Original Article

Differences in C-reactive Protein Level Based on Clinical Severity and Outcome of COVID-19 Patients at Dr. M. Djamil Hospital, Padang

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Abstract

Background: Inflammatory processes in COVID-19 can increase inflammatory markers such as C-reactive protein (CRP), procalcitonin (PCT), and interleukin 6 (IL-6). The level of C-reactive protein describes the severity of viral infection. Several studies have been conducted to investigate the link between C-reactive protein levels and the severity of COVID-19. The purpose of this study is to identify differences in C-reactive protein levels based on clinical degrees and outcomes of COVID-19 patients treated at Dr. M. Jamil General Hospital, Padang.

Methods: This is a retrospective cohort study that analyzed all COVID-19 patients treated at Dr. M. Jamil General Hospital, Padang. This study lasted from December 1st, 2021 and June 1st, 2022. The data was analyzed using univariate, bivariate, and confounding analysis. Bivariate analysis explored differences in C-reactive protein levels in clinical severity and patient outcomes for COVID-19. The Kruskal-Wallis test determined the difference between the CRP level and clinical severity, while the Mann-Whitney test determined the difference between the CRP level, length of stay and final hospitalization status. The confounding test was performed using multiple linear regression tests.

Results: The majority of participants were women (51.0%) with a range of age between 50–59 years (28.0%) and suffered from hypertension (46.0%). Less than half of them had secondary infection (49.0%). The majority of them had a critical clinical severity (75.0%) and length of stay ≤14 days (77.0%) and more than half were deceased (65.0%). C-reactive protein levels were higher in patients with critical clinical degrees (89.00 mg/L) compared to moderate (37.50 mg/L) and severe (23.00 mg/L), C-reactive protein levels in patients with long hospitalization ≤14 days (97.00 mg/L) was higher than >14 days (88.50 mg/L), and C-reactive protein levels were higher in patients who died (93.00 mg/L) than those who survived (68.00 mg/L).

Conclusion: C-reactive protein levels differed significantly based on clinical severity, length of stay and end of stay status of COVID-19 patients.

Keywords: C-reactive protein, COVID-19, clinical severity

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 will bind to Angiotensin Converting Enzyme 2 (ACE2) receptors in target organs such as the lungs, heart, renal system, and gastrointestinal system.[1,2]

The COVID-19 clinical manifestations include asymptomatic, mild, moderate, severe, or multi-organ dysfunction caused by the inflammatory process of viral infection. The inflammatory process increases inflammatory markers such as C- reactive protein (CRP), procalcitonin (PCT), and interleukin 6 (IL-6) (IL-6).[1,2]

The study by Liu et al on 140 COVID-19 patients found elevated levels of IL-6 in 95 patients (67.9%), C-reactive protein in 91 patients (65.0%), and procalcitonin in 8 patients (5.7%).[3] Zeng et al reported an association between elevated inflammatory markers and severity of COVID-19 patients in their meta-analysis. Monitoring the rise in these inflammatory markers can facilitate in determining the severity and prognosis of COVID-19 disease.[4]

C-reactive protein is a highly sensitive systemic marker that can be used as an indicator of inflammation during the acute phase of inflammation, infection, and tissue damage.[5] Hepatocytes produce C-reactive protein, which is secreted 4-10 hours after inflammation. C-reactive protein levels peak after 48

hours of inflammation and have a half-life of 19 hours.[6] C-reactive protein normal values vary. In suspected cases of COVID-19 with fever and respiratory symptoms, CRP level of 4 mg/L has proven useful as triage.[7]

C-reactive protein levels indicate the severity of viral infection. According to Chen et al study, the average amount of C-reactive protein in COVID-19 patients with severe clinical symptoms was higher than in those without severe clinical symptoms.[6] A mild viral illness is indicated by slightly elevated C-reactive protein levels (10–20 g/mL). COVID-19 patients with moderately elevated C-reactive protein levels (>20-40 g/mL) may experience reversible tissue damage as a natural response to the disease. COVID-19 patients with significantly elevated C-reactive protein levels (>100 g/mL) have advanced tissue damage, coagulation abnormalities, and multipleorgan failure, all of which are associated with a life-threatening prognosis.[7]

Several studies have been conducted to investigate the association between C-reactive protein levels and the severity of COVID-19. Tan et al.found a significant increase in C-reactive protein levels in 27 COVID-19 patients in the early stages of the disease in their study involving 27 COVID-19 patients in China. High levels of C-reactive protein are associated with extensive lesions in the lungs, according to computed tomography (CT) analysis of disease severity. In this study, C-reactiveprotein is associated with disease progression and can be used to predict the initial severity of COVID-19 disease.[8]

According to Chen et al study, high levels of C-reactive protein were associated with severe pneumonia and longer duration of illness than low levels of C-reactive protein. C-reactive protein has also been used in several studies to predict inpatient mortality and the need for mechanical ventilation.[9] High levels of C-reactive protein were associated with systemic inflammation and also strongly associated with venous thromboembolism (VTE), acute kidney injury (AKI), the severity of critical illness, and death in COVID-19 patients, according to a study conducted bySmilowitz et al. in New York involving adult patients with confirmed COVID-19.[10]

Based on the information presented above, the authors were interested in investigating differences in C-reactive protein levels based on clinical degrees and outcomes of COVID-19 patients who were treated at Dr. M. Djamil General Hospital, Padang.

METHODS

This was a retrospective cohort study. The study was conducted from December 2021 to June 2022 in the COVID-19 isolation room at Dr. M. Djamil General Hospital, Padang. All COVID-19 patients treatedat Dr. M. Djamil General Hospital, Padang between January 1st, 2021, and December 31st, 2021 who met the inclusion and exclusion criteria were included in this study.

The results of RT-PCR/TCM SARS-CoV-2 taken from nasal or nasopharyngeal swabs of patients aged 18 years, as well as complete medical record data including name, age, sex, comorbidities, clinical degree, protein levels (C-reactive), and outcomes of COVID-19 patients, were used to determine study inclusion criteria. Patients with high C-reactive protein levels who were evaluated qualitatively were excluded from the study.

RESULTS

There were 100 participants who met the criteria for inclusion and exclusion. The characteristics of COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang are shown in Table 1. The majority of patients were female (51.0%) with age ranges between 50-59 years (28.0%). Hypertension (46.0%) and diabetes (34.0%) were the most prevalent comorbid. Secondary infections were found in 49.0% of participants. The majority of participants (75.0%) had a critical clinical degree and length of stay less than 14 days (77.0%) and more than half of them were deceased (65.0%) (Table 1).

Table 2 shows that patients with critical severity had higher levels of C-reactive protein (89.00 mg/L) than those with moderate (37.50 mg/L) or severe (23.00 mg/L). The analysis revealed significant differences in C-reactive protein levels based on the clinical severity of COVID-19 patients

being treated at Dr. M. Djamil General Hospital, Padang (*P*=0.006).

Table 1. Characteristics of COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

Variable	N (%)
Age (Years)	
<50	21 (21.0%)
50–59	28 (28.0%)
60–69	27 (27.0%)
≥70	24 (24.0%)
Gender	
Male	49 (49.0%)
Female	51 (51.0%)
Comorbid	
Cerebrovascular	4 (4.0%)
Hypertension	46 (46.0%)
Diabetes Mellitus	34 (34.0%)
Cardiovascular	9 (9.0%)
Pulmonary Disease	0 (0.0%)
Kidney Disease	5 (5.0%)
Chronic Liver Injury	0 (0.0%)
Immunodeficiency	0 (0.0%)
Pregnancy	7 (7.0%)
Obesity	1 (1.0%)
Malignancy	1 (1.0%)
Secondary Infection	
Yes	49 (49.0%)
Clinical Severity	
Moderate	22 (22.0%)
Severe	3 (3.0%)
Critical	75 (75.0%)
Length of Stay	
≤14 days	77 (77.0%)
>14 days	23 (23.0%)
End of Treatment Status	
Life	35 (35.0%)
Dead	65 (65.0%)

Table 2. Differences in C-reactive Protein Level Based on Clinical Severity of COVID-19 Patients at Dr. M. Djamil Padang

Clinical Severity	Median of C- reactive levels (min-max)	*P*
Moderate	37.50 (4.90 – >160.00)	
Severe	23.00 (4.90 – 126.00)	0.006*[a]
Critical	0.00 (0.20 – >160.00)	

Note: **P*<0.05 is significant; [a]Kruskal-Wallis test

According to Table 3, the levels of C-reactive protein in deceased patients were higher in those with a length of stay of <14 days (97.00 mg/L) than in those with a length of stay >14 days (88.50 mg/L). The analysis revealed that there were significant differences in C-reactive protein levels in deceased patients based on the length of stay of COVID-19 patients at Dr. M. Djamil General Hospital, Padang (*P*=0.42). C-reactive protein levels were lower in living patientswith <14-day stay (55.00 mg/L) than those with >14 days stay (93.00 mg/L). The result indicated significant differences in C-reactive protein levels in surviving patients based on the length of stay of COVID-19 patients at Dr. M. Djamil General Hospital, Padang (*P*=0.031).

Table 3. Differences in C-reactive Protein Levels Based on Length of Stay in COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

Stratification	Length of stay	Median of C-reactive levels (min-max)	*P*
Deceased (n=65)	≤14 hari	97.00 (0.20 – >161.00)	0.042[b*]
	>14 hari	88.50 (16.00 – >161.0)	
Alive (n=35)	≤14 hari	55.00 (0.20 – >161.00)	0.031[b*]
	>14 hari	93.00 (7.9 – >132.0)	

Note: **P*<0.05 is significant; [b]Mann-Whitney test

Table 4 shows that deceased patients had higher levels of C-reactive protein (93.00 mg/L) than those who survived (68.00 mg/L). According to the findings of the study, there were significant differences in C-reactive protein levels based on the final status of COVID-19 patients at Dr. M. Djamil General Hospital, Padang (*P*=0.017).

Table 4. Differences in C-reactive Protein Levels Based on Final Hospitalization Status in COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

Final Hospitalization Status	Median of C- reactive levels (min-max)	*P*
Deceased	93.00 (0.20 – >160.00)	0.017*[b]
Survived	68.00 (0.20 – >1600)	

DISCUSSION

According to the findings of this study, the majority of patients (28.0%) were between the age of 50 and 59, and female (51.0%). Most common comorbid diseases included hypertension (46.0%), diabetes (34.0%), cardiovascular disease (9.0%), pregnancy (7.0%), kidney disorders (5.0%), cerebrovascular disease (4.0%), obesity (1.0%), and malignancy (1.0%). Secondary infections were found in less than half of the total subjects (49.0%). The majority of patients (75.0%) had a critical clinical degree and a length of stay of 14 days (77.0%), and more than half of the subjects (65.0%) died.

This study shows that the majority of COVID-19 patients were female. The result is similar to a study conducted by Fortunato et al involving 1,175

patients, revealing the incidence of COVID-19 was higher in women than men. Research on East Asian women suggested higher expression of ACE2 in women, so they are more likely to get COVID-19.[11]

Surendra's study in Jakarta found different results, revealing that the majority of participants were male.[12] According to another theory, women are less susceptible to COVID-19 infection than men. It is linked to innate immunity, steroid hormones, and sex chromosome factors. When compared to men, the immune regulation gene encoded by the X chromosome in women causes a decrease in viral load and inflammation. Women have higher levels of CD4+ T cells and better immune responses. Women have higher TLR7 levels than men, and biallelic expression allows for a better immune response and increased resistance to viral infections. Men are also associated with a bad lifestyle, such as smoking and drinking more liquor than women.[13]

The Fresan study found an association between hypertension and the severity of COVID-19, although not statistically significant. Hypertension was linked to severe COVID-19 (OR=2.42; 95% CI=1.98-2.96), death (OR=2.60; 95% CI=2.11-3.20), and poor outcomes in patients of all ages (OR=2.50; 95% CI=2.49-4.88).[14] The severity of COVID-19 is related to immune system dysregulation in hypertensive patients. Monocytes in hypertensive patients are hyperactive, producing more IL-6 after stimulation with angiotensin II or lipopolysaccharide, and there is an increase in CD8+ T cells that produce TNF. These CD8+ T cells are unable to fight viral infections and produce an excessive amount of cytokine.[15]

Diabetes patients are 3.69 times more likely to die from COVID-19.[16] Diabetes mellitus was associated with an increased risk of developing severe COVID (OR=2.47; 95% CI=1.86-3.27), death (OR=2.11; 95% CI=1.63-2.73), and a fatal outcome in patients of all ages (OR=2.25; 95% CI=1.89-2.69).[17] The role of hyperglycemia, high cellular affinity binding, efficient viral input, decreased viral clearance, impaired T-cell function, hyperinflammation, cytokine storm syndrome, and the presence of cardiovascular disease are all potential mechanisms by which diabetic patients are more vulnerable to the risk and severity of COVID-19.[18]

Cardiovascular disease is a common comorbidity in COVID-19 patients. A meta-analysis of 8 studies from China on 46,248 COVID-19 patients suggested that the most common co-morbidities included hypertension, DM and cardiovascular disease. The explanation is common cardiovascular disease in elderly patients, as well as functional immune system disorders, make them susceptible to COVID-19 infection.[19]

Pregnant women experience milder COVID-19 symptoms than the general population, but the overall pattern is similar. Pregnant women with COVID-19 may require more ICU admissions and invasive ventilation than non-pregnant women. Mothers with pre-existing comorbidities, as well as those who are obese and of advanced maternal age, should be considered at high risk for COVID-19 infection.[20]

The prevalence of kidney disease in COVID-19 patients is up to 3%, with a mortality rate of around 9% and a cure rate of up to 2%. Kidney disease is linked to an increased risk of pneumonia, as well as an increase in mortality from infection in patients nearing the end of their lives. ACE2 expression in the kidney rises with chronic kidney disease but is unrelated to susceptibility to SARS-CoV-2 infection in other organs, such as the heart. In SARS-CoV-2 infection, the kidney disease underlying COVID-19 is prone to hyperinflammation and a cytokine storm, resulting in severe symptoms. IL-6, CRP, oxidative stress, and metabolic disorders are all factors that contribute to inflammation.[21]

Cancer patients are at a high risk of contracting COVID-19 due to their immunocompromised state and the cancer therapy they receive. The cytokine storm that occurs in cancer patients has a poor outcome with COVID-19 and can progress to ARDS and multiple organ failure. The interaction between SARS-CoV-2 and cancer suggests that patients with cancer are more likely to be infected by SARS-CoV-2, resulting in severe COVID-19 infections and death.[22]

Obesity has an indirect effect on increasing the expression of ACE2, which originates in adipose tissue as cells expressing ACE2. Abnormal cytokine and complement production, results in decreased activity of anti-inflammatory processes Obesity is also associated with an increased risk of blood clots and prolonged viral shedding, both of which contribute to increased mortality in COVID-19.[23]

Secondary bacterial infection is one of the major complications that contribute to the high mortality rate in hospitalized COVID-19 patients. Secondary bacterial infections were found in 19.7% of COVID-19 patients treated in the ICU. The incidence of secondary bacterial infection was found to be higher than previously reported data.[24] Study Secondary bacterial infection was reported to occur in 6.3% of patients by Li et al, and 15% of patients in Zhou et al study had a secondary bacterial infection.[25,26]

In this study, C-reactive protein levels were higher in patients with a clinically critical grade (89.00 mg/L) compared to moderate (37.50 mg/L) and severe (23.00 mg/L). According to the findings, there are significant differences in C-reactive protein levels based on the clinical degree of COVID-19 patients being treated at Dr. M. Djamil Padang. Age ≥70, male, comorbid diabetes mellitus, and pregnancy were the confounding variables for the differences in C-reactive protein levels with the clinical degree of the patients.

According to Luo et al retrospective study, the majority of patients with severe clinical conditions had much higher levels of C-reactive protein than those with mild-moderate clinical conditions (100 vs. 9.65 mg/L).[27] According to Velavan and Meyer's research, patients with high C-reactive protein levels had a worse CT scan than those with mild-moderate clinical manifestations.[28]

According to Acar et al. in Turkey, inflammatory parameters such as C-reactive protein are related to disease severity and can be used as a potentially important risk factor for disease progression (COVID-19.[29] According to Danwang et al, C-reactive protein levels increased in severe COVID- 19 cases in a meta-analysis.[30]

C-reactive protein is a sensitive indicator of tissue injury. During acute inflammation, serum C-reactive protein levels rise. By combining with C-polysaccharide in the bacterial cell wall, C-reactive protein can recognize various pathogens and injured or necrotic cell components. C-reactive protein forms complexes with C-polysaccharides and phospholipids and can activate the complement system to remove pathogens and necrotic cells. Through specific C-reactive protein receptors, C-reactive protein can increase phagocytosis and kill a variety of pathogenic microorganisms.[31]

SARS-CoV-2 infection can result in a cytokine storm, which is associated with high mortality in COVID-19. Cytokines (like IL-6 and TNF-) stimulate hepatocytes to produce C-reactive protein. C-reactive protein is a strong biomarker associated with the development of COVID-19 that rises significantly during the early stages of inflammation and before CT scanning reveals critical findings. A multicenter retrospective study found higher levels of C-reactive protein in thrombotic complications following COVID-19 infection. Obesity and the metabolic syndrome in COVID-19 are linked to chronic systemic inflammatory diseases such as atherosclerosis and hypertension, which have an impact on COVID-19 outcomes. C-reactive protein plays an important role in the inflammatory response and can be used to determine the severity of COVID-19.[31]

The inflammatory process is thought to be related to aging. Several studies have found that in the absence of acute infection, the levels of several cytokines, particularly IL-6, TNF-alpha, and C-reactive protein, rise with age. Other research has linked higher hs-CRP levels to aging. Tang et al. discovered that males had higher hs-CRP levels than females.[32]

C-reactive protein recognizes and binds to specific polysaccharides in the bacterial wall, causing further activation of the complement pathway and pathogen opsonization. C-reactive protein is involved in both proliferative and apoptotic processes via Fc receptor activation and the production of proinflammatory and proapoptotic cytokines. C-reactive protein is not only an indicator of

inflammation, but its level has been linked to type 2 diabetes. The mechanism of the relationship between C-reactive protein and type 2 diabetes is still unclear. Other factors that contribute include oxidative stress and genetic factors such as a family history of type 2 diabetes.[33]

Elevated C-reactive protein is a normal part of pregnancy and is linked to pregnancy complications. The study by Mei et al. compared a sample of women with elevated C-reactive protein (>5 mg/l) to those without elevated CRP (5 mg/l) at 28–32 weeks' gestation to see if there was a difference in stillbirth and premature birth. After 32 weeks, none of the pregnant women who delivered the fetus died. In contrast to previous research that found an increased prevalence of preterm birth in women with high C-reactive protein levels.[34]

C-reactive protein levels were higher in patients with a length of stay of more than 14 days (89.00 mg/L) than in those with a length of stay of 14 days (84.00 mg/L). The analysis revealed that there was no significant difference in C-reactive protein levels in COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. This is presumably because C-reactive protein levels in living and deceased patients were not separated, resulting in inconsistent results. The stratification test was then performed. Stratification results revealed that in patients who died, patients with a length of stay of 14 days (97.00 mg/L) had higher C-reactive protein levels than those with a length of stay of >14 days (88.50 mg/L). The analysis revealed that there were significant differences in C-reactive protein levels in COVID-19 patients who died based on the length of stay at Dr. M. Djamil General Hospital, Padang.

With a length of stay of 14 days, patients who are alive have lower C-reactive protein levels (55.00 mg/L) than patients who are dead (93.00 mg/L). The analysis revealed that C-reactive protein levels differed depending on the length of stay in COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. Variables in COVID-19 patients' length of stay were found to be confounded by differences in C-reactive protein levels.

The findings of this study are consistent with the findings of Lentner et al, who found that the first examination of C-reactive protein was a significant predictor (*P*=0.001) and was related to patient length of stay as well as age (*P*=0.002). LoS was also affected by the number of comorbidities (*P*=0.07). The length of stay (LoS) increased by 0.003 days for every unit increase in C-reactive protein, according to this study. LoS increased by 0.16 days for every 50-unit increase in C-reactive protein (95% CI=0.10–0.21), and by 0.31 days for every 100-unit increase (95% CI=0.20–0.42).[35]

C-reactive protein levels were higher in patients who died (93.00 mg/L) than in those who survived (68.00 mg/L). The findings of this study revealed significant differences in C-reactive protein levels based on the final hospitalization status of COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. The patient's age at the end of treatment was a variable confounder of the difference in C-reactive protein levels.

According to the findings of Devran et al study, C-reactive protein levels can be used to predict mortality in patients with respiratory failure due to sepsis who were treated with a sepsis protocol based on the initial APACHE II score and the SOFA score on the first and third days in the ICU.[36] The Villoteau study found that higher baseline C-reactive protein levels in COVID-19 patients were associated with higher 14-day mortality in COVID-19 geriatric patients.[37]

In 321 adult COVID-19 patients, Bannaga et al found that higher C-reactive protein levels and lower albumin levels on admission to the intensive care unit were associated with higher mortality.[38] In Valerio et al study of 577 middle-aged adults hospitalized with COVID-19, patients who died had higher levels of C-reactive protein than those who survived.[39]

It is unclear why C-reactive protein is associated with decreased survival in older COVID-19 patients.[37] Some of the potential causes include:

a. C-reactive protein levels are reported to be positively correlated with lung lesions in the early stages of COVID-19 and can be used as a biomarker of disease severity.[8]

b. Hepatocytes produce C-reactive protein, which is linked to IL-6, which is involved in the cytokine storm. This will result in increased VEGF secretion and decreased E-cadherin expression, both of which contribute to increased vessel permeability, arterial hypotension, organ failure, and ARDS.[40]
c. Inflammatory conditions associated with elevated C-reactive protein levels can cause prothrombin to be released, increasing the risk of stroke or venous thromboembolic events.[41]
d. As a compensatory response in respiratory distress, elevated C-reactive protein induces hypercatabolism associated with respiratory muscle protein consumption.
e. C-reactive protein levels in older people can be used to assess pre-COVID-19 health status and to describe chronic disease, both of which are major risk factors for severe COVID-19.[37]

LIMITATION

This study has limitations, such as the use of a retrospective cohort design based on data from patient medical records and the uneven distribution of patients in various clinical degrees. This study was also unable to assess C-reactive protein levels at all COVID-19 clinical levels.

CONCLUSION

The majority of COVID-19 patients in this study were women between the ages of 50-59 years, with the majority having hypertension and critical clinical severity. There are significant differences in levels of C-reactive protein based on the degree of clinical COVID-19 patients with confounder variable age ≥70 years, males with comorbid diabetes mellitus and pregnancy. There are significant differences in levels of C-reactive protein based on the duration of treatment of COVID-19 patients. There are significant differences in C-reactive protein levels based on the final hospitalization status of COVID-19 patients with confounder variable age ≥70 years.

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CONFLICT OF INTEREST

None.

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