



# Left ventricular global longitudinal systolic function predicts mortality in sepsis independent to the shock index

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**Background:** Whether left ventricular (LV) global longitudinal systolic dysfunction refines risk stratification in sepsis/septic shock independent to shock index is unknown.

**Methods:** Shock index [(SI), heart rate (HR)/systolic blood pressure (BP), bpm/mmHg], LV global longitudinal strain (GLS, 2D-speckle-tracking-based, %), ejection fraction (EF, by planimetry), Sepsis-related Organ Failure Assessment (SOFA) score, and blood tests were assessed in patients with sepsis/septic shock at the admission in the Emergency Department. Follow-up was performed at 7 and 28 days from admission, accounting for all-cause mortality, major co-morbidities and SOFA  $\geq 2$ .

**Results:** In consecutive patients meeting inclusion criteria (n=123, 79% of the cohort), SI was  $<0.7$  in 48 patients (39%, i.e., without hemodynamic instability), 50 (41%) had possible hemodynamic instability by SI between 0.7 and 0.99, 25 (20%) had hemodynamic instability by a SI  $\geq 1$ . More abnormal GLS, and not SI, predicted mortality day-28 follow-ups (adjusted hazard ratio 1.3 per 1% of GLS closer to 0,  $P<0.05$ ) independently of age, comorbidities and SOFA  $\geq 2$ ; a consistent trend was found with mortality data at day-7 follow-up (adjusted hazard ratio=1.3,  $P=0.05$ ). LV end-diastolic volume index, cardiac index, systemic vascular resistance index and the peak velocity of the mitral E wave did not differ according to SI-strata. Age, body mass index, GLS and EF did not differ among SI groups, whereas female gender tended to be higher with higher SI (all  $P>0.5$ ). Prevalence of SOFA  $\geq 2$ , of diabetes, coronary heart disease (CHD), and chronic kidney dysfunction were comparable among SI groups; prevalence of cancer was lowest in the group of patients with low SI, chronic obstructive pulmonary disease (COPD) was higher with high or low SI. Blood lactate at admission tended to be higher with SI  $\geq 1$  than  $<0.7$  while troponin did not differ among SI groups.

**Conclusions:** In sepsis/septic shock, LV GLS and not SI predicted all-cause mortality at day-28 follow-up independently of SOFA  $\geq 2$  and major co-morbidity.

**Keywords:** Myocardial; function; echocardiography; sepsis; mortality; risk

Received: 11 December 2017; Accepted: 30 March 2018; Published: 26 April 2018.

doi: 10.21037/jeccm.2018.04.01

View this article at: <http://dx.doi.org/10.21037/jeccm.2018.04.01>

## Introduction

Although sepsis is a relatively infrequent clinical syndrome (1), sepsis (2) remains a challenging issue worldwide (3), associated with high mortality rate (4,5), and elevated costs of medical management. In sepsis, fatal events may be accounted for by refractory cardiovascular failure in as many as 1 patient in 3, and myocardial injury can be found in approximately 1 patient in 2 in post-mortem necropsy data (6). In septic patients, left ventricular (LV), ejection fraction (EF) and the shock-index (SI), a metric of hemodynamic instability as defined by the ration between heart rate (HR) and systolic blood pressure (BP), are often assessed for risk stratification. However, LV EF does not represent LV myocardial contractility in intact human hearts due to its high dependency from LV loading conditions and geometry (7-10), and the relationships of LV EF to outcome in sepsis and septic shock is inconsistent literature (11-20). Moreover, the prognostic importance of the SI in sepsis has been not consistent in literature (21-29).

LV global peak systolic strain (GLS) is a measure of longitudinal myocardial contractility (30), found to be related to prognosis in sepsis in particular in short follow-ups (19,20). We hypothesized that GLS may contribute to risk stratification in sepsis or septic shock independently of SI, because in sepsis, impaired myocardial systolic function may not be a simple manifestation of unstable coronary perfusion secondary to hemodynamic instability (31-34).

## Methods

In a time window going from October 2012 to June 2015, consecutive patients not in dialysis, admitted to a High-Dependency-Observation Unit of the Emergency Department, with sepsis or septic shock by standard definition (2), were evaluated (n=155) for hemodynamic instability and assessment of LV structure and function (21% excluded from the current analyses due to poor quality of imaging). Outcome was evaluated in a prospective study design. Events comprised death by any cause, assessed in-hospital by medical records, or by telephone and chart reviews after discharge. Re-hospitalizations were not accounted as events. Mortality rate was censored at day-7 (16%) as well as at day-28 (30%) from hospitalization. Time to event was defined as the difference between date of event and date of hospitalization, whereas for survivors, the observation time was set at 7 and 28 days by definition. No patient was lost at follow-up.

As reported previously (19,35), sepsis was defined by the coexistence of two or more of the following criteria: temperature  $>38$  or  $<35$  °C, HR  $>90$  beats/minute, respiratory rate  $>20$  breaths/minute or arterial partial pressure of carbon dioxide  $<32$  mmHg ( $<4.3$  kPa), white cell count  $>12,000$  cells/mm<sup>3</sup>, or  $<4,000$  cells/mm<sup>3</sup>, or presence of immature forms  $>10\%$ , with further evaluation of arterial blood lactate concentration. Sepsis-related Organ Failure Assessment (SOFA) score was used to assess sepsis severity (36), and to increase the sepsis-related inflammatory syndrome as recommended more recently (37-39). Shock was defined as systolic BP below 90 mmHg, or abrupt systolic BP drop of at least 40 mmHg from initial values, unresponsive to intravenous fluids and persisting for more than 20 minutes. Coronary heart disease (CHD) was defined based on medical history, charts review, ECG and echocardiographic findings as specified previously (19,40). History of chronic obstructive pulmonary disease (COPD) was defined based on medical charts review and therapy. History of chronic kidney disease (CKD) was defined by laboratory findings (serum creatinine above 1.2 mg/dL or 106.1 mmol/L) within a year from the hospitalization. History of cancer was assessed based on medical chart review. The study protocol was approved by the "Toscana - Area vasta - Centro" inter-institutional ethic committee (registration number OSS.13.031).

Echocardiography was performed within 24 h from the admission by a standardized protocol (41-43) and settings (iE33, Philips Medical System, Andover, MA, USA) allowing acquisitions of digital loops of at least 2 cardiac cycles with frames per second (fps) of 45 or greater (mean value observed  $57 \pm 5$  fps). LV EF was assessed by ventricular planimetry (44). LV stroke volume was computed as the difference between end-diastolic and end-systolic volumes; stroke index was computed as stroke volume/body surface area; cardiac index was computed as stroke index X HR and converted to L/min/m<sup>2</sup>. Systemic vascular resistance index was computed as mean BP\*80/cardiac index (divided by 1,000, kdyne\*s/cm<sup>5</sup>\*m<sup>2</sup>). The early wave of the LV filling (E wave) was sampled by pulsed Doppler at the tips of the mitral valve. Speckle-tracking analysis was performed off-line days or weeks after the admission (Philips QLAB Advanced Quantification Software version 8.1) in random sequence, and by experienced personnel (VP as final arbiter) blind to clinical data and outcome, by a methodology applied widely (19,43,45). Briefly, myocardial deformation was analyzed from two-dimensional gray-scale loops of the apical views of the left ventricle, by automatic

tracking of myocardial speckles, granted a manual selection of the region of interest. GLS was calculated averaging the negative peak of longitudinal strain from ventricular segments from the apical 4-chamber, 2-chamber views and apical-long axis. Subnormal LV GLS was defined by values  $>-15\%$  (46); very depressed GLS was empirically defined based on GLS  $>-10\%$ . In-house test-retest reproducibility analyses for assessment of LV EF and GLS have been tested and reported previously (19).

### Statistical analysis

Statistical analyses were conducted using IBM SPSS® software package (version 22). Data in table are mean values  $\pm$  1 standard deviation of the mean, or counts and percent. Cases with missing data ( $<1\%$  of the study sample) were excluded analysis by analysis. Patients were stratified in three groups according to SI values  $<0.7$  or  $\geq 0.7$  but  $<1$ , or  $\geq 1$  bpm/mmHg (26). For continuous variables, the null hypothesis was tested using the Student's t test for independent groups, employing log-transformed variables in the case of excessively skewed distribution; Fisher's exact test was used to compare counts in cross-tables (47). Receiver operating characteristic (ROC) curve was employed to evaluate the performance of classification of events, and the area under the curve of positive rate (sensitivity) versus false positive rate (1-specificity) for values of single variables was assumed as indicator of accuracy of variable-specific performance of classification. According to current recommendations (48,49), based on day-28 mortality rate, Cox's proportional hazard function was employed to explore whether SI and GLS predicted time-dependent mortality accounting for age, SI, and history of CHD, CKD, COPD, SOFA  $\geq 2$ , diabetes and of cancer, using a stepwise selection method with entry testing based on the significance of the score statistic (for  $P<0.05$ ), and removal testing based on the probability of a likelihood-ratio statistic based on the maximum partial likelihood estimates (for  $P>0.1$ ) (50). Time-varying effects of SI, GLS and EF on prognosis were tested by time-varying Cox' proportional hazard models, generating separate interaction terms of time with SI, GLS and EF, added to the models along with primary variables. Correlates of prognosis at day-7 follow-up were also provided as pathophysiologically relevant in severe sepsis. Two-tailed  $P<0.05$  was used to reject null hypotheses.

### Results

Among the 123 patients, not mechanically ventilated, who comprised the study sample (21% excluded due to poor quality of echocardiographic imaging), 48 (39%) showed a SI below 0.7 bpm/mmHg, and 25 (20%) a SI  $\geq 1$  bpm/mmHg; hence, 50 participants had a SI comprised between 0.7 and 0.99 bpm/mmHg (Table 1, missing laboratory data  $<1\%$  of the sample). In univariate analyses, age did not differ among groups of patients stratified based on SI; female gender tended to be more frequent among the patients with higher SI values; prevalence of diabetes and proportion of those with history of CKD did not differ between groups; history of CHD showed a not statistically significant trend toward lower prevalence with higher SI. History of COPD was lowest with SI comprised between 0.7 and 0.99 bpm/mmHg while history of cancer was lowest in the group of patients with SI  $<0.7$  bpm/mmHg. BMI was comparable among the three groups. Almost by definition, mean BP was lower and HR was higher in patients with higher SI. Differences in blood lactate concentration showed a trend toward higher values with SI  $\geq 1$  vs.  $<0.7$  while differences in troponin I did not reach the statistical significance across SI strata. Proportion of subjects with SOFA  $\geq 2$  did not differ significantly across the SI groups.

As reported in Table 2 (no missing data), LV end-diastolic volume index and E wave peak velocity were comparable among groups by SI; stroke index was slightly lower with SI  $\geq 1$  vs. SI  $<0.7$  ( $P<0.01$ ), whereas cardiac index was comparable among groups according to SI; systemic vascular resistance index tended to be lower with higher SI without reaching the statistical significance. Percent change in inferior vena cava with a single rapid deep breath did not differ among groups (35% vs. 33% vs. 30% according to SI groups as in Table 2,  $P>0.1$ ).

In univariate analysis, LV EF (Figure 1) and LV GSL (Figure 2) did not differ across groups of patients according to SI. Mean duration of follow-up was of 23 days (range, 1–28 days). Mortality by day-7 ( $n=19$ , 16%) showed a trend toward higher incidence with higher SI without reaching the statistical significance in univariate analyses, whereas at day-28 follow-up, the mortality ( $n=37$ , 30%) was comparable among the SI strata at admission.

SI did not correlate with GLS ( $r=0.14$ ,  $P=0.13$ ) as well as with EF ( $r=-0.17$ ,  $P=0.07$ ). Figure 3 showed that GLS may vary widely per unit of SI; moreover, deaths by day-7 ( $n=18$ , 15%) tended to cluster according GLS  $>-15\%$  more than

**Table 1** Clinical characteristics and mortality by presentation according to the shock index

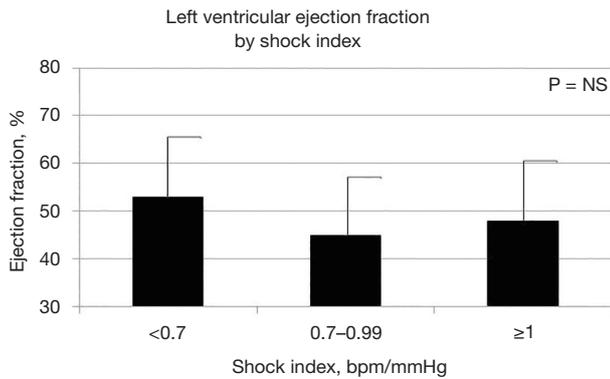
Characteristics	Shock index (SI), bpm/mmHg			P		
	Groups (cut-point) <0.7 (A)	Groups (cut-point) 0.7–0.99 (B)	Groups (cut-point) ≥1 (C)	A vs. B	A vs. C	B vs. C
N [% of total]	48 [39]	50 [41]	25 [20]	–	–	–
Age, years	73±12	75±13	71±14	NS	NS	NS
Female gender, %	29	46	58		0.04	
Diabetes, %	42	24	28		NS	
History of CHD, %	19	16	8		NS	
History of CKD, %	25	22	24		NS	
History of COPD, %	25	6	16		0.03	
Cancer, %	13	42	36		0.003	
BMI, kg/m <sup>2</sup>	25.5±5.0	23.4±3.6	23.4±4.3	NS	NS	NS
Mean BP, mmHg	86±14	79±11	66±10	0.016	0.000	0.003
HR, bpm	78±13	96±16	110±14	0.000	0.000	0.000
Lactate, mmol/L	1.25±0.71	2.17±2.6	3.19±2.27	NS*	0.001*	NS*
Troponin I, ng/dL	1.86±9.4	0.99±2.5	1.93±4.6	NS*	NS*	NS*
SOFA ≥2, %	38	41	20		NS (P=0.4)	
Deceased by day-7 follow-up, n [%]	5 [11]	8 [16]	7 [28]		NS (P=0.1)	
Deceased by day-28 follow-up, n [%]	12 [28]	15 [31]	9 [36]		NS (P=0.5)	

Shock Index: heart rate (HR, bpm)/systolic blood pressure (SBP, mmHg), with higher values indicative of greater hemodynamic instability. \*, after log-transformation. CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; BP, blood pressure; HR, heart rate; SOFA, Sepsis-related Organ Failure Assessment score (higher values indicative of more severe multi-organ failure); NS, not statistically significant.

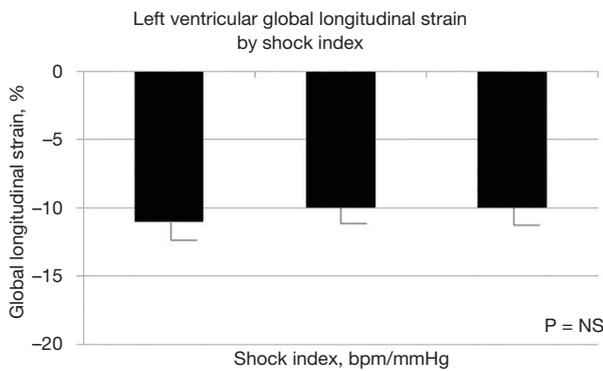
**Table 2** Echocardiographic characteristics by Shock Index

Characteristics	Shock index (SI), bpm/mmHg			P		
	Groups (cut-point) <0.7 (A)	Groups (cut-point) 0.7–0.99 (B)	Groups (cut-point) ≥1 (C)	A vs. B	A vs. C	B vs. C
N [% of total]	48 [39]	50 [41]	25 [20]	–	–	–
EDV index, mL/m <sup>2</sup>	46±17	47±21	41±16	NS	NS	NS
E wave peak velocity, cm/s	86±28	84±30	79±19	NS	NS	NS
Stroke index, mL/m <sup>2</sup>	24±9	21±9	17±6	NS	<0.01	NS
Cardiac index, L/min/m <sup>2</sup>	1.8±0.7	1.9±0.9	1.9±0.7	NS	NS	NS
Systemic vascular resistance index, kdyne*s/cm <sup>5</sup> *m <sup>2</sup>	4.4±1.7	3.8±1.9	3.5±1.8	NS	NS	NS

EDV index, left ventricular end diastolic volume/body surface area. NS, not statistically significant.



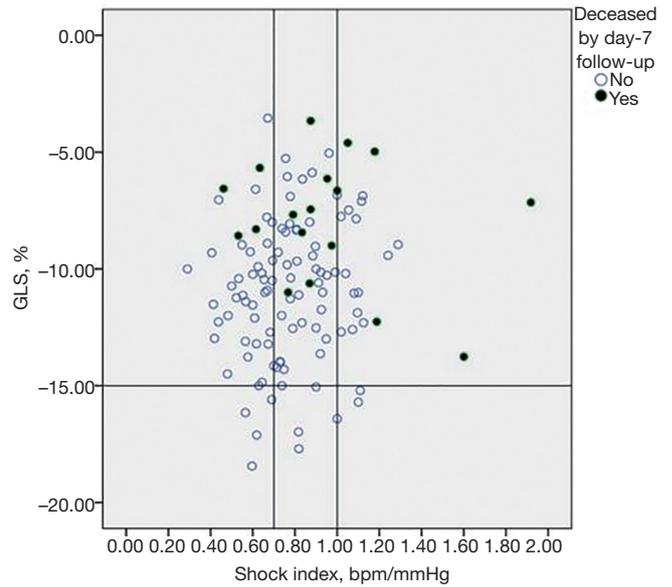
**Figure 1** Black bars represent mean values of left ventricular ejection fraction with 1 standard deviation of the mean represented by the black lines over each bar, by shock index values as indicated on the horizontal axis. Higher values of ejection fraction are indicative of better ventricular systolic performance. NS, not statistically significant.



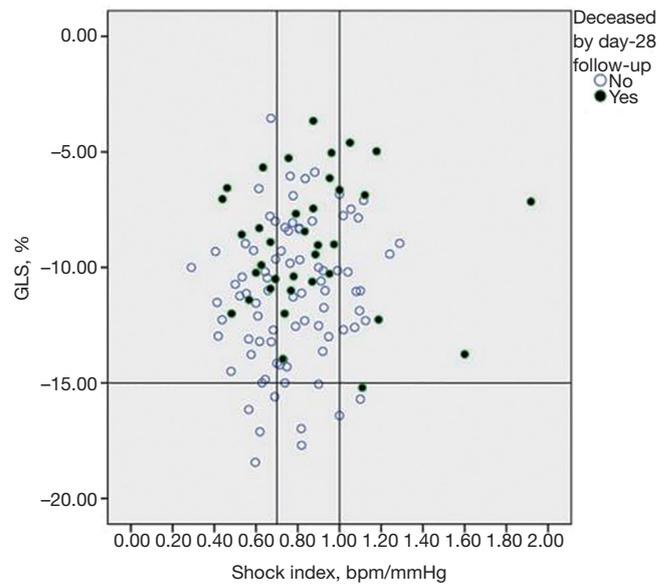
**Figure 2** Black bars represent mean values of left ventricular global longitudinal strain with 1 standard deviation of the mean represented by the black lines over each bar, by shock index values as indicated on the horizontal axis. More negative values of Global Longitudinal Strain are indicative of better longitudinal myocardial systolic performance. NS, not statistically significant.

according to SI, as demonstrated by the fact that events were recorded over a large interval of SI values, but almost never in the case of GLS <-15%, even for SI ≥1. Mortality data by day-28 follow-up (n=36, 30%) were consistent with those reported by day-7 follow-up (Figure 4).

By ROC curves, less negative GLS showed a statistically significant accuracy of the performance of classification of events by day 28 follow-up (area under the curve 0.68, 95% confidence interval 0.58–0.79, P=0.001), followed by lower LV EF (area under the curve 0.63; 95% CI, 0.51–0.75;



**Figure 3** Deceased by day-7 follow-up according to the global longitudinal strain (GLS, vertical axis) plotted against stroke index (SI, horizontal axis).



**Figure 4** Deceased by day-28 follow-up according to the global longitudinal strain (GLS, vertical axis) plotted against stroke index (SI, horizontal axis).

P=0.03), whereas increasing values of SI (area under the curve 0.57; 95% CI, 0.46–0.69; P=0.1) did not appear a significant and accurate predictor events. The interaction

**Table 3** Prediction of mortality in sepsis and septic shock: the Cox proportional hazard models

Parameters	Adjusted* hazards (95% confidence intervals, P)	
	Mortality at day 7, n=19	Mortality at day 28, n=37
Shock index (per bpm/mmHg)	11 (0.7–174, 0.09)	3 (0.5–20, 0.3)
GLS (per %)	1.4 (1.0–1.7, 0.05)	1.3 (1.0–1.6, 0.03)

\*, covariates in the model: age, left ventricular ejection fraction, sepsis related organ failure score  $\geq 2$  vs.  $< 2$ , history of coronary heart disease, kidney disease, chronic obstruction pulmonary disease, cancer. GLS, global longitudinal strain.

of GLS with SI (GLS\*SI, %\*bpm/mmHg) showed an accuracy of the performance of classification of events by day 28 follow-up not superior to GLS alone (area under the curve 0.60; 95% CI, 0.48–0.71;  $P=0.09$ ). Data using day-7 mortality were consistent (data not shown). In multivariable analyses, mortality rate at day-28 follow-ups was predicted by GLS and not by the SI, independent of covariates and cofounders (Table 3) while survival analysis considering day-7 follow-up showed a consistent trend despite a smaller number of events recorded by the follow-up. Results did not change when interaction terms of time and GLS, EF as well as SI were generated and added to the Cox's proportional hazard models (data not shown).

## Discussion

In patients with sepsis or septic shock, we provided novel information, as we showed that LV GLS is prognostically relevant at day-28 follow-up beyond the SI independently of a number of clinical confounders including history of cancer and of ischemic heart disease, and independently of SOFA score  $\geq 2$ . Furthermore, we showed that in sepsis or septic shock, LV systolic function, either assessed by EF or GLS, cannot be inferred by assessing SI, which is consistent with the notion that LV dysfunction in sepsis is not the simple result of myocardial ischemia (31,32). Therefore, assessment of LV GLS may add useful short-term prognostic information in the early phase of the risk stratification in sepsis/septic shock independent to the assessment of SI, and may be useful for triaging patients in the Emergency Department. Nevertheless, further studies are required to assessment whether LV GLS, and its change over time, may guide or influence treatment options, and contribute to change outcomes in sepsis as to date vasopressors/inotropes have been unable to change prognosis in septic shock (28,51-53).

SI has been indicated as useful tool for triaging patients with potentially critical clinical conditions requiring intensive

surveillance (21). Current guidelines suggest the use of SOFA to increase specificity of sepsis-related inflammation and prognosis (37). Adding a SOFA score equal or greater than 2 to the survival models did not impact the correlation of GLS with prognosis. SI and SOFA did not show strong inter-correlation in our study. In a previous study in a large cohort of patients with sepsis, SI  $\geq 1$  showed high specificity (80%) and negative predictive value (88%) with regard to outcome in the mid-term (28-day follow-up mortality) (27), but also showed relatively poor sensitivity (37%) and positive predictive value (23%); SI  $\geq 0.7$  had a negative predictive value as high as 95%, suggesting that such a simple, bedside no-cost index could be used in sepsis for early patient's characterization. Nevertheless, the most recent Protocol-Based Care for Early Septic Shock (ProCESS) study failed to reach the specific goal to change prognosis in group of patients with severe sepsis/septic shock specifically characterized by their hemodynamic conditions as expressed by the SI (28). Our study added new information by showing that the early assessment LV GLS predict all-cause death while SI was not prognostically relevant in patients with sepsis, in particular in the very short term. Interesting, LV end-diastolic volume, the peak velocity of the mitral E wave, cardiac index and systemic vascular resistance index did not differ significantly among SI-strata, suggesting that central hemodynamics was not the main player in determining the ratio between HR and systolic BP.

Although in experimental models in sepsis, cardiac output has being found to be increased and myocardial perfusion decreased (34), an increase in cardiac output may contribute to an increase in LV external myocardial work and oxygen consumption (34). Because SI tend to be higher with higher HR and with lower systolic BP, higher LV external work cannot be inferred by higher SI. In fact, in our study, cardiac index was not higher with higher SI while mean BP was lower with higher SI. Moreover, LV external work is proportional to stroke volume and to mean aortic pressure (54-56), as well as to systolic tension (or stress) applied to

the left ventricle (57). Of note, systolic BP is one of the determinants of systolic wall stress and of myocardial blood flow (58). In our study, stroke index was only marginally lower with higher SI, cardiac index was comparable among SI-based groups, and mean BP was lower with higher SI. Those results may explain at least in part the reason why SI did not correlate with GLS or with EF, along with the fact that LV systolic function is not the simple manifestation of myocardial under-perfusion (32-34). Myocardial injury in sepsis is associated with myocardial edema, inflammatory cell infiltration, cytokines-mediated damage and micro-vascular disease, and is more likely associated with impaired longitudinal LV myocardial contractility (6,59-62) rather than SI. A weak relationship between SI and GLS while the latter emerges as an important predictor of events in sepsis and septic shock, may help explaining the relatively low power of SI as prognostic factor in sepsis.

The present study has a number of limitations. Initial definition of sepsis was based on criteria (2), which have been considered not sufficiently specific as they are excessively oriented to account for the inflammatory response. More recently, new criteria for definition of sepsis have focused on more infection-related life-threatening inflammation (37). Retrospective analyses of current databases in the research field on sepsis suggest that the new definition including SOFA (36) is able to increase the specificity of sepsis-related inflammatory syndrome and predict greater mortality (38,39). At least in part, we accounted for the issue of the impact of sepsis definition on findings by considering a SOFA  $\geq 2$  as covariate in the survival analyses. The study focused on patients not mechanically ventilated, which may have contributed to the high feasibility of LV function quantification in our study, and could have characterized patients with less severe sepsis and shock; nevertheless, mortality rate by day-7 and day-28 was in line with expectations from a more general source of patients (27). Moreover, the study focused on data collected at the admission in the High-Dependency Observational Unit, without accounting for their changes over-time and initial scenarios in the emergency ward at first medical contact. History of CHD and of diabetes did not impact the relationship between LV GLS and prognosis, which suggests that values of LV GLS at admission in the Emergency Department are largely determined by sepsis. We did not assess circumferential strain systematically in the study population, which could be used to characterize the disease process involving differently oriented myocardial fibers in the LV wall (63); nevertheless, in our

hands, test-re-test variability was higher for circumferential than longitudinal strain, and early impairment of the LV longitudinal function compared to the relatively preserved circumferential function and LV EF in the early phase of the myocardial disease process has been reported previously (63).

In conclusion, in sepsis or septic shock, depressed LV longitudinal systolic performance, and not high SI, may predict all-cause mortality in short follow-ups independently of comorbidities including cancer, CAD, CKD and SOFA  $\geq 2$ .

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study protocol was approved by the “Toscana – Area vasta - Centro” inter-institutional ethic committee (registration number OSS.13.031) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). All patients gave informed consensus to enter the study.

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doi: 10.21037/jeccm.2018.04.01

**Cite this article as:** Palmieri V, Innocenti F, Guzzo A, Donnini C, Stefanone VT, Pini R. Left ventricular global longitudinal systolic function predicts mortality in sepsis independent to the shock index. *J Emerg Crit Care Med* 2018;2:38.