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Short Communication

Relationship between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with the severity of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease that spreads rapidly causing a high case fatality rate in vulnerable populations. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are known to be inflammatory biomarkers in certain infections. The aim of this study was to determine the relationship between NLR and PLR with the severity of COVID-19. A cross-sectional study was conducted at Tabanan Regency General Hospital, Bali, Indonesia, from January 2021 to December 2022. All patients included in the study tested positive for COVID-19 by real-time polymerase chain reaction (RT-PCR), aged 18–50 years with no comorbid. Laboratory examinations were carried out on admission. The patients were categorized into two groups based on the severity: moderate and severe/critical. The Mann-Whitney test was used to determine the association between NLR and PLR with the severity of COVID-19. A total of 104 patients were included in the study, the majority of COVID-19 patients had moderate (77.9%) severity. The average NLR was 5.8 and the PLR was 21.7. There was a significant relationship between NLR (p=0.002) and PLR (p=0.001) with the severity of COVID-19. The defined cut-off values of NLR and PLR were ≥3.8 and ≥106, yielding sensitivities of 95% and 70%, and specificities of 74% and 50%, respectively. This study highlights the promising role of NLR and PLR as predictive biomarkers to assess COVID-19 severity.

Keywords: COVID-19, NLR, PLR, COVID-19 severity, Bali

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. More than 511 million cases of COVID-19 have been confirmed based on the World Health Organization (WHO) data as of May 3, 2022. Over 6 million cases were reported in Indonesia by the Ministry of Health on the same date, with Bali reaching up to 157.166 cases [1,3,4] COVID-19 is diagnosed by several methods, such as detecting nucleic acids using the real-time polymerase chain reaction (RT-PCR), conducting radiological assessment with computerized tomography (CT), and carrying out laboratory examinations that support clinical diagnosis [5]. COVID-19 varies in severity, of which some patients experience severe and potentially life-threatening respiratory symptoms while some may present without signs or symptoms. Depending on the severity of the disease, COVID-19 could manifest in four types: mild, moderate, severe, and critical.

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are known inflammatory biomarkers that can be measured in a patient blood sample. NLR is an indicator of a systemic inflammatory response that can determine the prognosis of infection [6]. An elevated

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NLR may reflect an increased inflammatory process and is associated with a poor prognosis of COVID-19 [6,7]. In other cases of viral and bacterial pneumonia, NLR has a higher sensitivity than individual neutrophil and lymphocyte values [6].

PLR is an indicator of inflammation, caused by megakaryocytes in the bone marrow of hematopoietic tissue. Its primary function in inflammation is to transport neutrophils and other inflammatory cells to the site of injury [8]. This biomarker is closely related to mortality and disease severity in pneumonia [6]. A study revealed that elevated PLR levels correlated with prolonged hospital stays, suggesting that PLR could serve as an indicator of disease progression and prognosis in COVID-19 patients [8]. Both NLR and PLR are expressed as prognostic markers of heart disease, tumors, sepsis, acute respiratory distress syndrome (ARDS), and pneumonia [6], and even predictors in COVID-19 [9-11]. Therefore, the aim of this study was to determine the relationship between NLR and PLR with the severity of COVID-19.

Methods

Study design and patients

A cross-sectional study was conducted at Tabanan Regency General Hospital, Bali, Indonesia, between January 2021 and December 2020. All patients included in the study were tested positive for COVID-19 by RT-PCR, aged 18–50 years old, and hospitalized at the Tabanan Regency General Hospital. Patients with comorbidities, including diabetes mellitus, hypertension, cardiovascular disease and chronic obstructive pulmonary disease, were excluded from the study. The sampling method employed consecutive sampling from all COVID-19 patients during the study period that met the inclusion and exclusion criteria. A minimum sample size of 97 was achieved based on the calculation using the Lemeshow formula [12].

Study variables and data collections

Characteristics data (age and gender), length of stay in the hospital, clinical manifestation, COVID-19 severity, and laboratory examination test (hemoglobin, hematocrit, leukocytes, erythrocytes, neutrophils, lymphocytes, and platelets) of all patients were collected. COVID-19 severity was defined by its clinical manifestations and the presence of respiratory distress and hypoxemia. The COVID-19 severity was classified based on the Indonesian Society of Internal Medicine.

Moderate COVID-19 severity were cases without signs of respiratory distress and hypoxemia. A severe COVID-19 case was defined by fever with one of the following signs: (1) arterial partial pressure of O_2 (PaO_2)/oxygen concentration (FiO_2) ≤300mmHg; (2) oxygen saturation ≤93% at resting state; and (3) respiratory distress with respiration rate >30 times per minute. A COVID-19 patient with critical severity would experience respiratory failure and the need for ventilator use, along with multiple organ failures that require intensive care [13]. The laboratory examination test was carried out during admission time [14]. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and PLR was measured by dividing the platelet count by the absolute lymphocyte count.

Statistical analysis

The Kolmogorov-Smirnov normality test was conducted to assess the data distribution. To compare the NLP and PLR between the severity of COVID-19 groups, the Mann-Whitney test was employed since the data was not normally distributed. A value of $p<0.05$ was considered statistically significant. A receiver operating characteristic (ROC) curve was generated by plotting the sensitivity and specificity of NLR and PLR to measure the accuracy of the biomarkers to predict the severity of COVID-19. All data was analyzed using SPSS version 25 (IBM SPSS, New York, USA).

Results

Characteristics of the patients

A total of 104 patients were included in the study, as presented in **Table 1**. Most of the COVID-19 patients were women (70.2%) and the most frequent symptom reported was coughing (83.7%),

followed by fever (77.9%) and shortness of breath (54.8%). The average values of NLR and PLR were 5.8±8.5 and 21.7±33.8, respectively. A majority of COVID-19 patients were reported to have moderate severity (77.9%).

Table 1. COVID-19 patients' characteristics included in the study (n=104)

Characteristics	Frequency (%)
Sex	
Female	73 (70.2)
Male	31 (29.8)
Age, median (min-max), year	31.5 (18–50)
Length of stay, median (min-max), day	9 (2–16)
Clinical manifestations	
Cough	87 (83.7)
Fever	81 (77.9)
Shortness of breath	57 (54.8)
Nausea/vomiting	52 (50.0)
Headache	37 (35.6)
Runny nose	35 (33.7)
Anosmia	14 (13.5)
Laboratory results, mean (±SD)	
Hemoglobin, g/dL	12.9±1.7
Hematocrit, %	38.4±4.8
Leukocyte, /µL	$9.4\pm4.8\times10^3$
Erythrocyte, /µL	$4.5\pm0.6\times10^6$
Neutrophil, %	$69.5\pm14.3\times10^3$
Lymphocyte, /µL	22±12.2
Platelet, /µL	$279.6\pm140.6\times10^3$
NLR, mean	5.8±8.5
PLR, mean	21.7±33.8
COVID-19 severity	
Moderate	81 (77.9)
Severe/critical	23 (22.1)

Comparations of NLR and PLR based on severity of COVID-19

The mean NLR was significantly higher in the severe/critical COVID-19 patients compared to moderate severity (10.8±15.7 vs 4.3±4.0; p=0.002). Severe/critical COVID-19 patients also demonstrated a considerably higher mean PLR relative to patients with moderate severity (42.4±62.4 vs 16±15.7; p=0.001) (**Table 2**).

Table 2. Comparison of mean NLR and PLR based on COVID-19 severity (n=104)

Biomarkers	COVID-19 severity		p-value
	Moderate	Severe/critical	
NLR, mean±SD	4.3±4.0	10.8±15.7	0.002
PLR, mean±SD	16.0±15.7	42.4±62.4	0.001

Role of NLR and PLR as a predictor COVID-19 severity

Based on the ROC curve, a true positive value was demonstrated for both NLR and PLR, suggesting changes in NLR and PLR were associated with the severity of COVID-19 patients. At NLR and PLR cut-off values of ≥3.8 and ≥106, the sensitivity was 95% and 70%, and the specificity was 74% and 50%, respectively (**Figure 1**).

Discussion

Our study found that there was a relationship between the changes in NLR and PLR and the severity of COVID-19. In a previous study, severe COVID-19 cases demonstrated notable reductions in lymphocyte counts and elevated NLR values, with a positive correlation between NLR and hospital stay duration [16]. Another study showed that individuals with an NLR value greater than 3.3 had a 6.2-fold increased likelihood of experiencing severe COVID-19 compared to those with an NLR value of 3.3 or below [17]. However, a different study found a fairly high NLR value but with a large standard deviation in all severity categories, suggesting that the NLR value did not have a significant relationship with the severity of COVID-19 [18].

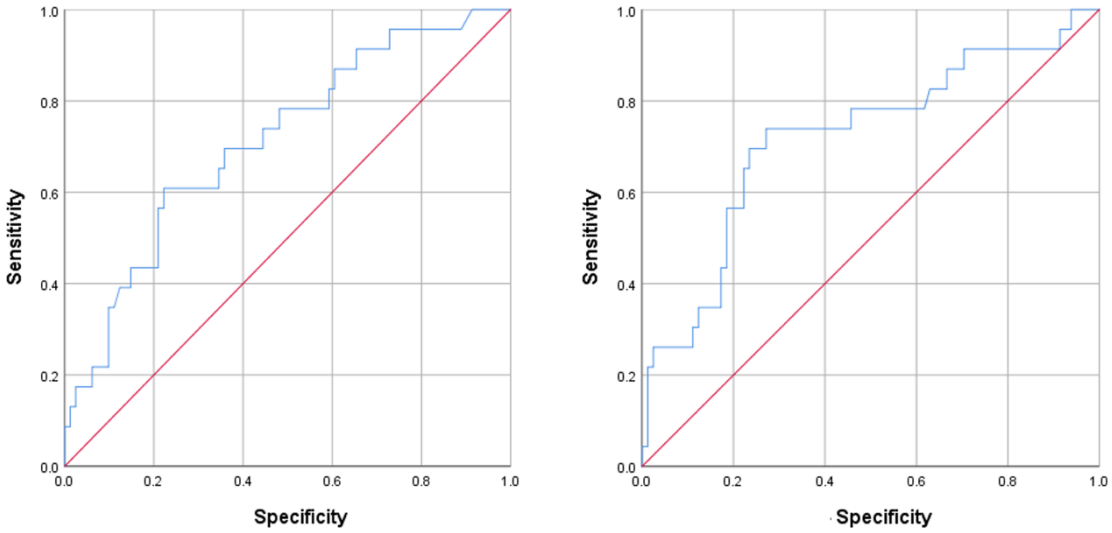

Figure 1. Receiver operating characteristic (ROC) curve of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) with cut-off values.

A study reported that an increase in PLR in COVID-19 patients correlated with prolonged hospitalization and disease prognosis [5]. Similarly, a distinct study speculated that changes in the PLR during treatment could reflect the disease progression and prognosis of COVID-19 patients. It was recommended that patients exhibiting PLR values greater than 126.7 undergo immediate intervention to prevent further disease worsening [8]. Additionally, PLR was observed significantly higher in non-surviving COVID-19 patients than COVID-19 survivors [19].

Neutrophils are crucial for pathogen elimination, constituting the most abundant leukocyte in the circulation and serving as the frontline defense in innate immunity. Neutrophils employ various antimicrobial mechanisms including phagocytosis, degranulation and the formation of neutrophil extracellular traps (NETs). Neutrophils also produce several cytokines and other inflammatory factors that influence and regulate inflammation and also the immune system [18]. Platelets also have considerable roles in inflammation and immune response. Platelets are recruited to inflammation sites, adhering to white blood cells (WBCs) to amplify their effect and secreting immune modulators that attract neutrophils, monocytes, and lymphocytes. They form platelet-granulocyte or platelet-leukocyte aggregates, further inciting inflammation, and stimulate neutrophils to also release NETs [19]. Lymphocyte, as part of adaptive immune system, also contribute significantly to inflammation, particularly T lymphocytes, which releases many proinflammatory cytokines [20].

Severe COVID-19 is characterized by an imbalance in coagulation and fibrinolysis. NETs contain tissue factors and DNA that stimulate intrinsic and extrinsic coagulation. CD16+ T cells are involved in the pathogenesis of microvascular endothelial damage and are known to release chemokines that activate both extrinsic and intrinsic coagulation pathways, leading to the formation of fibrin deposits [21]. Lung biopsy of severe COVID-19 patients showed evidences of ARDS, primarily driven by the cytokine storm. A cytokine storm is an uncontrolled systemic inflammatory response resulting from the release of large amounts of proinflammatory cytokines and chemokines by immune effector cells, especially neutrophils and lymphocytes [20]. Neutrophilia is commonly observed in patients with severe COVID-19 and low platelet counts are associated with severe COVID-19 [19,21]. While lymphopenia is linked to disease severity and mortality in COVID-19 patients due to the cytokine storm, which is associated with apoptosis of lymphocytes. Consequently, NLR can reflect the balance of innate and adaptive immune response, whereas PLR serve as an indicator of inflammation [20].

Conclusion

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) showed statistical significance in relationship with the severity of COVID-19, with *p*-value 0.002 and 0.001, respectively. The NLR and PLR cut-off value were ≥3.8 and ≥106, with sensitivity of 95% and

70%, and specificity of 74% and 50%, respectively. NLR and PLR have demonstrated to predict the severity of COVID-19.

Ethics approval

The protocol of this study was approved by the Ethical Committee of Tabanan Regency General Hospital, Bali, Indonesia (No: 800/2852/Kepeg/RSUD).

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Competing interests

The authors declare that there are no conflicts of interest.

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Underlying data

All data underlying the results can be requested from the corresponding author.

How to cite

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