**Original Research Report**

# CLINICAL PROFILES AND IL-6 LEVEL ANALYSIS OF CRITICAL COVID-19 PATIENTS RECEIVING LOPINAVIR-RITONAVIR

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## ABSTRACT

COVID-19 pandemic has infected more than 760 million patients, with more than 6.8 million deaths reported globally. Early detection of a patient's worsening condition can provide information for predictors and determine the priority of health services based on evidence-based indicators. Interleukin-6 (IL-6) is a cytokine that plays a role in the inflammatory process, so the detection of IL-6 levels has the potential to be used as a parameter that represents a patient's inflammatory state. This study aimed to analyze COVID-19 patients' characteristics, laboratory profiles, and IL-6 levels. A cohort-retrospective study design was used in this investigation, which utilised medical record data. The patients' characteristic (n=68) and IL-6 profiles (n=52) on the first, third, and sixth days of treatment were recorded consecutively. The patients had a mean age of 49 years, were mostly men (72%), had the most comorbid hypertension (29%), and were hospitalized for an average of 10.94 days. Shortness of breath was the most frequently reported manifestation (45.6%). The median neutrophil-lymphocyte ratio, C-reactive protein, procalcitonin, ferritin, and D-dimer were higher than the normal range. There were significant differences in lymphocytes (p=0.046), procalcitonin (p=0.023), and D-dimer (p=0.000) among the survivor and nonsurvivor patients. The dynamic changes in IL-6 were significant from day 1 to day 6 (p=0.014) and from day 3 to day 6 (p=0.041). In conclusion, risk stratification, laboratory profiles, and IL-6 levels are important in assessing COVID-19 patients' severity and outcomes.

**Keywords:** COVID-19; pandemic; IL-6; clinical characteristics, human and health

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**Highlights:**
1. Lymphocyte, procalcitonin, D-dimer, and high IL-6 levels in COVID-19 patients are associated with a poor prognosis.
2. IL-6 serial measurement for COVID-19 patients may be a potential indicator for evaluating the severity and patient outcomes.

## INTRODUCTION

Over 760 million people have been infected with COVID-19. The pandemic has reported more than 6.8 million deaths. The number of new COVID-19 cases has started to decrease globally. However, in several regions, the numbers continue to exceed one million patients every month, with 28,000 patients dying in February 2023 (World Health Organization 2022). The case fatality rate caused by the SARS-CoV-2 virus (3–4%) was lower than those of the Middle East respiratory syndrome (MERS) (34%) and severe acute respiratory syndrome (SARS) (11%). However, the total number of deaths from this virus has far exceeded the mortality rates of MERS and SARS (Park et al. 2020). Data from Southeast Asian countries revealed that Indonesia's case fatality rate remained over 1% in December 2022 (Minister of Health of the Republic of Indonesia 2020). Administering lopinavir-ritonavir resulted in a shorter length of stay in the intensive care unit (ICU), with a median of six days compared to eleven days for the standard care group. This is very important in a pandemic because of the limited capacity of the ICU (Owa & Owa 2020).

Clinical manifestations of COVID-19 can appear on a wide spectrum, from asymptomatic to critical symptoms. The critical symptoms are characterized by acute respiratory distress syndrome, which requires mechanical ventilation, and septic shock (World Health Organization 2022). Various studies have reported that the pathophysiology of COVID-19 is closely related to acute inflammation. Interleukin-6 (IL-6) is the main proinflammatory cytokine involved in controlling cell differentiation, migration, proliferation, and apoptosis (Rehman et al. 2017).

Several studies have revealed a strong correlation between serum IL-6 levels and impending respiratory failure (Coomes & Haghbayan 2020). In addition, serum SARS-CoV-2 nucleic acid (RNAaemia), which is highly associated with cytokine storms, is closely correlated with very high serum levels of IL-6 (Chen et al. 2020). As IL-6 is a key factor to indicate the degree of inflammation, evaluating the dynamic changes in IL-6 levels is important for identifying disease progression and predicting cytokine storms. Therefore, this study aimed to assess the IL-6 levels of critical COVID-19 patients receiving lopinavir-ritonavir therapy.

## MATERIALS AND METHODS

This study was a descriptive observational study with a cohort-retrospective study design. This study utilized the medical records of patients with positive polymerase chain reaction (PCR) results for COVID-19 as the study sample. The inclusion criteria were patients aged >18 years with critical symptoms who were hospitalized and received lopinavir-ritonavir therapy in the COVID-19 Isolation Room of the Intensive Care Unit at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in the period of June–October 2020. Lopinavir-ritonavir therapy was an antiviral therapy that was used at the beginning of the pandemic, according to the World Health Organization (WHO) guidelines (The Indonesian Society of Respirology 2020). The sampling technique used in this study was total sampling, with a total sample of 68.

Data collected included the patient's characteristics, the laboratory profiles that were examined on the first day of treatment, and IL-6 levels on the first, third, and sixth days of treatment. All data were statistically analyzed using IBM SPSS Statistics for Windows Version 20.0 (IBM Corp., Armonk, N.Y., USA). The Kolmogorov-Smirnov test was then applied to determine the homogeneity of the data. Data on hemoglobin and hematocrit that were normally distributed were analyzed using the independent t-test, while the other variables were analyzed using the Wilcoxon test. A p-value of <0.05 was considered statistically significant (Poudel et al. 2021). The tables and narratives in this article are used to present the research findings descriptively.

This study was approved by the Health Research Ethics Committee at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, with a reference number 149/113/Komitlitkes/VII/2021 dated 15/7/2023.

## RESULTS

The number of PCR-positive COVID-19 patients aged 18–65 years, who received lopinavir-ritonavir therapy in the Intensive Care Unit was 68 patients. However, only 52 patients had complete data on their IL-6 levels. Table 1 shows the COVID-19 patients' characteristics. The patients were 49 (±10.81) years old on average and mostly men (72%). The most common comorbidity was hypertension (29%), while the average length of stay was 10.94±8.1 days. Shortness of breath (45.6%) was the most prevalent clinical manifestation among the patients.

Table 1. The COVID-19 patients' characteristics.

| Variable | n (%) |
|---|---|
| Age (years) | |
| Mean±SD | 49.04 (±10.81) |
| Median (min-max) | 52.5 (24-65) |
| Sex | |
| Male | 49 (72.1) |
| Female | 19 (27.9) |
| Comorbid | |
| Hypertension | 20 (29.4) |
| Diabetes mellitus | 19 (27.9) |
| Obesity | 18 (26.4) |
| Coronary heart disease | 4 (5.8) |
| Asthma | 4 (5.8) |
| None | 26 (38.2) |
| Length of stay (days) | |
| Mean±SD | 10.94±8.1 |
| Median (min-max) | 9 (6-54) |
| Clinical manifestation | |
| Shortness of breath | 31 (45.6) |
| Dry cough | 10 (14.7) |
| Fever | 7 (10.3) |
| Anosmia | 6 (8.8) |
| Diarrhea | 6 (88) |
| Sore throat | 3 (4.4) |
| Myalgia | 3 (4.4) |
| Loss of consciousness | 2 (2.9) |

Table 2 demonstrates the patients' laboratory characteristics on the first day of treatment. The medians for the neutrophil-lymphocyte ratio (NRL), procalcitonin, C-reactive protein (CRP), ferritin, and D-dimer were found to be higher than the normal

Table 2. Laboratory profiles of the COVID-19 patients.

| Variable | Total (n=68) | Survivor (n=30) | Nonsurvivor (n=38) | p |
|---|---|---|---|---|
| Hemoglobin (g/dL) | | | | 0.239 |
| Median (min-max) | 13.52 (9.88-17.3) | 13.2 (9.88-17.02) | 13.65 (10.26-17.3) | |
| Mean±SD | 13.48±1.69 | 13.21±1.75 | 13.69±1.64 | |
| Hematocrit (%) | | | | 0.160 |
| Median (min-max) | 38.9 (27.89-52.2) | 38.05 (27.89-50) | 39.4 (30.6-52.2) | |
| Mean±SD | 39.49±5.32 | 38.47±5.01 | 40.3±5.48 | |
| Leukocyte ($x10^9$/L) | | | | 0.236 |
| Median (min-max) | 7.57 (1.96-38.89) | 7.05 (3.72-20.3) | 8.4 (1.96-38.89) | |
| Mean±SD | 8.85±5.78 | 7.82±3.46 | 9.66±7.04 | |
| Neutrophil ($x10^9$/L) | | | | 0.562 |
| Median (min-max) | 10.49 (4.3-22.7) | 9.92 (5.42-22.7) | 10.56 (4.3-19.12) | |
| Mean±SD | 11.04±3.69 | 10.75±4.02 | 11.27±3.45 | |
| Lymphocyte ($x10^9$/L) | | | | 0.046 |
| Median (min-max) | 1.05 (0.19-2.94) | 1.24 (0.59-2.7) | 1 (0.19-2.94) | |
| Mean±SD | 1.19±0.61 | 1.32±0.51 | 1.1±0.67 | |
| NLR | | | | 0.097 |
| Median (min-max) | 6.82 (1.72-49.26) | 5.7 (2.14-24.76) | 8.95 (1.72-49.26) | |
| Mean±SD | 9.61±8.47 | 7.01 ± 4.87 | 11.67±10.07 | |
| Trombosit ($x10^9$/L) | | | | 0.277 |
| Median (min-max) | 246.5 (96-673) | 272.5 (122-412) | 242 (96-673) | |
| Mean ± SD | 258.4 ± 96.27 | 267.9±85.39 | 250.89±104.57 | |
| Procalcitonin (ng/mL) | | | | 0.023 |
| Median (min-max) | 0.24 (0.01-70.41) | 0.15 (0.01-6.63) | 0.32 (0.06-70.41) | |
| Mean±SD | 1.78 ± 8.62 | 0.5±1.21 | 2.8±11.45 | |
| CRP (mg/L) | | | | 0.058 |
| Median (min-max) | 10.25 (0.6-89) | 7.15 (1.1-27.4) | 12 (0.6-89) | |
| Mean±SD | 12.6 ± 12.96 | 9.18±7.31 | 15.3±15.66 | |
| Ferritin (mcg/L) | | | | 0.394 |
| Median (min-max) | 1187 (38.5-7340.5) | 1161.1 (38.5-4361) | 1241.85 (71.73-7340.5) | |
| Mean±SD | 1460.84±1254.24 | 1299.91±1017.6 | 1587.89±1414.01 | |
| D-dimer (ng/mL) | | | | 0.000 |
| Median (min-max) | 1495 (310-9280) | 955 (380-6340) | 1950 (310-9280) | |
| Mean±SD | 1991.59±1706.83 | 1316.6±1168.73 | 2524.47±1882.48 | |

range. These were even higher in nonsurvivor patients. The statistical tests revealed significant differences in lymphocytes (p=0.046), procalcitonin (p=0.023), and D-dimer (p=0.000) among the survivor and nonsurvivor patients.

Table 3 shows the COVID-19 patients' IL-6 profiles. The mean IL-6 levels during the treatment were 256.42±475.99 on the first day, 224.97±515.49 on the third day, and 172.32±338.79 on the sixth day. The nonsurvivor group showed higher IL-6 levels than the survivor group. There was a significant difference in IL-6 levels on the third day (p=0.027) and sixth day (p=0.003), according to the statistical tests. The non-parametric Wilcoxon signed-rank test results indicated dynamic changes in IL-6 levels. There were significant changes in IL-6 levels from day 1 to day 6 (p=0.014) and from day 3 to day 6 (p=0.041), while there was no significant difference from day 1 to day 3 (p=0.321).

## DISCUSSION

In this study, men were more infected with the COVID-19 virus and fell into critical condition more often than women. Men also had higher levels of angiotensin-converting enzyme-2 (ACE2) expression and activity due to several factors (Liu et al. 2020a). ACE2 is found in many organs, such as the upper respiratory tract, the lungs, the heart,

Table 3. IL-6 level profiles of the COVID-19 patients.

| IL-6 variable (pg/mL) | Total (n=52) | Survivor (n=26) | Nonsurvivor (n=26) | p |
|---|---|---|---|---|
| Day 1 | | | | |
| Median (min-max) | 95.08 (1.77-3029.17) | 79.41 (1.77-1254.69) | 99.84 (52.95-3029.17) | 0.062 |
| Mean±SD | 256.42±475.99 | 185.76±272.00 | 327.07±614.67 | |
| Day 3 | | | | |
| Median (min-max) | 113.79 (2.50-3651.89) | 89.48 (2.50-486.63) | 146.48 (20.57-3651.89) | 0.027 |
| Mean±SD | 224.97±515.49 | 119.44±131.21 | 330.50±708.31 | |
| Day 6 | | | | |
| Median (min-max) | 91.61 (1.51-2187.50) | 35.73 (1.51-705.61) | 126.20 (3.1-2187.5) | 0.003 |
| Mean±SD | 172.32±338.79 | 82.41±138.53 | 262.22±445.14 | |

kidneys, and blood vessel linings. Its presence in the testis is very high (Sama et al. 2020, Wulandari et al. 2021). Furthermore, estrogen has been shown to protect women from COVID-19 (Acheampong et al. 2020).

Patients with comorbidities are more likely to develop critical conditions. These results are supported by other studies, which reported that cardiovascular disease, diabetes, and hypertension increase the risk of critical conditions and require intensive care (Honardoost et al. 2021). Chronic diseases (such as cardiovascular disease, hypertension, and diabetes) are associated with the pathogenesis of COVID-19. These diseases can circulate proinflammatory cytokines, weaken the innate immune response, and enhance viral entrance into cells because both ACE2 and viruses require glucose to perform their activities. In addition, metabolic disorders can lower immune function by interfering with macrophage and lymphocyte functions, making individuals more susceptible to infection and falling into a critical condition (Badawi & Ryoo 2016, Kusuma & Ardiany 2021).

This study showed that the critical COVID-19 patients' average length of stay in the intensive care unit was 10.9 days. These results are better when compared to a study in the Netherlands, where the patients' average length of stay in the intensive care unit was 20.6 days during the first wave of the pandemic (February–May 2020). However, the Netherlands study showed a decrease to 17.2 days during the second wave of the pandemic (October 2020–January 2021) and 16 days during the third wave of the pandemic (February–June 2021) (Dongelmans et al. 2022).

Shortness of breath and dry cough were the most common clinical manifestations in this study. These results agree with a study in China, which reported that 43% of critical COVID-19 patients complained of cough, sore throat, and shortness of breath (Ding et al. 2021). Coughing is caused by neurotropism (direct invasion of SARS-CoV-2 via ACE2 receptors), neuro-inflammation, and neuro-immunomodulation through the vagal sensory nerves (Song et al. 2021). The SARS-CoV-2 virus enters through the respiratory tract. Therefore, clinical manifestations in the upper and lower respiratory tracts are often found. It is not uncommon to find acute respiratory distress syndrome, which includes critical COVID-19 (Attaway et al. 2021).

Most of the critical COVID-19 patients showed lymphopenia, which is consistent with viral infection conditions (Zhong et al. 2021). A study reported that coronavirus infection induces lymphocyte clearance and inhibits immune function (Xu et al. 2020). This function acts as a potential immunological mechanism for disease progression. Apart from lymphopenia, critical COVID-19 patients also experience increased levels of inflammatory parameters (such as C-reactive protein, procalcitonin, ferritin, and D-dimer). Increased serum C-reactive protein, driven by IL-6 and other inflammatory cytokines, can be biomarkers for severe manifestations of COVID-19 because the patients may experience cytokine storms. This infection causes the activation of monocytes, macrophages, and dendritic cells (Melo et al. 2021). Other studies reported that increased procalcitonin is closely related to COVID-19 severity. This increase may be related to bacterial co-infection, which is mediated by an upregulation of tumor necrosis factor-alpha (TNF-α) and IL-6 (Hu et al. 2020). In addition, hyperinflammation occurs in COVID-19, causing a dysregulated immune response that may also trigger the production of procalcitonin (Tong-Minh et al. 2022). D-dimer is the most sensitive coagulation parameter in COVID-19 and indicates the risk of thrombosis (Conte et al. 2021). D-dimer levels are commonly elevated in elderly patients with comorbidities. The presence of viremia and cytokine storm syndrome in COVID-19 indicates a spike in pro-inflammatory cytokines that are uncontrollable by anti-inflammatory agents, thus overwhelming the coagulation cascade. Additionally, hypoxia predisposes to thrombosis through numerous signaling pathways (Poudel et al. 2021).

Critical COVID-19 patients may exhibit systemic hyperinflammation caused by macrophage activation syndrome or cytokine storms. The IL-6 profile analysis of the COVID-19 patients with severe symptoms showed that there were increased IL-6 levels among the nonsurvivors compared to the survivors. This increase correlated with the occurrence of systemic inflammatory response syndrome and multi-organ failure (Donoso et al. 2021).

IL-6 can act on all cell types by binding to the transmembrane or soluble IL-6 receptor (IL-6R). It can also form a complex with gp130 and activate the effector Janus kinase (JAK). Activation of several of these pathways will produce various biological effects. Some of the effects are the maturation of naive T cells into effector T cells, the expression of vascular endothelial growth factor (VEGF) in endothelial cells, and increased vascular permeability. Decreased myocardial contractility may also occur, which contributes to organ damage and the risk of death (Mehta et al. 2020, Nugroho et al. 2021).

Comorbidity is a factor that influences cytokine

levels. A study found that TNF-α and IL-6 increased significantly in patients with chronic kidney disease, diabetes, hypertension, and a history of atrial fibrillation (Luporini et al. 2021). Another study conducted in New York, USA, found that comorbidity was the main cause of elevated IL-6 levels in patients aged 65 and above (Del Valle et al. 2020). These findings may raise awareness of the important role of comorbidities in COVID-19 risk stratification.

IL-6 is a soluble mediator that has pleiotropic effects on inflammation, immunological response, and hematopoiesis. Physical exercise may cause the production of IL-6, which causes inflammation. IL-6 is considered one of the major pro-inflammatory interleukins and is involved in many immunological processes, including the induction of the acute phase response (Tanaka et al. 2014, Purwani et al. 2021).

Several studies have reported the association of high IL-6 levels with COVID-19 severity and poor outcomes. A study that examined the serum IL-6 levels several times during treatment in the ICU reported higher IL-6 levels in nonsurvivor patients compared to survivors (Gorham et al. 2020). In this study, there was a significant difference in IL-6 levels on day 3 between the survivor and nonsurvivor groups. A study on 37 critical COVID-19 patients in Turkey supports these findings. The study reported that on day 3 of treatment, there was a significant decrease in IL-6 levels in the survivor group. In contrast, the nonsurvivors showed high and stable serum IL-6 levels. These dynamic changes, especially the decrease in serum IL-6 levels among the survivors, showed the role of cytokines in the critical prognosis of COVID-19 with a prospective follow-up (Ozger et al. 2021).

Fluctuations in IL-6 levels have a fairly short duration. A study stated that the peak of IL-6 levels in the survivor group was around 7–10 days from the onset of disease symptoms. Within 10 days of treatment, IL-6 levels return to normal (Santa Cruz et al. 2021). In this study, IL-6 levels reached a peak on day 3. This difference could be due to the timing of measuring IL-6 levels, which generally took place only when the patient was admitted to the hospital. Due to limited resources and the fact that IL-6 measurement is not routinely carried out, IL-6 measurement at first admission in severe or critical COVID-19 patients is very important to predict the possibility of complications and severity (Liu et al. 2020).

**Strength and limitations**

This study can contribute to COVID-19 pandemic management and control through patient stratification, laboratory tests, and IL-6 level analysis to evaluate patient severity and outcomes. The limitation of this study was the lack of time parameters for sampling because changes in inflammatory cytokine levels (e.g., IL-6) during infectious disease occurrence are quite dynamic. Another limitation of this study was the small sample size, consisting of only the patients who received lopinavir-ritonavir. Future research can be conducted on a larger scale for all COVID-19 patients.

## CONCLUSION

Critical COVID-19 patients with comorbidities, poor laboratory profiles, and high IL-6 levels are associated with a poor prognosis. Therefore, patient risk stratification, laboratory profiles, and IL-6 levels can be important for evaluating the severity and patient outcomes.

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**Conflict of interest**

None.

**Ethical consideration**

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**Author contribution**

EAT contributed to the conceptualization, study design, data curation, formal analysis, data interpretation, methodology, supervision, manuscript writing, and content revision. NMR contributed to the conceptualization, study design, data interpretation, methodology, investigation, manuscript writing, and content revision. N contributed to the conceptualization, study design, formal analysis, data interpretation, methodology, investigation, project administration, writing, and content revision. FT contributed to the conceptualization, analysis, data interpretation,

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