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RESEARCH

The Relationship Of Lactate-Albumin Ratio To Mortality And Length Of Stay In Sepsis Patients At ICU Dr. Sardjito General Hospital

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ABSTRACT

Background : Sepsis is one of the causes of morbidity and mortality patients hospitalized in the intensive care unit (ICU) which requires early detection and management to predict outcomes. An increase in lactate together with decrease in albumin is encountered in severe inflammatory states. Lactate-albumin ratio has a predictive value of mortality in patient with sepsis that is similar to APACHE II and SOFA scores. These biomarkers can be done quickly, affordable, and available in many hospitals in Indonesia.

Objective : To determine the relationship between the lactate-albumin ratio and mortality and length of stay patient with sepsis in ICU of Dr. Sardjito Hospital.

Method : Research design using a retrospective cohort observational study method by collecting data from the medical records of sepsis patients treated at ICU of Dr. Sardjito Hospital. Data on lactate and albumin in plasma levels at admission and mortality events were collected to calculate the optimal cutoff using the ROC curve. The relationship between lactate-albumin ratio levels and mortality was analyzed using the chi-square test method followed by logistic regression in multivariate analysis.

Results : The total study subjects were 136 patients, wuth a median age of 55 years. The cut-off value for the Lactate-Albumin ratio in predicting mortality was found to be 0,878, with a sensitivity of 73.0 % and a specificity of 57.1% (AUC = 0,687; 95% CI 0,56-0,81; p=0,007). The cut-off value for the Lactate-Albumin ratio in predicting ICU length of stay was found to be 0,878, sensitivity 71,2% and specificity 63,6% (AUC = 0,684; 95% CI 0,53-0,84; p=0,043). Multivariate analysis showed that an increase in the Lactate-Albumin ratio was an independent and significant factor as a predictor of mortality (OR=3,43; 95% CI 1,29-9,16; p=0,013) and ICU length of stay (OR=4,33; 95% CI 1,19-15,68; p=0,036). Age, sex, hypertension, diabetes mellitus, cancer, obesity, and cerebrovascular disease were not independently associated with mortality dan ICU length of stay.

Conclusion : An increase in the Lactate-Albumin ratio is independently and significantly associated with an increased risk of mortality and length of stay in sepsis patients.

Background

The definition of sepsis based on The Third International Consensus Definitions for Sepsis and Septic Shock in 2016 is a life-threatening organ dysfunction caused by dysregulation of the host body's response to infection. Clinical evidence is in the form of abnormal body temperature (> 38°C or < 360C), tachycardia, metabolic acidosis, usually accompanied by respiratory alkalosis, tachypneu, and an increase or decrease in the number of white blood cells. Sepsis can be caused by an infection from bacteria, viruses or fungi.[1]

Data from the Center for Disease Control (CDC) shows that the incidence of sepsis increased by + 8.7% annually, from 164,000 cases (83 per 100,000 population) in 1979 to 660,000 cases (240 cases per 100,000 population) in 2000. There were 48.9 million cases and about 11 million sepsis-related deaths worldwide, accounting for nearly 20% of all deaths globally in 2017. Meanwhile, in developing countries, the death rate from sepsis is higher, which is around 35.5%. This death rate tends to rise and now ranks 10th in the cause of death in the United States.[1]

Sepsis is one of the most common causes of death in inpatients in intensive care units (ICU) even with the latest antibiotics and resuscitation therapy. The death rate from sepsis is much greater than due to acute coronary syndrome or stroke. Mortality can be as high as 30% in patients with sepsis who are treated in the intensive care unit.[2]

There are three main problems in the diagnosis of sepsis: 1) the clinical symptoms are not specific to sepsis; 2) no biomarker has sufficient sensitivity and specificity to identify sepsis due to complex pathophysiology; and 3) sepsis is a heterogeneous syndrome with no single cause, phenotype, or biological characteristics. These highly diverse and non-specific clinical parameters make it difficult to diagnose and evaluate sepsis, resulting in delays in identification and inadequate resuscitation, leading to high mortality. If the mortality of sepsis patients can be predicted so that resuscitation can be administered aggressively, then the survival rate is expected to increase.[3]

Of the several markers that are widely used, it is mentioned that lactate and albumin have a relationship with mortality in sepsis. Organ dysfunction syndrome in sepsis patients is related to tissue hypoperfusion where there is a maldistribution of blood flow in organs or microvessels or the inability of cells to use oxygen (cytotoxic hypoxia). Cytotoxic hypoxia results in anaerobic metabolism in the cytosol which will increase the formation of lactate. An increase in blood lactate levels indirectly indicates the overall severity of organ dysfunction associated with an increased risk of mortality.[4]

Hyperlactatemia is the main finding of sepsis that shows an increase in glycolytic flux due to hypermetabolism. A study conducted by Chebl et al (2017) on the relationship between increased lactate levels and length of stay of sepsis patients in the ICU showed that patients with elevated lactate who were alive and allowed to be outpatient had a longer length of stay than patients with normal lactate levels. This study also states that lactate levels are important prognostic markers for mortality where it is stated that at lactate levels of 2-4 mmol/l there is a mortality of 12% and at lactate levels > 4 mmol/l mortality is 40.7%.[5]

Albumin is a negative acute phase protein, which is a type of protein whose concentration decreases in response to inflammation, so albumin can describe the severity of inflammation. The condition hypoalbuminemia in sepsis is associated with increased vascular permeability and capillary leakage resulting in the loss of albumin from the intravascular compartment, which can also occur due to reduced synthesis and increased albumin catabolism. Some studies suggest that albumin may serve as an additional parameter for assessing mortality and prognosis, meanwhile serum albumin status can be affected by nutritional status and chronic inflammatory conditions. Research conducted by Qian et al (2019) found that albumin levels < 2.45 gr/dl is the optimal limit value of hypoalbuminemia which can independently predict mortality in sepsis patients and is a parameter that greatly affects the prognosis and increases ICU length of stay about 28% and hospital days 71%.[2,6]

Abnormal lactate and albumin levels in severe sepsis together can provide a prognostic index that positively correlates with infection. Both parameters can predict mortality independently so the combination of the two is intended to further improve the predictive value. A study conducted by Albee et al (2022) showed that patients with Lactate-Albumin ratio > 0.69 on the first day had a greater chance of decease within 28 days and were strongly correlated with prolonged ventilator use and prolonged hospitalization. Meanwhile, a study conducted by Lichtenauer et al (2017) showed that the Lactate-Albumin ratio > 0.15 was associated with long-term mortality that could occur even after correction.[7,8]

Several predictive assessment systems were developed to objectively evaluate the prognosis and mortality due to organ dysfunction in sepsis patients. Commonly used scoring systems including sequential organ failure assessment (SOFA) scores and acute physiology and chronic health evaluation (APACHE II) have been widely used as standard predictors of mortality in patients with critical illness, including patients with sepsis. This score has been validated and used in many countries due to its simplicity as a predictor of mortality. Research conducted by Erdogan, et al (2022) reported that the Lactate-Albumin ratio has a predictive value that is not much different from the APACHE II and SOFA scores in predicting mortality in sepsis patients consistently. This marker have several advantages, including that it can be done quickly in terms of the time needed for screening, cheap in terms of cost, practice in its examination method, and can be used as an alternative predictor in predicting mortality if the scoring system cannot be done.[8,9]

Methods

This study is an observational study of a retrospective cohort by taking secondary data from the medical records of patients with confirmed sepsis during admission who were treated in the ICU room of Dr. Sardjito General Hospital. The study was conducted by collecting medical record data of patients with confirmed sepsis (SOFA score > 2) who were examined for lactate and plasma albumin during admission. Data was taken from medical records at the Medical Record Installation of Dr. Sardjito General Hospital. The research was carried out after obtaining the approval of the Ethics Committee. The research population used was all patients with confirmed sepsis at the time of admission based on the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (SOFA score > 2) in the age group > 18 years who were admitted at ICU of Dr. Sardjito General Hospital since January 2022 until the number of samples was reached. The samples used were all subjects who met the inclusion and exclusion criteria of the study population. The inclusion criteria are patients aged 18 years or older who were confirmed to have sepsis (SOFA score > 2) during admission who are treated at ICU of Dr. Sardjito General Hospital.

The exclusion criteria are patients with chronic kidney disease (patients who routinely undergo dialysis), nephrotic syndrome, hepatic cirrhosis, post-return of spontaneous circulation (ROSC), burns, metformin treatment, and kwashiorkor, and those who receive albumin transfusions before being admitted to the ICU.

The data is checked for completeness and accuracy and then coded, tabulated and entered into a computer. The characteristic data of the research subjects were presented in the form of descriptive statistical values such as mean and standard deviation (numerical variables with normal distribution), median and range (numerical variables with no normal distribution), and frequency distribution (categorical variables). The normality test of numerical variable data was carried out using the Kolmogorov-Smirnov technique. If the test produces p>0.05, the data is declared to be normally distributed.

Data on Lactate-Albumin levels during admission were collected to calculate the optimal cut-off using the ROC curve. The relationship between the Lactate-Albumin ratio to mortality and length of stay was analyzed by the method of testing the difference in proportion between the two groups using the chi-square test. After obtaining univariate results and if the p value < 0.25 is obtained, it was followed by a multivariate analysis between the independent variable and other variables on mortality and length of stay. The test is declared significant if it produced p < 0.05.

Results

The data normality test was carried out using the Kolmogorov Smirnov technique and obtained abnormally distributed data. Thus, the data on the characteristics of research subjects are presented in the form of descriptive statistical values using median.

The characteristics of the research subjects are described in Table 1. Of the 136 samples, the median age of patients was 55.6 + 15.4 years and consisted of male (55.1%) and female (44.9%). The most common comorbidities were malignancy (33.8%), hypertension (25.0%), and diabetes mellitus (22.1%). The details of the distribution of basic characteristics of patients diagnosed with sepsis who are treated in the ICU of Dr. Sardjito General Hospital include age at diagnosis, gender, BMI (Body Mass Index), comorbidities, length of stay, and mortality. The median length of stay for all patients in the ICU is 10 days. The median admission lactate-albumin ratio was 1.1. The median SOFA score of all patients in the ICU is 8. The patients who deceased was more than the living about 115 patients (84.5%).

ROC analysis was performed to determine the cut-off of the Lactate-Albumin ratio of admission to clarify patients at high and low mortality risk. The selected cut-off is the farthest point from the curve to the diagonal line, which mathematically provides optimal prognostic performance (a combination of sensitivity and specificity).

The results of the ROC analysis showed AUC=0.687 with p=0.007. This shows that the Lactate-Albumin ratio is a significant predictor in predicting mortality but the quality of discrimination is in the weak category. The optimal cut-off using the Youden Index method, which is the farthest distance from the sensitivity – (1-specificity), obtained a lactate-albumin ratio of 0.878 with a sensitivity of 73.0% and a specificity of 57.1%.

Demographic data of research subjects were analyzed based on mortality, as shown in Table 4. The average age of the deceased patients was older than the living (56.4 vs 55.6), but showed no significant difference (p=0.132). Male patients experienced more mortality (53.9%) than female patients (46.1%) and showed no significant difference (p=0.498). In terms of comorbidities, patients with malignancies experienced more mortality (33.0%, p=0.653), and patients with cardiovascular disease experienced mortality with a statistically significant difference (16.5%; p=0.044). The median Lactate-Albumin ratio of deceased patients was higher than the survived patient, with a statistically significant difference (1.2 vs 0.8; p=0.007).

Table 1. Characteristics of Research Subjects

Parameters		Median minimal-maksimal)	N	% (n=136)
Age (years)		55,6 ± 15,4		
Gender	Male		75	55,1%
	Female		61	44,9%
BMI (kg/m²)		22.5 (13.9-54.7)		
Hypertension			34	25,0%
Cardiovascular disease			19	14,0%
Diabetes Mellitus			30	22,1%
Malignancy			46	33,8%
Obesity			11	8,1%
Cerebrovascular disease			29	21,3%
Admission Lactate		2,7 (0,7-16,8)		
Admission Albumin		2,6 (0,7-5)		
Lactate-Albumin ratio		1,1 (0,2-7,5)		
SOFA score		8 (3-15)		
ICU length of stay		10 (0-43)		
Output	Alive		21	15,5%
	Deceased		115	84,5%

Table 2. Table of Area Under Curve (AUC), Sensitivity, and Specifity of Lactate Albumin Ratio at Admission

Parameters	AUC	P	95% CI	Cut-off	Sensitivity	Specificity
Lactate-Albumin Ratio	0,687	0,007*	0,56-0,81	0,878	73,0%	57,1%

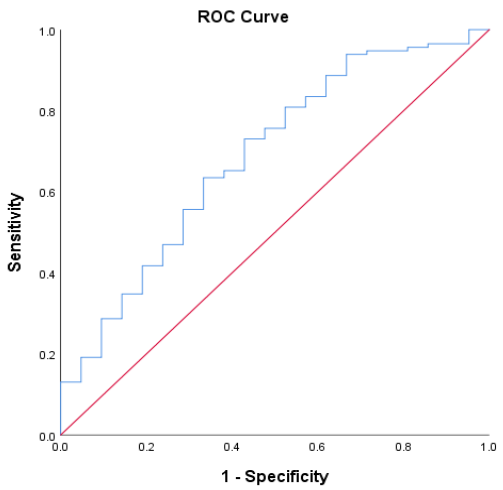

Figure 1. ROC Curve of Lactate-Albumin Ratio as a Predictor of Mortality

Table 3. Sensitivity, Specifisity, and Youden's Index Cut-off Value based on ROC Curve

Cut-off Value	Sensitivity	Specificity	Youden's Index
0,845	0,739	0,524	0,263
0,859	0,730	0,524	0,254
0,878	**0,730**	**0,571**	**0,302**
0,888	0,722	0,571	0,293
0,896	0,713	0,571	0,284

Table 4. Characteristics of Research Subjects based on Mortality

Parameters		Alive (n = 21)		Deceased (n = 115)		P
		N	%	N	%	
Age (years)	< 60 years	15	71,4%	61	53,1%	0,132*
	≥60 years	6	28,5%	54	46,9%	
Gender	Male	13	61,9%	62	53,9%	0,498
	Female	8	38,1%	53	46,1%	
BMI		23,4 (16,6-35,6)		22,5 (13,9-54,7)		0,418
Hypertension		4	19,0%	30	26,1%	0,493
Cardiovascular Disease		0	0,0%	19	16,5%	0,044*+
Diabetes Mellitus		3	14,3%	27	23,5%	0,567
Malignancy		8	38,1%	38	33,0%	0,653
Obesity		3	14,3%	8	7,0%	0,375
Cerebrovascular Disease		3	14,3%	26	22,6%	0,565
Lactate-Albumin Ratio		0.8 (0,2-2,8)		1.2 (0,3-7,5)		0,007*+

*)p < 0,05 is statistically significant, tested using *chi-square*
+)p < 0,25, will be tested in multivariate analysis
BMI : Body Mass Index

After the univariate analysis was carried out as presented in Table 4, a multivariate test analysis was carried out to determine the factors that had a significant influence on mortality from the independent variable and confounding variable. Variables that continued in the multivariate analysis were those that had p<0.25 in the univariate test.

The multivariate analysis showed that the Lactate-Albumin ratio remained significant in predicting mortality (OR 3.43; p=0.013), while the age and comorbidities of cardiovascular disease did not show significant differences.

Demographic data of the research subjects were analyzed based on the length of stay in ICU, as shown in table 6. The data showed that patients with younger age (<60 years) were treated in the ICU with longer days of treatment (54.4% vs 45.6%) but did not show a significant difference (p=0.346). Male patients were more treated in the ICU with longer days of treatment (54.4% vs 45.6%) than female and showed no significant difference (p=0.754). In terms of comorbidities, patients with malignancies were more likely to undergo treatment in the ICU with longer days of treatment (32.8%, p=0.508). The outcomes of patients with longer treatment (>3 days) were more than those with <3 days of treatment, which was 125 patients (91.9%).

Table 5. Results of Multivariate Analysis of Lactate-Albumin Ratio and Other Variables with Mortality in Sepsis Patients

	P	OR	CI 95%
Lactate-Albumin Ratio ≥ 0,878	0,013*	3,43	1,29-9,16
Age	0,241	1,02	0,99-1,05
Cardiovascular Disease	0,998	256295679	0-∞

*)p < 0,05 is statistically significant

Table 6. Characteristics of Research Subjects based on Length of Stay in ICU

Variable		Length of Stay (Days)						p
		< 3 days (n=11)		≥ 3 days (n=125)		Total		
		n	%	N	%	N	%	
Age	< 60 years	8	72,7%	68	54,4%	76	55,9%	0,346
	≥ 60 years	3	27,3%	57	45,6%	60	44,1%	
Gender	Male	7	63,6%	68	54,4%	75	55,1%	0,754
	Female	4	36,4%	57	45,6%	61	44,9%	
Obesity	Yes	1	9,1%	10	8,0%	11	8,1%	0,291
	No	10	90,9%	115	92,0%	125	91,9%	
Hypertension	Yes	1	9,1%	33	26,4%	34	25,0%	0,362
	No	10	90,9%	92	73,6%	102	75,0%	
Cardiovascular Disease	Yes	0	0,0%	19	15,2%	19	14,0%	0,455
	No	11	100,0%	106	84,8%	117	86,0%	
Diabetes Mellitus	Yes	1	9,1%	29	23,2%	30	22,1%	0,508
	No	10	90,9%	96	76,8%	106	77,9%	
Malignancy	Yes	5	45,5%	41	32,8%	46	33,8%	0,456
	No	6	54,5%	84	67,2%	90	66,2%	
Cerebrovascular Disease	Yes	1	9,1%	28	22,4%	29	21,3%	1,000
	No	10	90,9%	97	77,6%	107	78,7%	

ROC analysis was carried out to determine the cut-off of the Lactate-Albumin ratio of admission to clarify the risk of patients with long stay in the ICU >3 days and <3 days. The results of the ROC analysis were obtained AUC=0.684 with p=0.043. This shows that the Lactate-Albumin ratio is a significant predictor in predicting the length of stay in the ICU with the quality of discrimination in the weak category. The Lactate-Albumin ratio was obtained at 0.878 with a sensitivity of 71.2% and a specificity of 63.6%.

Table 7. Table of Area Under Curve (AUC), Sensitivity, and Specificity of Lactate-Albumin Ratio to Length of Stay in ICU during Admission

Parameter	AUC	P	95% CI	*Cut-off*	Sensitivity	Specificity
Lactate-Albumin Ratio	0,684	0,043*	0,53-0,84	0,878	71,2%	63,6%

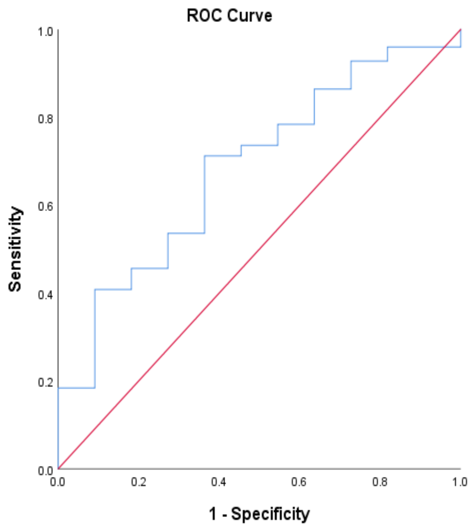

Figure 2. ROC Curve of Lactate-Albumin Ratio as a Predictor of ICU Length of Stay

Table 8. Sensitivity, Specificity, and Youden's Index Cut-off Value based on ROC Curve

Cut-off Value	Sensitivity	Specificity	Youden's Index
0,845	0,720	0,545	0,265
0,859	0,712	0,545	0,257
0,878	**0,712**	**0,636**	**0,348**
0,888	0,704	0,636	0,340
0,896	0,696	0,636	0,332

The multivariate analysis showed that patients with high Lactate-Albumin ratio significantly experienced a longer stay in the ICU compared to low Lactate-Albumin ratio (95.7% vs. 83.7%; p=0.036). The OR=4.33 (95% CI 1.19-15.68) showed that patients with high Lactate-Albumin ratio were 4.33 times more likely to experience prolonged hospitalization in the ICU than patients with low Lactate-Albumin ratio.

Table 9. Differences in the Proportion of Patients with Prolong Length of Stay based on Lactate-Albumin Ratio

Lactate-Albumin Ratio	Length of Stay n (%)		P	OR	95% CI
	≥3 days	<3 days			
Lactate-Albumin Ratio ≥ 0,878	89 (95,7%)	4 (4,3%)	0,036*	4,33	1,19-15,68
Lactate-Albumin Ratio < 0,878	36 (83,7%)	7 (16,3)			

Discussion

This study was conducted to assess the relationship between the Lactate-Albumin ratio during admission to identify its potential as a simple parameter in predicting mortality in sepsis patients. The simpler parameter, the easier it is to use it in various settings as a basis for clinical decision-making. A total of 136 patients were obtained in this study, with an average age of 55 years and the proportion of male and female gender was relatively balanced, namely 55.1% male and 44.9% female. In this study, more patients were found with an outcome of death (84.5%). This is possible because many patients are included in severe sepsis conditions which can be seen from the median of SOFA score at the time of admission is 8. In The Third International Consensus Definitions for Sepsis and Septic Shock (2016), it is stated that patients with a

SOFA score of 2 or more will have a risk of mortality 2 to 25 times higher than patients with a SOFA score of less than 2. In another study, it was also stated that the initial SOFA score in patients treated in ICU 2 to 7 was associated with a mortality rate of 37%, a SOFA score of 8 to 11 was associated with a mortality rate of 60% and a SOFA score of more than 11 was related with the highest mortality rate of more than 90%.1,21

The relationship between the Lactate-Albumin ratio in this study was analyzed as a nominal variable to make it simpler in its use. For this reason, ROC and Youden's Index were used to determine the optimal cut-off ratio of Lactate-Albumin to mortality in patients with sepsis. The analysis of this study showed that the optimal cut-off value of the Lactate-Albumin ratio was 0.878, with a sensitivity of 73.0% and a specificity of 57.1% and AUC of 0.687 (95% CI 0.56-0.81; p=0.007). This indicates that the Lactate-Albumin ratio is a significant predictor of death, but its discriminatory ability in distinguishing the decease and alive groups is in the weak category because it has AUC < 0.7. This result can be compared to a study conducted by Chebl, et al (2020) showed an AUC of 0.67 with a cut-off value of 1.22, sensitivity of 59% and specificity of 62%. The AUC of the Lactate-Albumin ratio in this study is similar to the study, namely in the category of weak discrimination. However, better AUC results were shown by the research of Albee, et al (2022) with an AUC value of 0.72 and a cut-off of the Lactate-Albumin ratio of 1.22 with a sensitivity of 62% and a specificity of 68%.7,10

Compared with the research of Chebl, et al (2020) and Albee, et al (2022), the cut-off point in this study has a higher sensitivity, but lower specificity. This means that with the cut-off, it can cause false positives, so that patients who are not at risk of death can have a Lactate-Albumin ratio of >0.878. When parameters with high sensitivity are used, the risk of mortality can be identified early. Low sensitivity leads to the possibility of undetected mortality, especially at the beginning of the course of the disease. The difference in AUC, sensitivity, and specificity of previous studies compared to this study can be caused by differences in the characteristics of the subjects, especially the comorbidities suffered by the study subjects. 7,10,11

The chi-square analysis in this study showed a significant relationship between the Lactate-Albumin ratio and mortality incidence. Lactate-Albumin ratio of >0.878 at admission showed a 3.43-fold increased risk of death (95% CI 1.29-9.16; p=0.013). These results are in line with the findings of several previous studies. A study by Chebl, et al (2020) showed that the value of the Lactate-Albumin ratio increased significantly in the deceased group (1.93+1.63) compared to the group that lived (1.20+1.03), p<0.001. Patients with a Lactate-Albumin ratio > 1.22 showed a 4.56 times greater risk of dying. Similar results were shown by Lichtenauer, et al (2017) on 348 sepsis patients with a higher Lactate-Albumin ratio value of deceased patients (median 0.31 ; 0.15-2.0) compared to living patients (median 0,09 ; 0,02-0,15), p<0,001 and Lactate-Albumin ratio > 0,15 increased the risk of mortality by 4,27 times. Meta-analyses conducted on seven studies with 10,264 patients also showed that higher lactate-albumin ratio were associated with increased mortality in sepsis and sepsis shock patients (OR 1,49, IK 95% 1,37-1,62;p<0,001).8,10,12

The pathophysiological mechanisms underlying the prognostic value of Lactate-Albumin have been consistently mentioned in several previous studies. Malnutrition, inflammation, and hypoperfusion problems occur in patients with sepsis. Hypoperfusion in sepsis patients accompanied by decreased peripheral oxygenation triggers an anaerobic glycolysis process that can increase lactate production. Checking lactate levels in the blood can be done easily and quickly. Lactate has been used as an indicator of tissue hypoperfusion and cellular hypoxia in sepsis patients that can predict mortality, organ dysfunction, and risk classification. Increased lactate levels in sepsis can also be caused by excessive stimulation of catecholamines that increase the activity of the Na-K-ATPase enzyme and increase pyruvate production. Lactate levels are said to be influenced by many factors, including due to the consumption of metformin and liver disease which interfere with the lactate clearance process in the blood so that it can increase lactate levels. This may limit the use of lactate as a reliable laboratory test.13

It is mentioned that albumin as the most widely circulated protein and is the main expander of plasma, plays an important role in the neutralization of free radicals and exogenous or endogenous substances, antioxidants, immune modulation, anti-inflammatory processes, and endothelial stabilization and is synthesized by the liver. Because it is the main protein in human blood, a decrease in albumin due to decreased synthesis and increased product degradation causes impaired regulation of intravascular oncotic pressure and manifests clinically as edema. Serum albumin concentrations in sepsis patients can be reduced due to intense systemic inflammatory processes, increased capillary leakage, tissue ischemic damage, reperfusion injury, and decreased immunological response.14

In the study Shadvar, et al., (2022), it was found that the prognostic value of the lactate-albumin ratio (AUC 0.963, 95% CI 0.918-0.987, $p<0.001$) was said to be better on mortality in sepsis patients compared to lactate levels (AUC 0.917, 95% CI 0.861-0.956, $p<0.001$). This study also explains the need for repeated lactate examinations to identify mortality risk. This is also similar to a study conducted by Shin, et al., (2018) which presented the results of the prognostic strength of the superior lactate-albumin ratio compared to a single lactate examination in predicting 28-day mortality in sepsis patients.15,16

The relationship of other variables to the output was also analyzed using chi-square. From the analysis, in terms of comorbidities, there was an increase in the proportion of mortality in sepsis patients with cardiovascular disease and showed a significant difference ($p=0.044$). This can be explained by the presence of hemodynamic instability conditions and increased lactic acid levels caused by perfusion insufficiency and hypoxia. This increase in lactate levels is associated with an increased risk of death in patients with acute heart failure. There is a severe and common decrease in ejection fraction in patients with heart disorders, usually receiving routine diuretic therapy for a long time, which can cause insufficiency of tissue perfusion. Hypoalbuminemia that occurs in patients with heart disorders caused by congestive to the liver is statistically stated to occur in 14% of patients with heart failure. A retrospective study of 2626 patients with heart disorders showed that patients with heart disorders had a significantly higher Lactate-Albumin ratio in patients who died compared to those who lived (1.36 vs 0.62, $p<0.05$). The survival analysis using kaplan meier also showed a lower curve in patients with a high lactate-albumin ratio compared to patients with a low lactate-albumin ratio ($p<0.001$) and further increased the risk of death (log rank $p<0.001$).17

The analysis in this study showed that

there was a significant relationship between the Lactate-Albumin ratio and the length of treatment. The lactate-albumin ratio >0.878 at admission showed a 4.33-fold increased risk for long-term prolongation with a sensitivity of 71.2% and a specificity of 63.6% (95% CI 1.19-15.68; p=0.036). This indicates that the Lactate-Albumin ratio in this study is a significant predictor in predicting the length of treatment, but the discriminatory ability is in the weak category. These results can be compared with a cohort study conducted by Mourya, et al., (2023) on 100 patients showing a significant relationship between the Lactate-Albumin ratio and the length of stay in the ICU (>3 days vs <3 days) with an AUC of 0.730 with a cut-off value of 1.30, sensitivity of 85.0% and specificity of 58.8% (p=0.006). Higher AUC results can be caused by differences in cut off points and differences in the characteristics of the samples used.18

Research on the ratio of Lactate-Albumin to the length of hospitalization of sepsis patients is still rare. The dependent variable commonly used to describe the prognosis by the value of the Lactate-Albumin ratio is mortality. However, there is a study by Shadvar, et al., (2022) which examined the relationship between the Lactate-Albumin ratio and the length of stay of treated sepsis patients and obtained the results that the Lactate-Albumin ratio as a good prognostic predictor of the outcome of hospital stay with a sensitivity of 76.7% and a specificity of 62.5% (AUC 0.693, 95% CI 0.611-0.766, p<0.001). Another study showed that sepsis patients with atrial fibrillation treated in the ICU with a Lactate-Albumin ratio > 0.5 more had an extended length of stay >10 days (p<0.001). A prospective cohort study of Chebl, et al., (2021) on 939 sepsis patients in the Emergency Department also showed similar results where the average length of hospitalization of sepsis patients who died was significantly longer than those who lived (16.25 vs 8.93, p<0.001).15,19,20

The lactate-albumin ratio in this study has a weak discriminatory ability, but its increase is an independent and significant factor in the occurrence of mortality and length of hospitalization in sepsis patients. This can be caused by other factors that affect mortality and length of hospitalization, such as differences in the cut-off of the Lactate-Albumin ratio, characteristics of the samples studied, sample size, race and ethnicity of the samples that are different from previous studies, and other confounding parameters.

This research has several limitations, namely with a retrospective research method based on existing medical records, not all information can be documented properly and completely. Apart from this, many sepsis sufferers do not have Lactate and Albumin checked at one time during admission, so many samples cannot be analyzed.

Conclusion

An increase in the Lactate-Albumin ratio is independently and significantly associated with an increased risk of mortality in sepsis patients. In addition, an increase in the Lactate-Albumin ratio is independently and significantly associated with an increased risk of length of stay in sepsis patients.

Suggestion

1. The researcher suggested that sampling be carried out prospectively, so that confounding factors could be controlled.
2. Further research is needed with a multi-center research sample so that the data obtained is more diverse and provides better research results.
3. Further meta-analysis studies are needed to determine the optimal cut-off value of

the Lactate-Albumin ratio with optimal sensitivity and specificity before it can be implemented in clinical practice.

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