Clinical and Experimental Emergency Medicine

Clin Exp Emerg Med 2020;7(3):161-169
https://doi.org/10.15441/ceem.19.075

Original Article

eISSN: 2383-4625

Usefulness of ischemia-modified albumin in the diagnosis of sepsis/septic shock in the emergency department

Seung Hwa Choo[1], Yong Su Lim[1,2], Jin Seong Cho[1,2], Jae Ho Jang[1,2], Jea Yeon Choi[1,2], Woo Sung Choi[1], Hyuk Jun Yang[1,2]

[1]Department of Emergency Medicine, Gachon University Gil Medical Center, Incheon, Korea
[2]Department of Emergency Medicine, Gachon University College of Medicine, Incheon, Korea

Objective No studies have evaluated the diagnostic value of ischemia-modified albumin (IMA) for the early detection of sepsis/septic shock in patients presenting to the emergency department (ED). We aimed to assess the usefulness of IMA in diagnosing sepsis/septic shock in the ED.

Methods This retrospective, observational study analyzed IMA, lactate, high sensitivity C-reactive protein, and procalcitonin levels measured within 1 hour of ED arrival. Patients with suspected infection meeting at least two systemic inflammatory response syndrome criteria were included and classified into the infection, sepsis, and septic shock groups using Sepsis-3 definitions. Areas under the receiver operating characteristic curves (AUCs) with 95% confidence intervals (CIs) and multivariate logistic regression were used to determine diagnostic performance.

Results This study included 300 adult patients. The AUC (95% CI) of IMA levels (cut-off ≥ 85.5 U/mL vs. ≥ 87.5 U/mL) was higher for the diagnosis of sepsis than for that of septic shock (0.729 [0.667–0.791] vs. 0.681 [0.613–0.824]) and was higher than the AUC of procalcitonin levels (cut-off ≥ 1.58 ng/mL, 0.678 [0.613–0.742]) for the diagnosis of sepsis. When IMA and lactate levels were combined, the AUCs were 0.815 (0.762–0.867) and 0.806 (0.754–0.858) for the diagnosis of sepsis and septic shock, respectively. IMA levels independently predicted sepsis (odds ratio, 1.05; 95% CI, 1.00–1.09; P = 0.029) and septic shock (odds ratio, 1.07; 95% CI, 1.02–1.11; P = 0.002).

Conclusion Our findings indicate that IMA levels are a useful biomarker for diagnosing sepsis/septic shock early, and their combination with lactate levels can enhance the predictive power for early diagnosis of sepsis/septic shock in the ED.

Keywords Sepsis; Shock, septic; Ischemia-modified albumin; Biomarkers

Capsule Summary

What is already known

The utility of ischemia-modified albumin was first recognized for the early diagnosis of acute myocardial infarction. Its diagnostic effectiveness for various diseases, including stroke, pulmonary embolism, ischemic vessel disease, sepsis, and septic shock, has also been reported.

What is new in the current study

This study showed the usefulness of ischemia-modified albumin in early diagnosis of sepsis/septic shock in the emergency department based on Sepsis-3 definitions.

Received: 2 September 2019
Revised: 16 October 2019
Accepted: 28 October 2019

Correspondence to: Hyuk Jun Yang
Department of Emergency Medicine, Gachon University Gil Medical Center, 21 Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Korea
E-mail: yanghj@gachon.ac.kr
ORCID
https://orcid.org/0000-0001-8324-9749

How to cite this article:
Choo SH, Lim YS, Cho JS, Jang JH, Choi JY, Choi WS, Yang HJ. Usefulness of ischemia-modified albumin in the diagnosis of sepsis/septic shock in the emergency department. Clin Exp Emerg Med 2020;7(3):161-169. https://doi.org/10.15441/ceem.19.075

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/).

Copyright © 2020 The Korean Society of Emergency Medicine

INTRODUCTION

Since the publication of the first edition of the *International guidelines for management of sepsis and septic shock* in 2004, many researchers have sought to promote the early diagnosis and appropriate treatment of sepsis and septic shock.[1-4] However, the mortality due to sepsis in patients remains between 20% and 30% worldwide.[5] The major causes of death in patients with sepsis are reduced intravascular volume, peripheral vasodilation, reduced myocardial function, and blood flow disturbances due to increased metabolism, which in turn results in an imbalance of oxygen distribution in the body; ultimately, this causes multiple organ dysfunction resulting from tissue hypoperfusion.[6]

Therefore, aggressive fluid therapy and the appropriate use of antibiotics in the early stage of sepsis are the focus of sepsis and septic shock treatment, and the early detection and diagnosis of sepsis are the basis for undertaking systematic clinical measures.[4,7,8] Given that most patients with severe sepsis in the intensive care unit are triaged at the emergency department (ED), and only 53% of patients with sepsis are diagnosed in the ED, identifying a diagnostic tool that enables early diagnosis of sepsis in the ED is crucial.[9,10] There is currently no established biomarker for the early diagnosis of sepsis and septic shock; however, several biomarkers have been investigated as candidates.[11-14] Procalcitonin (PCT) is the most reliable independent biomarker for diagnosing sepsis. PCT and lactate are currently reported to be the most useful biomarkers for diagnosing severe sepsis and septic shock.[14-16]

Ischemia-modified albumin (IMA) is albumin with structural modification at the N-terminal cobalt binding site due to free radicals released from ischemic tissues.[17] The usefulness of IMA was first reported in the early diagnosis of acute myocardial infarction,[18-20] and its diagnostic effectiveness for various other ischemic diseases including stroke, pulmonary embolism, and ischemic vessel disease has also been reported.[21-24] It has been reported that IMA levels rise during sepsis and severe septic shock.[25-27] Khashana et al.[28] and Yerlikaya et al.[29] reported the usefulness of IMA in the early diagnosis of neonatal sepsis. However, there have been no reports on the diagnostic value of IMA for the early detection of sepsis and septic shock in patients presenting to the ED. This study aimed to investigate the usefulness of IMA in diagnosing sepsis and septic shock in ED patients according to the Sepsis-3 definitions[30] by comparing the diagnostic performances of PCT, lactate, high sensitivity C-reactive protein (hsCRP), and IMA levels in these cases.

METHODS

Study design

This retrospective, observational study included a consecutive patient cohort that had been admitted to the ED of a tertiary teaching hospital located in an urban area in Incheon, Korea. The Institutional Review Board of Gachon University Gil Medical Center approved this study (GCIRB2019-283). Due to the retrospective study design, the requirement for informed consent was waived.

Participant selection and data collection

Adult patients (aged ≥ 18 years old) who had visited the ED between July 1, 2018 and December 31, 2018 and showed at least two of the systemic inflammatory response syndrome criteria (fever > 38.0°C or hypothermia < 36°C; tachycardia > 90 beats per minute; tachypnea > 20 breaths per minute; and leukocytosis with white blood cell count > 12,000/μL or leukopenia with white blood cell count < 4,000/μL) were considered to have a potential infection. Patients who had undergone laboratory tests for IMA, PCT, lactate, and hsCRP levels in the ED within 1 hour of admission were included in this study. We retrospectively reviewed the electronic medical records of these patients. Patients with non-infectious conditions, such as trauma, thermal injury, sterile inflammation, pancreatitis, heart failure, drug and gas intoxication, gastrointestinal bleeding, seizure, cardiac arrhythmia, and shock due to non-infectious causes were excluded based on clinical and laboratory information. Patients who had been diagnosed with a disease known to elevate IMA levels,[18-24] such as acute coronary syndrome, stroke, pulmonary embolism, peripheral vascular disease, and cardiac arrest, were also excluded, as were those who had undergone chemotherapy and those who required surgical intervention.

The following clinical and laboratory data were collected: age, sex, mean arterial pressure, length of hospital stay, 28-day hospital mortality, volumes of crystalloid infusion during ED stay, vasopressor use, and level of IMA, hsCRP, PCT, and lactate. The sequential organ failure assessment (SOFA) score and quick sepsis-related organ failure assessment (qSOFA) were calculated using the poorest physiologic results observed. Data of laboratory parameters measured within 1 hour of ED admission were collected.

Infection sources and microorganisms isolated from blood cultures

The source of infection was divided into six categories: respiratory infection (including pneumonia), urogenital infection, hepatobiliary infection, gastrointestinal infection, and other infections. When multiple infections were present, they were combined for calcu-

lations. For the identification of microbial pathogens, sampling and transportation of blood cultures were performed according to standard procedures.

Definition of sepsis and septic shock based on the Sepsis-3 guidelines

The Sepsis-3 guidelines redefined sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection. Organ dysfunction can be identified as an acute change of ≥ 2 points in the total SOFA score subsequent to infection. Septic shock is defined as a state in which vasopressors are required to maintain the mean arterial pressure at ≥ 65 mmHg and serum lactate levels at > 2 mmol/L (> 18 mg/dL), despite the use of adequate fluid resuscitation.[4]

Definition and application of the qSOFA

The qSOFA has three items: altered mentation, systolic blood pressure (≤ 100 mmHg), and a respiratory rate ≥ 22 bpm. A qSOFA score ≥ 2 has been reported to be a meaningful predictor of sepsis and poor outcomes.[4,30,31]

Albumin cobalt binding test

IMA levels were measured using the albumin cobalt binding test (Medical System Biotechnology, Ningbo, China) on an ADVIA Chemistry XPT analyzer (Siemens Healthineers, Erlangen, Germany) according to the manufacturer's specifications; this test has been previously validated.[18]

Statistical analysis

Categorical variables were presented as the number of patients (%), and continuous variables were presented as the mean ± standard deviation or median (interquartile range). For intergroup comparisons, categorical variables were analyzed using Chi-square tests and continuous variables were analyzed using independent t-tests or the Mann-Whitney U-test and Kruskal-Wallis test. All data were verified for normality using the Kolmogorov-Smirnov test.

To compare the diagnostic power for sepsis and septic shock based on the Sepsis-3 definitions and to determine the cut-off values, area under receiver operating characteristic (ROC) curve (AUC) analysis (with 95% confidence intervals [CIs]) was performed for PCT, lactate, hsCRP, and IMA levels, and for the qSOFA score. To determine the optimal cut-off value with maximum sensitivity and specificity, the Youden index (sensitivity+[specificity-1]) was calculated.

A multivariate logistic regression model with backward stepwise elimination was applied to identify independent predictors of sepsis and septic shock. Significant variables with P-values ≤ 0.10 in the univariate analysis were eligible for assessment in the multivariate logistic regression model. The variance inflation factor (VIF) was used as an indicator of autocorrelation or collinearity of independent variables included in the model. When the value of the VIF is > 10, multicollinearity is considered to be high. Odds ratios (ORs) and their 95% CIs for variables selected using the logistic model were also calculated.

Statistical analysis was performed using IBM SPSS Statistics ver. 23.0 (IBM Corp., Armonk, NY, USA) software, and P-values < 0.05 were considered statistically significant.

RESULTS

Clinical characteristics of the study population

In total, 557 patients were originally included in this study. Of these, 46 patients diagnosed with non-infectious disease, 207 patients diagnosed with a disease that could elevate IMA levels, and four patients with incomplete data were excluded. Finally, 300 patients were enrolled (Fig. 1). Of these, 148 (50.7%) patients were male; the median age was 75 (range, 66–81) years old; and 82, 134, and 84 patients had infection, sepsis, and septic shock, respectively. There were no significant sex distribution dif-

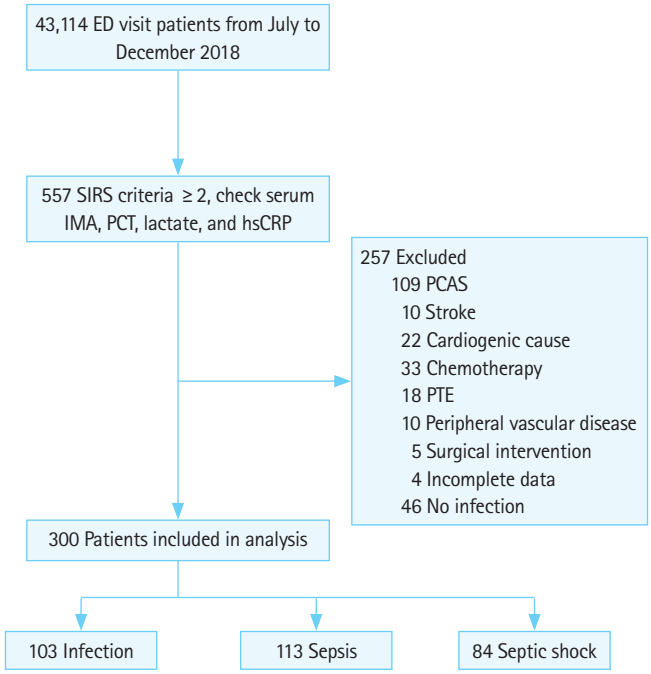

Fig. 1. Flow chart of patient selection based on inclusion and exclusion criteria. ED, emergency department; SIRS, systemic inflammatory response syndrome; IMA, ischemia-modified albumin; PCT, procalcitonin; hsCRP, high sensitivity C-reactive protein; PCAS, post cardiac arrest syndrome; PTE, pulmonary thromboembolism.

ferences among the three groups (P = 0.257). Patients with septic shock were the oldest (P < 0.001). All patients with septic shock met the sepsis criteria according to the Sepsis-3 definitions. Moreover, the patients with septic shock had the highest levels of hsCRP, lactate, PCT, and IMA (P < 0.001), and the highest SOFA and qSOFA scores (P < 0.001). The length of hospital stay was significantly longer for patients with septic shock (13 days; range, 7–25.5) than for patients with infection or sepsis (0 days; range, 0–0 days and 10 days; range, 5–16 days, P < 0.001), respectively (Table 1).

Classification according to the source of infection and microbial identification

Table 2 shows the classification according to the source and frequency of infection. Respiratory infections, including pneumonia, were the most common source of infection (n = 118, 39.3%), followed by urogenital infections (n = 87, 29.0%), hepatobiliary infection (n = 27, 9.0%), and infections of unknown cause or infections not classified into any of the above categories (n = 56, 18.7%). Of the 300 patients, 104 (34.7%) were found to have positive blood culture results; 66 (22%) of these patients had gram-negative bacillus infections, 32 (10.67%) had gram-positive coccus infections, 2 (0.67%) had polymicrobial infections, and 3 (1%) had fungal infections (*Candida albicans*). *Escherichia coli* was the most common pathogen (42 patients, 14%), followed by *Klebsiella pneumoniae*, which was identified in 14 (4.67%) patients (Supplementary Table 1).

Predictability of sepsis for each biomarker

Of the 300 patients, 218 (72.7%) had sepsis, while 82 (27.3%) had an infection according to the Sepsis-3 definitions. The ROC curve for sepsis prediction is shown in Fig. 2. IMA levels had the highest AUC values at 0.729 (95% CI, 0.667–0.791; cut-off ≥ 85.5 U/mL). Sensitivity and specificity were 58.7% and 79.3%, respectively. The AUC values for lactate, PCT, and hsCRP levels were 0.722 (95% CI, 0.663–0.782; cut-off ≥ 2.35 mmol/L), 0.678 (95% CI, 0.613–0.742; cut-off ≥ 1.58 ng/mL), and 0.667 (95% CI, 0.601–0.733), respectively.

Predictability of septic shock for each biomarker

According to the Sepsis-3 definitions, 84 of 300 (28.0%) patients were diagnosed with septic shock, and 216 (72.0%) patients were diagnosed with other infections. The ROC curve for septic shock prediction is shown in Fig. 2. Lactate levels had the highest AUC value at 0.751 (95% CI, 0.686–0.814) and cut-off value of > 2.35 mmol/L. Sensitivity and specificity were 66.7% and 75.0%, respec-

Table 2. Cumulative frequency in each infection category

Origin of infection	Number (%)
Respiratory	118 (39.3)
Genitourinary	87 (29.0)
Hepatobiliary	27 (9.0)
Gastrointestinal	10 (3.3)
Surgical	2 (0.7)
Other	56 (18.7)
Total	300 (100)

Table 1. General characteristics of the study patients

	Total (n = 300)	Infection (n = 82)	Sepsis (n = 134)	Septic shock (n = 84)	P-value[a]
Sex, female	152 (50.7)	48 (58.5)	63 (47.0)	41 (48.8)	0.257
Age (yr)	75 (66–81)	73 (66–81)	74 (66–80)	76 (67–83)	< 0.001[b]
BT (°C)	38.0 (36.8–38.6)	38.2 (37.7–38.6)	37.6 (36.7–38.5)	37.5 (36.4–38.8)	0.003[b]
RR (breaths/min)	20 (20–24)	20 (20–22)	20 (20–24)	20 (20–28)	< 0.001[c]
WBC (× 10^3/mm^3)	11.81 (7.13–17.47)	11.37 (7.11–14.95)	11.60 (7.48–16.23)	13.19 (6.48–21.94)	0.379
PLT (× 10^3/mm^3)	190 (137–244)	201 (159–247)	187 (137–257)	170 (113–225)	0.049[d]
hsCRP (mg/dL)	12.40 (2.84–20.81)	5.73 (1.46–13.31)	13.79 (2.90–21.94)	14.79 (6.11–23.40)	< 0.001[b]
Lactate (mmol/L)	1.9 (1.1–3.3)	1.2 (0.8–2.0)	1.90 (1.1–3.0)	3.05 (1.9–6.0)	< 0.001[b]
PCT (ng/mL)	0.73 (0.17–6.81)	0.34 (0.09–1.04)	0.63 (0.16–5.51)	4.69 (0.51–28.94)	< 0.001[b]
IMA (U/mL)	85.0 (81.0–90.0)	82.0 (79.0–85.0)	86.0 (81.0–89.0)	89.0 (84.0–92.8)	< 0.001[b]
SOFA score	3 (1–5)	1 (1–1)	3 (2–4)	7 (5–9)	< 0.001[b]
qSOFA	1 (0–2)	0 (0–1)	1 (0–2)	2 (1–3)	< 0.001[b]
LOS in hospital (day)	10 (3–17)	0 (0–0)	10 (5–16)	13 (7–26)	< 0.001[b]

Values are presented as number (%) or median (25th to 75th percentile).
BT, body temperature; RR, respiratory rate; WBC, white blood cell; PLT, platelet; hsCRP, high sensitivity C-reactive protein; PCT, procalcitonin; IMA, ischemia-modified albumin; SOFA, sequential organ failure assessment; qSOFA, quick sepsis-related organ failure assessment; LOS in hospital, length of stay in hospital.
[a]Compared using the Kruskal-Wallis test. [b]Results of the Mann-Whitney U-test, used in post hoc analysis for subgroup comparisons, were significant for all variables. [c]Results of the Mann-Whitney U-test, used in post hoc analysis, showed statistically significant differences between infection and septic shock. [d]Results of the Mann-Whiney U-test, used in post hoc analysis, showed statistically significant differences between infection and sepsis, and between infection and septic shock.

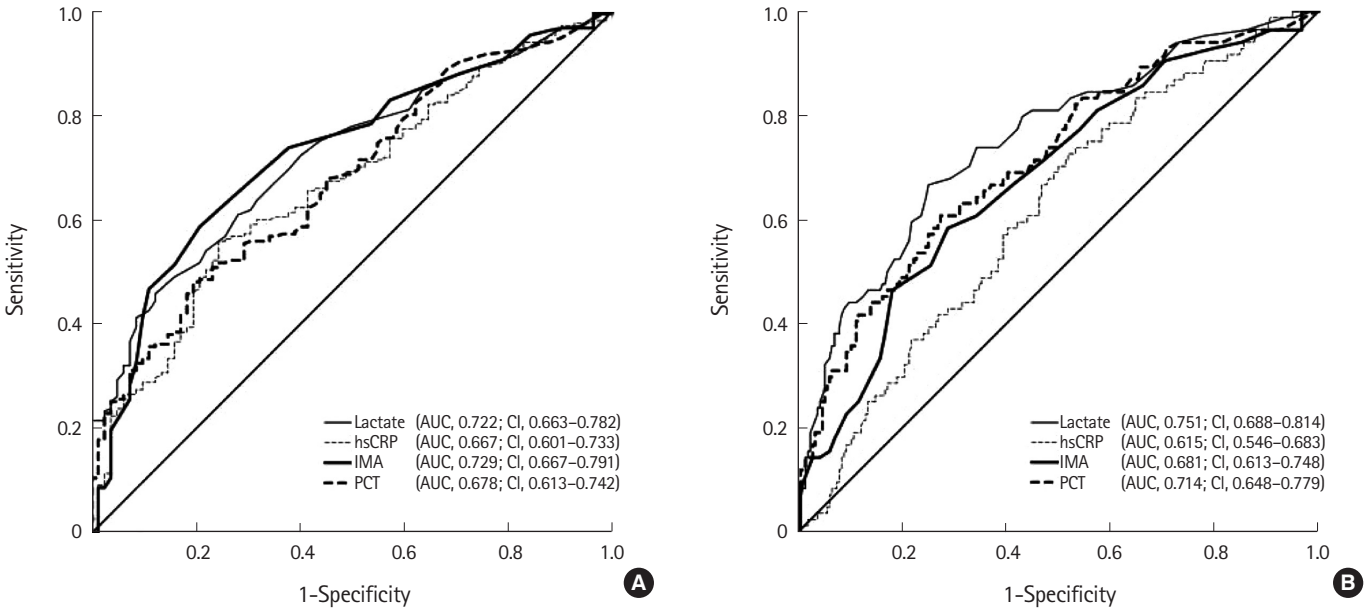

Fig. 2. Comparison of the receiver operating characteristic curves of ischemia-modified albumin (IMA), procalcitonin (PCT), lactate, and high sensitivity C-reactive protein (hsCRP) levels for the prediction of (A) sepsis and (B) septic shock. AUC, area under receiver operating characteristic curve; CI, confidence interval.

Table 3. Independent factors predicting sepsis and septic shock in patients with infection determined using multivariate logistic regression analysis

Variable		Sepsis		Septic shock	
		Adjusted odds ratio[a]	95% CI	Adjusted odds ratio[b]	95% CI
Mental status	Alert	Reference		Reference	
	Verbal response	0.89	1.40–10.84	2.19	0.95–5.06
	Painful response	12.48	2.67–58.30	2.46	1.15–5.29
	Unresponsiveness	Omitted		Omitted	
Mean arterial pressure (mm/Hg)		0.98	0.97–0.99	0.97	0.96–0.99
hsCRP (mg/dL)		1.05	1.02–1.10	-	-
Lactate (mmol/L)		1.85	1.36–2.50	1.31	1.14–1.56
IMA (U/mL)		1.05	1.00–1.09	1.07	1.02–1.11
Procalcitonin (ng/mL)		1.05	0.99–1.10	1.01	1.00–1.03

CI, confidence interval; hsCRP, high sensitivity C-reactive protein; IMA, ischemia-modified albumin.
[a]Age, body temperature, respiratory rate, pulse rate, white blood cell count, and platelet counts were removed using backward elimination in this analysis. [b]Age, body temperature, respiratory rate, pulse rate, white blood cell count, platelet count, and hsCRP levels were removed using backward elimination in this analysis.

tively. The AUC value for PCT levels was 0.714 (95% CI, 0.648–0.779) with a cut-off value of >2.67 ng/mL. Sensitivity and specificity were 60.7% and 72.7%, respectively. The AUC for IMA levels was 0.681 (95% CI, 0.613–0.824) with a cut-off value of >87.5 U/mL. Sensitivity and specificity were 58.3% and 71.3%, respectively. The AUC for hsCRP levels was 0.615 (95% CI, 0.546–0.683).

Identification of independent predictors of sepsis and septic shock using multivariate logistic regression analysis

Using multivariate logistic regression analysis, lactate (OR, 1.85; 95% CI, 1.36–2.50; P<0.001), hsCRP (OR, 1.05; 95% CI, 1.02–1.10; P<0.004), IMA (OR, 1.05; 95% CI, 1.00–1.09; P<0.029), and PCT (OR, 1.05; 95% CI, 0.99–1.10; P<0.099) levels were found to be independent predictors of sepsis in patients with infection. Regarding septic shock, multivariate logistic regression analysis indicated that lactate (OR, 1.31; 95% CI, 1.13–1.53; P<0.001), IMA (OR, 1.07; 95% CI, 1.02–1.11; P<0.002), and PCT (OR, 1.01; 95% CI, 1.00–1.03; P<0.027) levels were independent predictors, but hsCRP levels were not (Table 3). There was no evidence of autocorrelation or collinearity among the variables as the VIF for each pair of variables was <10 (data not shown).

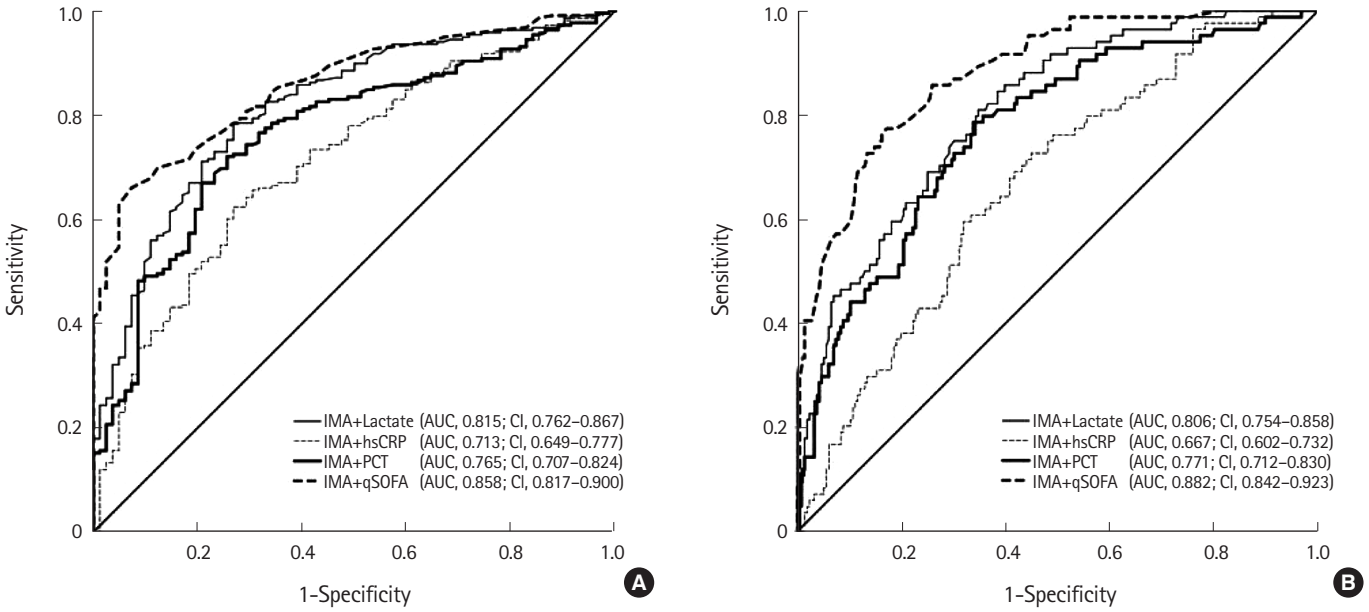

Fig. 3. Comparison of receiver operating characteristic curves of procalcitonin (PCT), lactate, and high sensitivity C-reactive protein (hsCRP) levels, and quick sepsis-related organ failure assessment (qSOFA) score combined with ischemia-modified albumin (IMA) levels for (A) sepsis and (B) septic shock prediction. AUC, area under receiver operating characteristic curve; CI, confidence interval.

Comparison of the predictive power of IMA levels combined with other biomarker tests and the qSOFA score for sepsis and septic shock

The diagnostic AUC for sepsis was the highest when IMA levels were combined with lactate levels (0.815 [95% CI, 0.762–0.867]; sensitivity, 78.4%; specificity, 73.2%). The AUC was 0.765 (95% CI, 0.707–0.824) when IMA levels were combined with PCT levels and 0.713 (95% CI, 0.546–0.683) when they were combined with hsCRP levels. When IMA levels were combined with the qSOFA score, the AUC was 0.858 (95% CI, 0.817–0.9; sensitivity, 66.1%; specificity, 92.7%).

The diagnostic AUC for septic shock was the highest when IMA levels were combined with lactate levels (0.806 [95% CI, 0.754–0.858]; sensitivity, 81.0%; specificity, 65.3%). The AUC was 0.771 (95% CI, 0.712–0.830) when IMA levels were combined with PCT levels and 0.667 (95% CI, 0.602–0.732) when they were combined with hsCRP levels. When IMA levels and the qSOFA were combined, the AUC was 0.882 (95% CI, 0.842–0.923; sensitivity, 77.4%; specificity, 82.9%). The details are shown in Fig. 3.

Value of the qSOFA for predicting sepsis and septic shock

For qSOFA scores ≥2, the AUC for the diagnosis of sepsis was 0.820 (95% CI, 0.772–0.867). Sensitivity and specificity were 44.5% and 99.8%, respectively. The AUC for the diagnosis of septic shock was 0.870 (95% CI, 0.828–0.912). Sensitivity and specificity were 75.0% and 83.8%, respectively.

DISCUSSION

Early diagnosis of sepsis in patients with infection in the ED is essential to start targeted therapy as quickly as possible. Although the Sepsis-3 definitions, revised according to the SOFA scoring system, provides guidelines to detect and diagnose sepsis, calculating the SOFA score is time-consuming, as multiple laboratory tests and data are needed. Such assessments are nearly impossible to perform in a crowded environment such as the ED, where many patients require urgent care. Hence, various biomarkers that require less time for assessment and diagnosis are utilized for early diagnosis, differential diagnosis, risk stratification, treatment monitoring, and prognostic evaluation. PCT, lactate, and hsCRP levels are several standard biomarkers used for this purpose.

Organ failure in sepsis and septic shock has been reported to result from ischemia-induced hypoxic damage and free radical-induced tissue damage.[32,33] The same mechanism has been reported to elevate IMA levels.[30] Ultimately, we inferred that IMA levels would be elevated in patients with sepsis or septic shock.

To our knowledge, this study is the first to demonstrate the usefulness of serum IMA levels as a predictor of sepsis and septic shock in patients with infection presenting to the ED. First, we investigated whether IMA levels could distinguish patients with sepsis from those without sepsis. At a cut-off of 85.5 U/mL, IMA levels were a significant predictor of sepsis (sensitivity, 58.7%; specificity, 79.3%; $P<0.001$). Moreover, IMA levels had the high-

est AUC (0.729) among all the biomarkers; this value was comparable to that of lactate levels (0.722) and higher than that of PCT (0.678) levels. Using logistic regression analysis, lactate, hsCRP, and IMA levels were found to be independent predictors of sepsis.

Second, we determined the usefulness of IMA in differentiating septic shock from other infections. At a cut-off of 87.5 U/mL, IMA levels differentiated patients with septic shock from those without septic shock (sensitivity, 58.3%; specificity, 71.3%). The AUC of IMA levels was 0.681, the third highest after that of lactate (0.751) and PCT (0.714) levels. As reported in a previous study, IMA, PCT, and lactate levels are meaningful markers for the monitoring and diagnosis of sepsis and sepsis-induced organ dysfunction, oxidative stress, and lactic acidosis in patients who are critically ill.[27] Using logistic regression analysis, we identified that lactate, IMA, and PCT levels were independent predictors of septic shock in patients with infection, but hsCRP levels were not.

As sepsis progresses to septic shock, tissue hypoperfusion occurs, leading to worsening of lactic acidosis. As a result, the diagnostic value of lactate seems to rise in patients with severe sepsis and septic shock, consistent with previous reports showing that a high lactate concentration reflects critical tissue hypoxia and severity.[14,34,35]

The AUC of IMA levels for septic shock was significant at 0.681; however, it was lower than that for sepsis. This finding was in contrast to our expectation that the predictive power of IMA would be enhanced as sepsis progresses to septic shock, as was the case for lactate. This may be because the elevation of lactate levels could have led to a lower IMA value, as reported in a previous study[36]; however, further studies are needed to clarify whether this is an issue with the measurement method or a result of the characteristics of IMA. Moreover, when a test was conducted by combining IMA and lactate levels for the diagnosis of sepsis and septic shock, the AUCs were 0.815 and 0.805, respectively (sensitivity, 78.4 [81%]; specificity, 73.2 [65.3%]). These results demonstrated that the predictive power, sensitivity, and specificity of IMA and lactate levels combined were all higher than those for IMA or lactate alone. Based on these results, additional studies are needed to determine the cut-off values and the protocol for clinical application.

Third, we examined the usefulness of the qSOFA score alone and the qSOFA score combined with IMA levels in the differential diagnosis of sepsis and septic shock. Since the introduction of the Sepsis-3 definitions, the qSOFA score has been used as a prognostic predictor and sepsis screening tool.[4,31] In particular, the qSOFA is quick, simple, and does not require additional blood work, which adds to its usefulness in the ED. Studies on the diagnosis of sepsis, septic shock, and organ dysfunction outside the intensive care unit, particularly in the ED, have been performed.[37,38] Previous studies have reported that the qSOFA score had high diagnostic specificity (>90%) but low sensitivity (10%–30%).[37,39] Our findings were similar, in that a qSOFA score of ≥1 had diagnostic sensitivity and specificity of 44.5% and 99.8% for sepsis, respectively, while a qSOFA score ≥2 had a diagnostic sensitivity and specificity of 14.7% and 99.9%, respectively. With such a low sensitivity, the clinical use of the qSOFA as a diagnostic tool for sepsis has been limited. Efforts to enhance its predictive power by combining it with biomarkers such as lactate and PCT levels have met with some success.[40,41]

In this study, we combined IMA levels and the qSOFA score to predict sepsis and septic shock and observed that the combined predictive power (AUCs of 0.858 and 0.882, respectively) was higher than that of the qSOFA score (AUCs of 0.820 and 0.870, respectively) and IMA levels (AUCs of 0.729 and 0.681, respectively) alone. These results suggest that adding IMA to qSOFA as a diagnostic tool for sepsis and septic shock could compensate for the low sensitivity of qSOFA alone.

This study had several limitations. This single-center study had a limited study period and a relatively small population of 300 patients and may have had a regional selection bias. In general, patients admitted to the ED were tested and treated according to the Surviving Sepsis Campaign guidelines.[4] As each patient was attended to by different medical staff, treatment could not be performed according to completely standardized guidelines and within a consistent timeframe. Further, our data may have low reliability due to the retrospective nature of the study, and selection bias may have occurred during the inclusion and exclusion process.

When selecting the study population, patients who met at least two of the systemic inflammatory response syndrome criteria and those who had been tested for PCT, IMA, lactate, and hsCRP levels were considered. Due to internal guidelines and national insurance policies, tests for biomarkers (with the exception of hsCRP) were performed for patients with suspected sepsis and for those who showed unstable vital signs and appeared to be severely ill. Additionally, because of the nature of the wide regional emergency medical center, there were numerous severely ill and transferred patients; therefore, the study population may have been biased towards severely ill patients. This may have resulted in a higher prevalence of sepsis and septic shock among patients in our study population than among the general patient population who presents to an ED. Therefore, a prospective, multicenter study with a large study population from multiple regions is needed to address these shortcomings. Moreover, subsequent studies should examine the clinical value of IMA in risk stratification, treatment

monitoring, and prognostic evaluation for patients with sepsis and assess the efficient clinical application of this biomarker.

In conclusion, IMA levels alone had diagnostic value for sepsis and septic shock among patients in the ED, in accordance with the Sepsis-3 definitions. Further, their predictive power could be enhanced when combined with lactate levels or the qSOFA score. IMA levels can serve as an important biomarker for the early diagnosis of sepsis and septic shock.

CONFLICT OF INTEREST

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

SUPPLEMENTARY MATERIAL

Supplementary Table is available from: https://doi.org/10.15441/ceem.19.075.

REFERENCES

1. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73.
2. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34:17-60.
3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165-228.
4. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486-552.
5. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther 2012;10:701-6.
6. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s: systemic inflammatory response and organ dysfunction. JAMA 1994;271:226-33.
7. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
8. Puskarich MA, Marchick MR, Kline JA, Steuerwald MT, Jones AE. One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: a before and after study. Crit Care 2009;13:R167.
9. Chamberlain DJ, Willis E, Clark R, Brideson G. Identification of the severe sepsis patient at triage: a prospective analysis of the Australasian Triage Scale. Emerg Med J 2015;32:690-7.
10. Lippi G, Montagnana M, Balboni F, et al. Academy of Emergency Medicine and Care-Society of Clinical Biochemistry and Clinical Molecular Biology consensus recommendations for clinical use of sepsis biomarkers in the emergency department. Emerg Care J 2017;13:6877.
11. Schmidt de Oliveira-Netto AC, Morello LG, Dalla-Costa LM, et al. Procalcitonin, C-reactive protein, albumin, and blood cultures as early markers of sepsis diagnosis or predictors of outcome: a prospective analysis. Clin Pathol 2019;12:2632010X19847673.
12. Luzzani A, Polati E, Dorizzi R, Rungatscher A, Pavan R, Merlini A. Comparison of procalcitonin and C-reactive protein as markers of sepsis. Crit Care Med 2003;31:1737-41.
13. Ljungstrom L, Pernestig AK, Jacobsson G, Andersson R, Usener B, Tilevik D. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. PLoS One 2017;12:e0181704.
14. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 1996;171:221-6.
15. Miglietta F, Faneschi ML, Lobreglio G, et al. Procalcitonin, C-reactive protein and serum lactate dehydrogenase in the diagnosis of bacterial sepsis, SIRS and systemic candidiasis. Infez Med 2015;23:230-7.
16. Hausfater P, Juillien G, Madonna-Py B, Haroche J, Bernard M, Riou B. Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department. Crit Care 2007;11:R60.
17. Bar-Or D, Curtis G, Rao N, Bampos N, Lau E. Characterization of the Co(2+) and Ni(2+) binding amino-acid residues of the N-terminus of human albumin: an insight into the mechanism of a new assay for myocardial ischemia. Eur J Biochem 2001;268:42-7.
18. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000;19:311-5.
19. Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of "Ischemia modified albumin", a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes. Heart 2004;90:644.
20. Lin S, Yokoyama H, Rac VE, Brooks SC. Novel biomarkers in

diagnosing cardiac ischemia in the emergency department: a systematic review. Resuscitation 2012;83:684-91.
21. Abboud H, Labreuche J, Meseguer E, et al. Ischemia-modified albumin in acute stroke. Cerebrovasc Dis 2007;23:216-20.
22. Balta S, Alemdar R, Erdogan S, Demir M, Ozturk C, Celik T. Ischemia modified albumin in cardiovascular disease. Am J Emerg Med 2016;34:1699.
23. Montagnana M, Danese E, Lippi G. Biochemical markers of acute intestinal ischemia: possibilities and limitations. Ann Transl Med 2018;6:341.
24. Turedi S, Gunduz A, Mentese A, et al. The value of ischemia-modified albumin compared with d-dimer in the diagnosis of pulmonary embolism. Respir Res 2008;9:49.
25. Erdem SS, Yerlikaya FH, Cicekler H, Gul M. Association between ischemia-modified albumin, homocysteine, vitamin B(12) and folic acid in patients with severe sepsis. Clin Chem Lab Med 2012;50:1417-21.
26. Prashanth AK, Anand U. Clinical significance of ischemia modified albumin in critically ill patients with sepsis. Indian J Clin Biochem 2015;30:194-7.
27. Ashok Kumar P, Anand U. Multiple biomarkers to assess the pathophysiological state in critically ill patients with sepsis. Indian J Clin Biochem 2016;31:310-4.
28. Khashana A, Ayoub A, Younes S, Abdelrahman A. Ischemia modified albumin in early neonatal sepsis. Infect Dis (Lond) 2016;48:488-9.
29. Yerlikaya FH, Kurban S, Mehmetoglu I, et al. Serum ischemia-modified albumin levels at diagnosis and during treatment of late-onset neonatal sepsis. J Matern Fetal Neonatal Med 2014;27:1723-7.
30. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
31. Rodriguez RM, Greenwood JC, Nuckton TJ, et al. Comparison of qSOFA with current emergency department tools for screening of patients with sepsis for critical illness. Emerg Med J 2018;35:350-6.
32. Galley HF. Bench-to-bedside review: targeting antioxidants to mitochondria in sepsis. Crit Care 2010;14:230.
33. Weiss SL, Deutschman CS. Elevated malondialdehyde levels in sepsis: something to 'stress' about? Crit Care 2014;18:125.
34. Freund Y, Delerme S, Goulet H, Bernard M, Riou B, Hausfater P. Serum lactate and procalcitonin measurements in emergency room for the diagnosis and risk-stratification of patients with suspected infection. Biomarkers 2012;17:590-6.
35. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004;32:1637-42.
36. Zapico-Muniz E, Santalo-Bel M, Merce-Muntanola J, Montiel JA, Martinez-Rubio A, Ordonez-Llanos J. Ischemia-modified albumin during skeletal muscle ischemia. Clin Chem 2004;50:1063-5.
37. Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AF, Lipman J. Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction: insights from a prospective database of ED patients with infection. Chest 2017;151:586-96.
38. Singer AJ, Ng J, Thode HC Jr, Spiegel R, Weingart S. Quick SOFA scores predict mortality in adult emergency department patients with and without suspected infection. Ann Emerg Med 2017;69:475-9.
39. Dorsett M, Kroll M, Smith CS, Asaro P, Liang SY, Moy HP. qSOFA has poor sensitivity for prehospital identification of severe sepsis and septic shock. Prehosp Emerg Care 2017;21:489-97.
40. Shetty A, MacDonald SP, Williams JM, et al. Lactate ≥ 2 mmol/L plus qSOFA improves utility over qSOFA alone in emergency department patients presenting with suspected sepsis. Emerg Med Australas 2017;29:626-34.
41. Spoto S, Cella E, de Cesaris M, et al. Procalcitonin and MR-proadrenomedullin combination with SOFA and qSOFA scores for sepsis diagnosis and prognosis: a diagnostic algorithm. Shock 2018;50:44-52.