Original Article

Inflammatory Markers of ARDS Events among Patients with Severe and Critical COVID-19 Infection at Adam Malik General Hospital, Medan, North Sumatera

Eva Susanti Debora Hutabarat[1*], Fajrinur Syarani[1], Syamsul Bihar[1], Putri Chairani Eyanoer[2]

[1]Department of Pulmonology and Respiratory Medicine Faculty of Medicine, University of North Sumatra/ Adam Malik General Hospital, Medan
[2]Department of Preventive and Community Medicine Faculty of Medicine, University of North Sumatra/ Adam Malik General Hospital, Medan

Corresponding Author:
Eva Susanti Debora Hutabarat | Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas of North Sumatra - Adam Malik General Hospital, Medan | drevasusantidh@yahoo.com

Submitted: November 22nd, 2022
Accepted: December 29th, 2022
Published: June 28th, 2023

Respir Sci. 2023; 3(3): 170-6
https://doi.org/10.36497/respirsci.v3i3.78

Abstract

Background: COVID-19 can cause fatal outcomes, especially acute respiratory distress syndrome (ARDS). It manifests as organ dysfunction during COVID-19's hyperinflammatory phase, which is associated with a high mortality rate. Data on the clinical characteristics and inflammation markers of patients with severe and critical degrees of COVID-19 with ARDS events are limited.

Method: This study is carried out at the Haji Adam Malik General Hospital in Medan. We grouped 204 medical records from February to July 2022 of hospitalized patients with severe and critical COVID-19 cases into two groups, ARDS and non-ARDS. Characteristics of demographic and laboratory inflammatory markers upon admission between each group were collected. After collecting data and serving as categorical data in the frequency distribution table by SPSS ver 25.0.

Results: We identified 116 patients (56.9%) who had ARDS event upon hospital admission. ARDS event are most commonly found in the elderly group and the median age of ARDS group patients was 59.5 years higher than the non-ARDS group. Male patients were more likely to have ARDS than female patients. Compared with the non-ARDS group, ARDS group patients had lymphocytopenia, neutrophilia, increased neutrophil-to-lymphocyte ratio (NLR), Procalcitonin and C-Reactive Protein levels.

Conclusion: Lymphocytopenia, neutrophilia, increased NLR, procalcitonin and CRP levels upon admission revealed that they were higher in ARDS patients compared to non-ARDS patients. It is critical to identify high-risk groups, such as male sex, the elderly, those with comorbidities, and patients with impaired inflammatory markers to prevent severe complications from COVID-19.

Keywords: ARDS, COVID-19, Indonesia, inflammatory markers, severe COVID-19

INTRODUCTION

In December 2019, the 2019 Coronavirus disease epidemic, also known as COVID-19, was first discovered in China, Wuhan Province. Coronavirus 2019 (COVID-19), caused by the SARS-COV-2 virus globally, hit the world, so the World Health Organization (WHO) declared this plague a significant threat to international health. COVID-19 is contagious and can cause fatal outcomes, especially acute respiratory distress syndrome (ARDS). COVID-19's disease progression may be divided into three stages: early infection, pulmonary phase, and hyperinflammation phase, each of which has a distinct alteration in particular biochemical markers.[1]

Virus infiltration into the lung parenchyma marks the beginning of the first phase, where SARS-CoV-2 infects ciliated bronchial epithelial cells through interaction with ACE2. This stage may be recognized by the presence of lymphopenia. During the pulmonary phase, the pneumonia virus causes localized inflammation of the lungs. Lymphopenia, elevated transaminase enzymes, and systemic inflammatory markers such as C-Reactive Protein are some of the biochemical parameters (CRP). At this stage, most patients need hospitalization. The last stage is the hyperinflammation phase, which is characterized by systemic inflammation or cytokine storm, which could also progress to ARDS and MOF (multiple organ failure). Some inflammatory markers increase significantly.[1]

Most patients with COVID-19 infections have mild flu symptoms, including fever, coughing, and myalgia. However, Acute Respiratory Distress Syndrome (ARDS) is one of the most frequent COVID-19 complications with a high enough mortality rate. ARDS appears as an organ dysfunction in the hyperinflammatory phase of COVID-19. COVID-19 patients who have ARDS have a mortality rate of 50% - 94%.[2–5]

Patients with severe COVID-19 infection exhibit a hyperinflammation state and markers related to inflammation that will be helpful for disease risk stratification. Many studies found that in patients with severe and critical degrees, a picture of hyperinflammation characteristics consisting of decreased lymphocyte levels, an increase in NLR (Neutrophil Lymphocyte Ratio), C-Reactive protein (CRP), which increased and increased procalcitonin. These findings show an essential role of cytokine storms in the pathophysiology of COVID-19.[6,7]

The disease progression begins with a time of incubation of about 3-14 days (an average of five days). Leukocyte and lymphocyte counts are still slightly decreased or normal level and patients are not symptomatic. The next stage in symptoms started to initiate, and the virus spreads hematogenously, majorly in the tissue expressing ACE-2, such as the lungs, digestive tract, and heart. Clinical symptoms in this stage are commonly mild. The second attack occurs 4-7 days after the

early symptoms arise. The patient still has a fever; the lung lesions worsen, and lymphocytes decrease. Inflammatory markers begin to rise in number, and hyperactivity of blood coagulation begins. If the problem is not handled, the following stage of inflammation will be uncontrolled, and a cytokine storm will occur, which will result in ARDS, sepsis, and other form of complications.[8]

Acute Respiratory Distress Syndrome is one of the emergencies in the field of pulmonology, characterized by alveolar-capillary membrane disruption, causing pulmonary edema and severe hypoxemia accompanied by diffuse infiltrate in both lung fields and without clinical signs or objective evidence of left heart failure, and as a one of the leading cause of death in COVID-19, with one of the main features of ARDS is cytokine storm, an inflammatory response systemically caused by the release of cytokines and pro-inflammatory chemical substances.[9,10] In 2008, Raghavendran et al. reported that the average mortality of ARDS was 40-70%. Hartini et al. at Cipto Mangunkusumo General Hospital in 2014 reported an incident of mortality of 75.3%.[11]

This study aims to identify the characteristics of neutrophils, lymphocytes, NLR, procalcitonin and C-Reactive Protein in severe and critical degree COVID-19 patients. However, still few studies have revealed that these inflammatory markers characteristics in severe and critical degree of COVID-19 patients and the correlation in ARDS event.

METHOD

This was a retrospective study from 204 medical records of hospitalized patients with severe and critical COVID-19 cases from February to July 2022 that was conducted at the Haji Adam Malik General Hospital in Medan, Indonesia with a total sampling method. Patients aged 18 years and older with confirmed COVID-19 with severe and critical disease from February to July 2022 that hospitalized were included in this study. COVID-19 diagnosis was made according to the guidelines released by the Ministry of Health and complied with WHO interim guidelines.[12]

When patients presented with one of the following symptoms, they were considered severe cases: 1) respiratory distress with a rate of respiration ≥30 breaths/min; 2) peripheral oxygen saturation ≤93% at resting state; 3) fraction of the oxygen tension in the arterial blood with inspiratory oxygen less than 300 mmHg. Critical cases were defined when patients presented with one of the following: 1) ARDS; 2) sepsis; 3) further organ failures that need critical care unit. [12]

Demographic data (age, age category, sex, comorbidities, onset of symptom to hospital admission and phase of disease) collected as well as laboratory inflammatory markers (neutrophils, lymphocytes, calculated neutrophil-to-lymphocyte ratio (NLR), C-Reactive Protein and procalcitonin). ARDS events defined using Berlin Criteria.[13]

All statistical analyses were carried out using the SPSS version 25.0 software (SPSS Inc). For categorical data, frequencies and percentages were used for descriptive analysis, whereas the median (minimum–maximum) was for quantitative variables.

RESULTS

Between February 2021 and July 2021, 204 COVID-19 confirmed cases' medical records with severe and critical cases were collected at Haji Adam Malik General Hospital.

Acute respiratory distress syndrome event are most commonly found in the elderly group, as shown in Table 1. We categorized the subjects into three following age groups. The median age of ARDS group patients was 59.5 years higher than the non-ARDS group, 57.50 years. Male patients were more likely to have ARDS than females (32.8% vs 24.1%).

We categorized the course of the symptoms into three groups, phase 1 (0-4 days), phase 2 (4-10 days), and phase 3 (≥11 days), more patients in the ARDS group were on phase 2 and 3 than in phase 1 (30.4% vs 18.6% vs 7.8%).

Table 1. Demographic characteristics of the samples

Variable	ARDS	Non-ARDS	Total
Sex			
Male	67 (32.8%)	52 (25.5%)	119 (58.3%)
Female	49 (24.1%)	36 (17.6%)	85 (41.2%)
Age [Median (min-max)] (years)	59.50 (21-84)	57.50 (21-81)	58.50 (21-84)
Young Adult (20-39)	11 (5.4%)	10 (4.9%)	21 (10.3%)
Adult (40-59)	47 (23.0%)	40 (19.6%)	87 (42.6%)
Elderly (≥60)	58 (28.4%)	38 (18.6%)	96 (47.1%)
Diabetes Comorbid			
Yes	40 (19.6%)	28 (13.7%)	68 (33.3%)
Hypertension Comorbid			
Yes	71 (34.8%)	38 (18.6%)	109 (53.4%)
Heart Disease Comorbid			
Yes	30 (14.7%)	20 (9.8%)	50 (24.5%)
Kidney Disease Comorbid			
Yes	13 (6.4%)	13 (6.4%)	26 (12.7%)
Malignancy Comorbid			
Yes	0 (0%)	6 (2.9%)	6 (2.9%)
Others			
Yes	9 (4.4%)	107 (52.5%)	116 (56.9%)
Comorbidities			
No comorbid	29 (14.2%)	22 (10.8%)	51 (25.0%)
1 comorbid	33 (16.2%)	32 (15.7%)	65 (31.9%)
>1 comorbid	54 (33.9%)	34 (16.7%)	88 (50.6%)
Symptom to admission [Median (min-max)] (days)	8 (2-20)	7 (2-15)	7.5 (2-20)
Phase			
Phase 1 (day 0-4)	16 (7.8%)	23 (11.3%)	39 (19.1%)
Phase 2 (day 5-10)	62 (30.4%)	62 (25.5%)	114 (55.9%)
Phase 3 (day ke ≥11)	38 (18.6%)	13 (6.4%)	51 (25.0%)

Table 2. Characteristics of inflammatory markers in ARDS and non-ARDS groups

Variable	ARDS	Non-ARDS	Total
Neutrophil [Median (min-max)]	9.76 (1.89-31.34)	7.57 (0.16-21.90)	8.39 (0.16-32.34)
Neutrophilia	89 (43.6%)	46 (22.5%)	135 (66.2%)
Lymphocyte [Median (min-max)]	0.91 (0.25-3.98)	0.92 (0.14-3.48)	0.92 (0.14-3.98
Lymphocytopenia	96 (47.1%)	74 (36.3%)	170 (83.3%)
NLR [Median (min-max)]	11.02 (1.72-50.14)	6.97 (0.47-71.43)	0.92 (0.14-3.98)
Increased NLR	86 (42.2%)	43 (21.1%)	129 (63.2%)
Procalcitonin [Median (min-max)]	0.40 (0.02-373)	0.14 (0.03-58.50)	0.24 (0.02-373)
Increased Procalcitonin	88 (43.1%)	44 (21.6%)	132 (64.7%)
C-Reactive Protein			
Increased CRP	68 (33.3%)	38 (18.6%)	106 (52.0%)

The median time from the beginning of the first symptom to hospital admission was 7.5 days. In ARDS patients, the median duration from the first onset of symptom to hospital admission was 8.05 days, longer than the non-ARDS group, 6.96 days.

We noted that more patients in the ARDS group had comorbid hypertension (34.8% vs 18.6%), diabetes (19.6% vs 13.7%), heart disease (14.7% vs 9.8%), and more than one comorbid (33.9% vs 16.7%).

Laboratory findings (Table 2) on admission showed that the inflammatory markers were increased in patients in the ARDS group. Neutrophilia was found in 43.6% of patients in the ARDS group, with a median value higher than the non-ARDS group (9.76 x 10^3/µL vs 7.57 x 10^3/µL). On admission, lymphocytopenia was present in 83.3% and more frequent in the ARDS group compared to the non-ARDS group (47.1% vs 36.3%). Using this data, we calculated the NLR and found a higher NLR in ARDS patients compared to the non-ARDS patients (42.2% vs 21.1%) with a higher median value (11.02 vs 6.97).

DISCUSSION

Despite significant control measures, the global COVID-19 epidemic is damaging, with high morbidity and fatality. We need accessible, cost-effective markers to simplify diagnostics and assess disease severity. In severe COVID-19, ARDS can arise from a dysregulated host response to SARS-CoV-2.

In this study, we revealed that male, elder patients, or patients with comorbidities, were more likely to develop ARDS. In healthy individuals, innate immunity neutralizes the virus early on, preventing it from infiltrating the alveoli. In older people, when innate immunity is compromised, the virus can get into the alveoli and replicate in large numbers. This causes macrophages and lymphocytes to initiate a robust reaction to eliminate virally infected cells. Enhanced levels of cytokines are related to this reaction. It can explain why the elderly are more prone to severe COVID-19 infections.[14,15]

It was hypothesized that the increased of neutrophils and decreased of lymphocytes were triggered by a cytokine storm in the body that triggers a series of

immunological reactions. In severe instances, the levels of inflammatory markers were found to be greater than in less severe cases. It indicates that a hyperinflammatory response could play an important role in the development of COVID-19. NLR is a simple inflammatory parameter that may be assessed in routine hematological examinations. Previous research has shown that increased NLR to clinical progressivity and fatality in COVID-19 cases.[15,16]

Furthermore, our present study showed that elevated procalcitonin and CRP were detected more in patients with ARDS compared with those without ARDS. It is attracting increased attention, as many COVID-19 patients with ARDS present with a dysregulated immune state. In addition, activated immune cells drive additional infiltration and increase the generation of reactive oxygen species and nitric oxide, which damages the epithelial-endothelial barrier and causes an imbalance in the ventilation/blood flow ratio, hence promoting the progression of ARDS.[17]

CONCLUSION

Placing high-risk patients in monitored isolation is crucial for tracking the fatal case of COVID-19. Identifying high-risk groups, such as elderly persons and those with comorbidities, and placing them in appropriate care is important. Neutrophilia, lymphocytopenia, increased NLR, and increased procalcitonin occurred in most patients in the ARDS group compared to the non-ARDS group. Consideration of inflammatory markers would help an early prediction for COVID-19 patients with ARDS event. These markers may be useful in determining how to allocate respiration equipment amongst patients in the intensive care unit. Nonetheless, further clinical research is required to determine the advantages of these inflammatory markers in anticipating ARDS.

REFERENCES

1. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. J Hear Lung Transplant. 2020;39(5):405–7.
2. Liang M, He M, Tang J, He X, Liu Z, Feng S, et al. Novel risk scoring system for predicting acute respiratory distress syndrome among hospitalized patients with coronavirus disease 2019 in Wuhan, China. BMC Infect Dis. 2020;20(1):1–10.
3. Navas-Blanco JR, Dudaryk R. Management of Respiratory Distress Syndrome due to COVID-19 infection. BMC Anesthesiol. 2020;20(1):4–9.
4. Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoğ Lu U. Severe covid-19 pneumonia: Pathogenesis and clinical management. BMJ. 2021;372.
5. Jang JG, Hur J, Choi EY, Hong KS, Lee W, Ahn JH. Prognostic factors for severe coronavirus disease 2019 in daegu, Korea. J Korean Med Sci. 2020;35(23):1–10.

6. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res. 2020;8(1).
7. Gong J, Dong H, Xia QS, Huang Z yi, Wang D kun, Zhao Y, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: a retrospective study. BMC Infect Dis. 2020;20(1):1–7.
8. PDPI, PERKI, PAPDI, PERDATIN, IDAI. Pedoman tatalaksana COVID-19 Edisi 3 Desember 2020. Pedoman Tatalaksana COVID-19. 2020. 36–37 p.
9. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? Crit Care. 2020;24(1):1–5.
10. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934–43.
11. Fatoni AZ, Rakhmatullah R. Acute Respiratory Distress Syndrome (ARDS) pada Pneumonia COVID-19. J Anaesth Pain. 2021;2(1):11–24.
12. WHO. WHO COVID-19 Case definition [Internet]. WHO. 2022. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2022.1
13. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8(12):1201–8.
14. Abdulamir AS, Hafidh RR. The possible immunological pathways for the variable immunopathogenesis of COVID—19 infections among healthy adults, elderly and children. Electron J Gen Med. 2020;17(4):1–4.
15. Khadke S, Ahmed N, Ahmed N, Ratts R, Raju S, Gallogly M, et al. Harnessing the immune system to overcome cytokine storm and reduce viral load in COVID-19: a review of the phases of illness and therapeutic agents. Virol J. 2020;17(1):1–18.
16. Ma A, Cheng J, Yang J, Dong M, Liao X, Kang Y. Neutrophil-to-lymphocyte ratio as a predictive biomarker for moderate-severe ARDS in severe COVID-19 patients. Crit Care. 2020;24(1):24–7.
17. Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: A global literature survey. Crit Care. 2020;24(1):1–4.