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C-Reactive Protein as The Predictor of Mortality for COVID-19 Patients in Indonesia

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) confirmed cases and deaths continue to rise. When a virus infects the body, the immune system tries to eliminate the virus. C-Reactive Protein (CRP) is a substance produced in the body in response to infection and inflammation. The study aimed to determine the role of CRP in predicting COVID-19 patients' mortality. From the 1st of March to the 31st of August 2020, data on patients confirmed with COVID-19 were collected from medical records. The correlation between CRP levels and patient mortality was determined using a Chi-Square test. A Receiver Operator Curve (ROC) analysis was used to determine the best CRP cut-off point, and a survival analysis was used to assess the patient outcome. This study included a total of 210 eligible patients. Survivors and non-survivors were divided into two groups of patients (159 patients and 51 patients, respectively). The CRP cut-off was 54 mg/L, with an AUC of 0.817 ($p<0.001$). C-reactive protein levels were related to COVID-19 patient mortality ($p=0.000$). According to the survival analysis, patients with CRP levels > 54 mg/L had a lower chance of 30-day survival ($p=0.0001$). This study presented that CRP levels can be used to predict mortality in COVID-19 patients.

Keywords: COVID-19, C-reactive protein, mortality, survival analysis

INTRODUCTION

An unknown disease spread rapidly by the end of December 2019, starting from Wuhan, China, to many other areas. Eventually, it was reported that this disease was caused by the novel Coronavirus type Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] The disease has been named Coronavirus Disease 2019 (COVID-19).[2] COVID-19 was declared a pandemic by the World Health Organization on March 11th, 2020. On 7 January 2022, there were more than 298 million confirmed cases of COVID-19 worldwide, with more than 5.4 million deaths.[3] In Indonesia, there are about 4.2 million confirmed cases with 144,129 deaths reported by 9 January 2022.[4]

SARS-CoV-2 belongs to the Sarbecovirus subgenus, commonly found in humans and other mammals.[2] There are severe acute respiratory infection symptoms in the early stages of the disease, which can progress to Acute Respiratory Distress Syndrome (ARDS) and other serious complications, eventually leading to multiple organ failure. Consequently, early detection and treatment of critical cases are essential.[5]

Several routine blood and serological parameters have been proposed for stratifying patients at higher risk of complications. C-Reactive Protein (CRP) is one of the tests performed.[6] C-reactive protein is an acute-phase protein synthesized by the liver in response to elevated inflammatory cytokine levels, particularly Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-).[7] C-reactive protein levels have been observed to rise in response to tissue damage, infection, and inflammation, and their concentration in the circulation will rise as well.[8] Laboratory markers including LDH, CRP, D-dimer, and lymphocyte count can be used to predict the prognosis and survival of COVID-19 patients, primarily when the risk stratification was only based on clinical presentation.[9,10]

C-reactive protein is a relatively inexpensive and simple way to measure acute-phase inflammatory response.[11] This test is commonly applied to

COVID-19 patients at several hospitals, including Dr. Mohammad Hoesin General Hospital. This study aimed to determine the role of CRP levels to predict mortality in COVID-19 patients.

METHODS

This study was performed at Dr. Mohammad Hoesin General Hospital in Palembang, which is the main referral hospital for COVID-19 in the southern region of Sumatera, from September 2020 to December 2020. Patients who were confirmed with COVID-19 using a Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test between March 1st and August 31st, 2020 were qualified to participate in this study. Patients with CRP levels below 5 mg/L and the laboratory tests not performed at Dr. Mohammad Hoesin General Hospital were excluded. The Ethics Committee for Medical and Health Research, Faculty of Medicine, Sriwijaya University approved this study protocol (approval number: 196-2020).

Personal and laboratory data were obtained from patient medical records. Age, gender, and comorbid diseases (hypertension, cardiovascular disease, diabetes mellitus, malignancy, and others) were collected as personal data. In contrast, laboratory data including CRP levels were obtained when the patient was first admitted to the hospital. The immunoturbidimetric method was used to evaluate CRP levels. C-reactive protein levels will be reported in milligrams per liter (mg/L).

The Chi-square or Fisher's exact tests were employed for categorical data analysis. Meanwhile, the Mann-Whitney U test was used to analyze numerical data with an abnormal distribution (presented with median and interquartile range (IQR) values). A Receiver Operator Curve (ROC) analysis determined the optimal cut-off point of the CRP level.

The patient's outcomes were determined using the Kaplan-Meier survival analysis. A p-value of less than 0.05 was considered statistically significant. SPSS version 26.0 and MedCalc version 19.5 were utilized as statistical software in this investigation.

RESULTS AND DISCUSSIONS

From March 1st to August 31st, 2020, 439 data entries on individuals diagnosed with COVID-19 were acquired for this study. The inclusion criteria were met by 210 patients. There were 51 non-survivors and 159 survivors among the 210 study participants. The non-survivor patients had an older median age [57 vs. 45 years] as compared with the survivor. The majority of non-survivor patients were males (31 subjects, 60.8%), whereas the majority of survivors were females (87 subjects, 54.7%). The most prevalent comorbidities found in both groups were diabetes, which was found in 18 people (35.3%) and 17 people (10.7%), respectively. Non-survivor patients had a higher median level of CRP (145 mg/L vs. 33 mg/L) than survivors. There were also significant differences in age, comorbidities (hypertension, diabetes), and CRP levels between both groups ($p<0.05$) (Table 1).

Receiver operator curve analysis was used to determine the prediction of mortality in COVID-19 patients based on CRP levels. The Area Under the Curve (AUC) was 0.817 ($p<0.001$). The analysis also found that the optimal CRP cut-off value was >54

Table 1. Distribution of age, gender, comorbidity, and levels of CRP in non-survivor and survivor patients

Characteristic	Non-Survivor (n=51)	Survivor (n=159)	p-value
Age (years)	57 (2–77)	45 (4–80)	**0.000****
Gender			
Male	31 (60.8%)	72 (45.3%)	**0.054***
Female	20 (39.2%)	87 (54.7%)	
Comorbidity			
Hypertension	10 (19.6%)	8 (5.0%)	**0.003*****
Cardiovascular disease	8 (15.7%)	16 (10.1%)	0.272*
Diabetes	18 (35.3%)	17 (10.7%)	**0.000***
Malignancy	6 (11.8%)	7 (4.4%)	0.088***
Other comorbidities	13 (25.5%)	23 (14.5%)	0.069*
C-reactive protein (mg/L)	145 (5–540)	33 (5–275)	**0.000****
> 54	44 (86.3%)	49 (30.8%)	**0.000****
≤ 54	7 (13.7%)	110 (69.2%)	

*Chi-Square test, **Mann-Whitney U test, ***Fisher's exact test

mg/L with a sensitivity of 86.27% and a specificity of 69.18% (Figure 1). Based on the results of the survival analysis (Figure 2), it was found that patients with CRP levels> 54 mg/L had a lower 30-day survival probability than patients with CRP levels ≤ 54 mg/L (p=0.0001).

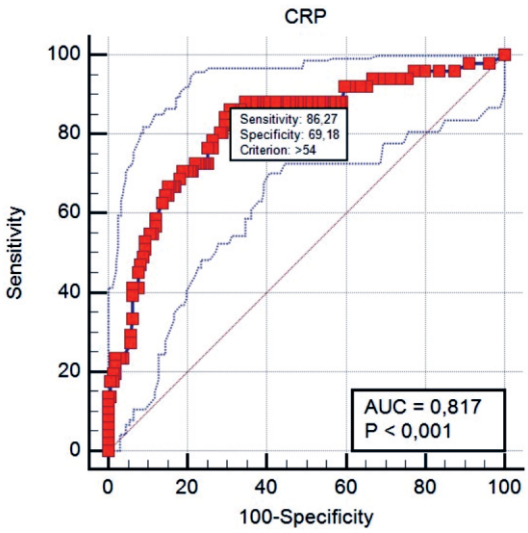

Figure 1. ROC curve for CRP levels

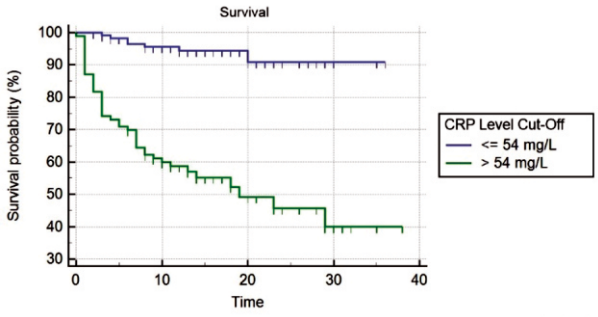

Figure 2. Kaplan-Meier survival curves for CRP levels

The median age of non-survivor patients was found to be higher than that of survivors in this study. This was in line with previous research, which found that patients with severe symptoms were older on average than those with mild symptoms.[12,13] The two studies revealed that the median age of patients with the severe condition was higher than that of non-severe status. This might be due to the immune system's vulnerability (immunosenescence and inflammaging) in advanced age and the presence of comorbidities, making elders more susceptible to COVID-19 illness and thus more likely to develop serious disease and even fatality.[14,15]

The majority of non-survivor patients in this study were males. It is also corroborated by some previous research that found comparable findings.[12,16] A study showed that males were more susceptible to SARS-CoV-2 infection and had more severe clinical symptoms than females.[17] Factors that might cause this to occur were different states in the immune system and respiratory tract in males and females, along with lifestyle choices such as smoking.[18]

Hypertension, diabetes, and cardiovascular diseases were the most common comorbid illnesses in this research with diabetes as the most prevalent in the non-survivor groups. This was consistent with previous research, which found that 64.3% of patients had comorbid diseases.[14] Previous research also reported that the most common comorbid diseases found in patients were hypertension at 30.7%, followed by diabetes at 14.3%, and cardiovascular disease at 11.9%.[9] Comorbidities including hypertension and cardiovascular diseases were also related to the severity of COVID-19 symptoms.[19] SARS-CoV-2 binds to target cells via ACE2, and ACE2 expression is significantly increased in patients receiving ACE inhibitors and ARBs who have type 1 or type 2 diabetes and hypertension. This can increase the chances of COVID-19 infection and the likelihood of developing severe COVID-19 infection.[16]

Non-survivor patients had a higher median CRP level than a survivor in this study. It could be used to indicate that the patient had been in a serious condition since their initial hospital admission. This suggested that there had been a significant amount of inflammation, which increased the risk of death.[20] Other studies found that the median level of CRP in severe patients was higher than in non-severe patients. C-reactive protein levels above a certain threshold had been related to adverse aspects of COVID-19, such as the development of ARDS and death. Thus, detecting levels of CRP in COVID-19 patients can be useful in assessing the severity of the disease.[21,22]

The cut-off value for predicting COVID-19 patient mortality was determined to be >54 mg/L, with a sensitivity of 86.27% and specificity of 69.18% (AUC: 0.817; p<0.001). This was similar to a previous study that reported an AUC value of 0.896 (p<0.001) for CRP, a cut-off point of >41.4 mg/L, including sensitivity and specificity at 90.5 and 77.6%, respectively.[23] With AUC levels of more than 80%, the CRP level is a fair marker to predict the outcome of COVID-19 patients.[23]

As presented in this study, most of the non-survivor patients had CRP levels of >54 mg/L, contrary to the survivor group (p=0.000), which indicated a correlation between CRP levels and

patient mortality. Another research showed that 93.9% of patients with high severity had levels of CRP> 8 mg/L, meanwhile, another study showed that all of the patients who died had CRP levels of more than 5 mg/L.[24,25] While CRP was linked to a need for mechanical ventilation, a baseline cut-off of >32.5 mg/L and a maximum cut-off of >97 mg/L might assume that events would occur.[26] Meanwhile, severe COVID-19 has been well correlated with CRP at the 20.42 mg/L cut-off (83% sensitivity, 91% specificity, AUC: 0.87; p<0.01), according to data on Computed Tomography (CT) severity scores.[27]

This study was consistent with the aforementioned studies suggesting that CRP levels were correlated with patient mortality. As one of the acute phase reactants, CRP concentration can be increased when there are infection, inflammation, and tissue damage.[28] Lung disease with inflammatory features such as in COVID-19 usually increases serum CRP levels in response to proinflammatory cytokines such as IL-6, IL-1, and TNF-α.[29] Therefore, the elevated levels of CRP in the non-survivor patients in this study indicated a high inflammatory response in COVID-19 patients.[30]

C-reactive protein levels of >54 mg/L were found to be associated with a lower 30-day survival probability (p=0.0001) in this study's survival analysis. This finding was consistent with previous research, which found that patients with CRP levels greater than 41.8 mg/L had a lower chance of survival.[24] COVID-19 heavily relies on the inflammatory response, which includes proinflammatory cytokines like IL-6. Increased levels of IL-6, a cytokine that regulates immune cells, can cause a cytokine storm, which can result in multiple organ failures and even death.[31] IL-6 can induce the production of CRP, which is a sensitive biomarker of inflammation, infection, and tissue damage.[29] C-reactive protein is produced in direct proportion to the amount of IL-6 released; therefore, a rise in CRP levels can demonstrate the progression of the disease and death.[32] C-reactive protein levels and mortality had a significant correlation according to this study, indicating that CRP levels can be used to predict COVID-19 patient mortality.

There were several limitations in this study. Patients with comorbidities including hypertension, diabetes, cardiovascular disease, and cancer were not excluded from the study, and their comorbidities might have influenced the increase in CRP levels irrespective of SARS-CoV-2 infection. Because CRP levels were correlated with the extent of inflammation, the dynamics of CRP over time should be included in future studies to provide more details about the disease's prognosis based on changes in CRP levels.

CONCLUSIONS AND SUGGESTIONS

Since there was a correlation between CRP levels and patient death, CRP levels can be used to predict COVID-19 patient mortality, allowing them to be used as an early marker and thus enhancing patient management. Serial CRP examination is advised to ascertain the dynamics of inspection results over time to determine the best time for the evaluation process. The test can be combined with other inflammatory markers to achieve optimal results.

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