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Correlation between NLR and PLR with the Severity of COVID-19 Inpatients

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ABSTRACT

When the COVID-19 outbreak is ongoing, the classification of COVID-19 patients based on the severity assessment is necessary to optimize the allocation of existing resources and early management interventions to improve prognosis. Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) are two of the most common, simple, inexpensive, rapid, and widely available tests in all health facilities, which indirectly indicate the inflammatory status of COVID-19 patients. This study aimed to analyze the correlation between NLR and PLR with the severity of COVID-19 inpatients. This cross-sectional study was conducted retrospectively using medical record data of COVID-19 patients hospitalized at Al Islam Hospital, Bandung, from January to March 2021. COVID-19 patients involved in this study were classified into moderate, severe, and critical degrees. Statistical analysis was carried out using ANOVA or Kruskal-Wallis and Spearman with a significant value of $p < 0.05$. The median NLR and PLR results based on the severity were 3.49; 6.27; 8.4 ($p<0.001$) and 159.2; 202.6; 250.9 ($p<0001$), respectively. There was a correlation between NLR and PLR and the severity with $r= 0.415$ ($p<0.001$) and $r=0.216$ ($p<0.001$), respectively. The correlation between NLR and the severity was stronger than PLR. Therefore, it was concluded that there was a correlation between NLR and PLR with the severity of COVID-19 patients.

Keywords: Neutrophil-to-lymphocyte ratio, platelet to lymphocyte ratio, the severity degree of COVID-19

INTRODUCTION

Coronavirus Disease (COVID-19) was previously found to be an unknown case of pneumonia that emerged in late 2019 in Wuhan (Hubei, China). COVID-19 was analyzed using a lower respiratory tract sample. A new virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was then identified as the causative agent, a single-stranded RNA-positive virus (+ssRNA).[1-3]

The transmission of COVID-19 occurs through droplets that can be exposed when talking, coughing, or sneezing. Another possible virus transmission is through direct contact with the surface (touching the surface containing the virus).[4] One of the disease symptoms is respiratory disorders ranging from moderate to severe, or even critical in some people, which require special attention.[3,5] Other common clinical symptoms are fever, cough, weakness, shortness of breath, joint pain accompanied by sputum, runny nose, sore throat, chest discomfort, anosmia, or no symptoms.[6] In severe cases, rapid and progressive deterioration, such as Acute Respiratory Distress Syndrome (ARDS), septic shock, metabolic acidosis, bleeding, and coagulation disorders.[7]

COVID-19 is currently an ongoing problem in more than 200 countries worldwide.[8] There were 149,234,519 confirmed cases of COVID-19 in April 2021 (CFR 2.1%) worldwide, of which 1,662,868 were confirmed cases in Indonesia (CFR 2.7%).[9] The diagnosis of COVID-19 is made based on the medical history, clinical symptoms, and the gold standard test such as molecular identification of SARS-COV-2 through nucleic acid amplification test with different possible methods such as Reverse Transcriptase-Quantitative Polymerase Chain Reaction (RT-qPCR), Real-time RT-PCR, Loop-mediated Isothermal Amplification (LAMP), and other isothermal or non-isothermal amplification methods.[7,10] Other additional tests are also needed for screening, diagnostic support, identification, and monitoring of the severity of COVID-19 patients.[11] However, not all healthcare facilities can perform such molecular screening tests due to facility limitations that can delay diagnosis and management of interventions. This delay may lead to the death of COVID-19 patients. One of the frequent, easy, inexpensive, quick tests performed in almost all health centers is a complete blood count test. Early identification and intervention are expected to improve the prognosis of COVID-19 patients.[11,12]

Inflammation plays an important role in the pathophysiology of COVID-19.[13] Hematology test of severe COVID-19 patients frequently shows leukocytosis, neutrophils, lymphopenia, thrombocytopenia, decreased eosinophils, and hemoglobin.[14] The NLR (calculated by absolute neutrophil count divided by total lymphocyte count) and the PLR (calculated by absolute platelet count divided by absolute lymphocyte count) play an essential role in the inflammatory process and can be used as indicators of the inflammatory process.[13,15,16] The NLR and PLR can indirectly exhibit inflammatory status in COVID-19 patients and predict the severity of the disease in confirmed COVID-19 patients, enabling early intervention to improve prognosis.[12,11] Clustering COVID-19 patients are significant, especially during the COVID-19 outbreak, to provide optimal health and treatment personnel. Neutrophils and lymphocytes are the first defenses and the primary human immune response to viral infections. Some of these cells express Angiotensin Converting Enzyme-2 (ACE2) receptors on their surface, and the virus can directly infect lymphocytes, causing lymphopenia.[17,18]

Platelets are important immune cells in the human body that play an important role in hemostasis, coagulation, maintenance of vascular integrity, angiogenesis, innate immunity, inflammatory response, and tumors. Platelet activation causes the adhesion of lymphocytes to endothelial cells, leading to a higher concentration of lymphocytes in areas of inflammation. All these processes contribute to an increase in PLR levels.[19,18]

Based on this background, the study aimed to analyze the correlation between the Neutrophil-to-Lymphocyte Ratio (NLR) and the Platelet-to-Lymphocyte Ratio (PLR) to the severity of COVID-19 inpatients at Al Islam Hospital, Bandung.

METHODS

This study was a retrospective study with a cross-sectional method using secondary data from laboratory medical records at Al Islam Hospital inpatients with confirmed COVID-19 from January to March 2021.

The population in this study was inpatients aged 18 years old at Al Islam Hospital who met the inclusion criteria and were confirmed with COVID-19 determined with nucleic acid amplification test using the POCKIT Central PCR analyzer, which is an Insulated Isothermal Polymerase Chain Reaction (IIPCR) test intended for the qualitative detection of nucleic acid from SARS-CoV-2 in oropharyngeal and nasopharyngeal swabs. Subjects in this study were hospitalized in a particular hospital treatment room of Al Islam Hospital according to the disease severity, such as moderate, severe, and critical (Table 1). They were also asked to undergo a complete blood test using the Mindray BC-5150 analyzer.

Data analysis was carried out using SPSS version 25 by presenting categorical variables in number (n) and percentage (%). Statistical tests used in this study were Chi-Square and Kolmogorov-Smirnov tests to ensure data normality. If the data were normally distributed, the difference between the degree of severity would be analyzed using ANOVA. However, Kruskall-Wallis would be used if the data had abnormal distribution. The correlation between the NLR and PLR with the severity was determined using the Spearman test. P-value < 0.05 was considered statistically significant. This study has been declared ethically feasible by the Research Ethics Committee of Al Islam Hospital, Bandung, with the number 017/KEPPIN-RSAI/08/2021.

RESULTS AND DISCUSSIONS

This study found 453 COVID-19 patients hospitalized at Al Islam Hospital who met the inclusion criteria consisting of 310 patients with moderate, 82 with severe, and 61 with the critical disease.

Table 2 shows that COVID-19 was more common in males (51%). Moderate and critical COVID-19 cases were more common in males, consisting of 159

Table 1. The severity of COVID-19 in the study

Mild	Severe	Critical
Clinical symptoms of pneumonia (fever, cough, dyspnea, shortness of breath) without symptoms of severe pneumonia SpO_2 ≥93% in room air	Clinical symptoms of pneumonia with meet any of the following criteria: Respiratory rate > 30x/minute Severe respiratory distress SpO_2 < 93% in room air	Acute Respiratory Distress Syndrome (ARDS) Sepsis Septic shock or other conditions that would generally require the provision of life-sustaining therapies Need intensive care unit monitoring

patients (35.1%) with moderate severity and 36 patients (7.9%) with critical severity. Severe COVID-19 was more common in females as many as 46 patients (10.2%), indicating no significant differences between gender with the severity of the disease. According to the age classification, there was a significant difference between age and disease severity (p <0.001). Moderate and severe degrees of COVID-19 were more common in patients aged 20-60 years as many as 222 patients (49%) with a moderate degree, 45 patients (9.9%) with a severe degree, and 36 patients (7.9%) with a critical degree were aged >60 years.

Table 3 shows the association between the laboratory results and disease severity. Although there were some significant results, there was no significant difference between hemoglobin and platelet levels and the severity degree, in line with a study by Qu *et al.,* which showed no significant association between platelet levels and the severity

Table 2. Characteristics of research subjects

Variable	Severity of Disease						Total	p-value
	Moderate	(%)	Severe	(%)	Critical	(%)		
Gender								
Male	159	35.1	36	7.9	36	7.9	231	0.199
Female	151	33.3	46	10.2	25	5.5	222	
Age								
20-60 y.o	222	49	45	9.9	25	5.5	292	<0.001
>60 y.o	88	19.4	37	8.2	36	7.9	161	
Total	310	68.4	82	18.1	61	13.5	453	

Table 3. The association between hematology and the severity of disease

Variable	Severity of Disease			p-value
	Moderate	Severe	Critical	
Hemoglobin (g/dL)				
Mean±SD	13.4±1.87	13.3±2.26	12.8±2.37	0.208
Median (min-max)	13.6 (6.3–18.4)	13.6 (6.1–19.9)	13 (6.9–16.7)	
Leukocytes, $10^3/\mu L$				
Mean±SD	7.59±3.57	10.42±4.3	10.34±4.99	<0.001
Median (min-max)	6.9 (2.2–30.8)	9.8 (3.7–26.1)	9.4 (2–28.7)	
Platelets, $10^3/\mu L$				
Mean±SD	231.75±98.57	247.09±100.3	243.46±127.85	0.544
Median (min-max)	217 (21–709)	222.5 (94–506)	220 (47–593)	
Neutrophil (%)				
Mean±SD	70.99±11.05	80.28±8.88	80.25±12.2	<0.001
Median (min-max)	72 (34–93)	82 (56–96)	84 (24–94)	
Lymphocytes (%)				
Mean±SD	21.1±9.99	13.27±7.33	12.67±9.86	<0.001
Median (min-max)	20.5(1–51)	13 (2–40)	10 (2–66)	
ANC, $10^3/\mu L$				
Mean±SD	5.59±3.34	8.48±3.93	8.49±4.41	<0.001
Median (min-max)	4.94 (1.23–26.79)	7.89 (2.77–21.66)	7.48 (0.48–22.96)	
ALC, $10^3/\mu L$				
Mean±SD	1.41±0.66	1.27±0.699	1.21±1.28	<0.001
Median (min-max)	1.32 (0.12–6.46)	1.06 (0.25–3.06)	0.86 (0.38–9.57)	
NLR				
Mean±SD	5.19±6.62	9.14±7.78	9.6±6.85	<0.001
Median (min-max)	3.49(0.71–91)	6.27 (1.40–48)	8.4 (0.49–42.5)	
PLR				
Mean±SD	198,78±158,1	261.86±184.8	294,15±219,95	<0.001
Median (min-max)	159,2 (14.15–1966,1)	202,6 (37.97–983,9)	250.9 (5.85–1225,9	

ANC: Absolute Neutrophil Count; ALC: Absolute Lymphocyte Count; NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio

of COVID-19 patients. The virus's ability to directly infect hematopoietic cells or bone marrow is one of the possibilities that can cause changes in the platelet count of COVID-19 patients, namely the corona virus that directly infects.[19,20]

Leukocytes have significantly higher at severe and critical COVID-19 compared to moderate COVID-19 disease (p < 0.001). A study by Rahman *et al*. showed a significant association between leukocytes and severity.[21] Leukocytes are an indicator of the inflammatory process that occurs in COVID-19; increased leukocyte count is associated with mortality and needs special attention during the treatment of COVID-19.[22]

There was a significant association between increased neutrophil levels and decreased lymphocyte levels with the severity (p <0.001). This research was in line with a study by Man *et al*., which found a significant association between high neutrophil levels, low lymphocyte levels, and the severity degree of COVID-19.[15] There was a significant association between the NLR and PLR and the severity (p < 0.001). This was in line with a study by Jain *et al*. and Man *et al*. indicating that the NLR and PLR were significantly higher in COVID-19 and severe patients.[18,15]

Table 4. The correlation between the NLR and PLR and the severity of disease

Variable	r	p-value
The correlation between the NLR with the severity of the disease	0.415	<0.001
The correlation between the PLR with the severity of the disease	0.216	<0.001

Table 4 shows that there was a positive correlation (p <0.001) between the NLR with the severity of the disease, indicating that there was a significant correlation between the NLR and the severity with a moderate correlation strength (r =0.415). This data was consistent with the study by Suhartono *et al*. showing a correlation between the NLR and the severity.[23]

There was a positive correlation (p <0.001) between the PLR and the severity, indicating that there was a significant correlation between the PLR and the severity with a weak correlation strength (r =0.216). This finding was in line with the study of Qu *et al.* showing an association between the PLR and the severity of COVID-19.[19]

This study showed no significant difference between gender and the severity of COVID-19; however, this study also found that 36 male patients (7.9%) and 25 female patients (5.5%) suffered critical COVID-19. Following the analysis of Jin *et al*., this data suggests a tendency for higher severity and death in male COVID-19 patients than in female patients aged 65. This fact can occur because the circulatory levels of ACE2 in male are higher than in female, and the expression of the high protein on the ACE2 receptor in specific organs is associated with organ failure.[24] Although the differences were not statistically significant, male patients suffered more critical cases than female patients. A higher number of male COVID-19 patients experienced the severity and worsening in the hospital as the result of a different immune response between males and females.[25,26] There is an association between the loss of T cell activation and age in males and the association between poor T cell response and disease worsening, which was only observed in males.[27] The study also found no difference between platelet and disease severity. Some studies mentioned that a decrease in platelet levels (thrombocytopenia) in COVID-19 patients may be associated with lung damage stimulating increased platelet use with platelet activation and aggregation. The decreased platelet levels may have resulted from cytokine storms or increased platelet destruction due to increased autoantibodies and immune complexes.[28]

Neutrophils and lymphocytes in this study showed a significant association with the severity of the disease. Critical COVID-19 cases in this study showed a higher neutrophil and lower lymphocyte count. This result was consistent with an investigation by Wu *et al*., which found that high neutrophil count was more frequently found in patients with ARDS than patients without ARDS.[29] Severe COVID-19 shows an increased neutrophil count, which that have been observed in the nasopharyngeal epithelium and the distal part of the lung.[30] There is a significant activity of cytokines causing secondary lymphatic organ atrophy, including spleen, and increased expression of FAS receptors and apoptosis leading to lymphopenia. There was a decrease in total lymphocyte levels, $CD4^+$ T cells, $CD8^+$ T cells, B cells, and Natural Killer cells (NK cells) in COVID-19 patients, indicating a possible link between lymphocytes and SARS-CoV-2 pathogenesis. Systemic inflammation significantly suppresses cellular immunity. Some studies showed that there might be a significant association between the severity of lymphopenia and the severity of COVID-19, which requires ICU treatment.[17,31,32]

Based on several studies, the NLR and PLR can be used as indicators of systemic inflammation.[33,34]

Abnormal laboratory test results, especially NLR and PLR in COVID-19 patients in this study, showed alterations that correlated with the severity of the disease. The increased NLR indicates the progressive increase of neutrophils and/or the decrease of lymphocytes. In some cases, the increase of neutrophils often suggests an underlying bacterial infection; however, neutrophilia in COVID-19 correlates with a hyperinflammatory state and cytokine storm as a part of the pathogenesis of COVID-19.[35] Neutrophil to lymphocyte ratio is a simple parameter for the inflammatory status of neutrophils playing a role as a marker of severe physiological stress in nonspecific inflammatory reactions and lymphopenia.[36,16] Some COVID-19 patients showed mild to severe pneumonia symptoms, and the NLR has been shown to be a good predictor of pneumonia. The increase in NLR indicates the severity of lymphatic damage, which may support the hypothesis that NLR is a simple and sensitive biomarker in patients with COVID-19.[34]

Neutrophils are involved in many viral respiratory diseases associated with ARDS. Lymphopenia is commonly considered to be an inadequate immunological response to viral infection, and it may be caused by virus attachment or indirectly caused by immune injuries from inflammatory mediators.[35] Neutrophils are the innate immune system at the time of viral infection. The central role of neutrophils is to eliminate pathogens and debris through phagocytosis. It also has other immune functions, such as the release of NETs for the inactivation of viral infections and the prevention of viral replication by cytokine production. Decreased number of cells or impaired leukocyte function may play a role in accelerating the condition of mild to severe disease.[37] Neutrophils express a complex array of receptors and adhesions of molecules, including immunoglobulins and inflammatory markers. Therefore, this is associated with increased levels of NLR in COVID-19 cases.[38]

There was a correlation between PLR and the severity of disease in this study, and the rise of PLR to a critical degree can result from decreased lymphocyte count. As one of the new types of inflammation indices, the PLR highly indicates the severity of systemic inflammation. In some previous studies, the PLR has been linked to tumor size, metastasis, and prognosis and can be used as a potential indicator of inflammation in the diagnosis of community acquired pneumonia. Platelets play an important role in the inflammatory response to neutrophils and other inflammatory cells in the injured part. The damaged part of platelets is rapidly activated and can become rapidly activated in response to proinflammatory cytokines or infectious factors. The advantage of the PLR selection is its ability to reproduce aggregation and inflammatory pathways and may be more informative in predicting various types of inflammation than the number of platelets or lymphocytes.[19,39,40]

Lung injury causes platelet aggregation and lung thrombus formation, leading to increased platelet consumption.[28] Platelet activation causes the adhesion of lymphocytes to endothelial cells, leading to an increased concentration of lymphocytes in the site of inflammation.[18] Direct stimulation mediated by SARS-COV-2 against NLRP3 inflammasomes leads to pyroptosis of lymphocytes that can predispose to lymphocytopenia. In addition, more severe lymphocytopenia than thrombocytopenia allows for an increase in PLR.[41] Abnormal hematology test result is closely related to the severity of COVID-19, the length of hospitalization, and the need for ICU support.[21] Monitoring the predictors of severity may assist clinicians in identifying and following-up on patients with a higher risk for progression.

CONCLUSIONS AND SUGGESTIONS

Neutrophil to lymphocyte ratio and PLR were significantly correlated with the severity in COVID-19 patients. NLR had a stronger correlation with the severity of COVID-19 patients compared to PLR. Higher NLR and PLR in critical degree indicate a higher urgency of intensive care in clinical practice. Due to some limitations of this research, further research was needed to determine the optimal cut-off value with a larger sample to obtain a more valid result.

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