

# Comparison of Platelet-to-Lymphocyte Ratio at Different COVID-19 Severity in Adam Malik Hospital, Medan, Indonesia

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## ABSTRACT

**Introduction.** Several inflammatory indicators such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphopenia have shown an inflammatory response of COVID-19. Nevertheless, not much research has been done in Indonesia. This study aims to determine the difference between PLR and severity of COVID-19 disease in Adam Malik Hospital, Medan.

**Method.** A retrospective study was conducted from September 2020 to February 2021 to analyze the medical records of patients with confirmed COVID-19. Patients' clinical severity was categorized according to the criteria of WHO. PLR is calculated by dividing the platelet count by the lymphocyte count obtained from a complete blood count of a COVID-19 patient at the time of hospital admission. A comparative analysis was performed to determine differences in PLR at different clinical severities of COVID-19.

**Results.** A total of 114 patients were enrolled in the study. Most of the COVID-19 patients are patients with non-severe grade, 57.1%, while the other 42.9% are patients with severe grade. In both severity grades, the platelet count is basically normal, while a low lymphocyte count is observed in the severe severity grades. Higher PLR values were found in severe COVID -19 patients, with a significant difference between severe and non-severe patients ( $p=0.00$ ).

**Conclusion.** There is a significant difference in PLR in severe and non-severe COVID -19 grades.

**Keywords:** Platelet-to-lymphocyte Ratio, Severity, COVID-19, Inflammation

## INTRODUCTION

The new coronavirus, or what is being called Coronavirus Disease 2019 (COVID -19), is an ongoing global health threat. Cases of COVID-19 were first reported in late 2019 in the city of Wuhan, Hubei Province, China.<sup>1</sup> The subsequent COVID-19 cases quickly compelled the World Health Organization (WHO) to declare pandemic or outbreak status that threatens global health.<sup>2</sup> The first cases of COVID -19 were reported in December 2019, when a group of people reported pneumonia-like signs and symptoms of unknown cause. The initial suspicion of animal-to-human transmission was based on the association of the ill people who had visited the fish market in Wuhan. However, further investigation shows that human-to-human transmission can occur.<sup>1,2</sup>

The pandemic COVID-19 not only has a high morbidity and mortality rate, but also has a significant impact on the economy. Efforts are being made in all parts of the world to understand the spectrum of the disease and to identify factors that influence its prognosis.<sup>3,4</sup> Given the tremendous strain on resources, particularly the need for oxygen and ventilatory support, time is needed to identify patients prone to complications at the time of arrival for

treatment or early detection to reduce the burden of personal expenditures.<sup>5</sup> Conditions range from those with no or mild symptoms to critical conditions. To date, most COVID -19 patients have mild symptoms.<sup>3</sup> Patients with COVID -19 may have mild symptoms without requiring oxygen, but on the other hand, there are quite a few patients who require ventilators even with more severe management. Different authorities have classified the severity of the disease differently. WHO classifies the disease into mild, moderate, severe, and critical. Mild disease was defined as polymerase chain reaction (PCR)-detected disease with symptoms but no evidence of hypoxia or pneumonia. Moderate disease was described as pneumonia with clinical signs but without signs of severe pneumonia or hypoxia ( $SpO_2 > 93\%$ ). The presence of signs and symptoms of severe pneumonia is a classification of severe disease. This is accompanied by one of three parameters: a respiratory rate greater than 30 breaths/minute, severe respiratory distress ( $PO_2/FiO_2 < 300$ ), and  $SpO_2 < 93\%$  in room air. Acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failure are hallmarks of critical illness.<sup>6</sup> Several recent studies have also made recommendations to identify simple hematologic and biochemical laboratory parameters that can help triage patients to better guide treatment. Several hematologic indicators that have been reported were neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphopenia.<sup>7,8</sup> All three are recognized as indicators of inflammatory response and help to assess the inflammatory response in patients with malignancies, cardiovascular disease<sup>9,10</sup>, diabetes<sup>11</sup>, chronic obstructive pulmonary disease (COPD)<sup>12</sup>, autoimmune diseases, hepatitis C virus infection<sup>10</sup>, and psychiatric disorders such as depression and bipolar disorder.<sup>13</sup> Studies of PLR as a marker of severity in COVID -19 cases have been conducted in a single center to date and show good

potential.<sup>14,15</sup> Chan and Rout concluded in their literature review that the benefit of PLR increased significantly in patients with severe disease compared with patients with milder symptoms, with 5 of 20 other studies finding the same.<sup>14</sup> Nonetheless, previous studies have generally compared the use of PLR with NLR or other markers, and the study conducted by Asghar et al. also did not show significance.<sup>16</sup> Simadibrata et al. stated that there were six studies on PLR in China, and their results were in the form that high PLR at admission was associated with the severity of COVID -19, and PLR research on the severity of COVID-19 disease is not widespread in Indonesia.<sup>17</sup> This study aims to investigate whether there is a difference between PLR and severity of COVID -19 disease. It is expected that this research will prove the utility of PLR in determining the severity of cases and can be used as an alternative biomarker investigation that is easier to obtain, more affordable, and comparable to other simple markers.

## MATERIALS & METHODS

This research is a retrospective study of medical records with a cross-sectional approach from September 2020 to February 2021 and was conducted at Adam Malik General Hospital Medan. All research procedures were reviewed and approved by the Ethics Committee with the ethical review number 0109/UN.5.2.1.1.1.12/PPL 2021.

Subjects of this study were adult patients aged  $> 18$  years who were diagnosed with confirmed COVID -19 based on the results of nasal and throat swabs, who were treated at H. Adam Malik General Hospital in Medan, and who had left the hospital under ideal conditions (cured and deceased). Patients with chronic obstructive pulmonary disease (COPD), blood disorders, other viral infections, and liver disease who underwent radiotherapy or chemotherapy were excluded because they could confound platelet count and blood group results. In addition, patients who did not have a

complete blood count were also excluded from the study.

The dependent variable in this study was the severity of COVID -19 according to the criteria recommended by WHO.<sup>2</sup> The independent variable in this study was the platelet-to-lymphocyte ratio (PLR), which was calculated by dividing the number of platelets by the lymphocytes obtained from the complete blood count of COVID -19 patients at the time of hospital admission.

SPSS Statistics 25 (IBM SPSS) was used for the statistical analysis of this study. The univariate analysis will determine the patient characteristics and the features of PLR in COVID -19 patients at Adam Malik General Hospital Medan. Bivariate analysis was used to see differences in PLR in the degree of COVID-19. Categorical variables are described as sum/total (%), and continuous variables are defined by the mean, median, and interquartile range (IQR). The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Standards for continuous variables were compared with the independent T test when the data were normally distributed. When the distribution was not normal, the Mann-Whitney U test was used. P <0.05 was considered statistically significant.

## RESULT

One hundred and fourteen patients with confirmed COVID -19 were included in the study (Table 1.). The mean age of the patients was 50.5±15.5 years. The proportion of female patients was 57%, which was higher than that of male patients (43%). In terms of clinical severity, non-severe had the highest proportion (57%), followed by severe (43%). Platelets below normal were found in 15 subjects (13.2%), followed by normal values in 93 subjects (81.6%) and platelets with above-normal values in 6 (5.2%). Low lymphocyte counts were found in 61 subjects (53.5%), normal lymphocytes in 50 subjects (43.9%), and more than three subjects (2.6%). The patient's mean platelet count was relatively

within normal limits ( $256.5 \pm 103.1 \times 10^3$  cells/ $\mu$ L), but the lymphocyte count was moderately decreased ( $1.52 \pm 0.84 \times 10^3$  cells/ $\mu$ L).

Table 1. Subject Characteristics

Characteristics	N=114
Age (year)	
Mean±St. Dev	50.5±15.5
Median (Min-Max)	53 (21-94)
Gender, n(%)	
Male	49 (43)
Female	65 (57)
Severity, n(%)	
Non-severe	65 (57.1)
Severe	49 (42.9)
Platelet Count, n(%)	
<150	15 (13.2)
150-450	93 (81.6)
>450	6 (5.2)
Mean±St. Dev (10 <sup>3</sup> cells/ $\mu$ L)	256.5±103.1
Lymphocyte Count (10 <sup>3</sup> cells/ $\mu$ L), n(%)	
<1,5	61 (53.5)
1,5-3,7	50 (43.9)
>3,7	3 (2.6)
Mean±St. Dev (10 <sup>3</sup> Cells/ $\mu$ L)	1.52±0.84
Platelet to Lymphocyte Ratio(10 <sup>3</sup> cells/ $\mu$ L)	
Mean±St. Dev	219.4±156.1
Median (Min-Max)	185.2 (17.6-1046.4)

Table 2 shows that in both degrees of disease severity, the platelet count is the highest, whereas in the non-severe, it is 53 individuals (81.5%). This compares to 40 subjects (81.6%) in the severe grade, and the average platelet count increased in patients with extreme grades compared to the non-severe grades. In the non-severe grade, the highest frequency was found in the average lymphocyte counts, 38 subjects (58.5%), while in the severe grade, lymphocytes below normal were found in most 37 subjects (75.5%). In contrast, in the extreme cases, the average number of lymphocytes is lower. The average number of PLRs is higher in the severe grades.

**Table 2. Platelet Count, Lymphocyte Count and PLR by Disease Severity**

Characteristics	Non-Severe (n=65)	Severe (n=49)
Platelet (10 <sup>3</sup> sel/μL), n(%)		
<150	9 (13.8)	6 (12.2)
150-450	53 (81.5)	40 (81.6)
>450	3 (4.5)	3 (6.1)
Mean±St. Dev (10 <sup>3</sup> cells/μL)	256.0±101.1	257.0±106.7
Limfosit (10 <sup>3</sup> sel/μL), n(%)		
<1,5	24 (36.9)	37 (75.5)
1,5-3,7	38 (58.5)	12 (24.5)
>3,7	3 (4.6)	0 (0)
Mean±St. Dev (10 <sup>3</sup> cells/μL)	1.84±0.82	1.10±0.66
Platelet to Lymphocyte Ratio (10 <sup>3</sup> cells/μL)	168.9±136.2	286.4±156.9

A comparative test of the platelet-to-lymphocyte ratio in each group is shown in Table 3. Based on the results of the analysis, a comparison of the mean and median PLR values in COVID -19 patients treated at Adam Malik Hospital in Medan showed significant differences between patients who had severe severity and those who did not (p value < 0.05).

**Table 3. Comparative Analysis of PLR in Severe and Non-Severe Patient**

Clinical Severity	Frequency	PLR		P
		Mean±St. Dev	Median	
Non-severe	65	168.9±136.2	141.2	0.000
Severe	49	286.4±156.9	245.1	

## DISCUSSION

Based on the study results, the characteristics of the confirmed COVID-19 patients had a mean age of 50.5 ± 15.5 years with the highest distribution at age 40-60 years (41.2%). This result is consistent with the age distribution of confirmed COVID -19 sufferers in Indonesia in the age range 31-59 years, which reaches 51.3% (COVID -19 Task Force). In addition, these age characteristics are also consistent with several single-center hospital studies in patients undergoing hospitalization, where the largest age distribution is in the range of 40-60 years.<sup>18-20</sup>

The characteristics of the patients in the study also showed that female patients dominated the population at 57% (n=62). These results are also consistent with the profile of COVID -19 sufferers in Indonesia, where the proportion of female

sufferers (51.1%) is higher than that of male sufferers (49.9%), although there is no significant difference (COVID 19 Task Force). A similar proportion was found among positively confirmed cases in South Korea, with female patients predominating at 56%.<sup>21</sup> The meta-analysis by Xie et al. (2020)<sup>20</sup> noted that this was consistent with the composition of study results, which found more female than male cases, although other studies in Korea and Iceland showed the opposite trend.<sup>22,23</sup> Other studies reporting differences in the distribution of the number of cases by sex were conducted in China and Italy, where the proportion of males is higher.<sup>24-26</sup> In various discussions of patient characteristics and epidemiology conducted in previous studies on the nature and pathophysiology of COVID -19, the characteristics of patients confirmed as positive varied widely depending on the habits and activity patterns in each country, province, and even specific communities. At the same time, the risk of death was consistently reported to be higher in male patients. A meta-analytic study on mortality risk stated that males had a 35% higher risk, which was related to the prevalence of smoking and drinking habits.<sup>20,27</sup> Uniformity is also more evident in the productive age group (30-65 years), confirming that different clusters are formed based on certain activity patterns, such as offices, social gatherings, and religious activities.<sup>28</sup> Based on the degree of clinical severity, non-severe is the spectrum of symptoms most experienced by COVID-19 patients (57%) in Adam Malik Hospital. Supported by the relatively young demographic characteristics of the majority, the proportion of mild to moderate severity is consistent with the characteristics of the age group in this study. A study conducted in South Korea on previous cases of 5628 patients also showed that the distribution of non-severe severity had the highest proportion of patients treated (85.4%).<sup>29</sup> A study conducted by Qu et al. (2020)<sup>30</sup> also showed that the number of non-severe cases

was higher (27 cases) than severe cases (3 cases). It is well known that the clinical severity of COVID -19 patients correlates significantly with increasing age, and deaths below 40 years of age are rare. This has been mentioned in several studies because of multifactorial causation that exacerbates symptoms with age, including multimorbidity, physical weakness, and decreased immune system function.<sup>18,31</sup>

In this study, both severity levels of COVID -19 were found to have normal platelet levels. This contrasts with Wool and Miller (2020)<sup>32</sup>, where platelet levels are lower in severe severity than in non-severe severity. Severely ill patients with sustained immune and coagulation activation can maintain their platelet count. This is demonstrated by a significant compensated platelet production response. In this study, lymphopenia in severe COVID -19 was found to be 75.5%. This was also noted in the study by Zhao et al. (2020)<sup>33</sup>, in which a significant decrease in lymphocytes was noted in severe grades of COVID -19 compared to non-severe grades.

The results of the comparison test in this study using the Mann Whitney test in two different clinical severity grades showed a p-value < 0.05. These results suggest that there is a significant difference in PLR values in severe and non-severe grades in COVID -19. These results are supported by a study by Huang et al. (2020)<sup>24</sup>, in which there are significant differences in PLR in severe and non-severe COVID -19. Research by Zhang et al. (2020)<sup>34</sup> also showed that there was a significant difference in PLR value for the severity of COVID -19. As an indicator of inflammation, PLR is primarily caused by megakaryocytes in the bone marrow recruiting neutrophils and other inflammatory cells to the site of injury. It appears in an inactive form and becomes active at the site of vascular injury and is rapidly activated in response to proinflammatory cytokines or infectious factors.

In a meta-analysis conducted by Simadibrata et al (2020)<sup>17</sup>, high PLR levels were found to be associated with severe COVID -19. The high PLR value at first arrival was also found in severe COVID -19, indicating a higher degree of cytokine storm. These findings may be useful in providing specialized care in severe cases of COVID -19 that require prolonged treatment.

Although PLR has been shown to be generally increased on admission in patients with severe and non-severe COVID -19 symptoms, Qu et al (2020) reported a decrease in PLR on admission in severe compared with non-severe COVID-19, although this was not statistically significant. Only three cases of severe COVID-19 were included in the analysis compared with 27 non-severe cases, which may lead to conflicting results. In addition, follow-up analysis of PLR in this study showed increased scores in cases of severe COVID-19 after hospitalization.<sup>30</sup>

Platelet-to-lymphocyte ratio (PLR) is also suggested as a good candidate to determine the severity and mortality of COVID-19. First, PLR is a well-established marker of inflammation. Inflammation plays an important role in the pathophysiology of COVID -19, with cytokine storms being the hallmark of severe disease and poorer prognosis. Thus, elevated PLR levels indicate an overactive inflammatory response and consequently a worse prognosis. Second, PLR is sensitive to innate and acquired immune responses. Third, PLR is an inexpensive and readily available measurement that can be used in institutions that are limited in measuring other inflammatory biomarkers.<sup>8,30</sup>

Although the results of the comparative test showed a significant difference in PLR values based on clinical disease severity, the investigators acknowledged several weaknesses of this study. First, due to the nature of cross-sectional studies, it is certainly difficult to analyze PLR values serially, so the observation of markers, both increases and decreases, cannot be

determined independently, considering that there are so many factors that can influence inflammatory markers, including response to treatment, type of medication, and other treatments. Second, this study was conducted in only one center, which may not represent the full spectrum of clinical severity or a broader demographic spectrum. Third, this study did not take into account the presence or absence of comorbidities in patients, which could introduce bias.

## CONCLUSION

Patients confirmed to have COVID -19 at Adam Malik hospital have a mean age of  $50.5 \pm 15.5$  years and are dominated by female patients (57%). The platelet-to-lymphocyte ratio in patients with confirmed COVID-19 showed an increased mean in severe clinical severity compared to non-severe and there were significant differences in PLR in severe and non-severe COVID -19 ( $p < 0.05$ ). Follow-up studies with serial PLR examinations in COVID -19 cases are needed to observe biases due to different pharmacological interventions in each case. There is a follow-up study evaluating the association between PLR and severity of COVID-19. It is recommended that a multicenter study can draw conclusions that are more general and apply to most cases of COVID-19 in Indonesia.

## Declaration by Authors

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