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The Correlation of D- Dimer and Neutrophil Lymphocyte Ratio (NLR) Levels on COVID-19 Mortality

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Abstract

Coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus or a new type of corona virus, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). D-dimer and Neutrophil Lymphocyte Ratio are parameters that can be used as a predictor of mortality in COVID-19, so this study aims to determine the relationship between D-dimer levels and NLR with mortality in COVID-19 patients. The study used an analytic observational method with a cross sectional approach from medical record data at UNS Hospital. The population in this study were COVID-19 patients at UNS Hospital who had their D-dimer and NLR levels checked in the period November 2020-January 2021. The sample was taken using a simple random sampling technique. Bivariate data analysis with Spearman Rank Correlation Test. Obtained 72 samples. 46 male patients and 26 female patients with the highest age range of 40-59 years as many as 34 patients. Patients who experienced mortality as many as 24 people while the rest survived. Spearman's Rank test obtained p-values of D-dimer and neutrophil lymphocyte ratio (NLR) with mortality of COVID-19 patients 0.009 and <0.001, respectively. While the correlation coefficients for D-dimer and NLR on mortality were 0.308 and 0.515, respectively. There is a relationship between D-dimer and NLR levels with mortality in COVID-19 patients with a positive correlation.

Keywords: COVID-19, D-dimer, Neutrophil Lymphocyte Ratio, Mortality.

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1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus or a new type of corona virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Baloch et al., 2020; Dhama et al., 2020; CDC, 2020). It was first discovered in Wuhan City, Hubei Province, China and then spread quickly throughout the world. The World Health Organization (WHO) then declared COVID-19 a global pandemic on March 11, 2021. Based on the latest WHO data update on February 9th, 2022, globally there were 2,893,613 new cases of confirmed COVID-19 while 11,378 patients died. Meanwhile, at the same time in Indonesia there were 46,843 new confirmed cases of COVID-19 while 65 patients died (Sarohan et al., 2021).

The SARS-CoV-2 virus spread rapidly because the virus is transmitted among humans via aerosol particles or droplets originating from the respiratory tract or through direct contact with surfaces contaminated with the virus (Liu et al., 2020; Prather et al., 2020; Sun et al., 2020). COVID-19 has a wide spectrum of symptoms from asymptomatic to mild symptoms such as cough, fever, shortness of breath, sore throat, headache, rhinorrhea and diarrhea (Çalıca Utku et al., 2020; El-Anwar et al., 2020; Guo et al., 2020; Hornuss et al., 2020; Lan et al., 2020; Menni et al., 2020). Patients with severe clinical manifestations may experience disseminated intravascular coagulation (DIC), septic shock, severe pneumonia, multiple organ dysfunction syndrome (MODS) and acute respiratory distress syndrome (ARDS) (Hu & Wang, 2021; Mellett & Khader, 2022; Tsai et al., 2021; Yu et al., 2020).

SARS-COV-2 attacks target organs that express angiotensin converting enzyme 2 receptors (ACE2R) (Cevik et al., 2020; Harrison et al., 2020; Lamers & Haagmans, 2022). ACE2R is expressed by various organs in the human body but the density is higher in the heart and lungs. In severe cases the inflammatory or inflammatory response can occur excessively (hyperinflammatory), which causes a cytokine storm or systemic cytokine storm. Systemic cytokine storm results in systemic endothelial injury and a hypercoagulable state. Hypoxia in COVID 19 patients will shift the anti-inflammatory and antithrombotic phenotype to a pro-inflammatory and procoagulation phenotype. Endothelial injury will cause the release of ultralarge von Wilebrand factor (UVWF) which functions in the process of hemostasis, named triggering platelet aggregation and initiation of thrombogenesis (Becker, 2020; Gomez-Mesa et al., 2021; Iba et al., 2020).

D-dimer is the final degradation product of fibrin cross-links in a blood clot degradation process called fibrinolysis. Increased D-dimer is a marker of thrombosis. Incidence of increased D-dimer levels often occurs in patients with severe COVID-19 and can be a predictor of acute respiratory distress syndrome (ARDS), the need for a long intensive care unit (ICU), and mortality (Farasani, 2021; He et al., 2021; Li et al., 2020; Ozen et al., 2021).

An increase in d-dimer levels associates with an increase 3 to 4 times worse outcomes. Increased d-dimer levels in COVID-19 patients can be triggered by underlying conditions such as diabetes, cancer, stroke and pregnancy. 71% of COVID-19 patients who experienced hypercoagulability died because they met the DIC criteria. Venous thromboembolism occurs in 25% of patients with severe COVID-19, and 30% of these patients develop pulmonary embolism. Based on existing research, 42% of COVID-19 patients had D-dimer levels > 1 μg/mL and 81% of them were reported die (Breakey & Escher, 2020).

Another parameter that can be used to determine the mortality rate of COVID-19 patients is the ratio of neutrophils to lymphocytes or the neutrophil lymphocyte ratio (NLR). NLR can be an indicator that is commonly used to see a systemic inflammatory response, including in COVID-19 infection. An increase in NLR indicates an increase in the inflammatory process and is associated with a poor prognosis. The NLR value is higher in patients with severe COVID-19 than in patients with mild symptoms. The intensity of the inflammatory response is indicated by an increase in the number of neutrophils while a decrease in the number of

lymphocytes is a marker of damage to the body's immune system. Out of a total of 15 studies consisting of 6033 patients with high NLR levels, 822 (14%) died in hospital (Simadibrata et al., 2021).

Examination of D-dimer and NLR levels can potentially be used as a marker parameter in determining the mortality rate of COVID-19 patients (Bastug et al., 2020; Liu et al., 2020; Singh et al., 2021). The purpose of this study was to determine whether there was a relationship between D-dimer levels and NLR on the mortality of COVID-19 patients.

2. RESEARCH METHOD

This study was an analytic observational study using a retrospective cross-sectional approach. The research was conducted at the medical record installation at UNS Surakarta Hospital, Central Java. The study population was confirmed COVID-19 patients at UNS Hospital with the inclusion criteria of patients confirmed for COVID 19 who show positive results for SARS-CoV-2 by rRT-PCR examination during the 1st wave of COVID-19, November 2020 to January 2021. The patients had a medical record with the results of the D-dimer and NLR examinations, and hospital inpatients. The exclusion criteria were patients with a history of immune disease and blood disorders, patients with incomplete medical record data, and patients with a history of coagulation disorders.

Samples were taken using simple random sampling technique. The total population is 300 patients. 72 respondents are obatained by random sampling technique. The independent variables are levels of D-dimer and Neutrophil Lymphocyte Ratio measured by a ratio scale. Dependent variable was the mortality rate of patients diagnosed with COVID-19, which was measured on a nominal scale which the patients died or survived.

Data analysis was performed using a computer application. Data on D dimer levels and NLR with mortality rates was analyzed using bivariate analysis to determine whether there were a correlation between D dimer and NLR levels with the mortality rate of COVID 19 hospital patients. A significant relationship is obtained if the p value <0.05. Ethical approval was obtained in dr Moewardi Hospital with ethical number: 916/VI/HREC/2022.

3. RESULTS AND DISCUSSION

The results of the study which obtained from 72 medical records of confirmed COVID-19 patients at UNS Hospital during the period November 2020 to January 2021 which were examined for D-Dimer and NLR levels. In data collection, the average value of D-dimer was 1709.5521 (SD 2131.6943) with the highest value of 10000 ng/ml and the lowest value of 195.60 ng/ml. While the mean value of NLR is 8.4479 (SD 12.469) with the highest value of 92.26 and the lowest value of 0.95. Distribution based on mortality in the study results showed that 48 out of 72 patients experienced mortality with an average D-Dimer level of 2490.32 (SD 2827.83) and an average NLR level of 14.30 (SD 19.24). There were 24 of the 72 patients who survived, with an average D-Dimer level of 1319.17 (SD 1576.18) and an average NLR of 5.52 (SD 5.22).

Table 1. COVID-19 Mortality.

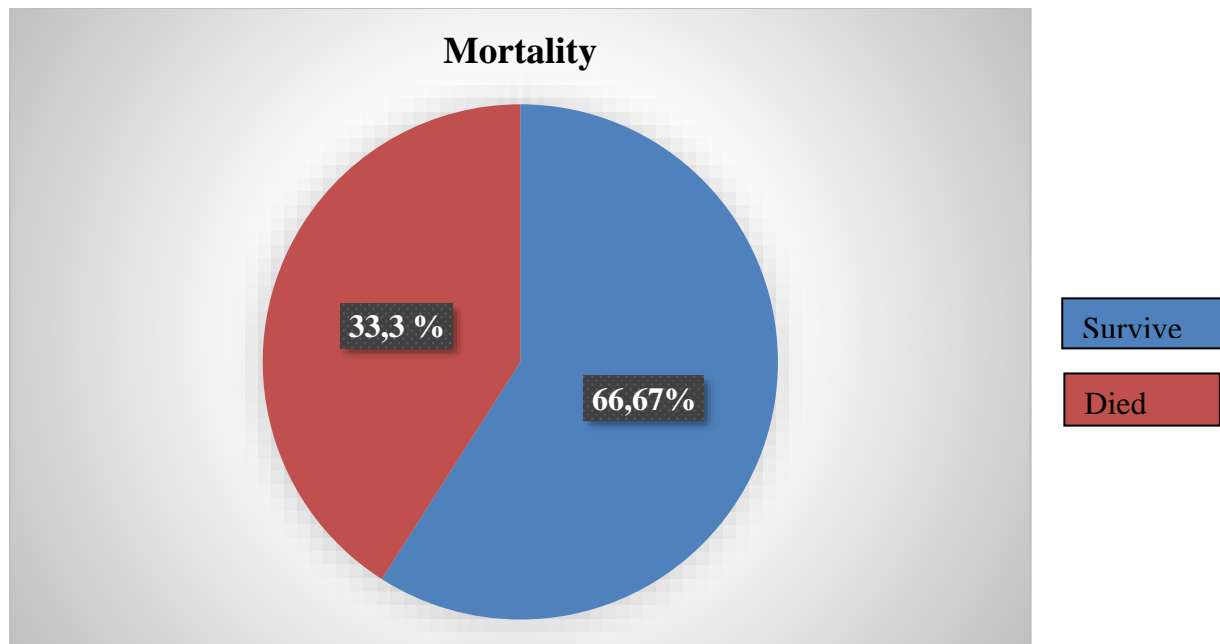|		Frequency (%)	D-dimer Mean (SD)	NLR Mean (SD)
Mortality	No	48 (66.7)	1319.17 (1576.18)	5.52 (5.22)
	Yes	24 (33.3)	2490.32 (2827.83)	14.30 (19.24)

Figure 1. Mortality Proportion of COVID-19. Patients in Universitas Sebelas Maret Hospital During November 2020- January 2021.

Table 2. Samples Distribution Based on Age and Gender.

Distribution	Total	Mortality		D-Dimer Mean (SD)	NLR Mean (SD)
		No (%)	**Yes(%)**		
Age (Years)					
0-18	0	0	0	0	0
19-39	5	4(80%)	1 (20%)	620.27 (386.28)	3.02 (1.86)
40-59	34	26 (76.47%)	8 (23.53%)	1416.72 (1742.02)	6.48 (5.36)
≥60	33	18 (54.54%)	15 (45.45%)	2147.06 (2511.99)	11.06 (17.27)
Sex					
Male	46	28(60.87 %)	18(39.13 %)	1483.57 (1903.77)	10.36 (15.19)
Female	26	20(76.92 %)	6 (23.08 %)	1340.91 (937.41)	5.07 (2.78)

Patients in the age group of 40-59 years were the group that had the highest number, namely 34 patients with 8 deaths and had an average D-Dimer level of 1416.72 (SD 1742.02) and an average NLR of 6.48 (SD 5.36). Meanwhile, the 60-year-old group had the highest mortality rate, which 15 out of 33 confirmed COVID-19 patients with an average D-Dimer level of 2147.06 (SD 2511.99) and an average NLR level of 11.06 (SD 17.27). The age group of 19-39 years had the lowest mortality rate, which 1 in 5 confirmed COVID-19 patients with an average D-Dimer level of 620.27 (SD 386.28) and an average NLR level of 3.02 (SD 1.86).

The results of the study including 72 patients were 46 male patients which 18 among them died with an average D-Dimer level of 1483.57 (SD 1903.77) and an average NLR of 10.36 (SD 15.19). While female patients with a total of 26 which 6 of them died. The average D-Dimer level in women was 1340.91 (SD 937.41) and the average NLR was 5.07 (SD 2.78).

Table 3. Distribution based on comorbidity.

Distribution	Total	Mortality No (%)	Mortality Yes (%)	D-Dimer Mean (SD)	NLR Mean (SD)
Comorbidity					
Hypertension	11	8 (72.7 %)	3(27.3%)	1292.72 (913.36)	12.66 (26.48)
Diabetes Mellitus	16	10(62.5%)	6 (37.5%)	1161.14 (721.08)	12.15 (21.69)
Congestive Heart Faillure	4	3 (75 %)	1 (25 %)	1106.04 (645.27)	4.53 (2.49)
Stroke	2	0 (0%)	2 (100%)	1274.50 (287.79)	5.92 (1.77)
Chronic Kidney Disease	1	0 (0%)	1 (100%)	1621.60 (0)	13.48 (0)
Tuberculosis	2	1 (50%)	1 (50 %)	1129.42 (1320.61)	2.71 (1.83)
None	46	31 (67.39%)	15 (32.61%)	1754.38 (2278.31)	7.92 (8.92)

The results of the analysis showed that diabetes mellitus was the most common comorbid which found in 16 patients, 6 of them were died. The highest mortality rate was in 46 patients without comorbidities written in the medical record, which 15 of them were died. The highest average D-Dimer level was found in patients without comorbidities which 1754.38 (SD 2278.31). Meanwhile, the highest NLR level was found in patients with chronic kidney disease, which was 13.48.

Table 4. Normality Test.

Variable	p-value
D-dimer	0.000
Neutrophil Lymphocyte Ratio	0.000

The number of samples exceeds 50 so that the normality test is interpreted by Kolmogorov-Smirnov using computer application. The results of the normality test show that the significance value for D-Dimer and NLR is 0.000 so that the data is not normally distributed because the significance value is <0.05.

Table 5. Spearman Correlation Test of D-dimer and NLR with COVID-19 Mortality.

Variable	p-value	Correlation Coefficient
D-dimer	0.009	0.308
Neutrophil Lymphocyte Ratio	0.000	0.515

The results of the Kolmogorov-Smirnov Normality Test showed that the results of the data were not normally distributed, so the Spearman correlation test was used to determine the relationship between D-Dimer and Mortality and NLR with Mortality. The interpretation of the D-Dimer correlation test with mortality showed a significance value of 0.009 and is interpreted as less than 0.05 so that there was a significant relationship between the two variables. The D-dimer correlation coefficient with mortality was 0.308, meaning that the relationship had moderate strength because it was in the range of 0.26 – 0.5 (Vidali et al., 2020). The correlation

coefficient of D-Dimer and Mortality was positive so it means that the two variables had a unidirectional relationship.

While the results of the Spearman Correlation Test on NLR and mortality showed a significance value of 0.000 meaning less than 0.05 so that there was a significant relationship between the two variables. The correlation coefficient value of NLR and mortality was equal to 0.515 so that the relationship between the two variables had strong correlation because it was included in the range 0.51-0.75 (Vidali et al.,2020). The correlation coefficient of NLR and Mortality was positive which means that the two variables had a unidirectional relationship.

DISCUSSION

The Correlation Between D-dimer Levels and Mortality of COVID-19 Patients.

The results of the Spearman correlation test to find out the relationship between the D-Dimer variable and Mortality showed a significance value of 0.009 which was interpreted as less than 0.05 so that there was a significant relationship between the two variables. The D-dimer correlation coefficient with mortality is 0.308, meaning that the relationship has moderate strength because it is in the range 0.26 – 0.5. The correlation coefficient of D-Dimer and Mortality is positive so it means that the two variables have a unidirectional relationship. So that the greater the level of D-Dimer, the greater the risk of mortality.

D-Dimer, which is one of the independent variables in this study, is the result of degradation of dissolved cross-linked fibrin (fibrinolysis) by plasmin activity. D-dimer is an indirect marker of coagulation activation and fibrinolysis (Demelo-rodríguez et al., 2020; Vidali et al., 2020; Yu et al., 2020). In this study, the results showed that 48 of 72 patients experienced mortality with a mean D-Dimer level of 2490.32 (SD 2827.83) ng/ml. The mean D-dimer value was greater than the patients who did not die, which is 24 patients with an average D-Dimer level of 1319.17 (SD 1576.18) ng/ml. These results are in accordance with previous studies which stated that D-dimer levels in COVID-19 are associated with a high risk of venous thromboembolism, disease severity, and risk of death (Giannis et al., 2020). Elevated D-dimer values contribute to the poor prognosis and high mortality in these patients (Giannis et al., 2020; Soni et al., 2020; Vidali et al., 2020; Yu et al., 2020). High D-Dimer values can be associated with activation of the coagulation cascade Secondary to Systemic Inflammatory Response Syndrome (SIRS) in COVID-19 patients. Incidence of increased D-dimer levels often occurs in patients with severe COVID-19 and can be a predictor of acute respiratory distress syndrome (ARDS), the need for a long intensive care unit (ICU), and mortality (Farasani, 2021). An increase in d-dimer levels causes a 3 to 4 times worsening. Increased d-dimer levels in COVID-19 individuals can be triggered by underlying conditions such as diabetes, cancer, stroke and pregnancy. 71% of COVID-19 patients who experienced hypercoagulability died because they met the DIC criteria. Venous thromboembolism occurs in 25% of patients with severe COVID-19, and 30% of these patients develop pulmonary embolism. Based on existing research, 42% of COVID-19 patients had D-dimer levels > 1 µg/mL and 81% of them were reported died (Breakey & Escher, 2020).

The Correlation Between Neutrophil Lymphocyte Ratio Levels and Mortality of COVID-19 Patients.

The Neutrophil Lymphocyte Ratio (NLR) is a biomarker of inflammation that can be measured during routine hematological examinations. An increase in NLR indicates an increase in the inflammatory process and is associated with a poor prognosis. The NLR value is higher in patients with severe COVID-19 than in patients with mild symptoms. The intensity of the inflammatory response is indicated by an increase in the number of neutrophils while a decrease in the number of lymphocytes is a marker of damage to the body's immune system. Previous

studies have shown that a higher NLR is associated with clinical deterioration and death in COVID-19 patients. NLR can be easily calculated from routine hematology tests by dividing the absolute neutrophil count by the absolute lymphocyte count. NLR has been reported as great value in demonstrating the inflammatory status of the patient. A recent study showed that severe cases of COVID-19 tend to have higher NLR (Channappanavar & Perlman, 2017).

In the study, patients who experienced mortality had an average NLR level that was greater than patients who were alive, with a value of 14.30 (SD 19.24). Meanwhile, 24 out of 72 patients who did not die had an average NLR of 5.52 (SD 5.22). The results of this study are in line with previous studies, namely NLR has proven prognostic value in cardiovascular disease, infection, inflammatory disease and in several types of cancer (Imran et al., 2021). The results of the Spearman Correlation Test on NLR and mortality showed a significance value of 0.000 meaning less than 0.05 so that there was a significant relationship between the two variables. The correlation coefficient value of NLR and mortality is equal to 0.515 so that the relationship between the two variables has strong strength because it is included in the range 0.51-0.75. The co rrelation coefficient of NLR and Mortality is positive so it means that the two variables have a unidirectional relationship. This means that the greater the NLR value, the greater the patient's risk of experiencing mortality.

4.   CONCLUSION

Based on research that conducted using the cross-sectional approach on 72 samples of confirmed COVID-19 patients' medical records at UNS Hospital during the period November 2020-January 2021, it was concluded that there was a relationship between D-Dimer levels and NLR on mortality in COVID-19 patients. The two relationships between D-Dimer and mortality and also NLR and mortality have a significant and positive correlation. A positive correlation means that increased levels of D-Dimer and NLR increase the risk of mortality in COVID-19 patients. With this research, it is hope that there will be further studies with a larger sample size.

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