Correlation of Neutrophil-Lymphocyte Ratio (NLR) With Sofa Score as a Parameter of Organic Dysfunction of Sepsis Patients in ICU Haji Adam Malik (HAM) General Hospital Medan

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Abstract:-

Background: The neutrophil-lymphocyte ratio (NLR) has received much attention and was recently investigated as a potential novel biomarker for sepsis and is cheaper and faster than SOFA scores. The aim of this study was to determine the relationship between neutrophil-lymphocyte ratio (NLR) and SOFA scores as a parameter of organ dysfunction in septic patients admitted to the ICU of Haji Adam Malik (HAM) General Hospital Medan.

Methods: This study is an analytic study with a case-control survey design that compares the NLR values in 25 septic patients (cases) and 25 patients without sepsis (controls) at the Intensive Care Unit (ICU) of HAM General Hospital Medan. Spearman correlation test was performed to find the relationship between NLR and SOFA scores and independent T test or Mann-Whitney test to examine differences between groups.

Results: A total 50 patients, it was found that the neutrophil value was higher in the case group (83.2) than the control group (79.3) with the result that there was no significant difference between the two groups (p=0.637), the lymphocyte value was lower in the case group (7.3±4.8) than the control group (11.6±6.3) with the result that there was a significant difference between the two groups (p=0.011), the NLR value was higher in the case group (18.0±15.3) than the group. control (9.7±8.8) with the result that there was a significant difference between the two groups (p=0.006), and the SOFA scores was higher in the case group (7.0±4.4) than the control group (44.3±1 ,8) with the result that there was a significant difference between the two groups (p=0.03). The results of the correlation test between NLR and SOFA scores found a very low positive correlation (p = 0.037; r = 0.296).

Kesimpulan: There is a very low positive correlation between NLR values and SOFA scores.

Keywords:- *Neutrophil-lymphocyte ratio, sepsis, SOFA score.*

I. INTRODUCTION

Sepsis is one of the leading causes of death worldwide. Based on data from the World Health Organization (WHO) in 2020, the incidence of sepsis worldwide reaches 49 million in 1 year and continues to increase every year, as the cause of death worldwide by 20%. Sepsis is a major cause of morbidity and mortality in intensive care units with a mortality rate of 42%.(1) According to the data obtained, a study conducted in 2009 in 150 intensive care rooms in 16 countries in Asia, including Indonesia, showed that severe sepsis and Septic shock constituted 10.8% of diagnoses in intensive care. In addition, according to data in Indonesia, septic shock was the highest cause of mortality for 3 consecutive years, namely in 49% of cases of mortality in 2009, increasing to 55% in 2011.(2)

The currently available organ failure assessment systems, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology II (SAPS II) are useful for assessing organ dysfunction and have been designated as a severity index. and a clinically useful prognosis.(3–5) The Surviving Sepsis Campaign's (2017) recommended severity rating is the SOFA scores, but this test is expensive and requires a large number of examination items, so there is a need for other simple biomarkers that can be easier and faster to do such as the neutrophil-lymphocyte ratio (NLR).

The neutrophil-lymphocyte ratio (NLR) has received much attention and has recently been investigated as a potential novel biomarker of sepsis as an abnormality in the immune system pathway which is the main pathophysiology of sepsis. NLR can be easily calculated from complete blood count and has been investigated as an index that can be used as a prognostic biomarker in several clinical conditions including sepsis. According to Hwang et. al (2017) in 1395 patients with severe sepsis and septic shock, NLR was independently associated with 28-day mortality.(6)

The role of NLR as a prognostic factor in sepsis is still debated, but many studies have proven that NLR is a potential test in assessing the severity of sepsis. A prospective observational study conducted by Liu et al.(7) in 333 patients with sepsis in the ICU showed that elevated NLR levels were associated with poor outcomes. Research by Salciccioli et. al. reported that NLR values were higher in

septic patients than in non-septic patients, although this study reported that there was no significant relationship between NLR and mortality in ICU patients.(8)

Neutrophils are animportant cellular component of the human body's defense system against infection and its decline in function during sepsis is characterized by the failure of neutrophils to phagocytize infecting pathogens. An increase in the number of neutrophils is a warning sign that the source of the infection cannot be addressed.(9,10) Apart from neutrophils, lymphocytes are also involved in the pathogenesis of sepsis. The subsequent dysregulated host response to infection causes a variety of changes, not only in the total number of circulating lymphocytes, but also in different T cell subpopulations.(11) Lymphocyte apoptosis also increases rapidly in the blood of patients with septic shock. and causes severe persistent and associated lymphopenia. with poor results.(12) Evans(13) demonstrated a positive correlation between disease severity in critically ill patients and the degree of neutrophilia and lymphocytopenia.

According to Liu et. Al. leukocytes are also capable of secreting potentially harmful substances, so they can also cause injury to normal cells and tissues in some situations and worsen septic conditions.(7) Another report observing 355 septic patients in America, found a negative correlation between lymphocyte count and mortality in septic patients, in addition, low absolute lymphocyte count is a good predictor of postoperative sepsis and a good predictor of bacteremia in the emergency department.(14)

II. METHODS

This study isan a casecontrolsurvey design to see the relationship between neutrophil-lymphocyte ratio (NLR) and SOFA score as a parameter of organ dysfunction in septic patients treated at the Haji Adam Malik General Horpital Intensive Care Unit (ICU) Medan from January to December 2020. The sample size in this study was calculated using the research formula for the number of case-control samples on the NLR variable. The sampling technique used is simple random sampling which first counts the number of subjects in the population, then each subject is numbered and partially selected with the help of random software (www.randomizer.org).

The inclusion criteria in this study were patients aged 18 to 60 years, patients treated in the ICU of RSUP HAM, and patients who had neutrophils and lymphocytes examined during treatment in the ICU of RSUP HAM. The exclusion criteria in this study were patients who did not have complete medical record data, patients with hematological disorders, patients with major congenital malformations, patients with cyanotic congenital heart disease, and patients with malignancy. Data analysis was performed using Statistical Product and Service Solution (SPSS) version 25.0. Subject descriptive data which includes age, gender, neutrophil count, lymphocyte count, neutrophil-lymphocyte ratio, and SOFA score will be displayed in the form of mean and standard deviation if the data is normally or medially distributed, minimum value, and maximum value if data is not normally distributed. Spearman correlation test was performed to find the relationship between NLR and SOFA scores and independent T test or Mann-Whitney test to test differences between groups.

All septicpatients were selected as cases, while non-septic patients were controls taken randomly from the population. Then tabulated to excel, starting from the characteristic data, the NLR ratio value, and the SOFA score value. The case were analyzedusing a computerapplication SPSS.

III. RESULTS

A. Demographic Characteristics and Intergroup Difference Test

This study was followed by 50 samples consisting of 25 septic patients (cases) and 25 non-septic patients (controls) who met the inclusion and exclusion criteria. The description of the characteristics and test of the differences in the samples of this study can be seen in table 1 below.

Sample Characteristics	Cases (n=25)	Control (n=25)	P value
Age, year (mean±SD)	44,8±16,7	46,9±16,3	0,717
Sex - Male, n (%) - Female, n (%)	8 (32) 17 (68)	10 (40) 15 (60)	0,560
Neutrophil (mean±SD)	79,1±16,4	79,5±9,3	0,367
Lymphocytes (mean±SD)	7,3±4,8	11,6±6,3	0,011*
NLR, median (min-maks)	11,9 (2,5-69,4)	9,7 (1,9-41,8)	0,006*
SOFA score, median (min-maks)	6 (2-18)	5 (1-6)	0,03*

Table 1. Demographic Characteristics and Test for Differences Between Groups

Description: Mann-Whitney test (gender comparison, NLR, and SOFA scores in case and control groups); t-test (comparison of age in case and control groups); *= significantly different if <0.05.

Table 1 shows that the mean age of the sample in this study was higher in the case group at about 44.8 ± 16.7 years compared to the control group at 46.9 ± 16.3 years. The female sample was the most in the case group and the largest number of males in the control group. SOFA scores and NLR scores in this study had a higher median value in the case groupthan in thecontrolgroup.

B. Neutrophil Values In Critically Ill Patients Admitted To The ICU

Neutrophil values in critically ill patients admitted to the ICU are shown in Table 2.

Neutrophil Value	Cases (n=19)	Control (n=19)	p value
Mean±SD	79,1±16,4	79,5±9,3	
Median (Min-Maks)	83,2 (23,6-97,1)	79,3 (56,7-95,9)	0,367
Cut-Off	60,3	76,3	

Table 2. Neutrophil values in critically ill patients admitted to the ICU.

Description: Mann-Whitney test, significant <0.05

Based on Table 2, it is known that the neutrophil value was higher in the case group (83.2) compared to the control group (79.3). However, the results of the study found that there was no significant difference between the neutrophil values in the case (sepsis) and control (non-sepsis) groups.

C. Lymphocytes Values In Critically Ill Patients Admitted To The ICU

Lymphocytes values in critically ill patients admitted to the ICU are shown in Table 3.

Lymphocytes Value	Cases (n=19)	Control (n=19)	p value
Mean±SD	7,3±4,8	11,6±6,3	
Median (Min-Maks)	6,6 (0,5-18,6)	10,6 (2,2-26,10)	0,011*
Cut-Off	9,5	14,1	

Table 3. Lymphocytes values in critically ill patients admitted to the ICU.

Description: Mann-Whitney test, significant <0.05

Based on Table 3, it was found that the lymphocyte values were lower in the case group (7.3±4.8) compared to the control group (11.6±6.3). The results of the study proved that there was a significant difference between the lymphocyte values in the case (sepsis) and control (non-sepsis) groups and was statistically significant (p=0.011).

D. NLR values in critically ill patients admitted to the ICU

NLR values in critically ill patients admitted to the ICU are shown in Table 4.

Neutrophil-Lymphocyte Ratio	Cases (n=19)	Control (n=19)	p value
Mean±SD	18,0±15,3	9,7±8,8	
Median (Min-Maks)	11,9 (2,5-69,4)	6,9 (1,9-41,8)	0,006*
Cut-Off	35,9	21,8	

Table 4. NLR values in critically ill patients admitted to the ICU.

Description: Mann-Whitney test, significant <0.05

Based on Table 4, it was found that the NLR value was higher in the case group (18.0±15.3) compared to the control group (9.7±8.8). The results of the study proved that there was a significant difference between the NLR values in the case (sepsis) and control (non-sepsis) groups and was statistically significant (p=0.006). The cut-off value of NLR in the sepsis group was 35.9 which was also higher than the control group (21.8).

E. Correlation of NLR scores with SOFA scores

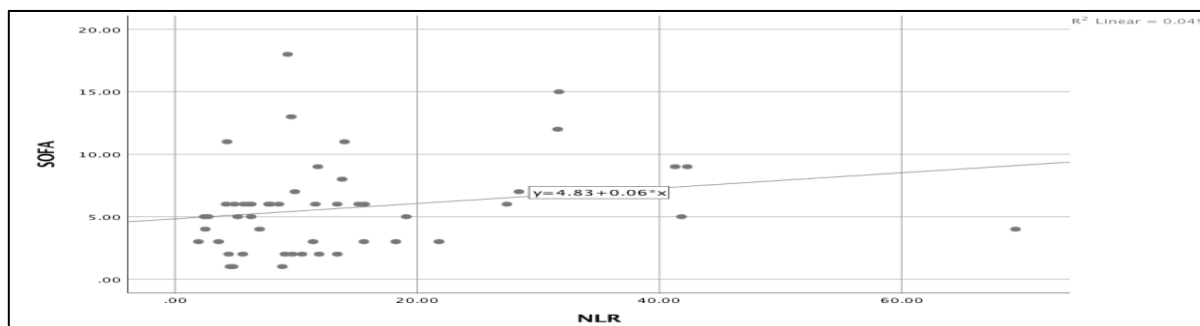The correlation between NLR scores and SOFA scores is shown in Figure 1 below.

Fig. 1: Scatter Plot Trend of SOFA Score Against NLR Values in Critically ICU Patients

Figure 1 Correlationbetweenthe NLR score and the SOFA score, meaning that the higher the NLR score, the greater and more significant the SOFA score increase (p = 0.037; r = 0.296).

IV. DISCUSSION

This study found that the male gender (40%) was more in the control group while the female gender (68%) was more in the case group. This is different from research by Angele et al.(15) that sepsis was most common in women compared to men because of the influence of the female hormone estrogen which has a protective effect against infection, sepsis and trauma. The hormone estrogen has an effect on increasing the immune system by increasing the production of IL-4 and IL-10 so that antibodies increase.(15) This difference in results may be due to the minimal number of samples.

The results of this study indicate that the mean age of the research subjects is 44.7 years in the septic group and 47 years in the non-septic group, thus indicating that the age range of patients treated in the ICU room at Haji Adam Malik Hospital Medan is in the productive age range. This is in accordance with research in the United States in 2001 which obtained results that were close to the results of this study, namely the incidence of sepsis in general was more common in the age range of 20-85 years.(16)

The mean neutrophil-lymphocyte ratio in this study was 11.9 and higher than the median control group of 6.9. This study showsthat in severe systemic inflammation such as sepsis, the body's immune system responds by increasing the neutrophil-lymphocyte ratio.(19) The increase in NLR occurs due to direct or indirect stimulation from the marrow.(20) This increase in neutrophils is caused by proinflammatory cytokines such as IL-6, IL-1 and TNF-α which are produced by macrophages and a decrease in the number of lymphocytes caused by increased secretion of glucocorticoid hormones which will also suppress lymphocyte production.(21)

Pro-inflammatory cytokines (IL-1, IL-6, and TNF-) will stimulate polymorphonuclear neutrophilic leukocytes (PMN) to adhere to vascular endothelial cells.(22) Leukocytes release proteases, oxidants, prostaglandins and leukotrienes which will cause surface damage. endothelium so that tissue factor is released.(23) The tissue factor triggers the coagulation process through the release of thrombin. The release of thrombin will cause the conversion of fibrinogen to fibrin resulting in the formation of a fibrin clot.(24) In sepsis, the fibrinlysis process is disrupted due to high levels of plasminogen activator inhibitor-1 (PAI-1) which prevents the conversion of plasminogen to plasmin, resulting in reduced fibrin destruction, while activation coagulation continues to cause the buildup of fibrin clots.(25) Fibrin clots that are formed will go to the circulation and small blood vessels, so that the oxygen supply to the tissues and organs of the body is disrupted. As a result, tissue ischemia and organ dysfunction such as respiratory, cardiovascular, kidney and liver organs occur as well as decreased consciousness.(15)

This study found that there was a very low positive correlation between the NLR score andthe SOFA score. The results of this study are in accordance with the study reported by Velissari et al.(26) that NLR and SOFA scores showed a significant relationship although this relationship did not have a correlation with the source of infection in septic patients. This was also reported by Zhou et al.(27) in septic patients with acute pancreatitis, an increase in NLR was accompanied by an increase in SOFA scores. Rehman et al. (2020) reported that NLR has a significant SOFA score with p value = 0.01, so it can be a cheaper and faster examination as an alternative to SOFA score assessment which is relatively more expensive and time-consuming.(28)

V. CONCLUSION

There is a very low positive correlation between NLR scores and SOFA scores. The cut-off value of NLR in septic patients is 35.9 while in non-septic patients it is 21.8. The cut-off value of SOFA score in septic patients was 10 while in non-septic patients it was 3.5.

SUGGESTION

This study is expected to be input for other studies that want to examine the NLR examination as analternative SOFA score in sepsis. This study is expected to add to the author's experience in researching patients in the ICU.

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