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# THE ASSOCIATION OF INTERLEUKIN-6 AND PROCALCITONIN LEVELS WITH CLINICAL OUTCOME OF COVID-19 DISEASE

**Renata Evelyn Ramadhani[1], Amanatus Solikhah[2], Rizka ariani [3]**

**AFFILIATIONS**

1. Faculty of Medicine, Universitas Ahmad Dahlan, Yogyakarta, Indonesia
2. Departement of Clinical Pathology, Universitas Ahmad Dahlan, Yogyakarta, Indonesia
3. Departement of Microbiology, Universitas Ahmad Dahlan, Indonesia



**ABSTRACT**

*Severe and potentially fatal complications can arise from COVID-19, especially when the immune system triggers an exaggerated inflammatory reaction. This study examines the possible relationship between serum levels of Interleukin-6, Procalcitonin and clinical outcomes in hospitalized COVID-19 patients. Using a retrospective cross-sectional design, this study evaluated data from 71 patients hospitalized at RSUD Wates in 2021. Biomarker level differences between survivors and non-survivors were assessed using the Mann-Whitney U test and binary logistic regression. IL-6 concentrations were significantly higher in non-surviving patients and continued to serve as an independent predictor of mortality after adjustment. Conversely, while PCT levels were higher in non-survivors, they did not retain independent prognostic significance in multivariate analysis. IL-6 is crucial in forecasting severe outcomes, likely because of its role in cytokine storms and immune dysregulation. Initial IL-6 measurement may help detect patients at higher risk and support decisions regarding intensive care. Meanwhile, raised PCT levels require careful interpretation within the broader clinical picture. Additional research involving larger sample sizes and robust methodologies is required to determine the value of combined biomarkers in COVID-19 risk evaluation.*

**KEYWORDS:**

Interleukin-6, Procalsitonin, COVID-19, Biomarker, Mortality

**CORRESPONDING AUTHOR:**
**Amanatus Solikhah**
amanatus.sholihah@med.uad.ac.id

## INTRODUCTION

Since the pandemic peak, SARS-CoV-2 infection rates and the associated mortality rate have declined. But the public remains at risk due to the emergence of the new variants of SARS-CoV-2, including KP.2, KP.3, and LB.1, which have the potential to increase transmission and affect the effectiveness of the immune response.[1] The main route of transmission of the contagious is through the respiratory droplets.[2] addition, the coronavirus can also be transmitted through feces.[3] As a systemic disease, COVID-19 exhibits highly diverse clinical presentations, ranging from mild and self-limiting symptoms to life-threatening complications with a higher likelihood of death.[4]

As our understanding of COVID-19 pathophysiology continues to evolve, numerous studies have identified laboratory biomarkers such as D-dimer, serum creatinine, and the platelet-to-lymphocyte ratio (PLR) as potential indicators of disease severity. Although the sensitivity and specificity of these parameters may vary, their role in guiding clinical decision-making remains significant. In this context, interleukin-6 (IL-6) and procalcitonin (PCT)

have also emerged as key focus areas, due to their involvement in cytokine storms and systemic inflammation—both of which are closely associated with increased mortality in COVID-19 patients.[5,6] Serum procalcitonin (PCT) levels in COVID-19 patients are typically very low or undetectable, as procalcitonin production is suppressed by interferon-gamma, which is elevated during viral infections. [7,8] Procalcitonin is useful for distinguishing bacterial infections from viral ones. Compared to acute-phase proteins like CRP and IL-6, procalcitonin serves as a more reliable biomarker due to its superior sensitivity and specificity in detecting systemic bacterial infections.[9]

In high-severity COVID-19 patients, elevated levels of procalcitonin do not necessarily reflect bacterial infection, but can result from a massive cytokine storm, in which a surge of proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) induce CALC-1 gene expression through activation of NF-κB and STAT3 signal transduction pathways, thus triggering procalcitonin synthesis in various body tissues such as lung, liver, and kidney, although theoretically interferon gamma (IFN-γ) as a typical response to viral infection has a role in suppressing PCT production; however, in severe systemic inflammatory conditions such as cytokine storms, the suppressive effect of IFN-γ is not dominant and unable to prevent systemic PCT spikes.[10]

Interleukin-6 plays a role in cytokine storms with poor patient outcomes.[11] Critically ill COVID-19 patients show a surge in immune system activity, especially humoral immune pathways, including an increase in interleukin-6, which contributes greatly to respiratory failure, shock and overall organ damage. This phenomenon, known as cytokine release syndrome (CRS), is one of the main factors contributing to the severe condition of COVID-19.[12]

Early identification of disease severity is the important component of patient management. Therefore, laboratory biomarkers are needed as predictive tools to assess the level of infection severity. This information plays an essential role in supporting timely and accurate clinical decision-making and

contributes to efforts aimed at reducing COVID-19-related mortality[13].

This journal aims to examine the assosiation between Interleukin-6 (IL-6) and Procalcitonin levels on the clinical outcome of COVID-19 patients, which are categorized based on clinical outcomes: alive or dead. This study is important to identify inflammatory biomarkers that play a role in patient prognosis, so that it can be used as an early indicator in determining intensive therapy and making clinical decisions quickly and accurately.

**METHODS**

This research was an observational analytic study using a cross-sectional design that was conducted retrospectively at RSUD Wates, a COVID-19 referral hospital in Kulon Progo Regency, during the period January to December 2021. The population of this study included all COVID-19 confirmed patients through real-time reverse transcription polymerase chain reaction (RT-PCR) examination and underwent hospitalization during the period. The technique of sampling used a total sampling method, by including all patients who had fulfilled the inclusion criteria and excluding the exclusion criteria.

The inclusion criteria is COVID-19 positive RT-PCR patients, those with complete medical record data including the results of Interleukin-6 (IL-6) and Procalcitonin (PCT) levels performed at the time of hospitalization, and those admitted during the study period, while the exclusion criteria were patients known to have other active infections other than COVID-19, such as severe bacterial infections, active tuberculosis, or other opportunistic infections, and also comorbid diseases such as diabetes, hypertension and other comorbid diseases.

The number of total subjects in this research was 71 patients, with the main variables being Interleukin-6 and Procalcitonin levels. Examination of interleukin 6 and procalcitonin levels using ichroma II with the fluorescence immunoassay method. IL-6 is defined as a proinflammatory cytokine measured in picograms per milliliter (pg/mL) with a normal reference value of ≤7 pg/mL, while PCT is a systemic inflammatory marker measured in nanograms per milliliter (ng/mL) with a normal reference value of <0.1 ng/mL.[14,15]

The data were retrospectively collected using an electronic medical record system, which included the patient's age, gender, IL-6 and PCT test results, and clinical outcomes.

This was analyzed using SPSS software version 27, beginning with normality testing using Kolmogorov-Smirnov and/or Shapiro-Wilk, because the data were not normally distributed, the Mann-Whitney U test was performed to assess differences in biomarker levels between the living and deceased patient groups, and binary logistic regression analysis to evaluate the independent association of IL-6 and PCT levels with mortality risk, with p values <0.05 considered statistically significant.

This research has received permission from the Ethics Committee of Health Research at RSUD Wates with a number KEPK/035/RS/XII/2024, and all data is treated confidentially and used only for research purposes in accordance with the principles of medical research ethics.

## RESULT AND DISCUSSION

Subject characteristics are in table 1. In this research, women were the most subjects (50.7%) and the age average of the subjects was 56.30 years with a standard deviation of 17.412 which showed that the subjects had varying ages. There were (80.3%) subjects who had increased Interleukin 6 levels and there were (69%) subjects who had increased procalcitonin levels.

**Tabel 1.** Subjects Characteristic

| Variable | N(%) | Mean (SD) |
|---|---|---|
| **Gender** | | |
| Male | 35 (49.3) | |
| Female | 36 (50.7) | |
| Age | | 56.30 (17.412) |
| **Interleukin-6 Levels (pg/mL)** | | |
| Normal | 14 (19.7) | |
| Increased | 57 (80.3) | |
| **Procalsitonin Levels (ng/mL)** | | |
| Normal | 22 (31.0) | |
| Increased | 49 (69.0) | |

Different findings were found in several research studies. In Alsan *et al.*'s study involving 5,198 research subjects, COVID 19 incidence in men was four times higher than in women.[16] The same thing was also founded in a research by Pijls *et al.* involving 229 researches and involving more than 10 million patients, the outcome of this research showed that men had a higher risk of covid infection compared to women, with a Relative risk (RR) value = 1.14 (95% Cl 1.07-1.21).[17]

The increased infection risk in males may be linked to elevated ACE2 receptor expression in organs such as the lungs and heart. Conversely,

estrogen reduces ACE2 levels in females, who also benefit from dual X chromosomes harboring vital immune genes like TLR7, TLR8, and CD40L, enabling a more rapid immune response.[18]

Based on the results of the analysis using the Mann-Whitney U test (table 2), it was found that there was a difference in the levels of interleukin-6 that was significant between the living and deceased patient groups. The median (IQR) value of interleukin 6 levels in the living group was 25.13 (77.2-6.865) pg/mL, while in the deceased group it was 85.97 (449.04-24.4) pg/mL.

The mean rank value of the living group was 30.51, while the dead group was 43.08 with a p value = <0.011. These results show that in patients who died, interleukin 6 levels tended to be significantly higher than those of living patients. These findings indicate that elevated levels of interleukin 6 may contribute to the worsening of the patient's clinical condition and increase the risk of death.

A statistically significant difference in procalcitonin levels was also observed between the survivors and non-survivors. The median procalcitonin level among survivors was 0.12 ng/mL (IQR: 0.06–0.4375), whereas among non-survivors, it was 0.42 ng/mL (IQR: 0.25–2.05). The mean rank of the living group was recorded at 28.74, while that of the deceased group was 45.37, with a p value = <0.001. These results confirmed that deceased patients had significantly higher procalcitonin levels compared to surviving patients.

**Table 2.** Comparison of Biomarkers Based on Clinical Outcomes of Subjects

| Variable | Group | Median (IQR) | Mean Rank | *p*-value |
|---|---|---|---|---|
| **Interleukin 6** | Survive | 25.13 (77.2-6.865) pg/mL | 30.51 | |
| | Deceased | 85.97 (449.04-24.4) pg/mL | 43.08 | <0.011 |
| **Prokalsitonin** | Survive | 0.12 (0.4375-0.060) ng/mL | 28.74 | |
| | Deceased | 0.42 (2.05-0.25) ng/mL | 45.37 | <0.001 |

The results of the analysis in this study show alignment with a study conducted by Zhou and colleagues in 2020. This research included COVID-19 patients in Wuhan and reported that Interleukin-6 levels were elevated in non-surviving patients, with an average of 11.0 pg/mL, compared to surviving patients with an average level of 6.3 pg/mL. This was statistically significant different (p<0.0001), and Interleukin-6 was identified as one of the

independent predictors of mortality in the multivariate analysis model.[19]

In line with these findings, a study by Herold *et al.* (2020) in Germany showed that patients who required mechanical ventilation tended to have significantly higher IL-6 levels, at around 121 pg/mL, compared to patients who did not require ventilators who had average levels of only 19.6 pg/mL. The study also determined that an IL-6 threshold of 80 pg/mL can be used as an early indicator to predict the risk of acute respiratory failure, which is one of the main factors associated with mortality in COVID-19 patients.[20]

In addition to these two studies, a meta-analysis conducted by Coomes and Haghbayan (2020) reinforced this relationship. The analysis of more than 1,400 patients showed that individuals who experienced severe COVID-19 or died had significantly higher IL-6 levels compared to those who experienced mild symptoms or recovered. This study confirms that IL-6 plays an important role as an inflammatory marker that is closely related to disease severity and likelihood of death.[21]

Elevated levels of Interleukin-6 (IL 6) are known to play a central role in the worsening clinical condition of COVID 19 patients. IL 6 is one of the major proinflammatory cytokines produced by respiratory epithelial cells, monocyte-macrophages, and T cells during the immune response to SARS-CoV-2 infection. When IL 6 production is excessively elevated, it can interfere with the function of immune system effectors such as Natural Killer (NK) cells and cytotoxic T cells ($CD8^+$), while inhibiting the differentiation of regulatory T cells that are important in maintaining immune balance. This results in hyperactivation of the immune response known as a cytokine storm, which can cause vascular endothelial damage, increased vascular permeability, and lead to acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and multiorgan failure.[22,23]

One systematic review published by Frontiers in Immunology mentioned that in the advanced phase of the disease, elevated IL 6 can cause a condition resembling macrophage activation syndrome, characterized by lymphocyte exhaustion, decreased immune system effectiveness, and uncontrolled escalation of systemic inflammation.[22] In addition, the meta-

analysis conducted by Coomes and Haghbayan also reinforced that high IL 6 levels are closely associated with severity and mortality in COVID 19 patients, through these pathophysiological mechanisms.[21]

Elevated procalcitonin levels in both mean and median values were shown to be significantly associated with an increased risk of death in COVID-19 patients, as demonstrated by a Belgian ICU study that reported a median PCT in deceased patients of 4.22 ng/mL compared to 0.53 ng/mL in survivors (p = 0.0004), as well as a retrospective study by Heidari *et al.* which showed that a mean PCT >0.05 ng/mL increased the risk of death almost twofold independently (OR = 1.99; 95% CI: 1.14-3.47; p = 0.015).[24,25]

In the univariate binary logistic regression analysis (table 3), Interleukin-6 levels showed a statistically significant association with clinical outcomes, with an odds ratio (OR) of 1.003 (95% CI: 1.000-1.005; p = 0.020). This means that each one-unit increase in Interleukin-6 levels was associated with a 0.3% increased risk of clinical outcomes. Meanwhile, procalcitonin levels did not show a significant association in the univariate analysis, with an OR of 1.037 (95% CI: 0.985-1.091; p = 0.165), so it cannot be concluded as a factor that plays a role in influencing outcomes independently.

**Table 3.** Results of Univariate Binary Logistic Regression Analysis

| Variabel | OR | 95% CI | P-value |
|---|---|---|---|
| **Interleukin-6** | 1.003 | 1.000 – 1.005 | 0.020 |
| **Prokalsitonin** | 1.037 | 0.985 – 1.091 | 0.165 |

On multivariate analysis, interleukin-6 still showed a statistically significant association (OR: 1.002; 95% CI: 1.000-1.005; p = 0.020), indicating that this variable was an independent predictor of clinical outcomes. Each one-unit increase in Interleukin-6 was associated with a 0.2% increased risk of outcome after controlling for other variables. In contrast, procalcitonin still did not show a statistically significant association in the multivariate model (OR: 1.033; 95% CI: 0.984-1.085; p = 0.189), so it cannot be considered as an independent predictor in this model.

Several previous studies have also shown that levels of interleukin-6 are a significant indicator in predicting mortality in COVID 19 patients. Research by Galán Román *et al.* (2020) showed that IL 6 has an important

role in a multivariate logistic regression-based mortality prediction model. In the study, IL 6, along with the neutrophil-lymphocyte ratio (NLR) and $SpO_2/FiO_2$ ratio, were included in a predictive model that produced a very high level of accuracy, with an area under curve (AUC) value of 0.94. This confirms that IL 6 is one of the most powerful indicators in estimating the risk of death from COVID 19.[26]

Meanwhile, Cheng *et al.* (2021) through univariate logistic regression analysis also found that IL 6 levels play a significant role as a predictor of short-term mortality. In their study, an IL 6 threshold of 163.4 pg/mL was able to predict death within 30 days with a sensitivity of 91.7%, indicating that IL 6 can be used as an important parameter in the assessment of patient prognosis.[27]

Something similar was found in a retrospective study by Liu *et al.* (2023), where IL 6 was still shown to be a significant independent predictor of mortality in a multivariate logistic regression model, despite adjusting for other clinical variables such as age, comorbidities and other inflammatory biomarkers. Interestingly, in the comparison of predictive performance, IL 6 showed the highest AUC value (0.898) compared to other biomarkers such as D-dimer and C-reactive protein (CRP), suggesting that IL 6 has a prognostic advantage in predicting poor clinical outcomes.[28]

The findings on procalcitonin in this study are in line with the study conducted by Nielsen *et al.* (2022), which evaluated the role of procalcitonin in predicting clinical outcomes in hospitalized COVID-19 patients. In that study, although PCT showed increased levels in patients with higher clinical severity, multivariate logistic regression analysis showed that PCT did not play a significant role as an independent predictor of mortality, with an odds ratio value close to one (OR = 1.00; 95% CI: 0.97-1.02; p = 0.713). Moreover, Kaplan-Meier analysis found no significant difference in the duration of hospitalization or intensive care based on baseline PCT levels. These findings reinforce that although PCT may reflect inflammatory activity or secondary infection, its role in determining the mortality risk of COVID-19 patients remains limited if not combined with other clinical parameters such as age, comorbidities, or more specific inflammatory indicators. Therefore, interpretation of PCT as a single predictive biomarker should be done with

caution, and not used as the sole basis for critical clinical decision-making.[29]

Although procalcitonin (PCT) levels were elevated in severe COVID-19 patients, this increase did not show significance in multivariate regression because PCT may be triggered by a systemic inflammatory response via interleukin-6 rather than a specific bacterial infection, and after controlling for other inflammatory variables such as IL-6 or CRP, the predictive effect of PCT on mortality was not significant.[30,31]

This is because biomarker collinearity and low PCT cut-off values (<0.5 ng/mL) are not strong enough to predict mortality independently, and the heterogeneity of the COVID-19 patient population causes inconsistencies in results between one study and another.[32,33]

**CONCLUSION**

Based on the results of this study, it can be concluded that Interleukin-6 (IL-6) levels have statistically significant associations with COVID-19 patient clinical outcomes, both through univariate and multivariate analysis, so that it can be categorized as an independent predictor of mortality risk. Elevated levels of IL-6 reflect excessive activation of the immune system, which contributes to a cytokine storm and triggers severe clinical complications like respiratory failure, multiple organ dysfunction and mortality.

On the other hand, although procalcitonin (PCT) levels were also found to be significantly higher in patients who did not survive, logistic regression analysis showed that PCT had no independently significant predictive power of clinical outcomes, and thus could not be used as the sole marker in predicting mortality. Overall, these findings confirm that IL-6 has a prognostic advantage over PCT in assessing severity and mortality risk in COVID-19 patients.

In this regard, the examination of IL-6 levels is recommended to be integrated into the early assessment protocol of COVID-19 patients in health care facilities, especially to detect patients who are at risk of worsening clinical conditions. The application of IL-6 as a predictive biomarker is expected to help clinicians determine the need for intensive therapy in a more timely and efficient manner. Meanwhile, interpretation of PCT levels should still be done carefully, taking into account the broader clinical context, including the possibility

of bacterial co-infection or the effects of cytokine storms. To strengthen these findings, further studies with prospective designs, larger sample sizes, and analyses that control for confounding variables are needed to more accurately evaluate the potential use of combined biomarkers in predicting the prognosis of COVID-19 patients in the future.

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