**SHOCK,** Vol. 50, No. 5, pp. 545–550, 2018

# PROGNOSTIC VALUE OF THE LACTATE/ALBUMIN RATIO FOR PREDICTING 28-DAY MORTALITY IN CRITICALLY ILL SEPSIS PATIENTS

**Jikyoung Shin,[*] Sung Yeon Hwang,[*] Ik Joon Jo,[*] Won Young Kim,[†] Seung Mok Ryoo,[†] Gu Hyun Kang,[‡] Kyuseok Kim,[§] You Hwan Jo,[§] Sung Phil Chung,[||] Young Seon Joo,[||] Jin Ho Beom,[||] Young Hoon Yoon,[¶] Kap Su Han,[**] Tae Ho Lim,[††] Han Sung Choi,[‡‡] Woon Yong Kwon,[§§] Gil Joon Suh,[§§] Sung-Hyuk Choi,[¶] Tae Gun Shin[*], for the Korean Shock Society (KoSS) Investigators**

*[*]Department of Emergency Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [†]Department of Emergency Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [‡]Department of Emergency Medicine, Hallym University College of Medicine KangNam Medical Center, Seoul, Korea; [§]Department of Emergency Medicine, Seoul National University Bundang Hospital, Seongnam, Korea; [||]Department of Emergency Medicine, Yonsei University College of Medicine, Seoul, Korea; [¶]Department of Emergency Medicine, Guro Hospital, Korea University Medical Center, Seoul, Korea; [**]Department of Emergency Medicine, Korea University Anam Hospital, Seoul, Korea; [††]Department of Emergency Medicine, Hanyang University College of Medicine, Seoul, Korea; [‡‡]Department of Emergency Medicine, Kyung Hee University Hospital, Seoul, Korea; and [§§]Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Korea*

Received 3 Jan 2018; first review completed 22 Jan 2018; accepted in final form 9 Feb 2018

ABSTRACT—**Aim:** The aim of this study was to evaluate the clinical utility of the lactate/albumin (L/A) ratio as a predictive factor of 28-day mortality in critically ill sepsis patients. **Methods:** This is a retrospective observational study from a prospectively collected multicenter registry of 10 emergency departments (EDs) in teaching hospitals that participated in the Korean Shock Society. It enrolled patients who were 19 years of age or older who had a suspected or confirmed infection and evidence of refractory hypotension or hypoperfusion. The prognostic performance of the L/A ratio and lactate level for predicting 28-day mortality was assessed. Lactate and albumin levels were measured immediately after ED arrival. **Results:** A total of 946 patients were included, with 22.5% overall 28-day mortality. The area under the receiver operating characteristic curve (AUROC) value of the L/A ratio (0.69, 95% confidence interval [CI] 0.64–0.73, $P < 0.01$) was higher than that of lactate (0.65, 95% CI 0.61–0.70, $P < 0.01$) for predicting 28-day mortality. The optimal cutoff of the L/A ratio was 1.32. The AUROC value of the L/A ratio was better than that of lactate regardless of lactate level (normal [<2.0 mmol/L]: 0.68 vs. 0.55; intermediate [≥2.0, < 4.0 mmol/L]: 0.65 vs. 0.50; high [≥4.0 mmol/L]: 0.66 vs. 0.62). In the subgroup with decreased lactate elimination, the AUROC value of the L/A ratio was also significantly higher than that of lactate (hepatic dysfunction: 0.70 vs. 0.66; renal dysfunction: 0.71 vs. 0.67). The L/A ratio cut-off and hypoalbminemia showed further discriminative value for 28-day mortality even in patients with normal or intermediate lactate levels. **Conclusions:** The prognostic performance of the L/A ratio was superior to that of a single lactate measurement for predicting 28-day mortality of critically ill sepsis patients. L/A ratio can be a useful prognostic factor regardless of initial lactate level and the presence of hepatic or renal dysfunction.

KEYWORDS—Albumin, lactate, lactate/albumin ratio, mortality, septic shock

## INTRODUCTION

Sepsis and septic shock are life-threatening conditions caused by tissue hypoperfusion and hypoxia leading to organ dysfunction (1, 2). Despite advances in intensive care and sepsis management, the mortality rate is 20% to 30% in sepsis and septic shock patients, resulting in 30% to 50% of all hospital deaths (3–5). Therefore, predictive biomarkers of mortality in septic shock patients are important for early detection and timely management.

Increased lactate levels are associated with mortality and are widely used for early diagnosis, management, and risk stratification in patients with septic shock (6, 7). However, lactate elevation can be affected by a number of different conditions including decreased lactate elimination due to hepatic or renal dysfunction as well as accelerated glycolysis, and the diagnostic value of initial lactate level alone might be low (8–11). In addition, there are patients among those with normal or intermediate lactate levels that are at high risk of early death. As a negative acute-phase protein, serum albumin can also serve as a biomarker for prognosis in septic patients (12). Similar to lactate levels, serum albumin levels are also affected by multiple conditions including inflammation, malnutrition, and liver cirrhosis (13).

The lactate/albumin (L/A) ratio has been proposed as a prognostic marker because the ratio is associated with multiple

Address reprint requests to Tae Gun Shin, MD, Department of Emergency Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. E-mail: taegunshin@skku.edu

Co-correspondence: Sung-Hyuk Choi, MD, PhD, Department of Emergency Medicine, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 152-703, Korea. E-mail: kuedchoi@korea.ac.kr

JS and SYH contributed equally to this work.

S-HC and TGS contributed equally to this work.

The authors report no conflicts of interest.

DOI: 10.1097/SHK.0000000000001128

organ failure and mortality in critically ill septic patients (14, 15). The L/A ratio may be a reasonable prognostic marker of sepsis considering that there are many physiological changes that need to be taken into consideration during sepsis; however, the use of the L/A ratio will require further validation prior to clinical application. In this study, we evaluated the prognostic performance of the L/A ratio and lactate levels for predicting 28-day mortality. Use of the ratio was also assessed according to lactate levels, decreased lactate elimination, and suspected focus of infection.

## PATIENTS AND METHODS

### *Study design*

This retrospective observational study used data from a prospectively collected multicenter registry of the Korean Shock Society (KoSS Septic Shock Registry) of patients admitted between October 2015 and February 2017. The KoSS is a collaborative research network to investigate and improve the quality of diagnosis and management for sepsis. It was organized in 2013 and the KoSS investigators have been prospectively collecting data from septic shock patients treated at the emergency department (ED) of 10 teaching hospitals throughout South Korea from October 2015. The study was approved by the institutional review boards (IRBs) of the individual participating centers and informed consent was obtained according to local IRB policy. Patients who were 19 years of age or older who had a suspected or confirmed infection and evidence of refractory hypotension or hypoperfusion were enrolled (16–19). Hypotension was defined as systolic blood pressure (SBP) <90 mm Hg, mean arterial pressure <70 mm Hg, or SBP decrease >40 mm Hg from baseline (20). Refractory hypotension was defined as persistent hypotension after 1 L or more intravenous fluid challenge or as the need for vasopressors after fluid resuscitation. Hypoperfusion was defined as a serum lactate level of 4 mmol/L or greater (7). Patients who signed a ''Do Not Attempt Resuscitation'' order, met the inclusion criteria 6 h after ED arrival, were transferred from other hospitals without meeting the inclusion criteria upon ED arrival, or were directly transferred from the ED to other hospitals were not enrolled in the KoSS registry.

### *Data collection*

The case report form included standard definitions of 200 variables including clinical characteristics, therapeutic interventions, and outcome of patients with septic shock (21). All data were anonymized and collected using standardized web-based report forms by research coordinators at each participating hospital. For data quality control, data were centrally reviewed at the coordinating hospital. From the registry, demographic characteristics, comorbidities, vital signs, suspected infection source, blood culture, laboratory data, interventions including use antibiotics, initial fluid resuscitation, vasopressor use, mechanical ventilation, renal replacement therapy, and outcomes were retrieved. Lactate and albumin values were measured immediately after ED arrival. Lactate levels were categorized into low (<2 mmol/L), intermediate ($2 \leq \times$ <4 mmol/L), and high ($\geq$ 4 mmol/L) groups. Hypoalbuminemia was defined as albumin levels <3.0 g/dL.

For calculated Maximum Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health evaluation (APACHE) II scores, the worst parameters within 24 h after ED arrival were used (22, 23). Organ dysfunction was defined as a SOFA score of 2 or more (22). The clinical criteria for septic shock outlined in the Third International Consensus Definitions were sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure $\geq$ 65 mm Hg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation (24). The primary outcome was 28-day mortality.

### *Statistical analyses*

Data are presented as the median with interquartile range (IQR) or number of patients with percentage. Categorical variables were analyzed with Chi-square tests and continuous variables were analyzed with Wilcoxon rank-sum tests. Prediction accuracy of 28-day mortality was assessed using the area under the receiver operating characteristic (AUROC) curve. Prognostic accuracy was assessed in all patients and in subgroups based on lactate levels, decreased lactate elimination (hepatic and renal dysfunction), and suspected focus of infection (intra-abdominal infection, urinary tract infection, and respiratory infection). For comparison of AUROC curves of two diagnostic modalities (L/A ratio, lactate), we used a test for dependent receiver operating characteristic curves (25). The cut-off point was determined using the Liu method that maximizes sensitivity and specificity. To adjust for potential confounders in the association between the L/A ratio and 28-day mortality, individual factors with a $P$ value less than 0.05 were used for multiple logistic regression. Statistical significance was defined by a $P$ value <0.05. STATA 13.0 software (STATA Corporation, College Station, Tex) was used for all computational analyses.

## RESULTS

A total of 1,046 patients were registered in this septic shock registry after the exclusion of 230 patients who signed a ''Do Not Attempt Resuscitation'' order, 136 patients who did not meet the inclusion criteria 6 h after ED arrival, 69 patients who were directly transferred from the ED to other hospitals and 624 patients without informed consent. Among them, finally, 946 patients with septic shock were analyzed in this study (Fig. 1). The mean time from ED arrival to meeting enrolment criteria was 1.3 h. Baseline characteristics are presented in Table 1. The overall 28-day mortality was 22.5% in all the patients and 90-day mortality was 30.0% (90-day follow-up loss, 14.9%). The median age of patients was 70.4 (IQR 60.2–78.3) and 543 (57.4%) patients were male. The most common infection focus was intra-abdominal infection (32.4%), followed by respiratory infection (25.6%). The median maximum SOFA score in 24 h was 8 (IQR 5–11). In laboratory tests, the non-survivor group showed lower albumin levels (median, 2.6 g/dL vs. 3.0 g/dL), higher lactate levels (median, 4.5 mmol/L vs. 3.0 mmol/L), and higher L/A ratio (median, 1.7 vs. 1.0) than the survival group ($P < 0.05$, all). In total, 423 (44.7%) patients met the clinical criteria for septic shock outlined in the Third International Consensus Definitions for Sepsis and Septic Shock (survivor vs. non-survivor, 41.9% vs. 54.5%; $P < 0.01$) (24).

Table 2 shows comparisons between AUROC values and the cut-off point of the L/A ratio for 28-day mortality. The AUROC value of the L/A ratio for predicting 28-day mortality (0.69, 95% confidence interval [CI] 0.64–0.73; $P < 0.01$) was higher than that for lactate alone (0.65, 95% CI 0.61–0.70; $P < 0.01$); the results for 90-day mortality were similar (Fig. 2). The AUROC value of the L/A ratio was significantly higher than that of lactate regardless of lactate level (normal: 0.68, 95% CI 0.59–0.77 vs. 0.55, 95% CI 0.46–0.64, $P < 0.01$; intermediate: 0.65, 95% CI 0.56–0.73 vs. 0.50, 95% CI 0.41–0.59, $P < 0.01$;

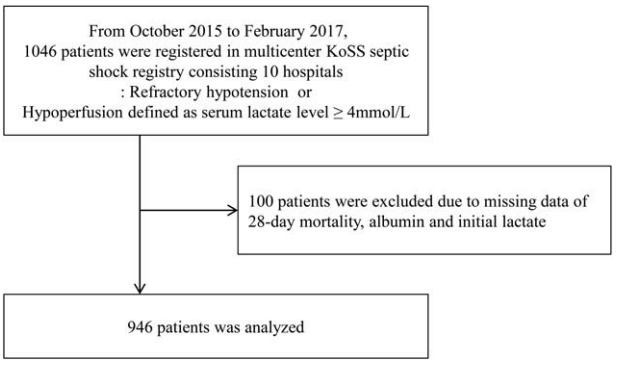


Fig. 1. **Study flow.**

Table 1. **Baseline characteristics**

| Variables | Overall (n = 946) | Survivors (n = 733) | Non-survivors (n = 213) | *P* |
|---|---|---|---|---|
| Age (years) | 70.4 (60.2–78.3) | 69.9 (60.2–77.4) | 72.9 (60.9–79.4) | 0.02 |
| Sex (male) | 543 (57.4) | 406 (55.4) | 137 (64.3) | 0.02 |
| Comorbidities | | | | |
| Hypertension | 402 (42.5) | 312 (42.6) | 90 (42.3) | 0.94 |
| Diabetes | 277 (29.3) | 210 (28.7) | 67 (31.5) | 0.43 |
| Cardiac disease | 129 (13.6) | 100 (13.6) | 29 (13.6) | 0.99 |
| Cerebrovascular disease | 140 (14.8) | 107 (14.6) | 33 (15.5) | 0.75 |
| Chronic lung disease | 72 (7.6) | 46 (6.3) | 26 (12.2) | <0.01 |
| Chronic renal disease | 83 (8.8) | 56 (7.6) | 27 (12.7) | 0.02 |
| Chronic liver disease | 117 (12.4) | 87 (11.9) | 30 (14.1) | 0.39 |
| Metastatic solid cancer | 217 (22.9) | 165 (22.5) | 52 (24.4) | 0.56 |
| Suspected infection focus | | | | |
| Respiratory infection | 242 (25.6) | 161 (22.0) | 81 (38.0) | <0.01 |
| Urinary tract infection | 171 (18.1) | 153 (20.9) | 18 (8.5) | <0.01 |
| Intra-abdominal infection | 306 (32.4) | 245 (33.4) | 61 (28.6) | <0.01 |
| Other or unknown | 227 (24.0) | 174 (23.7) | 53 (24.9) | <0.01 |
| Initial vital signs | | | | |
| Mean atrial pressure (mm Hg) | 68 (58–83.7) | 68 (58.7–83.3) | 68.7 (56.7–87) | 0.69 |
| Respiratory rate (per minute) | 20 (18–24) | 20 (18–23.5) | 22 (20–27) | <0.01 |
| Heart rate (per minute) | 108 (91–126) | 106 (90–125) | 114 (95–128) | <0.01 |
| Body temperature (°C) | 37.5 (36.6–38.5) | 37.7 (36.7–38.7) | 36.9 (36.3–37.9) | <0.01 |
| Blood culture-positive | 403 (42.6) | 320 (43.7) | 83 (39) | 0.47 |
| Maximum SOFA score in 24 h | 8 (5–11) | 7 (5–10) | 10 (7–13) | <0.01 |
| Organ dysfunction* | | | | |
| CNS | 233 (24.6) | 138 (18.8) | 95 (44.6) | <0.01 |
| Respiratory | 405 (42.8) | 277 (38.8) | 128 (60.1) | <0.01 |
| Cardiovascular | 781 (82.6) | 595 (81.2) | 186 (87.3) | 0.04 |
| Renal | 316 (33.4) | 225 (30.7) | 91 (42.7) | <0.01 |
| Hepatic | 242 (25.6) | 167 (22.8) | 75 (35.2) | <0.01 |
| Coagulopathy | 321 (33.9) | 235 (32.1) | 86 (40.4) | 0.02 |
| Multi-organ failure (two or more) | 700 (74.0) | 512 (69.9) | 188 (88.3) | <0.01 |
| APACHE II score | 18 (13–25) | 17 (12–23) | 22 (17–31) | <0.01 |
| Laboratory test | | | | |
| Albumin (g/dL) | 2.9 (2.5–3.3) | 3.0 (2.6–3.4) | 2.6 (2.2–3.1) | <0.01 |
| Initial lactate (mmol/L) | 3.3 (1.8–5.4) | 3.0 (1.7–4.8) | 4.5 (2.5–7.5) | <0.01 |
| Lactate/albumin ratio | 1.2 (0.6–1.9) | 1.0 (0.6–1.7) | 1.7 (1–3.0) | <0.01 |
| Interventions | | | | |
| Antibiotics within 3 h | 635 (67.1) | 491 (67.0) | 144 (67.6) | 0.87 |
| Fluid resuscitation within 3 h (30 mL/kg) | 743 (78.5) | 581 (79.3) | 162 (76.1) | 0.32 |
| Vasopressors | 844 (89.2) | 654 (89.2) | 190 (89.2) | 1.0 |
| Mechanical ventilation | 281 (29.7) | 147 (20.0) | 134 (62.9) | <0.01 |
| Renal replacement therapy | 158 (16.7) | 73 (10.0) | 85 (39.9) | <0.01 |
| ICU care | 601 (63.5) | 435 (59.4) | 166 (77.9) | <0.01 |
| Septic shock criteria of the Sepsis-3 consensus definition | 423 (44.7) | 307 (41.9) | 116 (54.5) | <0.01 |

Data are shown as the median with interquartile range or n (%).
*Organ dysfunction was defined as a SOFA score of two or more.
APACHE indicates acute physiology and chronic health evaluation; ICU, intensive care unit; SOFA, sepsis-related organ failure assessment.

high: 0.66, 95% CI 0.60–0.72 vs. 0.62, 95% CI 0.56–0.68, $P = 0.02$). In the decreased lactate elimination subgroup, the AUROC value of the L/A ratio was also significantly higher than that of lactate (hepatic dysfunction: 0.70, 95% CI 0.63–0.77 vs. 0.66, 95% CI 0.58–0.74, $P < 0.01$; renal dysfunction: 0.71, 95% CI 0.64–0.77 vs. 0.67 95% CI 0.60–0.73, $P < 0.01$). A higher prognostic value of the L/A ratio was also observed in infection focus subgroups including intra-abdominal and respiratory infections.

We compared 28-day mortality, septic shock corresponding to the Sepsis-3 definition and multi-organ failure according to initial lactate level using the cut-off point for L/A ratio and albumin level (Table 3). The 28-day mortality rates were significantly higher when the L/A ratio was above the cut-off point regardless of lactate level (normal: 21.7% vs. 7.6%, $P < 0.01$; intermediate: 28.9% vs. 12.6%, $P < 0.01$; high: 46.4% vs. 21.7%, $P < 0.01$). A significant trend in higher mortality was also observed in hypoalbuminemia patients compared with patients with normal albumin. Multi-organ failure rates were also higher in patients with an L/A ratio above the cut-off point in the intermediate and high lactate subgroups, and in patients with hypoalbuminemia regardless of lactate level. Regarding the sepsis-3 clinical criteria, there was a significant difference by the L/A ratio cut-off in the normal lactate group.

After adjusting for several confounding factors such as age, sex, chronic lung disease, chronic renal disease, infection focus, maximum SOFA score, and APACH II score, we found a

Table 2. **Area under the receiver operating characteristic curve (AUROC) and lactate/albumin ratio cutoff for 28-day mortality**

| | AUROC curve of 28-day mortality (95% confidence interval) | | | Lactate/albumin ratio cut-off point | | |
|---|---|---|---|---|---|---|
| | Lactate | Lactate/albumin ratio | *P* | Cut-off value | Sensitivity | Specificity |
| Overall patients | 0.65 (0.61–0.70) | 0.69 (0.64–0.73) | <0.01 | 1.32 | 0.66 | 0.62 |
| Lactate level | | | | | | |
| Normal lactate (<2.0 mmol/L) | 0.55 (0.46–0.64) | 0.68 (0.59–0.77) | <0.01 | 0.48 | 0.69 | 0.63 |
| Intermediate lactate (2.0≤ x <4.0 mmol/L) | 0.50 (0.41–0.59) | 0.65 (0.56–0.73) | <0.01 | 1.16 | 0.50 | 0.75 |
| High lactate (≥4.0 mmol/L) | 0.62 (0.56–0.68) | 0.66 (0.60–0.72) | 0.02 | 2.35 | 0.59 | 0.68 |
| Decreased lactate elimination | | | | | | |
| Hepatic dysfunction (n = 242) | 0.66 (0.58–0.74) | 0.70 (0.63–0.77) | <0.01 | 1.94 | 0.63 | 0.70 |
| Renal dysfunction (n = 316) | 0.67 (0.60–0.73) | 0.71 (0.64–0.77) | <0.01 | 1.39 | 0.71 | 0.57 |
| Infection focus | | | | | | |
| Intra-abdominal infection (n = 306) | 0.70 (0.62–0.78) | 0.76 (0.69–0.83) | <0.01 | 2.24 | 0.61 | 0.82 |
| Urinary tract infection (n = 171) | 0.77 (0.65–0.89) | 0.82 (0.72–0.92) | 0.10 | 1.69 | 0.67 | 0.86 |
| Respiratory infection (n = 242) | 0.59 (0.51–0.67) | 0.63 (0.55–0.70) | <0.01 | 1.41 | 0.54 | 0.70 |

significant association between the L/A ratio and 28-day mortality (adjusted odds ratio [OR] 1.51, 95% CI 1.33–1.72; $P < 0.01$; Table 4).

## DISCUSSION

In this study, we used the multicenter KoSS registry to evaluate the L/A ratio as a prognostic factor of mortality in critically ill sepsis patients. The diagnostic performance of the L/A ratio was better than that of single lactate for predicting 28-day mortality in sepsis patients with refractory hypotension or hyperlactatemia. Improved prognostic accuracy was consistent in subgroups of lactate levels (low, intermediate, high), decreased lactate elimination (hepatic or renal dysfunction), and suspected focus of infection. In patients with hepatic or renal dysfunction and intra-abdominal or urinary tract infection foci, the AUROC of the L/A ratio was relatively fair for predicting 28-day mortality (AUROC $\geq$ 0.70). In addition, the L/A ratio cutoff and hypoalbminemia showed further discriminative value for 28-day mortality than single lactate even in patients with normal or intermediate lactate levels.

Lactate is a well-known prognostic factor in critically ill patients with infection and trauma. Serum lactate level in the ED has been used as a prognostic factor of mortality in patients with clinically suspected infections (26, 27). However, interpretation of serum lactate levels is often complicated because some patients have high serum lactate levels due to lactate elimination impairment by hepatic or renal dysfunction and patients with normal or intermediate lactate levels might be at high mortality risk (11). In addition, mechanisms other than infection leading to cellular hypoxia can also increase serum lactate level (28).

Albumin is associated with mortality in sepsis patients, and is included in APACHE II scores (29, 30); however, chronic disease and amino acid supplements affect serum albumin level. Albumin is synthesized by the liver and hepatic dysfunction impairs albumin synthesis; therefore, serum albumin level in patients with hepatic dysfunction is lower than normal (31). Thus, serum albumin level is affected by chronic disease, nutrition support, and inflammation, and prognostic value of single measurement might be limited.

The L/A ratio has been proposed as a marker for combined interpretation of lactate and albumin levels; some studies have investigated its usefulness as a prognostic marker in sepsis patients. Wang et al. (14) evaluated the correlation of the L/A ratio to multi-organ failure and mortality in 54 sepsis patients in intensive care unit (ICU) and showed a strong association. Lichtenauer et al. (15) evaluated 348 patients with sepsis and reported similar results. These earlier studies were

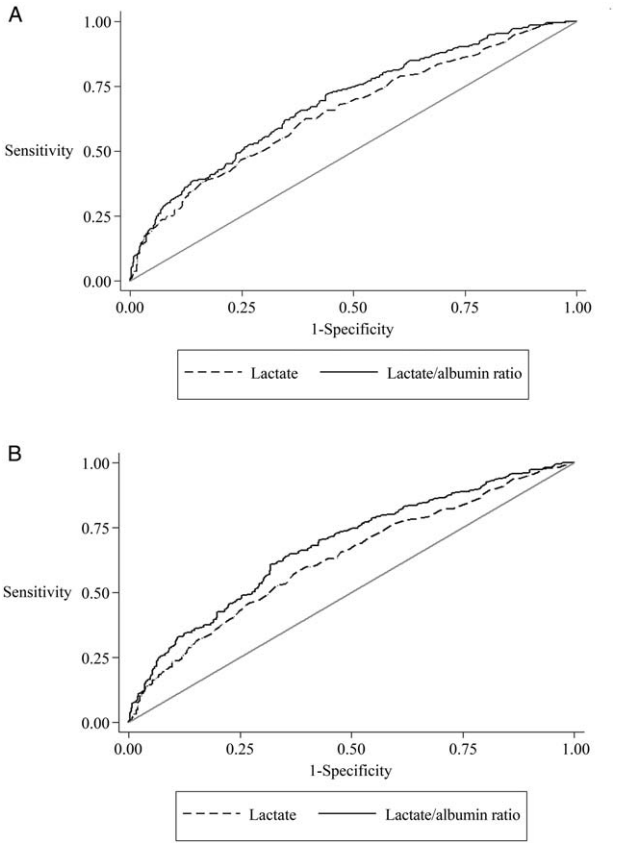


Fig. 2. **Receiver operating characteristic (ROC) curves of mortality.** A, ROC curves of 28-day mortality. The area under the operating characteristic (AUROC) for lactate is 0.65 (95% CI 0.61–0.70, $P < 0.01$) and that for lactate/albumin ratio is 0.69 (95% CI 0.64–0.73, $P < 0.01$). B, ROC curves of 90-day mortality. The AUROC for lactate is 0.63 (95% CI 0.59–67, $P < 0.01$) and that for lactate/albumin ratio is 0.68 (95% CI 0.64–72, $P < 0.01$).

Table 3. **28-day mortality, sepsis-3 definition, and multi-organ failure according to lactate level, lactate/albumin (L/A) ratio, and albumin level**

| | 28-day mortality | *P* | Sepsis-3 definition | *P* | Multi-organ failure | *P* |
|---|---|---|---|---|---|---|
| Lactate and L/A ratio | | | | | | |
| Normal lactate level (<2.0) | | | | | | |
| L/A ratio <cut-off point (0.48) (n = 157) | 12 (7.6) | <0.01 | 7 (4.5) | <0.01 | 93 (59.2) | 0.42 |
| L/A ratio ≥ cut-off point (0.48) (n = 106) | 23 (21.7) | | 16 (15.1) | | 68 (64.2) | |
| Intermediate lactate level (2.0 ≤ × <4.0) | | | | | | |
| L/A ratio <cut-off point (1.16) (n = 190) | 24 (12.6) | <0.01 | 95 (50.0) | 0.23 | 140 (73.7) | <0.01 |
| L/A ratio ≥ cut-off point (1.16) (n = 83) | 24 (28.9) | | 48 (57.8) | | 73 (88.0) | |
| High lactate level (≥4.0) | | | | | | |
| L/A ratio <cut-off point (2.35) (n = 244) | 53 (21.7) | <0.01 | 150 (61.5) | 0.54 | 181 (74.2) | <0.01 |
| L/A ratio ≥ cut-off point (2.35) (n = 166) | 77 (46.4) | | 107 (64.5) | | 145 (87.4) | |
| Lactate and albumin level | | | | | | |
| Normal lactate level (<2.0) | | | | | | |
| Albumin <3.0 (n = 119) | 26 (21.9) | <0.01 | 11 (9.2) | 0.80 | 83 (69.8) | 0.01 |
| Albumin ≥3.0 (n = 144) | 9 (6.3) | | 12 (8.3) | | 78 (54.2) | |
| Intermediate lactate level (2.0 ≤ × <4.0) | | | | | | |
| Albumin <3.0 (n = 142) | 36 (25.4) | <0.01 | 74 (52.1) | 0.93 | 119 (83.8) | 0.02 |
| Albumin ≥3.0 (n = 131) | 12 (9.2) | | 69 (52.7) | | 94 (71.8) | |
| High lactate level (≥4.0) | | | | | | |
| Albumin <3.0 (n = 217) | 87 (40.1) | <0.01 | 144 (66.4) | 0.10 | 188 (86.6) | <0.01 |
| Albumin ≥3.0 (n = 193) | 43 (22.3) | | 113 (58.6) | | 138 (71.5) | |

Lactate values are given in mmol/L and albumin values are given in g/dL.

ingle-center studies and targeted only ICU care patients. To the best of our knowledge, our study is the first to use data from a multi-center registry of 10 EDs for evaluating the L/A ratio and 28-day mortality with more detailed subgroup analysis.

The L/A ratio has potential benefits for prognostication of sepsis patients considering the results from our study and previous studies. First, the two markers independently predict mortality, and the values inversely change by different mechanisms. Thus, a comprehensive combination of both parameters might increase the predictive value. Second, normal or intermediate levels of lactate might be misinterpreted as a good prognosis. The L/A ratio might be used for additional identification of high-risk patients. In addition, our study suggests that a simple approach might provide further prognostic information using hypoalbuminemia and categories of lactate level. Third, the lactate/albumin ratio can increase the predictive value in patients with hepatic and renal dysfunction showing hyperlactatemia due to lactate elimination impairment.

There are some limitations in this study. First, the KoSS registry used in this study prospectively enrolled patients with septic shock to investigate clinical characteristics and improve the quality of ED management. The primary objective did not involve the L/A ratio. Second, we could not analyze data from patients excluded due to missing lactate or albumin values or lack of informed consent. Although this is one of the potential limitations of our study, we think that the characteristic of multi-institutional study with a relatively large number of patients might reduce the drawback. Third, because this study was a multicenter study, enrollment periods and case volumes were different for each hospital. Although sepsis management generally depends on the Surviving Sepsis Campaign guidelines, institutional characteristics might be different and were not adjusted in this study. Fourth, the L/A ratio showed moderate performance for predicting 28-day mortality in terms of AUROC. Based on our findings, the L/A ratio can be used for comprehensive interpretation of a single lactate value because lactate measurement is a simple, widely used method for screening patients at high-risk. Further research for prospective validation and risk stratification using the lactate/albumin ratio is needed. Finally, we focused on early septic shock patients in the ED and not the ICU, which might have led to selection bias.

## CONCLUSIONS

The prognostic performance of the L/A ratio was better than a single lactate measurement for predicting 28-day mortality in critically ill septic patients. This ratio was a useful prognostic factor regardless of initial lactate level and the presence of hepatic or renal dysfunction.

Table 4. **Multivariable logistic regression**

| Variables | Odds ratio | 95% CI | *P* |
|---|---|---|---|
| Age | 1.02 | 1.00–1.03 | 0.03 |
| Sex | 0.92 | 0.64–1.32 | 0.66 |
| Lactate/albumin ratio | 1.51 | 1.33–1.72 | <0.01 |
| Chronic lung disease | 1.74 | 0.98–3.10 | 0.06 |
| Chronic renal disease | 1.40 | 0.79–2.47 | 0.26 |
| Infection focus | | | |
| Intra-abdominal infection | | Reference | |
| Respiratory infection | 2.28 | 1.46–3.56 | <0.01 |
| Urinary tract infection | 0.66 | 0.35–1.22 | 0.18 |
| Other or unknown | 1.40 | 0.88–2.23 | 0.16 |
| Maximum SOFA score in 24 h | 1.11 | 1.04–1.17 | <0.01 |
| APACH II score | 1.02 | 1.00–1.05 | 0.07 |

APACHE indicates acute physiology and chronic health evaluation; SOFA, sepsis-related organ failure assessment.

## ACKNOWLEDGMENTS

The authors thank Sunyoung Kim, clinical research coordinators, for their assistance with data collection.

## REFERENCES

1. Vincent JL, De Backer D: Circulatory shock. *N Engl J Med* 369:1726–1734, 2013.
2. Vincent JL, Pereira AJ, Gleeson J, Backer D: Early management of sepsis. *Clin Exp Emerg Med* 1:3–7, 2014.
3. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K, International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 193: 259–272, 2016.
4. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, Vincent JL, Townsend S, Lemeshow S, Dellinger RP: Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. *Lancet Infect Dis* 12:919–924, 2012.
5. Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW: Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med* 31:670–675, 2003.
6. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, et al.: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 45:486–552, 2017.
7. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, Reinhart K, Selvakumar N, Levy MM: Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. *Crit Care Med* 43:567–573, 2015.
8. Shin TG, Jo IJ, Hwang SY, Jeon K, Suh GY, Choe E, Lee YK, Lee TR, Cha WC, Sim MS: Comprehensive interpretation of central venous oxygen saturation and blood lactate levels during resuscitation of patients with severe sepsis and septic shock in the emergency department. *Shock* 45: 4–9, 2016.
9. Park J, Hwang SY, Jo IJ, Jeon K, Suh GY, Lee TR, Yoon H, Cha WC, Sim MS, Carriere KC, et al.: Impact of metformin use on lactate kinetics in patients with severe sepsis and septic shock. *Shock* 47:582–587, 2017.
10. Sterling SA, Puskarich MA, Jones AE: The effect of liver disease on lactate normalization in severe sepsis and septic shock: a cohort study. *Clin Exp Emerg Med* 2:197–202, 2015.
11. Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, Kluge S: Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. *Intensive Care Med* 42:202–210, 2016.
12. Yin M, Si L, Qin W, Li C, Zhang J, Yang H, Han H, Zhang F, Ding S, Zhou M, et al.: Predictive value of serum albumin level for the prognosis of severe sepsis without exogenous human albumin administration. *J Intensive Care Med*; 2016 [Epub ahead of print].
13. Caironi P, Langer T, Gattinoni L: Albumin in critically ill patients: the ideal colloid? *Curr Opin Crit Care* 21:302–308, 2015.
14. Wang B, Chen G, Cao Y, Xue J, Li J, Wu Y: Correlation of lactate/albumin ratio level to organ failure and mortality in severe sepsis and septic shock. *J Crit Care* 30:271–275, 2015.
15. Lichtenauer M, Wernly B, Ohnewein B, Franz M, Kabisch B, Muessig J, Masyuk M, Lauten A, Schulze PC, Hoppe UC, et al.: A valuable tool for risk stratification in septic patients admitted to ICU. *Int J Mol Sci* 18:pii: E1893, 2017.
16. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R: Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 372:1629–1638, 2015.
17. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, et al.: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 372:1301–1311, 2015.
18. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, et al.: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 370:1683–1693, 2014.
19. Arise Investigators, Anzics Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, et al.: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 371:1496–1506, 2014.
20. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al.: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 41:580–637, 2013.
21. Shin TG, Hwang SY, Kang GH, Kim WY, Ryoo SM, Kim K, Jo YH, Chung SP, Joo YS, Beom JH, et al.: Korean Shock Society septic shock registry: a preliminary report. *Clin Exp Emerg Med* 4:146–153, 2017.
22. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG, The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22:707–710, 1996.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. *Crit Care Med* 13:818–829, 1985.
24. DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44:837–845, 1988.
25. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al.: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 315:801–810, 2016.
26. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, Weiss JW: Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 45:524–528, 2005.
27. Suetrong B, Walley KR: Lactic acidosis in sepsis: it's not all anaerobic: implications for diagnosis and management. *Chest* 149:252–261, 2016.
28. Curtis SE, Cain SM: Regional and systemic oxygen delivery/uptake relations and lactate flux in hyperdynamic, endotoxin-treated dogs. *Am Rev Respir Dis* 145:348–354, 1992.
29. Artero A, Zaragoza R, Camarena JJ, Sancho S, Gonzalez R, Nogueira JM: Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. *J Crit Care* 25: 276–281, 2010.
30. Goldwasser P, Feldman J: Association of serum albumin and mortality risk. *J Clin Epidemiol* 50:693–703, 1997.
31. Franch-Arcas G: The meaning of hypoalbuminaemia in clinical practice. *Clin Nutr* 20:265–269, 2001.