Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock*

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Principle: **Serum lactate is a potentially useful biomarker to risk-stratify patients with severe sepsis; however, it is plausible that elevated serum lactate is simply a manifestation of clinically apparent organ dysfunction and/or shock (i.e., refractory hypotension).**

Objective: **To test whether the association between initial serum lactate level and mortality in patients presenting to the emergency department (ED) with severe sepsis is independent of organ dysfunction and shock.**

Design: **Single-center cohort study. The primary outcome was 28-day mortality and the risk factor variable was initial venous lactate (mmol/L), categorized as low (<2), intermediate (2–3.9), or high (≥4). Potential covariates included age, sex, race, acute and chronic organ dysfunction, severity of illness, and initiation of early goal-directed therapy. Multivariable logistic regression analyses were stratified on the presence or absence of shock.**

Setting: **The ED of an academic tertiary care center from 2005 to 2007.**

Patients: **Eight hundred thirty adults admitted with severe sepsis in the ED.**

Interventions: **None.**

Measurements and Main Results: **Mortality at 28 days was 22.9% and median serum lactate was 2.9 mmol/L. Intermediate (odds ratio [OR] = 2.05, $p = 0.024$) and high serum lactate levels (OR = 4.87, $p < 0.001$) were associated with mortality in the nonshock subgroup. In the shock subgroup, intermediate (OR = 3.27, $p = 0.022$) and high serum lactate levels (OR = 4.87, $p = 0.001$) were also associated with mortality. After adjusting for potential confounders, intermediate and high serum lactate levels remained significantly associated with mortality within shock and nonshock strata.**

Conclusions: **Initial serum lactate was associated with mortality independent of clinically apparent organ dysfunction and shock in patients admitted to the ED with severe sepsis. Both intermediate and high serum lactate levels were independently associated with mortality. (Crit Care Med 2009; 37:000–000)**

KEY WORDS: severe sepsis; lactic acid; infection; hypotension; mortality

Severe sepsis and septic shock result in 751,000 estimated cases and 215,000 deaths annually in the United States, with an associated cost in excess of $16 billion (1). Given the morbidity and mortality associated with severe sepsis, the ability to risk-stratify patients in the most proximal phase of their illness may assist clinicians to more effectively manage the care of these patients to improve their outcomes.

The presence of an elevated serum lactate level is strongly associated with morbidity and mortality in diverse populations of critically ill patients (2–7). Clinically, serum lactate is a potentially useful biomarker to risk-stratify patients with severe sepsis presenting to the emergency department (ED) (8–11). In sepsis, elevated serum lactate level may be due to either impaired lactate clearance or excessive production (12, 13). It is, therefore, plausible that an elevated serum lactate level is simply a manifestation of organ dysfunction, given that the clearance of lactate is dependent on hepatic and renal functions (14, 15). Furthermore, investigators demonstrated an association between organ dysfunction and mortality in septic ED patients (16). Whether the apparent association between mortality and serum lactate is independent of organ dysfunction and refractory hypotension (shock) is unclear.

The primary aim of our study was to determine whether, in patients presenting to the ED with severe sepsis, the association between initial serum lactate level and mortality is independent of clinically apparent organ dysfunction and shock. Secondary exploratory aims were to describe the clinical characteristics of patients with elevated serum lactate levels and to determine which demographic and clinical variables distinguish these patients from those with normal serum lactate levels.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the University of Pennsylvania with an informed consent exemption.

Study Population. This was a retrospective cohort of patients with severe sepsis admitted to the ED of the Hospital of the University of Pennsylvania from January 2005 to December 2006. In 2004, the ED institutionalized an aggressive screening protocol based on a serum lactate measurement drawn at the time when sepsis was suspected to determine EGDT eligibility. All ED subjects were screened for

*See also p. XXX.

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inclusion if serum lactate level was measured or a physician documented one of the following indicators of severe sepsis in the ED electronic medical record: sepsis, severe sepsis, septic shock, cryptic septic shock, or EGDT. Subjects were excluded if they were discharged from the ED, left against medical advice, transferred to another institution, or were patients with trauma. Repeated patient visit(s) were excluded to focus on the index case and to comply with the assumption of independent observations.

Sepsis was defined as suspected infection in the presence of two or more systemic inflammatory response syndrome criteria (17). Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension (17–20). Hypoperfusion was primarily defined as a serum lactate ≥2 mmol/L (2, 3) and as >3 mmol/L in a sensitivity analysis based on the 2001 International Sepsis Definitions Conference criteria (18). Hypotension and organ dysfunction were defined according to the 2001 criteria (18). Alternative definitions for organ dysfunction, based on objective measurements, were created for variables based on subjective assessments (e.g., change in mental status and oliguria). Septic shock was defined as hypotension (systolic blood pressure <90 mm Hg) despite adequate fluid resuscitation (>1500 mL) or the use of vasoactive agents (17, 19, 21). The electronic medical records of subjects passing the initial screen were then evaluated for evidence of severe sepsis in the ED and excluded if two or more systemic inflammatory response syndrome criteria were not present, infection was not suspected (e.g., no documented concern for infection or sepsis and no administration of antibiotics), criteria for severe sepsis were not met (18), or if a lactate was not measured in the ED (<2% of exclusions).

Data Collection. The following data were recorded from the electronic medical record: sociodemographics, comorbidities, initial and worst vital signs, laboratory measurements, therapy (e.g., EGDT, intravenous fluids, vasoactive agents) received in the ED, and infection source. Therapy provided in the ED was at the discretion of the covering providers. Baseline variables from the ED were used to calculate the Acute Physiology and Chronic Health Evaluation II score (22). Three trained investigators (D.F.G., A.N.M., and M.E.M.) performed the data collection using a predrafted data abstraction form. Serum lactate levels and mortality information were recorded during chart abstraction. Each abstraction form was verified for completeness and accuracy by one of the other investigators. Adjudication, if necessary, was performed by one investigator (D.F.G.).

Initial serum lactate levels (millimole per liter) were measured with a serum-based assay catalyzed by lactate oxidase (Vitros, Ortho Clinical Diagnostics, Rochester, NY). Subsequent serum lactate measurements were not included in the analysis. Mortality information was obtained from the hospital record and the Social Security Death Index (http://ssdi.genealogy.rootsweb.com/). The primary outcome was 28-day mortality, with 60-day mortality as a secondary outcome. Initial venous lactate was *a priori* stratified as low (<2 mmol/L), intermediate (2–3.9 mmol/L), or high (≥4 mmol/L) (2, 3, 10).

On the basis of previous studies suggesting biological plausibility and/or a relationship with serum lactate or mortality, we considered age, sex, race, initiation of EGDT, blood transfusion, and severity of illness as potential confounders (8–13, 19). To best address the primary research question of whether the association between mortality and initial serum lactate level is independent of organ dysfunction, we considered organ dysfunction (acute and chronic) as a potential confounder (14–16). Acute organ dysfunction was defined based on the 2001 Conference criteria (18). We considered the following chronic organ dysfunction variables based on documented comorbidities: congestive heart failure, chronic renal insufficiency (including end-stage renal disease), chronic liver failure (i.e., cirrhosis or end-stage liver disease), diabetes mellitus, malignancy, and organ transplantation (14, 15, 23–28). Candidate variables hypothesized to be associated with elevated serum lactate levels were broadly categorized into three mechanisms: increased lactate production, decreased lactate clearance (14, 15, 23–28), and definitional-based risk factors (e.g., medical history of hypertension as a marker of relative hypotension [17, 18]). Our *a priori* hypotheses are presented in Tables 2 and 3.

Statistical Analysis. Wilcoxon's rank sum test or the Kruskal-Wallis test was used to compare continuous variables and the chi-squared statistic or Fisher's exact test was used to compare categorical variables. We used a fractional polynomial regression model to graph the fitted relationship between observed 28-day mortality and initial serum lactate concentration (29). An advantage of a fractional polynomial regression is that the model permits a nonlinear relationship in the fitted regression line.

Multivariable logistic regression, stratified on the presence or absence of shock, was used to adjust for potential confounding in the association between initial serum lactate level and mortality. Potential confounding variables were added one at a time to the base model and maintained in the final model if the point estimate for the odds ratio (OR) was altered by >10% (30). An *a priori* decision was made to force age and initiation of EGDT into the final models. Statistical analyses were performed using Stata 9.0 software (Stata Datacorp, College Station, TX) and two-sided p values ≤0.05 were considered significant.

For potential confounding variables that had a large proportion of missing values (>5%), namely coagulation, hepatic, and respiratory failure measurements, we used dummy variable adjustment in our primary analysis (31). We compared the dummy variable adjustment models with two separate regression models. First, organ dysfunction was categorized as present based on available measurements and as absent when values were missing consistent with the methods of Acute Physiology and Chronic Health Evaluation score calculations (22). Second, we imputed bilirubin, coagulation, and oxygenation measurements using the median values observed to determine organ dysfunction, which yielded an identical model to the first given the distribution of these variables. Comparison of these models with the dummy variable adjustment models found similar, significant associations in both shock strata. The final analyses using dummy variable adjustment are presented.

RESULTS

Baseline Characteristics. Eight hundred thirty adults were included in this study of severe sepsis and septic shock in the ED (Fig. 1). The age range of the patients was 18–101 years (median: 58; interquartile range: 45–71) and 53% were men. The initial median serum lactate level was 2.9 mmol/L (interquartile range: 2.0–4.4) and 28-day mortality for the cohort was 22.9% (95% confidence interval [CI]: 20.1–25.9). Mortality at 60 days was 28.3% (95% CI: 25.3–31.5). The proportion of patients meeting criteria for organ dysfunction, hypotension, or hypoperfusion are presented in Table 1. Two thirds of the cohort met two or more of the three severe sepsis criteria; one third of the cohort fulfilled only one of the three definitional criteria. The most common sources of infection in the cohort were respiratory (29.6%), urologic (22.8%), bacteremic infections including catheter-related infections (21.0%), gastrointestinal (15.3%), and soft tissue-related infections (9.1%). Microbiologically proven infection was observed in 58.3% (n = 484) of the cohort. Specifically, 25.2% (n = 209) had microbiologically proven urinary tract infection and 37.1% (n = 308) had proven bloodstream infection.

Characteristics of Lactate Strata in Shock and Nonshock Subjects. As detailed in Tables 2 and 3, statistically significant differences were apparent in the clinical markers of the systemic inflammatory response across increasing lactate

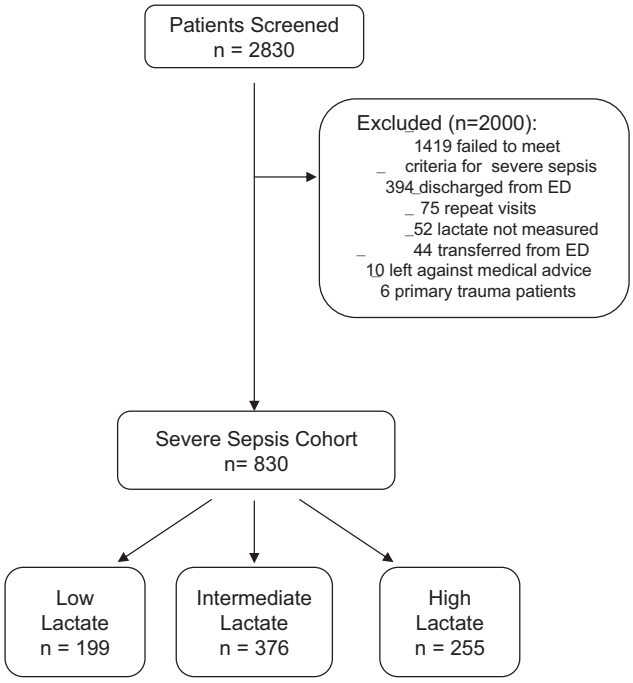

Figure 1. Enrollment and outcomes (serum lactate strata) for severe sepsis cohort. *ED*, emergency department.

Table 1. Criteria for inclusion in severe sepsis cohort (n = 830) based on the 2001 International Conference criteria (17)

Severe Sepsis Criteria Met in the Emergency Department	Severe Sepsis, n (%)
Organ dysfunction criteria	
Cardiovascular failure	
Systolic blood pressure <90 mm Hg	351 (42.3)
Mean arterial pressure <60 mm Hg	250 (30.1)
Shock (refractory hypotension)	196 (23.6)
Central nervous system failure	
Change in mental status	226 (27.2)
Glasgow Coma Scale <15[a]	172 (20.7)
Coagulation failure[b]	
International normalized ratio >1.5 or partial thromboplastin time >60	91 (11.0)
Hematologic failure	
Platelets <100	127 (15.3)
Hepatic failure[b]	
Total bilirubin >2[a]	99 (11.9)
Total bilirubin >4	62 (7.5)
Renal failure	
Creatinine increase >0.5 above baseline	272 (32.8)
Oliguria[c]	52 (6.3)
Creatinine >2.0 mg/dL[a]	223 (26.9)
Respiratory failure[b]	
Pao_2/Fio_2 <300	94 (11.3)
Hypoperfusion criteria	
Lactate ≥2 mmol/L	631 (76.0)
Lactate >3 mmol/L[a]	382 (46.0)

[a]These alternative definitions were used as secondary definitions in the analyses, but were not used as inclusion criteria; [b]these measurements were not recorded routinely in all subjects. Coagulation measurements were obtained in 588 subjects (70.8%), hepatic injury measurements in 484 subjects (58.3%), and arterial blood gas measurements in 195 subjects (23.5%); [c]patients were categorized as "oliguric" if documentation of anuria or oliguria was noted despite fluid resuscitation. Only one patient met this criteria alone for inclusion.

strata: lower temperatures, higher heart and respiratory rates, and higher white blood cell counts. Patients with an elevated serum lactate were severely ill as reflected in higher baseline Acute Physiology and Chronic Health Evaluation II scores; more likely to meet criteria for acute organ dysfunction; and treated more aggressively in the ED.

Association between Blood Lactate Levels and Mortality. In the nonshock subgroup, the initial median serum lactate level was significantly higher in nonsurvivors compared with survivors at 28 days (3.4 vs. 2.6 mmol/L, $p < 0.001$). In the shock subgroup, nonsurvivors also had significantly higher initial median serum lactate levels compared with survivors (5.2 vs. 3.3 mmol/L, $p < 0.001$). Each of the 28 patients with an initial serum lactate <1 mmol/L survived, including four in the shock subgroup.

The fitted relationship between initial serum lactate measurements and 28-day mortality for the shock and nonshock subgroups is shown in Figure 2. Although the relationship between serum lactate and mortality seemed different in the presence of shock, the interaction term was not significant ($p = 0.48$). In the nonshock subgroup, the predicted mortality reached a plateau at serum lactate levels >8 mmol/L, whereas higher serum lactate values were associated with increasing mortality in the shock subgroup until level exceeded 18 mmol/L.

Intermediate and high serum lactate levels, compared with low serum lactate levels, were significantly associated with increased 28-day mortality in both the nonshock and shock subgroups (Fig. 3). After adjusting for potential confounding variables, intermediate and high serum lactate levels remained significantly associated with 28-day mortality (Tables 4 and 5).

The association between 28-day mortality and serum lactate levels remained significant in our sensitivity analyses, using the more conservative definition of hypoperfusion (serum lactate >3 mmol/L) for inclusion criteria (17). In the nonshock subgroup, including 569 patients, we found that the intermediate and high serum lactate levels were significantly associated with 28-day mortality: OR 2.33 (95% CI: 1.23–4.39; $p = 0.009$) and 4.87 (95% CI: 2.56–9.27; $p < 0.001$). When the analysis was limited to those patients with microbiologically proven infection, 28-day mortality remained sig-

Table 2. Baseline characteristics in the 830 subjects by serum lactate stratum and shock status

Variable	Lactate Stratum for Nonshock Subjects (n = 634)				Lactate Stratum for Shock Subjects (n = 196)			
	Low (n = 160)	Intermediate (n = 317)	High (n = 157)	p	Low (n = 39)	Intermediate (n = 59)	High (n = 98)	p
Age (yrs)[a]	58 (44–69)	56 (45–71)	57 (44–71)	0.82	58 (44–71)	57 (48–72)	60.5 (52–73)	0.46
Sex (male), n (%)	87 (54.4)	168 (53.0)	87 (55.4)	0.79	17 (43.6)	29 (49.2)	53 (54.1)	0.52
Race								
White, n (%)	71 (46.7)	132 (43)	70 (46.3)	0.75	23 (60.5)	33 (60)	35 (36.1)	0.01
African American, n (%)	71 (46.7)	159 (51.8)	75 (49.7)		15 (39.5)	21 (38.2)	60 (61.9)	
Other, n (%)	10 (6.6)	16 (5.2)	6 (4.0)		0 (0)	1 (1.8)	2 (2.0)	
Temperature (°C)	38 (36.8–38.8)	37.9 (36.8–38.8)	37 (36.4–38.3)	<0.001	37.3 (36.4–38.7)	37 (36.4–38.9)	36.7 (36.0–37.8)	0.02
Heart rate	110 (97–122)	111 (100–126)	116 (102–131)	0.003	114 (93–123)	108 (90–135)	114 (91–132)	0.88
Respiratory rate	18 (16–23)	18 (16–22)	20 (18–25)	0.003	18 (16–20)	18 (16–22)	20 (16–27)	0.02
Mean arterial pressure	84 (71–95)	87 (73–98)	86 (73–100)	0.19	70 (60–82)	66 (57–80)	68 (60–83)	0.77
White blood cell count	12 (7.2–16.1)	12.8 (8–17.5)	13.7 (10.1–19.7)	0.002	10.7 (6.4–15.1)	12.6 (7.1–19.5)	11.7 (5.4–19.1)	0.32
Hematocrit	33 (28–37)	35 (31–40)	38 (31–43)	<0.001	32 (26–36)	33 (30–38)	34.5 (28–40)	0.12
Platelets	234 (147–342)	230 (167–348)	237 (156–319)	0.67	216 (145–303)	204 (142–280)	196 (114–283)	0.85
Serum creatinine (mg/dL)[a]	1.3 (0.9–2.1)	1.2 (0.9–1.8)	1.3 (1.0–2.0)	0.13	1.6 (1.0–3.8)	1.1 (1.3–2.8)	2.0 (1.3–3.2)	0.16
Glucose (mg/dL)[a]	110 (96–138)	123.5 (100–164)	155 (101–217)	<0.001	105 (94–129)	106 (84–130)	115 (89–177)	0.27
Total bilirubin[a,b] (mg/dL)	0.6 (0.3–0.9)	0.7 (0.4–1.3)	0.9 (0.5–3.0)	<0.001	0.5 (0.2–1.0)	0.6 (0.4–1.1)	1.2 (0.7–4.2)	<0.001
Prothrombin time (sec)[b]	13.6 (12.5–15.4)	13.8 (12.9–15.5)	14.4 (13.1–16.8)	0.18	14.2 (12.9–15.4)	14 (13–15.6)	16.1 (13.7–20.1)	0.002
Partial thromboplastin time (sec)[b]	28.4 (26.2–33.4)	28.6 (25.6–33.7)	28.4 (24.9–34.6)	0.78	28.9 (26.2–34.1)	29.2 (25.9–34.1)	29.5 (25.5–36.2)	0.77
Lactate (mmol/L)	1.3 (1.1–1.6)	2.8 (2.4–3.3)	5.3 (4.5–6.7)	<0.001	1.5 (1.1–1.7)	2.9 (2.5–3.3)	6.3 (5–8.6)	<0.001
Acute Physiology and Chronic Health Evaluation II (baseline)	14 (11–18)	14 (10–18)	16 (11–21)	0.001	18 (14–24)	16 (12–22)	21.5 (17–26)	<0.001
28-day mortality[a] (n, %), 95% confidence interval	14 (8.7), 4.9–14.2	52 (16.4), 12.5–20.9	50 (31.8), 24.6–39.7	<0.001	6 (15.4), 5.9–30.5	22 (37.3), 25.0–50.8	46 (46.9), 36.8–57.3	0.003

[a]Factors hypothesized to be associated with elevated serum lactate levels; [b]reported in those in whom a measurement was obtained.

Continuous measures are presented as medians with interquartile ranges (25th, 75th percentile). Categorical variables are presented as counts and percentiles.

nificantly greater across increasing lactate strata in both the nonshock and shock subgroups ($p < 0.001$).

At 60 days, the high serum lactate stratum was likewise associated with mortality in both the nonshock (OR 3.89, 95% CI: 2.25–6.71; $p < 0.001$) and shock (OR 2.76, 95% CI: 1.24–6.16; $p = 0.013$) subgroups. However, at 60 days, the intermediate stratum was no longer significantly associated with mortality in the nonshock (OR 1.51, 95% CI: 0.90–2.53; $p = 0.12$) or shock (OR 1.7, 95% CI: 0.73–4.16; $p = 0.21$) subgroups.

DISCUSSION

We found that initial serum lactate was associated with mortality independent of organ dysfunction in this study of ED patients with severe sepsis. Furthermore, we demonstrated that the relationship between serum lactate levels and mortality was independent of the presence of clinically apparent shock. Therefore, serum lactate, in its association with mortality, does not seem to function solely as a marker of clinically apparent organ dysfunction or hypotension. These observations suggest that a single serum lactate measurement provides useful information in patients with severe sepsis and support the notion that an initial serum lactate measurement could potentially be used to inform medical decision making to improve patient outcomes.

Our principle finding—serum lactate levels are associated with mortality independent of clinically apparent organ dysfunction—enhances our understanding of the information provided by a single serum lactate measurement. It is well established that lactate metabolism is dependent on hepatic and renal functions (14, 15), and it is plausible that the rise in serum lactate concentration in sepsis is, in part, due to impaired lactate clearance (12, 13). Nevertheless, despite observing an association between elevated serum lactate levels and liver dysfunction, we found that the association between serum lactate level and mortality was independent of clinical evidence of organ dysfunction in the proximal phase of sepsis. Furthermore, we found that serum lactate was associated with mortality independent of hemodynamic stability. A recent study by Howell et al (11) suggested that serum lactate was associated with mortality independent of blood pressure. However, the mortality in this sepsis cohort was only 5.7% and it seemed that the association between serum lactate levels and mortality was modified in the presence of shock (11). In our stratified analysis of patients with severe sepsis, we found that serum lactate was associated with mortality independent of overt shock. As such, our work, a validation and expansion on the recent work by Howell et al (11), supports the notion that a single serum lactate measurement seems to risk-stratify patients independent of organ dysfunction and hemodynamic stability.

The second important finding in our study questions the traditional serum lactate threshold used to identify at-risk patients who are not in overt circulatory dysfunction. Currently, a serum lactate threshold of ≥4 mmol/L is used to initiate protocol-based resuscitation (2, 19, 20). Our findings support the notion that such patients are at an increased risk of death. In addition, as also reported by Howell et al (11), we found that hemodynamically stable patients with intermediate serum lactate levels (2–3.9 mmol/L) experienced mortality twice that of the low serum lactate group. We believe that these patients constitute a potentially large at-risk group that may benefit from an aggressive resuscitation strategy. Future studies could test whether the intermediate serum lactate, nonshock subgroup may

Table 3. Comorbidities, organ dysfunction, and treatment received in the emergency department in the 830 subjects by serum lactate stratum and shock status

Variable	Lactate Stratum for Nonshock Subjects (n = 634)				Lactate Stratum for Shock Subjects (n = 196)			
	Low (n = 160)	Intermediate (n = 317)	High (n = 157)	*p*	Low (n = 39)	Intermediate (n = 59)	High (n = 98)	*p*
Comorbidities[a,b]								
Coronary artery disease, n (%)	15 (9.4)	31 (9.8)	10 (6.4)	0.45	5 (12.8)	10 (17.0)	10 (10.2)	0.44
Chronic renal insufficiency, n (%)[b]	32 (20.0)	42 (13.3)	19 (12.1)	0.08	6 (15.4)	13 (22.0)	13 (13.3)	0.36
Congestive heart failure, n (%)[b]	16 (10.0)	31 (9.8)	12 (7.6)	0.71	7 (18.0)	11 (18.6)	15 (15.3)	0.85
Chronic obstructive pulmonary disease, n (%)	11 (6.9)	19 (6.0)	8 (5.1)	0.72	5 (12.8)	2 (3.4)	9 (9.2)	0.22
Diabetes mellitus, n (%)[b]	48 (30.0)	93 (29.3)	40 (25.5)	0.61	9 (23.1)	17 (28.8)	26 (26.8)	0.82
End-stage renal disease, n (%)	11 (6.9)	21 (6.6)	6 (3.8)	0.41	2 (5.1)	7 (11.9)	7 (7.2)	0.48
Human immunodeficiency virus, n (%)	6 (3.8)	12 (3.8)	7 (4.5)	0.93	4 (10.3)	1 (1.7)	8 (8.2)	0.14
Hypertension,[b] n (%)	64 (40.2)	128 (41.4)	59 (39.1)	0.89	13 (33.3)	18 (31.0)	44 (47.3)	0.09
Liver failure, n (%)	7 (4.4)	17 (5.4)	19 (12.1)	0.009	1 (2.6)	4 (6.8)	13 (13.4)	0.13
Oncology, n (%)	55 (34.4)	91 (28.7)	52 (33.1)	0.38	15 (38.5)	21 (35.6)	30 (30.6)	0.66
Transplant, n (%)	21 (13.3)	36 (11.4)	12 (7.6)	0.27	4 (10.3)	8 (13.6)	6 (6.1)	0.29
Organ failure observed in emergency department[b]								
Cardiovascular failure								
Mean arterial pressure <60 mm Hg, n (%)	36 (22.5)	49 (15.5)	24 (15.3)	0.12	27 (69.2)	45 (76.3)	69 (70.4)	0.67
Central nervous system failure[b]								
Change in mental status, n (%)	38 (23.8)	64 (20.2)	57 (36.3)	0.001	6 (15.4)	15 (25.4)	46 (46.9)	<0.001
Glasgow Coma Scale <15, n (%)	29 (18.1)	43 (13.6)	52 (33.1)	<0.001	7 (18.0)	11 (18.6)	30 (30.6)	0.14
Coagulation failure								
International normalized ratio >1.5 or partial thromboplastin time >60, n (%)	6 (3.8)	18 (5.7)	28 (17.8)	<0.001	2 (5.1)	4 (6.8)	33 (33.7)	<0.001
Hematologic failure								
Platelets <100, n (%)	31 (19.4)	39 (12.3)	25 (15.9)	0.12	6 (15.4)	8 (13.6)	18 (18.4)	0.72
Hepatic failure[b]								
Total bilirubin >2, n (%)	8 (5.0)	28 (8.8)	30 (19.1)	<0.001	3 (7.7)	5 (8.5)	25 (25.5)	0.005
Total bilirubin >4, n (%)	6 (3.7)	14 (4.4)	17 (10.8)	0.008	3 (7.7)	4 (6.8)	18 (18.4)	0.078
Renal failure[b]								
Creatinine >0.5 baseline, n (%)	53 (33.1)	80 (25.2)	50 (31.8)	0.13	17 (43.6)	22 (37.3)	50 (51.0)	0.24
Creatinine >2.0 mg/dL, n (%)	42 (26.2)	60 (18.9)	36 (22.9)	0.17	18 (46.2)	22 (37.3)	45 (45.9)	0.53
Oliguria, n (%)	7 (4.4)	10 (3.2)	13 (8.3)	0.046	4 (10.2)	4 (6.8)	14 (14.3)	0.40
Respiratory failure								
Pao_2/Fio_2 <300, n (%)	17 (10.6)	24 (7.6)	21 (13.4)	0.12	6 (15.4)	3 (5.1)	23 (23.5)	0.01
Treatment received in emergency department[a,b]								
EGDT, n (%)	1 (0.6)	13 (4.1)	89 (56.7)	<0.001	17 (43.6)	42 (71.2)	74 (75.5)	0.001
Intravenous fluids (mL)	1635 (1125–2500)	2100 (1250–3000)	2750 (2000–4070)	<0.001	3400 (2350–5250)	3975 (2250–5500)	4000 (3000–5000)	0.38
Blood transfusion received, n (%)	4 (2.6)	12 (3.9)	15 (9.6)	0.008	7 (18.4)	7 (11.9)	20 (20.4)	0.39
Vasoactive agent,[c] n (%)	0	0	0	NA	11 (28.2)	17 (28.8)	50 (51.0)	0.006

NA, not available.

[a]Percentiles are based on those in whom data were recorded (missing in <5% in each instance); [b]factors hypothesized to be associated with elevated serum lactate levels; [c]vasoactive agents used in shock: norepinephrine (n = 66), dopamine (n = 9), dobutamine (n = 10), epinephrine (n = 1), and vasopressin (n = 3). A combination of agents was used in 11 subjects. Continuous measures are presented as medians with interquartile ranges (25th, 75th percentile). Categorical variables are presented as counts and percentiles.

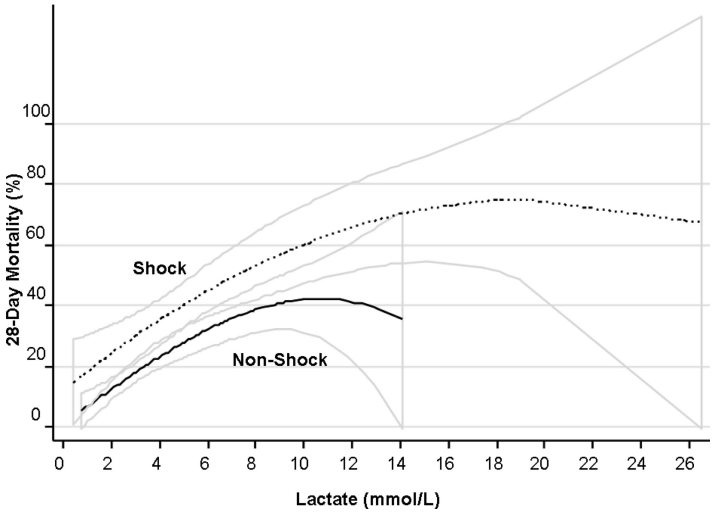

Figure 2. Relationship between initial venous lactate level and fitted 28-day mortality, using a fractional polynomial regression.

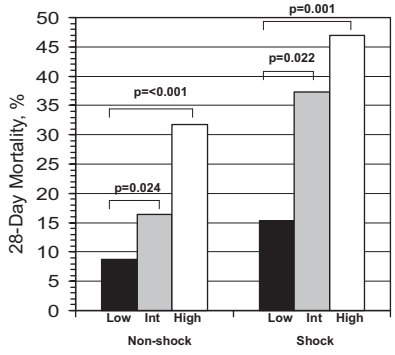

Figure 3. Association between serum lactate level and 28-day mortality, stratified by the presence of shock. Serum lactate categorized as follows: low = 0–1.9 mmol/L, intermediate (*Int*) = 2–3.9 mmol/L, and high = ≥4 mmol/L.

Table 4. Multivariable logistic regression demonstrating odds ratio of 28-day mortality by serum lactate strata in nonshock subgroup

Nonshock Model (n = 634)	Adjusted Odds Ratio (95% Confidence Interval)	*p*
Lactate stratum		
Low	Reference	Reference
Intermediate	2.05 (1.1–3.82)	0.024
High	4.87 (2.56–9.27)	<0.001
Adjusted for age and EGDT		
Intermediate	1.98 (1.05–3.75)	0.035
High	3.56 (1.67–7.61)	0.001
Adjusted for age, EGDT, and coagulation failure		
Intermediate	2.07 (1.08–3.97)	0.028
High	3.38 (1.56–7.30)	0.002
Adjusted for age, EGDT, and hepatic failure[a]		
Intermediate	1.90 (1.00–3.62)	0.050
High	3.21 (1.49–6.91)	0.003
Adjusted for age, EGDT, coagulation and hepatic failure[a]		
Intermediate	1.97 (1.03–3.79)	0.041
High	3.10 (1.42–6.75)	0.004
Adjusted for age, EGDT, coagulation and hepatic failure,[a] and APACHE II		
Intermediate	2.00 (1.04–3.83)	0.038
High	2.91 (1.33–6.39)	0.008
Adjusted for age, EGDT, blood transfusion, coagulation and hepatic failure,[a] and APACHE II[b]		
Intermediate	2.40 (1.21–4.79)	0.013
High	3.33 (1.47–7.56)	0.004

APACHE, Acute Physiology and Chronic Health Evaluation.

[a]The secondary definition of hepatic failure (total bilirubin >2 mg/dL) altered the odds ratio for the high serum lactate strata significantly; [b]nonshock model adjusted for blood transfusions (n = 620). potential confounding variables (e.g., malignancy) not included in the model did not alter the odds ratio of 28-day mortality by serum lactate strata significantly (>10%).

Table 5. Multivariable logistic regression demonstrating odds ratio of 28-day mortality by serum lactate strata in overt shock

Shock model (n = 196)	Adjusted Odds Ratio (95% Confidence Interval)	*p*
Lactate strata		
Low	Reference	Reference
Intermediate	3.27 (1.18–9.05)	0.022
High	4.87 (1.87–12.66)	0.001
Adjusted for age, malignancy, and EGDT		
Intermediate	4.26 (1.42–12.73)	0.009
High	6.65 (2.33–18.96)	<0.001
Adjusted for age, malignancy, EGDT, and hepatic failure[a]		
Intermediate	4.41 (1.45–13.46)	0.009
High	5.87 (2.01–17.12)	0.001
Adjusted for age, malignancy, EGDT, hepatic failure,[a] and APACHE II		
Intermediate	5.34 (1.69–16.83)	0.004
High	5.14 (1.74–15.18)	0.003

APACHE, Acute Physiology and Chronic Health Evaluation.

[a]The secondary definition of hepatic failure (total bilirubin > 2 mg/dL) altered the odds ratio for the high serum lactate strata significantly. Potential confounding variables not included in the model did not alter the odds ratio of 28-day mortality by serum lactate strata significantly (>10%).

benefit similarly from protocol-based resuscitation and consideration should be given to whether the serum lactate threshold used to define severe sepsis needs to be adjusted downward (17, 19).

Serum lactate seems to be a useful biomarker to risk-stratify patients with severe sepsis; however, some important questions remain unanswered regarding the pathophysiologic role of serum lactate in sepsis. Traditionally, increased serum lactate has been attributed to anaerobic glycolysis due to inadequate tissue oxygenation (32). However, hyperlactatemia in sepsis may be due to aerobic glycolysis or may be inflammatory mediated (33–38). Our study suggests that serum lactate levels correspond to the clinical variables that reflect the response to the systemic inflammatory response syndrome, along with alterations in glucose metabolism, coagulopathy, and hepatic dysfunction. One theory is that serum lactate serves as an early biomarker of the systemic inflammatory response of sepsis as a prelude to clinically apparent organ dysfunction and death (39, 40). Lactate production, therefore, may not be driven by a singular mechanism, but may result from several pathways, each driven by the inflammatory response of sepsis.

Our study has several strengths. First, as a center that protocolized venous lactate measurements as part of a sepsis clinical management pathway, we were able to study a large cohort of severe sepsis patients. Second, we used established consensus definitions for organ dysfunction and hypotension (17, 18). Third, in our sensitivity analyses, we demonstrated that our findings were robust over varying definitions of hypoperfusion (18) and in the subset of patients with microbiologically proven infection. Fourth, our use of venous lactate measurements in this study, which provide reliable results within minutes (2), demonstrates how serum lactate may be used effectively to risk-stratify patients in the ED.

There are several limitations to our study. First, our retrospective cohort study is potentially prone to selection, ascertainment, and misclassification bias. The protocolization of a severe sepsis clinical pathway before the initiation of this study and the use of serum lactate measurements as evidence of suspected infection serve to minimize the potential for selection bias. We acknowledge that a temporal delay potentially exists between the identification of sepsis and the measurement of serum lactate. Nevertheless, our results are internally valid and represent actual practice at a single center. The potential for ascertainment bias would most likely affect patients who presented in overt shock because they may receive protocol-based resuscitation regardless of a lactate measurement. However, of 2830 eligible patients, only 52

patients (1.8%) were excluded because they did not have a serum lactate obtained. We chose covariates that were readily available, easy to classify, and routinely documented in our ED. In addition, we performed sensitivity analyses to account for missing data and determined that our model was robust to different assumptions. Nevertheless, we acknowledge the potential for misclassification bias because of missing data and concede that our severity of illness measure (Acute Physiology and Chronic Health Evaluation II) was not used as originally described (22). Furthermore, we recognized that therapy received in the ED could confound the association between an initial serum lactate level and subsequent mortality. How the use of EGDT, which was underutilized at our center for unclear reasons, affects this relationship is unknown and warrants further study. Nevertheless, our adjustment for therapy received in the ED demonstrated that our findings were robust and, if anything, our reported findings may be biased toward the null.

Second, in our secondary aims that sought to describe the clinical characteristics of patients with elevated serum lactate levels, we acknowledge that although statistically significant, these observations should be interpreted with caution and confirmatory studies are warranted. Finally, our findings may not be generalizable to other centers based on the case mix of our study population (e.g., transplant and oncology patients).

CONCLUSIONS

Our study reveals that initial serum lactate is associated with mortality independent of clinically apparent organ dysfunction and shock in patients admitted from the ED with severe sepsis. From this perspective, measurement of serum lactate on presentation to the ED seems to be a useful, simple strategy to identify at-risk severe sepsis patients. Further studies are necessary to better understand the etiology of elevated serum lactate levels.

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