The sensitivity and specificity of neutrophil lymphocyte count ratio in diagnosing sepsis patients at Dr. Saiful Anwar General Hospital, Malang, Indonesia

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ABSTRACT

Background: Sepsis is the most severe manifestation of acute infection which can cause death in 30-50% of cases. Rapid and accurate diagnosis of sepsis is a challenge for clinicians and laboratories. *Neutrophil Lymphocyte Count Ratio* is a potential index to detect the occurrence of sepsis. This examination is easy, fast and cheap. Procalcitonin is currently widely used as a newer indicator in diagnosing pre-shock but is rarely done because of its cost. This study aims to compare the diagnostic value of *Neutrophil Lymphocyte Count Ratio* with procalcitonin as a marker in septic patients.

Method: A Case-control analytic research was conducted from March to June 2018. Examination of neutrophils and lymphocytes using Sysmex XN-1000 while procalcitonin examination used Elecsys BRAHMS PCT using ECLIA method. Diagnostic values are analyzed using the ROC curve, and the cut-off value is determined. The sensitivity, specificity, positive predictive value, negative predictive value, accuracy are calculated with 2x2 tables.

Result: The subjects of the study were 60 patients who hospitalized and examined for procalcitonin with 30 patients diagnosed based on clinical symptoms and SOFA score ≥ two by clinicians as sepsis patients and also 30 control patients. ROC analysis with procalcitonin cut-off values of 2,24 ng / mL obtained a sensitivity of 93%, specificity of 86,7%, *PPV* of 86,9%, and *NPV* of 92,4%.. At the cut-off value of *Neutrophil Lymphocyte Count Ratio* 5,06, there was a sensitivity of 80%, specificity of 76,7%, *PPV* of 76,9%, and *NPV* of 79,1%.

Conclusion: Procalcitonin has a better diagnostic value than *Neutrophil Lymphocyte Count Ratio* in diagnosing sepsis.

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INTRODUCTION

Sepsis causes one of the world health problems because of the complex treatment and high mortality rates. Sepsis according is an organ dysfunction caused by dysregulated host response against infection, which is evaluated using SOFA score ≥ 2.[1] A study conducted in England during 2001-2010 period observed that 1 of 20 deaths in England was caused by sepsis, with a prevalence of 5.5% and 4.8% for women and men, respectively.[1]

Research conducted at Dr. Soetomo Hospital in 2012 found that the mortality of sepsis caused by beta-lactamase (ESBL) extended-spectrum producing bacteria were 16.7% with an average incidence of 47.27 cases per year. The study reported that 27.08% of cases were severe sepsis, 14.58% of septic shock and 53.33% of cases were cases of sepsis.[2] Sepsis begins with the occurrence of a systemic inflammatory response syndrome (SIRS) accompanied by infection. Although an infection characterizes the incidence of sepsis, bacteremia is not always present. This is possible because of the presence of endotoxins and exotoxins in the bloodstream while the bacteria are in the tissues.[3]

Diagnosing an acute infection such as sepsis is clinically complex, because the signs and physical examination of sepsis were not specific despite the presence of bacteremia. Moreover, a conventional clinical and laboratory parameters for the diagnosis of sepsis are less sensitive and specific. Hence, in 1990, Procalcitonin (PCT) was used as a specific sign of bacterial infection. A serum procalcitonin levels increase in acute infections such as sepsis. The normal level of procalcitonin was below 0.5 ng / mL, and the serum level > 2ng / mL have a high risk for sepsis. A Meta-analysis by Uzzan and colleagues found that procalcitonin was better than CRP in distinguishing SIRS and sepsis.[4]

Zahorec et al. were the first to propose using Neutrophil Lymphocyte Count Ratio (NLCR) as an additional infection marker for sepsis in clinical practice.[5] Previously, NLCR has been found to correlate with the severity of the disease and has been suggested as a predictor of bacteremia. This

examination is relatively easy, fast, and inexpensive.

On the other hand, procalcitonin is widely used as a more recent indicator to diagnose a pre-shock condition. However, this is rarely done because it is expensive. Therefore, this study aims to compare the diagnostic values of the ratio of neutrophil lymphocytes with the procalcitonin as a marker in sepsis patients. Given the previous results and the importance of timely and accurate diagnosis of treatment of bacterial sepsis, we conducted this study to determine the diagnostic values of PCT and NLCR.

METHODS

This is an analytic observational case-control research conducted in the dr. Saiful Anwar Public Hospital, Malang between Maret to June 2018. A procalcitonin serum sample examination was done using Elecsys BRAHMS PCT with ECLIA method in Cobas e401. Neutrophil and Lymphocyte count was done using Sysmex XN-1000 from a venous blood sample with EDTA.

The subject was selected with consecutive sampling. The inclusion criteria were Dr Saiful Anwar Hospital patients diagnosed with clinical sepsis based on clinical symptoms and SOFA score more than or equal to two from medical records. The subjects blood sample was obtained for neutrophil and lymphocyte count and procalcitonin

as a biomarker for predictions of septic shock. The data will be analyzed using the SPSS version 23. The normality of the data distribution is evaluated using Saphiro Wilk test. The diagnostic value is analyzed using the ROC curve, and the cut off value is determined. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy are calculated with a 2x2 table.

RESULT

A total of 60 subjects was included in this research based on the clinical diagnosis from the medical record. The proportion of women and men were 28 (46,6%) and 32 (53,4 %), respectively.

A Cut-off point of 2.24 ng/Ml for procalcitonin shows sensitivity, specificity. positive and negative predictive value of 93%, 86.7%, 86.9% and 92.4%, respectively. While the NLCR cut-off point of 5.06 shows the sensitivity, specificity. positive and negative predictive value of 80%, 80%, 76.9%, and 79.1%, consecutively. The ROC curve analysis showed that PCT is significantly better than NLCR in diagnosing bacteremia.

DISCUSSION

Several studies found that found that men are more susceptible to sepsis. They tend to have infections in the lungs, while women tend to experience urinary tract infections. The most common cause for sepsis is a lung infection.[6] In this study, there was no significant difference between sex and age with the incidence of sepsis. We observed similar findings showing the same proportion of men and women who have diagnosed with sepsis. Hence, the sepsis incidence is not influenced by gender and age.[9]

In this study, we measured the diagnostic value of PCT and NLCR in patients diagnosed with sepsis. De Jager et al. state that the NLRC ratio is a simple and good laboratory test in diagnosing sepsis due to bacterial infections compared to the routine parameters, such as total leukocytes and CRP.[8] Holub et al. agreed that the NLCR is an excellent diagnostic test for sepsis. They find that it had high sensitivity and specificity of 91% and 96%, respectively, for bacterial infection.[9]

The increase in neutrophil counts in septic patients is caused by the proinflammatory cytokines, such as IL-6, IL-1, and TNF-a produced by macrophages. On the other hand, the lymphocyte count decreases in bacterial sepsis as a result fro the increase in the secretion of the glucocorticoid hormone which suppressed the lymphocyte production. Other theories suggest that the mechanism responsible for lymphocytopenia in sepsis involves the process of marginalization and redistribution of lymphocytes

Table 1. Characteristics

Variables	Cases		Control	
	Mean (Range)	N (%)	Mean (Range)/	N (%)
Age	46 (18-65)		47(18-65)	
Sex (n)				
Male		15 (50)		16 (50)
Female		15 (50)		14 (50)
Systolic Blood Pressure (mmHg)	125 (90 –165)		120(110-130)	
Heart Rate (times/minute)	108 (94–121)		85 (80-90)	
Repiratory Rate (times/ minute)	26 (24–32)		19(18-20)	
Temperature (ºC)	38.3(37.6–38.8)		36.4(36.0-37.0)	

Table 2. The Profile of PCT and NLCR

Characteristics	Cases	Control	P-value
	Mean(Range)	Mean(Range)	
Procalcitonin	36.9 (2.01-100)	0.23(0.01-0.78)	0.000
NLCR	16.6 (1.74-50.68)	2.79(1.63-6.31)	0.020
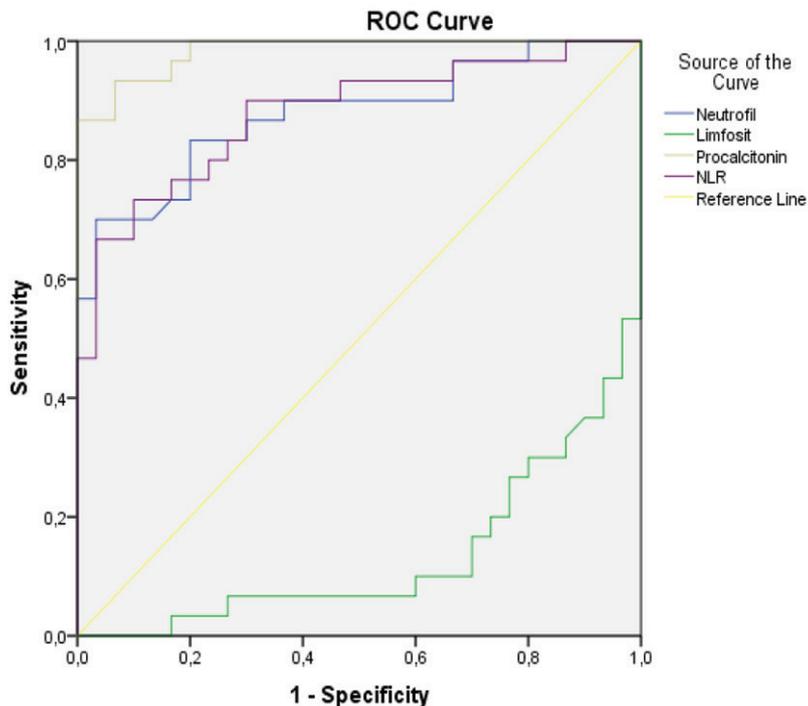
Picture 1. ROC Curve for PCT, NLCR, neutrophil, and lymphocyte

Table 3. The AUC, Sensitivity and specificity, cut-off and positive and negative predictive value for PCT, NLCR, Neutrophil, and Lymphocyte

Variable	AUC	P Value	Sensitivity (%)	Specificity (%)	Cut-off	+ PV (%)	- PV (%)
PCT	0.983	0.000	93	86.7	2.24	86.9	92.4
NLCR	0.878	0.000	80	76.7	5.06	76.9	79.1
Neutrophil	0.877	0.000	80	78	77.05	78.4	79.5
Lymphocyte	0.133	0.000	53	40	7.9	46.9	45.9

in the lymphatic system and the acceleration of the apoptotic process.

The process of apoptosis has occurred since the onset of sepsis, when bacteria or products stimulate macrophages to release pro-apoptotic substances, such as TNF-a, Nitrite Oxide (NO) and glucocorticoids. These will suppress the lymphocyte production. Along with the disease development, there will be an accumulation of apoptotic lymphocyte products acting as anti-inflammatory stimuli.[10]

In this study, it was found that there was a correlation between the ratio of lymphocyte neutrophil counts and the clinical symptoms in patients diagnosed with sepsis. However, this finding is limited by the small sample size. Therefore, further research with more significant sample size is needed to explore the correlation.

Research conducted in 2012, by Purba Donald

Roy found that PCT can be used as a sepsis marker and correlates with the sepsis severity. In this study, it was found that the AUC of procalcitonin was higher than the AUC of NLCR in patients diagnosed with sepsis. The results of this study are in line with the results of previous studies. However, this finding might be confounded with the antibiotic therapy which can affect the outcome of the NLCR. Although the NLCR is affected by antibiotic treatment, unlike the procalcitonin, it provides an easy, fast and, inexpensive examination. Moreover, it has been found to correlate with the severity of the disease and suggested as a predictor of bacteremia. Therefore, the can be useful in predicting the severity and diagnosis of sepsis.

CONCLUSION

From the results, it can be concluded that the procalcitonin is more superior than the ratio of neutrophil lymphocyte counts in diagnosing sepsis. Further research is needed with bigger sample size and cohort design for evaluating the new biomarkers.

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