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RESEARCH

CORRELATION OF MONOCYTE COUNT, MLR AND NLCR WITH PRESEPSIN LEVEL IN SIRS

(Hubungan Jumlah Monosit, MLR dan NLCR dengan Kadar Presepsin pada SIRS)

Nurmalia PS[1], N. Suci W[2], Imam BW[2]

ABSTRAK

*Systemic Inflammatory Response Syndrome (SIRS) mempunyai kebahayaan tinggi terjadi sepsis dan kematian. Nilai jumlah keseluruhan leukosit merupakan salah satu peramal pasien SIRS dengan bakteriemia. Pemeriksaan jumlah monosit, angka banding limfosit Monocyte-Lymphocyte Ratio (MLR), Neutrophil-Lymphocyte Count Ratio (NLCR) dapat diketahui dengan pemeriksaan leukosit. Presepsin telah diteliti untuk mencerminkan kondisi sepsis. Penelitian ini bertujuan untuk mengetahui keberadaan hubungan jumlah monosit, MLR dan NLCR dengan presepsin di SIRS lewat pembuktian. Ada 34 pasien SIRS di ICU RSUP Dr. Kariadi, diambil secara berturutan antara selama bulan Januari–Februari 2014. Pemeriksaan darah rutin dengan hematology analyzer. MLR dan NLCR di hitung secara manual. Kadar presepsin ditentukan dengan metode Chemiluminescent Enzyme Immunoassay (CLEIA). Uji kenasaban Pearson untuk hubungan MLR dan NLCR dengan presepsin. Uji kenasaban Spearman untuk jumlah monosit dengan presepsin. Kadar presepsin subjek penelitian 286–15687 pg/mL. Terdapat 23(67,8%) subjek yang mempunyai jumlah monosit dalam rentang nilai rujukan. 24(70,6%) dan memiliki jumlah neutrofil absolut lebih besar dari rentang nilai rujukan, sedangkan 21(61,8%) mempunyai jumlah limfosit absolut dalam rentang nilai rujukan. Hubungan jumlah monosit dengan presepsin mempunyai nilai r= -0,204; p=0,247; yang terkait MLR dengan presepsin r=0,163; p=0,358; sedangkan NLCR dengan presepsin r=0,345; p=0,046. Didasari telitian ini, dapat disimpulkan tidak terdapat hubungan bermakna antara jumlah monosit dan MLR dengan presepsin, selain itu didapatkan pula hubungan positif berarti antara NLCR dan presepsin di SIRS***.***

Kata kunci*: Monosit, MLR, NLCR, presepsin*

ABSTRACT

Systemic Inflammatory Response Syndrome (SIRS) has a high risk of mortality and sepsis. The total value of leukocytes is an indicator of SIRS with bacteremia. The examination of monocyte count, Monocyte-Lymphocyte Ratio (MLR) and Neutrophil-Lymphocyte Count Ratio (NLCR) can be determined by the examination of leukocyte count. The marker of presepsin can be investigated to reflect the condition of sepsis. Therefore, this research aimed to know the correlation between monocyte count, MLR and NLCR with presepsin in SIRS patients. This research was a cross sectional research conducted on 34 clinically SIRS patients at Dr. Kariadi Hospital taken consecutively from January to February 2014. Complete blood count test was carried out with a hematology analyzer. Meanwhile, MLR and NLCR was counted manually. Presepsin level was then determined by chemiluminescent enzyme immunoassay method (CLEIA). Next, Pearson test was conducted for analyzing the correlation of MLR and NLCR with presepsin, while Spearman test was conducted for analyzing the correlation of monocyte count with presepsin. The presepsin level of the subjects found was between 286–15687 pg/mL. 23 subjects (67.8%) had monocyte count in the range of the reference values, 24 subjects (70.6%) had absolute neutrophil count greater than the range of the reference values and 21 subjects (61.8%) had absolute lymphocyte count within the range of the reference values. The correlation of monocyte count with presepsin measured was r=-0.204 (p=0.247). Meanwhile, the correlation of MLR with presepsin measured was r=0.163 (p=0.358). The correlation of NLCR with presepsin measured was r=0.345 (p=0.046). Finally, it can be concluded that there was no significant correlation between monocyte count and MLR with presepsin, but there was a positive significant correlation between NLCR with presepsin in SIRS.

Key words: Monocyte, MLR, NLCR, presepsin

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INTRODUCTION

Systemic Inflammatory Response Syndrome/SIRS is a systemic inflammatory activation condition with various causes. In high risk level, it will cause sepsis and death.[1] One third of patients hospitalized in the Intensive Care Unit (ICU) were in SIRS condition.[2,3] The number of patients with infectious diseases has increased as the number of SIRS criteria has been met. Sepsis is SIRS with infection and positive culture. The systemic inflammatory response syndrome has a high risk of sepsis and death.[4] Sepsis is one of the top ten causing deaths in the United States. The prevalence of sepsis even has increased significantly in the past decade. In the ICU of Dr. Kariadi Hospital Semarang (RSDK) in 2012, the prevalence of sepsis was 172, while in 2013 it was 159 (Based on medical records of Dr. Kariadi Hospital, Semarang).

The research conducted by Pal *et al*[5], moreover, shows that patients with infections will have a risk of sepsis twice compared the patients without infections.[5] The results of blood cultures usually will take between 3–7 days to identify the bacteria and antibiotic sensitivity.[6,7] The research conducted by Marco *et al*[8] also shows that 19.9% of the patients with sepsis in the ICU have positive culturing results.[8] Thus, the diagnosis of sepsis is important by conducting rapid, accurate and relatively inexpensive laboratory investigation

To diagnoze the sepsis marker, presepsin must be investigated to reflect the condition of sepsis. Presepsin is a terminal fragment of Cluster of Differentiation (CD) 14, the fraction of the subtype of sCD14 (sCD14-ST). CD14 is a cell surface receptor that binds lipopolysaccharide (LPS) or LPS Binding Protein/LBP (known as LPS-LBP complex). Presepsin is released from monocytes through the mechanism of shedding/realeasing.[7] CD14 is expressed on the surface of monocytes, macrophages, and granulocytes cells. CD14 can bind and react with other bacterial ligands in between Lipotheoic Acid (LTA) and Peptide-glycan (PGN). Fraction soluble CD14 (sCD14), as a result, will be generated due to the presence of infection.[9–12] The research conducted by Shozushima *et al*[11] proves that presepsin can be used for diagnosing sepsis better than procalcitonin (PCT). The cut off presepsin about 415pq/mL can have a sensitivity of 80.1% and 81% for diagnosing the peculiarities of sepsis.[11]

In addition, the total number of leukocytes can also be used to indicate bacteremia in patients. Neutrophils and monocytes play an important role in phagocytosis. Therefore, the examination of serial changes in the circulation of neutrophils, monocytes and lymphocytes must be conducted. The number of lymphocytes will decrease between 4-6 hours after endotoxemia, while the number of monocytes will decrease after 90 minutes, but the number of neutrophils will increase.[13]

Furthermore, the ratio of lymphocytes, especially MLR and NLCR, is often associated with severity of disease.[14] *Neutrophil-Lymphocyte Count Ratio* (NLCR) is a benchmark that is cheap and easy to be examined, derived from the results of routine blood check in the laboratory. *Neutrophil-lymphocyte count ratio* under physiological condition is less than five, but will increase more than six in severe infection condition or SIRS.[15] The research conducted by Jager *et al*[16] shows that NLCR can be considered as an indicator of bacteremia in patients at the emergency wards.[16] Holub *et al*[15] even concludes that NLCR with cut off of 6.2 has a sensitivity of 91% and 96% for patients with bacteremia, so NLCR has an important diagnostic role for bacteremia.[15] Similarly, the research conducted by Meita *et al*[17] shows a strong positive correlation between NLCR and PCT in SIRS.[17]

In short, presepsin can be considered as a new marker for diagnosis of sepsis. Unfortunately, it is still not clear enough. For those reasons, this research aimed to examine the correlation of monocyte count, MLR and NLCR with presepsin in SIRS patients in ICU of RSDK.

METHODS

This research was an observational research with cross sectional approach. This research was conducted at Dr. Kariadi Hospital Semarang (RSDK) from January to February 2014. The examination of specimens was performed at the Laboratory Installation of Dr. Kariadi Hospital. Population of this research was adult patients in the ICU of Dr. Kariadi Hospital Semarang. Subjects of this research were selected with consecutive nonrandom technique based on several criteria. First, the age of patients had to be more than 14 years old. Second, patients had to meet two (2) or more SIRS indcators, such as temperature >38° C or <36° C, rapid heart rate >90 ×/min, respiratory rate >20 ×/min or PaCO2 <4.3 kPa (32 mmHg), leukocyte count >12,000/mm^3 or <4000/mm^3, or more than 10% of immature neutrophils stab.[18] Third, patients had to be willing to participate in this research by signing letter of consent. Fourth, patients did not have autoimmune disease.

Next, the patients' data were collected from medical, history, physical examination, and laboratorical records. The specimens of their blood were put in an EDTA tube to be checked by *hematology*

analyzer with *optical* methods (*Celldyn*). MLR and NLCR were measured manually. Afterwards, the number of monocytes was measured to examine the number of leukocytes using *hematology analyzer* instrument and then expressed in unit of percent (%). *Neutrophil-lymphocyte count ratio* was obtained by dividing absolute neutrophil count with the same number of lymphocytes.[15] *Monocyte-lymphocyte ratio*, on the other hand, was obtained by dividing absolute monocyte count with the same number of lymphocytes.[14] Finally, presepsin serum level was measured by *chemiluminescent enzyme immunoassay* method (CLEIA) using *Pathfast autoanalyzer* with a unit of pg/mL.

The data analysis was conducted using Pearson correlation test to know the correlation of NLCR and MLR with presepsin. Meanwhile, Spearman correlation test was conducted to know the correlation of monocyte count with presepsin. When the correlation of monocyte count, MLR and NLCR was statistically significant, it was then analyzed using the multivariate variables with the significance research value less than 0.05 ($p<0.05$).[19,20]

RESULTS AND DISCUSSION

This research was conducted on thirty-four SIRS patients, 17 males (50%) and 17 females (50%). The mean of the research subjects' age was 52.68±17.56 years old. The youngest age of the subjects was 16 years old and the oldest one was 89 years old. Presepsin level of the research subjects was between 286–15,687 pg/mL. Data of the characteristics of the research subjects can be seen in Table 1.

Furthermore, monocyte count obtained was in the range between 1-9% with a median of 3%. There were twenty-three research subjects (67.8%), who had monocyte count in the range of the reference values, while ten research subjects (29.4%) had monocytopenia. The range of the absolute monocyte count in the research subjects was between 62–1,036 cells/mm^3 and the median was 298 cells/mm^3. There were thirty-two subjects (94.1%), who had lower monocyte count than the reference value (<850 cells/mm^3).

The range of the absolute neutrophil count in the research subjects, moreover, was between 1,408–25,662 cells/mm^3 and the mean was 10,650.15 cells/mm^3. The number of the research subjects who had lower absolute neutrophil count than the reference values was one (2.9%). Meanwhile, the number of the research subjects who had greater absolute neutrophil count than the reference value (> 7,350 cells/mm^3) was 24 (70.6%).

In addition, the range of the absolute lymphocyte count in the research subjects was between 260–3,321 cells/mm^3 and the median was 1089 cells/mm^3. The number of the research subjects who had lower absolute lymphocyte count than the reference values (<1000 cells/mm^3) was thirteen subjects (38.2%). The number of the research subjects who had absolute lymphocyte count within the reference value was twenty-one subjects (61.8%). There were ten subjects (29.4%) who had lower monocyte count than the reference values. But, there was one subject (2.9%) with high monocyte count and presepsin level (see Table 2).

After the correlation of monocyte count and presepsin level was statistically tested, the results showed that the correlation was weak (r=-0.204)

Tabel 2. The distribution of monocyte count and presepsin level

	Monocyte count (%)			n
	<2	2-8	>8	
Presepsin level (pg/mL):				
<600	0	5	0	5
≥600	10	18	1	29
Total	10	23	1	34

Table 1. Tthe characteristics Data of of the research sujects

Chacteristics of the subjects	Mean±SD	Median (range)
Age (years old)	52.68±17.56	
Blood pulse (x/min)		93 (80–100)
Respiratory rate (x/min)		24 (20–30)
Temperature (°C)		38.3 (35.6–38.8)
Hb (gr%)	10.55±2.23	
Leukocyte count (thousand/mm^3)	12.52±5.86	
Thrombocyte count (thousand /mm^3)		199.50 (3–58)
Presepsin (pg/mL)		1134.50 (286–15687)
Length of stay before entering ICU (day)		3 (1–5)

Description: SD: Standard Deviation; minimum-maximum value range

Table 3. The distribution of NLCR and presepsin level

	NLCR		n
	<6.2	≥6.2	
Presepsin level (pg/mL):			
<600	3	5	8
≥600	5	21	26
Total	8	26	34

with the negative risk direction, but not significant (p=0.247).

The range of MLR value found was between 0.07-1.33 (with the median of 1.09). After the correlation of MLR and presepsin level was statistically tested, the results showed that the correlation was very weak (r=0.163) with the positive risk direction, but not significant (p=0.358).

The range of NLCR value found in the subjects was between 2.6-22.0 (with a median of 10.56). Most of the subjects, twenty-one subjects (61.2%), had high NLCR and presepsin level (see Table 3). It indicates that the correlation of NLCR and presepsin after the test was statistically significant with weak power (r=0.345; p=0.046) and a positive direction. Multivariate statistical analysis of the correlation of monocyte count, MLR and NLCR with presepsin could not be conducted since the results of the bivariate statistic test showed that the correlation of NLCR and presepsin was statistically significant.

Comparison of the distribution of the sexes in this research was similar between males and females aged between 16-89 years old with a mean of 52.68 years old (SD was 17.56 years old). The research conducted by Pal *et al*[5] found that 365 cases of SIRS in the ICU occurred in male subjects (47%) in the age between 15-96 years old.[5] Similarly, a research conducted by Nai *et al*[21] showed that SIRS mostly occurred in male subjects (57.9%) and the mean of age was 62 years old (SD was 17 years old).[21]

Furthermore, the results of the examination of the subjects' body temperature showed that the range of the body temperature was between 35.7–38.8°C. There were eight subjects (23.5%), who had a body temperature appropriate with SIRS. The lowest blood pulse rate of the subjects was 80x/minute, while the highest was 100×/min. However, there were nineteen subjects (55.91%) with blood pulse rate less than 90×/min, while the respiratory rate was between 20–30×/min. The lowest leukocyte count was 2,200/mm^3 and the highest one was 28,200/mm^3. The number of leukocytes in seventeen subjects (50%) was in accordance with SIRS and there was one subject (2.9%) in a state of leukopenia. The research conducted by Nai *et al*[21] in 2028 also found SIRS cases with abnormal body temperature (44.4%) and the same leukocyte count (50.5%) and rapid heart rate (62.8%).[21]

All subjects of this research, moreover, were treated using cultured antibiotic treatment although there still has been no result. The research on 3796 ICU patients conducted by Louis vincent *et al*[22] also showed that there were 51% of the infection cases, and as many as 71% of those patients got antibiotic treatment. The infections often occur in ICU patients since the risk of infection increases as the long duration of stay in the ICU, so the mortality rate will also increase.[22]

The results of this research, furthermore, show that there was no significant correlation between the monocyte count and presepsin in SIRS. This contrasts with the research conducted by Danikas *et al*[23] showing that there was a strong correlation between the phagocytosis of monocytes and neutrophils in SIRS. The systemic inflammatory response of the syndrome patients with phagocytic activity of neutrophils and monocytes was less than 37%, who had low expressions of CD64 and CD14 low and severe disease.[23]

In addition, the monocytes are located in the circulation. 10% of the total number of leukocytes only have a half-life between 1–3 days in the edge circulation and play an important role in phagocytosis. The mature monocytes will move into the tissue and change into macrophages. Monocyte-Derived Human Colony Stimulating Factor (MCSF) will stimulate the expression of monocyte chemotactic protein (MCP-1) in endothelial cells. The condition enhances the ability of monocytes in the blood circulation towards and into sub-endothelium.[24] Since the monocytes move into sub-endothelium, the number of monocytes in circulation will be reduced. Monocytopenia and lymphopenia will occur after administration of Escherichia coli endotoxin, and a decrease in the number of monocytes can be observed between 1–4 hours, whereas a decrease in the number of lymphocytes can be observed between 8-12 hours.[25]

The monocytes, moreover, have three (3) sub-populations based on the surface expression, namely classical, intermediate and non-classical. 90% of monocytes in bloodstream are in classical form (CD14 ++ CD16-). In the case of pathological conditions, such as sepsis, tumors, or trauma, the classical monocytes can be transformed into intermediate and non-classical ones, depended on the type of cytokine affecting.[26] The increasing number of sub-population of monocytes in inflammation and infectious diseases in humans indicates the role of CD14+CD16+monocytes in the

process. The roles of CD14+CD16+monocytes in inflammation and infection require certain changes or selective redirects of sub-populations of monocytes in vivo, but the mechanism is still not known clearly.[27] CD14 is a glycoprotein expressed by monocytes, macrophages, dendritic cells, and granulocytes. CD14 is a surface receptor that binds complex LPS-LPB, PGN, and LTA. CD14 will be detached from the cell membrane and change into a soluble form (sCD14). Presepsin (sCD14-ST) is a rebate form of sCD14, released from the cell membrane by cathepsin and other lysosomal enzymes due to phagocytosis.[28]

The monocytes, furthermore, will express CD14 and CD16 appropriate to improve their functions as phagocytes, antigen presenting cells and the body's immunity. The monocyte count usually declining in circulation, this can be caused by changes in monocytes into macrophages in tissues order to phagocyte bacteria.[29,30] The use of corticosteroids can induce monocyte apoptosis through activation of caspase cascade and also suppresses cytokines (IL-1β and M-CSF) allowing for the recovery of monocytes in blood circulation.[31] Presepsin can also be produced by neutrophil cells.[7,9,12]

The results of this research, moreover, showed that there was no significant correlation statistically between MLR and presepsin in SIRS. Monocytes and lymphocytes have an important role in systemic inflammation. These research subjects also experienced monocytopenia, a decrease in the absolute number of monocytes and lymphocytes, which make MLR not correlate with presepsin in SIRS.

Monocytopenia actually occurs because of an increased expression of MCP-1 in endothelial because of endotoxin or exotoxin exposure. This then triggers monocytes in the blood circulation move into the endothelium. Lymphopenia, on the other hand, occurs because of apoptosis, and new deployments of lymphocyte to the edge of the lymphoid tissue have been hypothesized, but the mechanism certainly still can not be known.[32]

The use of corticosteroids, furthermore, was found in 14.7% of the research subjects. The use of clinical anti-inflammatory corticosteroids as a treatment can reduce the degree of disease symptoms, but can not eliminate the causing factors. Corticosteroids can also reduce the expressions of intercellular adhesion molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule (VCAM) and Endothelial Leukocyte Adhesion Molecule-1 (ELAM-1) in endothelium. Thus, the adhesion and migration of leukocytes to sites of the inflammation, especially neutrophil cells, are inhibited.[33,34] Besides that, the corticosteroids can inhibit the release of monocytes from bone marrow.[35]

In addition, the results of this research show that there was a significant correlation between NLCR and presepsin with weak correlation power. The research conducted by De Jager *et al*[16] shows that NLCR can be considered as a good forecaster for bacteremia compared with CRP, lymphocyte and leukocyte counts.[16] Similarly, a research conducted by Fauzia *et al*[33] shows that NLCR can be associated with chronic systemic inflammatory conditions, such as hypertension, diabetes mellitus, asthma and arthritis.[33] *Neutrophil-lymphocyte count ratio* has been widely researched and proven to be a laboratory marker associated with systemic inflammation.[34]

The neutrophilia condition, moreover, often occurs because of inflammatory response of bacterial infections. The neutrophil count will increase one hour after the presence of a microbial infection. Neutrophils will be removed from the bone marrow in large quantities to get rid of microbes. There are some mechanisms triggering Neutrophilia. First, increasing of activated complement, Granulocyte Colony Stimulating Factor (G-CSF) and pro-inflammatory cytokine levels can lead to increased mobilization of neutrophils from the bone marrow into the bloodstream. Second, the increasing of neutrophils released from the bone marrow can become the location of inflammation. And, the last one is the increasing neutrophil products.[34,35]

The use of corticosteroids, furthermore, was found in 14.7% of the research subjects, especially SIRS patients with Chronic Obstructive Pulmonary Disease (COPD). Corticosteroids can prevent or suppress the inflammatory reaction due to infection or immunological agents and also inhibit early events of inflammation, such as edema, exudation cells, fibrin deposition, capillary dilation, leukocyte migration to sites of inflammation and phagocytic activity. The corticosteroid effect on inflammation is inhibition of neutrophil recruitment to the inflammatory place.[36] This condition makes the number of neutrophils in the blood circulation increase. The use of corticosteroids in various doses and duration of use will not cause an increase in leukocyte counts more than 20,000 cells/mm3 and/or shift to the left. The increase in the number of leukocytes, especially neutrophils is more because of the occurred infection.[37]

In addition, all research subjects had used antibiotics as treatment. Antibiotics are used for bactericidal and bacteriostatics to suppress expression of virulence factors of bacteria (e.g products of exotoxin, exopolysaccharides, flagellin, and lipopolysaccharide) and to attract inflammatory cells

in high density to the site of infection, thus providing more successful antibiotic shipping to the site of infection. Antibiotics are also used to downregulate the expression of integrin molecules affecting leukocyte adhesion and neutrophil accumulation at the site of infection. The use of antibiotics will make the number of neutrophils in the blood circulation increase.[38–40]

Finally, the use of β-lactam class of antibiotics (meropenem, cefotaxime, and ceftriaxon) with high doses and medication for ten days or more can cause neutropenia or agranulocytosis in 5–10% of patients with impaired liver function and 1–2% of patients without impaired liver function.[41,42] The specimen of the research subject was taken on the first day in the ICU with a period of hospitalization among 1–5 days before entering the ICU, so the side effects of antibiotic use in hematological system likely would not happen.

CONCLUSIONS AND SUGGESTIONS

The results of this research indicate that there were no significant correlation of monocyte count and MLR with presepsin in SIRS. However, there were significant correlation of NLCR and presepsin in SIRS with a weak positive direction.

Nevertheless, further researches are needed to be done, regarding to the correlation of hematology and presepsin in SIRS patients without using corticosteroids as a treatment. The inflammatory corticosteroids then can trigger inhibition of neutrophil recruitment to sites of inflammation. This condition can make the number of neutrophils in the blood circulation increase, thus affecting the results of the blood cell count.

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