Original Article

The Effect of Dexamethasone on IL-6 Levels in Confirmed COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

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Abstract

Background: Elevated IL-6 levels have been found in COVID-19 patients and are associated with a poor prognosis. According to COVID-19 management guidelines, several types of corticosteroids can be used as therapy modalities for COVID-19 patients, including dexamethasone, methylprednisolone, and hydrocortisone. The purpose of this study was to examine how dexamethasone administration affected changes in IL-6 levelsin confirmed COVID-19 patients at RSUP Dr. M. Djamil Padang.

Methods: This was a retrospective cohort study with a sample of all COVID-19 patients who met the inclusion and exclusion criteria and were treated in the COVID-19 isolation ward at Dr. M. Djamil General Hospital

Padang. The study began in June 2021 and concluded in July 2022. The data were analyzed both descriptively and analytically. The distribution of frequencies and proportions of each variable was included in the univariate analysis. The bivariate analysis employs data-scale-appropriate statistical tests such as the T-test to determine the relationship between independent and dependent variables.

Results: The characteristic of the patients were mostly 18-49 years old (37.22%), female (55.67%), of severe clinical degree (49.44%), had no comorbidities (52.78%) and the majority (77.78%) received dexamethasone in the recommended dose (1 x 6 mg). The study's findingsrevealed that there was no difference in IL-6 values before and after dexamethasone administration in patients with moderate clinical degrees, but there were differences in IL-6 values before and after dexamethasone administration in patients with severe and critical clinical degrees.

Conclusion: The IL-6 level has significantly decreased following dexamethasone administration. Dexamethasone administration causes significant changes in IL-6 values in severe and critical degrees but not in moderate clinical degrees.

Keywords: COVID-19, dexamethasone, IL-6

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Submitted: November 29th, 2022
Accepted: July 23rd, 2023
Published: July 30th, 2023

J Respirol Indones. 2023
Vol. 43 No. 3: 210–20
https://doi.org/10.36497/jri.v43i3.426

INTRODUCTION

The COVID-19 infection can be mild, moderate, severe, or critical. The most common clinical symptoms are fever (temperatures above 38 °C), cough, and difficulty in breathing. Other symptoms include severe shortness of breath, fatigue, myalgia, gastrointestinal symptoms like diarrhea, and other respiratory symptoms. Severe clinical deterioration occurs rapidly and gradually, such as in ARDS, septic shock, difficult-to-correct metabolic acidosis, and bleeding or coagulation system dysfunction within a few days.[1]

A viral infection causes an immune response against the virus, which can cause lung tissue damage, functional impairment, and decreased lung capacity if the immune response is uncontrollable. Macrophages initiate the immune response by presenting the SARS-CoV-2 antigen to T cells, which activate and release cytokines and chemokines such as interleukin (IL)-1, IL-6, IL-8, IL-21, tumor necrosis factor (TNF), and monocyte chemotactic protein (MCP)-1. Cytokine storms that stimulate lymphocytes and leukocytes to migrate to the site of infection can be caused by certain conditions.[2]

As the disease progresses, large amounts of cytokines are secreted, one of which is interleukin 6 (IL-6).[3] Interleukin 6 is a pleiotropic biomolecule that is secreted by many different cell types involved in inflammation, immune response, and hematopoiesis. Wan et al discovered elevated IL-6 levels in one-third of patients with mild symptoms and three-quarters of patients with severe symptoms in their study. Diao et al discovered an inversely proportional relationship between increased IL-6 levels and T-cell counts in

ICU patients. This discovery is based on the theory that SARS-CoV-2-induced cytokines can impair T cells' ability to eliminate pathogens.[4] High systemic IL-6 levels are associated with clinically severe COVID-19, which is mostly associated with respiratory distress syndrome.[5] Elevated IL-6 levels have been found in COVID-19 patients and are associated with a poor prognosis.

Corticosteroids are one of the therapeutic modalities that have a physiological role in inflammation and the immune system, as well as an effect on different cytokines.[6,7] Corticosteroids reduce the number and activation of inflammatory cells, including mast cells, macrophages, T lymphocytes, and eosinophils, as well as inflamed tissues, in all chronic inflammatory and immune diseases.[8] According to COVID-19 management guidelines, several types of corticosteroids can be used as therapeutic modalities for COVID-19 patients, including dexamethasone, methylprednisolone, and hydrocortisone.[9]

Awasthi et al discovered that after corticosteroid administration, 7 out of 10 patients had stable or decreased IL-6 levels.[10] Andre et al investigated the role of IL-6 as a biomarker of fatal SARS-CoV-2 pneumonia;IL-6 levels were measured when the patient was admitted, every 72 hours during hospitalization, and when the patient was discharged. This study discovered that the peak of IL-6 was time-limited and that IL-6 levels returned to normal after the 10th day.[11]

Another study from Julie et al took the first average measurement of IL-6 levels 4 (2-7) days after the patient was admitted, the second after 6 (6-11) days, and the third after 11 (10-15) days.[1212] This study found a significant difference in IL-6 levels in patients with a higher risk of death (720 pg/ml) versus those with a better prognosis (336 pg/ml).

METHODS

This research was a retrospective cohort study. From June 2021 to July 2022, this study was carried out in the COVID-19 isolation ward at RSUP Dr. M. Djamil Padang. All COVID-19 patients treated in the COVID-19 isolation ward at RSUP Dr. M. Djamil Padang who met the inclusion and exclusion criteria were included in the study. All confirmed COVID-19 patients aged >18 years who received dexamethasone therapy with IL-6 values >7, had complete medical record data in the form of pre- and post-IL-6 laboratory tests (6-11 days) and dexamethasone administration and had a diagnosis of clinical doctor in charge of service were eligible for the study. COVID-19 patients who had received dexamethasone therapy before being admitted to RSUP Dr. M. Djamil, as well as COVID-19 patients receiving IL-6 therapy, were excluded from the study.

RESULTS

The inclusion and exclusion criteria were met by 180 samples. Table 1 shows the characteristics of confirmed COVID-19 patients at RSUP Dr. M. Djamil Padang.

Table 1. The characteristics of COVID-19 patients (N=180)

Characteristic	n	%
Age		
18-49 years	67	37.22
50–59 years	44	24.44
60–69 years	42	23.33
≥70 years	27	15.00
Gender		
Male	80	44.44
Female	100	55.56
Clinical severity of COVID-19		
Mild	25	13.89
Severe	89	49.44
Critical	66	36.67
Comorbid		
No comorbid	95	52.78
1 comorbid	56	31.11
>1 comorbids	29	16.11
Corticosteroid dose		
According to the guideline	140	77.78
Above the guideline	40	22.22

The majority of study participants (37.22%) were between the ages of 18 and 49 and were female (55.56%). The most common degree was severe clinical degree (49.44%), followed by critical degree (36.67%). The majority of subjects had no comorbidities (52.78%). The majority of patients (77.78%) received dexamethasone at the recommended dose (1 x 6 mg).

Table 2. The relationship between dexamethasone administration and changes in IL-6 values in COVID-19 patients based on clinical degrees.

Dexamethasone Administration	IL-6 Level (pg/mL)			*P*
	Min-Max	Median (Q1-Q3)	Mean±SD	
Before	8.1–2342.00	77.00 (26.43– 182.88)	156.91±244.68	0.0001*
After	1.5–732.5	45.25 (15.45 – 120.60)	83.84±45.25	

Note: *Wilcoxon rank test

Table 3. The relationship between dexamethasone administration and changes in IL-6 values in COVID-19 patients based on clinical degrees.

Severity Degree	IL-6 Level (pg/mL) [Median Min–Max)]		*P*
	Before Dexamethasone Administration	After Dexamethasone Administration	
Mild (n=25)	54.70 (9.20–528.00)	20.20 (1.50–271.00)	0.137
Severe (n=89)	77.20 (8.10–999.00)	31.50 (1.50–491.50)	0.0001
Critical (n=66)	81.65 (8.20–2342.00)	70.35 (0.50–732.50)	0.0001

Note: *Wilcoxon rank test

According to Table 2, the IL-6 level before dexamethasone administration ranged from 8.1 to 2,342 pg/mL. After dexamethasone administration, IL-6 levels ranged from 1.5 to 732.5 pg/mL. Because the normality requirement for data distribution for changes in IL-6 values was not met, the correlation between dexamethasone administration and changes in IL-6 values was analyzed using a non-parametric unpaired 2-group difference test, namely the Wilcoxon signed ranks test (from the Kolmogorov-Smirnov test results with *P*=0.0001 was obtained). The Wilcoxon signed ranks test yielded *P*=0.0001, indicating that there was a significant difference in IL-6 values before and after dexamethasone administration, indicating the existence of a relationship between dexamethasone administration and changes in IL-6 values.

Table 3 depicts the relationship between dexamethasone administration and changes in IL-6 values based on the clinical severity of the disease. For moderate clinical degrees, the Wilcoxon signed ranks test yielded *P*=0.137 and *P*=0.0001 for severe and critical clinical degrees, respectively. Dexamethasone administration did not affect IL-6 values at moderate clinical levels, but it did have an effect on IL-6 values at severe and critical levels.

Table 4 demonstrates a link between clinical comorbidities and changes in IL-6 levels in confirmed COVID-19 patients. The Kruskal-Wallis test yielded *P*=0.030 for a comparison of changes in IL-6 values in moderately severe and critically ill COVID-19 patients.

Based on the average value of changes in IL-6 levels, it can be seen that patients with comorbidities >1 have the smallest rate of decline (8.20 pg/mL), followed by patients with 1 comorbidity and those without comorbidities, who have higher rates, namely 10.20 and 40.90 pg/mL. COVID-19 patients with more than one comorbidity had lower changes (decreases) in IL-6 values than COVID-19 patients with only one comorbidity or no comorbidity.

Table 4. The relationship between dexamethasone administration and changes in IL-6 levels in COVID-19 patients based on comorbidities.

Comorbid	Changes in IL-6 Level (pg/mL) [Median (Min-Max)]	*P*
No comorbid	40.90 (-100.70 – 799.10)	0.030*
1 comorbid	10,20 (-101.00 – 2237.20)	
>1 comorbids	8,20 (-100.10 – 482.10)	

Note: *Kruskal-Wallis test

Table 5 demonstrates that there is no relationship between dexamethasone dose and changes in IL-6 levels in confirmed COVID-19 patients. This is demonstrated by the acquisition of *P*=0.715 from the Mann-Whitney test for a comparison of changes in IL-6 values in COVID-19 patients at the recommended dose of dexamethasone and the dose above the guideline. Based on the mean value of changes in IL-6 levels, it can be seen that the rates of decline in IL-6 values in patients who received dexamethasone at the recommended dose and above the recommended dose were relatively similar, namely 21.92 and 21.90 pg/mL.

Table 5. Relationship between the dose of dexamethasone and changes in IL-6 values in COVID-19 patients

Dose of Dexamethasone	Changes in IL-6 Level (pg/mL) [Median (Min-Max)]	*P*
According to the guideline	21.92 (-100.10 – 799.10)	0.715
Above the guideline	21.90 (-101.00 – 2,237.20)	

Note: *Mann-Whitney test

DISCUSSION

The patients in this study were mostly between the ages of 18 and 49 (37.2%), with only a small proportion over the age of 70 (15.0%). The findings of this study are consistent with the study conducted in 2020 by Mudhaffer in Iraq, which discovered that the majority of COVID-19 patients were between the ages of 20 and 50.[13] The high prevalence of COVID-19among patients aged 18-49 years can be attributed to the fact that this age group is in the working-age category with the highest mobility and is followed by more interpersonal interactions. According to a study conducted in 2022 by Tabernero et al in Spain, the number of COVID-19 cases among young adults worldwide was increasing rapidly. Wider use of diagnostic tests has identified individuals in this population group as accounting for 75% of COVID-19 cases.[14]

This study's findings are inversely proportional to the findings of a 2020 study conducted by Belda in Spain, which obtained the highest prevalence of COVID-19 patients aged 70 years (44.6%) and only 15.3% of patients aged 18-49 years.[15] The elderly are at a higher risk of developing COVID-19, which can be accompanied by progressive clinical deterioration. Inflammaging is associated with immunosenescence, which is characterized by disturbances in the innate and adaptive immune systems as well as the continuous production of inflammatory mediators and cytokines. In older people, abnormal ciliary function and ciliary ultrastructure can also interfere with the successful cleaning of SARS-CoV-2 virus particles; this puts patients at a higher risk of contracting COVID-19.[16]

Older people, immunosenescence, and co-morbidities are more likely to set off a viral-induced cytokine storm, which can lead to life-threatening respiratory failure and multisystemic involvement.[16] The age of the patient is a risk factor for disease severity and mortality. According to a 2020 study from Liu et al in China, COVID-19 patients over 60 had a higher rate of respiratory failure and required more hospitalization than patients under 60.[17] According to other sources, the mortality rate rises with age. The risk of death was 3% in patients over the age of 50, 16% in those aged 50-59, 22% in those aged 60-69, and 34% in those over 70.[18]

More than half of the patients (55.6%) in this study were female. These findings are similar to those of Fortunato in Foggia in 2020, who discovered that 50.7% of COVID-19 patients were female.[19] There is evidence that men and women are equally at risk of SARS-CoV-2 infection, but men are at a higher risk of death when compared to women.[20]

A study from Doerre in 2021 in Germany using contact matrices discovered a pattern in which women had a higher presentation of contact with COVID-19 (13-26%) at the age of 20-39 years, but as age increases, especially in the range 50-69 years, men had a 9-14% higher contact presentation. Due to a greater number of contacts, young and middle-aged women contribute to an increase in the incidence of infection. Sex differences in contact rates may be one of the pathways that contribute to disease spread and lead to sex-specific infection rates and mortality outcomes.[21]

This study is inversely proportional to the findings of a 2020 study conducted by Raimondi in Italy, which discovered that the majority of COVID-19 patients (72.4%) were male.[22] The mechanism underlying the gender bias in COVID-19 is unknown, but it is thought to be linked to angiotensin-converting enzyme 2 (ACE2) expression, which is an important enzyme of the renin-angiotensin system (RAS) and a functional receptor for SARS-CoV and SARS-CoV2 infection. It has been demonstrated that ACE2 protects against chronic diseases such as hypertension, cardiovascular disease, and acute respiratory distress syndrome (COVID-19).[23]

According to research, SARS-CoV infection causes ACE2 down-regulation by binding the viral spike protein to ACE2, reducing ACE2 expression in the lungs, and causing acute respiratory failure. Because COVID-19 and SARS patients have similar acute respiratory distress syndromes and gender biases in disease susceptibility and mortality rates, this pathogenic mechanism is also present in COVID-19 cases.[23]

Different lifestyles between sexes, such as behaviors more commonly found in males than females, are also thought to be potential risk factors for COVID-19 occurrence. In general, women have more intense and stronger innate and adaptive immune systems than men, which aids in viral clearance. Estrogen, the primary female sex hormone, has been shown to protect against SARS by not only activating the immune response but also directly suppressing SARS-CoV replication. Estrogen is also known to inhibit the activity or expression of various renin-angiotensin system components, and it has been shown to specifically increase ACE2 expression.[23]

According to the clinical degree of COVID-19, the majority of respondents (49.4%) were in the severe category, followed by the critical category (36.7%) and the moderate category (13.9%). This study's findings are consistent with a study conducted by Li et al in Wuhan, China, which found that 49.1% of patients were in a severe category. This was because Wuhan experienced the highest peak of the COVID-19 outbreak, with family clusters and a high prevalence of COVID-19 in older adults, from mid-January to early February.[24]

The findings of this study are not similar to a 2020 research by Liu in Beijing on the use of corticosteroids in different clinical categories of COVID-19. According to this study, the majority of the patients (49.53%) were in the moderate category, followed by the critical (23.88%), and severe category (12.31%).[25] In 2020, Gong conducted a study in Shanghai on the severity of COVID-19 with inflammatory parameters and discovered that 34% of patients were in the severe category and 32% were in the critical category.[26]

According to this study, about 52.8% of subjects had no comorbidities. These findings are similar to a study by Surendra, which pointed out that 69% of patients with confirmed COVID-19 had no comorbidities. Only 31% of the patients in that study had one or more comorbidities, such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD), or chronic kidney disease.[18] Endothelial dysfunction is promoted by inflammatory cardiovascular risk factors such as dyslipidemia, obesity, and diabetes. Mast cells, T lymphocytes, dendritic cells, activated neutrophils, and platelets collaborate to produce an inflammatory response that includes increased production of pro-inflammatory cytokines, reactive oxygen species (ROS), and adhesion molecules.[27]

Bordallo et al discovered that 57% of patients with severe COVID-19 had hypertension, 42% were obese, and 34% had diabetes in a 2020 study in Brazil. The metabolic syndrome and obesity, according to the literature, develop as a result of chronic inflammation caused by increased NF-B activity and the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. Patients with hypertension also have endothelial cell dysfunction and immunometabolic changes, which contribute to higher inflammatory cytokine levels in the blood.[28] In general, the mortality rate is 3% in patients without comorbidities, 8% in patients with one comorbidity, and27% in patients with more than one comorbidity.[18]

Dexamethasone was administered to all patients as corticosteroid therapy. About 77.8% of patients received corticosteroid doses following the guidelines. According to the COVID-19 management guidelines, corticosteroids can be considered for initialuse in moderate, severe, and critical COVID-19 patients.[9] The dose of dexamethasone corresponds to the COVID-19 management guidelines, namely 0.15 mg/kg BW per day given every 24 hours with a maximum dose of 6 mg.[9,29] Dexamethasone is strongly recommended by the Infectious Diseases Society of America (IDSA) for critically ill patients with acute respiratory distress syndrome (ARDS) and systemic inflammation. Dexamethasone at a total daily dose of 6 mg IV or PO for 10 days (or until discharge) is recommended, as are other glucocorticoids such as methylprednisolone (32 mg) and prednisone (40 mg). As the severity of the disease decreases, so does the recommendation rate. Glucocorticoids are not recommended in non-severe COVID-19 patients due to a lack of strong evidence.[29]

Granholm et al concluded that there was no statistically significant difference in mortality or

health-related quality of life (HRQoL) between the use of dexamethasone 12 mg and 6 mg in patients with COVID-19 and severe hypoxemia, but the benefits of high-dose dexamethasone were more compatible.[30] Fakhriravari et al found a reduction in 28-day all-cause mortality in 2104 patients who received low-dose dexamethasone (6 mg) orally or IV once daily for 10 days compared to patients who received usual care.[31]

Elevated IL-6 levels have previously been observed in patients with respiratory dysfunction, implying that COVID-19 may cause cytokine-mediatedlung damage. SARS-CoV-2 infection is also extremely pathogenic, with rapid viral replication and a proclivity to infect the lower respiratory tract, which increases the severity of IL-6-induced severe respiratory distress. Serial measurement of circulating IL-6 levels may be useful in identifying disease progression in COVID-19-infected patients.[32] According to Table 2, the IL-6 value before corticosteroid administration ranged from 8.1 to 2,342 pg/mL, with a mean of 156.91 pg/mL and a median of 77.00 pg/mL. Ananda et al discovered that 83.9% of patients had IL-6 levels of 100 pg/mL, with only a small number of patients (16.1%) having normal IL-6 levels. According to their study, the lowest IL-6 level was 2.7 pg/mL, while the highest level was 244 pg/mL.[33]

Interleukin-6 is found in healthy people's blood at very low levels, around 1-5 pg/mL. In inflammatory conditions, IL-6 concentrations rise gradually and can reach the g/mL range in cases of sepsis.[34] Han et al investigated the predictive value of various cytokines and obtained that IL-6 was the best predictor of severe COVID-19.[35] A meta-analysis of nine studies concluded that elevated IL-6 levels were strongly related to disease severity. According to this study, patients with severe COVID-19 had an average IL-6 value of 58 pg/mL. This was a very high value when compared to the IL-6 level in patients with mild disease, which was only 17 pg/mL.[36] According to Herold et al, IL-6 levels greater than 80 pg/mL can predict the likelihood of respiratory failure and the need for mechanical ventilation in COVID-19 patients.[37] Chen et al discovered a cutoff of 80 pg/mL to distinguish between living and dead patients.[38]

The inflammatory process in COVID-19 begins with the novel coronavirus binding to the ACE2 receptor, which is expressed by alveolar epithelial cells, allowing the virus to enter the cell endosomally. Infected cells can undergo apoptosis or necrosis after virus replication, assembly, and release, triggering an inflammatory response by producing proinflammatory cytokines. TLRs, which aid innate immunity in recognizing infectious pathogens, can also activate macrophages and monocytes, causing them to release IL-6.[32,36]

After corticosteroid administration, IL-6 levels ranged from 1.5 to 732.5 pg/mL, with a mean of 83.84 pg/mL and a median of 45.25 pg/mL. Corticosteroids are anti-inflammatory medications that have long been known to inhibit pro-inflammatory cytokines like IL-2, IL-3, IL-4, IL-5, and IL-6.[39] Awasthi discovered IL-6 values more than twice the upper limit of normal (normal reference range 0.31-5 pg/mL) before corticosteroid administration in a study on IL-6 values after corticosteroid administration. After corticosteroid administration, five of ten patients had mean IL-6 levelsless than twice the upper limit of normal (10 pg/mL), and four of ten patients had IL-6 levels less than 5 pg/mL.[10]

A retrospective study of 90 confirmed severe and critical COVID-19 cases in Wuhan following treatment with various types of corticosteroids revealed a significant improvement in clinical parameters and chest CT images in patients receiving corticosteroids. This study provided experimental and clinical evidence that corticosteroids at medium to low doses could protectthe respiratory and digestive systems by activating ACE2 and suppressing cytokine storms.[39]

The Wilcoxon signed ranks relationship between dexamethasone administration and changes in IL-6 values obtained a P=0.0001, indicating that there was a significant difference in IL-6 values before and after dexamethasone administration, implying that there is a relationship between dexamethasone administration and changes in IL-6 values. These findings are consistent with those of Valle et al, who stated that patients treated with corticosteroids and remdesivir had a

rapid and gradual decrease in IL-6 levels when compared to patients who did not receive this treatment. This study observed that among several types of corticosteroids, dexamethasone had the greatest IL-6-lowering effect. Namazi stated in his research conducted in Saudi Arabia in 2022 that glucocorticoids could reduce SARS-CoV-2 infection by lowering IL-6 levels. Dexamethasone is reported to be the drug of first choice for the treatment of respiratory disorders among all glucocorticoids.[40]

The findings of this study are inversely proportional to those of Awasthi, who found a weak correlation between changes in the average plasma IL-6 value after corticosteroid administration and outcomes 10 years later.[10] Similarly, a retrospective analysis of outcomes in COVID-19 patients who received and did not receive corticosteroid therapy revealed that inflammatory markers (e.g., CRP, PCT, white blood cells (WBC), D-dimer, IL-6, and IL-10) and some serum biochemical indicators did not differ significantly between the two groups.[41]

According to Fujino's research, dexamethasone therapy alone did not affect IL-6 levels. An analysis of transcriptomic data supports this, demonstrating that the mechanism of dexamethasone therapy in patients with severe COVID-19 does not involve the IL-6 pathway. The odds ratio (OR) of IL-6 was high when adjusted for previous dexamethasone administration, implying that IL-6 levels might reflect ongoing respiratory system damage even when the patient was receiving dexamethasone therapy.[42]

The mechanism of corticosteroid potential effect on IL-6 levels is linked to the expression profile of the NR3C1 gene, which is the highest affinity target for dexamethasone, methylprednisolone, and prednisone. T cells, B cells, monocytes, natural killer cells, dendritic cells, and macrophages were the immune cells with the highest NR3C1 expression. NR3C1 expression is particularly high in alveolar macrophages. In patients with confirmed COVID-19, both macrophages and T cells expressed high levels of NR3C1, whereas plasma, neutrophils, and epithelial cells in recovered patients expressed lower levels of NR3C1. If there is a bond between glucocorticoids and the glucocorticoid receptor of GR/NR3C1), it can suppress transcription of inflammatory genes directly through protein synthesis-independent processes (transrepression) or transcriptional activation (transactivation) of several anti-inflammatory/repression factors, thereby reducing IL-6 production locally and systemically, restoring immune homeostasis and reducing the development of acute respiratory failure.[10,43]

This study found no link between dexamethasone administration and changes in IL-6 values at moderate clinical levels, but there was a link between dexamethasone administration and changes in IL-6 values at severe and critical levels. Eric et al found that serum IL-6 levels were significantly higher inpatients with severe COVID-19 in a systematic review and meta-analysis. According to a meta-analysis of available data, elevated levels are significantly associated with adverse clinical outcomes such as ICU admission, ARDS, and death. Serum IL-6 levels in patients with clinically severe COVID-19 are nearly three times higher than in those without complications.[44]

Wang et al pointed out that patients with clinically severe COVID-19 were more likely to require additional corticosteroid therapy.[45] Patients with severe COVID-19 who have high IL-6 levels are more likely to benefit from cytokine blockade. A study conducted by Valle et al observed that dexamethasone had the highest IL-6 lowering effect among several types of corticosteroids, which was thought to underpin the effectiveness of treatment in these patients.[40]

A study by Chen et al on the relationship between the clinical phenotype of COVID-19 and response to corticosteroid therapy found that corticosteroid therapy was associated with lower 28-day mortality in patients with a hyperinflammatory phenotype (i.e., a condition characterized by increased levels of proinflammatory cytokines and SOFA score) but had no effect on patients with a hypoinflammatory phenotype.[46]

In confirmed COVID-19 patients, researchers obtained a correlation between clinical comorbidities and changes in IL-6 levels. COVID-19 patients with

>1comorbidity had lower changes (decreases) in IL-6 values than COVID-19 patients without comorbidities or with 1 comorbidity. COVID-19 patients with comorbidities have a rapid and severe disease course, which often results in death. According to Sanyaolu et al, the most common comorbidities among COVID-19 patients are hypertension (15.8%), cardiovascular and cerebrovascular disease (11.7%), and diabetes (9.4%). Meanwhile, the most common comorbidities were HIV and hepatitis B (1.5%), cancer (1.5%), respiratory disorders (1.4%), kidney disorders (0.8%), and immune deficiencies (0.01%).[47]

The response of patients to corticosteroid therapy varies. Many factors influence the effectiveness of corticosteroid therapy, including disease severity, inflammatory conditions, and comorbidities.[46] Due to the low comorbidity assessment, drug interactions, and lack of knowledge regarding pathway crosstalk between COVID-19 and comorbidities required to understand the complexity of pathogenesis, the management of COVID-19 patients with comorbidities is becoming more complex.[48]

This study found no correlation between dexamethasone administration doses and changes in IL-6 levels in COVID-19 patients. This is demonstratedby a Mann-Whitney test with *P*=0.715 for a comparison of changes in IL-6 values among COVID-19 patients at the recommended dose of dexamethasone and a dose higher than the guideline. These findings are consistentwith the study by Zuniga et al of COVID-19 patients with IL-6 levels of at least 40 pg/mL.[49] There were no clinically significant differences between patients who received high-dose corticosteroids, namely dexamethasone equivalent to 125 mg methylprednisolone, and patients who received low-dose corticosteroids, according to this study.[49]

A study of 65 COVID-19 cases in Beijing stated that corticosteroids could inhibit IL-6 production,but there was no statistically significant difference in IL-6 levels between patients receiving low doses (2 mg/kg/day) and high doses (>2 mg/kg/day). In other words, low doses of corticosteroids (2 mg/kg/day) could inhibit IL-6 production just as well as higher doses.[25]

According to the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, patients with severe and critical COVID-19 should take 6 mg of dexamethasone daily for 10 days. In his study, Perner pointed out that higher doses of corticosteroids were beneficial for patients with a more severe course of the disease. According to several meta-analyses, the most commonly used daily dose was dexamethasone at a dose of 6-16 mg (a median dose of 12 mg).[50]

LIMITATION

This was a retrospective cohort study using medical records data with uneven distribution of data and only assessed changes in IL-6 values in the administration of one corticosteroid.

CONCLUSION

In general, the characteristics of clinically confirmed COVID-19 patients at RSUP Dr. M. Djamil Padang revealed that respondents were mostly female, aged 18-49 years, and nearly half of them had comorbidities. Following dexamethasone administration, the IL-6 level decreased significantly. The administration of dexamethasone was associated with significant changes in IL-6 values in severe and critical clinical degrees, but not in moderate clinical degrees. In patients with comorbidities, the effect of dexamethasone administration on changes in IL-6 values was significant, but there was no relationship between dexamethasone administration dose and changes in IL-6 values.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

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