

## ORIGINAL ARTICLE

# Comparison Between C-Reactive Protein and D-Dimer Serum in Pneumonia Phase as the Predictors of COVID-19 Patients' Mortality

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## ABSTRACT

**Introduction:** COVID-19 was declared a global pandemic in March 2020 by WHO. Until July 2022, there have been 555 million people suffering from this disease with a death toll of 6.35 million worldwide. Systemic inflammation triggered by a cytokine storm in a hypercoagulable state is the leading cause of COVID-19 patients' mortality. CRP and D-dimer are biomarkers that can clearly illustrate pathogenesis. This research aims to compare C-reactive protein (CRP) and D-dimer as a better predictor of mortality in COVID-19 patients. **Methods:** It is an analytical observational research supported by a retrospective cohort design. The research subjects were COVID-19 patients treated in the isolation room of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, between August 2020 and August 2021. CRP and D-dimer was taken during pneumonia phase and then was compared on the next steps using univariate, bivariate and prognostic statistical tests. The quality of the prognostic value was examined using the Receiver Operating Characteristic (ROC) curve to set the Area Under Curve (AUC) and discrimination value. **Results:** There were 195 subjects confirmed with COVID-19. CRP value was significant in mortality with a cut-off of 230.1 mg/dl (RR 1.561, 95% CI 1.117-2.182,  $p=0.05$ ). D-dimer value was significant on mortality with a cut off of 1,810 ng/ml (RR 21,613, 95% CI 8,266-56,508,  $p= 0.0001$ ). Prognostic test results showed the discrimination value for D-dimer set by the AUC was 96.8% (strong), while the CRP discrimination value was 65.7% (weak). **Conclusion:** It can be concluded that as a predictor of mortality in COVID-19 patients, D-dimer value has a better discriminatory value than CRP value.

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## INTRODUCTION

COVID-19 was declared a global pandemic in March 2020 by the World Health Organization (WHO). Until July 2022, there have been 555 million people suffering from this disease with a death toll of 6.35 million worldwide. In Indonesia 4,219,284 cases were reported until October 2021. The most significant death rate was in the fourth week of August 2021 where 12,887 people died with an average death rate of 754 per day (1,2,3). The Ministry of Health reported a Case Fatality Rate (CFR) of 3.4% in October 2021 (4).

The high number of mortality was due to an inflammatory mechanism that develops rapidly, where there is also a complication of hypercoagulable state in the next phase. In COVID-19 patients who are suffering from severe conditions, there is an increase in proinflammatory

chemokines and cytokines. The patients experienced Acute Respiratory Distress Syndrome (ARDS) which was a severe and uncontrolled systemic inflammatory response due to the release of proinflammatory cytokines (cytokine storm) and large amounts of chemokines, causing lung damage and fibrosis. These were shown by a significant increase in inflammatory markers such as Interleukine-6 (IL-6), C-Reactive Protein (CRP), ferritin, Lactate Dehydrogenase (LDH), and other proinflammatory cytokines (5,6,7).

The next stage is endothelial damage caused by inflammation. This problem causes microvascular dysfunction, inflammation, and hypercoagulable conditions. The hypercoagulable state is shown by a prolonged prothrombin time and an increasing number of D-dimer. In an uncontrolled inflammatory response, the symptoms will come to a more severe or critical state which trigger organ failure and require mechanical ventilation. The death risk may reach 50% (8).

Parameters of laboratory values are related to the pathophysiology of the COVID-19 disease course.

Laboratory abnormalities commonly found in COVID-19 patients decreased in lymphocyte counts but increased in several parameters: neutrophils counts, LDH, and CRP, procalcitonin (PCT), and D-dimer (11,12).

Laboratory values influenced by COVID-19 mortality converged on D-dimer. It is a product of fibrin degradation that describes the hypercoagulation process. Research had been conducted in China showed that based on the results of a meta-analysis of six studies involving 1,379 patients, the levels of D-dimer in non-survival patients were significantly higher than in the survivors (SMD = 0,91, CI 95% = 0,79 - 1,03). Therefore, increasing D-dimer levels were affected by increasing death risk in COVID-19 patients (10).

CRP is produced by the liver. It aims to respond to increasing levels of inflammatory cytokines, especially interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ) due to tissue damage, infection, and inflammation. The CRP concentration will increase in the circulation during the inflammatory process (11,12).

The high mortality rate of COVID-19 in Indonesia is a serious issue to be solved by advanced research development. The main problem of this study lies in finding quality laboratory values as the predictors of mortality outcomes for COVID-19 patients. CRP and D-dimer are the parameters that are strongly related to the pathogenesis of COVID-19 (i.e. cytokine storm and hypercoagulable state). CRP and D-dimer are two laboratory parameters that must be regularly examined in the early treatment of COVID-19 patients. They could be checked in laboratories at regional and central referral hospitals. It was possible to get more samples and the sampling time by observing and identifying the first day of the COVID-19 in pneumonia phase (day 7th to 10th after the patient is firstly sick). Such a method can minimize unnecessary bias (13,14). This research aims to compare prognostic value between serum concentrations of D-dimer and CRP as the better predictors of COVID-19 patients' mortality rate. Hypothesis of this study is D-dimer has better prognostic values as a predictor of COVID-19 patients' mortality than CRP.

## MATERIALS AND METHODS

### Study Design and Samples

It was a retrospective observational cohort study to determine the prognostic values of CRP and D-dimer for COVID-19 of electronic medical records at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The study was conducted after obtaining a permit from the Ethics and Research Committee of Dr. Hasan Sadikin General Hospital / Padjadjaran University with the number: LB.02.01/X.6.5/373/2021/ Dr. Hasan Sadikin General Hospital is the main referral hospital of Indonesia Ministry and Health at West Java, Indonesia.

The research subjects were adult patients (more than 17 years old) that had been diagnosed with COVID-19 and treated at Dr. Hasan Sadikin General Hospital in Bandung City from August 2020 to August 2021. The exclusion criteria were cases of post operative during treatment, multiple trauma and pregnancy. Information retrieval on the patient had obtained the consent from the patient and families beforehand. For determining the sample size, this research used the rule of thumb formula that calculated total independent variables ( $N=9$ ) times 10 and then divided by 0.5 with the result was a minimum sample size : 180 subjects . The sampling process used the probability technique with systematic random sampling. The CRP and D-dimer were taken once between day 7th -10th of illness. The index test for diagnosis of COVID-19 was RT-PCR for detection of viral RNA in nasopharyngeal swab. This test was used according to WHO guidelines for diagnosis of COVID-19 and it's done by governmental center (Central Laboratory of Dr. Hasan Sadikin General Hospital). The laboratory records that had been recruited from study individuals included: CRP, and D dimer. CRP level was measured by latex enhanced immunoturbidimetric method and D dimer was determined by immunofluorescent method.

### Statistical Analysis

Descriptive analysis aimed to set the characteristics of the research subjects. Some numerical scale data such as patients' ages and serum CRP and D-dimer values were presented in the form of mean, standard deviation, median, and range. The sample's characteristic data covered categorical figures such as gender was coded and presented as a distribution of frequency and percentage. Severity of COVID-19 was classified based on COVID-19 Therapeutic Protocol Guidelines issued by Indonesian Association of Anesthesiologist and Intensive Care (Perdatin) (6). Numerical data were analyzed for checking data distribution (normality test) using Shapiro-Wilk and Kolmogorov Smirnov test.

This research used a statistical test which is the prognostic test. Bivariate analysis used a categorical measurement scale, Chi-square value, and relative risk analysis. The significance test aimed to compare the characteristics of the two study groups (survivors and non-survivors). If the data were normally distributed, the data would be tested using an unpaired t-test. However, the Mann-Whitney test became another option if the data were not normally distributed. Categorical data were statistically analyzed using the Chi-square test (if the Chi-Square conditions have been met). The statistics processed through the SPSS version 25.0 for the Windows program. If the p-value is lower or the same as 0.05, it is statistically significant but if the p-value is higher than 0.05, it is not statistically significant.

### Prognostic Quality Test

The cut-off value of CRP and D-dimer would be determined by looking at sensitivity and specificity

values. The prognostic quality of variables measured calibration and discrimination values. The calibration value was measured by Hosmer and Lemeshow test. The calibration value was declared as good if the p-value is higher than 0.05. The discrimination value of the prognostic model was calculated by the AUC value. The discrimination value was good if AUC was higher or equal to the expected value (80%). The data obtained were recorded in a form to be processed through the SPSS version 25.0 for the Windows program.

## RESULTS

Subjects consisting 195 patients were selected by systematic random sampling technique. They had already met the inclusion criteria and did not include the exclusive ones.

### Significance of CRP and D-dimer on Mortality

The subjects were classified based on age, gender, comorbidities, and the severity of COVID-19 as described in Table I. The median for age category was 60.00 years old, and there were more male than female patients. The most commonly found comorbidities were hypertension 65(33.3%), diabetes mellitus 62(31.8%), and cardiovascular diseases 27(13.8%). Based on severity of COVID-19 findings, severe case was the highest with 153 cases (78.5%), moderate case 20(10.3%), critical case 12(6.2%) and mild case 10(5.1%). The data were then grouped based on the outcome, namely survivors and non-survivors. Cardiovascular comorbid variable

**Table I: Characteristics of Subjects**

Variables	N=195
<b>Age</b>	
<i>Mean Std</i>	57.38±14.268
<i>Median</i>	60.00
<i>Range (min-max)</i>	21.00-93.00
<b>Gender</b>	
Male	114(58,5%)
Female	81(41.5%)
<b>Comorbidities</b>	
Diabetic	62(31.8%)
COPD	2(1.0%)
Cardiovascular	27(13.8%)
Hypertension	65(33.3%)
Chronic Kidney Disease	9(4.6%)
Others	95(4.7%)
<b>Diagnosis COVID-19</b>	
<i>Mild case</i>	10(5.1%)
<i>Moderate case</i>	20(10.3%)
<i>Severe case</i>	153(78.5%)
<i>Critical case</i>	12(6.2%)

was statistically significant (Table II). The serum CRP and D-dimer values with mortality in COVID-19 patients were compared and statistically analyzed in Table III. In the non-survivors group, the serum CRP value had a median of 365 mg/dl, and the D-dimer had a median of 4.080 ng/ml. The results show that the p-values of the serum CRP and D-dimer were statistically significant.

**Table II: Comparison Between Characteristics of Subjects and Outcomes**

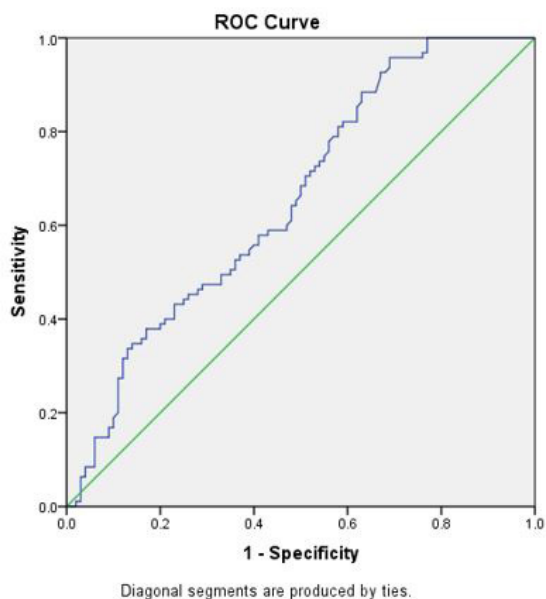
Variables	Outcomes		P value
	Mortality N=95	Survival N=100	
<b>Age</b>			
<i>Mean Std</i>	59.59±12.189	55.28±15.771	0.037*
<i>Median</i>	62.00	57.50	
<i>Range (min-max)</i>	30.00-88.00	21.00-93.00	
<b>Gender</b>			
Male	53(55.8%)	61(61.0%)	0.461
Female	42(44.2%)	39(39.0%)	
<b>Comorbidities</b>			
Diabetic	26(27.4%)	36(36.0%)	0.196
COPD	2(2.1%)	0(0.0%)	0.236
Cardiovascular	19(20.0%)	8(8.0%)	0.015*
Hypertension	34(35.8%)	31(31.0%)	0.478
Chronic Kidney Disease	7(7.4%)	2(2.0%)	0.094
Others	44(46.3%)	51(51.0%)	0.513
No Comorbidities	26(27.4%)	30(30.0%)	0.685

**Table III: Comparison Between CRP and D-Dimer Values on Outcomes of Subjects**

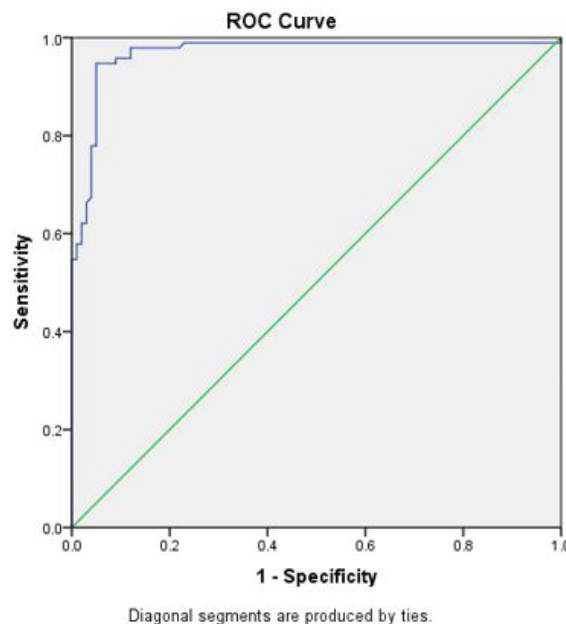
Variables	Outcomes		P value
	Mortality N=95	Survival N=100	
<b>CRP (mg/dl)</b>			
<i>Median</i>	365.00	237.50	0.0001**
<i>Range (min-max)</i>	105.00-2,650.00	11.00-26,600.00	
<b>D-Dimer (ng/ml)</b>			
<i>Median</i>	4,080.00	555.00	0.0001**
<i>Range (min-max)</i>	9.45-78,700,00	97.00-3,630.00	

**Prognostic Value Between D-dimer and CRP on Mortality**  
The analysis of the CRP value on mortality generated the cut-off value of 230.10 mg/dl with a sensitivity value of 70.5% (moderate sensitivity) and a specificity value of 49.0% (very weak specificity) (Table III). The value of the relative ratio (RR) for serum CRP was higher than 230.10 mg/dl with a death risk of 1.561 times compared to patients treated with serum CRP (the value was lower than 230.10), with a confidence interval of 1.117-2.182. The ROC curve showed that the serum CRP had a good diagnostic value because the curve moves away from the 50% line and approached 100%. The AUC value obtained from the ROC method is 65.7%, and a p-value of 0.000, which showed that the discrimination value is weak (Figure 1).

Based on the analysis of the D-dimer value on mortality,



**Figure 1: The ROC of Serum CRP.** The AUC value obtained from the ROC method is 65.7%, and a p-value of 0.000, which shows that the discrimination value is weak.



**Figure 2: The ROC of Serum D-Dimer.** The AUC value obtained from the ROC method is 96.8% with a p-value of 0.000, meaning that the discrimination value is good.

the cut-off point of the serum D-dimer value is 1,810.00 ng/ml with a sensitivity value of 95.8% (very strong sensitivity) and a specificity value of 91.0% (very strong specificity). RR value of serum D-Dimer is higher than 1,810.00 ng/ml with the death risk of 21.613 times compared to patients with serum D-Dimer values lower than 1,810.00 ng/ml with a confidence interval of (8.266-56.508). The ROC curve showed that the serum D-dimer had a good diagnostic value because the curve moved away from the 50% line and approached 100%. The AUC value obtained from the ROC method was 96.8% with a p-value of 0.000, meaning that the discrimination value was good (Figure2).

The calibration values of the CRP and D-dimer variables as the predictors were checked using the Hosmer and Lemeshow test with a p-value lower than 0.05. Thus, H0 was rejected. The model cannot be accepted or hypothesis testing cannot be carried out because there was a significant difference between the model and the observed values.

## DISCUSSION

The comparison of the two groups shows that they have the same characteristics during the initial examination. It means that both groups are homogeneous except for cardiovascular comorbidities, age and severity of COVID-19. In this research, cardiovascular comorbidities are experienced by 20% of subjects with the mortality outcomes, compared to 8% of survived subjects with a p-value lower than 0.05 (0.015). These findings may still emerge biases in terms of cardiovascular comorbidities, age and severity of the disease, affecting the mortality outcomes of COVID-19 patients. The influence of

these characteristics on mortality outcomes should be examined in further studies.

A test instrument with good validity has a strong sensitivity and specificity value. In this research, the sensitivity values between CRP and D-dimer were compared as the predictors of mortality in COVID-19 patients. This research found sensitivity value of D-dimer is 95.8% (very strong) compared to 70.5% CRP (medium). It also seems that the D-dimer was 91% (very strong) compared to 49.0% CRP (very weak).

Based on the calculation of the sensitivity and specificity values taken from the ROC curve, the cut-off point value of serum CRP was 230.10 mg/dl with a sensitivity value of 70.5% and a specificity value of 49.0%. It meant that 65.7% of patients treated with serum CRP values higher than 230.10 mg/dl were predicted to pass away (Figure 1). According to ROC curve, the value of serum D-dimer is 1.810.00 ng/ml with a sensitivity value of 95.8% and a specificity value of 91.0%. It meant that 96.8% of patients treated with serum D-dimer values higher than 1.810.00 ng/ml were predicted to pass away (Figure 2). Those findings were in line with a case-control study conducted in 2020. It involved 248 subjects in China regarding D-dimer as a biomarker of severity and mortality in COVID-19. The research found that the average D-dimer level was 1,690 (910 – 5,060) ng/ml, and the average CRP was 48.4 (10.98 – 92.25) mg/dl with  $p < 0.05$ . The findings revealed that the cut-off value of D-dimer  $\geq 2,140$  ng/ml, which meant that it was significant for the mortality rate of COVID-19 patients (14).

Another research was conducted in Bali in 2020. It discussed the relationship between CRP and D-dimer with the severity and mortality of COVID-19 in 242



patients. The average CRP was 133 mg/dl (34-200 mg/dl), and the average D-dimer value was 7,851 ng./ml (1,139-16,944 ng/ml) with the p-value was lower than 0.001 (statistically significant). This research found the best cut-off value for D-dimer is 4.181 ng/ml, while CRP was the best at the cut-off value of 72.50 mg/dl with an 88% AUC value (fair) (13).

The cut-off value of D-dimer obtained in this research was almost the same as that from the research in China in 2020, whereas the cut-off values of D-dimer and CRP were quite different from those found in Bali (13,14). It might be because there are differences in the data and the number of samples. The sampling method is based on the patients' sick days (from day 7 to 10 of illness) that made it different from the research in Bali used the first day of treatment. In this research we used day 7-10 of the disease because it's best describe the pneumonia phase that's the start point of inflammation process begin (16). The discrimination value was a statistically prognostic model validity test that aimed to select a model to distinguish existing data based on the probability of an event. The discrimination value for D-dimer set by the ROC curve through the AUC value was 96.8% (strong), while the CRP discrimination value was 65.7% (weak). Based on the calibration test, the concentration of CRP and D-dimer on the mortality of COVID-19 patients had a significance value lower than 0.05. Therefore, the model was not accepted because this test did not compare the model that consists of some prognostic variables. Laboratory parameters as predictors of mortality are important to be researched because clinicians can make appropriate and early therapeutic intervention decisions based on the selection of appropriate laboratory parameters, especially those capable of predicting death from COVID-19.

Based on the statistical tests of prognostic factors between serum CRP and D-dimer, the D-dimer is a better predictor than CRP. The results are supported by the pathogenesis of COVID-19. The patients who experience severe conditions perform a pathological host immune response, especially in the lungs, characterized by a cytokine storm. The presence of IL-6 plays a vital role in the pathogenesis and correlates with an increasing amount of CRP. It is a marker of IL-6 activation (5,6,7). From the side of cost effectiveness, IL-6 costs 20 USD compared to CRP examination of 3 USD for one patient in Indonesia. D-dimer is a molecule generated from the degradation of fibrin in fibrinolysis. D-dimer describes a hypercoagulable state in COVID-19 which can increase the risk of thrombotic and thromboembolic complications, particularly venous thromboembolism in the lungs. The increasing D-dimer is a marker of thrombosis found in severe COVID-19 patients. It is associated with the severity of the disease in the next phases (11,12). Increasing the concentration of D-dimer in serum means that there is an intravascular coagulation process. Previous findings have shown that D-dimer is constantly associated with the severity and mortality of COVID-19 patients. D-dimer examination

costs 20 USD for one patient in Indonesia.

## CONCLUSION

D-dimer and CRP are two of many laboratory parameters which from an economic and pathophysiological point of view, best describe the mortality of COVID-19 patients. This research concluded that as a predictor of mortality in COVID-19 patients, the serum D-dimer value has a better discrimination value than the serum CRP. However It was not enough to determine mortality predictors with single parameter, so further research should involve multiple parameters in identifying the quality of mortality predictors for COVID-19 patients.

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