

СООТНОШЕНИЕ ЛАКТАТ / АЛБУМИН ПРИ СЕПСИСЕ

LACTATE/ALBUMIN RATIO IN SEPSIS

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THE PROFILE OF LACTATE, ALBUMIN, AND LACTATE/ALBUMIN RATIO AS PREDICTORS OF MORTALITY IN SEPSIS PATIENTS

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**ПРОФИЛЬ ЛАКТАТА, АЛЬБУМИНА И ОТНОШЕНИЯ ЛАКТАТ /
АЛЬБУМИН КАК ПРОГНОСТИЧЕСКИЕ МАРКЕРЫ СМЕРТНОСТИ
У ПАЦИЕНТОВ С СЕПСИСОМ**

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Abstract.

Background. Oxygenation disturbances in sepsis patients may cause increase lactate levels which is proportional to the severity of the inflammation, followed by decrease in albumin levels. Combination of these two parameters is expected to be predictor of mortality in patients with sepsis. The aim of this study is to investigate the profile of lactate, albumin, and lactate/albumin ratio as mortality predictors in patient with sepsis.

Methods. This prospective cohort study was conducted in the ICU of dr. Saiful Anwar Hospital Malang from January to May 2019. Subjects were 82 patients with sepsis (SOFA score >2). Lactate and albumin levels were measured on the first day of hospitalization. Lactate levels were examined by colorimetric method, albumin were examined by BCG method. The instrument used was Cobas 501. Comparison was carried out using the T-Test/Mann-Whitney test. Prediction of mortality risk was done using relative risk (RR) determination.

Results. Significant difference was observed in albumin levels between sepsis patients who survived and who died ($p = 0.045$). No significant differences were observed in lactate levels and lactate/albumin ratio between sepsis patients who survived and who died ($p = 0.211, 0.119$, respectively). Relative risks were 3.034 for lactate, 3.667 for albumin, and 4.400 for lactate/albumin ratio.

Conclusions In patients with sepsis, lactate/albumin ratio is the best variable in predicting mortality, followed by albumin and lactate value. Further study that implements repeated measurement of lactate and albumin 6 and 12 hour is required to better predict the mortality of sepsis patients.

Keywords: lactate, albumin, lactate/albumin ratio, mortality, sepsis, prognosis

Резюме. История вопроса. Нарушения оксигенации у пациентов с сепсисом могут вызывать повышение уровня лактата пропорционально тяжести воспаления, с последующим снижением уровня альбумина. Ожидается, что сочетание этих двух параметров может служить предиктором смертности у пациентов с сепсисом. Целью этого исследования являлось изучение профиля лактата, альбумина и соотношения лактат / альбумин как предикторов смертности у пациентов с сепсисом.

Методы. Настоящее проспективное когортное исследование было проведено в отделении интенсивной терапии Больницы д-ра Сайфул Анвар, Маланг, с января по май 2019 г. Испытуемые: 82 пациента с сепсисом (оценка SOFA > 2). Уровни лактата и альбумина измеряли в первый день госпитализации. Уровень лактата определяли колориметрическим методом, альбумин - методом БЦЖ на приборе Cobas 501. Сравнение проводилось с использованием Т-теста / теста Манна-Уитни. Прогнозирование риска смертности производилось с использованием определения относительного риска (ОР).

Полученные результаты. Достоверная разница наблюдалась в уровнях альбумина между выжившими и умершими пациентами с сепсисом ($p = 0,045$), без значительных различий в уровнях лактата и соотношении лактат / альбумин между выжившими и умершими пациентами с сепсисом ($p = 0,211, 0,119$, соответственно). Относительные риски составили 3,034 для лактата, 3,667 для альбумина и 4,400 для соотношения лактат / альбумин.

Выводы У пациентов с сепсисом соотношение лактат / альбумин является лучшим параметром для прогнозирования смертности, за ним следуют значения альбумина и лактата. Для более точного прогнозирования смертности пациентов с сепсисом требуется дальнейшее исследование, в котором следует повторно провести измерение лактата и альбумина через 6 и 12 часов.

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Ключевые слова: лактат, альбумин, соотношение лактат / альбумин, смертность, сепсис, прогноз.

1 INTRODUCTION

2 Sepsis is a life-threatening organ dysfunction caused by an unregulated host
3 response to infection.¹ Sepsis, including severe sepsis and septic shock, is a major
4 health problem and one of the leading causes of death. It is estimated that sepsis
5 occurs in 30 million people worldwide each year and has the potential to cause 6
6 million deaths. The mortality rate due to sepsis is approximately 6% of all causes
7 of death in hospital. Given the high mortality rate, it is important to determine the
8 prognosis in septic patients, to determine subsequent management.² Therefore, it is
9 necessary to develop biomarkers that can be used as predictors of mortality in
10 septic patients.

11 Several studies have shown that lactate levels are a reliable parameter in
12 predicting prognosis in septic patients.² Lactate levels may increase in septic
13 patients through several mechanisms.³ Low peripheral oxygenation in septic
14 patients leads to anaerobic glycolysis which leads to lactate production. In clinical
15 practice, lactate levels are commonly used to detect tissue hypoxia. However,
16 elevated lactate levels seem to reflect more than just tissue hypoxia.
17 Hyperlactatemia is also found in septic patients with normal tissue oxygenation
18 who experience excessive $\text{Na}^+\text{-K}^+\text{-ATPase}$ stimulation, where activation of $\text{Na}^+\text{-}$
19 $\text{K}^+\text{-ATPase}$ will cause release of lactate from muscle tissue.² Mitochondrial
20 insufficiency in metabolizing pyruvate caused by stress can also cause an increase
21 in lactate in septic patients.³ However, the source, clearance and metabolic function
22 of lactate in sepsis are still not well known.⁴

23 Other than elevated lactate, a study by Magnussen et al showed that in septic
24 patients, there was a decrease in albumin.⁵ Albumin is an acute phase protein
25 produced in the liver.² Decreased albumin levels have been linked to various
26 chronic conditions such as liver failure, malnutrition or enteropathy. However,
27 studies in critically ill patients have shown that albumin levels are more of an
28 indicator of inflammation reflecting the severity of inflammation rather than a
29 marker of nutritional status.^{2, 5} This supports the suggestion that albumin may serve

30 as an additional parameter as predictors of mortality and prognosis in septic
31 patients.^{2,6}

32 Both lactate and albumin are parameters that can independently predict
33 mortality. The combination of the two is expected to increase the predictive value
34 of mortality in septic patients. The aim of this study is to determine the profile of
35 lactate, albumin, and lactate/albumin ratio as predictors of mortality in septic
36 patients.

37

38 MATERIALS AND METHODS

39 This study was conducted in a prospective cohort study design. The research
40 was conducted at the Intensive Care Unit (ICU) of RSUD dr. Saiful Anwar
41 Malang, from January to May 2019. The subjects involved in this study were 82
42 patients who were treated in ICU RSUD dr. Saiful Anwar Malang, who met the
43 criteria for sepsis (Sequential Organ Failure Assessment score/SOFA score ≥ 2).
44 Inclusion criteria in this study were age >16 years, SOFA score ≥ 2 . While the
45 exclusion criteria were patients who had received albumin therapy. The study was
46 carried out after obtaining approval from the ethical committee of the Faculty of
47 Medicine, Brawijaya University/RSSA Malang.

48 Lactate and albumin levels were checked from serum samples taken on the
49 first day the patients were admitted. Lactate levels were checked by colorimetric
50 method using Cobas501, expressed in mmol/L. While albumin levels were checked
51 by colorimetric method bromcresolgreen (BCG) using Cobas501, expressed in
52 g/dL. The ratio of lactic acid/albumin was calculated from the results of the
53 examination of lactate levels divided by albumin levels.

54 Statistical analysis was carried out using IBM SPSS Statistics 25 software.
55 Comparison test was done using the T-test/Mann-Whitney with p level < 0.05
56 considered as significance. The prediction of the risk of mortality was done by
57 determining Relative Risk (RR), while the cut-off value was determined using
58 previous research data.

59

60 RESULTS

61 There were 82 subjects participating in this study, 22 (26.8%) of them were
62 discharged and 60 (73.2%) died. Complete lactate and albumin levels were only
63 found in 58 subjects, which were then analyzed in this study. Of 58 subjects, 13
64 (22.4%) were discharged, and 45 (77.6%) died. All of the subjects only undergone
65 the albumin and lactate examinations once when admission. The characteristic of
66 study subjects according to age and sex in the group of patients who were
67 discharged and died are shown in Table 1. Furthermore, the comparison test was
68 carried out with the T-test/Mann-Whitney test, and the p-values were 0.025 and
69 0.065, respectively.

70 There was a significant difference in albumin levels between septic patients
71 who were discharged and died with p levels of 0.045. There were no significant
72 differences in lactate levels, as well as lactate/albumin ratio in septic patients who
73 were discharged and died with p values of 0.211 and 0.119, respectively (Table 1).

74 The cut off value determined for lactate levels, albumin levels and
75 lactate/albumin ratio variables were 4.00 mmol/L, 2.45 g/dL and 1.32,
76 respectively. With this cut off value, the RR was 3.034 for lactate variable, 3.667
77 for albumin, and 4.400 for lactate/albumin ratio.

78 **Table 1. Study's Subjects Characteristics. Lactate Acid Levels. Lactate**
79 **Acid/Albumin Ratio in Patients Who Were Survived and Died**

80

81 DISCUSSION

82 The results showed that the median of lactate levels in patients who died was
83 higher than in patients who were discharged. Lactate levels in the group of patients
84 who died were in the range of 1.60-8.20 mmol/L. Of the 13 patients who were
85 discharged, 9 (69.2%) had high lactate levels (>2 mmol/L). In contrast, of the 45
86 patients who died, 6 (13.3%) had normal lactate levels (≤ 2.0 mmol/L). These
87 results correspond with the study conducted by Nichol et al which showed that not

88 only hyperlactatemia (>2.0 mmol/L), but relative hyperlactatemia and lactate
89 levels in the upper normal range, were also associated with increased mortality.^{7,8,9}

90 Although the mean lactate level was higher in patients who died than in
91 patients who were discharged, there was no significant difference between the two
92 groups. These results can be explained as follows: (1) not every hyperlactatemia is
93 associated with acidosis, which is an important contributor to poor prognosis.⁷
94 Lactic acidosis is better at predicting mortality in patients with severe sepsis and
95 septic shock, compared with hyperlactatemia. Acid-base status needs to be
96 considered in predicting the prognosis of septic patients when using serum lactate
97 levels.¹⁰ (2) the mechanisms that cause hyperlactatemia may play an important role
98 in predicting mortality, rather than the hyperlactatemia itself. Lactate levels depend
99 not only on lactate production but also on its clearance. It is not known which
100 mechanism is more important in the prediction of mortality,^{7,9} study by Haas et al
101 demonstrated that severe hyperlactatemia correlates with ICU mortality,
102 particularly if lactate clearance does not occur within 12 hours of admission.¹¹ (3)
103 comorbidities, such as renal failure, may also have an additional role in the
104 incidence of mortality.⁷

105 However, the results of this study indicate that lactate levels ≥ 4.0 mmol/L
106 have an RR value of 3.034 in predicting mortality in septic patients. These results
107 are consistent with the study conducted by Thomas Rueddel et al which showed
108 that at lactate levels of ≥ 4.0 mmol/L, an OR of 3.0 was obtained in predicting
109 mortality 28 days after treatment in septic patients.¹² The study by Mikkelsen et al
110 also showed that moderate (2.0-3.9 mmol/L) and severe (≥ 4.0 mmol/L) increase in
111 lactate levels can predict mortality by 2.05-3.27 times and 4.87 times in patients
112 with sepsis.¹³ The study by Hasegawa et al showed that an increase in lactate levels
113 can predict mortality within 90 days in septic patients with Disseminated
114 Intravascular Coagulation (DIC) with an Odds Ratio (OR) of 2.31, but not in the
115 group of septic patients without DIC.

116 Dynamic changes in lactate levels are better than single lactate assays in
117 predicting outcome in critically ill patients.⁸ Normalization of lactate levels
118 suggests an improvement in tissue oxygenation and aerobic metabolism.^{4, 7} The
119 study conducted by Nguyen et al showed that high lactate clearance in septic
120 patients occurring within the first 6 hours, has been shown to be associated with a
121 reduction in 60-day mortality. Lactate clearance occurred in 38% of the patient
122 group who survived. Whereas in the group of patients who died, lactate clearance
123 was only obtained by 12%.¹⁴ However, lactate clearance could not be assessed in
124 this study because serial lactate levels were not examined.

125 Lower mean albumin levels were found in patients who died than in patients
126 who were discharged, with a significant difference between the two groups. This
127 result corresponds with studies by Gupta et al and Takegawa et al which showed
128 that the mortality in patients with sepsis, severe sepsis, septic shock with
129 hypoalbuminemia was higher than without hypoalbuminemia.^{15, 16} The study by
130 Yin et al also showed that 28-day survival rate in patients with serum albumin
131 <2.92 g/dL was lower than in patients with serum albumin ≥ 2.92 g/dL.¹⁷ In ICU
132 patients, serum albumin can be used as a clinical prognostic predictor, although its
133 levels may also reflect an acute phase response. The decrease in albumin levels is
134 in line with the increase in pulmonary vascular permeability, which may play a
135 role in mortality. Decrease in albumin that occurs within 1-3 days has a higher
136 mortality risk than the decrease in albumin that occurs within 7-14 days.¹⁶ In
137 addition to affecting vascular permeability, patients with low serum albumin levels
138 are more likely to experience infection from abdominal/pelvic sources, acute
139 kidney or liver damage, septic shock, and generally have a higher APACHE II and
140 SOFA score.¹⁷

141 The study by Qian et al showed that the optimal cut off value of albumin
142 which indicates a poor outcome is <2.45 g/dL, where the albumin level can predict
143 both short and long term mortality in patients with septic shock.¹⁸ The result

144 corresponds with this study which showed that albumin levels (<2.45 g/dL) is a
145 good predictor of mortality with a RR value of 3.667.

146 Kendall H investigated baseline albumin levels at presentation, the trends in
147 albumin decline and the lowest albumin levels in relation to predictors of mortality
148 in septic patients. The results showed that the mortality rate in septic patients with
149 initial albumin levels ≤ 2.45 g/dL was 63.4%. The mortality rate became 70.6% if
150 there is a decrease in albumin levels.¹⁹ The lowest albumin level is the best
151 predictor of mortality, compared to the initial albumin level and the decreasing
152 trend in albumin.⁶ The examination of serial albumin levels was not carried out in
153 this study, so the trend of decreasing albumin and the lowest albumin levels cannot
154 be evaluated.

155 There was a higher lactate/albumin ratio in patients who died than in patients
156 who were discharged. However, there was no significant difference between the
157 two groups. The optimal cutoff value of lactate/albumin ratio in the study
158 conducted by Jikyoung et al was 1.32.²⁰ In this study, the cut-off value could be
159 used as a predictor of mortality in septic patients with an RR of 4.400. The study
160 by Wang et al showed similar results where the lactate/albumin ratio on the first
161 day of admission was higher in the MODS patient group (median of 2.295)
162 compared to the group of patients without MODS (median of 1.550). The
163 lactate/albumin ratio can predict mortality with AUC of 0.84.²¹ These results also
164 correspond with the study by Jikyoung et al and Thapa et al which showed that
165 lactate/albumin ratio can predict mortality within 28 days, with AUC of 0.69 and
166 0.90.^{20, 22} Lactate/albumin ratio is better than lactate levels in predicting mortality
167 in septic patients,²⁰ according to the study.

168 The results of this study indicate that the lactate/albumin ratio is the best
169 predictor of mortality, followed by albumin levels and lactate levels. Limitations of
170 this study include: (1) bias from the variation of therapy is an uncontrollable factor.
171 For example, administration of epinephrine, metformin, nucleoside analog, high
172 volume hemofiltration with lactate-buffered fluid, will cause an increase in lactate

173 levels,⁹ (2) comorbidity is also an uncontrollable factor in this study, (3) lactate and
174 albumin examination was only performed once on the first day of admission so the
175 normalization of lactate levels and the trend of decreasing albumin levels could not
176 be evaluated.

177 In septic patients, the albumin level is the best predictor of mortality,
178 followed by lactate/albumin ratio and lactate level. Further study is needed with 6
179 and 12 hours of lactate and albumin serial examination, so that the prediction of
180 mortality in septic patients can be better.

181

182 **CONFLICT OF INTEREST STATEMENT**

183 We declare that we have no conflict of interest.

184

185 **ACKNOWLEDGEMENTS**

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189 for best collaboration in this research.

TABLES

Table 1. Study's Subjects Characteristics. Lactate Acid Levels. Lactate Acid/Albumin Ratio in Patients Who Were Survived and Died

Characteristics	Survived	Died	p value	RR*
Amount of subjects	13 (22.4%)	45 (77.6%)		
Age (year old)	45.85 ± 16.58	56.75 ± 14.50	0.025	
Gender				
Male	4 (12.9%)	27 (87.1%)	0.065	
Female	9(33.3%)	18 (66.7%)		
Lactate levels^a				
Median	2.80	3.30	0.211	3.034
<4 mmol/L	11 (27.5%)	29 (72.5%)		
≥ 4 mmol/L	2 (11.1%)	16 (88.9%)		
Albumin levels^b				
Mean ± SD	3.02 ± 0.56	2.68 ± 0.52	0.045	3.667
Range	2.68 – 3.36	2.53 – 2.84		
≥ 2.45 g/dL	11 (28.9%)	27 (71.1%)		
< 2.45 g/dL	2 (10.0%)	18 (90.0%)		
Lactate/Albumin ratio				
Mean ± SD	1.01 ± 0.59	1.35 ± 0.70	0.119	4.400
Range	0.66 – 1.37	1.14 – 1.56		
<1.32	11 (30.6%)	25 (69.4%)		
≥ 1.32	2 (9.1%)	20 (90.9%)		

*RR: *Relative Risk*; SD = Standard Deviation. ^aResults in mmol/L; ^bResults in g/dL

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The Profile of Lactate, Albumin, and Lactate/Albumin Ratio as Predictors of Mortality in Sepsis Patients

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