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The effect of lactate/albumin ratio on mortality in patients with sepsis

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Abstract

The aim of study was to evaluate the lactate/ albumin ratio, procalcitonin (ProCT) and C reactive protein (CRP) levels in patients with sepsis. For the study, 207 patients with sepsis who were treated in intensive care between January 1st, 2016 and January 1st, 2021 were analyzed retrospectively. The patients' age, sex, diagnosis for hospitalization, lactate levels during the admission (lactate 1) and discharge (lactate 2), CRP, ProCT and albumin, levels registered in patients' files were recorded from the hospital automation system and their effect on the mortality was statistically analyzed. The patients were grouped as those aged older than 65 and younger than 65, and those with and without mortality. The study included 207 patients diagnosed with sepsis (96 female, 111 male). ProCT levels were found significantly higher in the group older than 65 in the present study. In this study, according to the data obtained, there was no difference in lactate1/albumin and lactate2/albumin ratio in terms of age groups and sex. However, lactate1/albumin and lactate2/ albumin ratio were significantly higher in the group with mortality than the group without mortality. According to our ROC analysis results; The AUC for lactate1, lactate2, lactate1/albumin and lactate2/albumin ratio was 0.649, 0.680, 0.690, 0.771, respectively. The lactate/albumin ratio is a readily available parameter with consistently better prognostic performance than initial serum lactate for in-hospital mortality in adult patients with sepsis. Raised lactate/ albumin ratio showed significant association with increased mortality in patients with sepsis.

Keywords: C-Reactive Protein, lactate/ albumin ratio, mortality, procalcitonin, sepsis

Introduction

Sepsis is a common disease that is hard to diagnose and treat, and it becomes costly especially in intensive care patients and the geriatric patient population. The most current definition of sepsis is a life-threatening organ dysfunction developed against the infection as a result of irregular host response [1,2]. Even though new treatment models have been developed, the mortality rate in sepsis is still high due to delays in diagnosis and treatment. It is more common among men than women and its incidence is gradually increasing due to the increasing mean age and resistance to drugs [1-3].

There is no standard test for the recognition of sepsis and the clinical and laboratory findings are not specific to the disease and may sometimes be misleading. Generally used laboratory tests are complete blood count, blood gas, coagulation tests, lactate, ProCT and C-reactive protein (CRP) based on the findings and symptoms [1,4].

CRP, which is the most commonly used biomarker used in the routine practice, is the acute phase protein secreted by liver after inflammation or tissue damage. It has low specificity and may sometimes be insufficient to determine the severity of the sepsis [5, 6].

Procalcitonin is mostly secreted by thyroid gland C cells and liver as a response to bacterial endotoxins and proinflammatory cytokines especially in case of inflammation. The fact that ProCT has high sensitivity and specificity in sepsis, and a short half-life (<24 hours), and is easily measurable and inexpensive makes it an ideal biomarker. It is beneficial in early diagnosis but it may not be sufficient alone in determining the response to treatment and prognosis in sepsis due to its sensitivity and specificity change at different thresholds. However, studies have shown that procalcitonin levels are highly associated with the severity of sepsis and mortality compared to CRP [7-9]. Garnacho-Montero et al. examined ProCT and CRP levels in the Systemic Inflammatory Response Syndrome and found that ProCT might be a more reliable biomarker and is a superior marker than CRP in the admission to the hospital [10].

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Hypoxia and tissue hypoperfusion seen in sepsis play a key role on the development of multi-organ failure in patients. Lactic acidosis is one of the best indicators of the insufficient perfusion or development of anaerobic metabolism during septic shock. The inability of liver to metabolize lactate as a result of the deterioration of liver perfusion also increases lactate levels [11,12]. The tissue hypoxia level is important in determining mortality estimation. The measurement of blood lactate levels used to determine tissue hypoxia is rapid, inexpensive and easy [11,13]. On the other hand, among the limitations of serum lactate measurement; the interaction between the production and elimination of lactate also affects the results. For instance, the lactate levels of a patient with sepsis with hepatic dysfunction might be higher. Because lactate and albumin levels progress differently as the development of sepsis proceeds, a ratio between the two rather than analyzing lactate and albumin alone may be a new and perhaps better indicator for the patient's prognosis [12]. Wang et al. (2015) recommended using lactate/albumin ratio as a mortality indicator by using both onset lactate and albumin predictive values [14].

Symptoms and signs of sepsis are nonspecific. Parameters that will guide the monitoring of the response to sepsis treatment and timely termination of the treatment in addition to the early and correct diagnosis of sepsis are needed. Therefore, this study was conducted to evaluate the lactate/albumin ratio, ProCT and CRP levels in patients with sepsis, and investigate the effects of these parameters on mortality and the duration of hospital stay. The most important feature that distinguishes our study from other studies is the use of both input lactate measurement and final lactate measurements.

Materials and Methods

After the approval of the ethics committee in the study, retrospectively examined patients who were hospitalized in the Intensive Care Unit in Health Sciences University Van Province Training and Research Hospital between January 1st, 2016 and January 1st, 2021, who were discharged with the diagnosis of sepsis or who died due to sepsis.

The exclusion criteria for this study included: age <18 years, patients with metabolic or liver diseases, pregnancy, acute coronary syndrome, active gastrointestinal bleeding, requirement for immediate surgery, transfer to another institution.

The patients' age, sex, diagnosis for hospitalization, lactate levels during the admission (lactate1) and discharge (lactate2), CRP, ProCT and albumin, levels registered in patients' files were recorded from the hospital automation system and their effect on the mortality was statistically analyzed. All parameters, (except lactate2), are the values measured at the first hospitalization day of the patient. The patients were grouped as those aged ≥65 and <65, and those with and without mortality. Blood lactate measurements were made with the blood gas device (ABL 800; Radiometer) while procalcitonin, albumin CRP levels were measured with analyzer (Cobas Integra C6000; Roche Diagnostic). Samples with results indicating the presence of hemolysis (8 samples) and missing blood lactate (22 samples) and albumin (12 samples) results were excluded from the study.

The study was approved by KTO Karatay University Faculty of Medicine Non-Drug and Medical Devices Studies Ethics Committee (Number: 2020/008, Date: 15.12.2020).

Statistical analysis

Data obtained during the data collection stage were transferred into computer medium and analyzed. The data were analyzed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA) package program. The conformity to normal distribution of the data was examined using visual (histogram and probability graphics) and analytic methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests). Arithmetic mean, standard deviation, minimum and maximum values were used in the data abstraction while frequency distributions and percentages were used for the abstraction of categorical data. The Mann-Whitney U test was used to test whether there was a statistically significant difference between the two independent groups. The correlations of numerical variables without normal distribution were analyzed with the Spearman correlation coefficient. In order to examine the effect of lactate1/albumin ratio on mortality in groups determined according to gender, 2-way ANOVA test was applied. The backward method was used in logistic regression analysis to identify independent predictors for predicting mortality using possible risk factors that were significant in pairwise comparisons and were identified in previous studies. The model fitness was evaluated with the Hosmer-Lemeshow test. Two-way analysis of variance was used to measure the common effect of the variable on the dependent variable. Using Receiver operating characteristic (ROC) curve the area under the curve (AUC) was calculated for diagnostic value and accuracy of different parameters with the best sensitivity and specificity for given cut-off values. The significance level was $p<0.05$.

Results

The study included 207 patients diagnosed with sepsis (96 female, 111 male). The patients were aged between 18 and 99, and 64.25% of the patients were older than 65. The number of patients with mortality due to sepsis was 157. The mean age of the patients was 67.24±17.17. The patients' mean albumin value was 5.21±7.29 g/dL while the mean lactate levels were lactate1=3.92±3.59 mmol/L and lactate2=4.47±4.35 mmol/L. Furthermore, the mean ProCT value was 22.77±99.22 ng/mL while the mean CRP was 130.18±108.37 and the mean duration of hospital stay was 21.58±30.58. The patients' data according to the grouping in terms of age, sex and mortality are presented in Table 1, 2 and 3.

Considering the correlations, a weak negative correlation was found between ProCT, lactate1, lactate2, lactate1/albumin, lactate2/albumin and the durations of hospital stay (r=-0.241, r=-0.379, r=-0.379, r=-0.363, r=-0.380, respectively). There was a moderate negative correlation between albumin, lactate1/albumin and lactate2/albumin (r=-0.519, r=-0.529) while a strong positive correlation was found between lactate1 and lactate1/albumin, and between lactate2 and lactate2/albumin (r=0.785, r=0.797). A weak positive correlation was found between CRP and ProCT (r=0.329).

In the ROC analysis made between the groups with and without mortality in terms of lactate1/albumin, the serum cut off value was calculated as 0.775 with 66.2% sensitivity and 58% specificity ($p<0.001$, AUC=0.690, 95% CI=0.605-0.776). In the ROC analysis made between the groups with and without mortality in terms of lactate2/albumin, the serum cut off value was calculated as 0.749 with 86.6% sensitivity and 53.6% specificity (p<0.001, AUC=0.771, 95% CI=0.690-0.852) (Figure 1). In addition, in the ROC analysis performed between groups with and without mortality in terms of lactate1, lactate2, albumin, CRP, ProCT, we found the AUC values of 0.649, 0.680, 0.580, 0.483, 0.478, respectively.

When the effect of lactate2/albumin ratio on mortality in groups made according to gender is examined; It was observed that the lactate 2/albumin ratio affected the mortality in both female and male (p=0.003) (Figure 2).

When the effect of hospital stay on mortality in groups made according to gender is examined; It was observed that the length of hospital stay affected the mortality in both female and male, and the longer the duration of the stay, the lower the mortality (p=0.030). The hospitalization period of the patients who died of sepsis was short, and those who were discharged were long (Figure 3).

Table 1. Data of the patients aged above and below 65

Variables	Age <65 (median ± SD) (n: 74)	Age ≥65 (median ± SD) (n: 133)	p value
Sex (F/M)	36/38	60/73	0.801
CRP (mg/L)	133.42±114.5	128.36±105.08	0.915
ProCT (ng/mL)	22.45±35.13	22.95±121.39	0.010*
Albumin (g/dL)	5.49±7.68	5.06±7.09	0.176
Lactate1 (mmol/L)	4.20±4.05	3.77±3.30	0.989
Lactate2 (mmol/L)	4.13±4.57	4.66±4.23	0.101
Lactate1/albumin	1.64±1.87	1.31±1.38	0.669
Lactate2/albumin	1.69±2.37	1.47±1.54	0.202
Duration of hospital stay (day)	22.98±22.91	20.80±34.17	0.209
Discharge/ exitus	24/50	26/107	-

n: number of cases, SD: standard deviation, CRP: C-reaktif protein, ProCT: prokalsitonin, -: not suitable for statistical comparison as the number is small, *p<0.05 statistically significant

Table 2. Data of the patients in terms of sex

Variables	Female (median ± SD) (n: 96)	Male (median ± SD) (n: 111)	p value
CRP (mg/L)	128.46±109.91	131.67±107.48	0.680
ProCT (ng/mL)	14.35±27.85	29.94±132.42	0.352
Albumin (g/dL)	4.00±5.22	6.26±8.58	0.028*
Lactate1 (mmol/L)	3.87±3.55	3.77±3.30	0.189
Lactate2 (mmol/L)	4.21±4.44	4.72±4.27	0.373
Lactate1/albumin	1.50±1.62	1.37±1.54	0.614
Lactate2/albumin	1.56±1.93	1.54±1.83	0.541
Duration of hospital stay (day)	25.55±39.02	18.15±20.28	0.405
Discharge/ exitus	18/78	32/79	0.400

*p<0.05 statistically significant

Table 3. Data of the patients in the groups with and without exitus

Variables	Discharge (median ± SD) (n: 50)	Exitus (median ± SD) (n: 157)	p value
Age	62.88±17.60	68.63±16.85	0.014*
Gender (F/M)	18/32	78/79	0.400
CRP (mg/L)	115.41±79.78	134.78±115.69	0.715
ProCT (ng/mL)	12.54±22.73	26.00±113	0.644
Albumin (g/dL)	8.56±8.25	4.14±5.61	0.090
Lactate1 (mmol/L)	8.57±10.39	4.29±3.85	0.002*
Lactate2 (mmol/L)	3.45±4.46	4.91±4.25	0.000*
Lactate1/albumin	0.86±1.19	1.61±1.64	0.000*
Lactate2/albumin	0.93±1.59	1.82±1.93	0.000*
Duration of hospital stay (day)	28.96±21.44	19.23±32.68	0.000*

*p<0.05 statistically significant

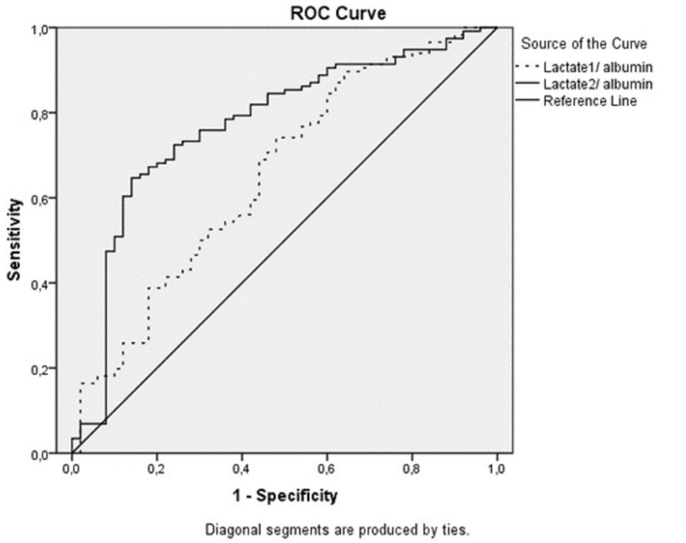

Figure 1. ROC curve for the performance of serum lactate1/albumin and lactate2/albumin ratio as a predictor of mortality in sepsis

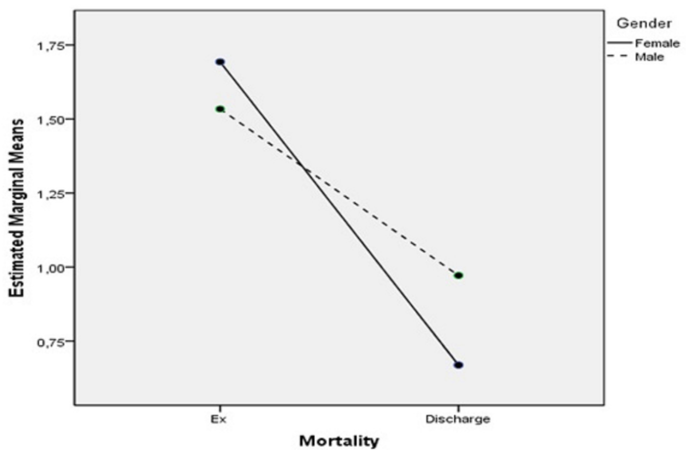

Figure 2. The effect of lactate2/albumin ratio on mortality in groups made according to gender

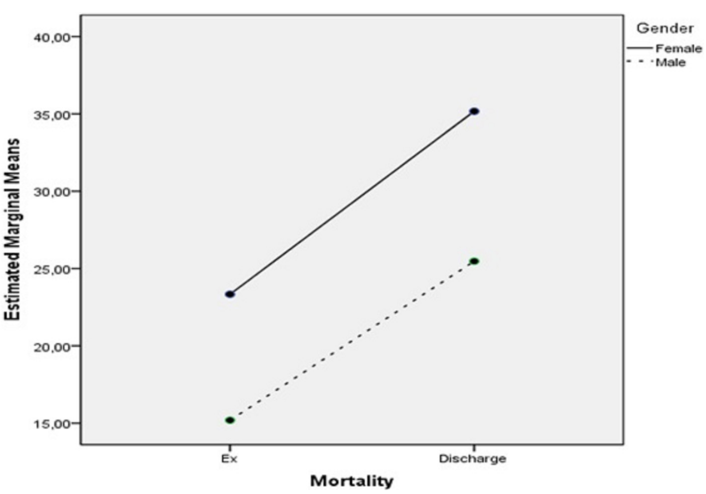

Figure 3. The effect of hospital stay on mortality in groups made according to gender

According to the Hosmer-Lemeshow test performed, having an age older than 65 increases mortality by 2.094 times while 1 unit decrease in albumin increases mortality by 1.067 times (p=0.035, p=0.002, respectively).

Discussion

Sepsis, septic shock and subsequent multi-organ failure continue to be the most important cause of mortality in intensive care units today. The increase in molecular cell damage and stress-causing factors, a decrease in physiological capacity are expected in the elderly and this increases the potential of elderly patients to become critically ill [2,15]. Most of the studies on sepsis found that the age was older than 60. In our study, the mean age of the patients was 67.24±17.17, and 111 (53.6%, 111/207) of them were male. In addition, the mean age was significantly higher in the group with mortality compared with the discharged group. In studies in the literature, as in our study, the incidence of sepsis in men was found to be higher than in women [1,15,16].

The acute phase protein, CRP, is an important marker of the inflammatory response and is frequently used in sepsis screening despite its low specificity [5,17]. A study examining the factors that affect the prognosis in elderly patients with sepsis, the mean CRP levels was found as 184.2 mg/L in the group with mortality and as 135 mg/L in the discharged group and the difference between them was significant [18].

The correlation between ProCT and sepsis was determined for the first time in 1993 [19]. ProCT values have an important role in the follow-up of the clinical condition of the patient and the monitoring of the effectiveness of the treatment. Rapid normalization of high ProCT values shows that the clinical status is getting better. On the contrary, a slightly decrease in ProCT value in time and remaining at the pathological levels (above 2 ng/mL) mean that the critical condition of the patient continues. ProCT levels rapidly increases in the terminal period. Some studies reported that the procalcitonin levels measured in deceased patients due to sepsis were significantly higher compared to living patients [7,19,20]. Clec'h et al. [7] found that ProCT levels were higher in patients experiencing septic shock than patients not having a septic shock. They also found that ProCT levels were higher in deceased patients compared to surviving patients. Chebl et al. [21] conducted a study with 1381 patients in 2020 and found that the mean procalcitonin levels were 12.27±26.42 ng/ml in the group with mortality and 12.60±26.20 ng/ml in the group without mortality. They also reported no significant difference between these groups in terms of procalcitonin (p=0.884).

Both CRP and ProCT are commonly used tests in the routine practice in the diagnosis and follow-up of sepsis. Müller et al. [22] revealed that there was a significant correlation between the severity of sepsis and serum procalcitonin and CRP levels, and that high procalcitonin levels were associated with bad prognosis. Furthermore, Claeys et al. [8] reported that initial procalcitonin and CRP levels might be the indicator of bad prognosis in sepsis cases. Luzzani et al. [6] compared the ProCT and CRP levels of cases in the diagnosis of sepsis and found that ProCT levels is a better marker than CRP. Oberhoffer et al. [23] reported that ProCT had higher sensitivity and specificity both as an inflammation parameter and prognosis indicator in septic cases compared to leukocyte count, body temperature and CRP, and that this superiority was approved with the ROC curves. They also categorized patients with sepsis as patients who died in the intensive care and surviving patients and found that ProCT values were significantly higher in deceased patients. Unlike studies reporting that there is a significant correlation between the severity of sepsis and serum procalcitonin and CRP levels, some studies asserted that CRP levels were lower in patients experiencing septic shock compared to patients with sepsis and severe sepsis and that CRP levels cannot be a marker determining the severity of the disease [24]. Liu Y et al. [25] conducted a study with 63 patients with sepsis and found no difference between the groups with and without mortality in terms of ProCT and CRP (p=0.44; and p=0.672, respectively).

ProCT levels were found significantly higher in the group older than 65 in the present study. In the evaluation of ProCT and CRP parameters between the groups with and without mortality, both values in the group with mortality were higher but there was no significant difference between the groups. Additionally, a weak positive correlation was found between ProCT and CRP. We believe that methodological differences in the studies may have caused the differences between the groups. According to these data we have obtained, it would not be correct to say that the increase in ProCT and CRP values can significantly affect the prognosis in sepsis. In order to evaluate its effect on prognosis, there is a need for more comprehensive studies involving a much higher number of patients.

Serum albumin levels can be indicator of systemic inflammation [26]. Several studies have suggested that albumin is a biomarker of mortality and prognosis. The concentration of albumin, a negative acute phase reactant, decreases with sepsis and metabolic disease [26,27]. Furthermore, the halflife of albumin (i.e.,~20 days) can be significantly reduced by systemic inflammation, malnutrition, and liver disease [28]. A large population study demonstrated that serum albumin is an important marker of mortality and morbidity [29]. In another study, serum albumin levels were the laboratory finding that was most closely associated with mortality in adult patients with sepsis [30]. Chebl et al. [21] conducted a study with 1381 patients in 2020 and found that the albumin values were 2.58±0.64 g/dl in the group with mortality and 2.95±0.66 g/dl in the group without mortality, and that the difference between the groups was significant (p<0.001). In our study, although the albumin levels were high among patients older than 65, there were no significant difference with the group younger than 65 in terms of albumin. The albumin value was significantly higher among men than women. Contrarily, albumin levels were lower in the group with mortality than the group without mortality but the difference was not significant. However, the low albumin levels in the group with mortality may explain the increase in lactate2 levels seen in this group.

Lactate is a glucose metabolite produced by tissues in the body in situations of oxygen deficiency. Specifically, it has been used as an indicator of tissue hypoperfusion and cellular hypoxia in patients. Latest studies have revealed that high lactate levels are associated with bad clinical results [11,13]. Oh DH et al. [31] conducted a study with 1043 patients having septic shock in 2019 and reported that patients in the high lactate group had worse prognosis. Mikkelsen et al. [13] reported that initial lactate was independently related to mortality in patients with severe sepsis. The first and last lactate measurements of the patients were made in the present study but lactate follow-up was not included in the analysis as not every patient had it. In the group with mortality, lactate1 measurements were significantly lower while the lactate2 values were significantly higher. In addition, lactate1 values were found to be lower than lactate2 values in patients older than 65 years of age, but there was no significant difference between the groups. A weak negative correlation was found between lactate1 and lactate2 levels and the duration of hospital stay. Similar to the present study, the lactate levels were significantly higher in the group with mortality compared to the group without mortality in the study by Chebl RB et al. [21] conducted with 1381 patients with sepsis in 2020 (p<0.001) and this study was the largest sampled study evaluating the lactate/albumin ratio and the association of sepsis. However, the first and last lactate measurement values were not used in that study unlike the present study.

Serum lactate and albumin levels change during sepsis. More recently, it was reported that the combination of lactate and albumin is a better predictor of mortality in critically ill patients [32-34]. Rather than evaluating separately lactate and albumin, which have an important effect on the prognosis of sepsis, combining these factors by using the ratio between lactate and albumin will provide a new and important variable. Wang et al. investigated the lactate/albumin ratio for the first time in an adult ICU setting and proved that it correlated well to the development of multiple-organ dysfunction syndrome (p<0.0001) and mortality (p=0.0122) [33]. The study conducted by Chelb RB et al. [21] with 1381 patients with sepsis found the AUC value of 0.61 (95% CI 0.57–0.65, p < 0.001) for lactate and 0.67 (95%CI 0.63–0.70, p < 0.001) for the lactate/albumin ratio. This study additionally reported that the lactate/albumin ratio was a predictor of in-hospital mortality. Another large study on the lactate/ albumin ratio was done by Shin et al. [33], who received data from the multicenter registry of 10 emergency departments (n = 946). Their AUC for the lactate/ albumin ratio was 0.69 and was significantly higher than that of lactate (0.62) for predicting 28-day mortality, and these results are comparable with ours and reinforce the finding that the lactate to albumin ratio outperforms lactate alone as a prognostic marker in sepsis. Lichtenauer M et al. [35] conducted a study with 348 patients with sepsis in 2017 and found that lactate/albumin ratio was independently related to the mortality in patients with sepsis and AUC was found as 0.70. Moustafa AA et al. [36] conducted a study with 199 pediatric patients with sepsis in 2017 and found that lactate/albumin ratio was a better marker than lactate in terms of mortality. In our study, both the first and last measured lactate values were used. According to our ROC analysis results; The AUC for lactate1, lactate2, lactate1/albumin and lactate2/albumin ratio were 0.649, 0.680, 0.690, 0.771, respectively. The results are consistent with other studies.

In this study, according to the data obtained, there were no difference in lactate1/albumin and lactate2/albumin ratio in terms of age groups and sex. However, lactate1/ albumin and lactate2/ albumin ratio were significantly higher in the group with mortality than the group without mortality. In the analysis of lactate and albumin values between groups, not much definite information was obtained for mortality, but lactate/albumin ratios provided important information in terms of mortality. Although the lactate1 values were low in the group with mortality, both the lactate1/ albumin ratio and the lactate2/ albumin ratio values were high. If patients were given albumin treatment, the lactate2/albumin ratio would be expected to be low. We do not know whether they received albumin treatment or not in the intensive care unit, but the high AUC value of lactate2/albumin ratio indicates that the lactate2/albumin ratio provides better information than lactate or albumin in estimating mortality. These results showed the importance of using lactate/albumin ratio rather than using lactate or albumin values alone.

Limitations

First, the current study was a retrospective study and the data was collected from a single center limiting the generalizability of these results. Second, the study did not have serial lactate measurements. Thirdly, we could not analyze data from patients excluded due to missing lactate, albumin, CRP and ProCT values. Moreover, we do not have data on albumin replacement, the start of antibiotic treatment, or the total amount of fluids administered. However, the efficacy of albumin as a prognostic factor can be negatively affected by health conditions that directly reduce the concentration of serum albumin (i.e., chronic malnutrition and inflammation). Finally, we did not have enough information to evaluate the performance of the lactate/albumin ratio with validated ICU scoring systems.

Conclusion

The lactate/albumin ratio is a readily available parameter with consistently better prognostic performance than initial serum lactate for in-hospital mortality in adult patients with sepsis. Raised lactate/albumin ratio showed significant association with increased mortality in patients with sepsis. Since lactate and albumin levels show a different course as sepsis progresses, the lactate/albumin ratio may be a new and perhaps a better indicator for the patient's prognosis. The lactate/albumin ratio is very easy to obtain and might therefore be very useful for risk stratification in critically ill patients. Larger, multicenter trials may be needed to further verify these findings.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study was approved by KTO Karatay University Faculty of Medicine Non-Drug and Medical Devices Studies Ethics Committee (Number: 2020/008, Date: 15.12.2020).

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