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PROGNOSTIC TEST OF SOFA SCORE WITH THE ADDITION OF LACTATE LEVELS IN PREDICTING 28-DAY MORTALITY OF SEPSIS PATIENTS IN THE INTENSIVE CARE UNIT AT RSMH PALEMBANG

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ABSTRACT

Sepsis is defined as a life-threatening organ dysfunction caused by the host's unresolved response to infection. Many scoring or biomarkers can be used as a prognostic scoring scoring. Lactate is an indirect measurement of tissue perfusion. SOFA scores and can be applied in predicting independent mortality. Also recently found an increase in SOFA along with an increase in lactate. This study aims to determine the ability of SOFA scores with addition of lactate in predicting mortality in sespsis patients. Observational analytic study with a cross-sectional design using data of sepsis patients treated from January - December 2018 at RSMH Palembang. Inclusion criteria in this study were patients who were treated in intensive care with a diagnosis of sepsis and aged > 18 years with exclusion criteria had incomplete medical record data, referral patients from other hospitals, patients treated less than 24 hours in RSMH Palembang and readmission patients to the intensive unit in the same maintenance period. SOFA scores with additional Lactate levels had a cut-off point of ≤ 12 with a sensitivity value of 85.0%, specificity: 85.4%, AUC: 92.8%, while the SOFA score had a cut-off point of ≤7 with a sensitivity value of 80%, Specificity: 72.9%, AUC: 81.1% in predicting the 28-day mortality of sepsis patients at RSMH Palembang. There was a difference in the prognostic value of the SOFA score with the addition of lactate levels compared to the SOFA score in predicting 28-day mortality of sepsis patients in the intensive care unit of RSMH Palembang.

Keywords: Lactate, Mortality, Sepsis, SOFA

1. INTRODUCTION

Sepsis is a syndrome of physiological, pathological and biochemical disorders caused by infection, which is a major public health problem. Based on JAMA 2016, sepsis is defined as life-threatening organ dysfunction caused by an irregular host response to infection.[1] Accurate early identification of patients with sepsis is essential to improve outcomes through better targeted medical management, but still challenging. However, there is no single "gold standard" diagnostic test for sepsis, and case definitions vary greatly.[2] Based on The Third International Consensus for Sepsis and Septic Shock, screening for sepsis patients is carried out using qSOFA (quick Sequential Organ Failure Assessment) which assesses 3 parameters namely decreased consciousness, decreased blood pressure ≤ 100 mmHg and respiratory rate ≥ 22 times per minute. Patients who have an infection if they have at least 2 of the 3 clinical criteria are positive qSOFA.[1,3] When the qSOFA score is positive, scoring will then be performed using the SOFA (Sequential Organ Failure Assessment) method. Khie et al. use SOFA scores to assess sepsis

outcomes in Southeast Asia. The aim is to evaluate management, outcome, adherence to sepsis bundles, and predictions of death of a maximum Sequential Organ Failure Assessment (SOFA) score in patients with sepsis obtained by the community in Southeast Asia.[4] The number of SOFA scores at the time of admission that later dies is significantly higher than survivors. The number of organ failure shows a significant correlation with 28-day mortality, which ranges from 7% in patients without organ failure to 47% in those with failure of at least four organs. He concluded in this population, calculation of SOFA scores can be applied and related to mortality.[4]

Seymour, et al. assess clinical criteria for sepsis by comparing SOFA to LODS (Logistic Organ Dysfunction System) scores, SIRS (Systemic Inflammatory Response Syndrome) and qSOFA criteria.[5] In this study, the predictive validity of SOFA did not differ much with LODS, but had higher predictive validity than qSOFA and SIRS in infected patients from the hospital, so SOFA can be used to support the assessment of clinical criteria for sepsis. Whereas, in patients infected with infections from outside the hospital, qSOFA is statistically higher than SOFA and SIRS.[5] In the 2018 Surviving Sepsis Campaign (lsc), lactate is one step in the first hour of surviving sepsis campaign bundle of care. Lactate is an indirect measurement of tissue perfusion.[6] Lactate was first discovered by Karl Scheele in 1780 in sour milk. About 70 years later, Joseph Scherer, a doctor from Germany, proved the presence of lactate in the blood by analyzing blood taken from a woman who had died of septic shock. In 1858, Carl Folwarczny proved the presence of lactate in the blood in living patients. Araki and Zillessen found a link between lactate levels and tissue hypoxia.[7] Lactate is a crucial metabolite in the two energy formation processes of ATP, which is a life force, namely glycolysis and oxidative phosphorylation. Glycolysis is a process that converts glucose into 2 pyruvate molecules while simultaneously producing 2 ATP molecules. The process of glycolysis can increase 2 to 3 times, for example in stressful conditions of the body, excess pyruvate is converted to lactate. At rest, lactate will again be converted into pyruvate to continue the oxidative phosphorylation process.[8]

Lactic acidosis and septic shock as a result of tissue hypoxia when oxygen fails throughout the body to meet oxygen demand. In sepsis patients, the basal metabolic rate increases, causing an increase in glucose metabolism. Glycolytic surges can exceed the capacity of pyruvate dehydrogenase to catalyze the conversion of pyruvate to acetyl coenzyme A. As a result, pyruvate is converted to lactate by lactate dehydrogenase. An increase in endogenous epinephrine and norepinephrine concentrations determines an increase in sodium-potassium ATP-ase activity through β2 stimulation so that the inhibition of β2 and sodium potassium ATP-ase determines the decrease in lactic acid production in patients with septic shock.[8] The SSC database shows that acute mortality in the hospital in hospital the lactate group> 2 mmol / L and without the need for vasopressors, had similar results to the group of hypotensive patients who needed vasopressors with serum levels of lactate <2 mmol / L. Serum lactate levels can increase rapidly under conditions of low blood pressure that require vasopressors because vasopressors constrict blood vessels resulting in tissue hypoxia.[9]

In 2017, Chebi, et al. conducted a retrospective study of serum lactate in predicting hospital mortality in the emergency room and found an increase in lactate levels had an effect on increasing hospital mortality and extending the length of stay in the emergency department and hospital.[10]

Filho, et al. conducted a retrospective cohort study, and concluded that an increase in lactate levels above 2.5 mmol /

L was the best threshold for predicting 28-day mortality in patients with severe sepsis and septic shock.[11] Liu, et al. try to assess the accuracy of prognostic mortality by comparing serum lactate levels, SOFA scores and qSOFA. Based on the results of the study, lactate is an independent prognostic predictor of mortality in patients with sepsis.[12] Lactate also has a discriminatory power that is superior to qSOFA, and shows discriminatory abilities similar to SOFA.[12]

Jansen, et al. in his research found that blood lactate levels were strongly associated with SOFA scores. This relationship was stronger during the initial phase of being treated in the intensive care unit, which provided indirect support in addition to early resuscitation to prevent organ failure. The results confirm that hyperlactatemia can be considered as a warning signal for organ failure.[13] Chen, et al. found that lactate was a prognostic predictor in septic patients in the ED, and could improve the performance of APACHE II, SOFA, and MEDS (Mortality in Emergency Department Sepsis) scores in predicting death.[14] Whereas Anderson, et al. found the same thing when the scoring system used was SAPS-3 (Simplified Acute Physiology Score-3).[15] Jung, et al. adding lactic acid levels to predict mortality in surgical patients assessed using qSOFA. In this study he found that the addition of these parameters could improve the prognostic of qSOFA to be comparable to SOFA itself.[15] Jemie et al. stated that there was a relationship between increased lactic levels and SOFA scores.[16]

As lactic acid levels increased, so did SOFA scores and vice versa.[16] In ICU Brazil, Bessen, et al. examined the new definition of Sepsis-3, is accurate in stratification of mortality and is superior to the previous definition. They also observed that the accuracy of the new definition increased progressively with severity. The lactate serum increased accuracy to values higher than 4 mmol / L in the group without organ dysfunction and septic shock.[17]

2. METHODS

This study was an observational analytic study using a cross sectional design. The data is taken from the patient's medical record which is stored in the Medical Record and Casemix Installation at Dr. Mohammad Hoesin General Hospital Palembang. The study will be conducted in January 2020 until the completion of data collection. Data was collected at the Medical Record and Casemix Hospital Installation Dr. Mohammad Hoesin General Hospital Palembang. The population in this study were all sepsis patients in the intensive care unit that were recorded at the Medical Record Installation and Casemix Hospital Dr. Mohammad Hoesin General Hospital Palembang from 1 January 2018 to 31 December 2018 (total population is the total sample). Samples were taken non-randomly, using a purposive sampling technique, where the study sample was taken based on inclusion criteria.

The inclusion criteria in this study were patients who were admitted to the intensive care unit of Dr. Mohammad Hoesin General Hospital Palembang, a patient with a diagnosis of sepsis, and a patient aged ≥ 18 years.

Exclusion criteria in this study were patients who did not have complete medical record data, referral patients or transfer from the intensive care unit of another hospital before, patients treated in the intensive care unit of Dr. Mohammad Hoesin General Hospital Palembang, less than 24 hours, the patient was re-admitted to the intensive care unit within the same treatment period.

The instrument used in this study was a checklist sheet to recap data collected from medical records. Lactate levels assessed were lactate levels that were examined through the laboratory at the

time the patient entered the intensive care unit and were divided based on scoring according to Chen's study.

Data collection methods in this study were data taken from the medical records of all sepsis patients treated in the intensive care unit of Dr. Mohammad Hoesin General Hospital Palembang from January 2018 to December 2018. Sepsis patients were taken as many as the number of samples based on the calculation using the total sample. Sampling was taken non-randomly by using a purposive sampling technique in which samples were taken based on criteria. The data taken is in accordance with the variables studied from the characteristics of the subject and the main variables of the study (SOFA score, lactate levels and mortality). After the data collected, the data is recap then the data is analyzed in accordance with the statistical test analysis design used. The way of processing this research data is using software, the SPSS program. Analysis of research data was done descriptively and analytically.

3. RESULT

There were 88 study samples that met the inclusion and exclusion criteria. The distribution of research variables on mortality can be seen in table 1. There were 35 (72.9%) subjects with ages 18 - 65 years in the group who died and 36 (90%) subjects with the same age in the survived group. There were 27 (56.3%) subjects with male gender and 21 (43.8%) subjects with female sex in the group who died.

Table 1 Distribution of Research Variables on Mortality (n=88)

Variable	Mortality		p_Value
	Death	Survived	
Age			0,043
18 – 65 y.o	35 (72,9%)	36 (90,0%)	
> 65 y.o	13 (27,1%)	4 (10,0%)	
Gender			0,185
Male	27 (56,2%)	28 (70,0%)	
Female	21 (43,8%)	12 (30,0%)	
Care Room			0,882
ICU IGD	20 (41,7%)	16 (40,0%)	
GICU	26 (54,2%)	21 (52,5%)	
P1	2 (4,2%)	3 (7,5%)	
Type of Diseases			0,050
Respiratory Tract Infection	24 (50,0%)	12 (30,0%)	
Gastrointestinal Infections	20 (41,7%)	18 (45,0%)	
Others	4 (8,3%)	10 (25,0%)	
Comorbid			0,000
0	4 (8,3%)	21 (52,5%)	
1	44 (91,7%)	19 (47,5%)	

Note: Analysis using Chi-Square, p <0.05 = significant relationship.

Based on Figure 1., it is known that an SOFA score cutoff point ≤7 is obtained with a sensitivity value of 80%, Specificity: 72.9%, Accuracy 82%, Likelihood ratio positive: 2.95, Likelihood negative ratio: 0.27, Positive predictive value: 83%, Negative predictive value: 80%, AUC: 81.1% in predicting the mortality of sepsis patients. Based on the correlation analysis, it was found that the sofa score correlated statistically with the direction of a positive correlation with moderate strength (0.633) on the mortality of sepsis patients. However, lactate levels have a cutoff value ≤ 2.6 with a sensitivity value of 85%, specificity: 95.8%, positive Likelihood ratio: 20.40, negative Likelihood ratio: 0.16, accuracy 80%, Positive predictive value: 86%, Negative predictive value 75%, AUC: 96.6% in predicting the mortality of sepsis patients.

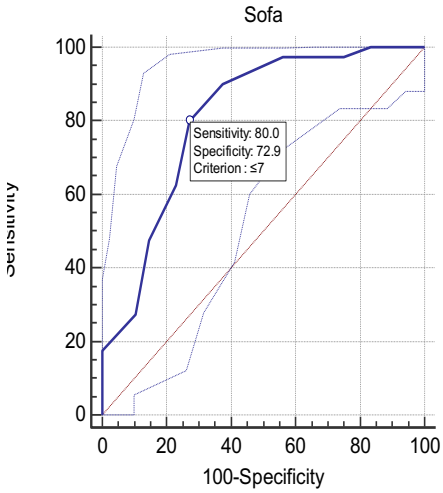

Figure 1. ROC SOFA Score on Mortality

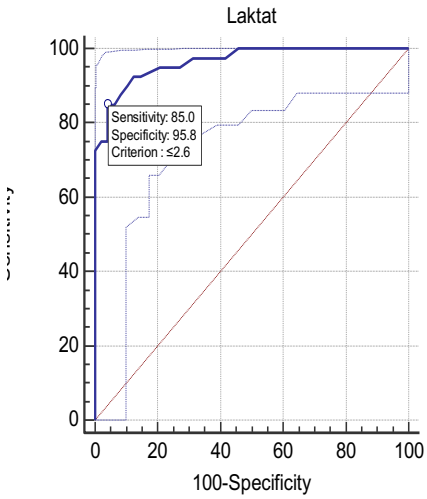

Figure 2. ROC Lactate Levels for Mortality

While, the SOFA + Lactate Score cutoff point ≤ 12 with a sensitivity value of 85.0%, specificity: 85.4%, Likelihood ratio positive: 5.83, Likelihood ratio negative: 0.18, Accuracy 85.22%, Positive predictive value: 91.1%, Negative predictive value 79.0%, AUC: 92.8% in predicting the mortality of sepsis patients. Based on correlation analysis, the sofa + lactate score is statistically correlated with the direction of a positive correlation with strong strength (0.703) on the mortality of sepsis patients.

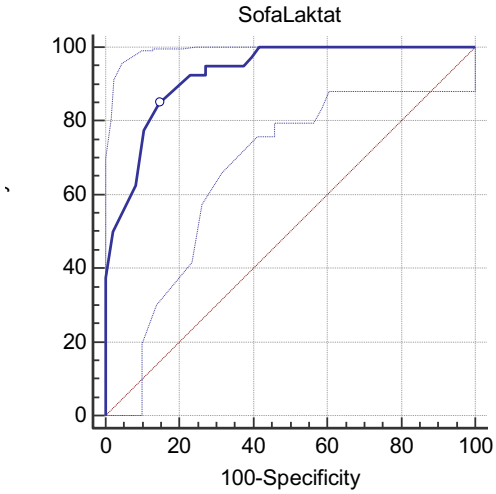

Figure 3. ROC SOFA Score + Lactate Score on Mortality

4. DISCUSSION

Based on the chi-square analysis it was found that age has a relationship with the mortality of sepsis patients while gender does not have a significant relationship with the mortality of sepsis patients. According to a report from the Center for Disease Control, it is estimated that sepsis attacks about 1.5 million individuals in the United States annually and causes the death of 250,000 individuals and accounts for 1 in 3 deaths in hospitals.[18] Based on a meta-analyst study from 1979-2015 by Fleischmann et al. regarding the incidence of sepsis in the adult population and cases of sepsis and severe sepsis treated were 288 and 148 cases out of 100,000 population / year, respectively.[18]

The incidence of sepsis follows a bimodal distribution, with higher rates at extreme ages. The rate of sepsis is in infants (5 per 1000 people) is at a moderate level, while in children and young adults (<5 per 1000 people) is at the lowest level, and then increases exponentially from the age of 50 to 85 years and over.[19] In developed countries, the majority (58%) of sepsis are hospitalized and the majority of hospital-related sepsis deaths (71%) are in patients aged 65 years or more.[20] The greater incidence of sepsis in older patients is likely explained by both a greater prevalence of chronic medical conditions that can predispose patients to sepsis and changes in decreased immune function, known as immunosenescence. In studies using administrative data, the fatality rate of sepsis seems to increase steadily with increasing age, from less than 10% in infants to more than 35% in patients 85 years and older.[21]

Research conducted by Nasir in 2015 found that male sex showed a higher risk of mortality than women. This phenomenon has been observed in animal studies where women have been known to have survival benefits both in terms of immunological and cardiovascular responses. However, most clinical studies have failed to show consistent differences in the results of sepsis in relation to gender.[22] A study by Pietropaoli in patients treated in intensive care showed that the odds of female vs. male mortality (OR 1.11) were slightly higher in the subgroup with sepsis. Pietropaoli conducted a multivariate analysis to show that gender had an independent effect on mortality, the analysis showed a higher mortality in women with sepsis.[23] The age variable is a bias variable in the results of sex analysis of mortality, because this study sample had 81.3% of subjects who were >40 years old. There were 48.8% of subjects with male sex and 66.7% of subjects with female sex > 40 years old in the group who died. This is also supported by the results of Denison's study which says that mortality rates in study subjects aged <40 years are lower in patients with female sex, whereas if age >40 years is lower in patients with male sex.[24] Differences in population samples cause the results of this study to differ from several other studies. The results of this study are in line with the theory and several studies that have been mentioned that age is related to mortality while gender is not related to mortality, due to the presence of a bias variable, namely age.

There were 26 (54.2%) subjects treated at GICU in the group who died and 21 (52.5%) subjects who were treated at GICU in the survived group. There were 24 (50.0%) subjects with a diagnosis of respiratory infection in the group who died and 18 (45.0%) subjects with a diagnosis of gastrointestinal infections in the survived group. In the chi-square analysis, it was found that the type of disease had a significant relationship to the mortality of sepsis patients, while the ward did not have a significant relationship to the mortality of sepsis patients.

The incidence of sepsis is higher in patients with chronic medical conditions that impair immune function, especially in

patients with cancer, obtaining immunodeficiency syndrome (AIDS), diabetes, and chronic obstructive pulmonary disease (COPD), in patients using immunosuppressive drugs, and in patients in hemodialysis. For example, the incidence of sepsis is about 40 times higher in patients who undergo hemodialysis compared to patients who do not undergo hemodialysis. Nationally, US hospital records estimate the incidence rate of sepsis is 755 per 100,000 patients with COPD. Patients with diabetes have a 2.5 times higher risk of hospitalization for sepsis compared to patients without diabetes.[19] The results of this study are in line with the theory mentioned above, that the type of disease has a significant relationship to the mortality of sepsis patients, but for the treatment of mortality of sepsis patients there is no further research, so it cannot be compared.

There were 44 (91.7%) subjects with the number of comorbid 1 in the group who died and 21 (52.5%) subjects with the number of comorbid 0 in the survived group. More than half of patients who have sepsis have at least one chronic medical condition, generally COPD (10-12%), congestive heart failure (15%), chronic kidney disease (5-12%), diabetes (3-20%), or alcohol abuse (2-5%), with varying frequency depending on the population studied. Among pediatric cases with sepsis, three out of four have at least one chronic condition, most commonly respiratory (30%), gastrointestinal (25%), or cardiovascular conditions (24%).[19] The results of this study are in line with the theory that the number of comorbidities is related to the mortality of sepsis patients, the more comorbidities are expected to increase mortality.

Based on Ghaini's research in 2019, SOFA and qSOFA scores both increased significantly in the group who died. SOFA shows good accuracy (AUROC) = 0.83 (95% CI, 0.76 - 0.90) for 28-day mortality compared with qSOFA (AUROC = 0.67, 95% CI, 0.54 - 0.80) and SIRS (AUROC = 0.62, 95% Cl 0.49 - 0.74).[25] Ghaini said that SOFA scores ≥2 can predict 28 days of mortality in sepsis patients better than qSOFA and SIRS, while other studies conducted by Raith in 2017 also found that SOFA had better AUROC values than qSOFA and SIRS in predicting mortality with comparison as follows SOFA: 0.753 (99% CI 0.750 - 0.757), qSOFA: 0.607 (99% CI 0.603 - 0.611) and SIRS: 0.589 (99% CI 0.585 - 0.593).[25,26] The results of this study are in line with Ghaini's study which found that SOFA was a strong predictor of mortality in sepsis patients. It is known that there were 37 patients with lactate levels > 2.6 in the group who died and 6 patients in the living group. Based on correlation analysis, it was found that lactate levels were statistically correlated with the direction of a positive correlation with moderate strength (0.618) on the mortality of sepsis patients.

Based on Ralphe's research in 2017, the mean age of the study sample was 64.87 ± 18.08 years in the lactate <2 mmol / L group, 68.51 ± 18.01 years in the lactate group 2-4 mmol / L , and 67.46 ± 17.67 years in the lactate group >4 mmol / L. All three groups are comparable in terms of age, sex and comorbidity except for diabetes, with the lactate group 2-4 mmol / L and lactate > 4 mmol / L has a higher proportion of diabetic patients. The average level of lactate was 1.42 ± 0.38 (<2 mmol / L), 2.72 ± 0.55 (2-4 mmol / L) and 7.18 ± 3.42 (> 4 mmol / L). Hospital mortality was found in 4 (2.7%), 18 (12%) and 61 (40.7%) patients in the low, medium and high lactate groups. The emergency room and hospital stay were longer for the lactate group >4 mmol / L compared to the other groups. Patients with medium and high lactate had OR 7.13 (95% CI 2.22-22.87 p = 0.001) and OR 29.48 (95% CI 9.75-89.07 p = <0.001) likely greater mortality in each hospital.[10]

Based on Doshi's research in 2018, there were 338 patients who met the

inclusion criteria and were divided into the lactate expressor group (n = 197; lactate expressor was a subject who had an initial lactate ≥2.5 mmol / L) and the non-expressor group (n = 141; non -expressors are subjects who have lactate <2.5 mmol / L). The mortality rate was 46.2% for lactate expressors and 24.8% for non-expressors. Both groups had initial differences: the expressor group had a higher median APACHE II score, and none had an increased prevalence of comorbid conditions. Patients who had a higher APACHE II score (odds ratio [OR] 1.10 (1.07-1.14), P <0.001) and were in the expressor group (OR 1.72 [1.03-2.89], P = 0.039) increases mortality.[27] The results of this study are in line with the research of Ralphe and Doshi who found that high lactate levels were related to the mortality of sepsis patients. Based on Chen's research in 2014, he found that AUC scores on SOFA, MEDS, and APACHE II scores in predicting 28-day mortality were AUROC 0.75 (95% CI 0.71 - 0.80), AUROC 0.74 (95% CI 0.69 - 0.78) and AUROC 0.74 (95% CI 0.70 - 0.78). When the score was added to lactate, the AUC value increased to AUROC 0.82 (95% CI 0.78 - 0.85), AUROC 0.81 (95% CI 0.77 - 0.85) and AUROC 0.81 (95% CI 0.77 - 0.84) and when set as a modified score into AUROC 0.81 (95% CI 0.77 - 0.85), AUROC 0.80 (95% CI 0.76 - 0.84) and AUROC 0,80 (95% CI 0.76 - 0.84).[14]

Based on Arif Aksu's research in 2018, getting that SOFA-Lactate Score$_{2.3}$ (lactate level ≥ 2.3 mmol / l) showed the highest discriminatory performance for hospital mortality (AUROC 0.791, 95% CI 0.761-0.819 p <0.001) sensitivity of 69.2% and specificity of 77.2%. SOFA-Lactate$_4$ (lactate levels mm4 mmol / l) also showed high discriminatory performance (AUROC 0.766, 95% CI 0.735-0.795 p <0.001) with a sensitivity of 64.5% and specificity of 76.3% compared to SOFA scores ≥ 3 (AUROC 0.755, 95% CI 0.724-0.784, p <0.001) sensitivity of 77.9% and specificity of 59.2% for hospital mortality. In the comparison of ROC analyzes conducted, the predictive nature of the SOFA-Lactate$_{2.3}$ value was found to be statistically significant compared to the SOFA-Lactate$_4$ value (p = 0.0066).[28] Tissue hypoxia and the onset of lactate are associated with reducing systemic oxygen delivery components (hemoglobin levels, oxygen saturation, and cardiac output) until oxygen extraction can no longer maintain oxygen supply to cells to meet cell needs. At the critical level of oxygen delivery, oxygen consumption is limited, and this is accompanied by a drastic increase in lactate levels.[7] Changes in microcirculation perfusion can also cause limited oxygen availability. Especially in sepsis, microcirculation or shunting abnormalities may cause oxygen deprivation to be sent to cells, thereby increasing lactate levels, from this whole process can cause an increase in lactate levels in the body.[7] The results of this study are in line with the research of Chen and Arif Aksu who found that the addition of lactate levels or lactate scores to SOFA was related to the mortality of sepsis patients.

5. CONCLUSIONS

SOFA score with the addition of Lactate levels with a cut-off point of ≤ 12 with a value with a sensitivity value of 85.0%, specificity: 85.4%, AUC: 92.8% in predicting 28-day mortality of sepsis patients at RSUP Dr. Mohammad Hoesin Palembang. SOFA scores have an average value of 7.58 + 3.11, while lactate levels have an average value of 3.63 + 2.05 and SOFA scores + lactate levels have an average value of 16.39 + 8.19 in patients sepsis at RSUP Dr. Mohammad Hoesin Palembang. SOFA and SOFA + lactate scores were significantly correlated (p value = 0,000) with the direction of a positive correlation with strong strength (0.749). Sepsis in this study had a mortality rate of 54.5% or 48 subjects from 88 study samples.

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