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Original Article

The Influence of Inflammatory Factors (IL-6, CRP, NLPR, D-Dimer, LDH) on the PaO2/FiO2 Ratio, in Patients with Severe and Critical Degrees of COVID-19

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Abstract

Background : Several types of inflammatory biomarkers that are important in severe and critical Covid-19 infections include: levels of IL-6, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-Dimer and neutrophil-lymphocyte platelet ratio (NLRP), which are independent variables. Meanwhile, the severity of Covid-19 infection can be determined by measuring the PaO2 /FiO2 ratio. However, the relationship between the PaO2/FiO2 ratio as the dependent variable is not yet known. The aims of this study was to analyze the relationship between PaO2/FiO2 ratio and inflammatory biomarkers in COVID-19 patients

Methods : An analytic observational study with a retrospective, cross-sectional approach. The research sample consisted of PCR-confirmed severe and critical COVID-19 patients who were treated in the isolation room of the Ulin Hospital in Banjarmasin from AugustDecember 2021, who met the inclusion and exclusion criteria. Data analysis used the Spearman test to see the relationship between the PaO2/FiO2 ratio and various inflammatory markers.

Results : 52 severe and critical patients were observed according to the research flow. The number of male and female subjects (32/20) was found. The mean age was 55.38 years. The correlation test found that: there was no significant relationship between the PaO2/FiO2 ratio and IL-6 ($p = 0.964$), but there was a negative correlation between the PaO2/FiO2 ratio and: a) CRP ($p = 0.038$), b) LDH ($p<0.001$), c) NLPR ($p = 0.013$), and d) D-dimer ($p<0.001$). The inflammatory biomarkers NLPR, LDH, and D-dimer are important independent variables for the severity of COVID-19, namely the PaO2/FiO2 ratio.

Conclusion : There are a significant correlation between the PaO2/FiO2 ratio to measure the severity of Covid-19 and several inflammatory biomarkers CRP, LDH, NLPR and D-dimer.

Keywords : COVID-19, PaO2/FiO2 ratio, NLPR, LDH, D-dimer

INTRODUCTION

The most frequent coronavirus 2019 (COVID-19) complication is acute respiratory distress syndrome (ARDS). Patients with SARS-CoV-2 illness can cause cytokine levels increases, which are indicative of the viral load and cause lung injury.[1,2] PaO2/FiO2, which is the ratio of arterial partial pressure of oxygen to inspired oxygen, can define ARDS and indicate the severity of low tissue oxygenation.[3] Some research exploring the relationship of various biomarkers to the severity of COVID-19, such as the Neutrophil Lymphocyte Platelet Ratio (NLPR), C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), D-Dimer, and Interleukin-6 (IL-6).[4–7] Decreased CD4+ and CD8+ T cells level in SARS-CoV-2 infection can increase several ratios, such as NLPR.[7] Increased inflammation in COVID-19 causes CRP, LDH and d-dimer to increase, so that they can describe COVID-19's severity.[8–10] Also, IL-6 levels will increase sharply in individuals infected with SARS-CoV-2 because it is involved in cytokine release syndrome (CRS), and this cytokine is involved in the differentiation and formation of B lymphocytes and also T lymphocyte differentiation and proliferation. Excess IL-6 can harm organs by increasing the permeability of vessels and decreasing myocardial contractility. The movement of fluid and blood cells in the alveoli causes ARDS, which can lead to death.[4,11,12]

COVID-19 causes many acute respiratory disorders, which can increase mortality. We suspect that PaO2/FiO2 is related to NLPR, CRP, LDH, D-dimer, and IL-6 because they both describe the severity of COVID-19 patients. So far, there is still no research on the relationship between PaO2/FiO2 and inflammatory biomarkers in COVID-19 patients. The aim of this study was to analyze the relationship between PaO2/FiO2 with NLPR, CRP, LDH, D-dimer and IL-6 in patients with severe and critical COVID-19.

MATERIALS AND METHODS

Study Design and Participants

This research is an analytic observational study with a retrospective study, with cross-sectional approach. It was carried out at the Ulin Hospital in Banjarmasin from February to March 2023. Our study population was all patients with severe and critical degrees of COVID-19 confirmed by PCR and being treated in the isolation room of the Ulin Hospital in Banjarmasin during the period AugustDecember 2021, and our study sample was all patients with severe and critical degrees of COVID-19 confirmed by PCR and being treated in the isolation room of the Ulin Hospital in Banjarmasin during the period August–December 2021, which meets the inclusion and exclusion criteria. The research sample in this study used a purposive sampling technique with a minimum sample size of 33 people.

Inclusion Criteria: 1) COVID-19 patients are over 18 years old; 2) Patients with severe and critical degrees of COVID-19 confirmed by PCR at Ulin Hospital, Banjarmasin; 3) COVID-19 patients who underwent routine blood tests (blood gas analize, IL-6, CRP, LDH, and D-Dimer) when admitted to hospital at Ulin Hospital in Banjarmasin during the August–December 2021 period.

Exclusion Criteria: 1) Patients with incomplete medical record data; 2) Patients with blood hematological malignancies.

COVID-19 patients was classified by Indonesian Pulmonary Doctors Association (2021) with the following criteria:

- Severe: Patients with confirmed COVID-19 who have oxygen saturation <94% in room air, PaO2/FiO2 ratio <300 mmHg, respiratory rate > 30 breaths per minute, or pulmonary infiltration > 50%.
- Critical: Patients with confirmed COVID-19 who have respiratory failure (ARDS), septic shock, and multi-organ dysfunction.

Measurement Method

All study subjects who met the inclusion criteria were measured for the ratio of PaO2/FiO2 using the i-STAT1 tool. Then measurements of IL-6, NLPR, CRP, LDH, and D-dimer were assessed in each study subject. IL-6 examination was carried out using the specification iCHROMA-II, NLPR with the specification SYSMEX XN-1000, as well as examination of CRP, LDH, and D-dimer using the ARCHITECT C-4000.

Statistic analysis

Data analysis was performed using SPSS computer software version 26.0. Gender, age, PaO2/FiO2 ratio, NLPR, CRP, LDH, D-dimer, and IL-6 were presented as mean PaO2/FiO2 ratio, NLPR, CRP, LDH, D-dimer, and IL-6 are presented as mean SD and median. The normality test was assessed using the Shapiro-Wilk test. The relationship between the PaO2/FiO2 ratio and NLPR, CRP, LDH, D-dimer, and IL-6 was the Spearman correlation test. A multiple linear regression analysis test was used to determine the independent variables that affect the ratio of PaO2/FiO2.

Ethical Clearance

Each action in this study was carried out only after information was provided and with parental consent. This research with human subjects was carried out in accordance with the ethical guidelines of each institution. In accordance with ethical guidelines, the Ethics Commission of the Research and Development Agency at the Ulin Hospital in Banjarmasin and the Faculty of Medicine at the University of Lambung Mangkurat endorsed this research protocol.

RESULTS

This study consisted of 52 samples from patients with severe and critical degrees of COVID-19 confirmed by PCR and being treated in the isolation room of the Ulin General Hospital in Banjarmasin during the period of August to December 2021 who met the study criteria.

Subject Characteristics

There were more male than female, namely 32 male subjects (61.5%) vs. 20 female subjects (38.5%). The median age of the patients was 57.50 years, with a range between 25 and 80 years for the youngest and oldest patients, respectively, with a mean age of 55.38 years (Tabel 1).

Relationship of PaO2/FiO2 Ratio with NLPR, CRP, LDH, D-dimer, and IL-6

Based on Table 2, NLPR, CRP, LDH, and D-dimer have a negative correlation with the PaO2/FiO2 ratio with p-value 0.013; 0.038; <0.001; <0.001, respectively. NLPR has a weak correlation with the ratio of PaO2/FiO2 (rs: -0.334); CRP has a weak correlation with the ratio of PaO2/FiO2 (rs: -0.289); LDH has a moderate correlation to the ratio of PaO2/FiO2 (rs: -0.580); and D-dimer has a moderate correlation to the PaO2/FiO2 ratio (rs: -0.538). IL-6 did not correlate with the PaO2/FiO2 ratio ($p > 0.05$).

Multiple Linear Analysis

Using multiple linear regression analysis and the backward method, a multivariate model of the relationship between the PaO2/FiO2 ratio in severe and critical COVID-19 patients with inflammatory biomarkers was obtained in the Table 3. This study has a t-table value of 1.676. In the partial test on model 3, which consists of 3 independent variables in the regression model, it can be seen that NLPR has a t value of -2.932 and a t count greater than the t table, so it can be concluded that partially NLPR has an influence on the ratio of PaO2/FiO2. LDH has a calculated t value of -4.163, and t calculated is greater than t table, so it can be concluded that LDH partially has an effect on the ratio of PaO2/FiO2. D-Dimer has a t count of -1.781; the t count is greater than the t table, so it can be concluded that partially D-Dimer has an effect on the ratio of PaO2/FiO2.

The F table of this research is 2,574. With the backward method, CRP and IL-6 are removed. After being removed, we then assessed three other inflammatory biomarkers, namely NLPR, LDH, and D-dimer. In model 3, F count > F table (11.089 > 2.574), so it can be concluded that NLPR, LDH, and D-dimer together have an influence on the PaO2/FiO2 ratio (Table 4).

Multiple linear regression equation as follows:

$$\gamma = 366.668 - 10.478X_2 - 0.145X_4 - 4.357X_5$$

TABLE 1
Characteristics of Research Sample

Characteristics		n	Mean ± SD	Median
Sex	Female	20		
	Male	32		
Age		52	55.38 ± 13.69	57.5
PaO2/FiO2 Ratio		52	186.73 ± 131.76	148.71
NLPR		52	3.85 ± 4.15	2.06
CRP		52	108.08 ± 71.43	99.05
LDH		52	863.92 ± 427.58	767.5
D-Dimer		52	3.28 ± 6.15	1.31
IL-6		52	35.87 ± 57.24	16.5

TABLE 2
Relationship of PaO2/FiO2 Ratio with NLPR, CRP, LDH, D-dimer, and IL-6

Variable		NLPR	CRP	LDH	D-dimer	IL-6
PaO2/ FiO2 Ratio	Spearman's rho	-0.344	-0.289	-0.580	-0.538	-0.006
	p-value	0.013	0.038	<0.001	<0.001	0.964

TABLE 3
Partial test results for the backward method

Model		B	t	Sig
1	Constant	363.049		
	NLPR	0.438	-2.423	0.019
	CRP	-8.919	-1.224	0.227
	LDH	-0.276	-3.359	0.002
	D-dimer	-0.124	-2.109	0.040
	IL-6	-6.336	1.364	0.179
2	Constant	352.241		
	NLPR	0.356	-2.799	0.007
	LDH	-10.035	-3.885	<0.001
	D-dimer	-0.137	-2.108	0.040
	IL-6	-6.368	1.129	0.265
3	Constant	366.668		
	NLPR	-10.478	-2.932	0.005
	LDH	-0.145	-4.163	<0.001
	D-dimer	-4.357	-1.781	0.081

TABLE 4
Analysis of variance for the backward method

Model	F	Sig.
1 (NLPR,CRP,LDH,D-dimer,IL-6)	7.320	<0.001
2 (NLPR,LDH,D-dimer, IL-6)	8.683	<0.001
3 (NLPR, LDH, D-dimer)	11.089	<0.001

The value of -10,478 in the above model means that for every addition of X2 (NLPR) by one unit, Y (PaO2/FiO2 ratio) will decrease by 10,478 units; the value of - 0.145 in the above model means that for every addition of X4 (LDH) by one unit, Y (PaO2/FiO2 ratio) will decrease by 0.145 units; the value of -4,357 in the above model means that for every addition of X5 (D-Dimer) by one unit, Y (PaO2/FiO2 ratio) will decrease by 4,357 units.

DISCUSSION

Males were found to be more prevalent than female in our study. This is due to the fact that female are more likely to produce larger amounts of antibodies against influenza vaccinations that have been inactivated. Female are also have immune systems that are twice as powerful as those of male. Because estrogen increases the action of vitamin D in female, infections will reduce more slowly than in male. On the other hand, male sex hormones are considered to boost ACE2 receptor activation, which might stimulate the virus to enter, making them more vulnerable to COVID-19 and worsening the prognosis of the illness.[13] The subjects in our research had a median age of 55.38 years, with the range of 25 years and 80 years. A person's ability to produce T and B cells declines with age, and their body's innate immune system becomes less effective. Finally, during an infection, the cells responsible for innate immunity go dormant. As a result, eliminating viruses is less likely to be successful and raises the risk of setting off a dysregulated immune response, in which highly active immune cells generate a plethora of cytokines, leading to a cytokine storm that will worsen the situation.[14,15]

The study revealed a negative correlation between NLPR and the PaO2/FiO2 ratio. The NLPR tends to decrease when the PaO2/FiO2 ratio rises, and there is a

statistically significant correlation between the two variables. It is the same with other studies by Syahrini H. *et al*., which showed that there was a significant relationship between neutrophils, lymphocytes, and platelets and the degree of severity of COVID-19 (16), and also research by Haryati H. *et al*., showed a substantial correlation between NLPR and COVID-19 patient outcomes ($p<0.005$). In patients who died (75.4%) had a higher rise in NLPR (≥0.037) than those who survived (23.6%). The NLPR defines how neutrophils, lymphocytes, and platelets interact with acute immunological processes to cause immunoembolism.[17]

The pathogenesis of inflammatory injury to the kidney, cardiovascular system, gastrointestinal tract, and lung, with necrosis and subsequent apoptosis of these tissues, are influenced by dysregulation of neutrophil activation by the release of cytotoxic chemicals, including reactive oxygen species (ROS) and proteinases such as leukocyte elastase. Neutrophils alone may not be the dominant component affecting the PaO2/FiO2 ratio's outcomes. In addition, the pathogenicity of SARS CoV-2, which harms type II alveolar cells, the cytokine storm (TNF-alpha, IL-1, IL-6, and L-8), and neutrophil products (ROS and MMP) are further probable causes of epithelial and endothelial damage in the lungs. All organs, including the lungs, experience increasing neutrophil recruitment and activation as a result of the cytokine storm. Increased neutrophil counts result in the activation and release of neutrophil elastase, as well as ROS and MMP, which damage the lung's alveoli-capillary membrane and diffusely injure the alveoli. Both the beginning of acute lung injury (ALI) and the progression of ARDS are characterized by these two mechanisms.[18]

One of the key laboratory indicators that may be utilized to help with diagnosis and prognosis in COVID-19 patients is lymphopenia. The primary immune cells that respond to viral infections are lymphocytes. The amount of systemic inflammation is thought to be adversely associated with the lymphocyte count. Increased systemic inflammation resulted in a considerable reduction in CD4+ T cells, an increase in CD8+ suppressor T cells, and a rise in lymphocyte death.[19,20] Thrombocytopenia has been reported in hospitalized patients with COVID-19, and lower platelet counts are associated with poorer clinical outcomes.[21] Research by Zaid Y. *et al*., showed higher platelets in the COVID-19 group with ARDS ($159.90x10^3/L$) compared to the COVID-19 group without ARDS ($194.55x10^3/L$).[21] Low platelet counts cause platelet counts to aggregate, platelet-leukocyte complexes to form, and the release of chemicals that support cell adhesion and inflammation. Increased adhesion molecules and pro-inflammatory factors have a detrimental effect on patient survival. Platelet count and ARDS mortality are closely correlated, as shown by platelet-mediated thrombosis and enhanced capillary-endothelial barrier permeability.[22]

An inflammatory biomarker that can be used to gauge the severity of COVID-19 is C-reactive protein (CRP).[23] Our research showed that there was a weak negative correlation between the PaO2/FiO2 ratio and CRP. Research regarding the direct relationship between the PaO2/FiO2 ratio and CRP is still rare. Our result are in line with the research of Erika P. *et al*., indicated a significant negative correlation between the PaO2/FiO2 ratio and CRP. Due to an aberrant inflammatory condition, CRP in COVID-19 patients may be a manifestation of lung injury and may indicate respiratory distress as measured by the PaO2/FiO2 ratio. The creation of a cytokine storm is thought to be one of the key contributors, despite the fact that the precise mechanism of SARS-CoV-2 in ARDS is not well understood.[24]

In metabolic processes, lactate dehydrogenase is crucial because it participates in the incomplete conversion of pyruvate, the glycolysis product, to lactate in the absence of an adequate oxygen supply. A shortage of oxygen in biochemical or tissue processes, or multiorgan failure, is indicated by elevated LDH activity. A rise in LDH activity might be a sign of cell death, hypoxia, or injury.[9] Our findings indicated a weakly negative correlation between the PaO2/FiO2 ratio and LDH. According to our research, LDH tends to decrease when the ratio of PaO2/FiO2 rises. The link between the PaO2/FiO2 ratio and LDH in severe or critical COVID-19 patients have not been studied. However, Zinelu A *et al*., showed that patients with more severe COVID-19 had a lower PaO2/FiO2 ratio than patients with less severe COVID-19 ($p=0.002$). In the severe group, the PaO2/FiO2 ratio was 25251, whereas it was 31466 in the mild to moderate group.[12] PaO2/FiO2 may be used to determine how much COVID-19 pneumonia lesions have affected the overall lung tissue by measuring LDH. The SARS-CoV-2 virus can induce cytotoxicity and a cytokine storm. After being infected with COVID-19, several cells also perish, which ultimately results in the production of extracellular LDH and an instantaneous rise in serum LDH. In other words, the LDH level will rise and the PaO2/FiO2 ratio will decrease if there is more cell damage, such as a bigger pneumonia lesion.[25]

The COVID-19 virus has been linked to hemostatic conditions. Numerous investigations have also discovered a considerable rise in D-dimer levels among patients with severe illnesses and those who did not survive.[26] The same conclusion is drawn from our study. The PaO2/FiO2 ratio and D-dimer have a moderately strong negative correlation that is statistically very significant. Patients with severe and critical COVID-19 might experience hypoxia, which can activate clotting. Numerous studies also suggested that hypoxemia might result in venous and arterial thrombosis. This physio-pathological process appears to be influenced by Virchow's triad of hypercoagulability, endothelial damage, and stasis. Hypoxia-inducible transcription

factors (HIF), which control the genes that govern coagulation and fibrinolysis, can also be activated by local and systemic hypoxia brought on by various risk factors (such as cancer, high altitude, immobility following serious trauma or surgical intervention, etc).[27,28]

Our finding demonstrated a negative correlation between IL-6 and the PaO2/FiO2 ratio. However, there was no statistically significant correlation between the two variables. However, it still seems that a rise in IL-6 will lead to a fall in the PaO2/FiO2 ratio. The association between the PaO2/FiO2 ratio and IL-6 in COVID-19 has not yet been studied. We speculate that there may be a correlation between the PaO2/FiO2 ratio and IL-6, which is connecting to the development of ARDS and extensive inflammatory activity and reduce the PaO2/FiO2 ratio. Gu Y *et al*.'s[4] research backs up our theory, they showed that COVID-19 patients who died from ARDS had high IL-6 and a low PaO2/FiO2 ratio ($p < 0.0001$). When infection occurs, the downstream JAK signaling pathway will bind to transmembrane or soluble IL-6R through IL-6. However, if IL-6 is excessive, it can cause organ damage, such as increased vascular permeability and decreased myocardial contractility revealed that in severe COVID-19 patients, IL-6 level, an important cytokine upstream of the inflammatory cytokine cascade, are raising prior to ARDS, followed by acute phase proteins level elevating, such as CRP. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 are examples of pro-inflammatory cytokines that can be promptly released by pathogenic Th1 cells after SARS-CoV-2 activation.[4,22,29]

After doing a multiple linear regression analysis between the ratio of PaO2/FiO2 and IL6, NLPR, CRP, LDH, and D-dimer As a consequence, only NLPR, LDH, and D-dimer, three independent factors, influence the PaO2/FiO2 ratio in severe and critical COVID-19 patients. There hasn't been any research done yet that compares different biomarkers as independent factors impacting the PaO2/FiO2 ratio. Neutrophils are thought to be the first cell type to be drawn to inflammatory areas. Neutrophils will transform into various phenotypes with different cell activities after they have reached the location of the inflammation. Additionally, neutrophils can attempt to modify innate and adaptive immune responses directly or indirectly through cytokines, chemokines, and other immune cells.[30] Although initially only neutrophils can be shown to be present, it is likely to affect NLPR. We further speculate that LDH may be present in large quantities across all organs and be intricately linked to the existence of the SARS-CoV02 infection, making LDH an independent factor influencing the PaO2/FiO2 ratio. Increased LDH activity can also be a sign of multiple organ failure, tissue oxygen deprivation, or oxygen deprivation in metabolic processes.[9] Another independent factor that might impact the PaO2/FiO2 ratio is D-dimer. Infection with SARS-CoV-2 increases the likelihood of developing ARDS, which affects lung oxygenation. One of the causes of a thrombus, which is indicated by an increase in D-dimer, is hypoxia. Numerous cellular and molecular signaling pathways are impacted by oxygen deprivation, which results in thrombus development.[30]

The strength of this study is that it is the only study that directly analyzes the relationship between the PaO2/FiO2 ratio and IL-6, LDH, CRP, NLPR, and D-dimer in severe and critical COVID-19 patients. It is hoped that this research can explain the relationship between the PaO2/FiO2 ratio and IL-6, LDH, CRP, NLPR, and D-dimer in patients with severe and critical degrees of COVID-19. However, our study has several limitations. First, the sample size of our study was small. Second, it did not separate the severe group from the critical group. Third, we only assessed the relationship of severity with COVID-19 inflammatory biomarkers, without separating mild or moderate degrees. Fourth, we did not analyze factors that had received medical intervention for concomitant diseases or comorbidities during treatment.

CONCLUSION

There are a significant correlation between the PaO2/FiO2 ratio to measure the severity of COVID-19 and several inflammatory biomarkers CRP, LDH, NLPR and D-dimer

Conflicts of interest

There is no conflicts of interest.

Authors' contributions

YOH designed, typed, and compiled the manuscript; AA, DIN, MI, IN, and EK participated in supervising this manuscript. All authors read and approved the final version of the manuscript.

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