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Prognostic stratification in septic patients with overt and cryptic shock by speckle tracking echocardiography

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Abstract
We evaluated the prevalence and prognostic value of left (LV) and right (RV) ventricular systolic dysfunction in the presence of overt and cryptic shock.In this prospective study, between October 2012 and June 2019, we enrolled 354 patients with sepsis, 41% with shock, among those admitted to the Emergency Department High-Dependency Unit. Patients were grouped based on the presence of shock, or by the presence of lactate levels ≥ (LAC +) or < 2 mmol/L (LAC-) evaluated within the first 24 h. By echocardiography performed within 24 h from the admission, LV systolic dysfunction was defined as global longitudinal strain (GLS) > -14%; RV systolic dysfunction as Tricuspid Annular Plane Systolic Excursion (TAPSE) < 16 mm. All-cause mortality was assessed at day-7 and day-28 follow-up. Mean values of LV GLS (-12.3 ± 3.4 vs -12.9 ± 3.8%) and TAPSE (1.8 ± 0.7 vs 1.8 ± 0.5 cm, all p = NS) were similar in patients with and in those without shock. LV GLS was significantly worse in LAC + than LAC- patients (− 11.2 ± 3.1 vs − 12.9 ± 3.7%, p = 0.001). In patients without shock, as well as in those LAC-, LV dysfunction was associated with increased day-28 mortality rate (78% vs 57% in non-survivors and survivors without shock and 74% vs 53% in non-survivors and survivors LAC-, all p < 0.01). LV (RR 2.26, 95% CI 1.37–3.74) and RV systolic dysfunction (RR 1.85, 95% CI 1.22–2.81) were associated with increased 28-day mortality rate in addition and independent to LAC + (RR 1.81, 95% CI 1.15–2.84). In conclusion, LV and RV ventricular dysfunction were independently associated with an increased mortality rate, altogether with the presence of cryptic shock.

Keywords Septic shock · Lactate levels · Systolic dysfunction · Prognosis

Introduction

Septic shock is characterized by both vasodilation and cardiac dysfunction, leading to a decrease in blood pressure. An abnormal vascular resistance has been reported as the major hemodynamic abnormality [1], and a key determinant of subnormal tissue perfusion and shock, which, during sepsis, is considered a marker of poor prognosis.

Based on Sepsis-3, the shock is identified by the presence of hypotension unresponsive to fluid challenge and increased lactate levels [2]. In fact, during shock, normal macrohemodynamics do not guarantee normal microcirculation in patients with circulatory failure [3, 4]. In several experimental models, during the development of acute circulatory failure, a simultaneous deterioration of the systemic circulation and microcirculation has been demonstrated [5]. Conversely, during the resuscitation phase, the relationship was not maintained. Therefore, the administration of fluid can normalize systemic hemodynamic, but microcirculatory alterations can persist and impair tissue perfusion [6–8]. During the earliest hours of shock, the lactate level increase is common and parallels the systemic hemodynamic derangement. As compared to the relationship between macro- and microcirculation, during the following phases, the correlation between the decrease in lactate level and improvement in microcirculation is less obvious. The marked heterogeneity of experimental and clinical models, where this relationship has been studied, could justify these

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results. However, an early normalization of lactate levels has been correlated with a good prognosis [9].

A systolic dysfunction, involving left as well as right ventricle, frequently occurs [10–13] and it predicts prognosis in septic patients independent to shock [14]. However, the prognostic value of LV and right ventricular (RV) systolic dysfunction in septic patients with or without shock remains unclear.

Aim of the present study was to evaluate the prevalence and the prognostic impact of LV and RV systolic dysfunction in septic patients stratified by the presence of shock or by the presence of persistently high lactate levels within 24 h from hospitalization.

Methods

Study design and setting

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 consent to enter the study.

In this observational prospective study, we included consecutive patients admitted to the Emergency Department–High-Dependency Unit (ED-HDU) between October 2012 and June 2019; sepsis diagnosis was based on 2001 criteria [15] for patients included until June 2016; since then, patients were selected based on Sepsis-3 [2, 16]. Septic shock was defined as persistent hypotension, requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg despite the administration of the initial bolus (20–30 ml/kg), based on current guidelines.

Patients in whom LV walls could not be evaluated through standard apical views, as well as those with left heart valvular disease more than moderate were excluded. Intubated patient was not admitted because invasive mechanical ventilation is not feasible in this clinical setting.

Criteria to define the presence of coronary artery disease (CAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and neoplasia have already been defined elsewhere [17]. Based on previous medical records, we defined known LV or RV systolic dysfunction respectively as LV ejection fraction < 50% and TAPSE < 16 mm. Clinical and laboratory data were collected at the admission into the ED (T0) and re-evaluated within 24 h from the admission to the ED-HDU; at the same time intervals, Sequential Organ Failure Assessment (SOFA) score was calculated. Lactate levels were collected upon ED admission (T0), and after 6 (T6), 12 (T12) and 24 (T24) hours and a value ≥ 2 was defined abnormal [2]. Treatments followed current guidelines [18].

Echocardiographic measurements

Echocardiography was performed within 24 h from the admission by a standardized protocol following recommendations of the American and European Societies of Echocardiography. We used two echocardiographic machines (iE33, Philips Medical System, Andover, MA and Vivid 5, General Electrics, Horten, NW) equipped with phased-array cardiological probes and standardized settings allowing acquisitions of digital loops of at least two cardiac cycles with at least 45 frames per second (mean value obtained, 57 ± 5 frames per second). LV ejection fraction (EF) was assessed by 2-plane Simpson's method, bedside, as part of the clinical workup at admission [19]. LV assessment has been described previously, as well as measurements reproducibility (12). Speckle-tracking analysis was performed off-line several days or weeks from the admission using a commercially available software by standard methodology previously applied in other studies, in random sequence, and by experienced physicians (VP and FI as final arbiters) blind to clinical data and outcome [20, 21]. LV systolic dysfunction (LVSD) was defined as LV Global Longitudinal Strain (GLS) ≥ -14%, based on the value with a 91% sensitivity and 75% specificity for 28-day mortality rate obtained by the ROC curves analysis [22].

The RV was assessed at end-expiration from a right ventricle-focused 4-chamber view; we measured RV basal, mid and longitudinal diameters (abnormal above 42, 35 and 86 mm, respectively). RV systolic function was estimated through Tricuspid Annular Plane Systolic Excursion (TAPSE), and fractional area change (FAC). We defined RV systolic dysfunction (RVSD) as TAPSE < 16 mm and/or FAC < 35% [23]. Physicians fully trained in echocardiography (FI, VP) analyzed the images.

Outcomes

Outcome was defined as all-cause mortality recorded by tracing medical records within the hospitalization or by phone calls and chart reviews after hospital discharge, irrespective of re-hospitalizations. Mortality rate was censored at day-7 and day-28 from hospital admission. No patient was lost at follow-up.

Statistical analysis

Statistical analyses were conducted using IBM SPSS software package (version 25). Data in table are mean values ± standard deviation or counts and percentage. For continuous variables, the null hypothesis was tested using the Student's *t* test for independent groups; Fisher exact test was used to compare counts in cross tables. Survival analysis

was performed by Cox's proportional hazard function and was used to explore the independent prognostic value of the variables of interest. Two-tailed $p < 0.05$ was used to reject null hypotheses.

Results

The total number of patients was 432. Of those, 23 patients were excluded due to the aforementioned criteria and another 54 due to incomplete echocardiographic assessment of LV and RV function. Therefore, the study population included 354 patients. The SOFA score (6.5 ± 2.3 versus 5.7 ± 4.8, p = NS), the proportion of patients with septic shock (41 vs 38%) and the frequency of all-cause mortality at day-7 (16% vs 17%) and at day-28 (31% vs 29%, all p = NS) were similar between patients excluded and those included in the study. We compared patients included based on Levi's criteria (n = 122) and Sepsis-3 (n = 232). T0 SOFA (5.9 ± 2.7 versus 6.3 ± 2.9), T24 SOFA (6.1 ± 2.8 versus 6.1 ± 3.1, all p = NS) as well as day-7 and day-28 mortality rate (respectively 19% vs 15% and 35% vs 29%, all p = NS) were similar regardless of the selection criteria and only 2 patients included in the first period had a T0 SOFA < 2.

We divided the study population based on two different criteria: 1) patients with and without shock, based on the aforementioned definition and 2) patients with lactate level persistently ≥ 2 mEq/L over the first 24 h (LAC +) or lactate level < 2 mEq/L (LAC-). In Table 1, we compared the clinical characteristics of the study population, based on these selection criteria. Subgroups were similar for age, gender distribution, and prevalence of previous medical conditions, except for a lower prevalence of COPD respectively among patients with shock and LAC + patients. The prevalence of previously known LV and/or RV systolic dysfunction was similar between subgroups.

The source of the infection was similar in patients with and without shock and in LAC + and LAC- patients. Both patients with shock and LAC + patients showed significantly higher heart rate and lower mean arterial pressure, compared to their counterparts. Almost by definition, SOFA score, as well as lactate levels, were higher in patients with shock both at T0 and at T24. We confirmed significant higher values of the SOFA score in LAC + patients, compared with those LAC-. Among LAC + patients, 71% had septic shock, as compared to 35% among LAC- patients ($p < 0.001$). Patients with shock received a higher amount of fluids, both as bolus and infusion, than those without. LAC + and LAC- patients received a similar volemic expansion. Non-invasive ventilation (NIV) or renal replacement treatment were employed in a similar portion of patients in the two sub-groups.

Based on the presence or absence of shock, we did not find any significant difference in terms of RV and LV dimensions and systolic function (Table 2). Conversely, LAC + patients showed a significantly lower LV ejection fraction and LV GLS compared to LAC- patients, in the absence of other relevant differences. We defined LVSD as LVGLS ≥ -14% and RVSD as TAPSE < 16 mm. We identified 103 patients (29%) with normal LV and RV systolic function, 131 (37%) with isolated LVSD, 28 (8%) with isolated RVSD and 92 with both LVSD and RVSD.

Day-7 and day-28 mortality rates were similar in patients with and those without shock (respectively 19% vs 14% and 35% vs 28%, all p = NS), whereas LAC + patients showed a significant higher day-7 and day-28 mortality rate than LAC- patients (29% vs 13%, $p = 0.004$, and 45% vs 28%, $p = 0.01$). As reported in Figs. 1 and 2 (top and bottom), the presence of LVSD or RVSD was associated with an increased all-cause mortality.

To evaluate whether LV and RV systolic dysfunction showed an independent prognostic value, we performed a Cox proportional survival analysis, where we introduced age, the presence of shock, persistent high lactate levels and the presence of LV and RV dysfunction (Table 3). The presence of LVSD and/or RVSD and the persistence of high lactate levels in the first 24 h, were independent predictors of increased mortality rate both at day-7 and day-28 follow-up. The presence of shock did not retain an independent prognostic value.

Discussion

In a population of spontaneously breathing patients with sepsis, LV or RV ventricular structural and functional parameters, as well as laboratory tests, were comparable between patients with and those without shock. Conversely, patients who showed the persistence of lactate levels ≥ 2 in the first 24 h had a significantly worse LV systolic function than those with normalization of lactate levels. The presence of LVSD and RVSD was a predictor of an increased mortality rate, independent to the presence of shock or high lactate levels. However, while shock did not retain an independent prognostic value, the persistence of high lactate level was associated with an increased short- and medium-term mortality rate.

Previous studies failed to demonstrate significant differences in terms of LV and RV structure and function between patients with and without septic shock [11, 12], and they did not definitively establish the association between a LV and/or RV systolic dysfunction and an unfavorable prognosis. These discrepancies could be justified by a marked heterogeneity among the available studies, in terms of entry selection criteria, study populations' size and methods

Table 1 Clinical characteristics of patients with and without shock and of LAC + and LAC- patients

	Patients with shock ($N=144$)	Patients without shock ($N=210$)	LAC + patients ($N=63$)	LAC- patients ($N=291$)
Age (years)	74 ± 12	74 ± 14	77 ± 11	74 ± 13
Male gender (%)	81 (57%)	121 (58%)	27 (44%)	172 (60%)
Previous medical conditions				
Hypertension (%)	74 (53%)	126 (60%)	32 (54%)	167 (58%)
Diabetes (%)	32 (23%)	63 (30%)	14 (24%)	78 (27%)
COPD (%)	15 (11%)	51 (24%)*	5(9%)	60 (21%)*
CKD (%)	36 (26%)	37 (18%)	12 (20%)	59 (21%)
Cirrhosis (%)	13 (9%)	5 (2%)*	6 (10%)	11 (4%)
Neoplasia (%)	49 (35%)	60 (29%)	17 (29%)	88 (31%)
LV and/or RV dysfunction	12 (9%)	19 (9%)	7 (12%)	24 (9%)
Infection source				
Pulmonary	58 (41%)	116 (57%)	23 (38%)	149 (53%)
Urinary tract	35 (25%)	33 (16%)	13 (22%)	55 (20%)
Abdominal	25 (18%)	22 (11%)	10 (17%)	35 (13%)
Soft tissue	8 (6%)	8 (4%)	6 (10%)	9 (3%)
Device	4 (3%)	8 (4%)	0	12 (4%)
Others	12 (9%)	16 (8%)	8 (13%)	20 (7%)
Sepsis severity				
Heart Rate (b/min)	94 ± 21	89 ± 19*	100 ± 20	89 ± 19°
MAP (mmHg)	71 ± 12	82 ± 14°	74 ± 15	78 ± 14*
T0 SOFA	8.4 ± 2.4	4.7 ± 2.1°	7.7 ± 2.7	5.8 ± 2.7°
T24 SOFA	8.1 ± 2.9	4.8 ± 2.2°	8.0 ± 3.3	5.7 ± 2.8°
T0 Lactate (mEq/L)	3.6 ± 2.9	2.9 ± 2.6*	6.0 ± 3.4	2.6 ± 2.2°
T24 Lactate (mEq/L)	2.2 ± 2.4	1.8 ± 2.2	3.7 ± 2.6	1.6 ± 2.1°
T0 Procalcitonin (ng/mL)	86 ± 106	33 ± 76*	86 ± 106	33 ± 76*
T24 Procalcitonin (ng/mL)	78 ± 90	36 ± 77*	78 ± 90	36 ± 77*
Biomarkers				
T0 Troponin (ng/mL)	1.3 ± 3.7	0.7 ± 4.2	1.3 ± 3.7	0.7 ± 4.2
T24 Troponin (ng/mL)	1.6 ± 3.7	0.7 ± 2.7	1.6 ± 3.7	0.7 ± 2.7
T0 NT-proBNP (ng/mL)	18,425 ± 19,680	15,512 ± 29,352	18,425 ± 19,680	15,512 ± 29,352
T24 NT-proBNP (ng/mL)	25,540 ± 31,102	17,271 ± 51,558	25,540 ± 31,102	17,271 ± 51,558
Treatment				
Fluid bolus (ml)	1545 ± 1204	1178 ± 843*	1565 ± 1143	1279 ± 987
Fluid infusion (ml/h)	113 ± 66	97 ± 41*	109 ± 48	102 ± 54
NIV (%)	36 (25%)	70 (34%)	18 (29%)	88 (31%)
Dialysis (%)	11 (8%)	17 (8%)	11 (3%)	17 (5%)

COPD Chronic obstructive pulmonary disease; *CKD* Chronic kidney disease; *MAP* mean arterial pressure; *SOFA* sepsis-related organ failure assessment; *NIV* non-invasive ventilation

*$p<0.05$; °$p<0.001$

employed to evaluate LV and RV systolic function. Even if we consider the studies, which included only patients with septic shock, results did not consistently confirm a worse prognosis in patients with myocardial systolic dysfunction. Our results could be explained by the large study population and the evaluation of LV systolic dysfunction by mean of LV GLS, a less load-dependent measure of LV function compared to conventional echocardiography. TAPSE already demonstrated a good prognostic value [21] and it represents a parameter easily measurable at the bedside, feasible in an Emergency Medicine setting.

To the best of our knowledge, no previous study compared LV and RV dimensions and function between patients with persistently high or normal lactate levels in the first 24 h. Approximately 25% of our patients showed persistently high lactate levels despite an adequate

Table 2 Echocardiographic parameters in patients with and without shock and in patients with (LAC +) and without (LAC-) persistently high lactate levels

	Patients with shock (*N* = 144)	Patients without shock (*N* = 210)	p	LAC + patients (*N* = 63)	LAC- patients (*N* = 291)	*p*
LVEDVI (ml/m^2)	41 ± 18	43 ± 18	NS	40 ± 15	43 ± 19	NS
LV EF (%)	51 ± 16	53 ± 14	NS	46 ± 16	53 ± 15	0.002
LV GLS	− 12.3 ± 3.4	− 12.9 ± 3.8	NS	− 11.2 ± 3.1	− 12.9 ± 3.7	0.001
TDI S wave (m/sec)	8.4 ± 5.9	8.2 ± 4.1	NS	8.2 ± 6.0	8.2 ± 4.6	NS
MV E/A ratio	1.04 ± 0.50	1.03 ± 0.53	NS	1.06 ± 0.57	1.02 ± 0.51	NS
E/E'	9.2 ± 5.6	9.6 ± 5.7	NS	9.6 ± 4.4	9.3 ± 6.0	NS
LA volume(ml)	45 ± 25	43 ± 20	NS	42 ± 20	44 ± 22	NS
RV basal diameter (cm)	3.6 ± 0.8	3.5 ± 0.7	NS	3.6 ± 0.8	3.5 ± 0.7	NS
RV longitudinal diameter (cm)	7.6 ± 1.1	7.6 ± 1.2	NS	7.4 ± 1.2	7.7 ± 1.2	NS
TAPSE (cm)	1.8 ± 0.7	1.8 ± 0.5	NS	1.8 ± 1.0	1.8 ± 0.5	NS
Tricuspid systolic gradient (mmHg)	29 ± 11	29 ± 10	NS	27 ± 12	30 ± 10	NS
Vena cava collapsibility index (%)	21 ± 22	25 ± 25	NS	31 ± 27	22 ± 23	NS

LVEDVI left ventricular end-diastolic volume index; *LV EF* left ventricular ejection fraction; *LV GLS* left ventricular global longitudinal strain; *TDI* tissue Doppler imaging; *MV* mitral valve; *LA* left atrium; *RV* right ventricle; *TAPSE* tricuspid annular posterior systolic excursion

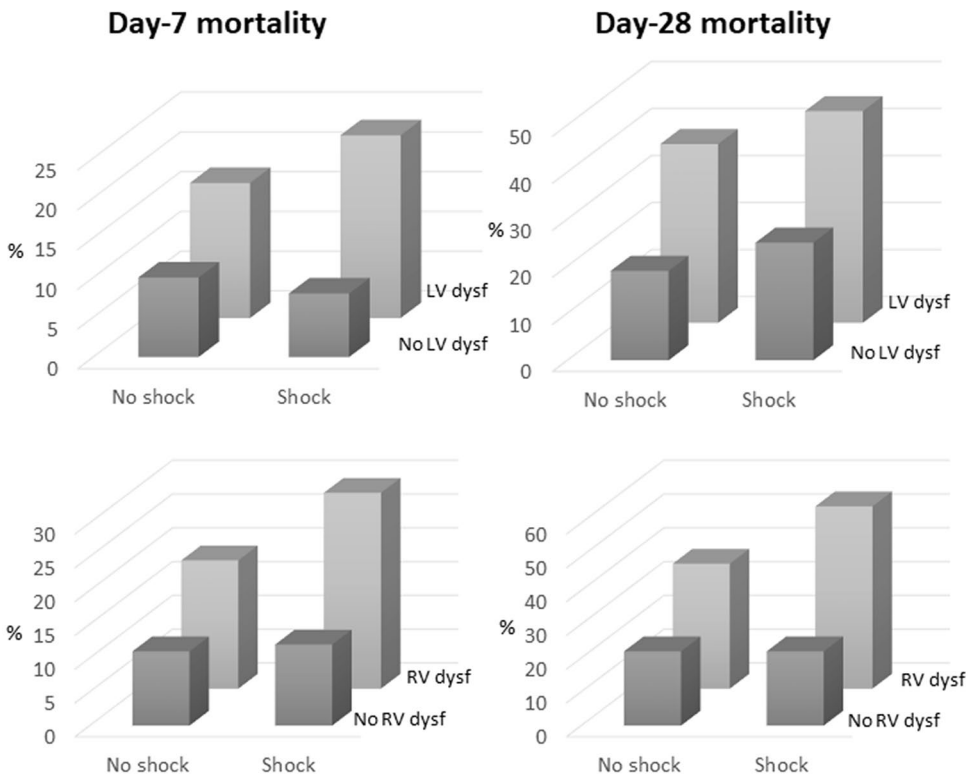

Fig. 1 Day-7 and Day-28 mortality rate by septic shock and LV (top, $p = 0.012$ and $p = 0.003$ by day-7 and day-28 follow-up) and RV (bottom, $p = 0.002$ and $p < 0.001$ by day-7 and day-28 follow-up) systolic dysfunction, defined respectively as LV GLS > -14% and TAPSE < 16 mm

resuscitation and, as in one third of the LAC + subgroup, in the absence of shock. The prevalence of previous medical conditions, which could influence lactate levels, like cirrhosis or CKD, was similar in LAC + and LAC- patients, making a significant role of comorbidities unlikely [24, 25]. This situation has a multifactorial origin. The presence of hypoxia and the consequent activation of anaerobic glycolysis coexists with non-hypoxemic causes, such as inflammation and catecholamine-driven accelerated glycolytic flux, stimulation of sodium–potassium ATPase pump activity, inhibition of pyruvate dehydrogenase in specific compartments such as striated muscle and the lung, and decreased lactate metabolism by the liver [26]. In the early phases of resuscitation, hypoperfusion is probably the prevalent mechanism; after the first hours of treatment, hyperlactatemia should be considered a marker of

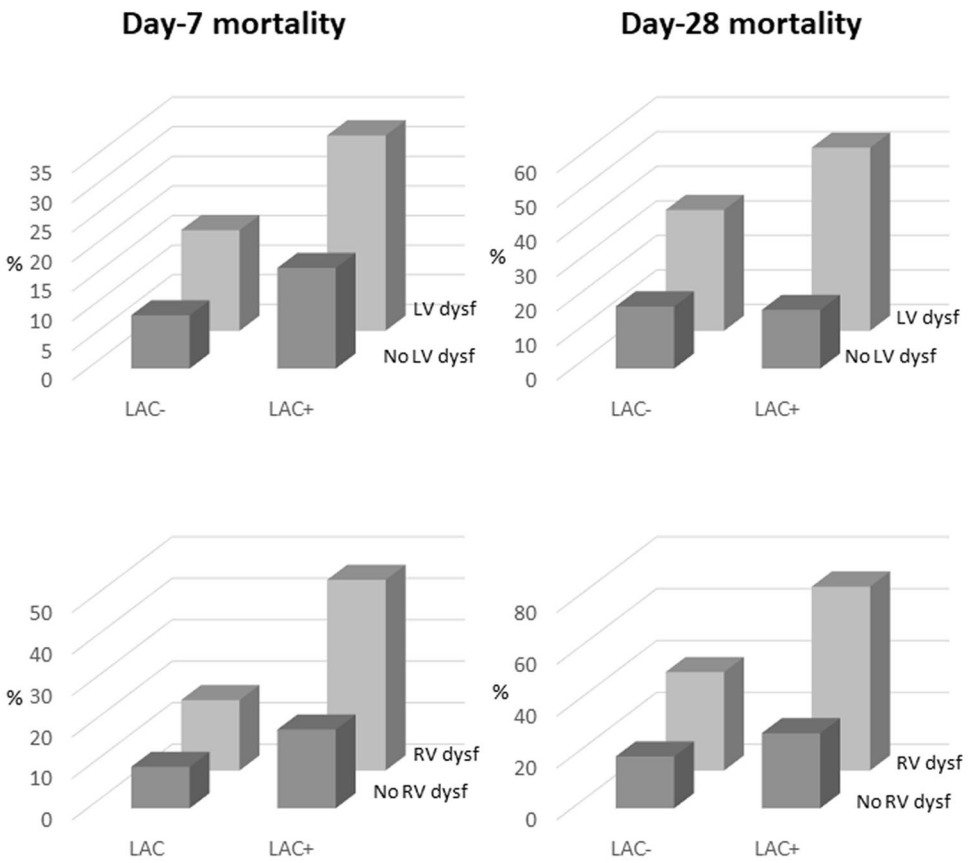

Fig. 2 Day-7 and Day-28 mortality rate by the persistence of high lactate levels and LV and RV systolic dysfunction (all $p < 0.001$), defined, respectively, as LV GLS > -14% and TAPSE < 16 mm

Table 3 Independent predictors of the day- 7 and day-28 mortality rates

	Day-7 mortality			Day-28 mortality		
	RR	95% CI	*p*	RR	95% CI	*p*
Age (years)	1.06	1.03–1.09	< 0.001	1.03	1.01–1.05	0.002
LV systolic dysfunction	2.23	1.11–4.48	0.025	2.07	1.23–3.46	0.006
RV systolic dysfunction	–	–	–	1.91	1.25–2.90	0.003
Septic shock	–	–	–	–	–	–
High lactate	1.94	1.07–3.52	0.030	1.77	1.12–2.80	0.014

the ongoing infection and metabolic derangement, poorly controlled by the treatment [27–29]. In experimental conditions, Correa and coll. demonstrated that the early decrease in lactate levels was associated with a better survival, a lower level of plasma interleukin-6 and an improved brain mitochondrial respiration [30]. Based on their data, it was not possible to ascertain whether the reduction in lactate was the effect of a better perfusion or a less severe inflammation. During sepsis, the impaired mitochondrial respiration despite normal oxygenation represents one of the mechanisms of organ damage, with a multifactorial etiology, and can reduce the ability of mitochondria to use lactate as an alternative source of energy [31]. In a group of septic patients, Hernandez and coll. demonstrated that lactate levels decreased by almost 50% of basal median value during the first 6 h of resuscitation. However, the normalization of different perfusion-related variables was inhomogeneous and lasted beyond the first 6 h, suggesting the involvement of non-flow dependent mechanism [28]. The presence or absence of shock is diagnosed by mean of macrohemodynamics, which does not take into account what happens at the cellular and subcellular level and, consequently, does not give a complete picture of the ongoing systemic inflammation. In the absence of an overt shock, the persistence of high lactate levels could be due to a severe activation of mechanisms of organ damage, sustained by non-flow dependent mechanism. In this condition, LVSD could represent a sign of organ damage due to the persistent activation of mechanisms

inducing cellular and subcellular dysfunction, with obvious prognostic consequences.

This study has several limitations. It is a single-center study, and local management strategies may have influenced patient selection as well as treatment and outcome. The clinical spectrum of septic shock is wide and highly dynamic, and although all patients were included within the first 24 h after HDU admission, time from the initial presentation of the disease to the echocardiogram varied.

Strain analysis has been employed by several authors to diagnose myocardial dysfunction during sepsis; it demonstrated to be a feasible technique and it allowed to unmask subtle alterations in myocardial contractility, that are not captured by the conventional echocardiographic evaluation. The increasing availability of strain software for LV function analysis on portable ultrasound machine will probably make this tool adequate for a bedside approach. Available data on RV systolic function during sepsis are limited and prognostic value of conventional echocardiographic measures compared with a more complex approach, like the strain analysis, has been incompletely explored. We could confirm a significant prognostic value for a standard parameter of RV systolic function like TAPSE: we, therefore, decided to employ this simple parameter, easily obtained during a bedside examination.

In conclusion, in a population of non-intubated septic patients, the persistence of high lactate levels during the first 24 h was associated with a worst LV systolic function, evaluated by mean of less load-dependent parameters, altogether with an adverse short- and medium-term prognosis. The presence of septic shock did not show an independent prognostic value.

Author contributions FI and VP gave substantial contributions to the conception and design of the work, drafted and revised the manuscript. FD, MC, MM, ADP, EC and SC gave substantials contributions in the acquisition, analysis, or interpretation of data for the work. FI, IT, SC drafted the manuscript; VP revised it critically for important intellectual content. RP gave the final approval of the version to be published.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest No conflict of interest to declare.

Statement of human and animal rights 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).

Informed consent All patients gave informed consent to enter the study.

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