Internal and Emergency Medicine (2019) 14:1321–1330
https://doi.org/10.1007/s11739-019-02196-z

EM - ORIGINAL

Prognostic value of serial lactate levels in septic patients with and without shock

Francesca Innocenti[1] · Federico Meo[1] · Irene Giacomelli[1] · Camilla Tozzi[1] · Maria Luisa Ralli[1] · Chiara Donnini[1] · Irene Tassinari[1] · Francesca Caldi[1] · Maurizio Zanobetti[1] · Riccardo Pini[1]

Received: 7 May 2019 / Accepted: 11 September 2019 / Published online: 25 September 2019

Abstract
To analyze the prognostic value of lactate levels for day-7 and in-hospital mortality, in septic patients with and without shock. In the period November 2011–December 2016, we enrolled 268 patients, admitted to our High-Dependency Unit with a diagnosis of sepsis. Lactate dosage was performed at ED-HDU admission (T0), after 2 h (T2), 6 h (T6) and 24 h (T24); lactate clearance was calculated at T2 and T6 [T2: ((LAC T0—LAC T2/LAC T0)*100)]; T6: [(LAC T0—LAC T6/LAC T0)*100]. The end-points were day-7 and in-hospital mortality. At every evaluation, the lactate level was higher in patients with shock than in those without (T0 3.8 ± 3.8 vs 2.4 ± 2.1; T6 2.9 ± 3.2 vs 1.6 ± 1.1; T24 3.0 ± 4.4 vs 1.4 ± 0.9 meq/L, all $p < 0.001$). Among patients with shock, an analysis for repeated measures confirmed a more marked lactate level reduction in survivors compared with non-survivors, both by day-7 and in-hospital mortality ($p = 0.057$ and $p = 0.006$). A Kaplan–MeIer analysis confirmed a significantly better day-7 survival in patients with T6 (with shock 86% vs 70%; without shock 93% vs 82, all $p < 0.05$) and T24 (with shock 86% vs 70%; without shock 93% vs 82, all $p < 0.05$) lactate ≤ 2 meq/L, compared with patients with higher levels. A T6 lactate clearance $> 10\%$ was more frequent among in-hospital survivors in the whole study population (57% vs 39%) and in patients with shock (74% vs 46%, all $p < 0.05$). Higher lactate levels and decreased clearance were associated with an increased short-term and intermediate-term mortality regardless of the presence of shock.

Keywords Lactate · Lactate clearance · Septic shock · Prognosis

Introduction

Upon ED admission, most septic patients show hyperlactatemia and serum lactate has been considered a marker of the severity of the septic process, alongside a guide for hemodynamic optimization [1]. Lactate is not a simple index of hypoperfusion, but a marker of the interplay of multiple pathways, which are involved in determining organ damages during sepsis [2].

Increased lactate levels may represent tissue hypoxia, accelerated aerobic glycolysis driven by excess adrenergic stimulation, or decreased clearance due to hepatic dysfunction [3].The 2018 Update of the Surviving Sepsis Campaign recommends to measure lactate level within 1 hour from the moment of the diagnosis and to repeat the measurement if the initial value is high [4]. However, our current knowledge of the prognostic value of lactate kinetics in septic patients with and without shock is incomplete, as well as the best time interval between different evaluations, to obtain prognostically valuable information.

Aims of the present study were: (1) to compare lactate levels and trends in patients with and without shock; (2) to analyze if the prognostic value of lactate was comparable in these two subgroups of septic patients.

Materials and methods

Study design and settings

This report utilized a portion of the data collected as part of a prospective study, which was conducted at the Emergency Department High-Dependency Unit (ED-HDU) of

✉ Francesca Innocenti
innocenti.fra66@gmail.com

[1] High-Dependency Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliero-Universitaria Careggi, Francesca Innocenti, Lg. Brambilla 3, 50134 Firenze, Italy

the University Hospital Careggi, Florence. The aim of the study was to identify reliable biomarkers, which could confirm the diagnosis of sepsis at an early stage in the course of the disease; in this paper, we reported the data regarding lactate levels. The study protocol was approved by the local Ethics Committee and all subjects provided oral and written informed consent. The study was conducted in compliance with the Declaration of Helsinki at the Careggi University Hospital (Florence, Italy), a 1600-bed tertiary care facility, with 82,000 ED visits per year from November 2011 to December 2016.

The ED-HDU is a sub-intensive care unit, with availability of advanced monitoring, managed by emergency physicians; all patients are admitted from the ED, according to bed availability. Within 48 h from ED admission, the ED-HDU physicians must decide the optimal patients' disposition, choosing between the ordinary ward and the intensive or sub-intensive care facilities. Because our ED-HDU does not have invasive mechanical ventilators, intubated patients or those potentially requiring intubation within 24 h are directly admitted into the ICU. In a previous analysis of a population of septic patients, we demonstrated that ED-HDU allows a significant reduction in ICU admissions, leading to a relevant cost reduction [5].

Selection of participants and outcomes

We included all subjects with a diagnosis of severe sepsis or septic shock according to the 2001 SCCM/ESICM/ACCP/ATS/SIS criteria [6]: as the most proportion of patients were enrolled before the publication of Sepsis-3, we maintained the previous diagnostic criteria. Exclusion criteria were: (1) age < 18 years; (2) severe bone marrow aplasia induced by recent chemotherapy; (3) dementia complicated by immobilization syndrome lasting at least 3 months; (4) refusal to participate.

Survival status was collected at hospital discharge; the primary outcomes were day-7 and in-hospital mortality rate.

Measurements

The Sequential Organ Failure Assessment (SOFA) scoring system was used to evaluate organ dysfunction during the first 24 h of ED-HDU stay. Study-related blood samplings were performed immediately after ED-HDU admission (T0), after 2 h (T2), after 6 h (T6) and after 24 h (T24). Lactate clearance was calculated at T2 and T6 [T2: ((LAC T0—LAC T2/LAC T0)*100)]; T6: [(LAC T0—LAC T6/LAC T0)*100].

Statistical analysis

The sample size was calculated, based on the levels of several biomarkers in survivors and non-survivors [7, 8]; due to the relevant difference between different markers, we finally decided to enroll 250 patients.

Continuous variables were reported as mean ± standard deviation; categorical data were analyzed using contingency tables and performing $\chi 2$ test. Between-group comparisons of continuous variables were calculated using the Mann–Whitney *U* test for data with a non-normal distribution (laboratory data) and with the Student *t* test for unpaired data with normal distribution.

To evaluate differences in trend among different scores we employed Analysis of Variance (ANOVA) for repeated measures. Survival analysis was performed with Kaplan–Meier method and Cox proportional hazard function. *P* values < 0.05 were considered as significant. All statistical analyses were carried out using SPSS version 25 (IBM-SPSS, IBM Corp, Armonk, New York, USA).

Results

During the study period, 369 patients were admitted to the ED-HDU due to sepsis; 94 patients were excluded according to study criteria (20 due to patients' refusal, 33 due to bone marrow aplasia induced by chemotherapy and 41 demented bed-ridden patients). Seven more patients were not included due to technical problems with blood sampling. The final study population included 268 patients; compared to participants, excluded patients showed a similar age (76 ± 13 vs 75 ± 13 years, p = NS) and T0 SOFA score (5.6 ± 3.0 vs 6.0 ± 3.0, p = NS). The in-hospital mortality rate was similar between participants and non-participants (26 vs 29%, p = NS). The mean of the door-to ED-HDU admission time was 4 ± 2 h [9].

In Table 1, we reported the clinical characteristics in the whole study population and based on the presence of shock. When comparing patients with and without shock, we found that both were of a similar age and had the same male/female ratio, as well as a similar prevalence of previous medical conditions. In patients with shock, the day-7 (23 vs 11%, p = 0.015) and in-hospital (33 vs 19%) mortality rate significantly increased. At every evaluation, MAP was lower and the lactate level was higher in patients with shock than in those without. In Table 2, we compared several parameters of organ damage in survivors and non-survivors, within the two subgroups of patients with and without shock. By day-7 end-point, among patients without shock we did not find any significant difference.

Table 1 Clinical characteristics in the whole study population and based on the presence of shock

	All patients ($n=268$)	Non shock ($n=153$)	Shock ($n=115$)	
Age (years)	74 ± 14	73 ± 15	75 ± 12	NS
Male sex (%)	157 (59%)	80 (54%)	75 (65%)	NS
PMC				
Arterial hypertension (%)	153 (60%)	87 (60%)	68 (59%)	NS
Diabetes (%)	83 (32%)	48 (33%)	35 (30%)	NS
Arterial disease (%)	46 (18%)	22 (15%)	24 (21%)	NS
COPD (%)	54 (21%)	34 (23%)	20 (17%)	NS
CKD (%)	59 (23%)	29 (20%)	30 (26%)	NS
Solid tumor (%)	41 (16%)	22 (16%)	19 (17%)	NS
Hematologic malignancy (%)	18 (7%)	9 (7%)	9 (9%)	NS
Source of infection				NS
Pulmonary (%)	119 (46%)	75 (50%)	44 (38%)	
Urinary tract (%)	45 (17%)	27 (19)	18 (16)	
Abdominal (%)	36 (14%)	16 (11%)	20 (18%)	
Skin (%)	9 (4%)	3 (2%)	6 (5%)	
Unknown (%)	34 (14%)	17 (12%)	17 (15%)	
Other (%)	16 (6%)	7 (5%)	9 (8%)	
Day-7 mortality	42 (16%)	16 (11%)	26 (23%)	0.015
In-hospital mortality	70 (26%)	29 (19%)	41 (35%)	0.006
Parameters at ED admission				
HR (b/min)	96 ± 20	97 ± 20	95 ± 21	NS
MAP (mmHg)	76 ± 16	80 ± 16	71 ± 13	< 0.001
Lactate (mmol/L)	3.0 ± 3.1	2.4 ± 2.1	3.8 ± 3.8	< 0.001
SOFA score	5.3 ± 2.7	4.8 ± 2.4	5.8 ± 2.8	0.002
Parameters after 6 h				
HR (b/min)	90 ± 18	90 ± 18	90 ± 18	NS
MAP (mmHg)	76 ± 13	79 ± 13	72 ± 12	< 0.001
Lactate (mmol/L)	2.2 ± 2.4	1.6 ± 1.1	2.9 ± 3.2	< 0.001
SOFA score	6.3 ± 3.0	5.0 ± 2.2	8 ± 3.1	< 0.001
Parameters after 24 h				
HR (b/min)	88 ± 18	89 ± 19	89 ± 17	NS
MAP (mmHg)	81 ± 14	85 ± 14	76 ± 12	< 0.001
Lactate (mmol/L)	2.2 ± 3.2	1.4 ± 0.9	3.0 ± 4.4	< 0.001
SOFA score	5.9 ± 3.1	4.9 ± 2.4	7.2 ± 3.5	< 0.001

PMC previous medical conditions, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *HR* heart rate, *MAP* mean arterial pressure, *WBC* white blood cells

Among those with shock, SOFA score was higher, and neurological and pulmonary dysfunction were more severe in non-survivors as compared with survivors. The SOFA score was higher and several organ dysfunctions were more severe among in-hospital non-survivors in both subgroups. Focusing on possible confounding factors for lactate prognostic value, prevalence of liver dysfunction was proportionate regardless of prognosis; conversely, PaO_2/FiO_2 was lower among non-survivors in both subgroups. Among patients with shock, a comparable proportion of survivors and non-survivors received a high dosage (>0.1 γ/kg/min) of noradrenaline (by day-7 mortality 75% vs 86%, by in-hospital mortality 75% vs 81%, all $p=$ NS).

We compared lactate levels in survivors and non-survivors according to day-7 and in-hospital mortality; we performed the analysis in the whole study population and in the subgroups of patients with and without shock. As shown in Table 3, at all the evaluations, lactate levels were significantly higher in non-survivors compared with survivors based on in-hospital mortality; day-7 non-survivors showed higher levels only at T6 and T24 evaluations. These results were confirmed in patients with shock. In those without shock, day-7 non-survivors showed comparable levels to survivors, while in-hospital non-survivors had significantly increased lactate levels at T6 and T24.

Table 2 Parameters of organ damage in patients with and without shock based on day-7 and in-hospital mortality rate

	Patients without shock ($n=153$)			Patients with septic shock ($n=115$)		
	Survivors ($n=137$)	Non-survivors ($n=16$)	p	Survivors ($n=91$)	Non-survivors ($n=26$)	p
Day-7 mortality rate						
Age (years)	72 ± 15	79 ± 15	NS	75 ± 12	77 ± 15	NS
T0 SOFA	4.7 ± 2.4	5.6 ± 2.3	NS	5.5 ± 2.5	7.1 ± 3.4	0.029
T1 SOFA	4.8 ± 2.4	6.0 ± 1.9	NS	6.2 ± 2.5	11.5 ± 3.6	< 0.001
T1 GCS	14.5 ± 1.8	14.4 ± 1.5	NS	14.4 ± 2.0	9.1 ± 5.5	0.001
T1 MAP	86 ± 14	83 ± 13	NS	76 ± 12	75 ± 16	NS
T1 creatinine (mg/L)	1.3 ± 1.0	2.5 ± 1.7	NS	2.1 ± 1.7	3.4 ± 3.8	NS
T1 platelets (n/mm^3)	171 ± 102	185 ± 87	NS	143 ± 101	120 ± 82	NS
T1 bilirubin (mg/L)	0.9 ± 1.0	0.6 ± 0.3	NS	1.0 ± 1.0	1.0 ± 0.6	NS
T1 PaO_2/FiO_2	236 ± 123	203 ± 98	NS	293 ± 129	160 ± 65	< 0.001
Hemoglobin (g/L)	10.9 ± 2.7	10.1 ± 1.4	NS	10.1 ± 1.8	11.0 ± 1.6	NS
Liver dysfunction (%)	6 (4%)	0	–	6 (7%)	1 (4%)	NS
	Survivors ($n=124$)	Non-survivors ($n=29$)		Survivors ($n=74$)	Non-survivors ($n=41$)	
In-hospital mortality rate						
Age (years)	71 ± 15	81 ± 12	0.001	74 ± 11	77 ± 14	NS
T0 SOFA	4.7 ± 2.5	5.1 ± 2.2	NS	5.3 ± 2.6	6.9 ± 3.0	0.003
T1 SOFA	4.6 ± 2.4	6.0 ± 2.0	0.015	5.9 ± 2.4	9.9 ± 3.7	< 0.001
T1 GCS	14.5 ± 1.8	14.4 ± 1.2	NS	14.6 ± 1.6	11.0 ± 5.1	0.001
T1 MAP	86 ± 14	83 ± 13	NS	76 ± 12	75 ± 13	NS
T1 creatinine (mg/L)	1.3 ± 1.0	2.1 ± 1.6	0.026	2.1 ± 1.8	2.8 ± 2.9	NS
T1 platelets (n/mm^3)	168 ± 103	195 ± 86	NS	148 ± 105	117 ± 77	NS
T1 bilirubin (mg/L)	0.9 ± 1.0	0.8 ± 0.7	NS	1.0 ± 1.0	1.1 ± 0.8	NS
T1 PaO_2/FiO_2	247 ± 123	172 ± 89	0.011	296 ± 132	214 ± 109	0.003
Hemoglobin (g/L)	10.8 ± 2.8	10.6 ± 1.4	NS	10.2 ± 1.8	10.6 ± 1.6	NS
Liver dysfunction (%)	6 (4%)	0	-	5 (7%)	2 (5%)	NS

GCS Glasgow Coma Scale, *MAP* mean arterial pressure

The Kaplan–Meier analysis confirmed a significantly better day-7 and in-hospital survival (Figs. 1 and 2) in patients with lactate ≤ 2 meq/L, compared with patients with higher levels. Both in the whole population and in patients with and without shock, the lactate level ≤ 2 meq/L at the baseline evaluation was not associated with a better survival rate (day-7 mortality rate: whole population survival 87% vs 80%, patients without shock 90% vs 87%, patients with shock 82% vs 71%; in-hospital mortality whole population survival 76% vs 71%, patients without shock 81% vs 80%, patients with shock 69% vs 62%, all p = NS). In patients with and without shock, day-7 survival was better in patients with lactate ≤ 2 meq/L at T6 and T24. In-hospital survival was better only in the presence of a lactate level ≤ 2 meq/L at T24, while the previous evaluations did not yield significant prognostic information.

An analysis for repeated measures confirmed a more marked lactate level reduction in survivors compared with non-survivors, whose mean values never decreased below 2 meq/l throughout the first 24 h, both by day-7 and in-hospital mortality (respectively, $p = 0.010$ and $p = 0.001$, Fig. 3). These trends were confirmed only in patients with shock, even though the difference by day-7 mortality tended to be significant, probably due to the limited number of events.

We included the lactate level in a Cox survival analysis, together with SOFA score, respectively, in the two subgroups with and without shock. Because type and entity of organ damage were not homogeneous among patients with and without shock and by different end-points, we preferred to consider the SOFA score as a global index of organ dysfunction. In patients with shock, a higher T6 lactate level was associated with an increased day-7 (RR 1.16, 95% CI 1.07–1.26) and in-hospital mortality (RR 1.15, 95% CI 1.07–1.24), independent to the SOFA score. Only in absence of shock, T24 lactate levels showed an independent association with an increased day-7 (RR 1.69, 95% CI 1.13–2.54) and in-hospital mortality (RR 1.58, 95% CI 1.13–2.21).

Table 3 Lactate levels in the first 24 h in day-7 and in-hospital survivors and non-survivors, in the whole study population and based on the presence of septic shock

	All patients ($n=268$)			Patients without shock ($n=153$)			Patients with septic shock ($n=115$)		
	Survivors ($n=226$)	Non-survivors ($n=42$)	p	Survivors ($n=137$)	Non-survivors ($n=16$)	p	Survivors ($n=91$)	Non-survivors ($n=26$)	p
Day-7 mortality rate									
T0 lactate (meq/L)	2.8 ± 2.6	4.1 ± 4.4	0.060	2.4 ± 2.2	2.5 ± 1.3	0.835	3.3 ± 3.1	5.2 ± 5.3	0.105
T2 lactate (meq/L)	2.5 ± 2.6	4.0 ± 4.5	0.060	2.0 ± 2.4	2.1 ± 1.2	0.872	3.0 ± 2.7	5.1 ± 5.4	0.093
T6 lactate (meq/L)	1.9 ± 1.7	3.9 ± 4.3	0.011	1.5 ± 1.1	2.1 ± 0.9	0.098	2.4 ± 2.2	4.9 ± 5.1	0.033
T24 lactate (meq/L)	1.7 ± 2.1	4.8 ± 6.3	0.018	1.3 ± 0.8	2.1 ± 1.4	0.081	2.3 ± 3.0	6.4 ± 7.6	0.042
T2 lac. clearance > 10%	97 (43%)	18 (43%)	0.855	56 (42%)	8 (50%)	0.757	41 (45%)	10 (38%)	0.938
T6 lac. clearance > 10%	130 (58%)	15 (36%)	0.123	77 (67%)	6 (38%)	0.585	62 (71%)	11 (44%)	0.085
	Survivors ($n=198$)	Non-survivors ($n=70$)		Survivors ($n=124$)	Non-survivors ($n=29$)		Survivors ($n=74$)	Non-survivors ($n=41$)	
In-hospital mortality rate									
T0 lactate (meq/L)	2.7 ± 2.5	3.9 ± 4.2	0.030	2.3 ± 2.0	2.6 ± 2.3	0.542	3.2 ± 3.0	4.9 ± 4.9	0.070
T2 lactate (meq/L)	2.4 ± 2.5	3.6 ± 4.0	0.038	2.0 ± 2.5	1.9 ± 2.5	0.970	2.9 ± 2.5	4.7 ± 4.8	0.043
T6 lactate (meq/L)	1.8 ± 2.4	3.5 ± 3.8	0.002	1.5 ± 1.0	2.0 ± 1.3	0.031	2.2 ± 1.8	4.4 ± 4.6	0.009
T24 lactate (meq/L)	1.5 ± 1.4	4.1 ± 5.6	0.002	1.2 ± 0.6	2.1 ± 1.5	0.020	1.9 ± 2.0	5.6 ± 6.8	0.008
T2 lac. clearance > 10%	88 (44%)	27 (41%)	0.896	50 (41%)	14 (50%)	0.906	38 (48%)	13 (34%)	0.752
T6 lac. clearance > 10%	119(57%)	26 (39%)	0.020	72 (69%)	10 (44%)	0.118	56 (74%)	17 (46%)	0.049

We performed several evaluations of lactate clearance to establish the shortest interval by which this measure acquires a prognostic stratification ability. The lactate clearance in a 2-h interval did not demonstrate any meaningful difference according to prognosis. A lactate clearance by at least 10% over the first 6 h was more frequent among in-hospital survivors (Table 2), both in the whole study population and in patients with shock. A Kaplan–Meier analysis showed a significantly better day-7 and in-hospital survival (Figs. 1 and 2) in patients with lactate clearance < 10%, compared with patients with lower levels; the result was confirmed in patients with or without shock.

We also included T6 lactate clearance > 10% in a Cox survival analysis alongside SOFA score. In patients with shock, a reduced lactate clearance was associated with a higher day-7 (RR 2.56, 95% CI 1.16–5.65) and in-hospital mortality (RR 2.23, 95% CI 1.17–4.23, together with the SOFA score, RR 1.13, 95% CI 1.01–1.25). In the absence of shock, a compromised lactate clearance was independently associated with a worse in-hospital mortality (RR 2.63, 95% CI 1.15–6.00).

Discussion

In a population of non-intubated septic patients, we found that patients with shock had significantly higher lactate levels, compared with those without shock. Among patients with shock, non-survivors showed a persistently high lactate over the first 24 h, whereas, in patients with a favorable outcome, lactate levels progressively decreased. Regardless of the presence of shock, a lactate level > 2 after a few hours of treatment was associated with the worst day-7 mortality. Only the persistence of a lactate level > 2 at T24 predicted a higher in-hospital mortality, independent to SOFA score in patients without shock. The separate evaluation of the

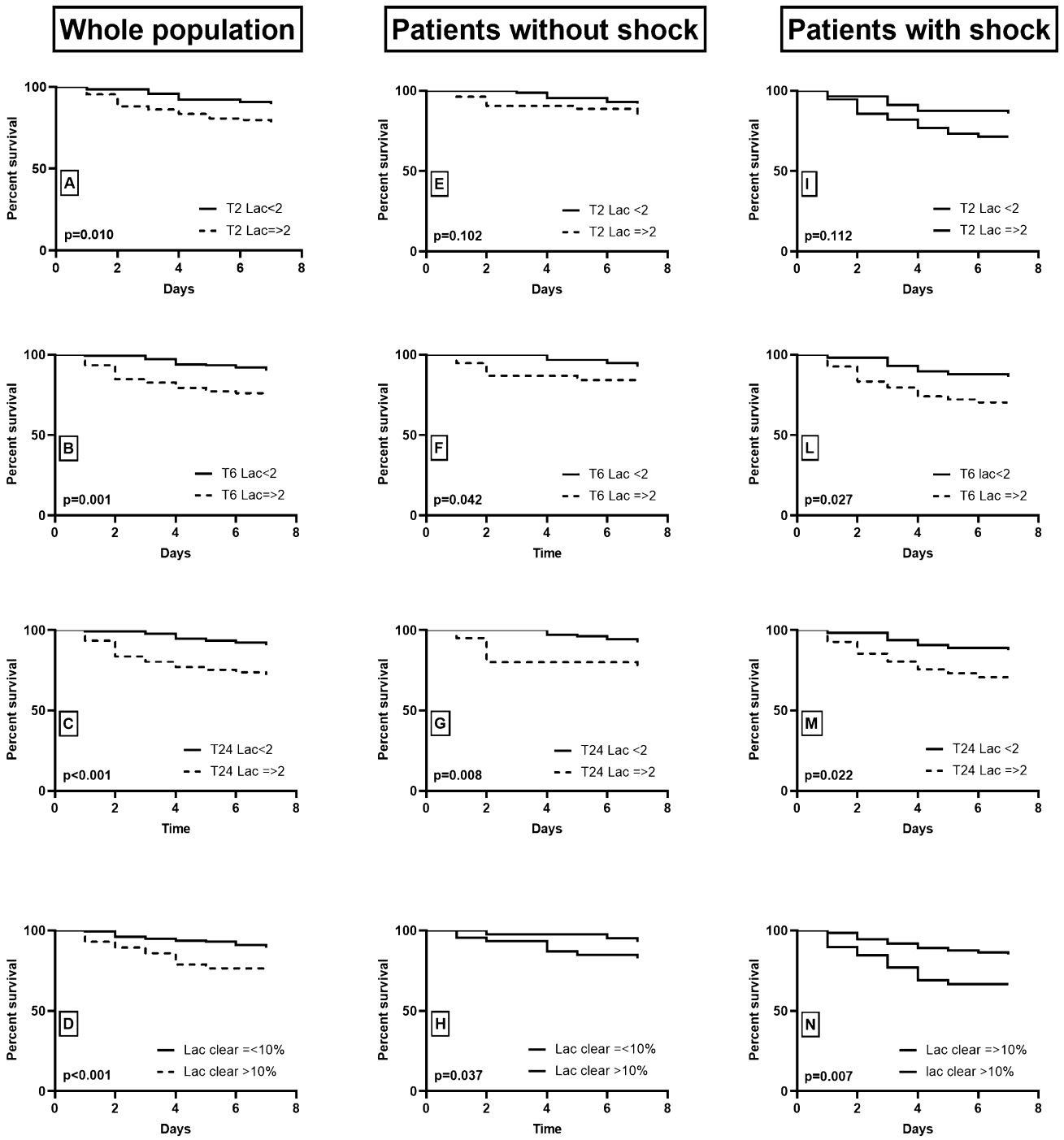

Fig. 1 Day-7 mortality rate in patients with lactate levels ≥ 2 meq/L compared to those with lactate levels < 2 meq/L by Kaplan–Meier survival analysis in the whole study population (**a**–**d**), in patients without shock (**e**–**h**) and in patients with shock (**i**–**n**)

prognostic value of lactate levels between patients with or without shock and the choice to include the day-7 mortality rate, represent the novelties of this study. We chose this early end-point because in Emergency Medicine, it is of utmost importance to identify patients at risk of an early adverse prognosis. The low number of adverse events in the first 7 days was a limitation for this analysis, especially among patients without shock. However, we confirmed a similar prognostic value of lactate levels with or without shock.

The larger portion of septic patients presents hyperlactatemia at the beginning of the disease. Several mechanisms can cause an increase in production: a

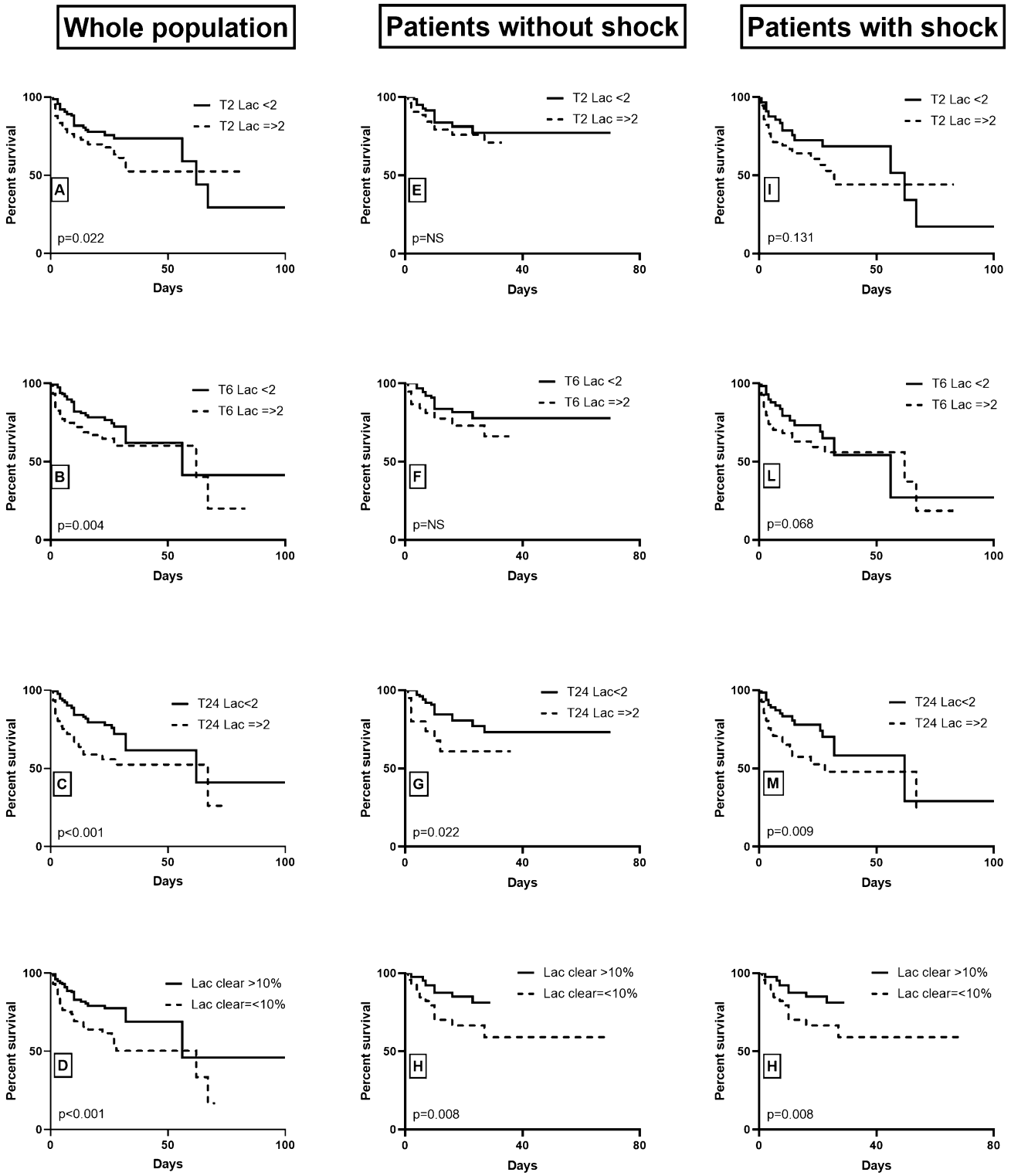

Fig. 2 In-hospital mortality rate in patients with lactate levels ≥ 2 meq/L compared to those with lactate levels < 2 meq/L by Kaplan–Meier survival analysis in the whole study population (**a**–**d**), in patients without shock (**e**–**h**) and in patients with shock (**i**–**n**)

hypoperfusion-induced anaerobic metabolism, alongside increased glycolysis, catecholamine stimulated Na–K pump activity and impaired pyruvate dehydrogenase activity [1]. A reduced lactate clearance, primarily because of liver hypoperfusion or dysfunction, may coexist with the production increase. Regardless of the causative mechanisms, the

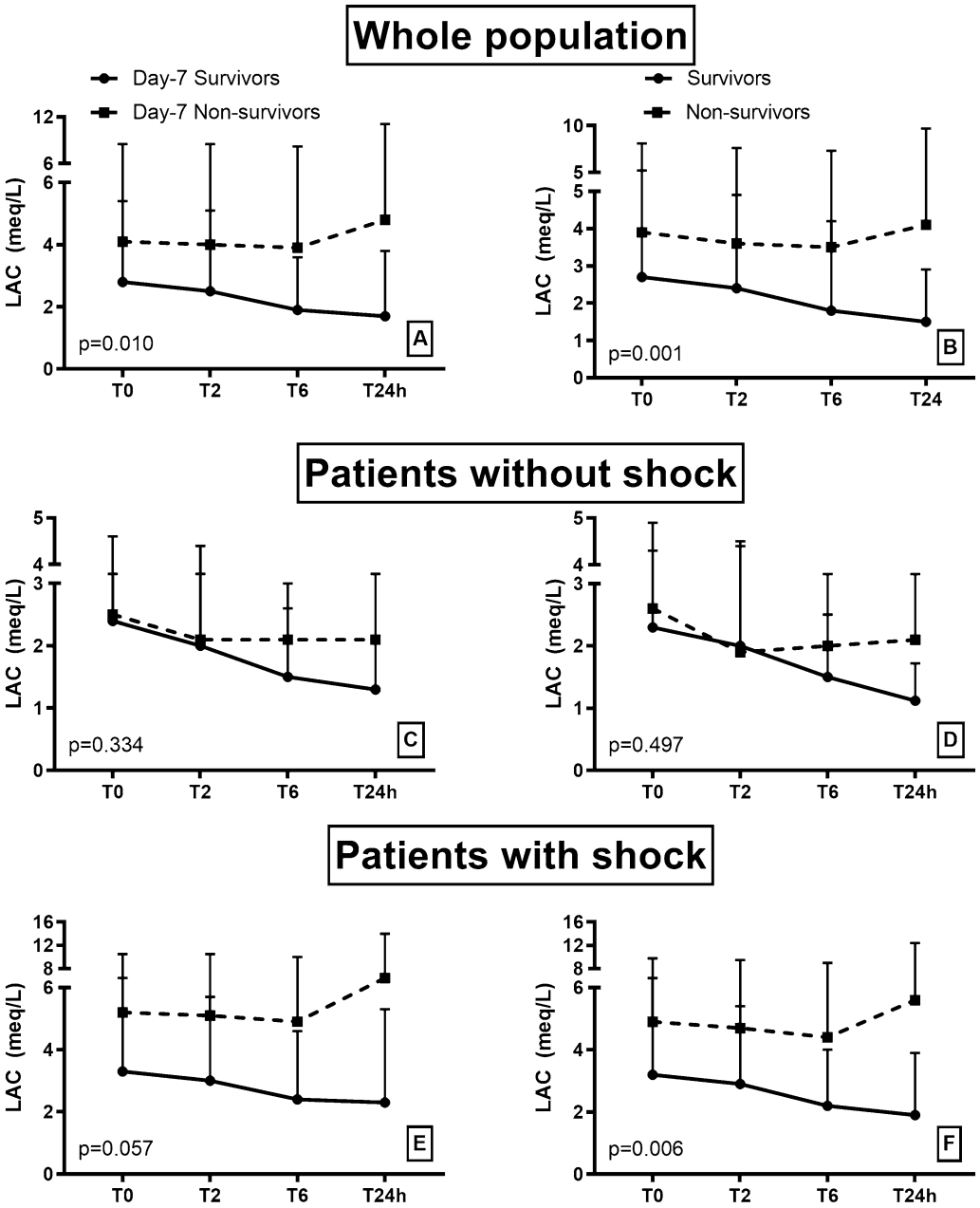

Fig. 3 Lactate trends by day-7 and in-hospital mortality in the whole study population (**a** and **b**), in patients without (**c** and **d**) and with shock (**e** and **f**)

degree of increase in lactate concentration correlated with the severity of the disease and with the mortality rate [10, 11]. According to the definition, septic shock is induced by more profound circulatory, cellular or metabolic abnormalities, compared with sepsis without shock [12]. We observed a higher lactate level in patients with shock compared to those without. This difference could be connected to a more pronounced hypoperfusion or to a more severe activation of the mechanisms of cellular dysfunction, like mitochondrial dysfunction or abnormal adrenergic stimulation. However, it indicated a more pronounced derangement of multiple pathways, leading to a worsening organ dysfunction in patients with shock compared to those without. This was confirmed by the higher SOFA score in the presence of shock [13]. On the other hand, regardless of less abnormal values, persistence of increased lactate levels was associated with an adverse prognosis even in the absence of shock. This could be one of the reasons why measurements obtained after several hours of treatment showed a better prognostic value compared with initial evaluations: while almost all septic

patients show elevated lactate at the moment of the diagnosis, persistence of high levels, despite the treatment, is a marker of an ongoing pathophysiologic derangement [14].

The analysis of lactate trends confirmed these findings. During the state of shock, lactate production and elimination is a dynamic process: therefore, several evaluations may be more informative than a single value. Many studies proved that a reduction of the lactate level over the first hours of treatment was associated with a better outcome [15-17]. Anyway, the concept of "lactate clearance" may be misleading. In fact, clearance is the removal of a substance from blood; conversely, changes in lactate levels are the sum of ongoing increased production and/or removal from the blood by the metabolism and excretion [18]. The persistence of high lactate levels despite the treatment could again represent a marker of an ongoing abnormal reaction of the organism to the infection, or a poor response to treatment. Vincent et al. [18] suggested that, based on recent evidence, measurements of every 1–2 h would give clinically relevant data. In our study population, an evaluation of lactate "clearance" before a 6-h interval did not yield any useful prognostic information. However, we confirmed an independent association of a normal lactate clearance with a reduced short- and medium-term mortality, both in the presence and absence of shock. We could interpret this decrease as a sign of a remission of the septic process at the cellular and subcellular levels and, therefore, a positive response to antibiotic therapy and hemodynamic stabilization.

There are some limitations in this report. The single-center study design and the clinical setting of the ED-HDU could limit the applicability of our results because it is not common, especially outside of European countries. Moreover, since all our patients were admitted to the ED-HDU, they were not intubated: we must keep in mind that a different selection criterion could have shown different results. Finally, as we had already explained, we added the day-7 mortality end-point: by the seventh day, the number of events was low but we were still able to show that a very short-term mortality rate depended on several parameters, and lactate levels seemed to play a role in prognostic stratification. Further studies are needed to confirm this very short-term prognostic stratification, which appears to be of utmost importance in Emergency Medicine.

Conclusion

In a population of non-intubated septic patients, abnormal lactate levels during the first 24 h of the ED stay, alongside an absence of lactate clearance, were associated with an increase in short- and medium-term mortality rate, both in the presence and absence of shock.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The study protocol was approved by the local Ethics Committee (Registration number 21/11).

Informed consent All subjects provided oral and written informed consent.

References

1. Fuller BM, Dellinger RP (2012) Lactate as a hemodynamic marker in the critically ill. Curr Opin Crit Care 18:267–272
2. Ryoo SM, Lee J, Lee YS, Lee JH, Lim KS, Huh JW et al (2018) Lactate level versus lactate clearance for predicting mortality in patients with septic shock defined by sepsis-3. Crit Care Med 46:E489–E495
3. Levy B (2006) Lactate and shock state: the metabolic view. Curr Opin Crit Care 12:315–321
4. Levy MM, Evans LE, Rhodes A (2018) The surviving sepsis campaign bundle: 2018 update. Crit Care Med 46:997–1000
5. Innocenti F, Bianchi S, Guerrini E, Vicidomini S, Conti A, Zanobetti M et al (2014) Prognostic scores for early stratification of septic patients admitted to an emergency department-high dependency unit. Eur J Emerg Med 21:254–259
6. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 31:1250–1256
7. Oberholzer A, Souza SM, Tschoeke SK, Oberholzer C, Abouhamze A, Pribble JP et al (2005) Plasma cytokine measurements augment prognostic scores as indicators of outcome in patients with severe sepsis. Shock 23:488–493
8. Shapiro NI, Schuetz P, Yano K, Sorasaki M, Parikh SM, Jones AE et al (2010) The association of endothelial cell signaling, severity of illness, and organ dysfunction in sepsis. Crit Care 14:R182
9. Innocenti F, Gori AM, Giusti B, Tozzi C, Donnini C, Meo F et al (2019) Prognostic value of sepsis-induced coagulation abnormalities: an early assessment in the emergency department. Intern Emerg Med 14:459–466
10. Nichol A, Bailey M, Egi M, Pettila V, French C, Stachowski E et al (2011) Dynamic lactate indices as predictors of outcome in critically ill patients. Crit Care 15:R242
11. Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M et al (2016) Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. Intensive Care Med 42:202–210
12. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS et al (2016) Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:775–787
13. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE (2005) Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet 365:871–875
14. Ryoo SM, Ahn R, Lee J, Sohn CH, Seo DW, Huh JW et al (2018) Timing of repeated lactate measurement in patients with septic shock at the emergency department. Am J Med Sci 356:97–102
15. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA (2010) Lactate clearance vs central venous oxygen

saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 303:739–746
16. Dettmer M, Holthaus CV, Fuller BM (2015) The impact of serial lactate monitoring on emergency department resuscitation interventions and clinical outcomes in severe sepsis and septic shock: an observational cohort study. Shock 43:55–61
17. Nguyen HB, Kuan WS, Batech M, Shrikhande P, Mahadevan M, Li CH et al (2011) Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: a multi-national evaluation. Crit Care 15:R229
18. Vincent JL, Silva QE, Couto L Jr, Taccone FS (2016) The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care 20:257