International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Platelet / Lymphocyte Ratio (PLR) in Severity of COVID-19 Patients at H. Adam Malik Hospital, Medan

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Abstract: ***Introduction: COVID-19 patients have broad-spectrum symptoms from asymptomatic to septic shock, multiorgan failure, and death. Fully monitoring its severity is very crucial to prevent higher mortality. The Platelet/Lymphocyte Ratio (PLR) reflects the connection between aggregation and inflammatory pathways that can be used as a predictive parameter of disease progression. This study was to analyze the difference of PLR levels of COVID-19 patients to obtain an easy and inexpensive biomarker in predicting its progression. Methods: It is a case-control design on RT-PCR confirmed COVID-19 adult patients who were treated at Haji Adam Malik Hospital. All samples were grouped into three classifications of severity (mild-moderate, severe, and critical). Subsequently, blood samples were taken to analyze the PLR levels of each patient. Results: From 54 patients, 18 patients in each group, an amount 59.3% was male and mean PLR of mild to moderate group was 154.11, severe group 326.38, and critical group 354.03. The ANOVA test found there was a significant difference between PLR levels of mild-moderate to severe and critical group (p-value = 0.004 and 0.001 respectively). Conclusion: PLR levels can be used as an easy and inexpensive parameter in predicting the severity of COVID-19.***

Keywords: COVID-19, Severity, PLR

1. Introduction

The clinical manifestations of patients with COVID-19 have a broad spectrum ranging from asymptomatic to septic shock, multiorgan failure, and death. The most common cause of death from COVID-19 is ARDS due to respiratory failure, sepsis, and cardiovascular complications.[1,2]Evidence suggests that the inflammatory response plays an important role in the course of the COVID-19 disease. The inflammatory response triggered by the rapid replication of the SARS-CoV-2 virus and the occurrence of cellular damage can lead to the recruitment of macrophages and monocytes, thereby inducing the release of cytokines and chemokines causing a cytokine storm. Several studies reported that among the many inflammatory markers, some inflammatory markers are easy to perform, inexpensive, and have been known to have a correlation to inflammation and prognosis in several conditions, such as Platelet/Lymphocyte Ratio (PLR) which indirectly describes the inflammatory status in the patient's body.[3–5]

Zhang, et al (2020) reported that platelets and lymphocytes decrease in COVID-19 patients when compared to healthy controls. Rong, et al (2020) also found a significantly higher Platelet/Lymphocyte Ratio level in severe cases compared to non-severe.[6,7]Regarding the infection with the SARS-CoV-2 virus, the Platelet/Lymphocyte Ratio level has a better predictive value on disease progression because it reflects the relationship between both aggregation and inflammatory pathways.[8,9]

2. Methods

Population and Research Design
This study is an analytic study with a case-control design conducted at the Department of Clinical Pathology, Faculty of Medicine, University of North Sumatra / Haji Adam Malik Hospital, Medan in collaboration with the Pediatrics Department, Infectious and Tropical Medicine Subdivision. The study began in January 2021 until March 2021. There were 54 samples that were classified into 3 categories of disease severity, included mild-moderate, severe, and critical.

The inclusion criteria in this study were confirmed positive for COVID-19 through RT-PCR examination patients,≥18 years old, who were hospitalized at H. Adam Malik Hospital Medan and were willing to participate in the study. The patients with previous malignancy/hematologic abnormalities (Leukemia, ITP), as well as patients who did not have complete blood count data at the time of admission, were excluded. Furthermore, complete blood collection of all subjects was carried out using the automatic cell counter analyzer Sysmex XN-1000 with the flow cytometry method and the number of the Platelet/ Lymphocyte Ratio was calculated.

Statistical analysis
Categorical variables will be presented descriptively by the distribution of frequency (n) and percentage (%). Numerical variables are presented with mean values and standard

deviations for data in a normal distribution, while data with abnormal distributions are presented in median and minimum-maximum values. Comparative analysis between the two groups used the ANOVA test. If the data is not normally distributed then the Kruskal Wallis test is used. Variables with a p-value <0.05 were considered statistically significant.

3. Results

This study was followed by 54 confirmed COVID-19 patients with mild-moderate, severe, and critical degrees who were treated at H. Adam Malik Hospital Medan and had met the inclusion criteria. 32 patients were male (59.3%) and 22 patients were female (40.7%). Other findings of the subjects of this study are presented in Table 1.

Table 1: Baseline Characteristics

Variables	*n=54 (%)*
Sex	
Man	32 (59.3)
Woman	22 (40.7)
Age (mean; years old)	
Mild-moderate	37,00±14,05
Severe	52,66±14,05
Critically	56,44±15,13

Statistical analysis showed the average value of the Platelet/Lymphocyte Ratio based on the severity of disease in COVID-19 patients (Table 2). The ANOVA test showed that there was a significant difference in the mean value of the Platelet/Lymphocyte Ratio between the three groups of COVID-19 disease. There was also a significant difference in the mean value of the Platelet/Lymphocyte Ratio between the mild-moderate group and the severe and critical grade group (p = 0.004 and 0.001, respectively). Meanwhile, there was no significant difference between the severe group and critical group.

Table 2: Analysis of Platelet/Lymphocyte Ratio Values Based on Severity of Disease

Variables	*PLR (x±sd)*	*P value*
Severity		
Mild-moderate	154,11±51,64	0.002
Severe	326,38±169,27	
Critically	354,03±234,41	
Mean differences of NLR		
Mild-moderate vs Severe		0.004
Mild-moderate vs Critically		0.001
Severe vs Critically		0.672

4. Discussion

Research by Yang et al showed the proportion of the subjects were dominated by males (56%) than females (37%) with a median age of 46 years. This male-dominated COVID-19 is influenced by several factors including genetic factors, immune system, and lifestyle.[10]The study of Zhao Y et al concluded that Asian ethnicities have a much higher ratio of ACE2 receptor expression than whites and African-Americans, where ACE2 expression in the lungs of men is much higher than women.[11]Elgendy et al stated that the hormone Estrogen and the X chromosome possessed by women had a blocking effect on viral infections. In addition, decreased expression of the CD200R receptor in men compared to women is known to correlate with a decrease in the body's ability to fight viral infections.[10]

In COVID-19, the balance between the inflammatory and anti-inflammatory responses is disturbed. Compensation for proinflammatory conditions often occurs excessively, resulting in suppression of the immune system (immunosuppression). This underlies the occurrence of impaired lymphocyte function, a decrease in the number of lymphocytes in circulation and tissues in COVID-19 patients. Excessive pro-inflammatory reactions will result in tissue damage, while excessive anti-inflammatory reactions will cause immunosuppression. An imbalance of these two reactions plays a role in the occurrence of cytokine storm and organ failure.[12]

In this study, Gong et al also got the same results where the severe group had a higher mean Platelet/Lymphocyte Ratio (174.8) than the non-severe (131.0).[13]Platelet/Lymphocyte ratio (PLR) has been used in various diseases, such as cardiovascular disease and autoimmune disease, as a predictor of inflammation and death. It has a better predictive value on disease progression when compared to using only the number of lymphocytes and platelets. It reflects the relationship between both the aggregation and inflammatory pathways.[14]In conclusion, PLR shows potential as a marker of inflammation as well as to determine the prognosis of COVID-19 patients.[15]

The reasons for using the Platelet/Lymphocyte Ratio can be used as an excellent candidate marker for determining the severity and mortality of COVID-19 include: (1) It is a good marker for inflammation; (2) It is sensitive to both natural and acquired immune responses; and (3) It is inexpensive and readily available examinations that can be used in places where resources are limited.[15]In our study, it was found that the critical group had a significantly higher mean level of PLR (354.0 /µl) than the mild-moderate (154.1 /µl) group and the severe group (326.3 / l). l) (p-value <0.05). The increase reflects higher levels of inflammation and cytokine storms. Significant differences were also found between the mild-moderate group to the severe and critical groups (p-value 0.004 and 0.001, respectively). This is in line with the research conducted by Sun et al which showed there was a significant difference in the Platelet/Lymphocyte Ratio in the severe category compared to the mild/moderate category.[16]

5. Limitations

All research subjects came from only one hospital which could allowed bias. Second, the measurement of platelets levels, lymphocytes levels, and Platelet/Lymphocyte Ratio is only done once, namely at the time of admission. Although some conditions were adjusted to the exclusion criteria that might affect the values of platelets and lymphocytes, they could not completely eliminate confounding variables that might affect the levels of the parameters in this study. Lastly, this study is limited to Indonesian ethnicity, where ethnicity and race factors may affect platelets and lymphocytes levels, therefore the results obtained in this study may not apply to the black population.

6. Conclusions

There is a significant difference in the mean levels of the Platelet/Lymphocyte Ratio between the mild-moderate group and the severe and critical group ($p<0.05$), so the Platelet/Lymphocyte Ratio can be used as an easy and inexpensive indicator parameter in predicting the severity of COVID-19.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

References

[1] Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis [Internet]. 2020 Jul;96:467–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1201971220303623

[2] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med [Internet]. 2020 Jul 1;180(7):934. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184

[3] Cascella M, Rajnik M, Cuomo A, Dulebohn S, Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Internet]. StatPearls Publishing. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

[4] Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, et al. Coronavirus Disease 2019–COVID-19. Clin Microbiol Rev [Internet]. 2020 Sep 16;33(4). Available from: https://journals.asm.org/doi/10.1128/CMR.00028-20

[5] Azhar EI, Hui DSC, Memish ZA, Drosten C, Zumla A. The Middle East Respiratory Syndrome (MERS). Infect Dis Clin North Am [Internet]. 2019 Dec;33(4):891–905. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0891552019300601

[6] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med [Internet]. 2020 Apr 3;46(4):586–90. Available from: http://link.springer.com/10.1007/s00134-020-05985-9

[7] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun [Internet]. 2020 May;109:102433. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0896841120300469

[8] Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol [Internet]. 2020 Jun 17;20(6):355–62. Available from: http://www.nature.com/articles/s41577-020-0331-4

[9] Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pão CRR, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood [Internet]. 2020 Sep 10;136(11):1330–41. Available from: https://ashpublications.org/blood/article/136/11/1330/461421/Platelet-activation-and-plateletmonocyte-aggregate

[10] Bwire GM. Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? SN Compr Clin Med [Internet]. 2020 Jul 4;2(7):874–6. Available from: https://link.springer.com/10.1007/s42399-020-00341-w

[11] Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-Cell RNA Expression Profiling of ACE2, the Receptor of SARS-CoV-2. Am J Respir Crit Care Med [Internet]. 2020 Sep 1;202(5):756–9. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202001-0179LE

[12] Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int [Internet]. 2020 Sep 3;44(9):1792–7. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cbin.11403

[13] Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis [Internet]. 2020 Jul 28;71(15):833–40. Available from: https://academic.oup.com/cid/article/71/15/833/5820684

[14] Qu R, Ling Y, Zhang Y, Wei L, Chen X, Li X, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol [Internet]. 2020 Sep 26;92(9):1533–41. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jmv.25767

[15] Simadibrata DM, Pandhita BAW, Ananta ME, Tango T. Platelet-to-lymphocyte ratio, a novel biomarker to predict the severity of COVID-19 patients: A systematic review and meta-analysis. J Intensive Care Soc [Internet]. 2020 Nov 2;175114372096958. Available from: http://journals.sagepub.com/doi/10.1177/1751143720969587

[16] Sun S, Cai X, Wang H, He G, Lin Y, Lu B, et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta [Internet]. 2020 Aug;507:174–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0009898120301790