

Neutrophils to Lymphocyte Ratio: Earliest and Efficacious Markers of Sepsis

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NEUTROPHIL-LYMPHOCYTE RATIO AND PROCALCITONIN LEVELS IN SEPSIS PATIENTS

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ABSTRACT

Background: Mortality in sepsis patients is still quite high. Delayed diagnosis will further increase mortality in septic patients. Microbiological culture examination is a standard diagnosis of sepsis which takes a relatively long time and low sensitivity. Currently procalcitonin is a reliable biomarker for the diagnosis and prognosis of sepsis patients. The neutrophil-lymphocyte ratio is a simple test that has been tested as a diagnostic marker for bacterial infection. We determined the correlation between neutrophil-lymphocyte ratio and procalcitonin level in sepsis patients.

Method: This study was an observational analytic with cross-sectional design conducted on sepsis patients aged of 18-60. The neutrophil-lymphocyte ratio was determined using Sysmex XN 1000 hematology analyzer. Procalcitonin levels were measured using VIDAS® BRAHMS PCT with the enzyme-linked fluorescence assay principle. The correlation between the ratio of neutrophil-lymphocytes and procalcitonin levels was statistically analyzed using Spearman correlation test.

Results: There were 30 subjects enrolled in this study. From microbial culture 63.3%-gram negative bacteria were identified. Median ratio of neutrophils-lymphocytes and procalcitonin was 12.05 (6.48-24.27) and 2.85ng/ml (0.75-88.42 ng/ml), respectively. The neutrophil-lymphocyte ratio in gram negative and procalcitonin were 12.07 ± 3.52 and 10.34 ± 22.92 ng/ml, respectively. While that of gram positive was 15.76 ± 4.36 , and 6.02 ± 4.26 ng/ml, respectively. The ratio of neutrophils-lymphocytes and procalcitonin in sepsis, severe sepsis, and septic shock were 10.08 ± 3.34 and 1.79 ± 1.39 ng/ml, 12.11 ± 4.08 and 3.56 ± 2.79 ng/ml, 15.78 ± 6.10 , and 23.19 ± 31.33 ng/ml, respectively. Spearman's correlation test showed a strong and significant correlation ($r_s = 0.68$, $p < 0.01$); $p < 0.01$) between the ratio of neutrophil-lymphocytes and procalcitonin levels in sepsis patients

Conclusion: There was a strong and significant correlation between the ratio of neutrophil-lymphocytes and procalcitonin levels in sepsis patients.

KEYWORDS: Neutrophil-lymphocyte ratio, procalcitonin, sepsis

INTRODUCTION

Sepsis is a systemic inflammatory response to infection (1). The incidence of sepsis in the United States is quite high, with estimation 13 million incidence per year and 4 million deaths per year (2). The standard of sepsis diagnosis is blood culture examination which takes relatively long time and positive blood culture resulting in only 26.6% in septic patients (3). Procalcitonin (PCT) is a rapid

and specific marker of sepsis that is currently in use. (4). The sensitivity, specificity, and under the curve area (AUC) of PCT were 77%, 79%, and 0.85, respectively.

Bacterial infection is characterized by the presence of neutrophilia and lymphocytopenia (5). The neutrophil-lymphocyte ratio is correlated with the severity of SIRS and sepsis. The neutrophil-lymphocyte ratios have been tested as markers for bacterial infections, with 91% sensitivity, 96% specificity and better accuracy rates compared to C-reactive protein (CRP) (6, 7).

Based on Surviving sepsis campaign (SSC) 2012, the severity of sepsis is categorized into sep-

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sis, severe sepsis and septic shock (4). Sepsis-induced mortality increases along with development of the sepsis severity and it is affected by comorbidities. Based on severity, the mortality rates in sepsis, severe sepsis and septic shock were 30%, 50% and 80%, respectively (8).

Delayed administration of appropriate antibiotics will increase mortality. 1 hour delay of antibiotics administration within the first 6 hours after hypotension will decrease the survival rate by 7.6%. In contrast, appropriate antibiotics within 1 hour contributes to a survival of 79.9% (9). In addition, the cost of treatment for sepsis patients is also very high.

Immune response to sepsis begins with the interaction between host components through pattern recognition receptors (PRRs) with pathogen-associated molecular patterns (PAMPs). There are four PRRs such as Toll-like receptors (TLRs), C-typelectin receptors (CLRs), and retinoic acid-induced genes (RIG)-1-like receptors. Lipoteichoic acid (LTA) of gram-positive bacteria will bind to TLR2 while lipopolysaccharide (LPS) of Gram-negative bacteria will bind to TLR4. This binding will activate innate and adaptive immune systems. Meanwhile, in lymphocyte cells occurs lymphopenia due to extensive apoptosis of lymphocyte cells (10). Increased PCT levels correlate with disease severity (11). PCT can increase CD16 surface marker expression in neutrophils (12) and is reported to have a suppressive effect of T cell lymphocyte activity (13).

Leukocyte population changes with a rapid kinetic, thus describing the role of neutrophils in the early stages of the inflammatory response. The ratio of lymphocyte neutrophils has been tested as a diagnostic marker and prognosis in septic patients (14). Based on the description above, the study aims to analyze the correlation between ratio of neutrophil-lymphocyte count and procalcitonin levels in sepsis patients.

10 METHODS

This study was an analytical observational research with cross-sectional design. The population were sepsis patients who came to the Emergency Installation and underwent treatment at the Inpatient Installation of Internal Medicine of Dr. Soetomo General Hospital Surabaya. Subjects were selected

through inclusion and exclusion criteria by consecutive sampling. Inclusion criteria were as follows: male or female, age 18 - 60 years, clinical sepsis patient according to criteria of consensus ACCP/SCCM year 1991 with two or more SIRS criteria accompanied by evidence/suspected infection source, procalcitonin level ≥ 0.5 ng/ml based on 2012 SSC criteria, and willing to participate in the study by signing informed consent. Patients with aplastic anemia, leukemia, myeloproliferative disease, malignancy or chemotherapy, HIV/AIDS, corticosteroid therapy, systemic lupus erythematosus, undergoing hemodialysis, surgery, burns, acute myocardial infarction were excluded in this study.

Sepsis is defined as a systemic response to infection. The diagnosis of sepsis is established based on the consensus criteria of ACCP/SCCM in 1991 consisted of two or more of the following SIRS criteria: 1) Body temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; 2) Heart rate of >90 times/min; 3) Tachypnea with respiratory frequency of >20 times/min or $\text{PaCO}_2 <32$ mmHg; 4) Leucocytes of $>12,000/\text{ul}$ or $<4,000/\text{ul}$, or $>10\%$ of immature/band form, accompanied by evidence/alleged source of infection (1) kadar prokalsitonin ≥ 0.5 ng/ml berdasarkan kriteria SSC 2012 (4), procalcitonin levels of ≥ 0.5 ng/ml based on SSC 2012 criteria.

The neutrophil-lymphocyte ratio is the result of the division of the absolute number of neutrophil counts against the absolute number of lymphocyte count. Sepsis occurs if the ratio of neutrophils-lymphocytes is >5 (7). Neutrophil and lymphocyte were measured using the Sysmex XN 1000 hematology analyzer. PCT is a precursor of calcitonin hormone and synthesized by C cells of the thyroid gland under the control of calcitonin gene related peptide 1 (CALC-1 gene). Examination with VIDAS®BRAHMS PCT Test technique was performed with linked fluorescent assay enzyme principle.

All data were entered into the computer through the SPSS statistical program edition 17 (SPSS, Inc., Chicago, IL.). The correlation between neutrophil-lymphocyte ratio and PCT level will be calculated using Pearson's parametric test if it was normally distributed or Spearman nonparametric test if it was abnormally distributed. Interpretation of correlation test results are based on p value, correlation strength and direction of correlation.

RESULTS:

The characteristics of 30 samples of sepsis patients undergoing hospitalization at Internal Disease Unit RSUD dr. Soetomo Surabaya which fulfilled inclusion and exclusion criteria are shown in table 1.

The obtained mean of age was 52.77 years, with the youngest age being 42 years old and the oldest 60 years old. Out 20 samples were male (66,7%) and 10 were female (33,3%). There were 18 DM patients (60%), 9 patients with DM and hypertension (30%), 1 patient with DM and urinary stones (3.3%), and 1 with no comorbid disease (3.3%) .

The source of infection in sepsis patients in this study indicated that soft tissue infection was the source of infection in 17 sepsis patients (56.7%), urinary tract infection in 7 patients (23.3%), and pneumonia in 6 patients (20%). Based on the severity of sepsis, in this study there were 53.3% subjects with severe sepsis, 30% with septic shock and 16.7% with sepsis.

The result of culture examination on 30 sepsis patients showed 19 gram of negative bacteria (63%), 4 gram positive bacteria (13.3%) and 7 gram with no growth of bacteria (23.3%). Gram-negative species based on positive culture results obtained 4 (13.3%) *Acinetobacter baumannii*, *E. coli* ESBL (+) of 3 (10%), *E. coli* 1 (3.3%), *Pseudomonas aeruginosa* 4 (13.3%), *Klebsiella pneumonia* 3 (10%), *Klebsiella pneumonia* ESBL (+) 2 (6.7%), *Enterobacter cloacae* 2 (6.7%). While gram-positive bacteria consisted of mammogram 1 (3.3%), *Enterococcus faecalis* 1 (3.3%), *Staphylococcus epidermidis* 1 (3.3%), and *Staphylococcus haemolyticus* 1 (3.3%).

The neutrophil-lymphocytes ratio and procalcitonin levels according to the severity of sepsis and culture of cultures in septic patients is shown in Table 2. There was an increase in the ratio of neutrophils to lymphocytes in the direction of severity of sepsis. Likewise with procalcitonin levels in subjects with septic shock, the procalcitonin levels were higher than in severe sepsis and sepsis. The ratio of neutrophil-lymphocyte according to culture result showed that the ratio of neutrophil-lymphocytes in gram-positive bacteria was higher compared to gram-negative bacteria. Meanwhile, procalcitonin levels were higher in gram-negative bacteria compared with gram-positive bacteria.

In this study, the ratio of neutrophil-lymphocyte

TABLE I.

Subjects' characteristics	
Characteristics	Results
Age (Years)	
Mean ± SD	52.77 ± 5.39 ²³
Median (min-max)	51.50 (42-60)
Gender	
Male	20 (66.7%)
Female	10 (33.3%)
Comorbid	
DM	18 (60%)
DM and Hypertension	9 (30%)
DM and urinal stone	1 (3.3%)
None	1 (3.3%)
Infection Source	
Soft tissue infection	17 (56.7%)
Urinary Tract Infection	7 (23.3%)
Pneumonia	6 (20%)
Severity degree	
Sepsis	16.7%
Severe sepsis	53.3%
Septic Shock	30%
Culture Results	
Gram-negative Bacteria	19 (63.3%)
<i>Acinetobacter baumannii</i>	4 (13.3%)
<i>Pseudomonas aeruginosa</i>	4 (13.3%)
<i>E. coli</i> ESBL (+)	3 (10%)
<i>E. coli</i>	1 (3.3%)
<i>Klebsiella pneumonia</i>	3 (10%)
<i>Klebsiella pneumonia</i> ESBL (+)	2 (6.7%)
<i>Enterebacter cloacae</i>	2 (6.7%)
Gram-positive Bacteria	4 (13.3%)
MRSA	1 (3.3%)
<i>Enterococcus faecalis</i>	1 (3.3%)
<i>Staphylococcus epidermidis</i>	1 (3.3%)
<i>Staphylococcus haemolyticus</i>	1 (3.3%)
No bacterial growth	7 (23.3%)

TABLE 2.

Description of the ratio of neutrophils-lymphocytes and procalcitonin levels			
	Frequency	Ratio of Neutrophils-lymphocytes	Procalcitonin ng/ml
Degree of Severity			
Sepsis	16.7%	10.08± 3.34	1.79± 1.39
Severe sepsis	53.3%	12.11± 4.08	3.56± 2.79
Septic Shock	30%	15.78± 6.10	23.19± 31.33
Culture Results			
Gram-negative bacteria	19 (63.3%)	12.07±3.52	10.34±22.92
<i>Acinetobacter baumannii</i>	4 (13.3%)	11.07±2.91	2.13±0.64
<i>Pseudomonas aeruginosa</i>	4 (13.3%)	12.56±3.48	17.17±27.83
<i>E. coli</i> ESBL (+)	3 (10%)	10.76±4.41	5.16±3.87
<i>E. coli</i>	1 (3.3%)	12.04	2.94
<i>Klebsiella pneumonia</i>	3 (10%)	13.45±7.05	30.54±50.12
<i>Klebsiella pneumonia</i> ESBL (+)	2 (6.7%)	13.74±0.25	3.55±0.96
<i>Enterobacter cloacae</i>	2 (6.7%)	11.34±1.01	1.09±0.13
Gram-positive bacteria	4 (13.3%)	15.76±4.36	6.02±4.26
MRSA	1 (3.3%)	20.00	0.92
<i>Enterococcus faecalis</i>	1 (3.3%)	11.05	10.95
<i>Staphylococcus epidermidis</i>	1 (3.3%)	18.91	4.65
<i>Staphylococcus haemolyticus</i>	1 (3.3%)	13.08	7.58
No bacteria growth found	7 (23.3%)	13.39± 8.05	7.71±12.43

levels in line with the increase in neutrophil-lymphocyte ratio. The neutrophil-lymphocyte ratio of >5 in all study subjects. Likewise with procalcitonin, procalcitonin levels of >0.5 ng/ml were found in all subjects and there were 3 subjects with very high procalcitonin values of 34.97 ng/ml, 58.87 ng/ml and 88.42 ng/ml.

From correlation analysis between the ratio of neutrophil-lymphocytes with procalcitonin levels by using Spearman correlation test rs value of 0.68 and p value <0.01 were obtained, suggesting a strong and significant correlation between the ratio of neutrophil-lymphocytes and procalcitonin levels in sepsis patients. The Correlation between the ratio of neutrophil-lymphocytes with procalcitonin levels was a positive or one-way correlation, which means that the higher the ratio

had an abnormal data distribution, with median value of 12.05 and the lowest value of 6.48 and the highest was 24.27. Procalcitonin content had abnormal distribution with median value of 2.85 ng/ml, the lowest level was 0.75 ng/ml and the highest was 88.42 ng/ml (table 3).

Description of the ratio of neutrophils-lymphocytes and procalcitonin levels (figure 1) in this study showed a tendency to increase procalcitonin

of neutrophil-lymphocytes in sepsis patients, the higher the procalcitonin level. The correlation linearity of neutrophils with lymphocytes with procalcitonin levels is shown in Fig. 2.

DISCUSSION

In this study, the mean value of procalcitonin level 9.15 ± 19.05 and median value 2.85 (0.75 - 88.42). Procalcitonin levels in this study increased

TABLE 3. The ratio of neutrophils-lymphocytes and Procalcitonin levels in septic patients

Variable	Result
Neutrophil-Lymphocyte Ratio	
Mean ± SD	12.87 ± 4.97
Median (min-max)	12.05 (6.48-24.27)
Procalcitonin	
Mean ± SD	9.15 ± 19.05
Median (min-max)	2.85 (0.75-88.42)

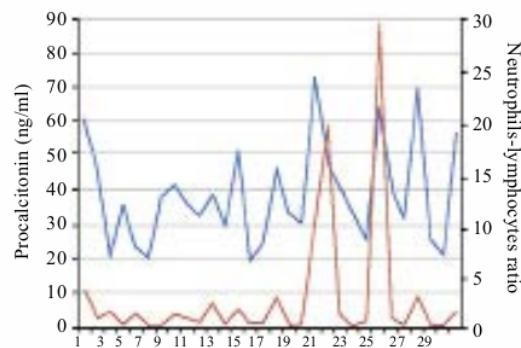


FIGURE 1. Description of the ratio of neutrophils-lymphocytes and procalcitonin levels

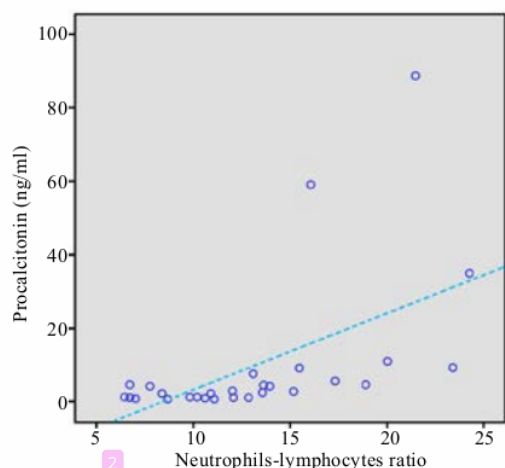


FIGURE 2. Correlation between Neutrophil-Lymphocyte Ratio and Procalcitonin Levels

in accordance with the severity of sepsis. The mean procalcitonin levels of 1.79 ± 1.39 ng/ml were obtained in subjects of sepsis, 3.56 ± 2.79 ng/ml in severe sepsis, and 23.19 ± 31.33 ng/ml in septic shock. The rate of procalcitonin in sepsis of gram-negative bacteria is higher than the sepsis of gram-positive bacteria. Median levels of procalcitonin in gram negative 13.8 ng/ml and 2.1 ng/ml in gram positive. In this study obtained levels of procalcitonin gram-negative bacteria higher than the procalcitonin content of gram-positive bacteria. In gram-negative bacteria found procalcitonin levels of 10.34 ± 22.92 ng/ml and gram-positive bacteria 6.02 ± 4.26 ng/ml.

The study conducted that the correlation between the ratio of neutrophil-lymphocytes with procalcitonin levels in sepsis and severe sepsis patients in the ICU room with r value of 0.598 and p value 0.001. In this study, correlation analysis between the ratio of neutrophil-lymphocytes with procalcitonin levels using Spearman correlation test obtained r_s value of 0.68 and p value <0.01 indicating there was a strong correlation between the neutrophil-lymphocyte ratio and procalcitonin levels in sepsis patients.

The incidence rate of sepsis continues to increase annually. A study found an incidence rate of sepsis from 82.7 cases per 100,000 population increased to 240.4 cases per 100,000 population with an increase of 8.7% per year. Previous research, got the average value of patients sepsis 52.77 ± 5.39 and median

value of 51.50 (42-60) years old. Age is one risk factor of sepsis. In neutrophil cells, in elderly patients there was a decrease in neutrophil phagocytosis capacity and decreased CD16 expression. This could underlies the susceptibility of elderly patients to bacterial infection (15). Thus, to reduce the effect of age on neutrophil cells and lymphocytes, this study only involved patients aged of 18-60.

Sepsis is more commonly experienced by men than women. Studies in 16 Asian countries with a total of 1,285 sepsis patients found men as many as 793 (61.7%) (16). Patients consisted of 159 (62.6%) male and 95 (37.4%) female. In accordance with the previous research, this study obtained men as many as 20 (66.7%) and women 10 (33.3%) (16). The influence of sex on the risk of sepsis is a complex involving the immunoneuroendocrine system.

Mortality in male patients is high. A retrospective study of 261,255 patients obtained higher mortality in men in the age group <50 years old than in women in the same age group. This difference does not occur in patients over the age of 50 years (17).

Various comorbid diseases also affect susceptibility, severity and mortality in sepsis patients. Comorbid disease in sepsis patients consisted of 18.7% DM, 18.6% hypertension, 15.2% chronic heart failure, 14.5% cancer, 12.1% chronic obstructive pulmonary disease, 2.0% HIV infection, and 0.3% pregnancy (18). This study obtained 60% DMD patients, DM and hypertension 30%, DM and urinary tract stones 3.3%, and no comorbid 3.3%.

DM is one of the factors that increase susceptibility to sepsis. In DM patients, hyperglycemia will disrupt the function of neutrophil cells and interfere with the production of various cytokines. In some studies using blood from DM patients showed a decrease in the function of neutrophil cells that included decreased endothelial adhesion capability, chemotaxis, phagocytosis, and bacterial killing ability (19). The condition of hyperglycemia is the main mechanism causing immune cell function impairment, while the type of DM, A1c levels are not found to affect the function of immune cells.

Source of infection in sepsis patients reported from lung infections as much as 48.8%, intra-abdominal infections 23.6%, urinary tract infections 10.6%, primary bloodstream 6.3%, Others (meningitis, bone or joint infections, infected) 9.1% and unknown 1.6% (20). In this study, soft-tissue in-

fections were the most common source of infection in sepsis patients, i.e. 56.7%, 23.3% urinary tract infection, and 20% pneumonia. Several factors influencing this difference were the majority of comorbid diseases of sepsis patients suffering from DM disease, the risk of developing skin and soft tissue infections is higher (21). In addition, lung infections in this study were only 20%. This is possible because the majority of lung infection patients were admitted to the Pulmunology Unit that was separated from the Internal Disease Unit.

Based on the severity of sepsis, subjects who experienced severe sepsis at most, namely by 53.3%, septic shock 30% and sepsis 16.7%. The results of culture in sepsis patients, gram negative bacteria more than with gram positive. Gram negative as much as 62.2%, consist of 19.9% *Pseudomonas*, 16% *E.coli*, 12.7% *Klebsiella*, 8.8% *Acinetobacter*, 7% *Enterobacter*, and 17% other bacteria. Meanwhile, 46.8% positive gram consisted of *Staphylococcus aureus* 20.5%, MRSA 10.2%, *Enterococcus* 10.9%, *S. epidermidis* 10.8%, *S. pneumoniae* 4.1%, and others 6.4% (22).

Bacteremia conditions always results in neutrophilia and lymphocytopenia (5). Neutrophil-lymphocyte stress factor (NLSF) is the ratio of neutrophil counts to lymphocytes. This prospective study obtained the manifestations of neutrophilia and lymphocytopenia that appear within 4-8 hours after insult. Under normal conditions NLSF is <5, in severe infections the NLSF is > 6 (23). In this research, the mean value of neutrophil-lymphocyte ratio was 12.87 ± 4.97 and median ratio of neutrophil-lymphocyte was 12.05 (6.48- 24.27). The ratio of neutrophil-lymphocyte increases with the

severity of sepsis. The mean neutrophil-lymphocyte ratio of 10.08 ± 3.34 was obtained in the subjects of sepsis, 12.11 ± 4.08 in severe sepsis, and 15.78 ± 6.10 septic pads.

Lymphocytopenia in sepsis conditions is due to extensive apoptosis of lymphocyte cells. In sepsis conditions, lymphocyte dysfunction is a significant decrease in CD4 + T cells, CD8 +, and NK cells in both the peripheral circulation and in the local organs of patients dying of sepsis (10, 24).

In sepsis conditions an increase in PCT levels is produced by various cells and tissues. LPS is an inducer potent release of PCT to the systemic circulation. After LPS administration increased CALC-1 gene expression in various extra-thyroid tissues, including renal parenchymal cells, lung, liver, pancreas, lymph, leucocyte, small intestine, colon, peritoneal macrophages, heart, brain, skin and fat tissue (25). PCT levels between 0.1 and 0.5 ng/ml indicate the presence of a bacterial infection such as a lower respiratory tract infection requiring antibiotic therapy. PCT levels >0.5 ng/mL indicate suspicion of a sepsis syndrome. For critically ill patients, the cut-off value for the diagnosis of sepsis with median cut-off was 1.1 ng/ml (interquartile range of 0.5-2.0 ng/ml).

CONCLUSION

There was a strong and significant correlation between the ratio of neutrophil-lymphocytes and procalcitonin levels in sepsis patients. Thus, an increase in the ratio of neutrophils-lymphocytes has the potential to be an indirect marker of increased procalcitonin levels. Although this still needs to be confirmed further with diagnostic tests.

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