# CORRELATION BETWEEN C-REACTIVE PROTEIN LEVEL AND OUTCOME IN CORONAVIRUS DISEASE 2019 PATIENTS AT COVID INTENSIVE CARE UNIT RSUP. Dr. M. DJAMIL PADANG

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***ABSTRACT***

***Background:*** *Coronavirus Disease 2019 (COVID-19) is a respiratory system disease transmitted to humans and has infected humans in almost every country. Plasma cytokine levels, such as C-reactive protein (CRP), are elevated inflammatory markers in most COVID-19 patients and are routinely examined, especially in the intensive care Unit (ICU). Elevated CRP levels are associated with higher rates of severity and death.*

***Objective:*** *This study aimed to determine the correlation between CRP levels and outcomes in COVID-19 patients at COVID ICU RSUP. Dr. M. Djamil Padang Period July – December 2021.*

***Method:*** *This research was conducted using by analytic observational method with a retrospective cohort design. Secondary data was collected from the medical records of COVID-19 patients treated in the ICU COVID RSUP. Dr. M. Djamil Padang from July – December 2021, using total sampling as a technique, 107 samples met the inclusion criteria. Data analysis was carried out using univariate and bivariate methods.*

***Result:*** *The result shows more male patients (51.4%) than women (48.6%). From the age range, most age was found in the range > 59 years (54.2%). The most common type of comorbid disease was diabetes (32.7%). The highest CRP level at the initial ICU admission was >160 mg/L (70.1%), and the highest ferritin level was >434 ng/mL (86.0%). The most common patient outcome was death (65.4%). There is a relationship between CRP levels (p = 0.029) and the outcome of COVID-19 patients in the COVID ICU.*

***Conclusion:*** *This study concludes that there is a correlation between C-Reactive Protein (CRP) levels and Outcomes in COVID-19 patients at COVID ICU RSUP. Dr. M. Djamil Padang Period July – December 2021.*

***Keywords :*** *COVID-19, CRP, Patient Outcome, ICU*

## INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is caused by a betacoronavirus (β-coronavirus) enveloped in Ribo Nucleic Acid (RNA), which appeared in December 2019 in Wuhan, China.[1] As of 18 October 2022, WHO reported that there were 621,797,133 confirmed cases of COVID-19 worldwide, and in Indonesia, there were 6,458,101 confirmed cases with a total death of 158,327 people.[2,3]West Sumatra was recorded as having 104,592 positive cases as of 13 September 2022, reported by the COVID-19 Handling Task Force. Epidemiological studies show that 6-10% of patients with mild COVID-19 rapidly progress to more severe diseases and require treatment in the intensive care Unit (ICU) for acute hypoxemic respiratory failure. The death rate reported in patients with severe COVID-19 in the ICU ranged from 50-65%.[4]

Based on the severity of symptoms, COVID-19 can be classified as asymptomatic, mild, moderate, severe, and critical. In patients without symptoms or with mild to moderate symptoms, patients can carry out independent isolation and be given treatment according to their condition. In contrast, patients with severe and critical symptoms usually require special treatment in the ICU because they have clinical signs of severe pneumonia with Acute Respiratory Distress Syndrome (ARDS). Intubation is required.[5,6]

Coronavirus disease 2019 is transmitted by droplets and aerosols from human to human. The estimated incubation period is 14 days from the time of exposure. During a viral attack, the immune system upregulates to eliminate the virus from the body, but the body can fail to downregulate it, and dysregulation of the immune system occurs. This dysregulation will later lead to a hyperinflammatory stage of COVID-19 called a Cytokine Storm. Hyperinflammation causes excessive secretion of pro-inflammatory, chemokines, and other inflammatory factors resulting in uncontrolled systemic inflammation.[7] Identifying markers of inflammation can help to know which patients are at risk of requiring intensive care or at risk of death. Inflammatory biomarkers such as C-Reactive Protein (CRP) were found to be increased in COVID-19 patients.[8,9]

The acute phase protein widely used as a marker of disease activity is CRP. Healthy individuals tend to have stable CRP concentrations, which will only increase if trauma, inflammation, or clinical or subclinical infection occurs.[10] In clinical medicine, the measurement of CRP levels is used as a multipurpose marker used as a screening tool for inflammatory diseases and differentiating between bacterial and viral infections.[11] High CRP levels due to IL-6

release have been reported in ARDS, Middle East respiratory syndrome, and H1N1 influenza. Recent studies report that CRP levels are increased in patients with COVID-19 and may correlate with disease severity and progression.[8] A previous study conducted by Yitbarek, et al. found that elevated CRP levels were seen in approximately 85% of severe COVID-19 patients who were observed before death.[12]

The inflammatory marker that is often examined in blood plasma is IL-6. But not all hospitals in West Sumatra can check these inflammatory markers, so the CRP biomarker can be used as an alternative. Besides being able to show a severe infection, it can also show the poor development of the disease. This could indicate that there is a gradual inflammatory reaction related to the prognosis of COVID-19.[13]

Based on the description above, researchers feel the need to conduct research on the relationship between CRP levels and outcomes in COVID-19 patients in the COVID ICU at RSUP. Dr. M. Djamil Padang.

## METHODS

This research is research with analytical methods with a retrospective cohort design. The population in this study were all medical records of COVID-19 patients treated in the ICU COVID RSUP. Dr. M. Djamil Padang in the July – December 2021 period. Sampling used the Total Sampling technique. The research sample is the medical records of COVID-19 patients treated in the COVID ICU at RSUP. Dr. M. Djamil Padang met the predetermined inclusion and exclusion criteria. The research sample that met the inclusion criteria obtained as many as 107 samples. Data analysis was carried out univariately and bivariate to see the frequency distribution of COVID-19 patients in the ICU and to determine whether there was a relationship between the variables. This research has passed an ethical review with letter number LB.02.02/5.

## RESULTS

Based on the results of research on research that has been carried out in RSUP. Dr. M. Djamil Padang in the period August 2022 – January 2023. There were 107 samples that met the inclusion criteria.

Based on Table 1, it is known that the sex of the COVID-19 patient in the ICU COVID RSUP. Dr. M. Djamil Padang was male, with 55 people (51.4%) and 52 women (48.6%). Most of the patients with COVID-19 were in the age range above 59 years, namely, 58 people (54.2%), followed by the age range 25-59 years with 48 people (44.9%), then in the age range 15-24 years as many as 1 people (0.9%), and there were no patients aged <15 years.

**Table 1. Frequency Distribution of Gender and Age in COVID-19 Patients in the COVID ICU**

| Category | n | Percentage (%) |
|---|---|---|
| Gender | | |
| Male | 55 | 51.4 |
| Female | 52 | 48.6 |
| Total | 107 | 100 |
| Age | | |
| < 15 years | 0 | 0 |
| 15 – 24 years | 1 | 0.9 |
| 25 – 59 years | 48 | 44.9 |
| > 59 years | 58 | 54,2 |
| Total | 107 | 100 |

Based on Table 2, it is known that the most common co-morbidities in COVID-19 patients in the COVID ICU at RSUP. Dr. M. Djamil Padang was diabetic, namely 35 people (32.7%), then followed by patients who had no co-morbidities, as many as 34 people (31.8), after that, patients with hypertension 20 people (18.7%), and 18 patients (31.8%) had two co-morbidities, namely hypertension, and diabetes.

**Table 2.Frequency Distribution of Comorbid COVID-19 Patients in the COVID ICU**

| Comorbid | n | Percentage (%) |
|---|---|---|
| Hypertension | 20 | 18.7 |
| Diabetes | 35 | 32.7 |
| Hypertension + Diabetes | 18 | 16.8 |
| No comorbid | 34 | 31.8 |
| **Total** | 107 | 100 |

Based on Table 3, it was found that the majority of COVID-19 patients were in the ICU COVID RSUP. Dr. M. Djamil Padang had high CRP levels in 75 people (70.1%), followed by very high levels in 27 people (25.2%), and normal levels were found in 5 people (4.7%).

**Table 3. CRP Levels in COVID-19 Patients in the COVID ICU**

| CRP Level | COVID-19 | |
|---|---|---|
| | n | Percentage (%) |
| < 5 mg/L (Normal) | 5 | 4.7 |
| 5 – 160 mg/L (High) | 75 | 70.1 |
| > 160 mg/L (Very high) | 27 | 25.2 |
| Total | 107 | 100 |

Based on Table 4, the final condition of the COVID-19 patient was obtained in the ICU COVID Hospital at the Hospital. Dr. M. Djamil Padang mostly died, namely 70 people (65.4%) and as many as 37 people (34.6%) patients who did not die.

**Table 4. The outcome in COVID-19 Patients in the COVID ICU**

| Outcome | COVID-19 | |
|---|---|---|
| | n | Percentage (%) |
| Non-Survive | 70 | 65.4 |
| Survive | 37 | 34.6 |
| Total | 107 | 100 |

Based on the results of statistical tests conducted in Table 5, a relationship was found between CRP levels with outcomes in COVID-19 patients in the COVID-19 ICU at the RSUP ICU. Dr. M. Djamil Padang with a value of p=0.029 (p <0.05).

**Table 5 Correlation between CRP levels and Outcome of COVID-19 Patients in the COVID ICU**

| CRP Level Category | Outcome of COVID-19 n(%) | | | p |
|---|---|---|---|---|
| | Non-Survive | Survive | Total | |
| < 5 mg/L | 2 (40) | 3 (60) | 5 (100) | |
| 5 – 160 mg/L | 45 (60) | 30 (40) | 75 (100) | 0.029 |
| > 160 mg/L | 23 (85.2) | 4 (14.8) | 27 (100) | |
| Total | 70 (65.4) | 37 (34.6) | 107 (100) | |

## DISCUSSION

The study results in Table 1 found that there were more male patients, namely 55 people (51.4%) and 52 women (48.6%). This finding aligns with a study conducted by Yang X, et al., which found more male patients with critical COVID-19 symptoms (67%) than women (33%). It was also explained that men and old age are more at risk of developing ARDS than women or younger patients.[14] This is because women are more immune to infection than men, which may be mediated by several factors, including sex hormones and high expression of the coronavirus receptor (ACE 2) in men.[15]

In patients with severe clinical symptoms, IFN levels will initially be low in mild and moderate symptoms, then increase, and may eventually become a cytokine storm. Men are significantly more at risk of experiencing more severe disease than women due to the release of TLR7 (toll-like receptor 7) XCI (X chromosome inactivation) in women. Severe COVID-19 disease has been associated with a delayed IFN response, and increased TLR7-mediated IFN production in women may prevent

progression to severe disease. TLR7 deficiency has been reported as a genetic mediator for severe COVID-19, mainly in younger males, with 1–2% rates found across cohorts.[16]

Based on Table 1, the largest age group was > 59 years, namely 58 people (54.2%). This finding aligns with a study conducted by Oliveira E, et al., which found that the average age of patients treated in the ICU was 71.5 years, with an age range of 62-80 years.[4] Elderly patients with COVID-19 are more susceptible to the disease and are at greater risk of being admitted to the ICU with a higher mortality rate. Older people are more susceptible to infection due to decreased natural immunity. Changes also occur in lung anatomy and muscle atrophy resulting in changes in physiological function, reduced lung reserve, and airway clearance.[17]

In contrast to the study of Gesmalah M, et al., it was found that the highest number of positive cases was in the age range 19-37 years (36.8%), followed by the age range 38-56 (32.5%) and ages 57-75 ( 18.9%).[18] Factors that may be related to this are that younger people have more contact than older people and are more driven to engage in social interaction, regardless of the health consequences. Older people feel vulnerable and are more likely to adhere to masks and social distancing, which younger people may neglect. However, it was found that older patients were associated with a higher risk of death compared to younger patients.[19]

Table 2 shows the co-morbidities that many COVID-19 patients who are in the COVID ICU have, namely diabetes in 50 people (46.7%), followed by hypertension in 37 people (34.6%). These findings are under research conducted by Biswas M, et al., who also found that diabetes and hypertension are the two most common co-morbidities in COVID-19 patients.[20]

People with diabetes tend to get infections due to impaired phagocytic cell abilities. In human monocytes, increased glucose levels directly enhance the replication of SARS-CoV-2. Poor T-cell function and elevated IL-6 levels play a role in developing COVID-19 disease in diabetics. It was found that uncontrolled blood sugar levels had a higher death rate. Epidemiological data on COVID-19 shows that 11-58% of all COVID-19 patients have diabetes, and an 8% death rate from COVID-19 has been reported in diabetic patients. The risk of ICU admission for COVID-19 individuals with diabetes is 14.2% higher than for individuals without diabetes.[21,22]

Hypertensive patients with COVID-19 are more at risk for developing severe complications. The mechanism starting from the activation of the conventional RAS axis (ACE/Ang II/AT1R) in parallel with the downregulation of the non-conventional axis (ACE2/Ang 1-7/Mas) is proposed to be a

factor underlying the outcome of severe COVID-19 in hypertension. In addition, hypertension is associated with endothelial dysfunction and a pro-inflammatory state, which includes higher levels of Ang II, chemokines, and cytokines, including IL-6 and TNF-α. In other words, endothelial dysfunction occurs when the walls of blood vessels become more rigid, and their vasorelaxant properties decrease.[23] Research conducted by Wang, et al. in Wuhan showed that the prevalence of hypertension was 31.2%, with 58.3% of patients being treated in the ICU.[24]

Patients with more than one comorbid are at greater risk of contracting COVID-19 and have a poor clinical impact. A study by Ganguli S, et al. in Bangladesh found multiple co-morbidities increased recovery time (15-27 days) and hospitalization (20-40%). An increase in symptomatic cases was found in DM+HTN patients, while CVD+Asthma patients had a higher percentage of severity.[25]

An overview of CRP levels in COVID-19 patients in the COVID ICU based on Table 3 found that most patients were in the RSUP COVID ICU. Dr. M. Djamil Padang had high CRP levels in the 5 – 160 mg/L range, namely, 75 people (70.1%). This finding aligns with research by IB Prasetya, et al. in Jakarta, which also showed that the initial CRP value in the group of patients with severe and critical symptoms was higher than the group with non-severe symptoms. Increased CRP is said to have a significant relationship with disease severity and death in COVID-19 patients.[26]

C-reactive protein is a nonspecific acute phase inflammatory protein whose expression increases in response to tissue injury, inflammation, and infection. This increase occurs due to the activation of the complement molecule C1q which leads to the opsonization of the pathogen. In addition, CRP binds to Fc receptors on the cell surface, releasing pro-inflammatory cytokines. Thus, CRP is a marker of inflammation and contributes to the inflammatory response. So the higher the production of CRP, the greater the inflammation that can occur.[8,27]

In Table 3, for very high levels above 160 mg/L, there were 27 people (25.2%). In a study conducted by Sharifpour, et al., almost all patients had evidence of a systemic inflammatory response to SARS-CoV-2 infection with a median CRP level of 169 mg/L at the time of initial ICU admission. Patients with very high CRP concentrations above the median value have a higher risk of developing complications such as venous thromboembolism, acute kidney injury, critical illness, and death compared to patients with lower CRP levels than the median. This explains that very high CRP levels affect poor clinical outcomes and increase patient mortality.[8]

In the early stages of severe and critical COVID-19, cytokine storms cause Mixed Antagonistic Response Syndrome (MARS), dominated by Systemic Inflammatory Response Syndrome (SIRS), and results in ARDS and organ dysfunction, which can result in multiple organ damage. In the late stages of the disease, elevated levels of anti-inflammatory cytokines inhibit immune cell activation, and the immune response is dominated by the Compensated Anti-inflammatory Response Syndrome (CARS), leading to decreased immunity and susceptibility to secondary infections.[28]

It can be seen in Table 3 that only 5 patients (4.7%) had normal levels below 5 mg/L. Normal CRP levels in severe and critical COVID-19 patients can be related to the patient's condition at the time of initial admission to the ICU who has entered the CARS phase, resulting in a decrease in pro-inflammatory cytokines in the patient's body.[28]

The final results of the patient's condition in the COVID ICU found that 70 people (65.4%) died, while 37 patients (34.6%) who did not die experienced improvement and moved from the ICU. Research conducted by Herlina, et al. found that the severe (severe-critical) group of patients had a 12 times greater risk of death than non-severe (mild-moderate) patients.[29] In severe COVID, there are two mechanisms: the first and second hits. If the first hit is severe, then systemic inflammation occurs. After the initiation of systemic inflammation, SIRS and CARS phases will ensue. If the patient's body condition and the therapy given to have a good impact on the patient, recovery will not be complicated, and the inflammatory response is considered a physiological process. This is related to the condition of the patient in the ICU.[30]

However, in some patients, immune dysregulation occurs. Excessive immune activation can occur, and additional damage to the parenchymal cells of vital organs can lead to organ system failure. In addition, patients may experience inflammatory complications due to immune paralysis in the CARS phase. Complications develop when the primary viral or secondary microbial infection is irreversible, resulting in organ failure and death. This is in line with a study conducted by Elezkurtaj, et al., which found that the most frequent cause of death was an infection, such as sepsis, septic shock, or multi-organ failure related to sepsis found in 16 patients (61.5%). Following a bacterial infection in two patients (7.7%) and one with viral pneumonia (3.8%).[31,30]

The results of data analysis in Table 5 used the chi-square test and obtained a p-value <0.05 (p = 0.029). This shows a relationship between CRP levels and the outcome of COVID-19 patients in the COVID ICU at RSUP. Dr. M. Djamil Padang. This finding is in line with researchSharifpour, et

al. found that the mean CRP levels in hospitalized patients were significantly higher in those who died, namely 206 mg/L (157–288 mg/L), and living patients had levels of 114 mg/L (72–160 mg/L). mg/L). Surviving patients had lower peak CRP levels and an earlier decline in CRP levels than deceased patients ($p<0.001$).[8]

In this study 75 patients with CRP levels between 5 – 160 mg/L, 45 of them died. There were 27 patients with CRP levels > 160 mg/L, and 85.2% died. This occurs through a local systemic response involving NK cells, dendritic cells, lymphocytes, neutrophils, and macrophages. Furthermore, SARS-CoV-2 changes the RAS and induces the increased activity of Ang II, which causes CRP production. If the immune response is inadequate to stop viral replication, tissue damage is sustained and increases in severity, which can result in a cytokine storm. If CRP increases by more than 20 units/day, the chance of death rises rapidly.[27,32]

In this study, there were also 5 patients with normal CRP levels, of whom 2 died, and 3 did not die. A survey by Luan Y, et al. found that CRP levels could stabilize or decrease in survived patients. This was also confirmed by a reduced inflammatory process or therapy that worked well.[33] CRP tests are widely available, easy to obtain, and inexpensive. Measurement of CRP levels is proving to be a valuable tool in the ICU, allowing risk stratification and rapid patient prognosis.[32]

## CONCLUSION

Based on research on the correlation between CRP levels and outcomes in COVID-19 patients at COVID ICU RSUP. Dr. M. Djamil Padang concluded that above-normal CRP levels were associated with increased mortality in COVID-19 patients, especially patients with severe and critical symptoms. This can be influenced by several factors, such as age over 59 years, male gender, and comorbid factors, such as diabetes and hypertension, which can play a role in the development of COVID-19 disease.

C-reactive protein is a convenient, inexpensive, and readily available prognostic biomarker associated with disease severity and mortality. This will help clinical practice when treating and monitoring COVID-19 patients to determine if they are developing a cytokine storm.

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