INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

PAGE 138
2024 March; 30 (2): 138-142
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

# Comparative Analysis of C-Reactive Protein and Procalcitonin Levels in the Severity of COVID-19 Patients

**Tuti Alawiyah[1], Asvin Nurulita[1], Uleng Bahrun[1,2]**

[1] Departement fo Clinical Pathology Faculty of Medicine, Hasanuddin University/ Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. E-mail: tuti1138@gmail.com
[2] Hasanuddin University Hospital, Makassar, Indonesia

## ABSTRACT

Coronavirus Disease 2019 (COVID-19) is a systemic disease characterized by mild to critical symptoms with a high risk of mortality. Fast and precise inflammatory markers are needed to predict the severity and prognosis of COVID-19 to decrease the mortality rate. The elevated levels of C-Reactive Protein (CRP) and procalcitonin may predict an increased risk of aggravation in COVID-19 patients. This study aimed to analyze the CRP and procalcitonin levels of COVID-19 severity. This was a cross-sectional retrospective study involving 160 COVID-19 patients at Dr. Wahidin Sudirohusodo Hospital. Subjects were grouped based on the severity of COVID-19 (mild, moderate, severe, critical). The difference in CRP and procalcitonin levels based on the severity of COVID-19 was analyzed using the Kruskal-Wallis test and the Spearman correlation test. The age of participants in this study ranged from 19-87 years old. The higher CRP and procalcitonin level shows heavier the severity of COVID-19 ($p<0.001$). This indicated a significant difference between CRP, procalcitonin levels, and the severity of COVID-19. This study showed that there was a significant correlation between CRP and procalcitonin with the severity of COVID-19, CRP ($p<0.001$) and procalcitonin ($p<0.001$).

**Keywords:** Severity of COVID-19, CRP, procalcitonin

## INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is a new type of coronavirus that has never been previously identified in humans.[1] The number of COVID-19 cases continues to increase rapidly and spread to various countries in a short time. The number of confirmed cases of COVID-19 by July 2022 reached 555,446,890 people worldwide and has resulted in more than 6,353,692 deaths. Confirmed cases of COVID-19 in Indonesia by July 2022 reached 6,120,169 people and resulted in 156,818 deaths.[2]

According to the World Health Organization (WHO), the degree of severity of COVID-19 is classified into 5 categories, such as asymptomatic, mild, moderate, severe and critical. The degree severity of a COVID-19 patient is determined based on the history, clinical symptoms, laboratory tests, and radiological tests.[3] Previous studies have shown that several markers such as Interleukin-6 (IL-6), D-dimer, lactate dehydrogenase (LDH), and Fibrinogen Degradation Product (FDP) are associated with COVID-19. Both the C-Reactive Protein (CRP) and procalcitonin test are two laboratory parameters, that can be used as biomarkers of increased inflammation and increased tissue injury.[4,5]

C-reactive protein is a type of protein produced by the liver, which serves as an early marker of infection and inflammation and a useful marker for monitoring the severity of disease. When inflammation occurs, natural and adaptive immune responses play an important role and lead to the production of many types of cytokines, including proinflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and IL-6. This cytokine will cause hepatocytes to secrete more CRP in COVID-19.[4]

Procalcitonin is a calcitonin precursor glycoprotein without hormonal activity, which is produced and released by parafollicular cells of the thyroid. During bacterial infection and sepsis, procalcitonin increases significantly because it is produced by extrathyroid sources in response to bacterial endotoxins and inflammatory cytokines, such as IL-1β, TNF-α, and IL-6. Procalcitonin levels are within the normal range in some uncomplicated COVID-19 patients. High procalcitonin levels in the severe symptom group indicate that COVID-19

patients with severe symptoms may experience bacterial superinfection, which contributes to complicating the clinical manifestation.[6]

Early data suggest that increased PCT concentrations may predict the severity of COVID-19. A meta-analysis of four studies from China showed that elevated PCT concentrations are associated with a five-fold higher risk of severe COVID-19, although the underlying pathophysiological mechanisms have not been elucidated.[7]

Based on this background, the authors were interested in comparison analysis of CRP and procalcitonin of severity in COVID-19 patients at Dr. Wahidin Sudirohusodo Hospital in Makassar.

## METHODS

This research was a retrospective study with a cross-sectional method using secondary data from patient medical records at Dr. Wahidin Sudirohusodo Hospital Makassar from May to June 2022. The study population was all inpatients who were diagnosed with COVID-19 by KSM Internal Medicine/Pulmonary Clinicians at Dr. Wahidin Sudirohusodo Hospital and met the inclusion criteria such as age > 18 years, had CRP and procalcitonin test results and information on the severity of COVID-19. According to WHO, the severity of COVID-19 is categorized into mild, moderate, severe and critical. Patients with malignancy, pregnancy, and patients recovering from previous surgery were excluded from this study. The laboratory data including CRP and procalcitonin levels were obtained when the patient was first admitted to the hospital. Demographic, clinical, and laboratory data were obtained from electronic medical records when the patient was first admitted to the hospital.

SPSS version 25, the Kolmogorov-Smirnov test to determine data normality, the Kruskal-Wallis test, and the Spearman correlation test. A $p<0.05$ was reported as significant.

The research was performed based on recommendations for ethical feasibility (Ethical Clearance) obtained from the Research Ethics Committee (KEPK) of the Faculty of Medicine, Hasanuddin University with number: 429/UN4.6.4.5.31/PP36/2022.

## RESULTS AND DISCUSSIONS

The research was conducted at the Medical Record Division at Dr. Wahidin Sudirohusodo Hospital in August 2022 and used data from 160 COVID-19 patients.

Most of the subjects were male (50.6%) and the most common age group was 46-65 years (45.6%). The most common category of COVID-19 in this study was moderate, which was found in 62 patients (38.8%). Table 1 also shows that the CRP levels varied between 0.10-340.20 mg/L and the procalcitonin levels in this study varied between 0.05-200.00 ng/mL. Based on the normality test with the Kolmogorov-Smirnov test, the data of CRP and procalcitonin were not normally distributed.

The highest median of CRP and procalcitonin levels was found in the critical grade and the lowest median was found in the mild grade of COVID-19 ($p<0.001$). The higher CRP and procalcitonin level shows heavier the severity of COVID-19 ($p<0.001$). This indicated a significant difference between CRP, procalcitonin levels, and the severity of COVID-19.

**Table 1.** Characteristics of research subjects

| Characteristics | n (%) | Min-Max | Median±SD |
|---|---|---|---|
| **Gender** | | | |
| Male | 81 (50.6%) | | |
| Female | 79 (49.4%) | | |
| **Age group (years)** | | | |
| 19-35 | 30 (18.8%) | | |
| 36-45 | 17 (10.6%) | | |
| 46-65 | 73 (45.6%) | | |
| >65 | 40 (25.0%) | | |
| **Severity of COVID-19** | | | |
| Mild | 26 (16.3%) | | |
| Moderate | 62 (38.8%) | | |
| Severe | 43 (26.9%) | | |
| Critical | 29 (18.1%) | | |
| **Variable** | | | |
| CRP (mg/L) | | 0.10-340.20 | 39.65±69.74 |
| Procalcitonin (ng/mL) | | 0.05-200.00 | |

**Table 2.** CRP and procalcitonin levels based on the severity of COVID-19

| Variable | Severity of COVID-19 | n | Median | SD | p* |
|---|---|---|---|---|---|
| CRP (mg/L) | Mild | 26 | 1.50 | 11.41 | 0.000 |
| | Moderate | 62 | 23.15 | 33.13 | |
| | Severe | 43 | 110.00 | 51.53 | |
| | Critical | 29 | 130.00 | 83.15 | |
| Procalcitonin(ng/mL) | Mild | 26 | 0.05 | 0.03 | 0.000 |
| | Moderate | 62 | 0.10 | 3.89 | |
| | Severe | 43 | 1.35 | 42.12 | |
| | Critical | 29 | 2.50 | 38.16 | |

*Abbrev : Kruskall-Wallis test

**Table 3.** Correlation test of CRP level with severity of COVID-19 disease

| Variable | n | Spearman Correlation | p-value |
|---|---|---|---|
| CRP levels with the severity of COVID-19 | 160 | 0.774 | 0.001 |

The results of the correlation test in Table 3 show that there is a significant positive correlation between CRP and the severity of COVID-19. Based on the correlation coefficient value, there was a very strong correlation between CRP and the severity of COVID-19 with R=0.774 (R>0.750).

**Table 4.** Correlation test of procalcitonin level with severity of COVID-19

| Variable | n | Spearman Correlation | p-value |
|---|---|---|---|
| Procalcitonin levels with the severity of COVID-19 | 160 | 0.655 | 0.001 |

Table 4 shows that there is a significant positive correlation between procalcitonin and the severity of COVID-19. Based on the correlation coefficient value, there was a strong correlation between CRP and the severity of COVID-19 with R=0.655 (R>0.500-R<0.750).

A total of 160 subjects met the study criteria; most of them were males with an age range of 19-91 years in the age group of 46-65 years (45.6%). The results of this study were in line with a study by Zhu *et al.*, which reported that the gender of the majority of COVID-19 patients was male.[8] Male sex hormones suppress the immune response, whereas female sex hormones give a natural protective effect on females.[9] The highest age group in the results of this study was in line with the results of research by Jiang *et al.* in several hospitals in China, which found that most COVID-19 patients had an age range of 49–56 years.[10]

Based on the classification of the severity of COVID-19, this study showed that subjects with more severe COVID-19 are likely to have higher CRP levels. Most of the research subjects in this study had moderate COVID-19 (38.8%) and the mean CRP levels in mild, moderate, severe, and critical COVID-19 in this study were 5.50 mg/L, 33.87 mg/L, 104.59 mg/L and 143.82 mg/L, respectively (Table 2). This difference in CRP levels was statistically significant (p<0.001). This was in line with the retrospective cohort study by Fang Liu *et al.*, and a study by Ruan *et al.*, which showed a significantly higher increase in CRP levels in severe disease compared to mild disease. This suggests that inflammatory factors play an important role in the development of mild to severe disease.[11,12]

C-reactive protein is an acute phase protein that can elevated to a hundredfold in infection or inflammation. The body experiences a natural and adaptive immune response while inflammation occurs, which triggers the production of many types of cytokines, including proinflammatory cytokines such as TNF-α and IL-6. These cytokines will cause hepatocytes to spend more CRP in COVID-19. In addition, they will also cause vasodilatation and increased vascular permeability resulting in fluid buildup in the lungs that ultimately interferes with breathing. Multiple organ failures may also occur. The CRP level is found to increase significantly in response to injury, infection, and inflammation. The CRP's capability to be a marker of acute inflammation is independent of demographic factors, such as age, gender, and initial physical condition.[13]

A cohort study by Liu *et al.* about the relationship between procalcitonin levels, progression, and prognosis of COVID-19 patients in 1,525 cases at the Leishenshan Hospital, Wuhan found that the group with elevated procalcitonin levels (≥0.05 ng/mL) had a higher risk of critical disease and mortality compared to the group with normal procalcitonin levels.[11]

Procalcitonin is a calcitonin precursor glycoprotein without hormonal activity, which is produced and released by parafollicular cells of the thyroid. High procalcitonin levels in the severe COVID-19 group indicate that patients with severe symptoms may experience bacterial superinfection, which contributes to complicating the clinical picture.[6] Procalcitonin is a biomarker of systemic inflammatory activity in the early phase after infection, which originates from the stimulation of proinflammatory cytokines. Procalcitonin levels increase in the presence of bacterial infections and are relatively low in viral infections; therefore, they can be used to distinguish between bacterial and viral infections.[14] Elevated procalcitonin levels in COVID-19 patients may indicate bacterial coinfection, which increases the severity of the disease and the possibility of sepsis and the occurrence of cytokine storms. Increased IL-6 levels in a cytokine storm can stimulate the release and increase of other acute-phase proteins, such as procalcitonin.[15]

Procalcitonin concentrations are not found to be elevated in COVID-19 patients on admission or during early disease, but patients with worse outcomes demonstrate a progressive increase in procalcitonin concentrations during the inpatient episode, a phenomenon, which this study aimed to capture through the use of peak procalcitonin value. It has been speculated that this increase could reflect bacterial co-infection, which likely occurs later in the course of illness, or the severity of COVID-19.[7]

Procalcitonin synthesis is upregulated by different cytokines such as IL-6 and TNF-α. Because hyperinflammation is shown to be an important factor in the progression of COVID-19 infections, the dysregulated immune response may also trigger PCT production.[16] Similar results of elevated procalcitonin levels were found in patients with isolated severe influenza virus infections, findings that support the hypothesis that procalcitonin is a marker of hyperinflammation.[17]

Viral proteins can increase the production of acute-phase reactants such as CRP, ferritin, and procalcitonin.[18] This is supported by the theory that SARS-CoV-2 proteins (ORF6 and NSP1) can increase PCT production by inhibiting IFN function and increasing STAT3 signaling in monocytes. This increase in STAT3 can increase PCT production. In addition, the increase in PCT production in COVID-19 patients may also be caused by the disrupted function of monocytes and their irregular secretion production.[19] In this case, the increase in procalcitonin due to viral infection may cause cytokines, Reactive Oxygen Species (ROS), and neutrophil/lymphocyte surface markers to upregulate. This positive feedback between procalcitonin and proinflammatory cytokines will lead to a severe systemic inflammatory response.[14]

The CRP and procalcitonin can be used to determine the severity of COVID-19. CRP levels in COVID-19 patients can effectively predict disease severity, adverse outcomes, prognosis, and mortality. High CRP levels in COVID-19 patients at hospital admission indicate CRP can be utilized as an independent biomarker for earlier detection of disease severity as severe patients are more likely to have high CRP levels as compared to non-severe patients, which indicates disease severity as well as the disease advancement.

In general, the results of this study indicated that there was a strong correlation between disease severity, CRP, and procalcitonin levels. Because CRP and procalcitonin levels have become inflammatory markers that are routinely tested and are widely available in health care centers, CRP and procalcitonin can be markers of the severity of COVID-19 disease. However, the use of secondary data and the limited information from medical records remained the limitations of this study. An incomplete medical recording system also contributed to the difficulty of this study, thereby excluding many subjects.

## CONCLUSIONS AND SUGGESTIONS

Therefore, the validity of PCT as an independent factor to predict the severity of COVID-19 needs to be further studied using a larger sample size. In conclusion, the serum levels of CRP have a significant correlation with the severity of COVID-19 and can be used as independent factors to predict disease risk. However, the validity of procalcitonin needs to be further investigated.

An increase in CRP and procalcitonin levels occurs along with the progression of COVID-19 into severe disease. It was suggested that CRP and procalcitonin can be markers of worsening patient conditions, thereby assisting in the selection of proper management strategies for COVID-19 patients.

## REFERENCES

1. Bchetnia M, Girard C, Duchaine C, Laprise C. The outbreak of the novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2): A review of the current global status. J Infect Public Health, 2020; 13(11): 1601-1610.
2. World Health Organization. WHO Coronavirus Disease (COVID-19) dashboard with vaccination data |

WHO Coronavirus (COVID-19) dashboard with vaccination data. World Health Organization, 2021; 1–5.
3. Kemenkes RI. Pedoman tatalaksana COVID-19. 2022; 1–112.
4. Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. Journal of Medical Virology, 2020; 92(11): 2409-2411.
5. Liu ZM, Li JP, Wang SP, Chen DY, Zeng W, *et al.* Association of procalcitonin levels with the progression and prognosis of hospitalized patients with COVID-19. Internat J Med Sci, 2020; 17(16): 2468-76.
6. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Internat J Antimicrob Agents, 2020; 56(2): 106051.
7. Lippi G, Plebani M. Procalcitonin in patients with severe Coronavirus Disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta, 2020; 505: 190–191.
8. Zhu J, Ji P, Pang J, Zhong Z, Li H, *et al.* Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. Journal of Medical Virology, 2020; 92(10): 1902-1914.
9. Kragholm K, Andersen MP, Gerds TA, Butt JH, Østergaard L, *et al.* Association between male sex and outcomes of Coronavirus Disease 2019 (COVID-19) – a Danish nationwide, register-based study. Clinical Infectious Diseases, 2021; 73(11): e4025-e4030.
10. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of Coronavirus Disease 2019 (COVID-19). Journal of General Internal Medicine, 2020; 35(5): 1545-1549.
11. Liu F, Li L, Xu M Da, Wu J, Luo D, *et al.* Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol, 2020; 127: 104370
12. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan China. Intensive Care Medicine, 2020; 46(5): 846-848.
13. Muhammad Sheshe S, Muhammad Labbo A, Garba Mohammed K, Sheshe S, Nazifi A, *et al.* Mechanism of antiviral immune response and COVID-19 infection. Asian J Immunol, 2020; 3(3): 1–8.
14. Shen Y, Cheng C, Zheng X, Jin Y, Duan G, *et al.* Elevated procalcitonin is positively associated with the severity of COVID-19: A meta-analysis based on 10 cohort studies. Medicina, 2021; 57(6): 594.
15. Boechat JL, Wandalsen GF, Kuschnir FC, Delgado L. COVID-19, and pediatric asthma: Clinical and management challenges. International Journal of Environmental Research and Public Health, 2021; 18(3): 1093.
16. Torres Acosta MA, Singer BD. Pathogenesis of COVID-19-induced ARDS: Implications for an ageing population. Eur Respir J. 2020; 56: 2002049.
17. Gautam S, Cohen AJ, Stahl Y, Valda Toro P, Young GM, *et al.* Severe respiratory viral infection induces procalcitonin in the absence of bacterial pneumonia. Thorax, 2020; 75(11): 974–81.
18. Gulhar R, Ashraf MA, Jialal I. Physiology, acute phase reactants. Publishing, 2023. Available from:https://www.ncbi.nlm.nih.gov/books/NBK519570/(accessed April 24, 2023).
19. Lugito NPH. Is procalcitonin a part of human immunological response to SARS-CoV-2 infection or just a marker of bacterial coinfection?. Curr Res Transl Med, 2021