therapy which have remarkably improved the prognosis of those patients. Nevertheless, not all patients with preserved LVEF after STEMI are equal when it comes to short- and long-term outcome. Therefore, measuring certain LV systolic parameters other than EF that could identify high-risk patients may be of
great value to define those who need more aggressive monitoring and therapies. The main focus in recent years has been on global longitudinal strain (GLS) which reflects the function of subendocardial longitudinal myocardial fibers that are very sensitive to ischemic damage. Previous studies have shown that GLS adds important prognostic data in patients with heart failure and in patients with STEMI across the whole spectrum of systolic function and even appears to be more accurate than LVEF in predicting major adverse cardiac events (MACEs). However, to the best of our knowledge, very few prospective studies have evaluated the utility of GLS to identify high-risk patients specifically among those with preserved LVEF following STEMI and no studies have explored its role for prediction of short-term outcome. The first month after STEMI is the most vulnerable period, during which critical treatment decisions that have a huge impact on the future outlook are taken, so identification of high-risk patients should take place during this period. Thus, we thought that it may be of considerable interest to explore the predictive value of early GLS on 30-day outcome among apparently low-risk patients with successful reperfusion and preserved LVEF following STEMI.

2 | METHODS

2.1 | Study design

This is a single-center prospective observational study that included 110 consecutive patients admitted with STEMI to coronary care unit at Benha University Hospital, Egypt, in the period from January to July 2017. STEMI was defined as chest pain typical for myocardial infarction of at least 30-minute duration and <6 hours, new ST-segment elevation in 2 contiguous leads with the cutoff points ≥0.2 mV in men or ≥0.15 mV in women in and <6 hours, new ST-segment elevation in 2 contiguous leads with the cutoff points ≥0.2 mV in men or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads on the 12-lead ECG. According to local protocol, all patients were candidates for reperfusion therapy by immediate fibrinolysis if timely PPCI was confirmed to be unavailable for whatever reason (unless fibrinolysis is contraindicated), with possible rescue PCI if fibrinolysis was found to be unsuccessful. Included patients were required to have successful reperfusion (either by fibrinolytic therapy using streptokinase “SK” or primary percutaneous coronary interventions “PPCI”) and normal LVEF (≥50%) measured by conventional echocardiography before discharge. Successful reperfusion was defined as disappearance or improvement of chest pain and/or resolution of ST-segment elevation by more than 50% in the lead with maximum elevation on baseline ECG 90 minutes of starting SK infusion or shortly after PPCI (culprit-only) that restores TIMI-II to III flow without major intra-procedural complications (defined as absence of no-reflow, dissections, perforations, or thrombus formation. This was adjudicated by an independent experienced attending interventional cardiologist). The study was approved by the local ethics committee at our institution, and patients were required to provide informed consent before echocardiographic examination.

Key exclusion criteria included the following:

- Patients <18 years old.
- Patients with missed MIs who did not receive any reperfusion and those who did not meet criteria for successful reperfusion.
- Patients with depressed LVEF (<50%) at discharge.
- Patients with noncardiac diseases that limit life expectancy.
- Patients with atrial fibrillation, paced rhythms or more than mild aortic stenosis, or other conditions that may hamper the quality of obtained echocardiographic data.
- Patients unable to give informed consent.

2.2 | Echocardiographic examination

Echocardiographic examination was performed using commercially available ultrasound system (Philips EPIQ 7 Ultrasound System, Andover, MA, USA) equipped with 3.5-MHz phased array transducer. Patients underwent echocardiographic study at baseline (within 48 hours of admission) and repeated during follow-up (at 30 days after discharge). All exams were performed by 2 experienced operators blinded to follow-up data. Before execution of the study and for reproducibility of measurements, these 2 experienced operators repeated 10 measurements of LVEF, WMSI, and GLS. Differences in measurements by the 2 observers were obtained for estimation of inter-observer variability. The same observers repeated the 10 measurements after a 2-month interval, and intra-observer variability was calculated.

The image was obtained at held end-expiration. LVEF was calculated using the Simpson’s biplane method in accordance with the European Association of Echocardiography and the American Society of Echocardiography recommendations. Wall-motion score index (WMSI) was assessed using the 17-segment model. For the two-dimensional speckle tracking echocardiography (2DSTE) image technique, sector depth and size were optimized to achieve perfect visualization of all LV myocardium in the 3 standard apical views (4-, 2-, and long-axis view) with a frame rate between 60 and 100 fps. End-systole was defined by the aortic valve closure in the apical long-axis view. The regions of interest were manually outlined at end-systole by outlining the endocardial borders in the apical views. Peak systolic longitudinal myocardial strain was automatically calculated throughout the myocardium for each LV apical view and reported spatially from base to apex and circumferentially in a polar plot map using a color-coded parametric representation. The global longitudinal strain (GLS) was calculated by taking an average of all peak systolic segmental strain values from the 3 standard apical views. Longitudinal peak strain values were averaged over 3 consecutive cardiac cycles. (Figure 1).
2.3 | Study endpoint

We used a primary outcome of composite 3-point major adverse cardiac events (MACEs) at 30 days (mortality due to cardiovascular causes, readmission due to heart failure (HF), and urgent revascularization). Adjudication of individual components of the endpoint was carried out by an independent reviewer committee blinded to echocardiographic data related to index MI. Data on mortality were obtained from hospital records and classified as cardiovascular and noncardiovascular. Readmission for HF was defined as hospitalization due to dyspnea with objective signs of pulmonary congestion together with treatment with intravenous diuretics. Urgent revascularization was defined as any urgent PCI or coronary artery bypass grafting (CABG) performed within 72 hours of hospital readmission.

2.4 | Sample size calculation

Sample size was calculated using Epi-Info software (v.7.2.2; Centers for Disease Control and Prevention, Atlanta, GA, USA) based on the results of the study by Munk et al., which reported 79% accuracy of GLS in predicting MACE. Precision level was adjusted to 0.08, and confidence level was adjusted to 95%. Calculated sample size was 100 patients.

2.5 | Statistical analysis

Data management and statistical analysis were performed using SPSS software vs 23 (IBM, Armonk, NY, USA). Numerical data were summarized using means and standard deviations. Categorical data were summarized as numbers and percentages. Comparisons between those reperfused by SK and those receiving PPCI were performed using Mann–Whitney U test for numerical variables and chi-square or Fisher’s exact test—if appropriate—for categorical variables. Difference between baseline echocardiographic parameters and follow-up parameters was analyzed using paired t test for normally distributed variables or Wilcoxon signed-rank test for nonnormally distributed variables. ROC analysis was carried out for using baseline GLS, WMSI, and LVEF in the prediction of MACEs. Cutoff point and diagnostic indices were calculated. Logistic regression analysis was carried out for prediction of risk of MACE. Odds ratio with 95% confidence interval was calculated. All P-values were 2-sided. P-values <.05 were considered significant. For determination of reproducibility, echocardiographic data were analyzed using correlation coefficients and mean ± SD of differences between the 2 measurements.

3 | RESULTS

3.1 | Study population

A total of 165 patients with successful reperfusion after STEMI were prospectively included. Sixteen patients were excluded because of AF (n = 8), ventricular paced rhythm (n = 3), and more than mild aortic stenosis (n = 5). Of the remaining 149 patients, 9 patients were excluded due to poor image quality. Finally, 30 patients had LVEF < 50%, leaving 110 patients with LVEF ≥ 50% for the final


analysis. Of those patients with LVEF ≥50%, the mean (SD) age was 58.8 ± 14 years, 58% were males, 27% had DM, 33% were hypertensives, 39% were smokers, 23% had obesity, 20% had known dyslipidemia, 16% had family history of premature coronary artery disease (CAD), 17% had past history of CAD, and 10% had history of previous coronary interventions (Table 1).

### 3.2 | STEMI

#### 3.2.1 | Location as suggested by ECG

Fifty-nine patients (53.6%) had anterior STEMI, 39 patients (35.4%) had inferior STEMI, and 12 patients (10.9%) had lateral STEMI.

#### 3.2.2 | Reperfusion strategies

Eighty-seven patients (79.1%) were reperfused using SK, and 23 patients (20.9%) underwent PPCI. All patients had criteria of successful reperfusion as previously defined.

#### 3.2.3 | Key time intervals

The mean total ischemic time for whole population was 203.3 ± 45.3 minutes, and the mean door-to-reperfusion time (device or needle) for the whole population was 44.1 ± 20.3 minutes. There was no statistically significant difference in total ischemic time between those reperfused by SK and those who received PPCI (202.6 ± 47 vs 205.7 ± 39.3 minutes, respectively, P = .937); however, door-to-needle time among those reperfused by SK was significantly shorter when compared to door-to-device time among those who underwent PPCI (35.6 ± 6.7 vs 76.3 ± 22.2 minutes, respectively, P < .001). Despite this difference in door-to-reperfusion time between those reperfused by SK and those receiving PPCI, symptom onset-to-ST resolution time was not significantly different between both groups (234.4 ± 45.7 minutes in SK vs 236.8 ± 37.8 minutes in PPCI, P = .99).

### 3.3 | Clinical outcome

#### 3.3.1 | In-hospital outcome

In-hospital MACEs were reported in 13 patients (11.8%) in the form of 4 patients with in-hospital heart failure (transient lowering of LVEF), 3 patients with in-hospital reinfarction, 1 patients with in-hospital ischemic stroke, and 5 patients with in-hospital resuscitated cardiac arrest. Mean length of hospital stay was 3.7 ± 1.2 days, and it was significantly longer among those who experienced in-hospital MACEs compared to those who did not (5.9 ± 0.8 vs 3.4 ± 0.9, P < .001). No statistically significant difference regarding in-hospital MACEs was found between those reperfused by SK and those who underwent PPCI (4 vs no heart failure events, 2 vs 1 reinfarctions, 1 vs no stroke, and 5 vs no resuscitated cardiac arrests in those reperfused by SK vs PPCI, respectively).

#### 3.3.2 | 30-day outcome

Thirty-day MACEs were reported in 24 patients (21.8%) in the form of 5 deaths due to cardiovascular causes (4 due to acute decompensated heart failure and one due to refractory VF), 13 patients with rehospitalization due to heart failure (10 due to transient lowering of LVEF and 3 due to diastolic HF), and 6 patients with urgent revascularization (all received PCI). No statistically significant difference regarding 30-day MACEs was found between those reperfused by SK and those who underwent PPCI (5 vs no cardiac deaths, 10 vs 3 rehospitalizations due to heart failure, and 5 vs 1 urgent revascularizations in those reperfused by SK vs PPCI, respectively).

### 3.4 | Echocardiographic parameters

Patients were followed up 29 ± 2.5 days after admission. The mean end-systolic volume (ESV) increased from 46 ± 14 mL at baseline to 52 ± 16 mL at 30-day follow-up (P = .005). The mean end-diastolic volume (EDV) increased from 104 ± 23 mL at baseline to 113 ± 28 mL at 30-day follow-up (P = .003). The mean LVEF decreased from 56 ± 8% at baseline to 48 ± 13% at 30-day follow-up (P < .001). The mean GLS value changed from −16 ± 4% at baseline to −12 ± 4% at 30-day follow-up (P < .001). The mean WMSI did not significantly differ when comparing baseline values to those at 30-day follow-up (1.3 ± 0.4 at baseline and 1.2 ± 0.3 at 30 days, P = .694) (Table 2).

At initial presentation, inter-observer variabilities were 5.6 ± 3.1% for LVEF, 4.2 ± 2.3% for WMS, and 6.8 ± 3.6% for GLS. Intra-observer variabilities were 4.6 ± 2.5% for LVEF, 5.7 ± 3.2 for WMS, and 5.8 ± 3.4% for GLS. At 30-day follow-up, inter-observer variabilities were 5.2 ± 2.9% for LVEF, 4.9 ± 3.3 for WMS, and 5.7 ± 3.3% for GLS. Intra-observer variabilities were 4.6 ± 3.0% for

### TABLE 1 Baseline characteristics of study population

| Age (years), mean ± SD | 58.8 ± 14 |
| Male gender, n (%)  | 64 (58.2) |
| DM                  | 30 (27.3) |
| HTN                 | 36 (32.7) |
| Smoking             | 43 (39.1) |
| Obesity             | 25 (22.7) |
| Known dyslipidemia  | 22 (20.0) |
| FH of premature CAD | 17 (15.5) |
| PH of CAD           | 19 (17.3) |
| PH of coronary interventions | 11 (10.0) |
| PCI                 | 10 |
| CABG                | 1 |

DM = diabetes mellitus; HTN = hypertension; FH = family history; CAD = coronary artery disease; PH = past history; STEMI = ST-elevation myocardial infarction; PCI = percutaneous coronary interventions; CABG = coronary artery bypass graft.

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LVEF, 4.8 ± 2.8 for WMS, and 5.2 ± 2.8% for GLS. The test–retest variability of GLS was 5.0 ± 2.1% (maximum 80.8, minimum −112.3).

### 3.5 Predictors of 30-day outcome

ROC analysis showed that (1) a cutoff value of baseline GLS > −12.65% predicted 30-day MACEs with a sensitivity and specificity of 77.8% and 83.7%, respectively (AUC 0.784, 95% CI 0.646–0.921, P < .001), (2) a cutoff value of baseline WMSI 1.25 predicted 30-day MACEs with a sensitivity and specificity of 72.2% and 74.4% (AUC 0.749, 95% CI 0.640–0.857, P = .001), (3) a cutoff value of baseline LVEF 54.5% predicted 30-day MACEs with a sensitivity and specificity of 55.6% and 72.1% (AUC 0.698, 95% CI 0.567–0.829). (Figure 2). Of note, and to consolidate the validity of our results, we excluded 6 urgent revascularization events from the ROC analysis as it is known that revascularization is totally independent of LV function and almost exclusively related to anatomy.

Moreover, a multivariate logistic regression analysis model adjusted for all other possible covariates (including method of reperfusion) using the occurrence of MACEs as a dependent factor showed baseline GLS value > −12.65% to be the only significant independent predictor for occurrence of MACEs (OR 19.54, 95% CI 6.3–61.1, P < .001).

Using the cutoff baseline GLS value of >−12.65% to stratify whole study population, it was found that those patients with GLS > −12.65% experienced the combined MACEs endpoint significantly higher than those with GLS < −12.65% (relative risk = 8.86, 95% CI = 3.6–21.7, P < .001). All individual components of the 30-day endpoint showed statistically higher rates in the group with GLS > −12.65% (Table 3).

## 4 DISCUSSION

Great interest is focused on improving short- and long-term prognosis of patients who recently sustained STEMI. Measurement of LVEF (whether performed by Simpson’s method or by the qualitative scoring of myocardial segments) following STEMI has long been a cornerstone step for risk stratification process that helps to guide treatment decisions and other secondary preventive measures. Currently, angiotensin-converting enzyme inhibitors (ACEIs) are indicated for those patients with impaired LV systolic function with LVEF 40%–45% following MI. Similarly, aldosterone antagonists are indicated in those with LVEF < 40% if accompanied by in-hospital heart failure or DM. This leaves patients with preserved LVEF following STEMI with weak and ambiguous treatment recommendations. Taking into account that LVEF lacks discriminative power within normal ranges and that not all patients with preserved systolic function after STEMI have good prognosis, one may realize that it is essential to look for novel measures for LV systolic function which could define high-risk patients among a group that has always been mistakenly thought to be at low risk.2
The prognostic value of GLS may in part be determined by the ability of GLS to reflect infarct size after MI, which has been demonstrated in several studies. Subendocardial longitudinal fibers are sensitive to hypo-perfusion in the setting of ischemia, so GLS may also reflect the area at risk.

The present study performed exclusively in patients with preserved LVEF following successful reperfusion of STEMI demonstrated that measurement of baseline GLS using a relatively rapid bedside semiautomated tool instead of the time-consuming post-processing methods allowed rapid risk assessment and predicted 30-day adverse outcome among patients with LVEF ≥ 50% with acceptable sensitivity and specificity (77.8% and 83.7%, respectively) using a cutoff value >-12.65%. We showed also that GLS is more predictive than WMSI and LVEF as regard to occurrence of 30-day MACEs. Additionally, baseline GLS value >-12.65% provided independent information concerning combined endpoint of cardiovascular mortality, readmission for heart failure, and urgent revascularization.

These results are similar to Ersbøll et al who showed in a much larger study (performed in a nearly identical population to ours) that baseline GLS >-14% was significantly associated with cardiovascular death (HR: 12.7; 95% CI: 3.0–54.6; P < .001) and heart failure hospitalization (HR: 5.31; 95% CI: 1.50–18.82; P < .001) and those with baseline GLS >-14% experienced the combined endpoint 3 folds higher than those with baseline GLS < -14% (HR: 3.21; 95% CI: 1.82–5.67; P < .001).

Several studies have previously evaluated the prognostic role of baseline GLS in unselected patient population in the setting of MI; Hung et al demonstrated the prognostic role of GLS in 603 high-risk patients with MI from the Valsartan in Acute Myocardial Infarction Study, and both Munk et al and Antoni et al demonstrated the prognostic value in STEMI. Although these studies had larger sample size, they were retrospective in nature and used a time-consuming algorithm for calculation of GLS. Furthermore, both studies carried out in STEMI patients included reinfarction in the combined endpoint which was not predicted by either GLS or LVEF in a much larger cohort of 849 patients evaluated by Ersbøll et al. The combined secondary endpoint in the study by Antoni et al was driven in large part by elective revascularization, which can often be anticipated from the coronary anatomy obtained at baseline. Taking these limitations of endpoint selection into consideration, we did not include either reinfarction or “elective” revascularization into our study’s follow-up endpoint in order not to make it a much complex one. Of note, none of the above-mentioned studies exclusively addressed population with preserved EF following STEMI (a group whose treatment decisions are still not clear), giving novelty to our findings.

5 | CONCLUSION

Semiautomated calculation of GLS significantly predicts 30-day adverse outcome in patients with preserved LVEF following STEMI above and beyond traditional identifiers of high risk. We recommend close monitoring to those patients by scheduling frequent follow-up visits and attention to proper prescription of guideline-directed medical and interventional therapies.

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STUDY LIMITATIONS

No analysis of the radial and circumferential deformation was performed.

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