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Original Article

The Effect of C-Reactive Protein Levels, Neutrophil, and Lymphocyte Count to Mortality of COVID-19 Patients with Sepsis in Referral Hospital

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by infection of Severe Acute Respiratory Distress Syndrome Coronavirus-2 (SARS CoV-2). COVID-19 patients may develop sepsis, the dysregulation of the immune system that causes organ dysfunction and life-threatening situations. High mortality of COVID-19 and sepsis make it important to study. The purpose of this study is to analyze the effect of CRP levels, neutrophil, and lymphocyte count to mortality of COVID-19 patients with sepsis. This study is an analytic observational study with a cross-sectional approach. Samples were randomly retrieved of COVID-19 patients with sepsis admitted in referral hospital. Univariate, bivariate, and multivariate analysis used SPSS 26th version of Windows. The results of this study indicate a significant effect of CRP levels and neutrophil count on mortality of COVID-19 patients with sepsis. Meanwhile, lymphocyte count had no significant effects. The multivariate analysis showed its significance value. Partially, the effect of neutrophils on the patient's mortality has a significant value. The conclusion of this study is CRP levels and neutrophil count simultaneously have an effect on higher mortality of COVID-19 patients with sepsis.

Keywords: COVID-19, Sepsis, CRP, Neutrophils, and Lymphocytes.

Highlights: This study examined the relationship of the C-Reactive Protein (CRP) levels, neutrophil, and lymphocyte count to COVID-19 with sepsis cases multivariately.

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INTRODUCTION

Coronavirus disease 2019 or more commonly called COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) and it could be spread.^{1,2} On March 11, 2020, COVID-19 was declared as a global pandemic.³ Sepsis is the biggest problem that causes the mortality of COVID-19 patients. Abumayyaleh *et al.*⁴ show that patients suffering from sepsis in COVID-19 had higher rates of comorbidity; 11% of COVID-19 patients fall into sepsis conditions based on the definition of Sepsis-3 International Consensus.⁴ The sepsis itself is defined as the state of organ dysfunction caused by immune dysregulation to an infection. Infected pathogens can be bacteria, fungi, and viruses. This can lead to both danger and tissue damage. The high prevalence of sepsis, which is about 31.5 million sepsis patients worldwide makes it increasingly important to study. The extent of the organ dysfunction that is usually measured in terms of Sequential Organ Failure Assessment (SOFA) score causes a high mortality, 5.3 million people each year.^{5,6}

C-reactive protein (CRP) is an acute phase protein released in response to infection. Increased release of IL-6 is also capable of stimulating the CRP secretion primarily produced by hepar cells.^{7,8} Neutrophils constitute polymorphonuclear leukocytes that occupy the largest proportion of white blood cells in the body. Neutrophils become the first line of body defense against substance invasion.⁹ Its activity is stimulated by increased proinflammatory cytokines. Lymphocytes are white blood cells responsible for controlling the adaptive immune system. If the number of T-lymphocyte cells is reduced, then there can be hyperinflammatory until death.

There have been studies that have studied the relationship between CRP levels and leukocytes of both mortalities and

clinical severities of COVID-19 patients. Additionally, some studies also link it with sepsis patients' mortality. Based on research conducted by Seung Mok Ryoo *et al.*¹³, a significant correlation was found between the increase of CRP and the mortality of sepsis with a value of $p = 0.003$. Meanwhile, a study proved that CRP levels were higher in severe COVID-19 patients.¹⁰ Leucocyte count has also been studied on deceased COVID-19 patients. Leucocytosis, neutrophilia, and lymphocytopenia are among the results. Of the deceased patients, most of them were COVID-19 in a severe stage.¹¹

The COVID-19 prevalence is high and continues to have profound effects on life in this part of the world. Severe and critical patients of COVID-19 with sepsis have also contributed to a high mortality rate. According to previous studies, CRP levels affect clinical disseminations of both COVID-19 and sepsis patients. Moreover, the number of neutrophils and lymphocytes also affects the mortality of the COVID-19 patient. The previous studies examined such independent variables univariately either to COVID-19 patients or sepsis patients only so researchers are interested to study the effect of C-reactive protein levels, neutrophil, and lymphocyte count to mortality of COVID-19 patients - with sepsis.

MATERIALS AND METHODS

The study is an observational analytic study with a cross-sectional approach. Research location is the Isolation Ward Dr. Moewardi Hospital, Surakarta, Indonesia. The actual population is COVID-19 patients with sepsis admitted to Dr. Moewardi's hospital in January until December 2021. The criteria for inclusion is a COVID-19 patient who was hospitalized at Dr. Moewardi surakarta in January - December 2021 and are over 18 years old, while the exclusion criteria are patients with immunodeficiency,

paraneoplastic syndrome, and patients taking immunosuppressant or steroid drugs. Samples were taken using the simple random sampling technique until it obtained 88 samples as a minimal number of samples and then an additional 10% so that 97 samples were used in the study.

CRP levels, neutrophil count, and lymphocyte count are the independent variables while the mortality is the dependent variable. Data analysis used the Statistical Program for the Social Sciences (SPSS) 26th version for Windows. The analysis used is univariate, bivariate, and multivariate. Bivariate used Spearman correlations test and

multivariate used binary regression logistic test. The study has been approved by Dr. Moewardi's health research ethics commission and has obtained an ethical clearance number 819/VI/HREC/2022.

RESULTS AND DISCUSSION

Results

This study is an observational analytic study with cross-sectional approach. Data were collected from COVID-19 patients with sepsis. Table 1 below shows the characteristic of samples with distribution based on age and gender.

Table 1. Sample Characteristic.

Distribution	Total (n=97)	Outcome		Neutrophils count, mean ± SD	Lymphocytes count, mean ± SD	CRP levels, mean ± SD
		Survivor (%)	Non Survivor (%)			
Age (years)						
0-18	0 (0%)	0 (0%)	0 (0%)			
19-39	15 (15.46%)	3 (20%)	12 (80%)	10.34 ± 8.58	1.24 ± 0.77	12.35 ± 7.50
40-59	42 (43.30%)	19 (45.24%)	23 (54.76%)	8.64 ± 5.09	1.14 ± 0.44	12.68 ± 9.16
≥60	40 (41.24%)	12 (30%)	28 (70%)	9.38 ± 5.60	0.92 ± 0.40	12.56 ± 10.78
Gender						
Male	60 (61.86%)	24 (40%)	36 (60%)	8.80 ± 5.45	0.99 ± 0.48	13.78 ± 9.83
Female	37 (38.14%)	10 (27.03%)	27 (72.97%)	9.86 ± 6.60	1.18 ± 0.52	10.62 ± 8.87

Table 2. Outcome of COVID-19 Patients with Sepsis.

Sample		Frequency (%)	Neutrophil count, average ± SD	Lymphocyte count, average ± SD	CRP, average ± SD
Outcome	Survivor	34 (35.05%)	6.78 ± 4.01	1.15 ± 0.49	9.08 ± 7.84
	Non Survivor	63 (64.95%)	10.52 ± 6.36	1.02 ± 0.51	14.47 ± 9.91

Table 2. shows that the mortality of COVID-19 patient with sepsis was 63 patients from 97 samples. The table also mentions the average of each independent variable in both categories, survivor and non-survivor. Independent variables have been analyzed bivariously to know the correlation of each independent variable to the dependent

variable. The significance of CRP levels is 0.005 and the significance of the neutrophil count is 0.001. At the same time, the significance of the number of lymphocytes is 0.151 (> 0.05). From the multivariate analysis, the determinant coefficient of the logistic regression is 0.193. From binary regression logistic test, the



significance value is 0.001 (<0.05) and thus it can be concluded that CRP levels and the number of neutrophils simultaneously affected the mortality of COVID-19 patients with sepsis.

Based on the binary regression logistic test, the significance of CRP levels is 0.098 (> 0.05) and the neutrophil count is 0.019 (< 0.05). From $\exp(b)$ it may be known as to the ratio of each independent variable. The $\exp(b)$ CRP levels are 1,047 and the variable neutrophil count is 1.150.

Discussion

CRP levels and mortality

The study found significant correlation ($p= 0.005$) between CRP levels and mortality of COVID-19 patients with sepsis. This coefficient correlation is positive, which means that the higher the CRP level, the higher the mortality rate of COVID-19 patients with sepsis. CRP levels have a 0.284 coefficient value of relations belonging to groups with weak correlation power. A study conducted by Wardika Sikesa¹² supports the results of the study. There is a significant CRP difference between a COVID-19 patient with moderate and severe symptoms. Thus, CRP levels affected the severity of COVID-19. In the same study, it has been suggested that there is a significant correlation between raising CRP levels to raising mortality in COVID-19 patients.¹² Seung Mok Ryou *et al.*¹³ conducted a sepsis related study and found a significant correlation between CRP increase and mortality of sepsis patients ($p = 0.003$).¹³

C-reactive proteins are acute phase proteins that are secreted more when inflammation occurs and reach peak values in 48 hours. Therefore, CRP can be used as an inflammation biomarker.¹²⁻¹⁴ The course of COVID-19 disease with sepsis involves an inflammatory response. The rapidly increasing CRP is part of the first line defense of the body as an innate immune system

enabled in order to fight off viral infections. At severe COVID-19, proinflammatory cytokines are oversecreted so as to affect CRP levels in the body. This extreme response can be harmful to the body because it leads to advanced organ dysfunction in a COVID-19 patient. The more severe the COVID-19 disease in patients, the higher the CRP rate.^{12,15} Wardika and Sikesa¹² indicate that the highest CRP rate is owned by severe and critical COVID-19 patients¹² who fit the diagnostic criteria of sepsis.¹⁶

Neutrophil Count and Mortality

The study found a significant correlation ($p= 0.001$) between the number of neutrophils and the mortality of COVID-19 patients with sepsis. This relationship is positive, which means that the higher the number of neutrophils, the higher mortality rate of COVID-19 patients with sepsis. The coefficient value of the neutrophils count is 0.348, which means having moderate correlation power. Patients with COVID-19 with severe disease had significantly higher absolute neutrophil counts.¹⁷ Sinurat *et al.*¹⁸ mention the distinct number of meaningful neutrophils in COVID-19 degrees, mild, moderate, and severe. That is illustrated by the higher number of neutrophils in severe groups than those of mild degrees (4.3 vs $3.2 \times 10^9/L$).¹⁸ Additionally, other studies cite the number of neutrophils measured within 24 hours after confirming diagnoses significantly correlated to COVID-19 mortality with a degree of significance of 0.002 ($p < 0.05$).¹⁹

The increasing number of neutrophils is due to some of the things described in the pathophysiology of COVID-19 that occur with sepsis. Once the SARS CoV-2 enters the body then infects the cell through its bound with the ACE-2 receptors, including the epithelial alveolar, it first activates the immune system. This is where the many neutrophils are activated as a body defense line against foreign invasion. Sepsis makes

the neutrophil's lifespan longer than normal conditions.²⁰ The rise in production of neutrophils is also set off by an increase in secretion mediator inflammation of viral infections, such as IL-6 and GCSF.²¹ Neutrophil will make a neutrophil's extracellular traps (NETs) that acts to trap and kill the virus. Overdeveloped NETs, however, can harm the body by damaging lung tissue. In addition, neutrophils are also responsible for the formation of Reactive Oxygen Species (ROS) that can destroy the DNA of the cell and expel the virus from the cells.^{18,22} Not only this, another mechanism for neutrophils is the direct destruction of the virus through Antibody Dependent Cell Cytotoxicity (ADCC).¹⁸ The severe increase of neutrophils count can cause tissue damage and lead to poor outcomes.²³ At the state of sepsis, neutrophils can induce obstructive nasal paths that will cause mismatch and hypoxia conduction. Thus, neutrophils contributed to sepsis in ARDS.²⁴

Lymphocyte count and mortality

The study results in that the number of lymphocytes and mortalities of COVID-19 patients with sepsis had no significant correlation ($p=0.151$). As for the coefficient value of correlation, the lymphocytes count of 0.174 means having weak correlation power. Negative value of coefficient correlation means lower levels of lymphocytes do not significantly affect mortality levels. Some studies support these results. The study mentioned that there is no correlation between the number of lymphocytes and the mortality of sepsis patients ($p=0.465$).²⁵ In addition, a diagnostic test of COVID-19 patients mentioned that lymphocytes had poorer diagnostic marks in COVID-19 patients than the number of neutrophils and NLR.²⁶

Characteristics of the immune suppression on sepsis conditions is apoptosis of T-helper, cytotoxic lymphocytes, B lymphocytes, and dendritic cells.²⁷ Other reference mentioned that. in the case of

sepsis. there will be an increase in the neutrophil count followed by an increase in the lymphocyte count. In turn, the number of lymphocytes may develop apoptosis if sepsis is not properly handled.²⁸ In a study from Martins et al. ²⁹, lymphocytes count were significant lower in patients with sepsis than the control group y.²⁹ In COVID-19 patients with sepsis they can either increase or decrease the number of lymphocytes. Some samples in the study also showed high levels of lymphocytes in COVID-19 patients with sepsis who passed away in either 48 hours or more. Thus, according to analysis data of this study, the number of lymphocytes does not significantly affect the mortality of a COVID-19 patients with sepsis ($p=0.151$).

However, there are other studies that contradict those results. Tarigan et al.¹⁹ analyzed the correlation of lymphocyte count measured in the first 24 hours of COVID-19 patient mortality and had significant results ($p=0.002$; $P < 0.05$).¹⁹ Other research also revealed that sepsis patients who have persistent lymphopenia were at a risk of dying by 5.66 times greater than being non persistent lymphopenia.³⁰ The differences in previous studies with these may be due to some factors. One is the patient's comorbidity, which has not been analyzed in this research. Based on a statistical analysis, comorbidity contributes more to affecting mortality than the number of absolute lymphocytes.²¹

CRP levels, neutrophil count, lymphocyte count, and mortality

The contribution of independent variables (CRP levels, neutrophil count, and lymphocyte count) to the dependency variable is 19.3%. CRP levels in a partial way have no significant impact on mortality while the number of neutrophils has a significant partial influence on mortality. Based on exp(b) ratio, patients with increasing CRP rates have a mortality risk of 1,047 times greater than those with low CRP levels. Meanwhile, patients with an increasing

number of neutrophils will have a mortality risk of 1,150 times greater than those with a low number of neutrophils.

No previous study has analyzed multivariately the number of neutrophils, the number of lymphocytes, and the CRP concentrations together in COVID-19 patients with sepsis. Previous studies analyzed the independent variable as Neutrophil Lymphocytes Ratio (NLR). The study from Nurhayatun *et al.*³¹ showed that NLR increase in COVID-19 patients increased the risk of death.³¹ Both neutrophils and CRP levels play a role and are directly involved in the human body's defense systems when there is both infection and inflammation. Previous studies have proved that each of these variables has significant correlation to the severity of both COVID-19 and sepsis and affects its mortality. Hyper-activated neutrophils lead to the formation of overloaded NETs and ROS results a danger condition to the body.¹⁸ In addition, neutrophils have a tendency to induce ARDS in sepsis patients.²⁴ CRP as a biomarker inflammation increases as the rate of inflammation increases. Increased CRP leads to increased risk of organ dysfunction and death in sepsis. The study proved that CRP levels and the neutrophil count simultaneously affected COVID-19 patients' mortality with sepsis.

STRENGTH AND LIMITATION

The strength of this study was the novelty of research about COVID-19 with sepsis and using a multivariate analysis. The limitation of this study was no analysis about patient comorbidities.

CONCLUSIONS

The increase in CRP levels and the neutrophil count simultaneously have an effect on higher mortality of COVID-19

patients with sepsis. The variable that has the most influence is neutrophils because in multivariate analysis neutrophils have significant partial influence value. Meanwhile the lymphocyte count had no significant correlation to mortality of COVID-19 patients with sepsis. For future research relevant to this study, comorbidities of the patients need to be analyzed beside the independent variables.

ETHICAL CLEARANCE

The research protocol was approved by Dr. Moewardi's health research ethics commission and has obtained an ethical clearance number 819/VI/HREC/2022.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

ANM collected and analyzed data, wrote the manuscript and generated the figure and tables. DRH proofread the manuscript and revised the manuscript. AS proofread the manuscript. EN designed this study.

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