Original Article

Differences in IL-6 Levels Based on Clinical Severity and Outcome of COVID-19 Patients at Dr. M. Djamil Hospital

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Abstract

Background: A cytokine storm is defined by elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6). In COVID-19 infection, IL-6 is superior to C-reactive protein (CRP) and other inflammatory markers in predicting respiratory failure. The IL-6 is the main cytokine triggered by T cells when a cytokine storm occurs. IL-6 is the most important driver of immune dysregulation and ARDS in COVID-19 infection. The purpose of this study is to assess differences of IL-6 levels based on clinical severity and outcomes in COVID-19 patients at Dr. M. Djamil Hospital.

Method: The study took place at Dr. M. Djamil Hospital from November 2021 to November 2022. This is a retrospective cohort study in which patients were tested for IL-6 levels between January 1st, 2021 and December 31, 2021. The distribution of the frequency and proportion of each variable is included in univariate analysis; bivariate analysis determines the correlation between the independent variables (clinical severity, length of stay, and final status of hospitalization) and the dependent variable (IL-6 levels in COVID-19 patients).

Results: Patients' characteristics in this study, the majority of patients aged 18-49 years. Women and patients with moderate disease were more common. The majority of patients were treated for less than 14 days, and the final status of hospitalization the patients showed that most of the patients recovered. IL-6 levels with median (min-max) was 32.00 (1.50-589.00). The IL-6 levels were higher in clinically critical COVID-19 patients (77.20 mg/L), in patients with a shorter length of stay (14 days) (36.00 mg/L), and at final status of hospitalization were death (58.90 mg/L).

Conclusion: There were differences of IL-6 level based on clinical severity and final hospitalization status of COVID-19 patients, but not from the length of stay in COVID-19 patients at Dr. M. Djamil Hospital.

Keywords: clinical severity, COVID-19, IL-6 length of stay, outcome

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has infected millions of people and has a high mortality rate, deeming it a global emergency.[1] The Severe Acute

Respiratory Syndrome Coronavirus-2 (SARS-Cov2) virus infection causes a variety of symptoms ranging from asymptomatic to severe. Fever, cough, difficulty breathing, other respiratory symptoms, and non-respiratory symptoms such as diarrhea, anosmia, ageusia, delirium, nausea, vomiting, and others are the most common clinical symptoms.[2] Around 80% of COVID-19 cases have mild-moderate symptoms, and 5% or more patients with critical-severe symptoms require intensive care unit (ICU) treatment, with a mortality rate of 1-2%.[3]

The pathogenesis of COVID-19 is divided into three stages: pulmonary, pro-inflammatory, and thrombotic.[4] COVID-19 infection has a diverse clinical picture in each phase, with 5-20% progressing to a severe level and requiring intensive care due to organ dysfunction. Therefore, it is important to identify patient characteristics that must be prioritized and have the potential to progress to a severe degree through hyperinflammation prevention. The challenge is determining how to detect early worsening conditions to aid in the management of COVID-19 patients. Effective markers can help with the detection, management, and prevention of serious complications.[5]

Acute respiratory distress syndrome (ARDS) and multi-organ failure can occur in patients with severe COVID-19 due to an increase in proinflammatory cytokines. Han et al discovered that lymphopenia and cytokine release syndrome (CRS) were related to disease severity.[6] Cytokine release syndromes, which cause single or multiple organ failure, have been thought to influence not only the severity but also the prognosis of COVID-19.[7] Cytokine storm is a systemic inflammatory response characterized by increased levels of proinflammatory cytokines, including IL-6, that can be triggered by a variety of factors such as infection, toxins, or idiosyncratic drug responses. Gubernatorova et al discovered that IL-6 levels had a strong correlation with the incidence of ARDS (P=0.001).[8]

Recent studies by Sabaka et al suggest using IL-6 testing in patient management and identifying patients at risk of aggravation.[9] Study by Renee et al, COVID-19 patients requiring hospitalization or experiencing acute respiratory failure had higher than normal levels of IL-6.[10] According to the findings of a recent meta-analysis, critically ill COVID-19 patients (ICU admission and/or acute respiratory failure) had nearly three times higher serum IL-6 levels.[11]

High IL-6 levels have been linked to a variety of clinical symptoms, including fever and the presence of bilateral lung involvement on computed tomography chest scans.[12] In the study by Ruan et al, higher levels of IL-6 were found in patients who died from COVID-19 when compared to survivors.[13] IL-6 levels may serve as an indicator of poor prognosis, according to Coomes et al research in Toronto.[3,14]

Sabaka et al found that IL-6 is superior to CRP and other inflammatory

markers in predicting respiratory failure in COVID-19. In COVID-19, interleukin-6 is the most important driver of immune dysregulation and ARDS.[9] During a cytokine storm, interleukin-6 is the primary toxic mediator produced by T cells.[11] The systematic role of IL-6 measurement and its ability to predict disease severity has yet to be determined.[6] Based on the foregoing information and the limited research on the effect of IL-6 on the clinical degree and outcome of COVID-19 patients at Dr. M. Djamil Hospital, the researcher wishes to investigate how IL-6 levels relate to the clinical degree and outcome of confirmed COVID-19 patients being treated at Dr. M. Djamil Hospital.

METHOD

This was a retrospective cohort study. The study took place at Dr. M. Djamil Hospital from November 2021 to November 2022. This research is part of the study "Relationship between initial CT values, inflammatory markers and onset of clinical symptoms with the outcome of treatment of COVID-19 patients at Dr. M. Djamil Hospital Padang" and has received approval from the Research Ethics Committee of Dr. M. Djamil Hospital with N0. LB 02.02/5.7/520/2022. Patients were tested for IL-6 levels at Dr. M. Djamil Hospital from January 1st 2021 to December 31st 2021.

Patients who met the inclusion and exclusion criteria were studied for IL-6 levels from January 1st, 2021 to December 31st, 2021. The COVID-19 patients over the age of 18 who were treated in the isolation room of Dr. M. Djamil Hospital and examined by IL-6 with complete medical record data including demograpfhic data, clinical degree description, and outcome were eligible for the study.

The study exclusion criteria were patients with mild clinical degrees of COVID-19 who were treated due to comorbidities; discharged patients at their request while still being treated for COVID-19; and patients with comorbid autoimmune diseases (rheumatoid arthritis, SLE, rheumatic heart disease, primary Sjogren's syndrome, fibrosis), bone dysplasia, JIA, and uveitis in JIA), chronic inflammation (Erdheim-Chester disease, Behcet's syndrome, systemic sclerosis, large cell arteritis, and type 2 diabetes mellitus), malignancy (ovarian cancer, colorectal cancer, prostate cancer, breast cancer, cancer of the bones, blood cancer, pancreatic cancer, lung cancer (non-small cell carcinoma), and lymph cancer), post-organ transplantation, patients receiving anti-IL6 therapy, and patients with extreme levels of IL-6.

RESULTS

There were 322 samples that met the inclusion and exclusion criteria. Table 1 shows the characteristics of COVID-19 patients treated at Dr. M. Djamil Hospital. The COVID-19 patients aged 18-49 years are the most common age group being treated (41.93%). Female COVID-19 patients were treated more frequently than male patients (45.34%).

Table 1. Characteristics of COVID-19 patients treated at Dr. M. Djamil Hospital (n=322)

Patient's Characteristic	N	%
Age		
18–49 years	135	41.93
50–59 years	82	25.47
60–69 years	61	18.94
≥70 years	44	13.66
Gender		
Male	146	45.34
Female	176	54.66
Clinical Severity		
Moderate	132	40.99
Severe	91	28.26
Critical	99	30.75
Length of stay		
<14 days	233	72.36
≥14 days	89	27.64
Final Status of Hospitalization		
Recovered	224	69.57
Recovered with sequelae	10	3.10
Died	88	27.33
IL-6 levels [median (min-max)]	36.00 (1.50-589.00)	

The majority of patients (40.99%) had a moderate clinical severity, while only 28.26% had severe and 30.75% had a critical severity. Most patients (72.36%) stayed for less than 14 days on average, while 27.64% stayed for more than 14 days. The final status of hospitalization of the patients revealed that the majority of them (69.57%) recovered, only 3.10% recovered with sequelae, and 27.33% died. For IL-6 levels, the median (min-max) is 32.00 (1.50-589.00).

Table 2. IL-6 Levels Based on Clinical Degree of COVID-19 Patients Treated at Dr. M. Djamil Hospital

Clinical Degree	IL-6 Levels [Median (min-max)]	P
Moderate	21.50 (1.50-528.00)	
Severe	53.00 (2.49-589.00)	0.0001*
Critical	77.20 (1.50-588.00)	

Note: *P<0.05 significant with the Kruskal-Wallis test

Table 2 shows that COVID-19 patients with critical severity (77.20 mg/L) have higher IL-6 levels than those with severe condition (53.00 mg/L) and moderate condition (21.50 mg/L). The analysis revealed significant differences in IL-6 levels based on the clinical severity of COVID-19 patients at Dr. M. Djamil Hospital.

Table 3. The IL-6 levels of COVID-19 patients treated at Dr. M. Djamil Hospital based on the length of their treatment

Length of Stay	IL-6 Levels [Median (min-max)]	P
<14 days	36.00 (1.50-589.00)	0.633*
≥14 days	35.60 (1.50-528.00)	

Note: *P<0.05 significant with the Kruskal-Wallis test

Table 3 shows that IL-6 levels were higher in patients with a length of stay of more than 14 days (36.00 mg/L) than <14 days 35.60 mg/L. The analysis revealed that there was no significant difference in IL-6 levels between COVID-19 patients at Dr. M. Djamil Hospital based on length of stay.

Table 4. IL-6 Levels Based on Final Hospitalization Status of COVID-19 Patients Treated at Dr. M. Djamil Hospital

Final Hospitalization Status	IL-6 Levels [Median (min-max)]	P
Recovered	33.90 (1.50-589.00)	
Recovered with sequelae	37.45 (9.20-173.00)	0.0001*
Died	58.90 (1.50-588.00)	

Note: *P<0.05 significant with the Kruskal-Wallis test

Table 4 shows IL-6 levels are higher at final hospitalization status were death (58.90 mg/L), recovery with sequelae (37.45 mg/L) and recovery (33.90 mg/L). The analysis found significant differences in IL-6 levels based on final hospitalization

status for COVID-19 patients at Dr. M. Djamil Hospital.

DISCUSSION

There were 322 confirmed COVID-19 patients at Dr. M. Djamil Hospital who met the inclusion criteria for this study. COVID-19 patients with a mild clinical condition were excluded because inflammatory markers were not examined. This is consistent with a study conducted in Istanbul by Esin et al, which found that in patients with mild clinical symptoms, there was no significant increase in serum IL-6 due to the small amount of cell damage caused by SARS CoV2. In these mild COVID-19 patients, the inflammatory response did not increase proinflammatory cytokines such as IL-6, IL1-, and TNF-.[15]

The characteristics of the patients in this study revealed that the majority of the COVID-19 patients treated at Dr. M. Djamil Hospital were between 18 and 49 years old as many as 140 patients (41.93%), and patients more than 70 years old as many as 46 patients (13.66%). This study is consistent with the study of Setiadi et al in Jakarta, who reported that the age range of patients treated was 40-60 years for as many as 29.6%, followed by young adults aged 19-40 years for as many as 24.2%.[16]

The cause of the large number of COVID-19 patients who are adults and young adults of productive age is the transmission of the SARS-CoV-2 virus, whose transmission that influenced by human mobility. The adult and young adult's outdoor activities, such as work and face-to-face learning, as well as domestic and international travel, provide opportunities for transmission.[16]

According to the findings of a separate study conducted by Liu et al, the average age of COVID-19 patients in China is 56 years old.[17] Khan et al discovered that 74% of patients were over the age of 50.[18] The severity of COVID-19 disease is related to age, which is caused by a decline in the immune system (immunosenescence) in old age.[18] This study supports the findings of Lee et al, who discovered that age influences the decrease in Angiotensin Converting Enzyme-2 (ACE-2) expression, implying that age has clinical implications in determining the prognosis of COVID-19 patients.[4]

According to a study conducted by Cummings et al in New York, old age is associated with high morbidity and mortality due to many comorbidities, longer length of stay, increase need for mechanical ventilation, and increase need for oxygen supplementation after hospital discharge.[19] In the elderly, cellular senescence, immunosenescence, and inflammaging cause phenotypic changes in immune cells such as telomere shortening, inhibition of immune cell proliferation, and accumulation of senescent macrophages (macrophageing), interfering with viral clearance in the respiratory tract. A decrease in the number of T cell receptors caused by aging results in the production of a small number of T cells and B cells, disrupting the adaptive immune response and making vaccinations less effective in the elderly.[20]

According to this study, there were more female patients than male COVID-19 patients treated at Dr. M. Djamil Hospital. The findings of this study are consistent with the findings of Liu et al, who discovered that female patients had 52.17% more severe cases than male patients, while male patients had 47.83% more severe cases.[17] These findings are also consistent with Shayan Kahn's research, which discovered 52.3% more female patients and 47.6% more male patients.[18]

Women have higher levels of ACE2 enzymatic expression than men, particularly ACE2 expression in the transverse colon. When compared to other symptoms, this increase in ACE2 expression causes gastrointestinal symptoms to predominate in COVID-19 infection in women.[21]

This study differs from Lee et al's study, which found that the morbidity and mortality rates of COVID-19 patients were higher in males because the ACE2 gene was located on the X chromosome, resulting in a more severe condition because of a decrease in the number of ACE2 receptors in male patients.[4] Another factor that contributes to more SARS-CoV-2 infections in men is the effect of sex hormones on immune and inflammation modulation. Estrogen boosts innate and adaptive immunity, improves vascular function, promotes regeneration, and has anti-inflammatory and antioxidant properties, whereas testosterone suppresses the immune system.[21]

According to the clinical severity of the disease, the number of patients in the moderate clinical category was 40.99%, the critical category was 30.75%, and the severe category was 28.26%. Patients treated for less than 14 days were as many as 72.36%, while those treated for more than 14 days were as many as 27.64%. According to the final hospitalization status of the patients, 69.57% recovered, 3.10% recovered with residual symptoms, and 27.33% died. Those 88 patients died with varying clinical severity, including 60 patients in critical, 15 in severe condition, and 13 in moderate condition.

According to Pal et al study in Romania, the death rate for COVID-19 patients ranged between 12.9% and 61.5%.[22] According to Goertz et al, COVID-19 symptoms were still present 90 days after recovery in patients who had been hospitalized for COVID-19, with 32% having one or two symptoms, 55% having three or more symptoms, and only 13% being symptom-free.[23]

The results of this study's examination of IL-6 levels in COVID-19 patients revealed a 92.2% increase in IL-6 levels >7 pg/ml and a 7.8% in normal IL-6 levels of <7 pg/ml. Most existing studies show that IL-6 levels in COVID-19 patients are higher than the normal range and that IL-6 levels are higher in severe cases of COVID-19 than in mild to moderate clinical cases.[24] Takashi's research demonstrates an association between serum IL-6 levels in COVID-19 patients and the likelihood of ICU hospitalization.[25]

The increase in IL-6 in COVID-19 is because this cytokine is produced by stromal cells as well as a variety of immune cells including macrophages, dendritic cells, mast cells, T lymphocytes, and B lymphocytes. In COVID-19 infection, these cytokines are also activated by IL-1 and TNF, and their secretion is influenced by TLRs, prostaglandins, adipokines, and other cytokines.[14]

Another important factor that contributes to higher IL-6 levels in SARS-CoV-2 infection when compared to other infectious or inflammatory conditions is the virus's ability to directly initiate IL-6 secretion. Protein N on the surface of the SARS-CoV-2 virus is a structural protein that can directly activate IL-6 secretion and expression (nucleocapsid). Apart from activating this protein, it also prolongs IL-6 secretion, so the amount of RNA viral load influences the severity of the patient.[14]

According to this study, IL-6 levels are higher in critical conditions (77.20 mg/L) compared to severe (53.00 mg/L) and moderate (21.50 mg/L). The analysis revealed significant differences in IL-6 levels based on the clinical severity of COVID-19 patients at Dr. M. Djamil Hospital. Herold's study found that a high increase in interleukin-6 (IL-6) above 80 pg/ml was sufficient to identify COVID-19 patients at high risk of respiratory failure.[26]

Patients with IL-6 levels of 80 pg/mL had a 92% risk of respiratory failure, which was 22 times higher than patients with lower IL-6 levels. The median time for mechanical ventilation after reaching IL-6 levels of 80 pg/mL was 1.5 days (range 0–4 days).[27] In the early stages of COVID-19 infection, monocytes and macrophages produce the cytokine IL-6, which if in excess, can cause severe lung damage (acute lung injury) and worsen the patient's condition.

Gorham's study concentrated on ICU patients with severe conditions (high SOFA score; 85% of patients were on mechanical ventilation, 68% were treated supine, and 20% were on ECMO). The overall mortality rate is 32%, indicating clinically critical COVID-19 patients with a poor prognosis. A larger cohort study of IL-6 levels in COVID-19 patients treated in the ICU is required to assess the significance and role of IL-6 in patient prognosis more specifically.[28]

In a study of 127 patients with severe COVID-19 in China, Zhu et al discovered that IL-6 levels as the sole parameter determining the severity of COVID-19 were superior to other inflammatory parameters, with an AUROC of 0.835, a sensitivity of 87.50% (95% CI=61.60-98.10), and a specificity of 74.77% (95% CI=65.60-82.50).[29] Sabaka et al discovered that patients with baseline IL-6 levels greater than 24 pg/ml had a 50% chance of developing hypoxia, with a 100% sensitivity and an 88.9% specificity; the positive and negative predictive values were 76.9% and 100%, respectively.[9] Mojtabavi et al discovered an average difference in IL-6 levels of 23.1 pg/mL (95% CI=12.42-33.79) in a meta-analysis study involving 1357 COVID-19 patients.[30]

Interleukin-6 stimulates T-cell activation and expansion, as well as B-cell

differentiation, both of which contribute to the acute phase response. When B cells are activated by antigen, these cytokines are required for B cell proliferation. They also cause B cells to differentiate into effector cells that produce IgM, IgG, and IgA antibodies. These cytokines promote the maturation of immature thymocytes into cytotoxic T cells while suppressing the induction of regulatory T cells via Th17 cells.[24]

Increased IL-6 levels, followed by excessive immune cell proliferation, cause the release of proinflammatory cytokines and chemokines, resulting in a worsening of systemic inflammation, known as a "cytokine storm." A cytokine storm damages the lungs, leading to ARDS and worsening the patient's clinical condition.[31]

The analysis revealed that there was no significant difference in IL-6 levels between COVID-19 patients at Dr. M. Djamil Hospital based on length of stay. The average length of stay for patients with moderate degrees was 12.36 days, 10.80 days for those with severe degrees, and 8.71 days for those with critical degrees. In this study, the average length of stay for recovered patients was 12.42 days, while patients with residual symptoms stayed for 13 days, and patients who died had the shortest stay, namely 6.42 days. This finding is consistent with the findings of Christel et al, who found no relationship between onset and outcome in COVID-19 patients (P=0.633).[32]

The median length of stay for patients who recovered ranged from 5 days (in the young) to 15.7 days (in the elderly), while the median length of stay for patients who died ranged from 5.7 days (in the elderly) to 12.2 days (in the elderly working age). The length of hospital stays for recovering patients increases with age, and men recover slightly slower than women. In contrast, the working-age population has the longest time between hospitalization and death, while the elderly have shorter survival times. Nursing home patients spend more time in the hospital than patients of the same age in the general population.[32]

In a separate study, Zhu et al discovered that IL-6 levels in severe COVID-19 cases were higher than those in the mild-moderate group at baseline, 5-10 days after the onset of the disease, and gradually decreased until they reached levels comparable to those in the mild-moderate group, following a 10-day course of treatment.[29] Cruz et al discovered high IL-6 levels in survivors, leading to clinical deterioration, but there was a rapid decrease in IL-6. Peak IL-6 levels in survivors occur 7-10 days after symptom onset. The critical inflammation peaks around days 7-10, accompanied by clinical worsening.[33]

Even though the patient had clinically progressed to the hypoxemic stage, IL-6 levels tended to decrease after the 10th day and were close to normal. The strongest predictor of age is IL-6.[33] Sun et al discovered a 23-fold increase in IL-6 levels in 8 patients who progressed to critical illness and respiratory failure in a retrospective study of 40 patients with severe degrees in China.[34]

High IL-6 levels can cause bilateral lung damage and pyrexia, worsening symptoms and necessitating oxygen therapy and mechanical ventilation. COVID-19 patients with high IL-6 levels stayed in the hospital for longer periods than COVID-19 patients with mild to moderate COVID-19 levels. In terms of length of stay, the average significant difference in IL-6 levels between patients with severe and non-severe COVID-19 is 38.6 pg/mL.[35] Other factors influencing COVID-19 patients' length of stay include age and the number and type of co-morbidities such as diabetes, hypertension, and cardiovascular disease.[36]

According to the findings of this study, IL-6 levels were higher at final hospitalization status death (58.90 mg/L) when compared to recovery with sequelae (37.45 mg/L) and recovery (33.90 mg/L). The analysis found significant differences in IL-6 levels based on final hospitalization status for COVID-19 patients at Dr. M. Djamil Hospital. The findings of this study are supported by Shimazui's research, which found that higher IL-6 levels (per tertile) are significantly associated with a higher 90-day in-hospital mortality rate (P=0.005).[25]

This is supported by research by Xiaohui who discovered that the IL-6 level can predict the severity of COVID-19 patients. The combined area under the curve (AUC) was 0.85 (95% confidence interval (CI) 0.821 to 0.931). According to research, there is a link between IL-6 levels and mortality. Pooled sensitivity, specificity, and AUC were 0.15 (95% CI=0.13-0.17; I^2=98.9%), 0.73 (95% CI=0.65-0.79; I^2=91.8%), and 0.531 (95% CI=0.451-0.612).[7]

The study by Abdul et al found the same correlation between IL-6 and the severity of COVID-19 patients; this is because IL-6 is an adequate predictor of disease severity in COVID-19 patients.[37] According to research conducted in Munich, high IL-6 levels can predict critical illness. In a cohort of 40 patients, increased IL-6 (>80 pg/ml) was found to be strongly associated with a 22-fold higher need for mechanical ventilation compared to patients with lower IL-6 levels.[27]

Interleukin-6 is a significant cytokine whose production is linked to a variety of inflammatory diseases.[9] Subjects infected with SARS-CoV-2 had elevated IL-6 levels, which correlated with patient symptoms such as pulmonary inflammation and extensive lung damage. Furthermore, patients infected with SARS-CoV-2 had low levels of suppressor cytokine signaling-3, which controls and stimulates the IL-6 negative feedback mechanism.[38]

Other studies have found that IL-6 levels are higher in patients with severe COVID-19, which can be used to predict the progression from mild to severe infection.[9] According to Diao et al, COVID-19 patients in intensive care had lower CD8+ T cell counts, and their total CD4+ and CD8+ T cell counts were also negatively correlated with TNF- and IL-6 levels.[39]

Recent research has revealed that higher levels of IL-6, CRP and IL-10 are more significant than other cytokines in a

subset of COVID-19 patients. This study examined the IL-6 parameter at the time of the patient's arrival at the hospital. Due to the dynamics of inflammatory processes during SARS-CoV-2 infection, Cruz et al concluded that measuring IL-6 only at the start of treatment was insufficient for accurately predicting outcomes or serving as a guideline for therapy. IL-6 kinetics analysis revealed that IL-6 levels increased transiently in patients who had received treatment.[33]

The mortality rate of COVID-19 patients can be divided into three stages based on the immune parameter of increased IL-6 levels. Stage 1 is the first four days of being sick with COVID-19, when significant viral replication occurs, resulting in viremia in the blood.[40] IL-6 levels were not significantly different between patients who recovered and those who died. Age, gender and co-morbidities such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease and obesity all have an impact on patient outcomes during this stage.[36,40]

Stage 2 occurs in 5-14 days when the disease's fatality rate rises due to amplification of the inflammatory response and accelerated progression to clinically severe or critical. Due to the massive production of immune cells and inflammatory cytokines, particularly IL-6, severe symptoms such as shortness of breath, sepsis, and ARDS appear at this stage. Excessive inflammatory mediators cause lung damage and impair lung function as a result of widespread inflammatory infiltration. COVID-19 patients in this stage are extremely vulnerable and will die. Survivors of COVID-19 who have a cytokine storm during this phase have sequelae after they recover.[40]

Stage 3 is the final stage, which occurs after 15 days, with a median time of 16-18.5 days from the onset of COVID-19 until the patient dies. Patients in this phase suffer severe organ injuries, particularly to the heart, kidneys, liver, and lungs; nearly all patients in this phase require life-sustaining mechanical ventilation. In this vase, IL-6 levels rise dramatically, causing vascular leakage, activation of complement pathways, and disseminated intravascular coagulation, which occurs in 71.4% of patients and leads to death from multiorgan failure.[40]

This study employed total sampling with a large sample size to discover a significant association between IL-6 levels and clinical severity and final hospitalization status, but it discovered limitations. This is a retrospective cohort study with data collected from medical records, and the patient distribution in each clinical degree is uneven. It only evaluates IL-6 levels during the first 24 hours of treatment.

CONCLUSION

The COVID-19 patients in this study were mostly women between 18-49 years old, with a moderate clinical severity of disease, a length of stay less than 14 days, and a final hospitalization status recovered. There were differences of IL-6 levels based

on clinical severity and final hospitalization status of COVID-19 patients, but not from the length of stay in COVID-19 patients at Dr. M. Djamil Hospital.

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