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RESEARCH ARTICLE

Correlation of NLR and D-dimer Levels with Clinical Severity of COVID-19 and Determination of Cut-off Values at a Hospital in Cirebon

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Abstract

Inflammation and coagulation markers play a crucial role in assessing the systemic involvement of COVID-19. Early identification of disease severity through neutrophil-lymphocyte ratio (NLR) and D-dimer levels can aid physicians in promptly identifying potentially severe cases and determining appropriate treatment strategies. This study explored the relationship between NLR, D-dimer levels, and clinical severity in COVID-19 patients. This retrospective cross-sectional study reviewed 237 medical records of adult COVID-19 patients treated at Permata Cirebon Hospital from July to October 2021. The seriousness of COVID-19 served as the outcome variable, while NLR and D-dimer values were considered independent variables. Correlation analysis examined the relationship between NLR, D-dimer, and COVID-19 severity. Receiver operating characteristic (ROC) curve analysis was employed to establish the cut-off values. The majority of COVID-19 patients exhibited moderate disease severity. Male gender, advanced age, and comorbidities such as diabetes, hypertension, CVD, and stroke were associated with a higher likelihood of severe disease. A significant positive correlation was found between NLR and disease severity, as well as between D-dimer and disease severity. Notably, the correlation between D-dimer and disease severity was more substantial than that of NLR. Furthermore, the cut-off values obtained from the ROC analysis were 3.79 for NLR (sensitivity=68.8%, specificity=68.1%) and 1,110 for D-dimer (sensitivity=79.2%, specificity=87.5%). The study revealed a significant positive correlation between the severity of NLR, D-dimer levels, and COVID-19. Therefore, NLR and D-dimer can serve as prognostic markers for COVID-19 patients.

Keywords: COVID-19, cut-off, D-dimer, NLR, severity

Introduction

Clinical symptoms of COVID-19 are categorized as asymptomatic, mild, moderate, severe, and critical.[1] Patients of advanced age (>65 years), smokers, patients with hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and malignancies are at higher risk for more severe disease progression and mortality when infected with COVID-19.[2] COVID-19 may also cause complications in the hematologic and neurologic systems.[3,4] Changes in the hematologic system include lymphopenia, elevated inflammatory markers, and hypercoagulopathy.[3–5]

COVID-19 spreads rapidly and has a relatively high mortality rate. Therefore, one of the keys to reducing the mortality rate of COVID-19 is early detection of COVID-19 severity. Several previous studies have found that several inflammatory and coagulation parameters, including neutrophil-lymphocyte ratio,[4,6] C-reactive protein, lactate dehydrogenase,[7] D-dimer,[8] and ferritin, have predictive value and are associated with COVID-19 severity, increased risk of intensive care unit (ICU) admission, and mortality.[3,5,7,8]

The neutrophil-lymphocyte ratio (NLR) indicates impaired cell-mediated immunity associated with systemic inflammation.[9] NLR is essential in determining the inflammatory status in COVID-19 patients and is more sensitive than neutrophils or lymphocytes alone. NLR values are markedly increased in COVID-19 patients with severe symptoms. This increase is due to dysregulated expression of inflammatory cytokines.[6,9,10] An exaggerated inflammatory response is characterized by a cytokine storm that can lead to systemic inflammatory syndrome. Inflammation-triggered viruses increase NLR, which then triggers the progression of

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COVID-19.[10] The NLR value is calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes. In the healthy adult population, NLR values have been reported to range from 0.78 to 3.53, with a cut-off value of 3.13. COVID-19 patients with an NLR value <3.13 are considered to have a good prognosis.[9,10]

In COVID-19 patients, hematologic abnormalities in hypercoagulopathy are frequently found in addition to lymphopenia, placing COVID-19 patients at high risk for venous thromboembolism. Coagulopathic disorders are common in COVID-19 patients.[3] Coagulopathic disorders may be characterized by elevated D-dimer. D-dimer is a fibrin degradation product or small protein fragment in the peripheral circulation after plasminogen activators have degraded fibrin. Elevated circulating D-dimers indicate activation of the coagulation system and ongoing fibrinolysis, support the presence of thrombus, and correlate directly with the amount of fibrin undergoing lysis but do not directly indicate the location of the thrombus. Fibrin degradation products, including D-dimer, cause platelet activation.[11,12] The normal value of D-dimer is <0.5 μg/ml. An increase in plasma D-dimer indicates an increase in hemostatic and thrombolytic activity. Elevated D-dimer levels are also associated with increased in-hospital mortality.[13,14] The incidence of thrombotic complications in COVID-19 patients is approximately 16–69%. High D-dimer levels are expected to predict the severity of COVID-19, pulmonary complications, and thromboembolic events. D-dimer levels can be used to evaluate coagulation and fibrinolytic activity in the body for early diagnosis and therapy to reduce morbidity and mortality.[14]

Based on the above description, inflammation, and coagulation are essential indicators that can be used to assess the systemic involvement of COVID-19. Early detection of disease severity with NLR and D-dimer can help physicians identify potentially severe cases early, determine appropriate treatment steps, and initiate effective therapy promptly, which can ultimately prevent the development of COVID-19, save medical resources, and reduce mortality and morbidity. This study investigated the relationship between NLR and D-dimer levels with clinical severity in COVID-19 patients.

Methods

A cross-sectional study was conducted retrospectively, reviewing the medical records of patients diagnosed with COVID-19 on the first day of admission in the Emergency Room in Permata Cirebon Hospital between July 2021 and October 2021. The inclusion criteria for the study were patients who had COVID-19 confirmed by RT-PCR and were ≥18 years of age. Patients with a comorbid history of coagulopathy and leukocyte disorders were excluded from this study. The Health Research Ethics Committee approved all research procedures, Universitas Islam Bandung (189/KEPK-Unisba/VI/2023).

The primary outcome of this study is the severity of COVID-19 patients. The seriousness of COVID-19 is classified as moderate and severe according to the criteria of the Indonesian COVID-19 guideline. Data on the severity of COVID-19 that were obtained were divided into moderate and severe degrees, regarded with mild degrees that had no recommendation for admission; therefore, D-dimer and NLR values were not obtained. Moderate-degree criteria in this study reported clinical symptoms of pneumonia (fever, cough, tightness, rapid breathing) but no signs of severe pneumonia, including SpO_2≥93% with room air. The severe-degree criteria are reported with moderate degrees plus one of the signs and symptoms: breathing frequency >30 ×/minute, severe respiratory distress, or SpO_2<93% in room air.[2,5] The independent variables in this study were NLR and D-dimer levels. The NLR value compares the number of neutrophils with the number of lymphocytes obtained from medical records. NLR values are categorized into average (<3.13) and abnormal values (≥3.13). D-dimer levels were obtained from medical records and reported as usual (<500 mg/ml) and abnormal (≥500 mg/ml). Data on patient characteristics such as age, sex, concomitant diseases such as diabetes, hypertension, renal diseases, cardiovascular diseases, lung disease, malignancies, and stroke, which is known as medical history, vital signs such as systolic blood pressure, respiratory rate, body temperature, and oxygen saturation, laboratory examination such as hemoglobin which divided into normal if hemoglobin count >13 g/dl for males, and >12 g/dl for females based on WHO criteria, thrombocyte count, leucocyte count, and random blood glucose which divided into normal

if glucose <200 mg/dl, and not normal if glucose >200 mg/dl. Data on patient characteristics were also collected on the first day of admission in the emergency room to describe patients according to clinical severity.

After collecting the data, we conducted double data entry using Microsoft Excel. Data analysis was performed using SPSS ver. 26 (IBM, SPSS, New York). The descriptive data for categorical variables were presented as relative proportions. In contrast, numerical variables were summarized using mean measures, including the minimum and maximum range of values and standard deviation. To examine the relationship between the severity of COVID-19 and NLR and D-dimer values, a bivariate analysis was conducted using the Spearman correlation test. The significance level set for this study was 0.05. Additionally, we employed the receiver operating characteristic (ROC) curve to determine the cut-off values for the NLR and D-dimer variables in predicting severe cases of COVID-19.

Results

Participants in this study were obtained from medical record data from July 2021 to October 2021—237 confirmed patients with COVID-19 were included. Based on clinical severity, 160 cases were classified as moderate (67.5%), and 77 others were classified as severe (32.5%). More than half of the patients were men (51.1%); the dominant age group was 18-60 (74.3%).

In addition, patient characteristics were

Table 1 COVID-19 Patient Characteristics

Characteristics	COVID-19 Severity Level			
	Moderate		Severe	
	n=160	%	n=77	%
Gender				
Male	75	31.6	46	19.4
Female	85	35.9	31	13.1
Age (years)				
18–60	121	51.1	55	23.2
>60	39	16.5	22	9.3
Diabetes				
Yes	33	13.9	23	9.7
No	127	53.6	54	22.8
Hypertension				
Yes	15	6.3	13	5.5
No	145	61.2	64	27
Renal disease				
Yes	5	2.1	1	0.4
No	155	65.4	76	32.1
Cardiovascular diseases				
Yes	11	4.6	12	5.1
No	149	62.9	65	27.4
Lung disease				
Yes	1	0.4	0	0.0
No	159	67.1	77	32.5
Malignancy				
Yes	0	0.0	4	1.7
No	160	67.5	73	30.8
Stroke				
Yes	0	0.0	1	0.4
No	160	67.5	76	32.1
Outcome				
Survivor	160	67.5	75	31.6
Non-survivor	0	0.0	2	0.8

Table 2 Vital Signs and Laboratory Characteristics by Severity Level

Characteristics	COVID-19 Severity Level			
	Moderate		Severe	
	n=160	%	n=77	%
Systolic blood pressure (mmHg)				
<140 (normal)	132	70.2	56	29.8
>140 (high)	28	57.1	21	42.9
Respiratory rate (×/minute)				
<30	158	69.9	68	30.1
≥30	2	18.2	9	81.8
Body temperature (°C)				
≤37.3	22	59.5	15	40.5
>37.3	138	69.0	62	31.0
SpO_2 (%)				
>93	107	99.1	1	0.9
≤93	53	41.1	76	58.9
Haemoglobin (g/dl)				
Normal	154	69.1	69	30.9
Not normal	6	42.9	8	57.1
Thrombocyte count (×109 /L)				
≥150	140	68.3	65	31.7
<150	20	62.5	12	37.5
Leucocyte count (×109 /L)				
4–10	148	75.9	47	24.1
>10	12	28.6	30	71.4
Random blood clucose (mg/dl)				
<200 (normal)	119	72.6	45	27.4
>200 (not normal)	41	56.2	32	43.8

subdivided according to disease severity (Table 1). Severe disease was relatively more common in men than in women (38% vs 26.8%) and in patients older than 60 years (36.1% vs 31.3%). The proportion of severe disease was also higher in patients with diabetes mellitus (41.1%), hypertension (46.4%), cardiovascular disease (52.2%), malignant disease (100%), and stroke (100%). Two of the 77 patients with severe disease died (2.6%).

Table 2 shows the characteristics of vital signs and laboratory values for COVID-19 patients based on the disease severity. High systolic blood pressure (>140 mmHg) is more common in patients with severe disease than in patients with moderate disease. Similarly, respiratory rate ≥30 ×/minute and SpO_2≥93 are more likely to be found in patients with severe than moderate disease. Among laboratory indicators, patients with severe disease are likelier to have abnormal Hb levels, higher leukocyte counts, and abnormal random blood glucose levels than patients with moderate disease.

Table 3 shows that the mean value of NLR and D-dimer is relatively higher in patients with severe disease than those with moderate disease.

Table 3 Correlation of NLR and D-dimer with COVID-19 Severity Level

Variables	COVID-19 Severity Level						r	p
	Moderate			Severe				
	Mean	Min–Max	±SD	Mean	Min–Max	±SD		
NLR	3.43	0.15–24.30	±2.93	7.79	1.00–47.47	±7.23	0.460	<0.001*
D-dimer	598.69	52.00–4,290.00	±660.81	4,545.27	200.00–14,430.00	±4,327.71	0.613	<0.001*

Note: r: correlation coefficient, *significant p<0.05

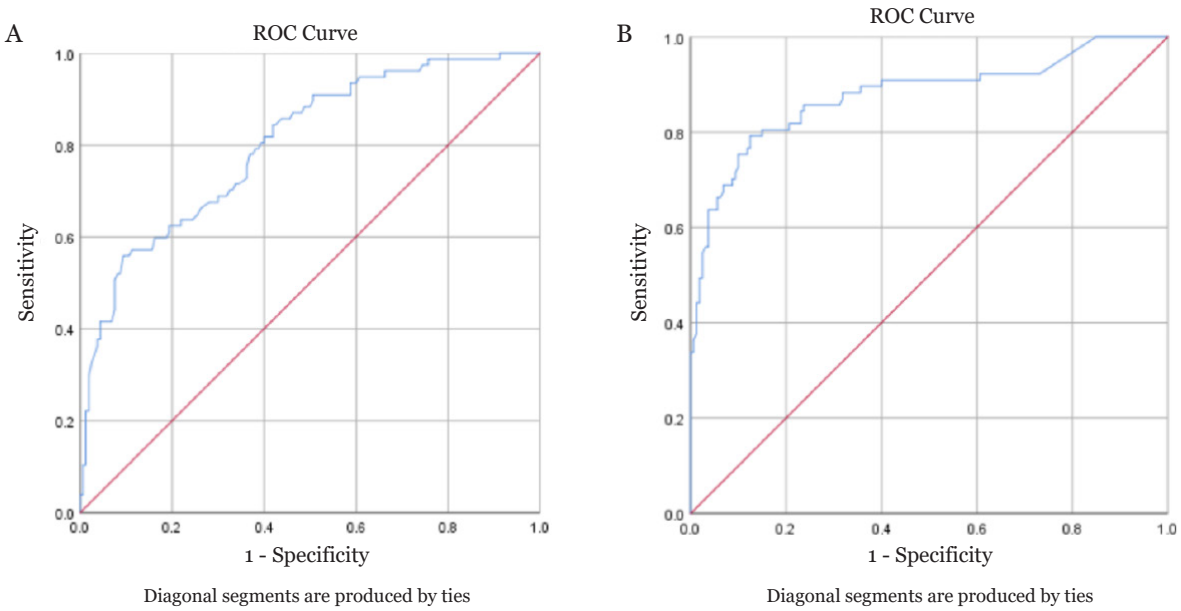

Figure (A) ROC Analysis for NLR and (B) ROC Analysis for D-dimer

In addition, the results of Spearman correlation analysis between NLR and COVID-19 severity showed a significant correlation (p<0.001) with moderate strength of positive direction (r=0.460). These results suggest that an increase in NLR value positively correlates with an increase in disease severity. A similar picture was found for the D-dimer value with a stronger correlation (r=0.613). These results suggest that an increase in D-dimer level has a strong positive correlation with an increase in the severity of COVID-19.

We further analyzed the ROC curve to determine the cut-off values for the NLR and D-dimer variables in predicting severe cases of COVID-19. The ROC analysis for NLR yielded an area under the curve (AUC) value of approximately 80.2%, with a 95% CI ranging from 74.3% to 86.1% and a p-value of 0.000. This analysis found that the optimal cut-off value for the negative likelihood ratio accurately predicted severe COVID-19 in 80 out of 100 individuals. Therefore, the NLR demonstrated an excellent ability to predict the severity of COVID-19. Similarly, the ROC analysis for D-dimer resulted in an AUC value of approximately 87.8%, with a 95% confidence interval ranging from 82.5% to 93.1% and a p-value of 0.000. The optimal cut-off value for D-dimer accurately predicted severe COVID-19 in 87 out of 100 individuals. Hence, D-dimer exhibited a good predictive ability for severe COVID-19 (Figure).

The determination of cut-off values from the graph resulted in an NLR value of 3.79, with a sensitivity of 68.8% and a specificity of 68.1%. Meanwhile, the cut-off value for D-dimer was 1,110, with a sensitivity of 79.2% and a specificity of 87.5% (Table 4).

Discussion

The results showed that more than half of the confirmed COVID-19 patients were male and in the age range of 18–60 years. Similarly, in most studies of COVID-19 patients, male patients were found to be more dominant than females and had a more severe disease course.[15,16] Males have

Table 4 Cut off Value of NLR and D-dimer for Severe COVID-19

Variables	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR ≥3.79	0.802	68.8	68.1	53	87
D-dimer ≥1,110.0	0.878	79.2	87.5	75	89

been reported to have a higher risk of disease progression than females. COVID-19 elevated levels of proinflammatory cytokines such as IL-8 were higher in men than women, whereas women were more likely to have a strong T-cell response.[15–17] In addition, men are also associated with a higher prevalence of smoking and tobacco use, but this needs further investigation.[16] The 18-to-60-year-old age group is the dominant age group affected by COVID-19 due to high mobility and activity outside the home.[18] However, older individuals (>60 years) are at higher risk of developing more severe diseases because overexpression of ACE2 is a sign of decreased immunity, decreased organ function, and concomitant diseases.[17]

The results showed a tendency toward severe disease in patients with diabetes, hypertension, heart disease, malignant disease, and stroke. Diabetes mellitus is an essential complication in COVID-19 patients. A systematic review by Singh et al.[19] found an increase in the frequency and severity of COVID-19 in patients with diabetes mellitus. Diabetes mellitus and its complications may increase the risk of morbidity and death during acute infection due to suppression of innate and humoral immune function. Several predisposing factors are thought to be the cause of the severity of COVID-19 in patients with diabetes mellitus, including increased expression of ACE2; increased furin, a membrane-bound protease that facilitates internalization of the virus; and impaired T-cell function leading to lymphopenia and increased IL -6, which is also known to increase in diabetes mellitus and plays an essential role in organ failure during COVID-19 infections.[19,20] Lippi et al.[20] reported that hypertension and cardiovascular disease are associated with a 2.5-fold increase in COVID-19 progression and death, particularly in patients >60 years of age. The involvement of hypertension and cardiovascular disease in the pathogenesis of COVID-19 through a direct role as a causative factor in ARDS and multiorgan failure. This condition may be due to an increase in converting enzyme inhibitors (ACEi) in hypertensive patients, which increases their susceptibility to COVID-19 and increases the risk of death.[21]

This study's characteristics of SpO_2 in COVID-19 patients were mostly ≤93%, regardless of disease severity. To date, there have not been many studies of differences in peripheral oxygen saturation based on the severity of COVID-19, and therefore, only brief generalizations can be made; according to referrals, patients with severe symptoms usually show an oxygen saturation <93%, resulting in a worse prognosis.[20] A study in Jakarta also showed that more patients with moderate to severe symptoms required hospitalization than patients with mild or no symptoms.[22]

In this study, NLR values were higher in patients with severe disease than those with moderate. In addition, a significant relationship was found between NLR and the severity of COVID-19 disease, with a moderate correlation strength. This is consistent with several previous studies that found the NLR higher on average in patients with severe COVID-19 than in patients with milder disease.[23] A high NLR in COVID-19 patients on admission may be an early sign of the patient's prognosis. In addition, a higher NLR is usually found in patients with more severe symptoms, such as fever, cough, respiratory tract infection, pneumonia, and a drop in oxygen saturation below 93%. Initial treatment is generally given immediately in the respiratory ICU for these various clinical signs.[6,22] Increased neutrophil counts are caused by an inflammatory response and lymphocytopenia due to the expression of ACE2 receptors, which make them one of the targets of infection, and by increased inflammatory cytokines, which can trigger a reduction in lymphocytes.[24] Lymphocytopenia in COVID-19 patients can trigger lymphocyte apoptosis and pyroptosis, bone marrow suppression due to the release of proinflammatory cytokines, thymic suppression, activation-induced lymphocyte cell death, lymphocyte tissue redistribution, and several other pathways.[24,25]

This study found that the average D-dimer level was higher in patients with severe disease than in moderate. A significant relationship was also found between D-dimers and the severity of COVID-19 disease, with a strong positive correlation. Luo et al.'s[25] study in Wuhan obtained similar results, according to which there was a significant correlation between D-dimer and mortality and severity of COVID-19 patients ($p<0.05$). Yao et al.'s[26] study in China found that elevated D-dimers were likelier in patients with severe grades (Kendall's tau-b=0.374, p=0.000). A meta-analysis study also showed that mortality and disease severity increased with elevated D-dimers. In addition, the study showed that the

risk of mortality was four times higher in patients with positive D-dimers than in negative ones, so D-dimer can be considered as a biomarker for testing the severity and mortality of COVID-19.[27]

D-dimer is a fibrin degradation product; its presence in the circulation indicates the degradation of fibrin polymer by plasmin so that it can be used as a parameter of coagulopathy. D-dimers >1,000 ng/ml indicate a 20-fold higher risk of death than patients with lower D-dimers.[27,28] The pathogenesis of coagulopathy in COVID-19 is not significantly different from disseminated induced coagulopathy (DIC), in which there is an excess of proinflammatory cytokines, increased damage-associated molecular activity, stimulation of cell death mechanisms, and damage to the vascular endothelium.[11,14] In coagulopathy due to COVID-19, there is widespread inflammation and dysfunction of endothelial cells, abnormal blood flow dynamics, and activation of platelets, cell-free DNA, histones, and viral RNA that cumulatively activates factor XI and the formation of thrombin and fibrin. Coagulopathy manifests as thrombosis and hemorrhage.[12–14] Vascular thrombosis contributes to tissue ischemia and organ dysfunction. In addition, the thrombus formed may break loose and travel through the blood vessels, resulting in embolism.[11] In a study, the incidence of venous thromboembolism associated with COVID-19 was 14.7%, involving pulmonary embolism and deep vein thrombosis, whereas the incidence of arterial thromboembolism in this study was 3.9%.[29] These thromboembolic events play an essential role in the severity and mortality of COVID-19 patients.

Based on the data analysis and ROC curve, the NLR was found to have an AUC of 0.802 (95% CI=0.743–0.861, p<0.000). The optimal cut-off value for NLR, ≥3.79, was determined as the minimum threshold for predicting the severity of COVID-19 upon admission to the hospital. This cut-off value demonstrated a sensitivity of 68.8% and a specificity of 68.1%. The positive predictive value (PPV) was 53%, while the negative predictive value (NPV) was 87%. These results indicate that NLR can serve as a reliable predictor for the severity of COVID-19. A study by Fei et al.[28] in China, which examined 72 COVID-19 patients on the second day of treatment, also supported the findings of this study. Fei et al.[28] obtained an AUC NLR value of 0.888, demonstrating the ability of NLR to differentiate between different degrees of severity. Based on the data, no other study observed the correlation and cut-off between NLR and the seriousness of COVID-19, especially in Indonesia when the analyses were performed.

Similarly, the analysis of the D-dimer values using the ROC curve revealed an AUC of 0.878 (95% CI=0.825–0.931, p<0.000). The cut-off value for D-dimer, ≥1,110.0, was identified as the minimum threshold for predicting the severity of COVID-19 upon admission to the hospital. This cut-off value showed a sensitivity of 79.2% and a specificity of 87.5%. The PPV was 75%, and the NPV was 89%. Therefore, D-dimer can be considered a valuable predictor of the severity of COVID-19. This study identified D-dimer levels higher than 1,500 ng/ml as a predictor of mortality in severe COVID-19 cases.[30] Additionally, Zhang et al.'s[30] study aligned with these findings, showing that a D-dimer level >2.0 ng/ml predicted mortality in patients with severe COVID-19 compared to non-severe degrees. Therefore, patients with elevated D-dimer levels should be closely monitored following the guidelines for managing coagulopathy in COVID-19.

The result of this study should be considered in the context of several potential limitations. First, these studies retrieved data from the first day the patient was admitted to the ER; therefore, developed results of NLR and D-Dimer when the patient was still inpatient were not being observed. Second, as the studies were only performed in the regent of Cirebon of Permata Hospital, the size of the samples in this study needed to provide more power for the responder analyses. Last, the inclusion and exclusion criteria may be limited in generalizability.

Conclusions

The study revealed a significant correlation between NLR and D-dimer levels and the severity of COVID-19. Notably, the correlation between D-dimer and disease severity was stronger. Therefore, NLR and D-dimer can be valuable prognostic markers for COVID-19 patients.

Conflict of Interest

The authors declare no conflict of interest.

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