

Evaluation of Serum Ischemia-Modified Albumin And Oxidative Stress Markers in Patients with Sepsis

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Purpose: The most common causes of mortality and morbidity in patients followed up in intensive care are bacterial infections and sepsis. Rapid and timely intervention is essential for the successful treatment of sepsis. Therefore, this study aimed to reveal the relationships between mortality and patients by examining ischemia-modified albumin, APACHE II, CRP, PCT, lactate, WBC, NLR, PLR, SII, platelet, and lactate/IMA (LIMA) values in patients with sepsis followed up in intensive care units.

Material Method: The study was planned as prospective and single-center. 31 patients diagnosed with sepsis were included in the study. The first 24 hours and 5th day values of patients diagnosed with sepsis were examined and recorded. The biomarkers and APACHE-II score of patients diagnosed with sepsis were examined for predictive power of 28-day mortality.

Results: Thirty-one patients diagnosed with sepsis from the Anesthesia Intensive Care Unit were included in the study. Of the total patients, 21 (67.7%) were male and 10 (32.3%) were female. The APACHE-II score of patients diagnosed with sepsis in the first 24 hours (AUC:0.891, 95% CI: 77.6–100, $p < 0.0001$) was determined to be the best indicator for predicting 28-day mortality. In addition, neutrophil/lymphocyte ratio on day 5 (AUC:0.765, 95% CI:59.3–93.7, $p = 0.013$), Lactate/IMA on day 1 (AUC:0.628, 95% CI:59.3–83.9, $p = 0.230$) and SII on day 5 (AUC:0.624, 95% CI:42.3–82.5, $p = 0.246$) were also determined as other biomarkers that can be used to predict 28-day mortality.

Conclusion: APACHE-II score still maintains its place in predicting mortality in patients with sepsis. No biomarker alone has been able to surpass this score, and markers obtained in combination such as NLR, LIMA and SII may be helpful in predicting mortality. New and large-scale studies are needed on this subject.

Keywords: sepsis, mortality, IMA, APACHE-II, SII, NLR

Introduction

Sepsis-3 describes sepsis as a dysregulated host response to infection resulting in life-threatening organ malfunction.¹ The most common causes of mortality and morbidity in patients monitored in intensive care are bacterial infections and sepsis.^{2,3}

From data published in 2020, there were 48.9 million cases and 11 million sepsis-related deaths worldwide, representing 20% of all global deaths.⁴ Determining the progression to sepsis at an early stage and thus reducing mortality rates is of great importance in intensive care patients.

Various biomarkers and scoring systems are currently used to determine the prognosis of patients in intensive care. APACHE II (Acute Physiology and Chronic Health Evaluation II), white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), and lactate are the most important of these. The APACHE II scoring is the gold standard for evaluating high-risk patients in intensive care. This scoring provides information about the prognosis of patients by risk stratifying them. However, sometimes incorrect scores may occur. For example, the APACHE II score is calculated as relatively low in a young patient with severe sepsis but no organ failure.^{5,6} Biochemistry Laboratory of KSU Application and Research Hospital.

The Society of Critical Care Medicine and the European Society of Intensive Medicine have suggested using the SOFA score to predict mortality in sepsis.¹ The use of the quick SOFA (qSOFA) system for out-of-intensive care units (ICU) and pre-hospital periods was recommended by consensus because the SOFA scoring takes time to apply and requires laboratory

testing.⁷ C-reactive protein (CRP) and procalcitonin (PCT) are commonly used to monitor critically ill patients in intensive care.⁸ However, measuring CRP is not ideal for monitoring sepsis, as its levels can also increase in postoperative conditions, autoimmune diseases, rheumatological disorders, and non-infectious conditions such as myocardial infarction. On the other hand, PCT levels are significantly higher in cases of bacteremia and sepsis. PCT and CRP have low prognostic values on the expected life expectancy of patients with sepsis.⁹

Although CRP and procalcitonin may not be specific to sepsis, they are useful in identifying critically ill patients who need closer monitoring, enabling earlier diagnosis and treatment.⁹

No single biomarker of sepsis may be ideal, but many are helpful in terms of at least identifying critically ill patients who need more careful monitoring so that the condition may be diagnosed and treated as soon as possible. Another parameter in the early progression to sepsis is the lactate level. Hyperlactatemia due to tissue hypoxia is observed. Since oxygen delivery to the cells decreases after sepsis develops, lactate values become quite difficult to interpret.

Complete blood count (CBC) is an easily accessible and inexpensive test. The WBC, neutrophil, lymphocyte, platelet (PLT) and mean platelet volume (MPV) values studied in this test and the ratios of these values to each other are used as inflammatory markers. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are some of the most important of these markers. Systemic immune-inflammation index (SII) is an index obtained by calculating with the formula (neutrophil x platelet)/lymphocyte.

Ischemia-modified albumin (IMA) is a biomarker whose level increases secondary to ischemia of the myocardium and skeletal muscle, measured with the albumin cobalt binding test.

Rapid and timely intervention is essential for the successful treatment of sepsis. Therefore, this study aimed to reveal the relationships between patients with mortality by looking at IMA, APACHE II, CRP, PCT, lactate, WBC, NLR, PLR, SII, platelet and lactate/IMA (LIMA) values in sepsis patients followed in the intensive care unit.

Materials and Method

This study was conducted prospectively in a single center over 6 months. Thirty-one patients diagnosed with sepsis were included in the study. The informed consent form was obtained from the patients or their relatives and study permission was obtained. Patients who were considered to have sepsis were ≥ 18 years old and stayed in the intensive care unit for ≥ 72 hours were included in the study. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) definitions and clinical criteria were used to describe septic shock and multiorgan dysfunction.⁷

In addition, terminal cancer patients, those who had received massive blood transfusions, ischemic heart disease, and patients with ongoing pregnancy were excluded from the study.

All patients' general evaluation (age, gender, patient diagnosis, additional diseases), blood biochemistry, complete blood count, arterial blood gas, and APACHE II and SOFA scores were calculated and recorded within the first day of admission to the intensive care unit.

The day the patient was admitted to the intensive care unit was considered day 1.

The values examined on the first day were planned to be compared with the APACHE II criteria, which evaluate many parameters. The values examined on the fifth day were aimed at evaluating the predictive power of mortality after the patient's clinical deterioration.

To evaluate IMA levels in patients hospitalized in the intensive care unit on days 1 and 5, 8 mL of blood was taken from the peripheral vein into a citrated tube. After the blood was clotted and centrifuged at 3000 g for 10 minutes. The obtained sera were stored at -80°C until the study day. Serum IMA levels were analyzed colorimetrically using the method developed by Bar et al.¹⁰ Complete blood counts were tested in the Biochemistry Laboratory of KSU Application and Research Hospital using SYSMEX XN3000 AND SYSMEX XT 1800i automatic hematology analyzers. Blood gas analyses were performed on the Radiometer ABL 700 device located in the Biochemistry Laboratory of KSU Application and Research Hospital.

Our study was conducted in accordance with the Declaration of Helsinki.

The Ethics Committee of Kahramanmaraş sütçü imam University, School of Medicine approves this study. (Ethics No. 2017/21).

Statistical Analysis

SPSS 25.0 package program (SPSS Inc, Chicago, Illinois, USA) was used to evaluate the statistical data obtained in the study. Continuous data were summarized as mean and standard deviation, while categorical data were summarized as numbers and percentages. Student's *t*-test was used to compare continuous variables in independent groups. The chi-square (χ^2) test was used to evaluate two categorical independent groups for comparisons between groups. The Receiver operating characteristic (ROC) curve was used to evaluate the predictive power of the markers for appendicitis. According to this method, the sensitivity of 100%, false positivity zero (1-Specificity=0), the area under the curve (AUC) being 1, and the diagnostic value of the AUC value being $p < 0.05$ were accepted as the basic criteria for the best test definition. In determining the cut-off value, the Youden index, which overlaps with the point closest to the upper left corner of the ROC graph and reflects the highest value of the sum of sensitivity and specificity, was used. In investigating the accuracy of the diagnostic test, sensitivity and specificity were calculated with a 95% confidence interval and presented as a table. The level of statistical significance was $p < 0.05$.

Results

Thirty-one patients diagnosed with sepsis from the Anesthesia Intensive Care Unit were included in the study. Twenty-one (67.7%) of the patients were male and 10 (32.3%) were female. The mean age of the patients was 76.77 ± 14.92 years (min-max: 30–96 years), and the median (min-max) APACHE II score values at the time of admission to the intensive care unit were 20.5 (12–30).

Of the patients included in the study, 64.5% ($n=20$) had septic shock on initial admission to the hospital, 35.5% ($n=11$) had acute renal failure, 16.1% ($n=5$) had acute liver injury, and 83.9% ($n=26$) required invasive mechanical ventilation.

The final status of the patients was evaluated as alive and exits, and 18 (58.1%) of the patients ended up as exits. The study included 18 patients, and the mean time to death was determined as 12.6 days. In addition to sepsis, the cases had diabetes mellitus, coronary artery disease, goiter, Alzheimer's, cerebrovascular disease, arrhythmia, and obesity.

Table 1 presents the first 24 hours and 5th-day IMA, CRP, PCT, lactate, WBC, platelet count, MPV, NLR, PLR, LIMA, and SII values of patients diagnosed with sepsis.

Table 1 IMA, CRP, PCT, Lactate, WBC, Platelet Count, NLR, PLR, LIMA and SII Values of Patients Diagnosed with Sepsis in the First 24 hours and on the 5th Day

	Day 1 Median (Min-Max)	Day 5 Median (Min-Max)	Z*	p
IMA (AbsU)	0.322 (0.242–0.385)	0.337 (0.279–0.432)	–1,034	0.301
CRP (mg/L)	138 (19–423)	98 (9–340)	–1,861	0.063
Procalcitonin (ng/mL)	6.1 (0.1–252)	20.2 (0.1–158.5)	–1,579	0.114
Lactate (mmol/L)	2.1 (0.5–34)	3.57 (0.8–26.0)	–0.608	0.543
Leukocyte count ($10^6/L$)	11580 (1860–32,180)	14,999 (5170–60,000)	–1,195	0.232
Platelet count ($10^9/L$)	211 (47–567)	173 (13,408)	–1,921	0.055
MPV (fL)	10.8 (8.3–12.6)	11.19 (8.0–13.2)	–2,657	0.008
NLR	12.2(2.78–55.7)	16.8 (1.82–52.13)	–0.294	0.769
PLR	0.28 (0.03–1.27)	0.21 (0.0–0.78)	–2,371	0.018
LIMA	6.4 (1.5–46.6)	13.1 (1.85–74.16)	–2,007	0.045
SII	4025.2 (340.8–16,030.1)	2665.0 (216.1–19,442.6)	–1,999	0.046

Notes: *Wilcoxon rank test was used to compare groups. The level of statistical significance is $p < 0.05$ and is shown in bold in the table.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; IMA, Ischemia modified albumin; CRP, C-reactive protein; MPV, Mean platelet volume; NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; LIMA, lactate/IMA; SII, Systemic immune-inflammation index.

Table 2 All Values of Patients Diagnosed with Sepsis Cut-Off, Sensitivity, Specificity, AUC, 95% Confidence Interval and p Values for Predicting 28-Day Mortality

	Cut-Off	Sensitivity	Specificity	AUC	95% CI	p
APACHE II	20	88.9	76.9	0.891	77.6 – 100	<0.0001
NLR Day 5	11.86	72.2	76.9	0.765	59.3–93.7	0.013
LIMA Day 1	6.2	66.7	61.5	0.628	59.3–83.9	0.230
SII Day 5	1782.2	61.1	61.5	0.624	42.3–82.5	0.246
CRP Day 1	131	46.2	50.0	0.477	23.6–71.8	0.852
CRP Day 5	79.8	53.8	60.0	0.646	40.8–88.4	0.239
PCT Day 1	8.25	46.2	60.0	0.550	30.7–79.3	0.687
PCT Day 5	9.09	53.8	70.0	0.508	26.1–75.4	0.951
Lactate Day 1	1.75	61.5	60.0	0.662	42.5–89.8	0.193
Lactate Day 5	2.0	69.2	60.0	0.669	43.8–90.1	0.172
WBC Day 1	11,205	53.8	50.0	0.492	24.9–73.6	0.951
WBC Day 5	15,425	46.2	80.0	0.623	38.6–86.0	0.321
Platelet Day 1	148.5	61.5	40.0	0.462	20.9–71.4	0.756
Platelet Day 5	132.0	53.8	40.0	0.308	8.7–52.8	0.121
NLR Day 1	10.8	69.2	70.0	0.631	37.9–88.3	0.292
PLR Day 1	0.26	53.8	50.0	0.608	37.1–84.4	0.385
PLR Day 5	0.16	69.2	70.0	0.604	36.1–84.6	0.402
LIMA Day 5	6.61	61.5	60.0	0.677	44.8–90.6	0.154
SII Day 1	2263.3	61.5	60.0	0.608	35.5–86.0	0.385

Notes: *ROC curve was used to calculate the values of the groups. The level of statistical significance is $p < 0.05$ and is shown in bold in the table.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; IMA, Ischemia modified albumin; CRP, C-reactive protein; NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; LIMA, lactate/IMA; SII, Systemic immune-inflammation index.

Cut-Off, Sensitivity, Specificity, AUC, 95% confidence interval, and p values of APACHE-II, NLR5, LIMA1, and SII5 values for predicting 28-day mortality of patients diagnosed with sepsis were calculated and presented in Table 2.

ROC curves of patients with sepsis are presented in Figure 1.

In patients diagnosed with sepsis, APACHE-II was the best statistical indicator in the first 24 hours, and NLR 5th-day values were the second-best statistical indicator. Although statistically significant values were not reached, LIMA1 and SII5 values could also give an idea about 28-day mortality.

Discussion

One of the most important events leading to morbidity and mortality in patients with severe sepsis is the development of global tissue hypoperfusion and oxidative damage. Ischemia-modified albumin (IMA), an albumin produced under ischemic and oxidative conditions, is a marker of oxidative stress and hypoperfusion. Sepsis causes an imbalance between reactive oxygen species and antioxidants.⁷ Changes in endothelium, neutrophils, macrophages, and mitochondrial signaling pathways during sepsis cause significant oxidative stress.¹¹ Ischemic damage is associated with oxidative stress, and the production of reactive

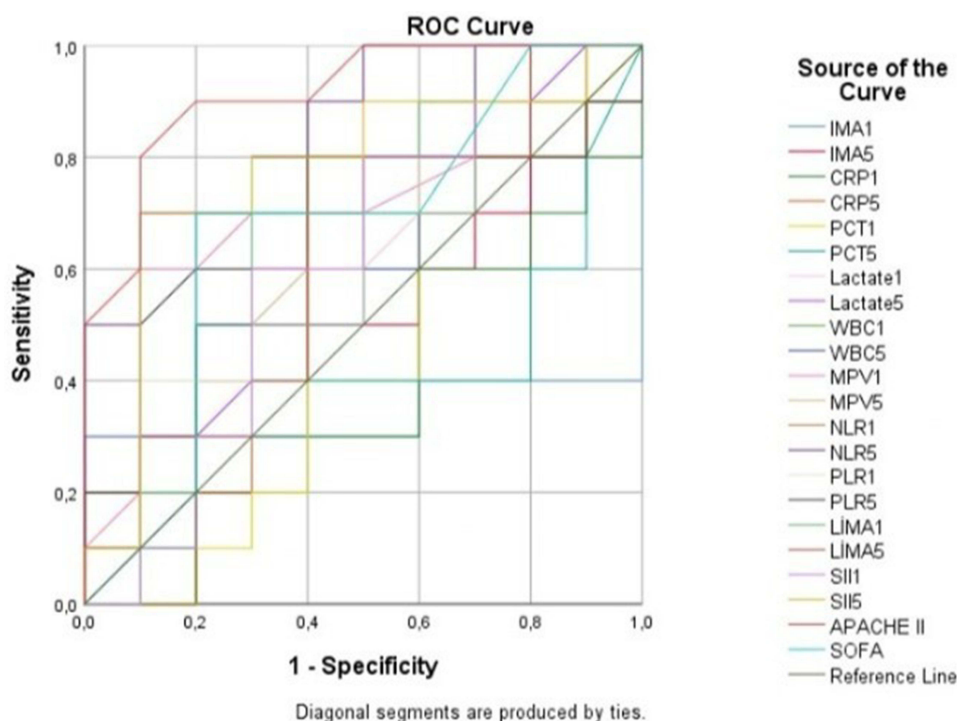


Figure 1 ROC curves of patients diagnosed with sepsis.

oxygen species affects albumin and produces IMA.¹² Mitochondrial dysfunction in sepsis causes increased anaerobic metabolism despite adequate oxygen delivery, which also leads to an increase in lactate levels.¹³

To our knowledge, this is the first study to compare serum IMA levels with APACHE-II, IMA, CRP, PCT, lactate, WBC, platelet count, MPV, NLR, PLR, LIMA and SII values on different days to predict mortality in patients with sepsis. In previous studies, IMA and APACHE-II were never studied together.

In our study, APACHE-II was found to be the best statistical indicator in the first 24 hours, and NLR values on the 5th day were found to be the second-best statistical indicator in patients with a diagnosis of sepsis. Although statistically significant values were not reached in our study, LIMA1 and SII1 values could also give an idea about 28-day mortality.

Kyoshi et al, in a study examining central line-related bloodstream infection in a general intensive care unit, APACHE-II (OR (95% CI) 1.051 (1.000–1.105), $p=0.048$) was found to be a prognostic factor in the deterioration of patients.¹⁴ In a study investigating the effects of APACHE-II on mortality at 30–60–180 days in oncological patients with sepsis by Kuo et al, APACHE-II (OR (95% CI) 1.07; 1.03–1.11) $p<0.001$ was found to be statistically significant.¹⁵ Suo et al. It was determined that APACHE-II score (AUC:0.568, sen: 61.2%, spe: 62.2, % 95CI:0.512–0.684) and lactate (AUC:0.810, sen:83.3% spe:79.4%, 95CI:0.738–0.882) values were significant in predicting mortality in patients with sepsis.¹⁶ In our study, the APACHE-II score was the most valuable indicator in predicting mortality in patients with sepsis, similar to the literature.

The current meta-analysis of 14 studies by Huang et al, including 11,564 patients with sepsis, showed that NLR was significantly higher in non-survivors than in survivors and that higher NLR was associated with prognosis in patients with sepsis. These results indicate that higher NLR is independently associated with adverse clinical prognosis in patients with sepsis.¹⁷ In the study by Hwang et al investigating the relationship between 28-day mortality and NLR in patients with sepsis, it was determined that NLR had a statistically significant predictive power for mortality in patients with sepsis.¹⁸ In our study, similar to the literature, NLR value was the most valuable parameter after APACHE-II value in predicting mortality. In the study by Park et al, among 124 patients evaluated, IMA was found to be higher in the non-survivor group than in the survivor group (92.6 ± 8.1 vs 86.8 ± 6.2 U/mL, $p<0.001$). IMA was found to be associated with 28-day mortality.¹⁹ Previous studies evaluating the prognostic value of IMA in patients with sepsis or severe sepsis reported a significant association between IMA

and short-term mortality.¹² In the study by Prashanth et al, significantly higher IMA levels ($p<0.0001$) were found in patients with sepsis compared to those without sepsis (0.085 ± 0.234).²⁰ In another study, statistically significantly higher IMA levels were found in patients with sepsis compared to the control group ($p<0.0001$).²¹ Yin et al, similarly, in the study conducted by, IMA levels were higher in those who died than in those who survived ($p<0.05$) and were found to be a strong determinant of 28-day mortality.²² In the study conducted by Yerlikaya et al, serum IMA, CRP, PCT and leukocyte counts were found to be significantly higher in the sepsis group before treatment than in the control group.²³ In the study conducted by Cetin et al, the effect of IMA on mortality was investigated in 81 sepsis patients. Serum IMA levels in the patient and control groups were found to be 117.8 ± 85 IU/g and 115.8 ± 134.0 IU/g, respectively ($p=0.072$). A weak but statistically significant positive correlation was found between IMA and lactate levels ($p:0.009$). The mortality rate of the patient group on the 28th day was found to be 79%. In this study, similar to our study, it was determined that serum IMA levels were not a prognostic marker in predicting mortality in patients with sepsis.²⁴ In our study, similar to the study by Çetin et al, although IMA levels were high in patients with sepsis, it was not found to be statistically significant. In the study by Choo et al, IMA levels are a useful biomarker for early diagnosis of sepsis/septic shock and its combination with lactate levels may increase the predictive power of early diagnosis of sepsis (AUC IMA: 0.729, AUC IMA and Lactate: 0.815).²⁵ In the study by Bo et al, IMA levels were found to be statistically significantly higher in the non-surviving group than in the surviving group ($p<0.001$). The predictive power of 28-day mortality in patients with sepsis showed a higher mortality risk compared to other groups in both the group with high IMA and the group with high IMA and lactate (AUC IMA: 0.712, $p<0.001$; AUC IMA and lactate 0.838, $p<0.001$).¹² In our study, although IMA values increased, they were not found to be statistically significant, and it was predicted that the combined evaluation of LIMA1 values could provide an idea about 28-day mortality. Systemic immune-inflammation index (SII) is an economical and useful parameter based on lymphocyte, neutrophil, and platelet counts and can simultaneously reflect the inflammatory and immune status of patients.²⁶ SII can be used not only to predict death in patients with sepsis but also to increase diagnostic accuracy by combining clinical scores of sepsis severity. A lower SII theoretically indicates that the body may be impaired by severe inflammation or myelosuppression and is generally associated with poor prognosis.²⁷ In the study by Jiang et al, a relationship was found between SII and 28-day mortality ($p:0.049$) (24). In the study by Mangales et al, in which 267 patients with sepsis were evaluated retrospectively, SII was found to be an independent predictor of sepsis mortality (AUC:0.848, sensitivity was 85.5%, specificity was 71.2% and cut-off was 564).²⁸ In our study, it was found that SII could be useful in predicting 28-day mortality of patients with sepsis, although it was not statistically significant. This study had some limitations. Our study was conducted in a single center with a limited number of patients. These results cannot be generalized to the entire population. IMA may differ according to measurement protocols in each laboratory environment. Results and measurements should be verified before application.

Conclusion

APACHE-II score still maintains its place in predicting mortality in patients with sepsis. No single biomarker has been able to surpass this score, and combined markers such as NLR, LIMA, and SII may help predict mortality. New and large-scale studies are needed on this subject.

Abbreviations

APACHE II, Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell count; CRP, C-reactive protein; PCT, procalcitonin; PLT, platelet; and MPV, mean platelet; NLR, Neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, Systemic immune-inflammation index; IMA, Ischemia modified albumin.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study is approved by the Ethics Committee of kahramanmaraş sütçü imam University, School of Medicine. (Ethics No. 2017/21).

Consent to Participate

Obtained.

Consent for Publication

Obtained.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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