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Prognostic Biomarkers in COVID-19: The Impact of Neutrophil-Lymphocyte Ratio, Ferritin, Platelet-Lymphocyte Ratio, and D-Dimer

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Abstract. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was declared a global pandemic by the World Health Organization (WHO) in March 2020. This indicates that identifying factors associated with mortality in affected patients is essential for optimizing clinical management. Therefore, this study aims to analyze the differences in Neutrophil-Lymphocyte Ratio (NLR), ferritin, Platelet-Lymphocyte Ratio (PLR), and D-dimer levels between COVID-19 patients who recovered and those who did not, as well as identify the key prognostic factors. The study was conducted using a cross-sectional method at RSUD Abdoel Wahab Sjahranie, Indonesia, from January to December 2021. The sample population consisted of adult COVID-19 patients with complete data on neutrophil, lymphocyte, and platelet counts, as well as ferritin and D-dimer levels. Among the 682 patients, the average age was 53.43 years, where 66.9% recovered and 33.1% died. The results showed that there were significant differences in NLR, ferritin, and D-dimer levels between the recovered and deceased groups ($p<0.05$), with the deceased group having higher levels. Although PLR also showed a significant difference ($p=0.017$), it was not significant in the multivariate analysis ($p= 0.896$). The multivariate analysis identified NLR (OR=1.064), ferritin (OR=1.001), and D-dimer (OR=1.086) as significant predictors of mortality. In conclusion, NLR, ferritin, and D-dimer were effective in predicting COVID-19 mortality, while PLR was ineffective. These findings provide valuable insights for improving clinical management strategies for COVID-19 patients.

Keywords. COVID-19, NLR, ferritin, PLR, D-dimer, prognosis, mortality

1. Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by SARS-CoV-2, with various clinical symptoms. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic due to its rapid spread across various regions worldwide. Since its initial report in Wuhan, Hubei Province, China, in late December 2019, it has spread to 114 countries, with over 118,000 confirmed cases and more than 4,000 deaths as of March 11, 2020. The WHO's declaration of a pandemic indicates the severity and rapid transmission of the disease [1-3].

According to previous studies, understanding the factors influencing mortality risk in COVID-19 patients is crucial in the context of the pandemic. Early exploration of mortality risk factors is essential to assist clinicians in making informed decisions and interventions, ultimately improving patient recovery and prognosis [4]. An effective approach to assess prognosis is through complete blood count results and a routine laboratory test. This test provides information on neutrophils, lymphocytes, platelet counts, and other blood cells [5]. Neutrophil-Lymphocyte ratio (NLR) has emerged as a potential prognostic tool for different diseases [6-7]. It is often calculated by dividing the number of neutrophils by the number of lymphocytes and is recognized as a systemic inflammation marker due to its quick and easy assessment [8-10]. In addition, NLR has shown greater prognostic power compared

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to other infection markers, such as C-reactive protein (CRP), leukocyte count, and neutrophil count in community-acquired pneumonia cases [11]. Platelet-Lymphocyte Ratio (PLR), calculated by dividing platelet count by lymphocyte count, is another prognostic tool, which reflects inflammation, atherosclerosis, and platelet activation [8]. Several studies have shown that NLR and PLR are often combined as inflammatory biomarkers in certain infections [12].

Serum ferritin is an inflammatory marker that increases in response to systemic infection and immuno-modulatory functions and exhibits both host-protective [13]. In addition, it can be used as a biological marker to assess morbidity and mortality. Elevated ferritin levels are often associated with cytokine storms triggered by SARS-CoV-2 infection, which can lead to pro-inflammatory and immunosuppressive changes. Increased ferritin levels are commonly observed in older COVID-19 patients (>65 years) or those with severe diabetes complications [14-15].

D-dimer, a marker of coagulation and fibrinolysis activation, also provides predictive value in infection conditions and in determining disease severity [16]. Several studies have reported that elevated D-dimer levels correlate with poor prognosis in community-acquired pneumonia and chronic obstructive pulmonary disease (COPD) [17]. In COVID-19 cases, significant differences in its levels were observed between severe and mild to moderate disease presentations [18]. Therefore, this study aims to analyze the differences in NLR, ferritin, PLR, and D-dimer between COVID-19 patients who recovered and those who died, as well as identify key prognostic factors. The results are expected to offer further insights into prognostic markers that could enhance clinical management and patient outcomes.

2. Methods

This was an analytical observational study with a cross-sectional design, conducted at the Medical Records and Clinical Pathology Laboratory of RSUD Abdoel Wahab Sjahranie, Samarinda, East Kalimantan. The study population consisted of adult COVID-19 patients treated at RSUD Abdoel Wahab Sjahranie from January to December 2021. A purposive sampling technique was applied to select patients who met the inclusion and exclusion criteria.

Inclusion criteria were patients who were confirmed COVID-19 positive, aged over 18 years, hospitalized, and with complete data on neutrophil, lymphocyte, platelet counts, ferritin, as well as D-dimer in their medical records. Patients who had undergone surgery, were pregnant, had HIV, congestive heart failure, chronic liver disease, chronic kidney disease, coagulation diseases, or cancer were excluded from the study.

Data were collected from medical records, such as information on age, sex, neutrophil count, lymphocyte count, platelet count, ferritin level, D-dimer level, and outcome status (recovered or deceased). NLR and PLR were calculated using the formulas, namely NLR = Absolute Neutrophil Count / Absolute Lymphocyte Count, and PLR = Absolute Platelet Count / Absolute Lymphocyte Count.

Data were processed using Microsoft Excel and SPSS version 26, univariate analysis described the data in terms of frequency and percentage distributions. The Kolmogorov-Smirnov test was used to assess distribution normality. The Mann-Whitney test was used to compare the recovered and deceased groups. Multivariate analysis was conducted using logistic regression to evaluate the predictive power of NLR, ferritin, PLR, and D-dimer on the prognosis of COVID-19.

3. Results and Discussion

Medical records were collected from 682 adult COVID-19 patients treated from January to December 2021. The average age of the respondents was 53.4 years, with the majority being male (59.4%). Among the patients, 66.9% recovered, while 33.1% died. Hematological parameters showed average values of 237.6 for platelet count, 6.7 for neutrophils, 1.2 for lymphocytes, 2.9 for D-dimer, and 1119.9 for ferritin. The average NLR was 6.9 and PLR was 244.2.

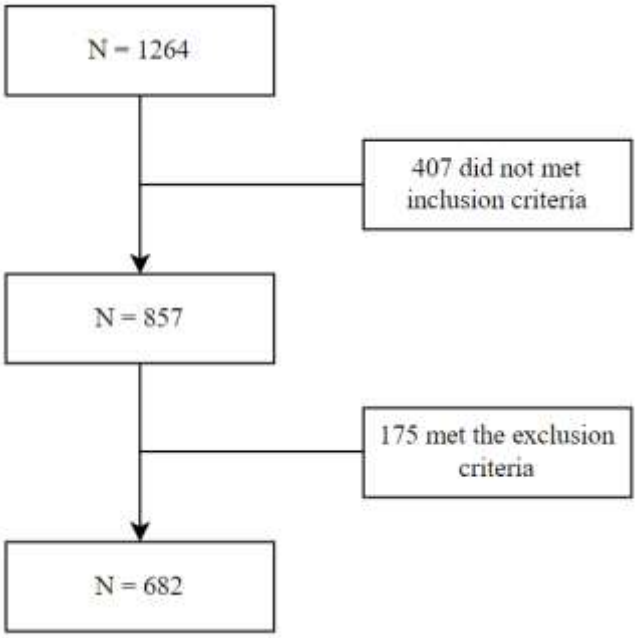

Figure 1. Study Flowchart

Bivariate analysis showed a significant difference in NLR between COVID-19 patients who recovered and those who died ($p < 0.001$). Respondents who died had a higher NLR compared to those who recovered. This result was consistent with previous studies showing a significant relationship between NLR on the first day of treatment and COVID-19 severity, with higher NLR observed in severe cases compared to mild-to-moderate cases [19-20]. [4] reported that NLR in deceased patients was significantly higher than in survivors, from day one to the last day of treatment.

Table 1. Analysis of Studied Variables

Variable	**N (%)**
Gender	
Male	405 (59,4)
Female	277 (40,6)
Patient Outcome	
Deceased	226 (33,1)
Recovered	456 (66,9)

Variable	**Mean (SD)**	**p-value**	**Logistic Regression**	
			Odds Ratio (95% CI)	**p-value**
Age	53,4 (12,9)			
Platelet Count (10^6/µL)	237,6 (95,8)			
Neutrophil Count (10^3/µL)	6,7 (4,4)			
Lymphocyte Count (10^3/µL)	1,2 (0,8)			
D-Dimer (µg/mL)	2,9 (4,8)	<0.001	1,086 (1,047 – 1,126)	<0.001
Ferritin (µg/mL)	1.119,9 (671,9)	<0.001	1,001 (1,000 – 1,001)	<0.001
NLR	6,9 (5,8)	<0.001	1,064 (1,023 – 1,106)	0,002
PLR	244,2 (187,9)	0.017	1,000 (0,999 – 1,001)	0,896

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Ferritin levels showed a significant difference between recovered and deceased patients ($p < 0.001$), with deceased patients having higher ferritin levels. This was consistent with previous studies showing that increased ferritin was a marker of poor prognosis in COVID-19 [21]. Besides its well-known function as an iron storage protein, it was also one of the acute-phase proteins that increased in both acute and chronic inflammation. As an acute-phase protein, elevated serum ferritin levels were modulated by pro-inflammatory cytokines [22-23].

D-dimer levels showed a significant difference between recovered and deceased patients ($p < 0.001$), with higher levels observed in deceased patients. [18] reported similar results, showing that elevated D-dimer levels were associated with severe COVID-19 symptoms and could serve as a marker of disease severity.

Logistic regression analysis showed that NLR (OR = 1.064; 95% CI 1.023–1.106), ferritin (OR = 1.001; 95% CI 1.000–1.001), and D-dimer (OR = 1.086; 95% CI 1.047–1.126) significantly predicted the risk of death in the patients. NLR, ferritin, and D-dimer were effective mortality predictors, while PLR was not significant in multivariate analysis. This confirmed their role as important prognostic indicators.

Increased NLR at hospital admission was predominantly observed in patients with critical symptoms and those who died [21][24-25]. The positive correlation of NLR with CRP and procalcitonin suggested its potential as a novel biomarker for systemic inflammation [12][26-27]. In addition, NLR correlated positively with chest CT scan scores in COVID-19 patients [27]. [28] emphasized that an NLR > 4.94 on the first day of treatment was associated with a 1.2 times higher risk of requiring intubation.

High NLR results were obtained from an increase in the number of neutrophils and a decrease in the number of lymphocytes. The nonspecific immune response included in respiratory infections was characterized by the mobilization of neutrophils to the lungs (alveoli). Inflammatory responses could stimulate neutrophil production and accelerate lymphocyte cell death [29]. Dysregulation of the immune cell response was believed to play a significant role in the severity of diseases caused by SARS-CoV-2. According to Selanno et al., an increase in NLR in severe cases resulted from an enhanced inflammatory response, which led to decreased cellular immunity [30].

Meta-analysis by [21] showed significantly elevated ferritin levels in severe cases compared to mild-moderate cases, with deceased patients exhibiting much higher ferritin levels. Elevated ferritin was linked to poor prognosis and worsening in COVID-19 patients. [31] emphasized ferritin's utility in early identification and management of patients at risk of clinical deterioration, leading to ICU admission or death. Changes in ferritin levels in respondents were not only higher in those who died compared to those who survived but also showed an increase as the disease worsened [32]. [33] observed that a D-dimer level > 2.0 mg/L at hospital admission was associated with increased mortality risk (OR 10.17; CI = 1.10 – 94.38; $p = 0.041$), with levels > 2.14 mg/L predicting mortality with sensitivities and specificities of 88.2% and 71.3%, respectively (AUC 0.85; 95% CI = 0.77–0.92). Coagulopathy, marked by elevated D-dimer levels, was common in COVID-19. Severe cases were significantly associated with higher risks of DVT and acute pulmonary embolism. Pulmonary intravascular coagulation (PIC) was a characteristic coagulopathy in COVID-19, manifesting locally in the lungs, unlike systemic coagulopathy from sepsis and DIC [19]. [34] proposed PIC as macrophage activation syndrome (MAS) linked to diffuse immunothrombosis in the lungs of the respondents. Elevated circulating D-dimer reflected pulmonary vascular thrombosis with fibrinolysis, while increased myocardial enzyme concentrations showed acute ventricular stress due to pulmonary hypertension. Several studies reported high macrophage and other immune cell infiltration in the lung tissue of deceased COVID-19 patients [35].

The mechanism of thrombosis was generally caused by an imbalance in Virchow's triad, which consisted of blood vessels, blood flow, and hypercoagulability. Viral infections disrupted the coagulation cascade by inducing a procoagulant state. In addition, inflammation of lung parenchymal cells and endothelial cells of pulmonary vessels also induced the release of procoagulant factors. This condition could increase the activation of the coagulation cascade leading to thrombosis and fibrin

deposition in the pulmonary vessels, uncontrolled inflammation damaged endothelial cells [36]. Hypoxemia in these patients also played a significant role in the thrombosis mechanism. This condition caused vasoconstriction and inflammation, by activating hypoxia-inducible factor, which activated cytokines, tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1), potentially leading to thrombosis [36].

4. Conclusions

In conclusion, this study showed that NLR, ferritin, and D-dimer could be used as prognostic predictors for mortality in COVID-19 patients, while PLR was not found to be significant in predicting mortality. These results enhanced the understanding of prognostic biomarkers for the disease and provided valuable insights for the clinical management of the disease.

5. Ethical Clearance

This study received ethical approval from the Health Study Ethics Committee of Abdoel Wahab Sjahranie Hospital, Samarinda with the number 117/KEPK-AWS/VII/2022.

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