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Overview of Interleukin-6 Levels in COVID-19 (Coronavirus Disease 2019) Patients at Dr. M. Djamil General Hospital, Padang, Indonesia

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ABSTRACT

Background: COVID-19 infection can cause an exaggerated immune response. This immune response is associated with an increase in proinflammatory cytokines, especially interleukin-6 (IL-6). High IL-6 levels are found in the acute stage of COVID-19, and IL-6 can induce an excessive humoral inflammatory response. This study aimed to provide an overview of IL-6 levels in coronavirus disease 2019 (COVID-19) patients at Dr. M. Djamil General Hospital, Padang, Indonesia. **Methods:** Descriptive observational study of 102 research subjects. Observations on sociodemographic, clinical, and laboratory data were carried out in this study. Univariate analysis was carried out using SPSS version 25. **Results:** Patients with symptom onset <7 days had higher IL-6 levels than those with an onset of more than 7 days. Patients with critical degrees have the highest IL-6 levels compared to moderate and severe degrees. Patients with more than 1 comorbid had higher IL-6 levels than patients who had no comorbid or only had 1 comorbid. Patients with <21 days of treatment had higher IL-6 levels than patients with more than 21 days of treatment. **Conclusion:** COVID-19 patients at Dr. M. Djamil General Hospital, Padang, Indonesia, with an onset of less than 7 days, a critical degree, and more than 1 comorbidity have higher IL-6 levels.

1. Introduction

The severity of COVID-19 varies. Some people are asymptomatic, and some have mild symptoms such as flu-like symptoms, but some develop severe, critical symptoms up to death. Acute respiratory distress syndrome (ARDS), pneumonia, and multiple organ dysfunction (MOD) are clinical manifestations of the progression of COVID-19. Approximately 3-29% of patients undergoing treatment at the hospital require treatment in the intensive care unit (ICU). COVID-19 infection can cause an exaggerated immune response. This immune response is associated with an increase in proinflammatory cytokines, especially interleukin-6 (IL-6). Excessive increase in IL-6 levels is thought to cause damage to the wall alveolus so that ARDS

occurs. This event is known as cytokine storm syndrome, which requires intensive care.¹⁻⁵

High IL-6 levels are found in the acute stage of COVID-19, and IL-6 can induce an excessive humoral inflammatory response. Excessive increase in IL-6 has a correlation with mortality and disease severity. Other research states that clinically critical COVID-19 patients with severe respiratory failure have immune dysregulation, which is characterized by an increase in proinflammatory cytokines, especially IL-6. This exaggerated immune response can cause lung damage and fibrosis, resulting in functional disability.⁶⁻⁹ This study aimed to provide an overview of IL-6 levels in coronavirus disease 2019 (COVID-19) patients at Dr. M. Djamil General Hospital, Padang, Indonesia.

2. Methods

This study was a descriptive observational study and used secondary data obtained from medical records at the medical records installation of Dr. M. Djamil General Hospital, Padang, Indonesia. A total of 102 research subjects participated in this study, where the research subjects met the inclusion criteria. The inclusion criteria were patients diagnosed with COVID-19 who were treated at Dr. M. Djamil General Hospital, Padang, Indonesia, aged more than 18 years, and have complete medical record data. This study was approved by the medical and health research ethics committee at Dr. M. Djamil General Hospital, Padang, Indonesia. This study explores various sociodemographic data, clinical data, and laboratory

data from research subjects. Data analysis was carried out univariately to present the distribution frequency of each data and variable. Analysis was carried out using SPSS software version 25.

3. Results

Table 1 presents the characteristics of COVID-19 patients at Dr. M. Djamil General Hospital, Padang, Indonesia. The majority of patients are over 60 years old and male. The majority of COVID-19 patients have IL-6 levels of more than 80 pg/mL. The majority of patients have symptom onset in less than 7 days. The majority of COVID-19 patients experience a critical degree, have comorbidities, and have a length of stay of less than 21 days.

Table 1. Characteristics of COVID-19 patients.

Variable	Total
Age	
18-60 years	40 (39,28%)
>60 years	62 (60,82%)
Gender	
Male	58 (56,91%)
Female	44 (43,19%)
IL-6 level	
<80 pg/ml	16 (15,77%)
>80 pg/ml	86 (84,33%)
Symptom onset	
<7 days	86 (84,33%)
≥7 days	16 (15,77%)
Clinical degree	
Moderate	18 (17,63%)
Severe	13 (12,74%)
Critical	71 (69,63%)
Comorbid	
No	29 (28,43%)
Yes	
1 comorbid	56 (54,94%)
>1 comorbid	17 (16,73%)
Length of stay	
<21 days	99 (97,19%)
≥21 days	3 (2,91%)

Table 2 presents a cross-tabulation between IL-6 levels associated with several variables in COVID-19 patients. Patients with symptom onset <7 days had higher IL-6 levels than those with an onset of more than 7 days. Patients with critical degrees have the highest IL-6 levels compared to moderate and severe

degrees. Patients with more than 1 comorbid had higher IL-6 levels than patients who had no comorbid or only had 1 comorbid. Patients with <21 days of treatment had higher IL-6 levels than patients with more than 21 days of treatment.

Table 2. Overview of IL-6 levels in COVID-19 patients.

Variable	IL-6 level (pg/mL), Mean
Symptom onset	
< 7 days	248,33
≥7 days	101,26
Clinical degree	
Moderate	77,3
Severe	180,33
Critical	272,67
Comorbid	
No	216,54
Yes	
1 comorbid	225,19
>1 comorbid	247,82
Length of stay	
<21 days	228,82
≥21 days	139,33

4. Discussion

IL-6 levels increase sharply in COVID-19 with critical clinical degrees, according to existing studies. Another study demonstrated an increase in serum IL-6, CRP, and procalcitonin in patients with the severe clinical disease who were admitted to the ICU. IL-6 levels in patients in the ICU increased significantly when compared to patients who were not treated in the ICU. In 2 patients who died in the ICU, IL-6 levels had reached the upper limit, which was > 240 pg/ml. Other studies have also shown an increase in IL-6 levels up to three times in patients with severe COVID-19. It is known that there is a dysregulated immune response to pathogens cause organ dysfunction. COVID-19 patients with ARDS experience hyperactivation of the humoral immune system called cytokine release syndrome (CRS). CRS can be triggered by various factors such as infection, toxins, and proinflammatory cytokines (TNF, IL-6, IL-1 β). The cytokine release syndrome that occurs in COVID-19 is triggered by an excess of IL-6 response. IL-6 increases pulmonary capillary permeability and stimulates coagulation pathways, causing microthrombi to form in the pulmonary circulation. Failed COVID-19 patients' breath suspected of having immune system dysregulation mediated by IL-6 upregulation. This dysregulation leads to the production of cytokines proinflammatory excess by monocytes, macrophages,

and decreased CD4 lymphocytes which causes inflammation of the lung parenchyma.¹⁰⁻¹⁴

IL-6 levels can also be used as a predictor of the severity of COVID-19, where IL-6 levels > 24.3 pg/ml together with D-dimer levels > 0.28 mg/L increase the risk of respiratory complications of COVID-19 with a sensitivity of 66.7% and a specificity by 96.4%. Another study compared IL-6 levels in COVID-19 patients in the ICU who died with patients who recovered. The result is that there is a significant increase in IL-6 and IL-10 in critical patients compared to non-critical patients. Other studies have also shown higher levels of IL-6 and IL-10 in COVID-19 patients treated in the ICU and the presence of IL-2, IL-4, TNF- α , and IFN- γ in very small amounts. Various studies have also presented similar results, namely increased levels of IL-6, IL-10, and TNF- α in critical patients. However, there have also been studies with results of IL-2 levels in asymptomatic and mild clinical patients and increased IFN- γ and IL-4 in the early stages of infection.^{15,16}

High IL-6 levels are associated with an increase in the neutrophil: lymphocyte ratio and CT severity score on high-resolution computed tomography (HRCT) examination of the thorax in critically ill patients in the ICU. This allows the use of IL-6 levels as a predictor of COVID-19 severity. However, IL-6 levels are not directly proportional to mortality rates, so they cannot be used as a predictor of mortality in COVID-19

patients in the ICU in this study. There is another study using measurement of IL-6 levels for 72 hours as a predictor of mortality in COVID-19 patients where patients with IL-6 levels of more than the 50% percentile have a high mortality rate in 21 days, and IL-6 levels of more than the 75% percentile has a high mortality within 18 days. Increased levels of IL-6 correlate with the progress of COVID-19 at the cellular level. High levels of IL-6 cause inhibition of CD8+ T-cell responses and, together with IL-17, induce cell death through PD-1 and PDL. Patients with IL-6 levels >80 pg/ml have a 22-fold higher risk of experiencing respiratory failure than patients with lower IL-6 levels. Elevated IL-6 levels also increase the risk of cardiovascular events in COVID-19. Early symptoms of COVID-19, which are predominantly upper respiratory infections, can develop into pneumonia, ARDS, and cardiovascular disorders such as myocardial infarction, pericarditis, and arrhythmias. Cardiovascular disorders in COVID-19 can be characterized by increased levels of C-reactive protein, NT-pro BNP, and creatinine. COVID-19 patients who died were found to have higher levels of IL-6 and ferritin, accompanied by higher rates of acute cardiovascular events and acute heart failure.¹⁷⁻¹⁹

5. Conclusion

COVID-19 patients at Dr. M. Djamil General Hospital, Padang, Indonesia, with an onset of less than 7 days, a critical degree, and more than 1 comorbidity, have higher IL-6 levels.

6. References

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