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Correlation between Neutrophil to Monocyte Ratio, C-Reactive Protein, and D-dimer Levels among COVID-19 Patients

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ABSTRACT

COVID-19 is a disease caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) and leads to various clinical manifestations. This condition can cause inflammation and cardiovascular disease that can result in increased Neutrophil-to-Monocyte Ratio (NMR), C-Reactive Protein (CRP), and D-dimer. The correlation between variables needs further investigation that can be a reference. This study aimed to analyze the correlation between NMR and CRP also NMR and D-dimer in COVID-19 patients with moderate dan severe illness. The research was an observational analytical study with a cross-sectional design on 40 subjects. Data were secondary data from COVID-19 patient's medical records in RSND Semarang. This study was carried out from April to September 2021. Correlation analysis using the Spearman Rank test with $p<0.05$ was considered significant. The Mean of NMR, CRP, and D-dimer was 16.69±10.65, 113.94±70.42 mg/L, and 1.72±2.35 mg/L, respectively. There was a weak positive correlation between NMR and CRP ($p=0.023$ and $r=0.358$) and there was no correlation between NMR and D-dimer ($p=0.638$ and $r=0.077$). It was expected that this knowledge about the correlation between NMR and CRP and D-dimer can help healthcare providers in planning therapy and preventing complications that may occur due to CRP and D-dimer increase.

Keywords: COVID-19, NMR, CRP, D-dimer

INTRODUCTION

China reported a case of pneumonia with symptoms of fever, shortness of breath, and cough with an unknown cause in December 2019. 2019 novel Coronavirus (2019-nCov) labeled from samples taken from the lower respiratory tract indicated the presence of the novel Coronavirus.[1] The rapid spread of the virus made WHO declare COVID-19 as a pandemic on March 11th, 2020.[2] Positive confirmation cases in Indonesia increased day by day. Until February 19th, 2021, there were 1.263.299 cases with a Case Fatality Rate (CFR) of 2.7%.[3]

Standard laboratory tests performed on COVID-19 patients include C-Reactive Protein (CRP), D-dimer, and leukocyte count.[4] The number of neutrophils divided by the number of monocytes determines Neutrophil-to-Monocyte Ratio (NMR). The NMR value in COVID-19 patients of more than 17.75 at admission to the hospital had a higher severity and mortality rate as conducted in a study in Mexico. The study also stated that NMR was more specific and sensitive than Lymphocyte-to-Neutrophil Ratio (LNR).[5]

Neutrophils are the most common leukocytes in the blood that appear as an early response to infection. COVID-19 patients with high neutrophils indicate a poor prognosis.[6] Monocytes are innate immune cells that play a role in the inflammatory response, phagocytosis, and antigen presentation. Previous research found an increasing number of monocytes in patients with mild COVID-19 and a decrease in the number of monocytes in patients with severe COVID-19.[7]

C-reactive protein is an acute-phase protein formed by liver hepatocytes due to an inflammatory or infectious process to minimize tissue damage.[8] The SARS-CoV-2 virus that infects the body will cause the release of proinflammatory cytokines, such as IL-6 and TNF-α, which induce the secretion of CRP by hepatocytes.[9] The normal CRP value in the blood is less than 10 mg/L.[10] Patients with severe pneumonia symptoms will have a high CRP value.[11] D-dimer is a degradation product of fibrin breakdown in the fibrinolytic system. Elevated levels of D-dimer are associated with hypercoagulation and increased fibrinolytic activity. Elevated D-dimer levels are found in patients with confirmed cases of

COVID-19.[12,13]

This study aimed to analyze the correlation between NMR with CRP and D-dimer in COVID-19 patients. It was expected that this study can be used as a reference and expand the knowledge about the correlation between NMR with CRP and D-dimer to assist health care providers in planning therapy and preventing complications, which may occur due to increased CRP and D-dimer levels.

METHOD

This study was carried out from April to September 2021, at the medical record installation unit of the Diponegoro National Hospital Semarang. The researcher used an analytic observational study with a cross-sectional approach. The inclusion criteria were patients aged 19-60 years old who were confirmed positive for COVID-19 based on a positive PCR test of a nasopharyngeal and oropharyngeal swab. The patients were in moderate and severe illness on the first day of admission. The exclusion criteria were pregnant patients, patients undergoing radiation or chemotherapy, and patients with a history of liver disease, kidney disease, stroke, and history of anticoagulant therapy.

The data were analyzed statistically using the computer program. A descriptive test was carried out on each data, followed by a normality test using the Shapiro-Wilk and a correlation test using the Spearman rank test. Ethical clearance was obtained from the Ethical Committee or Komisi Etik Penelitian Kesehatan (KEPK) of the Faculty of Medicine, Diponegoro University No.207/EC/KEPK/FK-UNDIP/VI/2021.

RESULTS AND DISCUSSIONS

Table 1 shows the characteristics of research subjects, including age, gender, hemoglobin level, leukocyte count, platelet count, NMR, CRP, D-dimer, and comorbidities.

The mean value of NMR was (14.97±10.18) with the lowest value of 3.53 and the highest value of 47. The elevated NMR was in accordance with a study conducted by Téllez *et al.*, which found that COVID-19 patients experienced an increase in NMR with moderate to severe hospitalized symptoms.[14] Therefore, to get more intensive care, they could be considered. Fei *et al.* also found an increase in NMR

Table 1. Characteristics of research subjects

Variables	F	%	Mean±SD	Median (min-max)
Age (year)			47.50±9.32	48.5 (22-60)
Gender				
Male	34	68		
Female	16	32		
Systole (mmHg)			141.32±20.8	139.5 (106-219)
Diastole (mmHg)			88.34±12.72	88.5 (63-133)
Heart rate (/minute)			96±17.10	95(36-130)
Respiratory rate			25.42±4.34	25(18-36)
Hb (gr/dL)			13.83±1.75	13.95 (9.7-18.30)
Leukocyte count (10^3/uL)			7.68±5.17	6.39 (2.69-31.61)
< 4 10^3uL	7	14		
4-11 10^3uL	34	68		
>11 10^3uL	9	18		
Platelet count (10^3/uL)			250.12±110.36	234.5 (120-658)
<150 10^3uL				
150-450 10^3uL	9	18		
>450 10^3uL	38	76		
	3	6		
NMR			14.97±10.18	11.47(3.53-47)
CRP (mg/L)			97.24±71.80	91.3 (5-333.2)
D-dimer (mg/L)			1.53±2.16	0.57 (0.11-10)
Comorbidity				
DM	19	38		
hypertension	16	32		

Description: F= frequency; %=proportion; SD=Standard Deviation

in COVID-19 patients, especially those with severe symptoms.[15] The mean value of CRP was (97.24±71.80) mg/L with the lowest CRP of 5 mg/L and the highest CRP of 333.2 mg/L. The result showed an increased CRP level in COVID-19 patients. C-reactive protein is an acute-phase protein synthesized by hepatocytes as a marker of inflammation. A study by Ahnach *et al.* suggested that there was a significant relationship between CRP and severity in COVID-19 patients.[16] Wang also expressed similar points in his research conducted in China.[11] There was a positive correlation between CRP and lung lesions, which can predict the severity of COVID-19 patients and as a reference in giving the therapy.

The mean value of D-dimer was (1.53±2.16) g/L with the lowest and the highest D-dimer of 0.11 mg/L and 10 mg/L, respectively. The results of the distribution of comorbidities showed that 19 (38%) subjects had DM, and 16 (32%) subjects had hypertension as the comorbid disease. According to a study conducted by Yao *et al.*, an increased D-dimer was found in patients infected with SARS-CoV-2.[17] Gungor *et al.* found that D-dimer levels were strongly correlated with severity and mortality in COVID-19 patients.[18]

In their study, Xiaokang *et al.* proved several factors, which might cause an increase in D-dimer in COVID-19 patients, an infection, which causes the release of proinflammatory cytokines resulting in a cytokine storm.[19] Cytokine storms can cause endothelial dysfunction, which leads to microvascular damage. Microvascular damage causes abnormalities in the coagulation system. Some patients also experience hypoxia and inflammation, which can lead to thrombosis or increased oxygen consumption. Oxygen demand tends to increase when there is an abnormality in hemodynamics that triggers thrombosis. In addition, severe infection or acute inflammation due to sepsis can activate the coagulation cascade that triggers thrombosis.

Table 2. Correlation between NMR with CRP and D-dimer

Variables	CRP		D-dimer	
	P	r	p	r
NMR	0.000	0.490	0.200	0.185

Description: p=significance value; r=correlation coefficient

Based on the Spearman Rank correlation test results in Table 2, there was a significant correlation between NMR and CRP with p=0.000 (p <0.05). This correlation was weak with r = 0.490. The direction of the correlation showed a positive correlation, which indicated a unidirectional relationship. The results showed no correlation between NMR and D-dimer with a significance value (p)=0.200 and a correlation coefficient (r) = 0.185. The results indicated no correlation because the p > 0.05. Figure 1 shows the graph of the correlation between NMR and CRP. A positive correlation indicated that increased NMR will lead to increased CRP. A weak positive correlation between NMR and CRP in COVID-19 patients was also found in a study conducted by Mortaz *et al.*, which found an important role of neutrophils during and after the occurrence of infection, tissue damage, and inflammation in the body.[20] The SARS-CoV-2 virus causes inflammation and the release of proinflammatory cytokines, including IL-6, which is influenced by monocytes. IL-6 is synthesized in the early phase of inflammation. Activation and secretion of IL-6 will induce acute-phase proteins, one of which is CRP, secreted by hepatocytes. The presence of infection and inflammation will be accompanied by an increase in the flow of neutrophils from peripheral blood vessels to the site of inflammation, causing an increased production of TNF-α, which will induce CRP production.

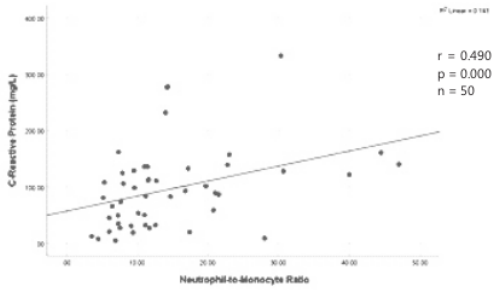

Figure 1. The graph of the correlation between NMR and CRP with the Spearman Rank correlation test

A study conducted by Qin *et al.* revealed a decrease in the number of monocytes in patients with severe COVID-19 due to challenges in the proliferation process. Monocytes also play a role in inducing CRP production; monocytes affect the release of IL-6 and TNF-α that play a role in the production of CRP.[7,21]

The history of DM and hypertension in research subjects influenced the study results by several factors. Kalma showed that inflammatory response

and vascular abnormalities caused the increase in CRP levels in type 2 DM patients.[22] The abnormalities occurred due to low-grade chronic inflammation of the endothelium due to complications from DM inflammatory response and vascular abnormalities. In their study, Pan *et al.* suggested that COVID-19 patients with hypertension had higher CRP and D-dimer levels than COVID-19 patients without hypertension. Immune system disorder can cause an increase in CRP.[23] COVID-19 patients with comorbidities of hypertension had a higher mortality rate with a poor prognosis and an increased risk of complications.

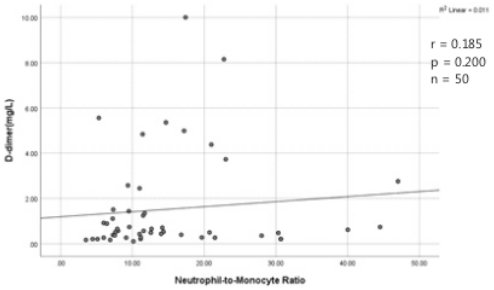

Figure 2. The graph of the correlation between NMR and D-dimer with Spearman Rank correlation test

Figure 2 shows the correlation graph between NMR and D-dimer. The inflammatory response that occurs in monocytes influences the production of thrombin, which plays a role in fibrinolysis. The thrombin will activate neutrophils to form Neutrophil Extracellular Traps (NETs), which activate the intrinsic pathway. An increase in the coagulation cascade and fibrinolysis will cause an increase in D-dimer.[24,25] However, when neutrophils and monocytes were combined in this study, there was no significant correlation between NMR and D-dimer. The study results were also influenced by the history of hypertension of the subject.

CONCLUSIONS AND SUGGESTIONS

The study concluded that there was a weak positive correlation between NMR and CRP levels, and there was no correlation between NMR and D-dimer levels. Further research was needed on COVID-19 patients, considering several factors such as the length of suffering, the severity of COVID-19 patients, and the patient's comorbidities, such as type 2 DM and hypertension.

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