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Early blood lactate area as a prognostic marker in pediatric septic shock

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Abstract *Purpose:* We attempted to evaluate whether the early lactate area is useful as an early prognostic marker of mortality in pediatric septic shock patients. *Methods:* We performed a retrospective study of pediatric patients with septic shock who were admitted to the pediatric intensive care unit of Asan Medical Center, Seoul, Korea. Serial arterial lactate levels were obtained immediately and then every 6 h after admission for a total of 24 h. The lactate area (mmol/lh) was defined as the sum of the area under the curve (AUC) of serial lactate levels measured during the 24 h following admission. We compared the lactate-associated parameters as a predictor of mortality. *Results:* A total of 65 patients were included in this study, and the overall 28-day mortality of these patients was 26.2 %. Survivors compared with non-survivors had an initial lactate level of 3.13 ± 2.79 vs. 6.16 ± 4.87 mmol/l, a lactate clearance of 32.8 ± 63.4 vs. −30.8 ± 75.6 %, and a lactate area of 59.7 ± 56.0 vs. 168.0 ± 107.0 mmol/lh ($p < 0.05$ for all variables). Receiver operating characteristic curves indicated a strong predictive power for the lactate area (AUC = 0.828), which demonstrated the largest AUC in comparison with the AUCs of the initial lactate level (0.699) or the 24-h lactate clearance (0.719). Using multivariate logistic regression analysis, the lactate area was a significant prognostic factor. *Conclusion:* The early lactate area is a potentially feasible and clinically useful predictor of mortality in pediatric septic shock patients.

Keywords Septic shock · Pediatrics · Blood lactate levels · Lactate area

Introduction

Septic shock in pediatric patients is one of the leading causes of morbidity and mortality despite advancements in the treatment of multiple organ failure [1–3]. In order to improve the clinical outcomes in these patients, it is crucial to obtain early recognition of patients who are at risk of death and to optimize the clinical decision-making in a timely manner [4–6].

In patients with septic shock, the failure to supply oxygen to meet the tissue oxygen demand causes tissue hypoxia and increases anaerobic metabolism. Elevated serum lactate levels reflect the anaerobic metabolism related to cellular hypoxia and are thought to be an important marker of impaired tissue perfusion in patients with sepsis [7]. Unresolved global tissue hypoxia, as indicated by inadequate lactate clearance, is associated with multiorgan dysfunction and increased mortality

during the early phase of resuscitation of patients with septic shock [8].

Although elevated serum lactate levels may result from tissue hypoxia and anaerobic metabolism, they can also develop in other ways [9–12]. However, regardless of the etiology, elevated lactate levels in patients with septic shock have been reported to be related to poor outcomes, although they might also be considered as an early marker of a potentially reversible state if there is rapid intervention [13–16]. Several recent studies have emphasized the prognostic value of lactate-associated parameters such as the initial lactate level or lactate clearance [8, 17, 18]. These results suggest that the duration as well as the severity of hyperlactatemia are related to mortality in septic shock patients [19–21]. However, the initial lactate level represents only a patient's initial status and, therefore, cannot reflect the changes over time of lactate levels, and lactate clearance cannot demonstrate the severity of hyperlactatemia. In our study we introduced the lactate area defined as the sum of the area under the curve of serial lactate levels, as this is a new concept reflecting the severity and duration of hyperlactatemia.

We measured serial lactate levels and evaluated the relationship between the lactate variables and patient mortality. We also attempted to determine whether the early lactate area is useful as an early prognostic marker in pediatric septic shock.

Materials and methods

This retrospective, observational study was performed in the pediatric intensive care unit (PICU) of Asan Medical Center Children's Hospital, Seoul, Korea. All data were retrospectively reviewed for consecutive patients admitted to the PICU and diagnosed with septic shock from February 2007 to August 2011. The definition of septic shock was based on the 2005 International Pediatric Sepsis Consensus Conference criteria (IPSCC) [22].

Patient demographics, laboratory results, sources of infection, and co-morbidities were collected at baseline. To assess the severity of illness and organ dysfunction, the Pediatric Risk of Mortality III (PRISM III) score [23] and the Pediatric Logistic Organ Dysfunction (PELOD) score [24] were calculated within 24 h after admission. All patients were monitored using an arterial catheter, and arterial blood gas and lactate levels were measured at least four times a day, according to our center's protocol for septic shock patients. Lactate levels were measured in arterial blood using a blood gas analyzer (GEM Premier 3000 with iQM, displayed ranges of lactate 0.3–15.0 mmol/l). The initial lactate levels were obtained immediately following the patient's admission to the PICU. Serial arterial blood lactate levels were then obtained every 6 h during the initial 24 h period following admission.

Lactate clearance was defined as the percent of change in the lactate level per hour from the baseline measurement. This was calculated using the equation [8],

$$[(\text{Initial lactate level} - \text{follow-up lactate level})/\text{Initial lactate level}] \times 100$$

In our study, the lactate level measured at 24 h after admission was used as the follow-up lactate level in the equation in order to compare it with the lactate area calculated 24 h after admission.

Lactate area (mmol/lh) was defined as the sum of the area under the curve of serial lactate levels during the first 24 h following each patient's admission using the trapezoidal rule.

We evaluated the 28-day mortality rate as the primary outcome. Statistical analysis was performed using Windows SPSS software, version 18. Continuous variables were presented as the means with the differences between survivors and non-survivors compared by means of an independent *t* test. Categorical explanatory variables were summarized as frequencies and percentages, and the differences between the two groups were analyzed using the χ^2 test and Fisher's exact

Table 1 Patient characteristics

	No. of patients (%)
Characteristics	
Age in months	119.9 ± 72.7 (1 month–19 years)
Male:female	38:27
Inotropic or vasopressor support	65 (100)
Referred from emergency room: ward	20:45
Mortality	17 (26.2)
Underlying disease	61 (93.8)
Hemato-oncologic disease	29 (47.5)
Neurologic disease	9 (14.8)
Cardiac disease	6 (9.8)
Chronic kidney disease on dialysis	6 (9.8)
Gastrointestinal disease	4 (6.6)
Post-liver transplantation	4 (6.6)
Other	3 (4.9)
Proven microorganism	39 (60)
Gram-positive bacteria	12 (30.8)
Enterococcus faecalis	4
Streptococcus viridans	3
Staphylococcus aureus	3
Streptococcus pneumoniae	2
Gram-negative bacteria	22 (56.4)
Escherichia coli	7
Pseudomonas aeruginosa	6
Klebsiella pneumoniae	5
Enterobacter aerogens	3
Stenotrophomonas maltophila	1
Fungus	3 (7.7)
Candida albicans	3
Others	2 (5.1)[a]

[a] Positive parainfluenza virus in one patient using real-time PCR from sputum; one patient with tsutsugamushi infection diagnosed according to the clinical findings and tsutsugamushi-specific IgG antibodies

test. Repeated measures analysis of variance was performed in order to determine the differences of arterial lactate levels between survivors and non-survivors.

To evaluate the relationships between mortality and lactate variables, multivariate logistic regression analysis with backward elimination was conducted to identify factors significantly related to mortality. The factors correlated with mortality at $p < 0.05$ were included in a logistic regression model. Receiver operating characteristic (ROC) curves were calculated to evaluate the reliability of lactate variables as a prognostic factor with a 95 % confidence interval (95 % CI), and the optimal cutoff point was chosen. We considered $p < 0.05$ as statistically significant for all of the analyses.

Results

We identified a total of 65 patients and evaluated their baseline characteristics as shown in Table 1. The overall mortality rate of the patients was 26.2 %. Most of the study patients (61 out of 65) had significant co-morbidities. Twenty-nine patients had hemato-oncologic malignancies, and all of these patients developed septic shock associated with neutropenic fever. The patients with hemato-oncologic disease showed significantly higher mortality (41.4 %) than the patients with no underlying disease or with a different underlying disease (Table 2). The non-survivor group had a significantly higher PRISM III score and PELOD score than the survivor group. All patients except for three had two or more organ dysfunctions. Respiratory, hematologic, and hepatic dysfunction was more frequently observed in non-survivors.

The initial lactate level, lactate clearance, and lactate area were significantly worse in non-survivors than in survivors (Table 2). Patients with initial lactate levels higher than 5 mmol/l showed a significantly higher mortality rate [>5 vs. ≤5 mmol/l = 47.1 % (8/17) vs. 20.8 % (10/48): OR = 3.38, 95 % CI 1.04–10.9, $p = 0.038$]. A multivariate logistic regression analysis was performed after adjusting for underlying hemato-oncologic

Table 2 Comparisons of the clinical characteristics of the survivors and non-survivors

	All patients	Survivors ($n = 48$)	Non-survivors ($n = 17$)	p value
Age in months	119.9 ± 72.7	125.1 ± 67.5	105.3 ± 86.5	0.34
Male, *n* (%)	38 (58.5)	28 (58.3)	10 (58.8)	0.97
Laboratory findings				
WBC, (/mm^3)	10,449 ± 13,066	12,441.7 ± 14,010	4,823.5 ± 7,795.5	0.038
Platelet, (×10^3/mm^3)	102.3 ± 116.0	118.7 ± 118.3	56 ± 98.0	0.055
AST, (IU/l)	185.4 ± 396.4	73.6 ± 85.0	501 ± 681.1	<0.001
ALT, (IU/l)	103.5 ± 192.3	55.8 ± 65.1	238.2 ± 330	<0.001
Total bilirubin, (mg/dl)	2.68 ± 3.34	2.05 ± 3.00	4.45 ± 3.71	0.010
Prothrombin time, (INR)	1.61 ± 0.59	1.45 ± 0.49	2.05 ± 0.65	0.002
Albumin, (mg/dl)	2.76 ± 0.60	2.73 ± 0.68	2.83 ± 0.29	0.417
BUN, (mg/dl)	31.93 ± 22.46	28.3 ± 19.8	42.0 ± 26.6	0.035
Cr, (mg/dl)	1.87 ± 2.25	1.99 ± 2.54	1.54 ± 1.11	0.323
CRP, (mg/dl)	15.01 ± 9.92	15.10 ± 10.14	14.74 ± 9.54	0.361
pH	7.35 ± 0.11	7.36 ± 0.10	7.31 ± 0.11	0.068
Base excess, (mmEq/l)	−4.45 ± 7.19	−3.45 ± 7.03	−7.28 ± 7.07	0.058
Initial lactate level, (mmol/l)	3.92 ± 3.67	3.13 ± 2.79	6.16 ± 4.87	0.015
Lactate clearance, (%)	0.65 ± 108.9	32.8 ± 63.4	−30.8 ± 75.6	0.021
Lactate area, (mmol/lh)	88.0 ± 86.4	59.7 ± 56.0	168.0 ± 107.0	0.001
Length of PICU stay	12.4 ± 15.1	13.73 ± 16.86	8.53 ± 7.31	0.220
PRISM III score	16.5 ± 8.2	14.0 ± 6.1	23.4 ± 9.5	0.001
PELOD score	19.8 ± 8.0	17.7 ± 6.4	25.5 ± 9.5	<0.001
Organ dysfunction				
Number of organ dysfunctions	3.3 ± 1.2	2.92 ± 0.96	4.29 ± 1.05	<0.001
Cardiovascular, *n* (%)	65 (100)	48 (100)	17 (100)	
Respiratory, *n* (%)	35 (53.8)	21 (43.8)	17 (100)	<0.001
Neurologic, *n* (%)	25 (38.5)	16 (33.3)	9 (52.9)	0.128
Hematologic, *n* (%)	40 (61.5)	26 (54.2)	14 (82.4)	0.036
Renal, *n* (%)	21 (32.3)	14 (29.2)	7 (41.2)	0.268
Hepatic, *n* (%)	25 (38.5)	15 (31.3)	10 (58.8)	0.044
Hemato-oncologic disease, *n* (%)	29 (44.6)	17 (35.4)	12 (70.6)	0.012
Mechanical ventilation, *n* (%)	38 (58.5)	21 (43.8)	17 (100)	<0.001
Dialysis, *n* (%)	22 (33.8)	15 (31.2)	7 (41.2)	0.324
Proven microorganism, *n* (%)	38 (58.5)	25 (52.1)	14 (82.4)	0.026

Values are shown as the mean ± SD

PICU pediatric intensive care unit, *PRISM III score* pediatric risk of mortality III score, *PELOD score* pediatric logistic organ dysfunction score

disease, proven microorganism, mechanical ventilation, PELOD score, PRISM III score, and organ dysfunction (Table 3). The variables identified as being significantly correlated with the 28-day mortality were underlying hemato-oncologic disease and the lactate area.

The lactate levels at each time point differed significantly between the survivors and non-survivors, and the levels gradually decreased in survivors (Fig. 1). The lactate variables, PRISM III score, and PELOD score were analyzed using the ROC curve. The areas under the curve (AUC) of the lactate levels that were measured every 6 h are shown in Table E1. The AUCs of the PRISM III score and the PELOD score were 0.820 (95 % CI, 0.690–0.945) and 0.811 (95 % CI, 0.696–0.932), respectively ($p < 0.001$). Figure 2 illustrates the ROC curves for the initial lactate levels, lactate clearance, and the lactate area as a predictor of mortality. The area under the ROC curves indicated a strong predictive power for the lactate area, which represents the largest AUC in comparison with the AUC of the initial lactate levels or lactate clearance. The cutoff point of 96 mmol/lh obtained for the lactate area had the maximum sum of sensitivity (58.0 %) and specificity (79.2 %) for predicting 28-day mortality.

When patients were categorized as being in the low lactate area group (<96 mmol/lh) or in the high lactate area group (≥96 mmol/lh), the mortality rate was significantly higher in the high lactate area group (10/20, 50 %) than in the low lactate area group (7/45, 15.6 %) ($p = 0.005$). The relative risk of mortality of patients with a lactate area above 96 mmol/lh was 1.92 (95 % CI, 1.07–3.46; $p = 0.005$). Figure E1 shows the Kaplan-Meier survival curves over time of the patient groups with lactate areas above and below 96 mmol/lh.

Table 3 A multivariate logistic regression with backward elimination was performed after adjusting for underlying hemato-oncologic disease, proven microorganism, mechanical ventilation, PELOD score, PRISM III score, and organ dysfunction

Variables	Odds ratio	95 % CI	*p* value
Hemato-oncologic disease	5.734	1.015–32.390	0.048
Lactate area	1.143	1.046–1.250	0.003
Lactate clearance	0.902	0.814–1.000	0.050

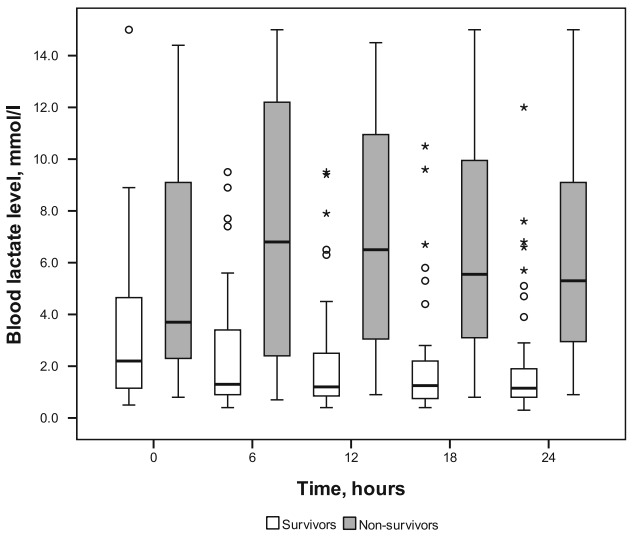
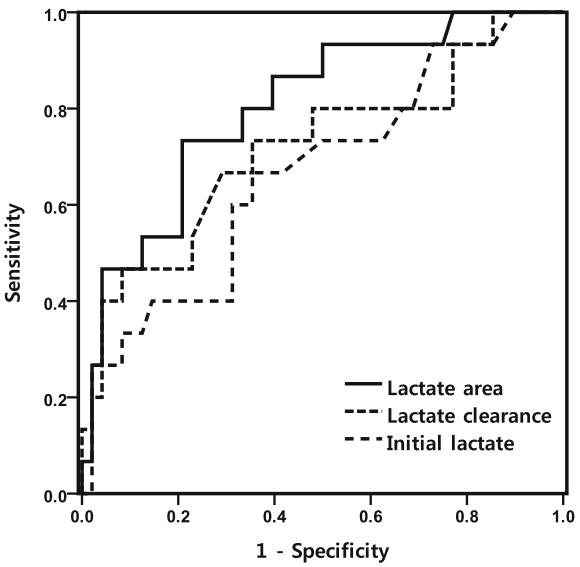


Fig. 1 Box plot showing the blood lactate levels in the survivor and non-survivor groups, which were measured every 6 h. The serial lactate levels demonstrate significant differences between the survivors and non-survivors. Mauchly's test of sphericity and a pairwise comparison were performed ($p < 0.001$)

Discussion

Since the 1991 study of Bakker et al. indicating that blood lactate levels are closely related to the survival of patients with septic shock, several studies have reported the prognostic importance of the lactate level and the usefulness of lactate reduction during the treatment of septic shock [13–15, 18, 21]. A recent study emphasized the efficacy of the use of lactate in critically ill patients for



Variables	AUC	*P* value	95% CI
Initial lactate	0.699	0.015	0.549 – 0.849
Lactate clearance	0.719	0.011	0.558 – 0.881
Lactate area	0.828	< 0.001	0.714 – 0.942

Fig. 2 ROC curves of the initial lactate level, 24 h lactate clearance, and the lactate area as a predictor of mortality

both the diagnosis and subsequent monitoring of their therapeutic responses [25].

In our study, the initial lactate levels presented significant differences between survivors and non-survivors, and the patients with an initial lactate level >5 mmol/l showed higher mortality, which is similar to the results of previous studies [18, 26]. However, the initial lactate levels were not significantly correlated with the mortality. The single initial lactate level in isolation is not much more useful for predicting the outcome than lactate clearance or the lactate area. As opposed to the initial lactate level, lactate levels at 12, 18, and 24 h were strong predictors of mortality (Table E1). As shown in Fig. 1, blood lactate levels in non-survivors tended to be elevated and persistently high, while blood lactate levels in survivors tended to decrease and normalize within 24 h. These tendencies seemed to result in the correlation of the blood lactate levels at 12, 18, and 24 h with mortality, which supports the importance of the time course of lactate levels in predicting the outcome [21]. Serial lactate measurement, not a single lactate level, may provide important information regarding the effectiveness of resuscitation, and the normalization of blood lactate has a timely association with patient recovery during septic shock [27].

Although lactate clearance showed a positive predictive value (AUC = 0.724), it only describes the change in lactate levels as a percentage. It cannot reflect the severity of hyperlactatemia, which is an important prognostic factor for septic shock. Furthermore, lactate clearance tends to be higher with changes in lower lactate levels.

Several studies have suggested that persistent elevation of lactate is associated with a high patient mortality rate and multiple organ damage [8, 14, 21]. Lactate area, a term used for the first time in this study and calculated at 24 h after admission, is related to the persistence and severity of the elevated lactate level during the early course of treatment. The lactate area includes the exposure time of hyperlactatemia as well as the actual lactate concentrations. The amount of organ damage and organ dysfunction occurring during the early period of septic shock depends upon the degree of hypoxia and the length of time that an organ is exposed to hypoxia [21]. In our study, the lactate area has a strong predictive value for mortality in pediatric septic shock patients. The multivariate logistic regression analysis results also support the value of the lactate area as being associated with patient mortality. These results indicate that the lactate area may be useful in the early recognition of patients with a high risk of mortality regarding septic shock. We therefore suggest to clinicians that aggressive management is needed in order to reduce the lactate concentration and to prevent long-lasting hyperlactatemia during the early period of septic shock.

There are some limitations to our study, including the use of data from a single medical center and the retrospective observational study design with a small sample size. Prospective, large, multicenter studies will be needed in order to confirm and generalize our results. We also noticed the limitation of the lactate area in that it cannot distinguish the patients with decreasing lactate concentration and those with increasing lactate concentration during a 24-h period.

We suggest a reasonable basis for the use of serial lactate laboratory tests for both the prognosis and subsequent monitoring of the therapeutic effectiveness in pediatric patients with septic shock. Our study reports the important result that the lactate area can be feasible and clinically useful as a good predictor of mortality in pediatric septic shock patients during 24 h of intervention.

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