Utility of the early lactate area score as a prognostic marker for septic shock patients in the emergency department

Gina Yu*, Seung Joon Yoo*, Sang-Hun Lee, June Sung Kim, Sungmin Jung, Youn-Jung Kim, Won Young Kim, Seung Mok Ryoo

Department of Emergency Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: The current Surviving Sepsis Campaign guidelines recommend the remeasurement of lactate levels if the initial lactate level is elevated; however, the prognostic value of lactate kinetics is limited and inconsistent. We attempted to determine the efficacy of the lactate area score (calculated from repeated lactate measurements during initial resuscitation) as a prognostic marker of septic shock in the emergency department (ED).

Methods: We performed a retrospective study of adult patients with septic shock in the ED of a single tertiary medical center. Serial lactate levels were measured five times within 12 hours. We also compared the initial lactate level, maximum lactate level, and lactate area score. The lactate area score was defined as the sum of the area under the curve measured at 2, 4, 6, and 12 hours following the initial measurement.

Results: A total of 362 patients were enrolled in this study, and the overall 28-day mortality was 31.8%. The lactate area score of serial lactate levels as well as the initial (median [interquartile range], 4.9 [3.4 to 10.5]; P=0.003) and maximum (7.3 [4.2 to 13.2]; P<0.001) lactate levels were significantly higher in the non-survivor group. However, in multivariate analysis, only the lactate area score (odds ratio, 1.013; 95% confidence interval, 1.007 to 1.019) was significantly associated with 28-day mortality.

Conclusions: The early lactate area score may be a possible prognostic marker for predicting the 28-day mortality of adult septic shock patients. Further prospective interventional studies should be conducted to validate our results.

Key Words: lactic acid; mortality; prognosis; sepsis; shock

INTRODUCTION

Septic shock remains an important cause of morbidity and mortality among critically ill patients; thus, the Surviving Sepsis Campaign guidelines have been going to consensus for septic shock management [1]. The recent Surviving Sepsis Campaign guidelines recommend 1 hour of bundle therapy, which includes repeated lactate measurements when the initial lactate level is elevated [2]. As an index for tissue hypoxia and accelerated aerobic metabolism, elevated serum lactate is associated with unfavorable outcomes among patients with severe illness [3]. Although elevated serum lactate may not directly reflect tissue hypoxia, it is ac-

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companied by a hypermetabolic state with enhanced glycolysis and hyperlactatemia in cases of severe illness, especially septic shock [3-7]. Serum lactate level is associated with mortality, and hospital mortality has been reported to increase linearly with increasing serum lactate level [8]. Therefore, lactate-guided therapy with repeated measurements has also been recommended in the Surviving Sepsis Campaign [9].

Lactate normalization is a proven prognosis marker among septic shock patients. Since Nguyen et al. [10] reported that over 10% of lactate clearance reduced mortality by 11%, various studies have demonstrated the prognostic value of lactate clearance [5,11-13]. In the previous studies, not only lactate clearance but also repeated lactate measurements could predict mortality among septic shock patients [14,15]. Moreover, other methods of using lactate levels to predict mortality have been investigated [16].

In a recent study of pediatric septic shock patients, the lactate area score, defined as the sum of the area under the curve (AUC) of measured lactate levels, was an independent prognostic factor for mortality with an odds ratio (OR) of 1.143 and 95% confidence interval (CI) of 1.046–1.250 [17]. However, there have not been enough studies of lactate area score in septic shock [13,17]. In this study, we assessed the lactate area score to predict the 28-day mortality of adult septic shock patients. The objective of this study was to determine the prognostic value of the lactate area score of critically ill patients with septic shock.

MATERIALS AND METHODS

Setting and Study Population
This study was a retrospective analysis of a prospective data registry and was performed in the emergency department (ED) of Asan Medical Center with an annual census of more than 100,000 patients in the Republic of Korea. It was approved by the Research Ethics Committee of the Hospital (No. 2015-1253).

Between January 2010 and December 2017, all adult patients with septic shock who were diagnosed in the ED and treated with protocol-driven resuscitation bundle therapy were enrolled with their data prospectively collected in our institution's Septic Shock Registry. Septic shock was defined as refractory hypotension with a systolic blood pressure of <90 mmHg or a mean arterial pressure of <70 mmHg requiring vasopressors despite adequate fluid resuscitation or a blood lactate concentration of at least 4 mmol/L [9].

Exclusion criteria were as follows: patients with a "do not

> **KEY MESSAGES**
> - The lactate area score is the sum of the area under the curve of serial lactate levels from repeated measurements using the trapezoidal rule, divided by the time interval.
> - The study involved adult septic shock patients in the emergency department, and measurements were performed within 12 hours from shock recognition.
> - The lactate area score may be an early prognostic marker of 28-day mortality.

attempt resuscitation" status, patients who were transferred to another hospital during initial resuscitation, and patients who lacked data for repeated lactate measurements. In addition, we excluded patients with missing data of five times on repeated lactate levels.

Data Collection
Patient demographics and clinical data, including age, sex, past medical history, initial vital signs, laboratory results (such as white blood cell count, prothrombin time, and the levels of hemoglobin, platelet, aspartate transaminase, alanine transaminase, total bilirubin, blood urea nitrogen, creatinine, albumin, and lactate), and disease severity determined by the Sequential Organ Failure Assessment (SOFA) score, were retrieved from the Septic Shock Registry (Table 1).

Lactate levels in arterial blood were measured using a blood gas analyzer (GEM Premier 3,000, display range, 0.3 to 15.0 mmol/L; Instrumentation Laboratory, Bedford, MA, USA). We measured the lactate level at the time of shock recognition (T_1), which was repeated at 2, 4, 6, and 12 hours following the initial measurement (T_2, T_3, T_4, T_5). The lactate area score was defined as the sum of the AUC of serial lactate levels $(L_1, L_2, L_3, L_4, L_5)$ measured for 12 hours using the trapezoidal rule, divided by the time interval [17].

$$\text{Lactate area score (mmol/L×hr)}=\sum_{n=1}^{4}(L_n+L_{n+1})\frac{1}{2}\times(T_{n+1}-T_n)$$

The maximum lactate level was the highest level of lactate obtained from serial lactate measurements (five times). The primary clinical outcome of this study was the 28-day mortality rate. We evaluated the predictive ability of each lactate level $(L_1, L_2, L_3, L_4, L_5)$, the maximum lactate level, and the lactate area score.

Statistical Analysis
Continuous variables are presented as the means with differ-

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Table 1. Baseline characteristics of the study population

Characteristics	All patients (n = 362)	Survivor (n = 247)	Non-survivor (n = 115)	P-value
Age (yr)	64.3 ± 12.5	64.1 ± 12.4	64.7 ± 12.9	0.669
Male sex	242 (66.9)	164 (66.4)	78 (67.8)	0.812
Past medical history				
Hypertension	108 (29.8)	77 (31.2)	31 (27.0)	0.460
Diabetes	74 (20.4)	48 (19.4)	26 (22.6)	0.485
Stroke	25 (6.9)	22 (8.9)	3 (2.6)	0.027
Coronary artery disease	40 (11.0)	27 (10.9)	13 (11.3)	1.000
Chronic lung disease	56 (15.5)	37 (15.0)	19 (16.5)	0.755
Liver cirrhosis	52 (14.4)	34 (13.8)	18 (15.7)	0.371
Vital sign				
Systolic blood pressure (mmHg)	106.5 ± 31.6	106.1 ± 30.8	107.4 ± 33.4	0.705
Diastolic blood pressure (mmHg)	65.7 ± 22.0	65.6 ± 51.6	65.9 ± 23.2	0.931
Respiratory rate (rates/min)	22.0 (20.0–30.6)	21.0 (20.0–28.0)	22.0 (20.0–26.0)	0.195
Pulse rate (beats/min)	105.1 ± 31.6	103.8 ± 30.3	108.0 ± 34.2	0.101
Body temperature (℃)	37.5 ± 1.4	37.5 ± 1.4	37.5 ± 1.3	0.125
Severity				
SOFA score	11.0 (8.0–14.8)	10.0 (8.0–13.0)	13.0 (11.0–16.0)	<0.001
Lactate area score	43.7 (26.4–71.4)	38.8 (22.7–58.0)	57.0 (33.9–98.0)	<0.001
Presumed site of infection				
Respiratory tract	155 (42.8)	98 (39.7)	57 (49.6)	0.077
Urinary tract	22 (6.1)	20 (8.1)	2 (1.7)	0.018
Gastrointestinal tract	40 (11.0)	27 (10.9)	13 (11.3)	0.916
Hepato-biliary tract	82 (22.7)	63 (25.5)	19 (16.5)	0.057
Bone or soft tissue	16 (4.4)	9 (3.6)	7 (6.1)	0.292
Other	44 (12.2)	28 (11.3)	16 (13.9)	0.485

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).
SOFA: Sequential Organ Failure Assessment.

ences or medians with interquartile ranges, which were compared between patients by independent t-test and Mann-Whitney test. Categorical variables are summarized as frequencies and percentages, and differences between two groups were analyzed by Fisher's exact test.

To evaluate the relationship between mortality and lactate variables, univariate and multivariate logistic regression analyses with backward elimination were performed. We presented the OR with 95% CI for each model. The factors associated with mortality such as past history of stroke, infection site of urinary tract, laboratory tests of platelet, prothrombin time, albumin, blood urea nitrogen, creatinine, C-reactive protein, initial lactate, maximum lactate, severity factors of lactate and lactate area score were included in a multivariate logistic regression model. The model performance was evaluated using the receiver operating characteristic (ROC) curve with the

AUC of each ROC curve. We considered $P < 0.05$ as statistically significant for all of the analyses.

RESULTS

Baseline Characteristics of the Study Population

A total of 362 adult patients were enrolled in this study, and their 28-day mortality was 31.8% (Figure 1). When we divided patients into the survivor and non-survivor group, age, sex, initial vital signs, and past medical history were not significantly different except for stroke, which was more frequent in the survivor group (88.0% vs. 12.0%, P = 0.027). However, the SOFA score (median [interquartile range], 10.0 [8.0 to 13.0] vs. 13.0 [11.0 to 16.0]; P < 0.001) and lactate area score (38.8 [22.7 to 58.0] vs. 57.0 [33.9 to 98.0]; P < 0.001) were significantly higher in the non-survivor group, whereas urinary tract infection
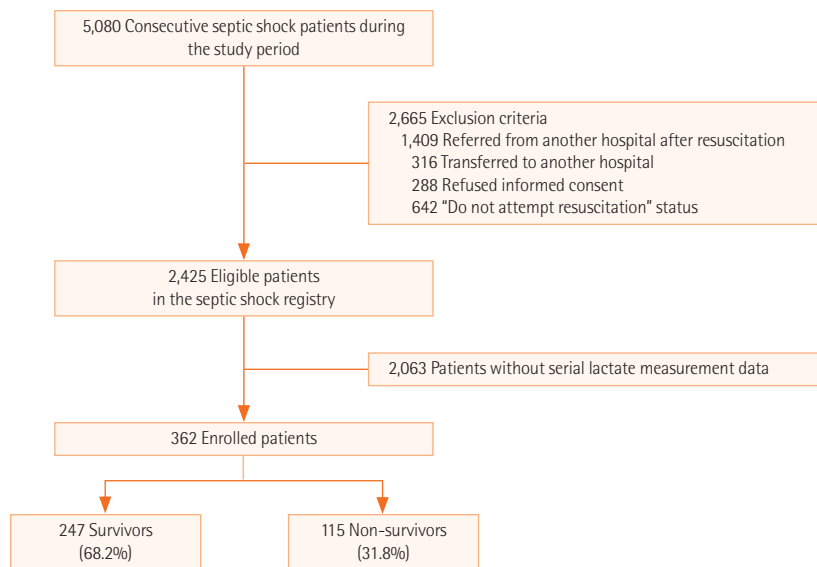
Figure 1. Flowchart of the selection and classification of patients.

Table 2. Laboratory findings of survivors and non-survivors

Characteristics	Survivor (n=247)	Non-survivor (n=115)	P-value
White blood cell (×10³/μl)	11.6 (4.9–19.1)	9.9 (4.6–18.0)	0.688
Hemoglobin (g/dl)	11.6±2.8	11.3±2.7	0.393
Platelet (×10³/μl)	183.5 (94.0–268.3)	140.5 (49.0–186.3)	0.049
Aspartate transaminase (IU/L)	44.0 (28.0–74.3)	46.0 (27.0–197.5)	0.664
Alanine transaminase (IU/L)	25.0 (14.8–46.3)	33.5 (14.0–69.3)	0.842
Total bilirubin (mg/dl)	1.0 (0.6–2.3)	1.3 (0.7–3.2)	0.435
Prothrombin time (INR)	1.3 (1.1–1.6)	1.4 (1.2–2.0)	0.001
Albumin (mg/dl)	2.8±0.7	2.5±0.6	<0.001
Blood urea nitrogen (mg/dl)	27.5 (17.0–41.3)	30.5 (18.8–47.0)	0.042
Creatinine (mg/dl)	1.4 (1.0–2.6)	1.6 (1.1–2.3)	0.004
C-reactive protein (mg/dl)	8.1 (3.0–20.5)	15.8 (7.4–24.0)	0.009
Initial lactate (mmol/L)	4.2 (2.4–6.6)	4.9 (3.4–10.5)	0.003
2-Hour lactate (mmol/L)	3.3 (1.9–5.4)	4.7 (2.3–7.5)	0.001
4-Hour lactate (mmol/L)	2.8 (1.7–4.7)	4.2 (2.2–8.2)	<0.001
6-Hour lactate (mmol/L)	2.7 (1.6–4.5)	4.5 (2.3–8.1)	<0.001
12-Hour lactate (mmol/L)	2.6 (1.6–4.8)	4.6 (2.6–9.9)	<0.001
Maximum lactate (mmol/L)	5.4 (3.2–8.1)	7.3 (4.2–13.2)	<0.001

Values are presented as median (interquartile range) or mean±standard deviation.
INR: international normalized ratio.

was significantly frequent in survivor group (8.1% vs. 1.7%, P=0.018) (Table 1).

Laboratory Findings of Survivors and Non-survivors
In the non-survivor group, the platelet count was lower (183.5 vs. 140.5×10³/μl, P=0.049), prothrombin time was longer (1.3 vs. 1.4, P=0.001), and albumin level was lower (2.8 vs. 2.5 mg/dl, P<0.001); however, the levels of blood urea nitrogen (27.5 vs. 30.5 mg/dl, P=0.042), creatinine (1.4 vs. 1.6 mg/dl, P=0.004), and C-reactive protein (8.1 vs. 15.8 mg/dl, P=0.009) were higher. All serial lactate levels and the maximum lactate level were significantly higher in the non-survivor group (4.2 vs. 4.9, 3.3

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Table 3. Multivariate analysis for predicting 28-day mortality

Characteristics	Univariate OR (95% CI)	Multivariate OR (95% CI)	P-value
Stroke	0.274 (0.080–0.935)		
Urinary tract infection	0.201 (0.046–0.875)		
Platelet (×10³/μl)	0.999 (0.997–1.001)		
Prothrombin time (INR)	1.141 (0.979–1.330)		
Albumin (mg/dl)	0.489 (0.347–0.690)	0.586 (0.407–0.843)	0.004
Blood urea nitrogen (mg/dl)	1.007 (0.998–1.016)		
Creatinine (mg/dl)	1.136 (1.001–1.289)		
C-reactive protein (mg/dl)	1.023 (1.003–1.042)		
Initial lactate (mmol/L)	1.100 (1.038–1.165)		
Maximum lactate (mmol/L)	1.143 (1.081–1.209)		
SOFA score	1.126 (1.060–1.197)	1.082 (1.014–1.153)	0.017
Lactate area score (mmol/L×hr)	1.016 (1.010–1.022)	1.013 (1.007–1.019)	<0.001

Multivariate analysis included logistic regression analysis and backward elimination.
OR: odds ratio; CI: confidence interval; INR: international normalized ratio; SOFA: Sequential Organ Failure Assessment.

Table 4. Comparison of the AUC between the initial lactate, maximum lactate, and lactate area score

| Variable	AUC	95% CI	P-value
Initial lactate (mmol/L)	0.596	0.532–0.659	0.003
Maximum lactate (mmol/L)	0.635	0.572–0.698	<0.001
Lactate area score (mmol/L×hr)	0.659	0.597–0.720	<0.001

AUC: area under the curve; CI: confidence interval.

vs. 4.7, 2.8 vs. 4.2, 2.7 vs. 4.5, 2.6 vs. 4.6, and 5.4 vs. 7.3 mmol/L with P=0.003, P=0.001, P<0.001, P<0.001, P<0.001, and P<0.001, respectively) (Table 2).

Predicting 28-Day Mortality

We analyzed disease severity using a logistic regression model, which revealed that the SOFA score and lactate area score were highly associated with 28-day mortality (OR, 1.126; 95% CI, 1.060 to 1.197 and OR, 1.016; 95% CI, 1.010 to 1.022, respectively). In multivariate analysis, the lactate area score (OR, 1.013; 95% CI, 1.007 to 1.019), serum albumin (OR, 0.586; 95% CI, 0.407 to 0.843), and SOFA score (OR, 1.082; 95% CI, 1.014 to 1.153) were significantly associated with mortality (Table 3).

A comparison of the AUC of the ROC curve between the initial lactate, maximum lactate, and lactate area score revealed that the lactate area score was higher (AUC [95% CI]: 0.596 [0.532 to 0.659], 0.635 [0.572 to 0.698], and 0.659 [0.597 to 0.720], respectively) (Table 4, Figure 2). However, the difference between the maximum lactate and lactate area score was not statistically significant (P=0.071).
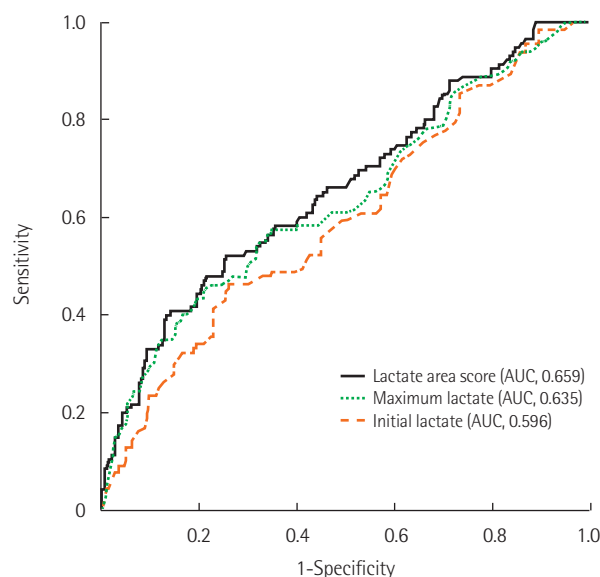
Figure 2. Receiver operating characteristic and area under the curve (AUC) in lactate area score, maximum lactate, and initial lactate.

DISCUSSION

In this study, we found that the lactate area score obtained from serial lactate measurements was independently associated with 28-day mortality among septic shock patients in the ED. However, the OR of the lactate area score for predicting mortality was not only lower than that in previous studies, which involved pediatric septic shock patients, but also lower than the SOFA score.

Although the initial lactate level is a biomarker that can be used to determine the prognosis and severity of septic shock [18], it represents only the initial status and cannot reflect the effect of initial resuscitation. As serial lactate measurements reflect the response to the initial management, they may be a suitable predictor. In this study, the initial lactate level as well as L_2, L_3, L_4, and L_5 were associated with mortality (Table 2). However, the discrepancy in the median values between survivors and non-survivors was increased with time (T_1, 0.7 mmol/L; T_2, 1.4 mmol/L; T_3, 1.4 mmol/L; T_4, 1.8 mmol/L; and T_5, 2.0 mmol/L). This result indicated that the prognostic value of lactate levels may increase with time. Our previous study showed that the optimal timing of lactate remeasurements for predicting mortality was 6 hours from shock development [15].

In studies by Kim et al. [17] and Wang et al. [13], the use of the lactate area score as a predictor of mortality has been proposed. In contrast to the initial lactate level, the exposure time to ischemia was considered by quantifying the accumulations of lactate at each time. In both studies, serial lactate measurements were performed in the early phase of septic shock for 24 hours every 6 hours from ICU admission, and the lactate area score was calculated using the trapezoidal rule. They demonstrated that the score was significantly associated with mortality. However, considering lactate kinetics, repeated lactate measurements for 24 hours might be too long to accurately reflect early mortality among septic shock patients [12,19-21]. In this study, we measured lactate levels for 12 hours (every 2 hours in the initial 6 hours) to give a more precise prognosis. The lactate area score was an independent predictor of mortality among adult septic shock patients (OR, 1.013; 95% CI, 1.007 to 1.019) in multivariate analysis. In the AUC of the ROC curve, the lactate area score was higher than the initial and maximum lactate levels. Although this result was similar to that of previous studies, the AUC value was lower, and the difference from the maximum lactate level was not statistically significant [13,17]. Unlike previous studies, our study was conducted in the very early phase of septic shock in the ED and not the ICU. In addition, we measured lactate levels more frequently (five times) within 12 hours. The association might be decreased because initial resuscitation includes hemodynamic stabilization, and early antibiotic administration is crucial for reducing mortality [2,22]. Although the lactate area score may be an independent predictor, its statistical relevance is limited.

There are several limitations in our study. First, it was a retrospective observational study in a single medical center. Although a large number of patients were included, many patients with missing data on serial lactate levels were excluded. Multiple measurements of lactate levels might include patients with more severe illness, and it can dilute the results of lactate area score assessment due to severe illness in the comparisons. Since the same reason, AUC of lactate area score might lower than other studies. The overall 28-day mortality was higher than that of other similarly designed studies involving patients with septic shock (26.2%–36%) [17,23,24]. One more important limitation was that the calculation method is not easy.

Despite these limitations, the early lactate area score may be an possible prognostic marker for predicting the 28-day mortality of adult septic shock patients. To generalize our results, further prospective multicenter interventional studies should be conducted to validate our results.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORCID

Gina Yu   https://orcid.org/0000-0002-7484-405X
Seung Joon Yoo   https://orcid.org/0000-0001-7774-1374
Sang-Hun Lee   https://orcid.org/0000-0003-4303-7375
June Sung Kim   https://orcid.org/0000-0002-9941-585X
Sungmin Jung   https://orcid.org/0000-0002-6992-7088
Youn-Jung Kim   https://orcid.org/0000-0003-1385-5836
Won Young Kim   https://orcid.org/0000-0002-6904-5966
Seung Mok Ryoo   https://orcid.org/0000-0002-2436-3311

AUTHOR CONTRIBUTIONS

Conceptualization: SMR. Data curation: SJ. Formal analysis: GY, YJK. Funding acquisition: SMR. Methodology: SJY. Project administration: SHL. Visualization: JSK. Writing – original draft: GY. Writing – review & editing: SMR, WYK.

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