BLOOD LACTATE LEVELS CUTOFF AND MORTALITY PREDICTION IN SEPSIS—TIME FOR A REAPPRAISAL? A RETROSPECTIVE COHORT STUDY

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ABSTRACT—The objective of this study was to identify the initial value of blood lactate that best correlates with 28-day mortality in resuscitated septic shock patients. This was a retrospective cohort study including 443 patients admitted to an intensive care unit (ICU) with severe sepsis or septic shock from the emergency department. A receiver-operating characteristic (ROC) curve was drawn to obtain the best cutoff value for initial blood lactate associated with 28-day mortality. Patients were then dichotomized according to the chosen lactate cutoff, and sensitivity, specificity, and positive and negative predictive values were calculated. Baseline blood lactate level more than 2.5 mmol/L showed the largest area under the ROC curve to predict 28-day mortality (ROC area, 0.70; 95% confidence interval [CI], 0.62–0.79), with sensitivity, specificity, and negative predictive value of 67.4%, 61.7%, and 94.2%, respectively. Mortality at 28 days was 16.9% (31/183) in patients with initial lactate more than 2.5 mmol/L and 5.8% (15/260) in patients with initial lactate at most 2.5 mmol/L (relative risk, 2.93; 95% CI, 1.63–5.28; $P < 0.001$). Initial blood lactate levels more than 2.5 mmol/L (hazard ratio [HR], 2.86; 95% CI, 1.53–5.33; $P = 0.001$) and Sepsis-related Organ Failure Assessment score at ICU admission (HR, 1.18; 95% CI, 1.09–1.27; $P < 0.001$) were associated with increased 28-day mortality in the adjusted Cox regression. In this retrospective cohort study, a lactate level more than 2.5 mmol/L was the best threshold to predict 28-day mortality among severe sepsis and septic shock patients. Further prospective studies should address the impact on morbidity and mortality of this threshold as a trigger to resuscitation in this population of critically ill patients.

KEYWORDS—Biological markers, cohort, lactic acid, mortality, prognosis, ROC curve, sepsis, septic shock

INTRODUCTION

Severe sepsis and septic shock represent leading causes of morbidity and death worldwide, with mortality rates approaching 20% to 30% in the most recent clinical trials (1–3). Incidence of severe sepsis and septic shock has been increasing over the years, despite efforts to improve early recognition and treatment (4, 5).

Increased blood lactate levels in severe sepsis and septic shock most commonly indicate impaired oxidative phosphorylation secondary to decreased oxygen availability to the cells (hypoxic hypoxia) and/or tissue hypoperfusion (stagnant hypoxia) (6). Because blood lactate levels can be easily and quickly determined, these have been used as a surrogate of tissue hypoperfusion in critically ill patients admitted to the emergency department (ED) or to intensive care unit (ICU) (7–13). Indeed, increased blood lactate levels have been used to identify critically ill patients at high risk of death even before the development of hemodynamic instability, i.e. cryptic shock, as well as to trigger resuscitation (14).

Current guidelines for severe sepsis and septic shock resuscitation recommend that patients with severe sepsis or septic shock with an initial blood lactate level twice above the normal limit (≥ 4 mmol/L) should be promptly resuscitated (15). Nevertheless, an increasing number of studies have been suggesting that lower elevations of blood lactate levels are also associated with increased risk of death (9–11, 13). Therefore, the optimal lactate cutoff that should trigger resuscitation in this population of critically ill patients remains unclear (11).

Our objective was to identify a cutoff value for initial blood lactate level that best correlates with 28-day mortality among medical patients with severe sepsis or septic shock admitted to the ICU from the ED.

PATIENTS AND METHODS

Study design and setting

This was a retrospective cohort study performed at a 41-bed, mixed ICU, in a private tertiary care hospital in São Paulo, Brazil. The study protocol was approved, and informed consent was waived by Hospital Israelita Albert Einstein institutional review board (protocol number 11057312.6.0000.0071).

Patients

All adult (≥ 18 years) medical patients admitted to the ICU from the ED with severe sepsis or septic shock, diagnosed between January 2008 and December 2012, were included in this study. Patients admitted to the ICU from other hospitals, from the ward, step-down unit, and operating room were excluded from this analysis. Patients without an initial blood lactate measure were also excluded.

Definitions

Sepsis was defined as a systemic inflammatory response syndrome (SIRS) secondary to a confirmed or suspected infection (15). SIRS was defined by the presence of two or more of the following criteria: body temperature more than 38°C or less than 36°C, heart rate more than 90 bpm, respiratory rate more than

20 ipm or partial arterial pressure of CO_2 less than 32 mmHg, white blood count more than 12,000/mm^3 or less than 4,000/mm^3, or the presence of more than 10% rods (16). Severe sepsis was defined as sepsis associated with organ dysfunction, and septic shock was defined as hypotension refractory to fluid infusion with the need for vasopressors (15).

According to our institutional protocol for severe sepsis and septic shock resuscitation, patients admitted to the ED who fulfilled criteria for severe sepsis and septic shock were submitted to blood sampling for lactate measurement and blood cultures, received a first dose of broad-spectrum antibiotics within 1 h from the admission, received a fluid load with 20 to 30 mL/kg of crystalloids, and were admitted to the ICU (17, 18).

Goal-directed therapy was applied to patients with severe sepsis associated with arterial lactate levels at least 4.0 mmol/L or those who remained hypotensive (systolic blood pressure <90 mmHg or mean arterial blood pressure [MAP] <65 mmHg) despite fluid resuscitation (17, 18). The following therapeutic goals were targeted during the first 6 h of resuscitation: central venous pressure between 8 and 12 mmHg (12–15 mmHg in mechanically ventilated patients), MAP at least 65 mmHg, central venous oxygen saturation ($ScvO_2$) at least 70 %, and diuresis at least 0.5 mL/kg/h (17, 18).

Collected variables

The following data were collected and recorded: demographic characteristics, comorbidities, admission diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score (19), Sepsis-related Organ Failure Assessment (SOFA) score (20), site of infection, hemodynamic parameters, administered treatments (fluids, vasopressors, blood transfusion, steroids, and antibiotics) during the first 24 h of ICU admission, the need for mechanical ventilation, mortality at day 28, and length of ICU and hospital stays.

Lactate clearance time (time span between the first two blood lactate measurements; hours), absolute lactate clearance (initial lactate value minus delayed value; mmol/L), relative lactate clearance (absolute clearance divided by initial value and the result multiplied by 100; %), and lactate clearance rate (relative clearance divided by clearance time; % per hour) were determined as previously described (21). Blood lactate levels were obtained after severe sepsis, and septic shock diagnosis at the ED and after ICU admission was measured by catalyzed lactate oxidase (VITROS; Jonhson & Johnson, New Brunswick, NJ) and expressed in mmol/L.

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies and continuous variables as median and interquartile range (IQR). Binary variables were compared with chi-square test or with Fisher exact test when appropriate. Continuous variables were compared with Mann-Whitney U test.

A receiver-operating characteristic (ROC) curve was constructed to assess the best blood lactate level cutoff related to 28-day mortality. Subsequently, patients were dichotomized according to the lactate cutoff chosen by ROC curve analysis. We calculated sensitivity, specificity, and positive and negative predictive value for this cutoff value. We also constructed ROC curves to test the ability of initial lactate levels, absolute lactate clearance, relative lactate clearance, and lactate clearance rate to predict 28-day mortality in the subgroup of patients who had more than one blood lactate measurement performed during the first 24 h of ED admission.

Survival analysis was performed using the Kaplan-Meier method with the dichotomized values of initial lactate levels, and the log-rank test was used to compare the groups. Unadjusted analysis was performed using the Cox proportional hazards regression model, using as censored variable, 28-day mortality, and time in days (up to 28 days), including sex, age, presence of comorbidities, severe sepsis or septic shock diagnosis, APACHE II score, SOFA score at ICU admission, vasopressor use, need for mechanical ventilation, and site of infection. Variables with $P < 0.20$ in the unadjusted analysis were included in the adjusted Cox regression and those with $P < 0.05$ were included in the final model. The hazard ratios (HRs) with their respective 95% confidence intervals (95% CIs) were estimated for each covariate.

Two-tailed tests were used, and when $P < 0.05$, the test was considered statistically significant. Stata version 13.0 (StataCorp, College Station, Tex) and SPSS version 21.0 (IBM Statistical Package for the Social Science) were used for statistical analyses.

RESULTS

Study patients and clinical presentation

Four hundred forty-three patients were included in this analysis. Demographics and clinical characteristics of studied patients are shown in Table 1. The median (IQR) age was 70 (55–82) years. Severe sepsis patients accounted for 58.2% (258/443) of patients and septic shock for 41.8% (185/443) of patients. The most prevalent comorbidities were systemic hypertension (32.7%) and diabetes mellitus (20.8%). The most common site of infection was the respiratory tract (50.6%), followed by the urinary tract (20.3%) (Table 1).

The median (IQR) APACHE II score was 20 (17–24), and the median SOFA score at ICU admission was 4 (3–7). The median (IQR) initial blood lactate level was 2.1 mmol/L (1.3–3.3 mmol/L) and median (IQR) $ScvO_2$ was 75% (71%–81%). Approximately 42% of patients (185/443) were on vasopressor drip and 19% (83/443) required mechanical ventilation during the first 24 h of ICU admission (Table 1).

Initial lactate levels as a predictor of death

The blood lactate cutoff of 2.5 mmol/L showed the largest area under the ROC curve (ROC area = 0.70) related to 28-day mortality (Fig. 1). The sensitivity, specificity, and negative predictive value of initial lactate levels more than 2.5 mmol/L for 28-day mortality were 67.4%, 61.7%, and 94.2%, respectively (Table 2).

Mortality at 28 days was 16.9% (31/183) in patients with initial lactate more than 2.5 mmol/L and 5.8% (15/260) in patients with initial lactate at most 2.5 mmol/L (absolute difference, 11.1% [95% CI, 5.0%–17.3%]; relative risk, 2.93 [95% CI, 1.63–5.28]; $P < 0.001$). Initial blood lactate levels more than 2.5 mmol/L were significantly associated with increased 28-day mortality (HR, 3.22; 95% CI, 1.74–5.98; $P < 0.001$) (Fig. 2).

Lactate kinetics as a predictor of death

Out of the 443 patients included in the primary analysis, 260 (58.7%) had more than one lactate measurement performed during the first 24 h of ED admission. Of those 260 patients, 33 (12.7%) died, whereas 227 (87.3%) were alive at day 28 (Table 3). Lactate clearance time, absolute lactate clearance, relative lactate clearance, and lactate clearance rate did not differ between survivals and nonsurvivals (Table 3). The AUC was highest for the initial lactate levels (0.664) followed by absolute lactate clearance (0.571), clearance rate (0.550), and relative lactate clearance (0.515).

Predictors of 28-day mortality

From the initial model containing 10 predictors (Table 4), the backward elimination Cox regression analysis yielded a final model containing lactate more than 2.5 mmol/L (HR, 2.86; 95% CI, 1.53–5.33; $P = 0.001$) and SOFA score at ICU admission (HR, 1.18; 95% CI, 1.09–1.27; $P < 0.001$) significantly associated with increased 28-day mortality. The presence of diabetes mellitus was an independent protective factor (HR, 0.25; 95% CI, 0.08–0.84; $P = 0.024$) (Table 4).

DISCUSSION

In our retrospective single-center cohort study with 443 severe sepsis and septic shock patients admitted to the ICU, initial lactate levels more than 2.5 mmol/L exhibited the highest

TABLE 1. **Baseline characteristics of 443 severe sepsis and septic shock patients admitted to the intensive care unit**

Characteristics	All (N = 443)	Lactate ≤2.5 mmol/L (N = 260)	Lactate >2.5 mmol/L (N = 183)	P*
Age, year, median (IQR)	70 (55−82)	71 (54−83)	70 (58−82)	0.845
Male, n (%)	273 (61.6)	156 (60.0)	117 (63.9)	0.428
Comorbidities, n (%)				
Systemic hypertension	145 (32.7)	80 (30.8)	65 (35.5)	0.305
Diabetes mellitus	92 (20.8)	51 (19.6)	41 (22.4)	0.478
Transplant	48 (10.8)	29 (11.2)	19 (10.4)	0.877
Oncologic	46 (10.4)	25 (9.6)	21 (11.5)	0.531
Chronic kidney failure	30 (6.8)	20 (7.8)	10 (5.5)	0.443
Congestive heart failure	28 (6.3)	19 (7.4)	9 (4.9)	0.329
Liver cirrhosis	14 (3.2)	4 (1.5)	10 (5.5)	0.026
COPD	14 (3.2)	5 (1.9)	9 (4.9)	0.098
Source of sepsis, n (%)				
Respiratory system	224 (50.6)	146 (56.2)	78 (42.6)	0.005
Urinary system	90 (20.3)	44 (16.9)	46 (25.1)	0.041
Abdominal	73 (16.5)	34 (13.1)	39 (21.3)	0.027
Skin and soft tissues	17 (3.8)	11 (4.2)	6 (3.3)	0.803
Bloodstream	10 (2.3)	6 (2.3)	4 (2.2)	1.000
Unknown	21 (4.7)	14 (5.4)	7 (3.8)	1.000
Other	8 (1.8)	5 (1.9)	3 (1.6)	1.000
Diagnosis at ED, n (%)				
Severe sepsis	258 (58.2)	166 (63.8)	92 (50.3)	0.005
Septic shock	185 (41.8)	94 (36.2)	91 (49.7)	0.005
APACHE II score, median (IQR)	20 (17−24)	19 (16−25)	20 (17−24)	0.542
SOFA score, median (IQR)	4 (3−7)	4 (3−6)	5 (3−8)	0.033
Initial lactate, mmol/L, median (IQR)	2.1 (1.3−3.3)	1.44 (1.11−1.89)	3.66 (3.00−5.77)	<0.001
ScvO₂, %, median (IQR)	75 (71−81)	75 (70−81)	75 (72−81)	0.406
Vasopressor use on day 1, n (%)	185 (42.3)	92 (37.5)	93 (52.0)	0.001
Mechanical ventilation on day 1, n (%)	83 (18.9)	48 (18.5)	35 (19.4)	0.806

*P values were provided by chi-square test or Fisher exact test for binary variables and Mann-Whitney U test for continuous variables.
APACHE II, Acute Physiology and Chronic Health Evaluation II (varies from 0 to 71, higher values indicate greater severity); COPD, chronic obstructive pulmonary disease; ED, emergency department; IQR, interquartile range; ScvO₂, central venous oxygen saturation; SOFA score, Sequential Organ Failure Score (range 0−24, higher values indicate greater number of organ dysfunction) at ICU admission.
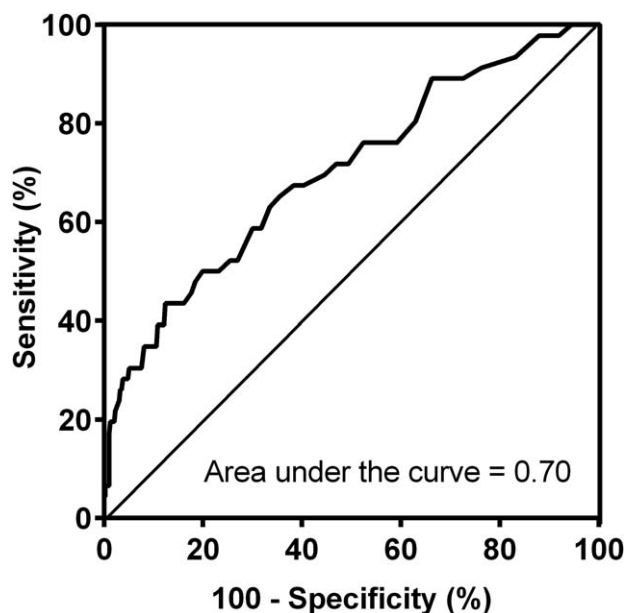Values represent median (IQR) or n (%).

Fig. 1. **ROC curve addressing the association between admission blood lactate and 28-day mortality.** ROC, receiver-operating characteristic.

sensitivity, specificity, and negative predictive value for 28-day mortality. Patients with initial lactate levels above this cutoff had a mortality rate 3.2 times higher than patients with initial lactate lower or equal to 2.5 mmol/L.

Clinical studies have emphasized tissue hypoxia, characterized by supply-dependent oxygen consumption, as a leading cause of increased lactate levels in septic patients (22, 23). During the acute phase, hyperlactatemia is often considered a marker of tissue hypoperfusion (15). Although the current guidelines for severe sepsis and septic shock resuscitation recommend that patients with severe sepsis or septic shock with an initial blood lactate level of at least 4.0 mmol/L must be promptly resuscitated (15), recent studies have shown that less expressive elevations in lactate levels have also been associated with poor outcomes (9–13), regardless of the presence of hepatic dysfunction (12).

TABLE 2. **Diagnostic assessment of initial blood lactate more than 2.5 mmol/L to predict 28-day mortality**

Measurement	Estimate	95% CI
Area under the ROC Curve	0.70	0.62−0.79
Sensitivity	67.4	52.0−80.5
Specificity	61.7	56.7−66.5
Positive predictive value	16.9	11.8−23.2
Negative predictive value	94.2	90.7−96.7

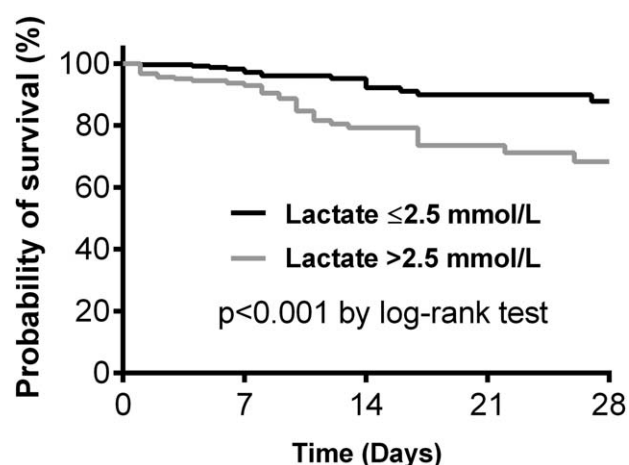CI, confidence interval; ROC, receiver-operating characteristic.

Fig. 2. **Kaplan-Meier survival curves for 28-day survival according to lactate levels.**

Several other studies are consistent with our findings of mild hyperlactatemia as a predictor of mortality in septic patients (9, 10, 13). A prospective single-center cohort study involving 1,287 patients admitted to the ED with suspected infection showed that initial venous lactate levels between 2.5 and 4.0 mmol/L were independently associated with an increased risk of 28-day in-hospital death (9). Another single-center cohort study including 830 patients with severe sepsis and septic shock admitted to the ED showed that initial venous lactate levels between 2.0 and 3.9 mmol/L, compared with initial lactate levels less than 2.0 mmol/L, were associated with increased mortality at day 28, regardless of the presence of shock (10).

A *post hoc* analysis of the Vasopressin in Septic Shock Trial, including 665 patients, showed that patients with lactate levels between 1.4 and 2.3 mmol/L had a significantly increased risk of 28-day mortality and organ dysfunction compared with those with lactate at most 1.4 mmol/L (13). In this study, baseline lactate values of 2.3 mmol/L exhibited 60% sensitivity and 55% specificity for 28-day mortality (13), which is similar to our findings. Therefore, initial blood lactate levels measure, commonly available in most EDs and ICUs, is a valuable tool to help clinicians at the bedside identify high-risk septic patients in need of additional resources of care, such as ICU admission, invasive hemodynamic monitoring, and varying degrees of organ support. Another *post hoc* analysis of a multicenter, noninferiority trial showed that initial venous lactate levels had an area under the ROC curve of 0.64 to predict in-hospital survival (21). In contrast to our study, only patients with initial

venous lactate levels at least 2.0 mmol/L were included, and the authors did not show the exact lactate threshold associated with the highest area under the ROC curve (21).

Along with our results, available evidence suggests that the current guidelines might be too conservative when recommending that resuscitation should be only reserved for those septic patients with blood lactate concentrations at least 4.0 mmol/L (15). Considering the increased risk of unfavorable outcomes reported in septic patients presenting to the ED with intermediate hyperlactatemia (9–13), aggressive resuscitation may be advisable and might improve morbidity and mortality. Nevertheless, a mild hyperlactatemia must be placed in the appropriate clinical context to prove value as a prognostication in sepsis (24). Indeed, a recent randomized controlled trial involving 348 critically ill patients used a lower cutoff of blood lactate concentration ($\geq$3.0 mmol/L) to trigger resuscitation (25). In this study, patients undergoing lactate-guided therapy exhibited a lower risk of in-hospital mortality than the control group (25).

We found diabetes mellitus to be a protective factor for 28-day mortality in patients with severe sepsis and septic shock. Although patients with diabetes have an increased risk of infections and sepsis (26, 27) due to depressed humoral and cellular immunity (28, 29), conflicting data exist on whether the outcomes of septic patients are affected by the presence of diabetes (30). Although some authors reported increased mortality among patients with diabetes with infection (31, 32), others reported improved survival (33–35). The exact mechanisms responsible for these controversial findings remain unclear (30, 36). It was demonstrated that administration of exogenous insulin was associated with improvement on host immunity and decreased production of proinflammatory mediators, such as tumor necrosis factor alpha (37), decreased production of macrophage migration inhibitory factor, and intranuclear factor kappa B and reactive oxygen species generation by mononuclear cells in obese patients (38). Therefore, we can hypothesize that blood glucose control with exogenous insulin administration, which is routinely used in ICU patients (39), could explain, at least partially, the mechanism related to the observed protective effect of diabetes on 28-day mortality in our study population. In addition, besides the effect of insulin on the immune and inflammatory response, diabetes has been associated with reduced risk of acute respiratory dysfunction, which may have positively affected our population of critically ill patients (40).

Our study has limitations. First, this was a single-center study. Therefore, our results may have limited external validity.

Table 3. **Measures of lactate kinetics and their association with 28-day mortality**

Characteristics	Dead at day 28, 33/260 (12.7%)	Alive at day 28, 227/260 (87.3%)	P*
Initial lactate, mmol/L	3.66 (2.00–7.10)	2.33 (1.44–3.44)	0.002
Second lactate, mmol/L	2.78 (1.56–5.22)	1.78 (1.22–2.67)	0.001
Lactate clearance time, h	6 (4–14)	6 (5–11)	0.481
Absolute lactate clearance, mmol/L	0.55 (0.00–1.88)	0.33 (−0.22 to 1.44)	0.186
Relative lactate clearance, %	17.5 (−0.11 to 39.1)	17.7 (−11.2 to 45.4)	0.778
Lactate clearance rate, %/h	2.84 (−0.01 to 6.64)	1.90 (−1.48 to 6.79)	0.353

*P values were provided by Mann-Whitney U test.
Values represent median (IQR).

TABLE 4. **Univariate and multivariate Cox proportional hazards regression models to assess which variables were independently associated with 28-day mortality**

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Lactate >2.5 mmol/L	3.22	1.74–5.98	<0.001	2.86	1.53–5.33	0.001
Systemic hypertension	0.54	0.26–1.11	0.095			
Diabetes mellitus	0.27	0.08–0.87	0.028	0.26	0.08–0.84	0.024
Liver cirrhosis	2.34	0.84–6.53	0.105			
Abdominal infection	1.98	1.03–3.83	0.042			
APACHE II score	1.04	0.90–1.10	0.124			
SOFA score	1.20	1.12–1.29	<0.001	1.18	1.09–1.27	<0.001
Septic shock	2.17	1.18–3.96	0.013			
Vasopressor use	1.94	1.05–3.56	0.034			
Mechanical ventilation	1.79	0.98–3.26	0.059			

CI, confidence interval; HR, hazard ratio; SOFA, Sequential Organ Failure Score (range 0–24, higher values indicate greater number of organ dysfunction); APACHE II score, Acute Physiology and Chronic Health Evaluation II (varies from 0 to 71, higher values indicate greater severity).

Second, because of the retrospective nature of our study, we are subject to selection and information bias. We analyzed variables that were routinely collected and documented as part of patient care. Third, patients admitted to the ED after 2010 could have received fluids, vasopressors, inotropes, and red blood cells transfusion guided by lactate clearance (41). Nevertheless, because all patients received their first dose of broad-spectrum antibiotics within 1 h from the admission and received an initial fluid load (20–30 mL/kg of crystalloids), it is unlikely that additional therapeutic interventions guided by the lactate clearance or ScvO$_2$ would have biased our results. Fourth, survival bias could have undervalued the observed association between lactate clearance and 28-day mortality in our study. Thus, our results must be interpreted with caution. Finally, patients recovering from surgery and those with a higher risk of delayed resuscitation (ward and hospital referrals) were not included in this analysis, which might have had an impact on our observed mortality rate and death prediction.

CONCLUSION

In our retrospective cohort study, severe sepsis or septic shock patients admitted to the ICU from the ED with initial blood lactate more than 2.5 mmol/L were at increased risk of death. Further prospective multicenter studies should address the impact of lower serum lactate cutoffs as a trigger to resuscitation on morbidity and mortality in this population of critically ill patients.

ACKNOWLEDGMENTS

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