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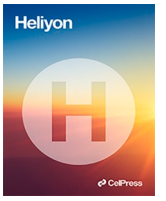

Research article

The prognostic utility of Lactate/Albumin*Age score in septic patient with normal lactate level

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ABSTRACT

Background: A previous study has shown that the lactate/albumin*age (LAA) score is useful for predicting mortality in patients with sepsis admitted to the ICU. We aimed to evaluate the clinical significance of the LAA score in patients with sepsis who presented to the emergency department (ED)

Methods: This retrospective observational study used data from the Korean Shock Society Registry collected between January 2017 and December 2021. The prognostic performance of the LAA score for predicting the 28-day mortality was evaluated. Lactate and albumin levels were measured immediately after arrival to the ED.

Results: Of the 5346 patients with sepsis, data from 3240 were analyzed. The area under the receiver operating characteristic curve (AUROC) of the LAA score (0.737, 95 % confidence interval (CI) 0.716–0.757), was higher than that of lactate (0.699, 95 % CI 0.677–0.720, $p < 0.001$), lactate/albumin (LA) ratio (0.730, 95 % CI 0.709–0.751, $p = 0.016$), and Sequential Organ Failure Assessment (SOFA) score (0.698, 95 % confidence interval 0.676–0.720, $p = 0.004$), and Acute Physiology and Chronic Health Evaluation (APACHE) II scores (0.672; 95 % confidence interval 0.649–0.694, $p < 0.001$). The optimal cut-off value for the LAA score was 119.9. In the Kaplan-Meier analysis according to the optimal cutoff value, the 28-day mortality rates were higher in the high LAA score group (log-rank test, $p < 0.001$). The LAA score was independently associated with 28-day mortality in the multivariate Cox proportional hazards model (adjusted hazard ratio 2.07, 95 % CI 1.76–2.43, $p < 0.001$). In the normal (<2 mmol/L) lactate group, the AUROC value for LAA score was higher than LA ratio (normal group 0.674 vs 0.634, $p < 0.004$). In patients over 65 years old, LAA score (0.731) showed a higher AUROC value than LA ratio (0.725). ($p < 0.001$)

Conclusion: The LAA score may be used as an independent predictor of mortality in patients with sepsis in the emergency department. Our results show that it performs better than serum lactate alone, LA ratio, and SOFA and APACHE II scores. While this suggests that the LAA could provide clinicians with a useful tool for timely early intervention and care planning in patients with a poor prognosis, further validation in large multicenter prospective studies are necessary to confirm its reliability and practicality as a readily available and objective biomarker.

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1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Although our understanding of sepsis has improved rapidly in recent years, it remains a significant global burden, with a global prevalence of 31.5 million and 5.3 million deaths annually [2]. Despite aggressive treatment, mortality rates in patients with sepsis and septic shock are more than 10 % and 40 %, respectively. Therefore, predicting mortality risk in patients with sepsis is crucial for early diagnosis and timely treatment.

There are several markers for the early diagnosis, treatment, risk stratification, and outcome measures associated with sepsis and severe sepsis, including serum lactate and albumin levels [3]. Lactic acidosis occurs in sepsis and severe sepsis due to cellular dysfunction, tissue hypoperfusion, and increased aerobic glycolysis [4]. As a surrogate for tissue perfusion in critically ill patients, serum lactate level is independently associated with mortality [5].

Albumin is produced by the liver and plays a role in the blood oncotic pressure [6]. Serum albumin is a negative acute-phase protein and hypoalbuminemia is a marker of inflammation that has a strong inverse association with sepsis severity [7,8]. Therefore, serum albumin concentration is not only a marker of nutritional status but also an important indicator of sepsis severity.

Several studies have shown that the lactate/albumin (LA) ratio is an important prognostic parameter in patients with sepsis and septic shock and has a better prognostic ability than lactate or albumin alone [9–12].

Although comorbidities play an important role in the prognosis of patients with sepsis, age is an independent risk factor for mortality [13,14]. Previous studies have shown that in-hospital mortality is 30–60 % in patients over 65 years of age and increases to 40–80 % in patients over 80 years of age [14–16].

This study aimed to evaluate and compare the value of the lactate/albumin*age (LAA) score as a predictor of mortality in patients with sepsis who presented to the emergency department.

2. Methods

2.1. Study design

This was a retrospective observational study using data from patients prospectively recruited to the Korean Shock Society (KoSS) Registry between January 2017 and December 2021. The KoSS is a cooperative research network organized to monitor and improve the diagnosis and treatment of sepsis [17]. KoSS was organized in 2013, and investigators prospectively collected data from patients with sepsis treated in the emergency departments of 15 teaching hospitals from October 2015. Patients aged 19 years with refractory hypotension or hypoperfusion were included in this study. Patients with a "Do Not Resuscitate" order, patients who met the inclusion criteria more than 6 h after arrival at the ED, patients transferred from other hospitals that did not meet the inclusion criteria at the time of arrival at the ED, and patients transferred directly from the ED to another hospital were not included in the KoSS registry. We further excluded patients with terminal malignancies and patients with missing laboratory results. Fig. 1 depicts the workflow of patient enrollment in this study. The Institutional Review Board of Ansan Hospital, Korea University approved this study (2023AS0144) and waived the requirement for informed consent due to the observational nature of the study.

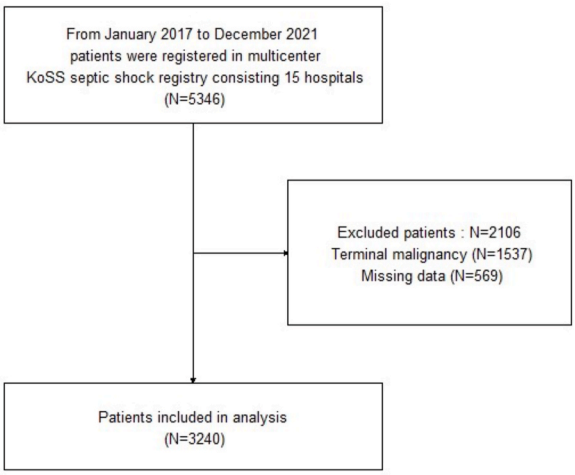

Fig. 1. Flow diagram of patient enrollment in the present study.
KoSS: the Korean Shock Society.

2.2. Data collection

The case report form contained standard definitions for more than 200 variables, including clinical characteristics, therapeutic interventions, and outcomes in patients with septic shock [17]. Lactate and albumin levels were measured upon arrival to the emergency department.

Based on The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis was defined as an increase in SOFA score ≥2 points in patients with suspected infection, and septic shock as the use of vasopressor to maintain mean arterial pressure ≥65 or lactate concentration ≥2 mmol/L despite sufficient volume resuscitation [1]. According to the lactate level, the comparison was divided into normal group (lactate <2.0 mmol/L), intermediate group (4.0 mmol/L > lactate ≥2.0 mmol/L), and high group (lactate ≥4.0 mmol/L). Subgroup analysis was performed for the septic shock group. The primary outcome was 28-day mortality, and the secondary outcomes were mechanical ventilation rate and 90-day mortality.

Demographic characteristics including age and sex, and clinical data including comorbidities such as hypertension and diabetes,

Table 1
Baseline characteristics of patients with sepsis.

	Survivor (N = 2494)	Death (N = 746)	Total (N = 3240)	*p* value
Age (years)	69.0 ± 13.3	72.7 ± 13.1	69.9 ± 13.3	<0.001
Gender (male)	1408 (56.5 %)	447 (59.9 %)	1855 (57.3 %)	0.102
Septic shock	1394 (55.9 %)	588 (78.8 %)	1982 (61.2 %)	<0.001
Comorbidities				
HTN	1139 (45.7 %)	349 (46.8 %)	1488 (45.9 %)	0.622
DM	896 (35.9 %)	278 (37.3 %)	1174 (36.2 %)	0.532
Cardiovascular disease	424 (17.0 %)	118 (15.8 %)	542 (16.7 %)	0.482
Cerebrovascular disease	368 (14.8 %)	127 (17.0 %)	495 (15.3 %)	0.146
Chronic lung disease	213 (8.5 %)	87 (11.7 %)	300 (9.3 %)	0.012
Chronic renal disease	292 (11.7 %)	93 (12.5 %)	385 (11.9 %)	0.619
Chronic liver disease	274 (11.0 %)	101 (13.5 %)	375 (11.6 %)	0.065
Infection focus				<0.001
Respiratory infection	526 (21.1 %)	259 (34.7 %)	785 (24.2 %)	
Urinary tract infection	572 (22.9 %)	88 (11.8 %)	660 (20.4 %)	
Intra-abdominal infection	717 (28.7 %)	159 (21.3 %)	876 (27.0 %)	
Others or Unknown	679 (27.2 %)	240 (32.2 %)	919 (28.4 %)	
Vital sign				
SBP (mmHg)	94.0 [79.0; 116.0]	93.0 [75.0; 117.0]	94.0 [78.0; 117.0]	0.162
DBP (mmHg)	56.0 [48.0; 68.0]	56.0 [45.0; 70.0]	56.0 [47.0; 69.0]	0.079
HR (beats/min)	106.0 [90.0; 123.0]	110.0 [91.0; 124.0]	108.0 [90.0; 123.5]	0.047
RR (breaths/min)	20.0 [18.0; 24.0]	22.0 [20.0; 28.0]	20.0 [18.0; 24.0]	<0.001
BT (°C)	37.7 [36.8; 38.7]	37.1 [36.2; 38.1]	37.6 [36.6; 38.6]	<0.001
SOFA max in 24hr	8.0 [6.0; 11.0]	11.0 [8.0; 14.0]	9.0 [6.0; 11.0]	<0.001
APACHE II	19.0 [14.0; 26.0]	25.0 [19.0; 33.0]	21.0 [15.0; 28.0]	<0.001
Laboratory results				
WBC (K/μL)	10.9 [5.7; 17.1]	10.5 [3.7; 17.8]	10.9 [5.2; 17.2]	0.093
Hb (g/dL)	11.1 ± 2.6	10.6 ± 2.8	11.0 ± 2.6	<0.001
PLT (K/μL)	39 [79 | 216]	118 [47; 222]	134 [72; 217]	<0.001
BUN (mg/dL)	28.6 [19.3; 42.4]	38.0 [25.8; 57.6]	30.4 [20.5; 46.0]	<0.001
Cr (mg/dL)	1.4 [0.9; 2.3]	1.8 [1.2; 2.9]	1.5 [1.0; 2.4]	<0.001
AST (IU/L)	40.0 [25.0; 82.0]	46.0 [28.0; 106.0]	41.0 [25.0; 86.0]	<0.001
ALT (IU/L)	26.0 [15.0; 56.0]	26.0 [14.0; 64.0]	26.0 [15.0; 57.0]	0.494
CRP	13.4 [5.3; 23.2]	16.7 [6.4; 26.0]	14.1 [5.5; 24.0]	<0.001
PH	7.4 [7.4; 7.5]	7.4 [7.3; 7.4]	7.4 [7.3; 7.5]	<0.001
PCO2 (mmHg)	29.0 [24.9; 33.9]	28.3 [23.2; 37.0]	29.0 [24.5; 34.0]	0.730
PO2 (mmHg)	79.5 [65.2; 97.0]	79.2 [61.5; 106.0]	79.4 [64.4; 99.0]	0.740
HCO3 (mEq/L)	19.5 [16.2; 22.4]	17.1 [12.5; 21.2]	19.1 [15.3; 22.2]	<0.001
Lactate (mmol/L)	3.0 [1.8; 5.0]	5.5 [3.0; 8.5]	3.5 [2.0; 5.8]	<0.001
Albumin (g/dL)	3.1 [2.7; 3.5]	2.7 [2.3; 3.2]	3.0 [2.6; 3.5]	<0.001
Latate/Albumin ratio	1.0 [0.6; 1.7]	2.0 [1.1; 3.4]	1.2 [0.7; 2.0]	<0.001
Lacate/Albumin*age	68.0 [39.7; 116.1]	142.1 [81.2; 235.2]	80.8 [44.0; 141.2]	<0.001
Intervention				
Crystalloid 30 ml/h for 3hr	1762 (70.6 %)	543 (72.8 %)	2305 (71.1 %)	0.278
Antibiotics within 3 h	1574 (63.1 %)	484 (64.9 %)	2058 (63.5 %)	0.403
Vasopressor use	2259 (90.6 %)	697 (93.4 %)	2956 (91.2 %)	0.019
Mechanical ventilation	604 (24.2 %)	525 (70.4 %)	1129 (34.8 %)	<0.001
Renal replacement Tx	295 (11.8 %)	301 (40.3 %)	596 (18.4 %)	<0.001
ICU adm	1570 (63.0 %)	577 (77.3 %)	2147 (66.3 %)	<0.001

HTN: hypertension, DM: diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, RR: respiratory rate, BT: body temperature, SOFA: The Sequential Organ Failure Assessment, APACHE: Acute Physiology And Chronic Health Evaluation, WBC: white blood cell, Hb: hemoglobin, PLT: platelet, BUN: Blood Urea Nitrogen, Cr: creatinine, AST: aspartate transaminase, ALT: alanine transaminase, CRP: C-Reactive Protein, ICU adm: Intensive Care Unit admission, Tx: therapy.

vital signs, suspected infection source, laboratory results, initial fluid therapy, inotropes, vasopressors, antibiotics, ventilators, renal replacement therapy, ICU admission, interventions, and 28- and 90-day mortality were extracted from the registry.

2.3. Statistical analysis

Data are expressed as mean ± SD, median with interquartile range (IQR) or percent. Continuous variables were analyzed using the *t*-test if normally distributed or the Mann-Whitney *U* test otherwise. Nominal variables were analyzed using the chi-square test or Fisher's exact test. The accuracy of the 28- and 90-day mortality predictions was measured using the area under the receiver operating characteristic (AUROC) curve. AUC difference tests were performed using De Long and bootstrap tests. The LAA score cut-off value was calculated using Youden's index to determine the optimal value. Kaplan-Meier analysis and the log-rank test were used to compare the 28-day and 90-day mortality of the LAA score according to the cutoff point. To identify the factors associated with mortality, the Cox proportional hazards model was used, and the LAA score was dichotomized according to the cutoff point. A multivariate Cox proportional hazard model was created, including significant factors at the 0.1 level of and variables selected by the researcher, and variables selected using the stepwise backward elimination method; Cox regression was performed with the remaining variables. To simultaneously assess the effects of several variables (quantitative or categorical) on the use of mechanical ventilation, a multivariate logistic regression model was applied. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using R software (Version 4.2.2).

3. Results

Between January 2017 and December 2021, 5346 patients with sepsis were enrolled in this study. After excluding 1537 patients with terminal malignancies and 569 patients with missing data, 3240 patients were included.

3.1. Baseline characteristics

Table 1 shows the demographic, clinical, and laboratory characteristics of the patients. The 28-day mortality rate was 23.0 % and the 90-day mortality rate was 32.8 %. The mean age of the patients was 69.9 ± 13.3 years and was younger in the survivor group than in the death group (survivor vs death group, 69.0 ± 13.3 vs 72.7 ± 13.1 years). There were 1855 (57.3 %) males. The most common comorbidities were hypertension (45.9 %) and diabetes (36.2 %). Most common, "other" or unknown origin were defined as the source of infection (919, 28.4 %). The medians for maximum SOFA and APACHE II scores within 24 h 9.0 [6.0; 11.0] and 21.0 [15.0; 28.0], respectively.

Vital signs analysis showed a higher respiratory rate, lower body temperature group ($p < 0.001$), higher lactate value (5.5 vs 3.0 mmol/L), and lower albumin (2.7 vs 3.1 g/dL) in the death group. The mean LA ratio was 1.2 [0.7; 2.0] and the mean LAA score was 80.8 [44.0; 141.2]. Both the LA ratio and LAA score were higher in the death group (LA ratio 2.0 vs 1.0, LAA score 142.1 vs 68.0). The death group also had higher rates of mechanical ventilation ($p < 0.001$), renal replacement therapy ($p < 0.001$), and vasopressor use ($p < 0.01$). The rate of fluid resuscitation in the first 3 h was 72.8 % in the death group and 70.6 % in the survivor group ($p = 0.278$). The ICU admission rates were also higher in the death group (77.3 % vs. 63.0 %, $p < 0.001$).

Table 2
Area under the curve (AUC) and lactate/albumin*age score cut-off thresholds for 28-day mortality among different patients' subgroups.

	AUC of 28-day mortality (95 % confidence interval)			LAA score cut-off thresholds				
	LA ratio	LAA score	P	Cut-off threshold	Sensitivity	Specificity	PPV	NPV
Overall	0.730 [0.709–0.751]	0.737 [0.716–0.757]	0.016	119.9	0.59	0.77	0.43	0.86
Lactate								
Normal <2.0 mmol/L	0.634 [0.565–0.703	0.674 [0.607–0.740]	0.004	44.6	0.46	0.85	0.27	0.93
Intermediate 2.0≤<4.0 mmol/L	0.62 [0.571–0.670]	0.635 [0.587–0.683]	0.3	59.57	0.77	0.45	0.21	0.92
High ≥4.0 mmol/L	0.692 [0.664–0.720]	0.703 [0.675–0.731]	0.1	175.1	0.60	0.72	0.53	0.77
Age								
<65 years	0.743 [0.704–0.783]	0.742 [0.702–0.781]	0.8	70.8	0.74	0.65	0.32	0.94
≥65 years	0.725 [0.701–0.750]	0.731 [0.707–0.756]	<0.001	120.2	0.64	0.73	0.45	0.86

LA ratio: lactate/albumin ratio, LAA score: lactate/albumin*age score, PPV: positive predictive value, NPV: negative predictive value.

3.2. Primary outcome

3.2.1. ROC curve of LAA score for 28-day mortality

The AUROC curve of the LAA score for 28-day mortality was 0.737 (95 % CI, 0.716–0.757), with an optimal cut-off value of 119.9, sensitivity of 0.59, specificity of 0.77, positive predictive value of 0.43, and negative predictive value of 0.86 (Table 2). As shown in Table 3, the AUROC value of the LAA score (0.737, 95 % CI 0.716–0.757) for 28-day mortality prediction was higher than that of lactate (0.699, 95 % CI 0.677–0.720, $p < 0.001$), albumin (0.651, 95 % CI 0.628–0.673) and age (0.586, 95 % CI 0.563–0.610). Moreover, LAA score (0.737, 95 % CI, 0.716–0.757) had a higher AUROC value than LA ratio (0.730, 95 % CI 0.709–0.751) ($P = 0.016$), but also SOFA (0.698, 95 % CI 0.676–0.720, $p = 0.004$) and APACHE II score (0.672, 95 % CI 0.649–0.694, $p < 0.001$) (Fig. 2, Table 3). There was also a significant difference in the mortality prediction value of the LA ratio and SOFA score (AUROC 0.730, 95 % CI 0.709–0.751 vs 0.698; 95 % CI 0.676–0.720, $p = 0.017$) (see Fig. 3).

In the normal and intermediate group of lactate, the AUROC curve of the LAA score was significantly higher than that of the LA ratio (normal 0.674, 95 % CI 0.607–0.740 vs 0.634, 95 % CI 0.565–0.703, $p = 0.004$; intermediate 0.737, 95 % CI 0.716–0.757 vs 0.730, 95 % CI 0.709–0.751, $p = 0.016$), whereas there was no statistically significant difference in the high lactate group (0.703, 95 % CI 0.675–0.731 vs 0.692, 95 % CI 0.664–0.720, $p = 0.1$). In patients ≥65yrs of age, the AUROC curve of LAA score was 0.731 (95 % CI 0. 707–0.756), which was higher than the LA ratio of 0.725 (95 % CI 0.701–0.750, $p < 0.001$). However, the predictive values of the LAA and LA ratios were similar and not significantly different (AUC: LAA score 0.742, 95 % CI 0.702–0.781 vs LA ratio 0.743, 95 % CI 0.704–0.783, $p = 0.8$) in those aged <65 years (Table 2).

3.2.2. Kaplan-Meier curve and Cox proportional hazard model for 28-day mortality

In the Kaplan-Meier analysis according to the optimal cutoff value, the 28-day mortality was higher in the high LAA score group (log-rank test, $p < 0.001$) (Fig. 4), whereas in the univariate Cox proportional hazard model, the high LAA score group was associated with 28-day mortality (hazard ratio 3.94, 95 % CI 3.40–4.56, $p < 0.001$) and was independently associated in the multivariate Cox proportional hazard model (adjusted hazard ratio 2.07, 95 % CI 1.76–2.43, $p < 0.001$). Other factors associated with 28-day mortality were body temperature (0.85, 95 % CI 0.81–0.90, $p < 0.001$), SOFA score (1.05, 95 % CI 1.03–1.07, $p < 0.001$), Hb (0.95, 95 % CI 0.93–0.98, $p < 0.001$), mechanical ventilation (2.84, 95 % CI 2.36–3.46, $p < 0.001$), and renal replacement therapy (1.70, 95 % CI 1.42–2.03, $p < 0.001$) (Table 4).

3.3. Secondary outcomes

3.3.1. Mechanical ventilation

The use of mechanical ventilation was higher in the high LAA score group (adjusted odds ratio 1.37, 95 % CI 1.11–1.68, $p = 0.003$). In addition to the LAA score, chronic liver disease, infection focus, respiratory rate, SOFA score, pH, and RRT were associated with mechanical ventilation (Supplementary Table 1). The predictive power of mechanical ventilation was not statistically different from the LA ratio of 0.693 (95 % CI 0.674–0.713) with an AUROC curve of 0.702 (95 % CI 0.683–0.722) for the LAA score ($p = 0.07$) (Supplementary Fig. 1).

3.3.2. 90-Days mortality

In the Kaplan–Meier analysis, the 90-day mortality was also higher in the high LAA score group (log-rank test, $p < 0.001$) (Fig. 5). As shown in Table 5, in the Multivariate Cox proportional hazard model, this high group was also independently associated with 90-day mortality (adjusted hazard ratio 1.78, 95 % CI 1.56–2.03, $p < 0.001$). The results of the ROC analysis for 90-day mortality prediction showed that the AUC of the LAA score was 0.702 (95 % CI 0.683–0.722), which was significantly better than that of the lactate (0.652, 95 % CI 0.632–0.672, $p < 0.001$), LA ratio (0.693, 95 % CI 0.674–0.713, $p < 0.001$), and APACHE II score (0.675, 95 % CI 0.656–0.695, $p = 0.03$). However, this was not statistically significant with respect to SOFA score (0.688; 95 % CI 0.669–0.708, $p = 0.2$) (Supplementary Table 2).

3.4. Subgroup analysis for septic shock

In the septic shock subgroup, a high LAA score was independently associated with 28-day mortality (adjusted HR 1.69, 95 % CI

Table 3
Area under the Curve (AUC) comparison for 28-day mortality in patients with sepsis.

Models for AUC comparison			AUC [95 % CI]	AUC [95 % CI]	Z	p
LAA score	vs	Lactate	0.737 [0.716–0.757]	0.699 [0.677–0.720]	8.47	<0.001
	vs	Albumin		0.651 [0.628–0.673]	6.43	<0.001
	vs	Age		0.586 [0.563–0.610]	10.51	<0.001
	vs	LA ratio		0.730 [0.709–0.751]	2.41	0.016
	vs	SOFA		0.698 [0.676–0.720]	2.88	0.004
	vs	APACHE II		0.672 [0.649–0.694]	4.76	<0.001

CI: confidence interval, LAA score: lactate/albumin*age score, LA ratio: lactate/albumin ratio, SOFA: The Sequential Organ Failure Assessment, APACHE: Acute Physiology And Chronic Health Evaluation.

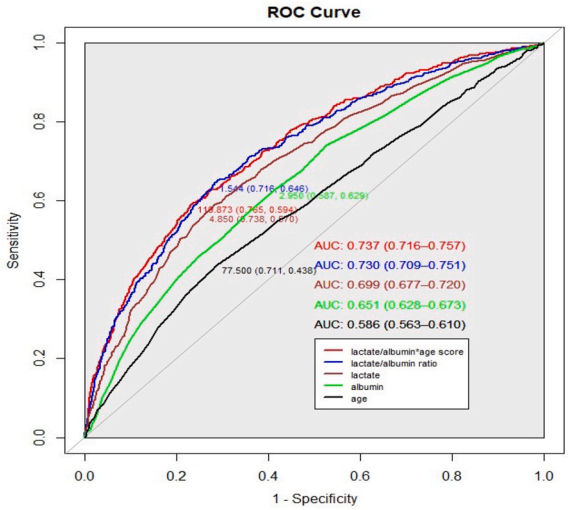

Fig. 2. Receiver-operating characteristic curves for lactate, albumin, age, lactate/albumin ratio, lactate/albumin*age score predicting 28-day mortality in patients with sepsis.

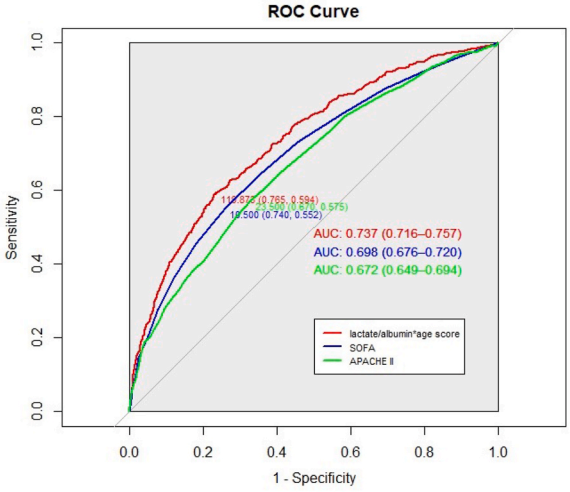

Fig. 3. Receiver-operating characteristic curves for SOFA, APACHE II score, lactate/albumin*age score predicting 28-day mortality in patients with sepsis.
SOFA: The Sequential Organ Failure Assessment, APACHE: Acute Physiology And Chronic Health Evaluation.

1.41–2.04, $p < 0.001$) (Supplementary Table 3). The AUROC for the LAA score was 0.700 (95 % CI 0.674–0.725, $p < 0.001$). However, in the septic shock subgroup, the AUROC curve for predicting 28-day mortality was highest for the SOFA score (0.743, 95 % CI 0.721–0.765), followed by the APACHE II score (0.726, 95 % CI 0.703–0.748) (Supplementary Table 4).

4. Discussion

In this study, we evaluated the performance of the LAA score as a predictor of mortality in patients with sepsis. Our study showed that the initial LAA score in the emergency department could independently predict mortality in patients with sepsis. The diagnostic performance of the LAA score in predicting 28-day mortality in patients with sepsis was better than that of lactate, albumin, and LA ratio alone and showed a higher AUROC curve than SOFA and APACHE II scores. In addition, the LAA score showed better discrimination than the LA ratio for 28-day mortality, even in patients with normal lactate levels, and better performance in patients over 65 years of age. Even though further validation and research are necessary, we anticipate that the LAA score could assist emergency physicians in assessing patient severity during initial evaluation, particularly in patients with normal lactate levels, by referencing the LAA score alongside vital signs and lactate level.

Hyperlactatemia (>2 mmol/L) has been shown to be an independent predictor of mortality in critically ill patients with sepsis,

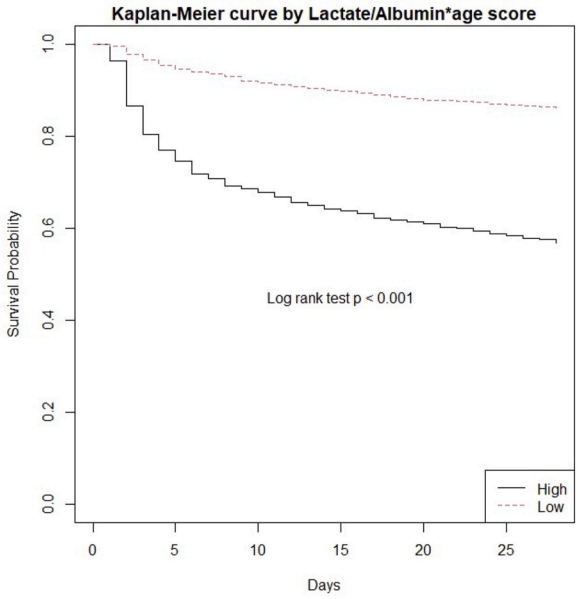

Fig. 4. Kaplan-Meier curve of 28-day mortality rate by lactate/albumin*age score for patients with sepsis.

Table 4
Cox proportional hazards model for 28-day mortality in patients with sepsis (n = 3240).

Variables	Univariate			Multivariate		
	HR	95 % CI	*p*	HR	95 % CI	*p*
LAA score	3.94	3.40–4.56	<0.001	2.07	1.76–2.43	<0.001
Underlying disease						
Chronic renal disease	1.06	0.85–1.32	0.608	1.07	0.67–1.30	0.67
Chronic liver disease	1.19	0.96–1.46	0.108	–	–	–
Infection focus						
Respiratory infection	1.99	1.63–2.42	<0.001	1.20	0.98–1.47	0.052
Urinary tract infection	0.71	0.55–0.92	0.011	0.81	0.62–1.05	0.11
Other or Unknown	1.51	1.23–1.84	<0.001	1.20	0.98–1.47	0.07
Vital Sign						
Respiratory Rate	1.06	1.05–1.07	<0.001	1.02	1.01–1.03	<0.001
Body Temperature	0.75	0.71–0.79	<0.001	0.85	0.81–0.90	<0.001
SOFA max score in 24 h	1.19	1.17–1.22	<0.001	1.05	1.03–1.07	<0.001
Laboratory results						
Hb	0.93	0.91–0.96	<0.001	0.95	0.93–0.98	<0.001
CRP	1.01	1.00–1.01	<0.001	–	–	–
PH	0.03	0.02–0.05	<0.001	–	–	–
Intervention						
Mechanical Ventilation	5.70	4.87–6.68	<0.001	2.84	2.36–3.46	<0.001
Renal Replacement Therapy	3.77	3.25–4.36	<0.001	1.70	1.42–2.03	<0.001

HR: hazard ratio, CI: confidence interval, LAA score: lactate/albumin*age score, SOFA: The Sequential Organ Failure Assessment, Hb: hemoglobin, CRP: C-Reactive Protein.

trauma, and other conditions, and elevated lactate levels are used worldwide for early diagnosis, treatment, and risk stratification in patients with septic shock [18,19]. In emergency departments, serum lactate levels have been used as prognostic factors for mortality in patients with clinically suspected infections [4,20]. Lactate is a well-studied prognostic factor; however, its interpretation is complicated by the many conditions that can result in increased lactate levels [21–25].

Hypoalbuminemia reflects nutritional status and is associated with the degree of the inflammatory response in critically ill patients [26,27]. Albumin is a predictor of debility, vulnerability to stressors, and unstable homeostasis, and is associated with prognosis in critically ill patients and patients with sepsis or bacteremia [12,28–30]. Although serum albumin concentration is a prognostic factor, it is affected by comorbidities, such as chronic liver disease, dietary supplementation, and inflammation [31,32]. Therefore, measurements alone may be a limited prognostic factor.

Older adults are disproportionately affected by sepsis, with more than 60 % of patients diagnosed with sepsis being over 65 years of age [15]. Furthermore, mortality from sepsis increases with age, with studies showing an OR of 2.26 for those aged 65 years and older

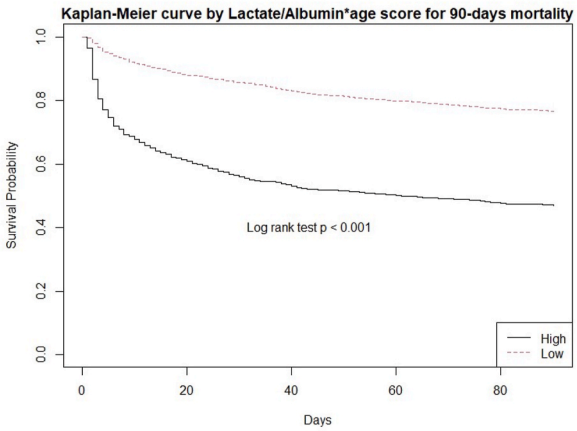

Fig. 5. Kaplan-Meier curve of 90-day mortality rate by lactate/albumin*age score for patients with sepsis.

Table 5
Cox proportional hazards model for 90-day mortality in patients with sepsis (n = 3240).

Variables	Univariate			Multivariate		
	HR	95 % CI	*p*	HR	95 % CI	*p*
LAA score	3.02	2.68–3.41	<0.001	1.78	1.56–2.03	<0.001
Underlying disease						
Chronic renal disease	1.23	1.04–1.47	0.017	–	–	–
Chronic liver disease	1.26	1.06–1.50	0.008	–	–	–
Infection focus						
Respiratory infection	1.88	1.60–2.22	<0.001	1.23	1.04–1.47	0.017
Urinary tract infection	0.66	0.53–0.82	<0.001	0.74	0.60–0.92	0.006
Other or Unknown	1.40	1.18–1.65	<0.001	1.13	0.96–1.34	0.152
Vital Sign						
Respiratory Rate	1.05	1.04–1.06	<0.001	1.01	1.01–1.02	0.004
Body Temperature	0.77	0.74–0.81	<0.001	0.87	0.83–0.91	<0.001
SOFA max score in 24 h	1.17	1.16–1.19	<0.001	1.05	1.03–1.07	<0.001
Laboratory results						
Hb	0.90	0.88–0.92	<0.001	0.92	0.90–0.94	<0.001
CRP	1.01	1.00–1.01	0.02	–	–	–
PH	0.05	0.04–0.08	<0.001	–	–	–
Intervention						
Mechanical ventilation	4.25	3.75–4.81	<0.001	2.32	1.99–2.69	<0.001
Renal Replacement Therapy	3.26	2.88–3.71	<0.001	1.51	1.31–1.75	<0.001

HR: hazard ratio, CI: confidence interval, LAA score: lactate/albumin*age score, SOFA: The Sequential Organ Failure Assessment, Hb: hemoglobin, CRP: C-Reactive Protein.

[13]. APACHE II, SAPS II, and SOFA scores are the leading predictors of mortality in critically ill patients, including those with sepsis, and APACHE II and SAPS II scores include age among their variables. However, APACHE II and SAPS II scores are inconvenient to apply in the emergency department because they collect too many variables and do not help determine the prognosis and treatment of the disease early or quickly.

Recent studies have suggested that LA ratio, a combination of serum lactate and albumin levels, may be a useful prognostic marker in patients with sepsis. In a multicenter study of 15 teaching hospitals (KoSS), the LA ratio showed better ability to predict 28-day mortality than lactate alone [32]. In patients with sepsis and septic shock admitted to the ICU, studies have shown that the LA ratio is superior to lactate and albumin levels alone as predictors of ICU mortality and MODS [10,12]. However, Gharipour et al. found the LA ratio to be useful as a prognostic marker of 28-day mortality but equivalent to lactate alone [33]. In a multicenter observational study of patients with sepsis admitted to the ICU, Shadvar et al. found that the LA ratio had a better prognostic performance for RRT, ICU LOS, and MV duration than lactate alone and lactate clearance [11]. Another study found that the LA ratio was useful in predicting the 28-day mortality and MODS in pediatric patients with sepsis aged 1 month to 13 years who were admitted to the PICU [34]. In addition to sepsis, recent studies have shown that the LA ratio is a useful prognostic factor in critically ill patients, such as those with heart failure, acute myocardial infarction, acute respiratory failure, liver failure, acute pancreatitis, traumatic brain injury, and cardiac arrest [35–44].

The Sequential Organ Failure Assessment (SOFA) score is widely used to predict the risk of hospitalization and mortality in patients with sepsis [11]. In our study, the AUROC of the LA ratio for 28-day mortality prediction was significantly higher than that of the SOFA

score ($p = 0.017$). However, the LAA score showed better predictive results than the SOFA score and LA ratio. (LAA score vs SOFA score $p = 0.004$, LAA score vs LA ratio $p = 0.016$) In a study of patients in the ICU, the LAA score showed better predictive performance than the SOFA score (AUC 0.67 vs 0.64, $p < 0.0001$), while the LA ratio was not superior to the SOFA score (AUC 0.61 vs 0.64, $P = 0.7384$) [30]. The AUC curve for the prediction of 28-day all-cause mortality in patients admitted to the ICU with acute pancreatitis showed that the LA ratio (74.262 %) was clearly superior to lactate (71.252 %) and albumin (65.917 %) but not to SOFA (75.153 %) [40].

The emergency room is an unpredictable environment with a diverse patient population and limited resources, requiring optimal untilization for the best possible care. To achieve this, various artificial intelligence-based studies are being conducted, utilizing vital signs, diverse blood test results, biomarkers, and genetic testing to enhance predictive accuracy. As mentioned above, there have been many studies on the utility of the LA ratio as a prognostic marker, but the only prior study on the LAA score was conducted by Chen el al. using data from the Medical information Mart for Intensive Care III (MIMIC-III) [30]. The LAA score is easily measurable, can be easily applied to clinical decision-making, and can help prioritize patients who may benefit more from intensive care services, especially during the initial stages of ED care. Due to the objective nature of the three variables, it may complement the limitations associated with other popular prognostic scoring systems, such as the SOFA and APACHE II scores, and may be more useful in older patients with initial normal lactate concentrations.

Despite the large sample size and the long duration of prospective data collection, this study has some limitations. First, we were unable to analyze data from patients with missing values, including lactate and albumin levels. Second, this was a multicenter observational study using data from the KoSS registry, but it was a single-nation study and therefore cannot be generalized. Third, Sepsis management generally follows the Sepsis Survival Campaign guidelines; however, institutional characteristics may vary and were not adjusted for in the present study.

5. Conclusion

The LAA score may be used as an independent predictor of mortality in patients with sepsis in the emergency department. While our results indicate that it has a statistically higher performance comparted to serum lactate alone, LA ratio, and SOFA and APACHE II scores, the difference in actual accuracy is marginal. This suggests that the LAA has potential, further validation as a readily available and objective biomarker is needed in large multicenter prospective studies to fully establish its clinical untility.

CRediT authorship contribution statement

Sungjin Kim: Writing – original draft, Conceptualization. **Sukyo Lee:** Writing – original draft. **Sejoong Ahn:** Writing – original draft, Methodology, Formal analysis. **Jonghak Park:** Supervision, Investigation. **Sungwoo Moon:** Investigation. **Hanjin Cho:** Writing – review & editing, Supervision, Conceptualization. **Sung-Hyuk Choi:** Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37056.

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