ORIGINAL ARTICLE

Platelet to Lymphocyte Ratio is an Accurate Biomarker for Predicting Case Severity in Covid-19

Ngakan Ketut Wira Suastika[1], Ketut Suega[2]

[1] Department of Internal Medicine, Faculty of Medicine, Udayana University/Udayana University Hospital, Bali, Indonesia
[2] Department of Internal Medicine, Faculty of Medicine, Udayana University/Sanglah General Hospital, Bali, Indonesia

ABSTRACT

Introduction: Identifying cases that can develop to be severe at an early stage and providing appropriate therapy to patients can reduce the mortality rate in coronavirus disease 2019 (Covid-19). This study aims to determine the diagnostic value of the platelet to lymphocyte ratio (PLR) to predict case severity in Covid-19. **Method:** This is a prospective study. Participants of the study are patients who had been confirmed with Covid-19 based on real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) who received treatment in the hospital from April to October 2020. The sample in this study was obtained by consecutive sampling technique. A total of 507 participants were included in this study. The receiver operating characteristic curve (ROC) method is used to obtain the area under the curve (AUC), cut off value, sensitivity, and specificity of the PLR to predict case severity. **Results:** PLR is significantly higher in severe cases compared to mild-moderate cases ($p < 0.001$). The cut off value of PLR to predict severe cases of Covid-19 is more than 150 with a sensitivity of 80.5%, a specificity of 66.3%, and an area under the curve (AUC) of 0.807 ($p < 0.001$, 95% confidence interval (CI) 0.759 - 0.855). In binary logistic regression analysis, PLR was independently associated with case severity with the adjusted odds ratio (OR) of 7.73 ($p < 0.001$, 95% CI 3.75 - 15.93). **Conclusions:** PLR can be used as a simple and accurate biomarker to predict the case severity in Covid-19.

Keywords: Biomarker, Covid-19, Lymphocytes, Platelets

Corresponding Author:
Ngakan Ketut Wira Suastika, MD
Email: wira.suastika@unud.ac.id
Tel: +623618953670

INTRODUCTION

Coronavirus disease 2019 (Covid-19) has spread to 223 countries. Data from the World Health Organization (WHO) until the end of February 2021, there are more than 113 million confirmed cases and more than 2.5 millions of deaths due to Covid-19 (1). Case Fatality Rate (CFR) was found significantly higher occurred in European countries (2). Until now, there is no specific therapy that has been proven to be effective in the management of Covid-19 (3). The symptoms of Covid-19 is vary widely from asymptomatic, mild symptoms, and can progress quickly to severe cases accompanied by acute respiratory distress syndrome (ARDS) and lead to death (4–6). Therefore, we need a biomarker that can predict the case severity at an early stage, so that proper management can be given and can reduce the mortality rate. Several biomarkers such as interleukin 6 (IL-6), C-reactive protein (CRP), and D-dimers were found to be associated with a poor prognosis in Covid-19 (7–9). However, these laboratory tests are expensive and are not widely available in health care facilities.

Inflammation plays an important role in the pathophysiology of Covid-19 (10). Platelets play a role in hemostasis and also in the response to inflammation and infection (11). Platelets are also potential hematologic biomarkers and have been associated with disease severity in Covid-19 (12). Lymphopenia is also the most common hematological disorder in Covid-19, especially in severe cases (10). The platelet to lymphocyte ratio (PLR) has been found to have diagnostic value in several diseases such as community acquired pneumonia and epilepsy (13,14). Platelet and lymphocyte counts can be obtained from a complete blood count (CBC), which is a routine laboratory examination performed on Covid-19 patients in all health care facilities.

Therefore, we conducted a study that aims to find an association between the PLR with disease severity and determine the diagnostic value of PLR in Covid-19.

MATERIALS AND METHODS

Study design, population, samples, and sampling

This study is an observational study with a prospective design. Patients were followed during treatment and clinical outcomes (severe or mild-moderate cases) were recorded. The study population was patients with a confirmed Covid-19 who underwent treatment at the

Udayana University Hospital, Bali, Indonesia, from April to October 2020. Patients were confirmed with Covid-19 through a real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) examination through a nasopharyngeal swab. The sample in this study was obtained by consecutive sampling technique. Patients over 18 years old were included in this study, while patients with pregnancy and hematological disorders were excluded in this study. A total of 507 patients were included in this study. The independent variable in this study is the PLR, which is calculated from the number of platelets divided by the number of absolute lymphocytes on a complete blood count. The dependent variable in this study is case severity which is a dichotomous variable, severe cases and mild-moderate cases. Severe case definitions include fever or symptoms of respiratory tract infection, plus one of: respiration rate greater than 30 breaths per minute, severe respiratory distress, or oxygen saturation ≤ 90% in room air (15). In mild-moderate cases, none of these criteria was found.

Instruments and procedure

Clinical, epidemiological and laboratory data were obtained from patient medical records. The rRT-PCR laboratory examination used the Roche Diagnostics Cobas 6800 SARS-CoV-2 test, and the complete blood count was examined using a Sysmex XN-series automated hematology analyzer.

Clinical, epidemiological data, and blood samples for laboratory examination were collected when the patient was admitted to the hospital and recorded in the medical record. This study has been approved by the Committee of Ethics of the Faculty of Medicine, Udayana University (approval number 1010/UN1422.VII.14/ LT/ 2020)

Data analysis

Categorical variables are presented as percentages, while continuous variables are presented as median and interquartile range. Mann Whitney test was used to determine the differences in continuous variables, while the Chi-square test was used for categorical variables. The receiver operating characteristic curve (ROC) analysis is used to obtain the area under the curve (AUC), cut off value, sensitivity, and specificity of the PLR to predict case severity. PLR and age variables were transformed into dichotomous variables based on the cut off value obtained through the ROC analysis. To determine the association between PLR, age, and comorbidity with case severity, we used binary logistic regression analysis. All analyzes used SPSS 25.0 software. The results obtained are statistically significant if $p < 0.05$.

RESULTS

Clinical, epidemiological, and hematological characteristics

A total of 133 (26.23%) patients met the criteria for severe cases, while 377 (73.77%) patients met the criteria for mild-moderate cases. The PLR value is significantly higher in severe cases compared to mild-moderate cases ($p < 0.001$) (Table I).

Diagnostic value of PLR and age

The cut off value of PLR obtained through ROC analysis was more than 150 with a sensitivity of 80.5%, a specificity of 66.3%, and an AUC of 0.807 ($p < 0.001$) (Figure 1 and Table II).

Association between PLR and case severity in Covid-19

Age and comorbid variables are transformed into dichotomous variables, under or equal to 45 years and over 45 years old, and the presence or absence of comorbid. By including age and comorbid variables to the binary logistic regression analysis, we found that PLR independently had a significant association with case severity in Covid-19. PLR has an adjusted OR of 7.73 (95% CI 3.75 – 15.93), p < 0001 (Table III).

Table I: Clinical, epidemiological, and hematological characteristics

Variable	Median (Interquartile range)			
	All patients (n = 507)	Mild – Moderate (n = 374)	Severe (n = 133)	p value
Age, years	43 (18 – 84)	35 (18 – 75)	54 (19 – 84)	0.001
Sex				
Male (%)	309 (60.95)	224 (59.90)	85 (63.91)	0.476
Female (%)	198 (39.05)	150 (40.10)	48 (36.09)	
Comorbid				
Yes (%)	108 (21.30)	33 (8.82)	75 (56.39)	< 0.001
No (%)	399 (78.70)	341 (91.18)	58 (43.61)	
Hemoglobin, gr/dl	14.0 (7.9 – 17.4)	14.1 (8.9 – 17.1)	13.6 (7.9 – 17.4)	0.001
Leukocyte, x10^3 µL	6.77 (2.36 – 17.25)	6.65 (2.55 – 13.82)	7.14 (2.36 – 17.25)	0.018
Neutrophil, x10^3 µL	4.05 (0.99 – 15.50)	3.80 (1.29 – 12.72)	5.26 (0.99 – 15.50)	< 0.001
Lymphocyte, x10^3 µL	1.61 (0.31 – 5.92)	1.83 (0.46 – 5.92)	1.06 (0.31 – 5.70)	< 0.001
Monocyte, x10^3 µL	0.57 (0.05 – 1.66)	0.57 (0.11 – 1.66)	0.59 (0.05 – 1.64)	0.513
Platelet, x10^3 µL	238 (54 – 672)	235 (84 – 590)	243 (54 – 672)	0.024
PLR	140.79 (22.9 – 1032.26)	124.20 (39.18 – 404.30)	237.80 (22.90 – 1032.36)	< 0.001

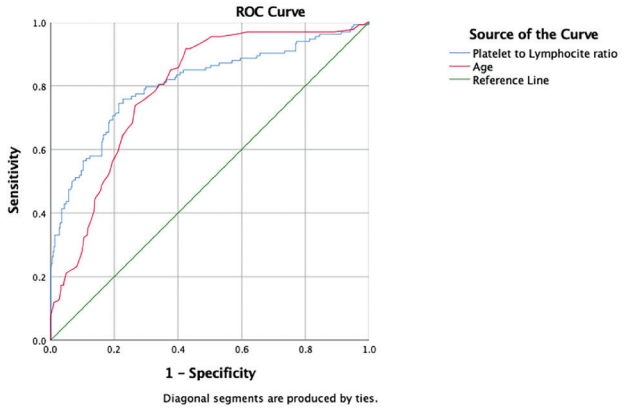

Figure 1: The ROC analysis of the PLR and age for predicting case severity in Covid-19

Table II: The cut off value, sensitivity, specificity, and AUC of PLR and age

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	95% CI	p value
PLR	> 150	80.5%	66.3%	0.807	0.759 – 0.855	< 0.001
Age, years	> 45	80.5%	65.8%	0.790	0.748 – 0.832	< 0.001

Table III: The OR and Adjusted OR of PLR, age, and comorbid

Variable	OR (95% CI)	p	Adjusted OR (95% CI)	P value
PLR	7.46 (4.62 – 12.03)	< 0.001	7.73 (3.75 – 15.93)	< 0.001
Age	7.91 (4.90 – 12.77)	< 0,001	3.27 (1.69 – 6.31)	< 0.001
Comorbid	19.59 (10.96 – 34.99)	< 0.001	9.84 (5.14 – 18.87)	< 0.001

DISCUSSION

We found that PLR was significantly higher in severe cases compared to mild-moderate cases. We also found the PLR adjusted odds ratio of 7.73, which means that patients with a PLR of more than 150 have a tendency to become severe cases by 7.73 times compared to PLR of less than or equal to 150. These results are consistent with several studies that have shown a significant increase in platelet counts in Covid-19 (16,17). Other studies have also shown that the median or mean platelet count at admission is significantly higher in non-survivors compared to survivors (18). The increase of platelet count can be caused by cytokine storms, some cytokines such as interleukin-6 (IL-6), thrombopoietin (TPO) and stem cell factors can stimulate an increase of the number of megakaryocytes (19). Interleukin-6 can also stimulate thrombopoiesis by increasing thrombopoietin production (20). Another mechanism, injury to the vascular endothelium causes the release of von Willebrand Factor (vWF) which can interact with megakaryocytes that cause increased of platelet production (21). The increased of thrombopoietin level in inflammation can also stimulate megakaryocytes in the lungs to produce platelets (22).

Same with the acute phase reactants such as D-dimer, C-reactive protein (CRP), ferritin and fibrinogen, PLR is also found to be increased in severe Covid-19 cases (23–25). The increase of inflammatory markers suggests that inflammation plays a vital role in the pathophysiology of Covid-19. However, several studies have found that thrombocytopenia occurs more frequently in severe Covid-19 cases compared to non-severe cases (16,26). Another study also found that the occurrence of thrombocytopenia on admission to the hospital was an independent risk factor for mortality in Covid-19 patients (27). A decrease or increase in platelet counts can occur in Covid-19, thrombocytopenia indicates that there is an increase in platelet consumption due to the formation of a thrombus or the occurrence of disseminated intravascular coagulation (DIC), whereas an increase of platelet counts indicates a cytokine storm phase (28). Because of the important role of platelets in hemostasis and inflammation, serial monitoring of platelet counts is necessary to monitor and predict the clinical outcome (17).

We found that the cut off value of PLR more than 150 has a sensitivity of more than 80%. Biomarker with high sensitivity are needed for screening patients who are at risk of developing severe cases. The AUC of PLR of more than 0.800 also means that the biomarker is accurate for predicting case severity in Covid-19 (29). PLR as a biomarker has several advantages over other inflammatory biomarkers, including it is cheap, simple, provides fast results, and is widely available in all health care facilities.

This study has several limitations. First, PLR data were collected only when the patient was admitted to the hospital, not collecting data on dynamic changes during treatment. Second, this study is a single centre.

CONCLUSION

PLR can be used as a simple and accurate biomarker to predict case severity in Covid-19. Multicentre studies are needed to confirm these finding. Future studies are also needed to determine the association of cytokine storms in Covid-19 with changes in platelet counts.

REFERENCES

1. World Health Organization. WHO Coronavirus Disease 2019 (COVID-19) Dashboard [Internet]. 2021 [updated 2021 February 28; cited 2021 February 28]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Bhattacharya S, Basu P, Poddar S. Changing epidemiology of SARS-CoV in the context of COVID-19 pandemic. J Prev Med Hyg. 2020; 61(2):E130–6.

3. Baden LR, Rubin EJ. Covid-19 - The Search for Effective Therapy. N Engl J Med. 2020; 382(19):1851-2.
4. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect. 2020; 80(6):656-65.
5. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ. 2020; 368:m1091.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; 323(11):1061-9.
7. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020; 71(15):762-8.
8. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J Intensive Care. 2020; 8(1):1–11.
9. Zhao C, Wei Y, Chen D, Jin J, Chen H. Prognostic value of an inflammatory biomarker-based clinical algorithm in septic patients in the emergency department: An observational study. Int Immunopharmacol. 2020; 80:106145.
10. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. Clinical Chemistry and Laboratory Medicine. 2020; 58(7):1021-8.
11. Jenne CN, Kubes P. Platelets in inflammation and infection. Platelets. 2015; 26(4):286-92.
12. Salamanna F, Maglio M, Landini MP, Fini M. Platelet functions and activities as potential hematologic parameters related to Coronavirus Disease 2019 (Covid-19). Platelets. 2020; 31(5):627–32.
13. Huang Y, Liu A, Liang L, Jiang J, Luo H, Deng W, et al. Diagnostic value of blood parameters for community-acquired pneumonia. Int Immunopharmacol. 2018; 64:10-5.
14. Güneş M, Büyükgul H. Relationship between generalized epileptic seizure and neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and neutrophil mediated inflammation. Int J Neurosci. 2020; 130(11):1095-100.
15. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. World Health Organization. 2020.
16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497-506.
17. Thachil J. What do monitoring platelet counts in COVID-19 teach us? Journal of Thrombosis and Haemostasis. 2020; 18(8): 2071-2.
18. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5):475-81.
19. Behrens K, Alexander WS. Cytokine control of megakaryopoiesis. Growth Factors. 2018; 36(3):89-103.
20. Senchenkova EY, Komoto S, Russell J, Almeida-Paula LD, Yan LS, Zhang S, et al. Interleukin-6 mediates the platelet abnormalities and thrombogenesis associated with experimental colitis. Am J Pathol. 2013; 183(1):173–81.
21. Poirault-Chassac S, Nguyen KA, Pietrzyk A, Casari C, Veyradier A, Denis C V., et al. Terminal platelet production is regulated by Von Willebrand factor. PLoS One. 2013; 8(5):e63810.
22. Lefrançais E, Ortiz-Mucoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, et al. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature. 2017; 544(7648):105-9.
23. Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. Thrombosis and Haemostasis. 2020; 120(5):876.
24. Favaloro EJ, Lippi G. Recommendations for Minimal Laboratory Testing Panels in Patients with COVID-19: Potential for Prognostic Monitoring. Seminars in Thrombosis and Hemostasis. 2020; 46(3):379-82.
25. Qu R, Ling Y, Zhang Y hui zhi, Wei L ya, Chen X, Li X mian, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020; 92(9):1533-41.
26. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18):1708-20.
27. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, et al. Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. Platelets. 2020; 31(4):490-6.
28. Amgalan A, Othman M. Hemostatic laboratory derangements in COVID-19 with a focus on platelet count. Platelets. 2020; 31(6):740-5.
29. Hajian-Tilaki K. Receiver operating characteristic (ROC) curve analysis for medical diagnostic test evaluation. Casp J Intern Med. 2013; 4(2):627–35.