CORRELATION OF NEUTROPHILS/LYMPHOCTES RATIO AND C-REACTIVE PROTEIN IN SEPSIS PATIENTS

by Henny Elfira Yanti

RESEARCH

CORRELATION OF NEUTROPHILS/LYMPHOCTES RATIO AND C-REACTIVE PROTEIN IN SEPSIS PATIENTS

(Kenasaban antara Rasio Neutrofil/Limfosit dan C-Reactive Protein di asien Sepsis)

Henny Elfira Yanti, Fery H Soedewo, Puspa Wardhani

ABSTRAK

Sepsis merupakan penyebab umum dari kesakitan dan kematian di seluruh dunia. Diagnosis yang cepat dan tepat sangat diperlukan. Salah satu respons fisiologis pada sistem imunitas terhadap inflamasi sistemik adalah peningkatan jumlah neutrofil dan penurunan jumlah limfosit. Rasio neutrofil/limfosit telah diketahui sebagai petanda inflamasi yang cepat, sederhana dan murah. Tujuan penelitian ini adalah membuktikan adanya kenasaban antara rasio neutrofil/limfosit dan c-reactive protein di pasien sepsis. Penelitian bersifat ptong lintang observasional, dilakukan masa waktu Januari hingga Juni 2015. Sampel penelitian terdiri dari 42 pasien sepsis yang dirawat di Instalasi Rawat Darurat RSUD Dr. Soetomo Surabaya. Semua sampel dilakukan pemeriksaan jumlah limfosit, neutrofil, CRP. Hasil dianalisis menggunakan uji kenasaban Spearman's. Rasio neutrofil/limfosit berkisar antara 3,42–57,47 (21,74±14,1). Kadar CRP antara 1,22 mg/L–361,86 mg/L (158 mg/L±97,4 mg/L). Hasil penelitian tidak terdapat kenasaban antara RNL dan kadar CRP di pasien sepsis (p=0,51). Tidak terdapat kenasaban antara RNL dan kadar CRP di pasien sepsis. Hal ini disebabkan adanya perbedaan jalur aktivasi antara neutrofil dengan CRP sehingga menyebabkan peningkatan CRP tidak sebanding dengan peningkatan jumlah neutrofil.

Kata kunci: *Sepsis, rasio neutrofil/limfosit, C-reactive protein*

ABSTRACT

Sepsis is the common cause of morbidity and mortality worldwide. Therefore, rapid and precise diagnosis is required. The physiological immune response against systemic inflamation is characterized by increased neutrophils and decreased lymphocyte counts. Ratio of neutrophil to lymphocyte count (RNL) is rapid, simple and an inexpensive marker of systemic inflammation. The aim of this study was to prove any correlation between RNL and the level of CRP. This study was done in January until June 2015 and design of the study was cross sectional observational. Study subjects consisted of 42 sepsis patients from the Emergency Department of the Dr. Soetomo General Hospital Surabaya. All samples were examined for the number of lymphocytes, neutrophils and CRP. The results were statistically analyzed using Spearman's correlation test. Ratio of neutrophil to lymphocyte count ranged between 3.42–57.47 (21.74±14.1). The level of CRP was between 1.22 mg/L-361.86 mg/L (158 mg/L±97.4 mg/L). There was no correlation between RNL and CRP levels in patients with sepsis. There was no correlation between RNL and CRP level in patients with sepsis. This was due to the differences between neutrophil activation pathway and CRP thus, the CRP level was not proportional to the increase in the number of neutrophils.

Key words: Sepsis, ratio of neutrophil to lymphocyte count, C-reactive protein

INTRODUCTION

Sepsis is a clinical syndrome characterized by a systemic response to infection which can rapidly lead to organ dysfunction and death. Sepsis is actually a normal reaction due to infection, but can last longer due to bacteria, viruses, parasites or fungi. Similar clinical incidence is often encountered due to non-infection, such as trauma, surgery and burns.[1]

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In the United States, the number of sepsis cases during the last decade has been as many as 750,000 people per year with a prevalence of three cases per 1,000 people. The improvement and development of pharmacotherapy and supportive care actually have increased survival rate. Unfortunately, mortality rate still ranges from 25% to 30% for severe sepsis and 40% to 70% for septic shock. Sepsis even has caused 20% of all deaths in hospitals in a year equal to the number of deaths caused by acute myocardial infarction.[2]

Sepsis ranked the third position of the most common diseases in the Dr. Soetomo Hospital in 2014. The incidence of sepsis in the Dr. Soetomo Hospital even has increased in the last 2 years. The incidence of sepsis was as many as 2446 cases in 2013 and 3,060 cases in 2014. The majority of sepsis cases was found in the age of 45–64 years. Death due to sepsis was 1653 out of 3060 cases (54%) during 2014 and 2446 out of 1487 cases (60.8%) in 2013.[3]

The American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference in 1991 proposed a definition of Systemic Inflammatory Response Syndrome (SIRS), sepsis and severe sepsis. This syndrome is a series of worsening inflammation, ranging from SIRS and developing into sepsis, severe sepsis, and septic shock. Criteria for SIRS are based on temperature, heart rate, respiratory rate and leukocyte count. At least two of four criteria must be met to determine SIRS. SIRS can frequently be triggered by either infections or non infections, such as burns, acute pancreatitis and trauma. Meanwhile, sepsis is defined based on SIRS criteria as well as suspected or proven infection. Severe sepsis is defined as sepsis accompanied by acute organ dysfunction.[4]

The 1991 consensus has limitations in defining sepsis, namely 2 of 4 SIRS criteria are not specific to sepsis. These criteria do not include biochemical markers, such as C-reactive protein, procalcitonin (PCT), or interleukin (IL)-6, often elevated in sepsis.[4]

In 2001, the Consensus Conference by the Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/ American Thoracic Society/Surgical Infection Society modified the definition of sepsis with certain criteria based on clinical and laboratory parameters as shown in Table 2. Nevertheless, the criteria of severe sepsis remains unchanged, namely sepsis with organ dysfunction. Septic shock is defined as persistent hypotension with a systolic blood pressure of <90 mm Hg or a mean arterial blood pressure of <70 mmHg, despite adequate fluid resuscitation.[4,5]

In addition, one of the physiological responses in the immune system against systemic inflammation is an increase in the number of neutrophils as well as a decrease in the number of lymphocytes. This is due to changes in the dynamics and regulation of apoptosis in a state of systemic inflammation when compared with non-inflammatory. The number of neutrophils and lymphocytes is also considered as parameters contained in CBC. CBC is an examination routinely performed in hospitals. For those reasons, many researches use simpler parameters, such as ratio of neutrophils/lymphocytes (RNL).[7]

The ratio of neutrophils/lymphocytes is an absolute number of neutrophils divided by an absolute number of lymphocytes. The ratio of neutrophil/lymphocyte under physiological conditions is 2: 1. In patients with sepsis, the ratio will increase.[7]

A research conducted by Gurol et al.[8] entitled "Are There Standardized Cutoff Values for Neutrophil-Lymphocyte Ratios in bacteremia or sepsis?" aimed to determine the cutoff value of RNL based on the level of procalcitonin with a total sample of 1,468 patients with sepsis. The results of the research then showed that the cut-off value of less than 5 could be used to diagnose sepsis.[8]

C-Reactive Protein (CRP), moreover, is an acute phase protein formed in the liver (hepatocyte cells) due to inflammation or infection. CRP levels will increase within 4 to 6 hours. The levels are even doubled within 8 hours after inflammation. Peak concentration is achieved within 36 hours to 50 hours. CRP levels will continue to increase along with the inflammatory process and then will decrease rapidly when healing. This is because CRP has a half-life of 5 to 7 hours. In other words, CRP levels are in line with the degree of inflammation and the degree of healing. Therefore, CRP can be used to assess disease activity. The normal value of CRP is <5 mg/L. Thus, the value can be said to increase when the value obtained in the examination is more than the normal one.[9,10]

The pathophysiology of sepsis, furthermore, involves a complex interaction of proinflammatory and anti-inflammatory mediators in response to pathogen invasion. This mechanism then can lead to a damage to the endothelium, vascular permeability, microvascular dysfunction, coagulation activation pathway, and impaired tissue oxygenation resulting in a sepsis cascade.[2]

As a result, RNL value in this research is expected to have a strong correlation with CRP. Consequently, RNL may be used as one of the parameters later, replacing CRP in aiding diagnosis as well as monitoring therapy and supporting indicators of clinical improvement in patients with sepsis, especially in areas that have limited facilities.

Table 1. Criteria for sepsis by SCCM/ACCP/ATS/ESCIM/SIS 2001 Consensus Conference[4,6]

Terms	Criteria
Sepsis	Suspected infection with one of the following clinical and laboratory criteria below
General parameters Fever (>38.3°C) Hyperthermia (<36°C) Heart rate >90×/min or >2 SD above the normal value according to age Tachypnea Changes in mental status Significant edema or *positive fluid balance* (>20 mL/kg over 24 hours) Hyperglycemia (plasma glucose >120 mg/dl without diabetes	
Inflammatory parameters Leukocytosis (leukocytes >12,000/uL) Leukopenia (leukocytes <4000/uL) Immature forms of leukocytes >0% Increased *C-reactive protein* more than 2 SD above the normal value Increase in procalcitonin more than 2 SD above the normal value	
Hemodynamic parameters Arterial hypotension (systolic blood pressure <90 mm Hg; mean artrial pressure <70 mmHg or a drop in pressure >40 mm Hg in adults or >2 SD below the age-adjusted normal values	
Parameters of organ failure Arterial hypoxemia (PaO 2/FiO 2<300) Acute oliguria (urine output<0.5 mL/kg/hour for at least 2 hours despite adequate fluid resuscitation) Increased creatinine>0.5mg/dL or 44.2 umol/L Coagulation disorders (INR>1.5 or aPTT>60) Ileus (absent bowel sounds) Thrombocytopenia (platelet count<100,000/uL) Hyperbilirubinemia (total plasma bilirubin>4 mg/dL or 70 umol/L)	
Tissue perfusion parameters Hyperlactataemia (>1 mmol/L) Decrease in capillary refill	

METHODS

The research subjects in this research were adult sepsis patients who came to the Installation of Emergency Unit, Dr. Soetomo Hospital from May 2015 to June 2015. Inclusion criteria were eligible patients with sepsis according to ACCP/SCCM Consensus Conference 2001 (see Table 1) as determined by peer specialists in the disease, at the age over 21 years, as well as willing to participate in this research and signed an informed consent. Meanwhile, exclusion criteria were patients consuming immunosuppressive drugs (steroids), having malignancy, receiving chemotherapy, refusing medical treatment and refusing to follow this research.

Next, the sampling technique in this research was performed using consecutive sampling with a sample

$$ n_1 = n_2 = 2\left[\frac{(Z\alpha + Z\beta)s}{(x_1 - x_2)}\right] $$

Note:
n: sample size
Zα: 1.96
Zβ: 0.84
x_1: Mean RNL in patients with sepsis *
x_2: Mean RNL in patients with sepsis *
s: Standard deviation
* Data taken from a research conducted by Nugroho.[7]

size of at least 42 people. Statistical analysis then was conducted to see the correlation between RNL values and CRP levels in those patients with sepsis. The date obtained then were tabulated to be processed using Spearman's correlation. Afterwards, the data were analyzed using R program.

By using the above formula, the minimum number of samples in this research was 42 samples. After receiving approval from the Research Ethics Committee of the Dr. Soetomo Hospital, patients who met the inclusion criteria were asked to have routine blood tests using ADVIA 2120i instrument to determine the value of neutrophils and lymphocytes to obtain the value of RNL. CRP levels, finally, were determined by using Achitect 4000.

RESULTS AND DISCUSSION

The number of the research subjects were 42 patients, consisted of 25 males (59.52%) and 17 females (40.48%) with a mean age of 55.04 years and an age range of 29 years to 86 years. Similarly, a research conducted by Sark et al.[11] also showed that females have a lower risk of sepsis than males. This was possibly related to their hormonal differences between the sexes that could contribute to the differences in their inflammatory response and sepsis. Increased estradiol in women is known to boost immune function and anti-inflammatory mediator dominance that may provide a protective effect.[11,12]

In addition, all samples in this research were sepsis patients with different underlying diseases. The percentage of patients with sepsis caused by diabetes mellitus was very high, namely 15 cases (35.7%). Similarly, a research conducted by Koh et al.[13] showed that patients with diabetes mellitus have an increased risk of infection and sepsis, about 20.1–22.7% of all patients with sepsis.[13]

Diabetes mellitus is usually associated with increased susceptibility to infection and sepsis. This is due to the disruption of the host response, especially chemotaxis, adhesion of neutrophils, intracellular killing and defects in humoral immunity associated with hyperglycemia.[13]

Based on the results of this research, moreover, the values of RNL increased in nearly all patients with sepsis, about 38 samples (90.5%). There were only 4 samples (9.5%) with normal RNL (<5). The range of RNL obtained was from 3.42 to 57.47 (with a mean of 21.74 and a standard deviation of 14.1). The lowest ratio of neutrophil/lymphocyte obtained was in sepsis patients with a diagnosis of type II diabetes mellitus, left multiple kidney stones, and urosepsis, while the highest RNL was found in sepsis patients with a diagnosis of type II diabetes mellitus and post-stroke with stage II hypertension.

The ratio of neutrophils/lymphocytes in this research increased in nearly all patients with sepsis, about 38 samples (90.5%). Similarly, a research reported by Gurol et al.[8] showed an increase in the cutoff values of RNL in sepsis patients with a cut-off of more than 5, so it can be considered as a marker for sepsis that can be used to diagnose sepsis with a sensitivity of 57.8% and a specificity of 83.9%. Like the previous research, a research conducted by Lowsby et al.[14] showed that RNL in bacteremia group was significantly higher than in the control group.[8,14]

Table 2. Characteristics of the research subjects

Characteristics of samples	Total	Percentage (%)
Sex, n (%)		
Males	25 samples	(59.52)
Females	17 samples	(40.48)
Age (years), Mean±SD		55.04±14.10
<45	9 samples	(21.42)
45–65	21 samples	(50)
>65	12 samples	(28.58)
The diagnosis of underlying disease, n (%)		
Diabetes mellitus	15 samples	(35.7)
Diabetes mellitus + diabetic nephropathy	8 samples	(19)
Community acquired pneumonie	5 samples	(11.9)
Chronic kidney disease	4 samples	(9.5)
Urinary tract infection	3 samples	(7.1)
Cirrhosis	2 samples	(4.8)
Cholecystitis	1 sample	(2.4)
Acute Cholangitis	1 sample	(2.4)
Acute pancreatitis	1 sample	(2.4)
Cerebrovascular attack thrombotic	1 sample	(2.4)
Peritoneal tuberculosis suspects	1 sample	(2.4)

Table 3. CRP classification based on severity

		CRP				
		<5	10–40	40–100	100–200	>200
RNL >5	+	12 (28.5)	1 (2.3%)	4 (9.5%)	4 (9.5%)	17 (40.5%)
	−	1 (2.3%)	0	0	2 (4.7%)	1 (2.3%)

In this research, there were also four samples that had normal RNL values, but with high CRP levels. It may be possibly because the patients that have been in a state of sepsis have already created depressed immune.

Furthermore, CRP levels obtained in this research increased in almost all patients with sepsis as many as 41 samples (97.6%) with an increase in CRP values up to above 5 mg/L. There was only one sample (2.4%) with a CRP value of <5 mg/L. The range of CRP values was from 1.22 to 361.86 (with a mean of 158 mg/L and a standard deviation of 97.4 mg/L). The lowest CRP levels were found in sepsis patients with a diagnosis of type II diabetes mellitus and ulcers pedis, while the highest CRP levels were found in sepsis patients with a diagnosis of type II diabetes mellitus and diabetic ketoacidosis (KAD).

Similarly, Gian Paolo et al.[15] reported that CRP levels increased significantly in patients with infection compared with those without infection. Therefore, the levels of CRP were in accordance with the severity of organ function. The same results were also reported in a research conducted by Hong-Xiang et al.[16]

Table 3 showed that the largest group (40.5%) was the samples of sepsis patients with RNL above 5 and CRP levels between 100–200. This indicated that sepsis in this research was most often caused by a bacterial infection. Similarly, a research conducted by Mayr, et al.[4] showed that bacteria were the most common organisms causing sepsis.[4,17]

One sample of sepsis patients in this research, nevertheless, had normal CRP levels. This is likely because the patient had taken antibiotics before. Another possibility is that the patient's early normal CRP level could be very low (normal range is 0.08 mg/L–3.1 mg/L), so a 10× increase in the patient's CRP level remained in the normal range.

Several researches have already proven that RNL and CRP are good markers for inflammation. Yong Xia et al.[18], for instance, reported that both RNL and CRP increased significantly in the group of bacteremia compared with the group of non-bacteremia.

Next, the correlation of RNL and CRP levels in this research was analyzed using Spearman's correlation test. This correlation test was conducted since the data from one of the variables analyzed, the RNL levels, were not normally distributed (p=0.008), whereas the data of CRP was normally distributed (p=0.29). The results of this correlation test showed that there was no correlation between RNL and CRP levels with a p value of 0.51.

Nevertheless, several researches have already proven that RNL and CRP are good markers for inflammation. Yong Xia et al.[18], for instance, reported that both RNL and CRP increased significantly in the group of bacteremia compared with the group of non-bacteremia. Another research conducted by Zahorec et al.[19] on RNL as parameters quick and simple in patients with systemic inflammation and critical illness also showed that RNL can be considered as a simple parameter used to monitor the clinical status in patients with sepsis and systemic inflammation.[17,19]

Therefore, it could be estimated that RNL and CRP in patients with sepsis will have a good correlation. The same opinion was delivered by Gunay et al.[19] that there was a positive correlation between RNL and CRP in patients with chronic obstructive pulmonary disease
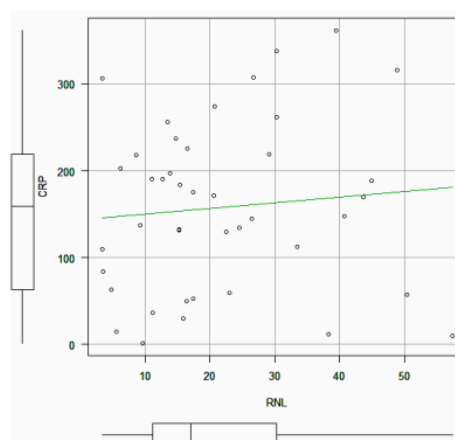

Figure 1. Correlation between RNL and CRP levels (p=0.51).

considered as a disease with chronic inflammation.[20] However, unlike the results of these previous researches, the results of this research showed that despite an increase RNL and CRP levels, there was no correlation between RNL and CRP.

In the early phases of inflammation, tissue macrophages and monocytes in the circulation produces a wide range of monokines, one of which is IL-1. IL-1 causes the release of neutrophils from the bone marrow resulting in an increase in the number of neutrophils in the circulation. CRP activation then occurs through a different route, preceded by the activation of cellular defense. Next, IL-6 is secreted by the Th-1 stimulating hepatocytes to secrete CRP, while IL-1 and TNF-α produced by monocytes also stimulates hepatocytes to secrete CRP.

IL-1 is also known to induce the production of IL-6 leading to the higher production of IL-6. All these processes then lead to an increase in CRP that is not comparable to an increase in the number of neutrophils. This possibility leads to the absence of a correlation between RNL and CRP.[21] Another possibility is that CRP levels have a wider range, while RNL has a narrower range. Thus, since the variation of the samples in this research was less wide, the samples were clustered only in certain areas.

CONCLUSION AND SUGGESTION

Based on the results of this research, it can be concluded that there was no correlation between RNL and CRP. It may be due to differences in the activation pathway between neutrophil and CRP. As a result, an increase in CRP was not proportional to an increase in the number of neutrophils.

Consequently, further research needs to be conducted on larger samples with a longer study time, so more accurate data representing the population can be obtained to get more meaningful results. Besides, unification of basic clinical state of patients with sepsis and correlation of RNL and more specific parameters, such as procalcitonin, need to be conducted to give more perfect results.

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