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Association of Inflammatory Markers with Acute Respiratory Distress Syndrome in Severe and Critical Degree COVID-19 Patients

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Abstract: ***Background: One of the most prevalent COVID-19 consequences, with a high fatality rate, is acute respiratory distress syndrome (ARDS). ARDS manifests as an organ malfunction during COVID-19's hyperinflammatory phase. However, there is a scarcity of information on the clinical features and inflammation markers of people with severe COVID-19 and ARDS. Therefore, this research aimed to evaluate the association of inflammatory markers with COVID-19-associated ARDS among patients hospitalized with COVID-19 cases in H Adam Malik Hospital Medan. Methods: This is an analytical cross-sectional study from 204 medical records on patients hospitalized with a confirmed COVID-19 with a severe and critical degree in RSUP H Adam Malik Medan between February and July 2021. The chi-square test was conducted to analyze the data with SPSS version 25. Results: We analyzed laboratory tests to identify the inflammatory marker in 204 COVID-19 majoritieswho were male (119 vs 85) admitted to the Department of Pulmonology and Respiratory Medicine, Adam Malik General Hospital. We investigated the association between inflammatory markers and ARDS. According to statistical research, neutrophilia is associated with a greater neutrophil-to-lymphocyte ratio (NLR) and high levels of the procalcitonin were associated risk factor for ARDS event (respectively: PR: 1.685, 95%CI: 1.651-5.486, p<0.05; PR: 1.515, 95%CI: 1.664-5.409, p<0.05; PR: 1.517, 95%CI: 1.731-5.705, p<0.05). Conclusion: There were associations between inflammatory markers with ARDS. Neutrophilia, elevated NLR, and high levels of procalcitonin prior to hospitalization could be considered risk factors for ARDS in severe COVID-19 allowing clinicians to adjust treatment strategies aggressively to reduce mortality.***

Keywords: SARS-CoV-2; COVID-19; ARDS; inflammation markers; Indonesia

1. Introduction

COVID-19 is highly contagious and can lead to fatal outcomes, especially Acute Respiratory Distress Syndrome (ARDS). (1–3) The number of confirmed positives in Indonesia is 1, 837, 126 and the number of cases died is 51, 095 cases. The clinical course of COVID-19 can be classified into three stages, and the third stage is the hyperinflammation phase, characterized by systemic inflammation, or cytokines storm, which results in acute respiratory distress syndrome and MOF (Multiple Organ Failure). In this situation, some inflammatory biomarkers were significantly elevated. (4) Markers in the laboratory as a tool to help predict the severity of COVID-19 in a pandemic situation are critical because the allocation of resources must be carefully planned, especially regarding the readiness of respiratory support devices. The purpose of this study is to assess the relationship between several inflammatory markers, including levels of lymphocytes, NLR, C Reactive Protein (CRP) and procalcitonin, and the incidence of ARDS in COVID-19 patients.

2. Methods

This is an analytical descriptive study from 204 medical records of patients diagnosed as COVID-19 patients with confirmed critical severity who were treated in the isolation room at H. Adam Malik Hospital Medan from February 2021 to July 2021. The sample in this study were all confirmed severe and critical COVID-19 patients who were hospitalized at H Adam Malik General Hospital Medan who met the inclusion and exclusion criteria. The inclusion criteria in this study were as follows: Age above 18 years, patients diagnosed with confirmed COVID-19, namely evidence of positive COVID-19-Reverse Transcriptase Polymerase Chain Reaction from nasopharyngeal or oropharyngeal swab, with severe and critical grade, which was established based on history, physical examination, radiological examination. Exclusion criteria in this study were incomplete medical records.

The information that has been gathered will be analysed by employing software designed for statistical analysis. The information that was gathered will undergo processing and descriptive analysis so that we can determine the frequency distribution of study participants depending on attributes.

The test used to analyse the relationship between the independent and dependent variables is the Chi-Square test. Before collecting data on the sample, the researcher first submitted ethical clearance to the Health Research Ethics Commission (KEPK) Faculty of Medicine Universitas Sumatera Utara, Medan. After collecting data and serving as categorical data in the frequency distribution table by SPSS version 25.0.

3. Results

We analysed laboratory tests to identify the inflammatory marker in 204 COVID-19 majorities were male (119 vs 85) admitted to the Department of Pulmonology &Respiratory Medicine, Adam Malik General Hospital.

Characteristics of subjects based on comorbid diseases suffered with a more significant proportion, namely subjects with hypertension, namely 109 people (53.4%), whereas from subjects with comorbid hypertension, 71 people (34.8%) with ARDS.

Table 1: Correlation of laboratory with ARDS in severe and critical COVID-19 patients

	ARDS (%)	Non-ARDS (%)	N (%)	*p-value*	CI (95%)
Neutrophilia					
Yes No	89 (43, 6) 27 (13, 2)	46 (22, 5) 42 (20, 6)	135 (66.2) 69 (33.8)	**<0.001 PR 1.69**	1.65-5.48
Lymphocytopenia					
Yes No	96 (47, 1) 20 (9, 8)	74 (36, 3) 14 (6, 9)	170 (83, 3) 34 (16, 7)	0.800	0.43 – 1.91
Increased NLR					
Yes No	86 (42, 2) 30 (14.7)	43 (21, 1) 45 (22, 1)	129 (63, 2) 75 (36, 8)	**< 0.001** **PR 1.52**	1.66 – 5.41
Increased Procalcitonin					
Yes Normal	88 (43, 1) 28 (13, 7)	44 (21, 6) 44 (21, 6)	132 (64, 7) 72 (35, 3)	**< 0.001** **PR 1.52**	1.73-5.70
Increased CRP					
Yes Normal	61 (29, 9) 55 (27, 0)	52 (25, 5) 36 (17, 6)	113 (55, 4) 91 (44, 6)	0.35	0.74-2.28

In this study, the relationship between the incidence of neutrophilia and the incidence of ARDS, where 89 (43.6%) study subjects who experienced ARDS had neutrophilia as well. Statistically, there is a very significant relationship between the incidence of neutrophilia and the incidence of ARDS with a p-value <0.05. by calculating the Prevalence Ratio value of 1.69, which is >1, so that the incidence of neutrophilia can be used as a sign or risk factor for patients with ARDS, where patients with neutrophilia have a risk of 1.685 times compared to those without, with 95% CI: 1.65-5.48.

In this study, the relationship between the incidence of increased N/L ratio and the incidence of ARDS, where 86 (42.2%) study subjects who experienced ARDS had an increased incidence of N/L ratio as well. There is a statistically significant link between the occurrence of increased N/L ratio and the occurrence of ARDS (p-value<0.05), with a calculation of the prevalence ratio of 1.52, which is >1, so that the incidence of increased NLR can be used as a sign or risk factor for patients with ARDS incidence, where patients with increased NLR had 1.52 times the risk compared to those who did not, with 95% CI: 1.66-5.41.

The relationship between the incidence of increased procalcitonin and the incidence of ARDS, where 88 (43.1%) study subjects who experienced ARDS had an increased incidence of procalcitonin as well. Statistically there is a significant relationship between the incidence of increased procalcitonin and the incidence of ARDS with a p-value of <0.05, with a calculation of the Prevalence Ratio value of 1.52, which is >1, so that the incidence of increased procalcitonin can be used as a sign or risk factor for patients with ARDS events, where patients with procalcitonin values those who increased had 1.52 times the risk compared to those who did not, with a 95% CI: 1.73-5.70.

4. Discussion

COVID-19 individuals' symptoms range from asymptomatic to moderate respiratory problems. even with severe respiratory symptoms with acute respiratory distress syndrome, or what is called Acute Respiratory Distress Syndrome, ARDS. The human immune system has a significant role in dealing with viral infections. Neutrophil Lymphocyte Ratio (NLR), or the ratio between neutrophils and lymphocytes, reflects the high systemic inflammatory response associated with infectious diseases with a poor prognosis.

Neutrophils, lymphocytes, procalcitonin neutrophil-lymphocyte ratio (NLR), and CRP are biomarkers the authors have chosen to give critical information on the level of systemic inflammation, and they are easily obtained via normal laboratory investigations. (2, 4, 5)

The human immune system plays an essential role in eliminating viral infections. The value of the N/L ratio reflects a high systemic inflammatory response associated with a poor prognosis in infectious diseases. (6–9)

Several studies have reported that severe cases (with death outcomes) of COVID-19 tend to have high neutrophil type counts and low lymphocytic values. Elevated NLR values can help predict the severity of COVID-19. (10–12) Qin et al. also reported through their retrospective analysis of 452 patients that critical cases tended to have higher N/L ratio values than severe patients. So that the N/L ratio can help early screening for COVID-19 with a critical degree. (13)

A procalcitonin value that was higher than the cut-off value was found in 99 patients (44.6%) of the total sample, where if grouped based on the incidence of ARDS, in the group with ARDS, there was a mean procalcitonin value of 5.43 ng/mL with a median of 0.40 ng/mL which was higher if compared with the group without ARDS with a mean value

of 2.81 ng/mL and a median of 0.14 ng/mL. Procalcitonin is an inflammatory marker of bacterial infection that has long been recognized. (11, 14, 15) The increase in procalcitonin values can assist clinicians in identifying the presence of secondary infection in COVID-19 patients with severe conditions.

5. Conclusion

There were associations between inflammatory markers with ARDS. Neutrophilia, elevated NLR, and high levels of procalcitonin prior to hospitalization could be considered risk factors for ARDS in severe COVID-19 allowing clinicians to adjust treatment strategies aggressively to reduce mortality.

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