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Research Article

Biomarker Profiles Associated with Covid-19 Mortality in East Java, Indonesia: A Tertiary Care Hospital Study

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ABSTRACT

Objective: This study aimed to compare the most useful biomarkers for predicting prognosis and response to therapy in COVID-19 patients. **Material and Methods:** This quantitative study involved 639 patients who were hospitalized with COVID-19 infection. Patients without any biochemical marker result; patients referred to another hospital; and peripheral oxygen levels measured using oxygen supplementation were excluded from the study. **Results:** There was a statistically significant difference in terms of demographics, vital signs on admission, and laboratory parameters. The risk of mortality in COVID-19 is significantly influenced by c-reactive protein (CRP) and interleukin-6 (IL-6) levels (p-value <0.05). **Conclusion:** Findings revealed these biomarkers could help the future development of more personalized treatment and diagnostic approaches.

Keywords: Biomarker, COVID-19, Outcome.

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INTRODUCTION

COVID-19 is a devastating disease that has spread since 2020 and caused many of deaths. COVID-19 primarily manifested as a severe acute respiratory syndrome and later, demonstrated diverse manifestations. The incidence of COVID-19 showed a rising trend during June- Augustus 2021 and this phenomenon is in line with the increase of mortality.[1] From 17 June 2021 to 22 August 2021, Indonesia reported more than 10,000 daily new and the average daily cases reached 30,475 in that specific time period. World Health Organization (WHO) reported as of 25 October 2023, there have been 6,813,429 confirmed cases of COVID-19 with 161,918 deaths. East Java as the second most populated province became the epicenter of COVID-19 in 2020.[2]

For medical professionals, the COVID-19 pandemic brings a number of concerns. To save lives, prompt diagnosis and hospitalization, risk assessment, and efficient use of critical care resources are crucial. While clinical assessment is essential, laboratory markers, also known as biomarkers, can offer extra, unbiased data that can have a big impact on these aspects of patient care. An increasing body of research suggests that immunological and inflammatory variables are important in the development of COVID-19 manifestation. Certain biomarkers, such as those associated with inflammation and immunity (procalcitonin (PCT), interleukin-6 (IL-6), c-reactive protein (CRP)), hematological parameters (lymphocyte count, neutrophil-to-lymphocyte ratio (NLR)), cardiac parameters (ferritin, D-dimer, red blood cell distribution width, creatinine kinase myocardial band (CK-MB), myoglobin, troponin), liver (albumin, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin), and lung injury (Krebs von den Lungen-6), have been previously demonstrated to be significant. In COVID-19, these indicators can be utilized as prognostic biomarkers to help identify high-risk patients and predict significant events like mortality. However, the majority are not frequently tested, readily available, costly, and uncomfortable.[3]

There is a reported association between worse clinical outcomes and higher levels of biomarkers, which indicate massive inflammatory response. Previous studies showed that in patients infected with SARS-CoV-2, elevated D-dimer levels at admission were linked to a higher risk of disease venous thromboembolism, severity, and mortality.[4-6] The results of other research also demonstrated a positive correlation between elevated PCT, ferritin, IL-6, CRP, and NLR and significant severe manifestations to a critical state of COVID-19 infection.[7-14] The inflammatory biomarker may be a crucial indicator that helps with COVID-19 management.

However, there are still gaps in our knowledge. Longitudinal studies are needed to ascertain the biochemical marker's prognostic significance. Through examining the relationship between the COVID-19 biochemical marker, patient characteristics, and treatment outcomes, our work aims to bridge these gaps and provide valuable management insights for future iterations. Routine blood exams and biochemical markers have not received much attention. Thus, the goal of the current study was to evaluate the potential utility of the complete blood count (CBC) parameter as a predictor of COVID-19 mortality. The study sought to determine the predictive usefulness of neutrophils to NLR, procalcitonin, ferritin, IL-6, CRP, and D-dimer.

MATERIAL AND METHODS

Study Design and Subject Recruitment

In this retrospective study, 639 patients were hospitalized with COVID-19 infection at Airlangga

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University Hospital, Surabaya, East Java. All patients with COVID-19 confirmed by RT-qPCR who were admitted to the hospital between June 1, 2021, and August 31, 2021, were included in the research. Clinical characteristics including age, gender, and comorbidities were gathered based on the medical records of the Airlangga University Hospital. The exclusion criteria were patients with insufficient records; patients without any biochemical marker result; patients referred to another hospital; and peripheral oxygen levels measured using oxygen supplementation.

Data Collection for Patient's Characteristics

We used the medical record to collect data on their demographic characteristics such as gender, age, history of hypertension, and history of diabetes. Vital sign examinations at admission were recorded including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), temperature (T), and peripheral oxygen saturation (SpO2). Laboratory work was performed including complete blood count, liver function test, renal function test, and electrolyte test. Several biochemical marker levels measured such as D-dimer, PCT, ferritin, IL-6, and CRP. The latest laboratory work were recorded.

Statistical Analysis

The SPSS program version 25 for Windows was used. Categoric data were tested with Pearson chi-square and numeric data were tested with Spearman correlation. We performed a Receiving Operator Curve (ROC) analysis to determine the cut-off value. Sensitivity and specificity are considered based on the highest Younden index. The data was calculated using binary regression to consider the odd ratio (OR) and compare the differences in categorical data between the two groups.

RESULTS

Following the completion of the inclusion criteria, 548 patients were enrolled in the study. 432 people did not survive and 118 people did.

Comparison of patient demographic characteristics

Table 1 shows that there was a statistically significant difference between survivors and non-survivors in terms of age, gender, and history of comorbidities. Comorbidities were classified as developing with or without asthma, diabetes mellitus, and hypertension. Between the two groups, there was a substantial age difference (survivor: 42(17.69) vs non-survivor: 57.09 (13.75); p-value <0.001). In the non-survivor group, the percentage of male patients was notably greater than in the survivor group (54.7% vs. 43.9%, p-value 0.039). In comparison to the survivor group, the non-survivor group had a higher proportion of hypertension and asthma (1.7% and 1.4%, respectively; p-value 0.8) and 32.5% vs. 24.4%, respectively. Additionally, fewer patients in the survivor group than in the non-survivor group (47% vs. 68.2%, p-value 0.076) had diabetes mellitus.

Comparison of vital sign

In terms of SBP, HR, temperature, RR, and SpO2, there was a significant difference between the two groups (Table 2). The SBP differed significantly between the two groups (survivor: 122.06 (20.75) vs non-survivor: 133.06 (26.81); p-value 0.021). A significant difference in HR, temperature, RR, and SpO2 was reported between the survivor and non-survivor group (97.26 (15.76) vs 105.7 (19.1), p-value < 0.001; 36.66 (0.96) vs 36.94 (0.98), p-value 0.02; 22.96 (4.67) vs 27.43 (6.17), p-value <0.001; and 94.74 96.44) vs 85.23 (14.91), p-value <0.001 respectively).

Table 1. Comparison of patient demographic characteristics.

Variable	Survivor	Non-survivor	Total		Total	P-value
	Mean (S.D)	Mean (S.D.)	Survivor	Non-survivor		
Age	42.00 (17.69)	57.09 (13.75)	432	117	549	<0.001*
Gender						
Male			190 (43.9%)	64 (54.7%)	254	0.039*
Female			242 (56.1%)	53 (45.3%)	295	
Hypertension						
Yes			105 (24.4%)	38 (32.5%)	143	<0.001*
No			326 (75.6%)	79 (67.5%)	405	
Asthma						
Yes			6 (1.4%)	2 (1.7%)	8	0.8
No			425 (98.6%)	115 (98.3%)	540	
Diabetes						
Yes			75 (68.2%)	55 (47%)	130	0.076
No			35 (31.8%)	62 (53%)	418	

*p-value <0.05 is considered as statistically significant. Categoric data were tested with Pearson chi-square and numeric data were tested with Spearman correlation.
**S.D.=standard deviation.

Table 2. Comparison of vital signs.

Variable	Survivor	Non-survivor	Survivor	Non-survivor	Total	P-value
	Mean (S.D.)	Mean (S.D.)				
SBP (mmHg)	127.06(20.75)	133.06(26.81)	417	117	534	0.021*
DBP (mmHg)	78.33(12.71)	79.11(14.24)	417	117	534	0.583
HR (bpm)	97.26(15.76)	105.7(19.1)	429	117	546	<0.001*
T (C)	36.66(0.96)	36.94(0.98)	429	116	545	0.02*
RR	22.96(4.67)	27.43(6.17)	430	115	545	<0.001*
SpO2	94.74(6.44)	85.23(14.91)	431	116	547	<0.001*

*p-value <0.05 is considered as statistically significant. Categoric data were tested with Pearson chi-square and numeric data were tested with Spearman correlation
**SBP=systolic blood pressure, DBP=diastolic blood pressure, HR= heart rate, T= temperature, RR=respiratory rate, SpO2= peripheral oxygen saturation

Comparison of patient laboratory result

All laboratory variables had significant differences between the two groups except hemoglobin as summarized in Table 3. There was a significantly higher mean value of WBC in the non-survivor group (12 (7.43) vs. 8.09 (4.59), p-value < 0.001). The mean value of platelet was lower in the non-survivor group (260.23 (129.67) vs 276.67 (116.64), p-value < 0.047) while the mean value of NLR was higher in the non-survivor group (13.63 (15.34) vs 5.6 (5.78), p-value < 0.001). Liver function tests including ALT and AST were significantly higher in the non-survivor group (109.15(174.25) vs 48.18(41.07), p-value <0.001; 83.9(162.39) vs 45.75(41.37), p-value <0.001 consecutively). Additionally, renal function tests differed considerably in the non-survivor group and the survivor group. (29.67(24.14) vs 16.54(17.32), p-value < 0.001; 2.07(3.1) vs 1.4(2.05), p-value < 0.001). Otherwise, electrolyte levels including Na, K, and Cl were significantly difference in the non-survivor group. (134.15(7.3) vs 134.55(12.5), p-value 0.002; 4.23(0.83) vs 4.97(11.26), p-value <0.001; 101.54(6.59) vs 101.72(11), p-value 0.035). Furthermore, biochemical markers including D-dimer, PCT, CRP, ferritin, and IL-6 were significantly elevated in the non-survivor group. (5.85(7.87) vs 2.48(6.76), p-value < 0.001; 7.03(20) vs 1.14(7.03), p-value <0.001; 146.85(88.15) vs 50.41(58.09), p-value <0.001; 2,044.27(2,160.25) vs 897.19 (855.87), p-value <0.001; and 499.49 (1,741.01) vs 94.83(673.75), p-value <0.001).

ROC-AUC analysis of biomarker

Figure 1 showed that IL-6 had greatest area under the curve followed by CRP and NLR respectively. The graph's area under curve was 0.861, 0.835, and 0.748 (p-value < 0.001). Based on Table 2 and Table 3, the ROC curve for IL-6's predictive role on patient mortality described 77.6% specificity and 81.5% sensitivity at the 8.23 mg/L threshold. CRP at the 9.5 cut off had 85.2% sensitivity and 72.4% specificity. Significantly from Hosmer and Lemeshow test is 0.982 (p-value > 0.005) and indicates good logistic regression model fit. Omnibus test of model coefficient shows sig value < 0.001. This indicates that the model obtained is influenced by at least one tested independent variable. The important parameters in the model are then determined by testing the partial parameters. The Model Summary shows Nagelkerke R Square 0.618 and indicates the ability of the independent variable (D-dimer, procalcitonin, CRP, ferritin, IL-6, and NLR) to describe the dependent variable (mortality) is 61.8%. We presented cut off levels based on the highest Younden index in Table 4. High sensitivity and specificity were observed in CRP, IL-6, and NLR. The binary logistics model from Table 5 below explains the mortality of patients with COVID-19 which is significantly influenced by CRP and IL-6 levels. An increase in CRP and IL-6 levels will result in a higher risk of mortality at 1,012 (95%CI 1,004-1,021, p-value 0.005) and 1,007 (95%CI 1,000-1,013, p-value 0.041) times consecutively.

DISCUSSION

The present study describes the concept of COVID-19 mortality prediction based on the immune system response rather than on the observation of clinical manifestations themselves. Furthermore, by using demographics, vital signs, and laboratory results, we were able to obtain more information to analyze the risk of mortality. These demographic factors can influence the severity and outcomes

Table 3. Comparison of patient laboratory results.

Variable	Survivor	Non-survivor	Survivor	Non-survivor	Total	P-value
	Mean (S.D.)	Mean (S.D.)				
Hb (mg/dl)	13.3 (1.95)	13.13(2.48)	429	117	546	0.992
WBC (x10^9/L)	8.09(4.59)	12(7.43)	429	117	546	<0.001*
Plt (x10^9/L)	276.67(116.64)	260.23(129.67)	429	117	546	0.047*
NLR	5.6(5.78)	13.63(15.34)	428	116	544	<0.001*
ALT (U/L)	48.18(41.07)	109.15(174.25)	390	113	503	<0.001*
AST (U/L)	45.75(41.37)	83.9(162.39)	390	113	503	<0.001*
Ureum (mg/dl)	16.54(17.32)	29.67(24.14)	393	114	507	<0.001*
Creatinine (mg/dl)	1.4(2.05)	2.07(3.1)	393	114	507	<0.001*
Na (mmol/L)	134.55(12.5)	134.15(7.3)	399	115	514	0.002*
K (mmol/L)	4.97(11.26)	4.23(0.83)	398	115	513	<0.001*
Cl (mmol/L)	101.72(11)	101.54(6.59)	395	114	519	0.035*
D-dimer (µg/mL)	2.48(6.76)	5.85(7.87)	382	102	484	<0.001*
Procalcitonin	1.14(7.03)	7.03(20)	224	97	321	<0.001*
CRP (mg/L)	50.41(58.09)	146.85(88.15)	364	101	465	<0.001*
Ferritin (ng/mL)	897.19(855.87)	2,044.27(2,160.24)	141	51	192	<0.001*
IL6 (pg/mL)	94.83(673.57)	499.49(1,741.01)	174	51	225	<0.001*

*p-value <0.05 is considered as statistically significant. Categoric data were tested with Pearson chi-square and numeric data were tested with Spearman correlation.
**Hb=hemoglobine, WBC= white blood cell, Plt= platelete, ALT= alanine aminotransferase; AST= aspartate aminotransferase, CRP= C-reactive protein, IL6= interleukin 6, NLR= neutrophil to lymphocyte ratio.

Table 4: Sensitivity, specificity, cut off levels of various biomarkers to predict mortality in COVID-19.

Biochemical parameters	Cut off levels	Sensitivity (%)	Specificity (%)
D-dimer	0.66	92.6	31
Procalcitonin	0.78	48.1	87.9
CRP	9.5	85.2	72.4
Ferritin	167.3	55.6	77.6
IL-6	8.23	81.5	77.6
NLR	171.98	70.4	69

*p-value <0.05 is considered as statistically significant.
**CRP= c-reactive protein, IL-6= interleukin-6, NLR= neutrophil-to-lymphocyte ratio

Table 5. Cut off level, sensitivity, and specificity of various biomarkers to predict mortality in COVID-19.

Biochemical parameters	Odd ratio	P-value	95%CI
D-dimer	0.983	0.721	0.894-1,081
Procalcitonin	1,024	0.263	0.982-1,067
CRP	1,012	0.005*	1.004-1,021
Ferritin	1,000	0.113	1.000-1,001
IL-6	1,007	0.041*	1.000-1,013
NLR	1,124	0.064	0.993-1,271

*p-value <0.05 is considered as statistically significant.
**CRP= c-reactive protein, IL-6= interleukin-6, NLR= neutrophil-to-lymphocyte ratio

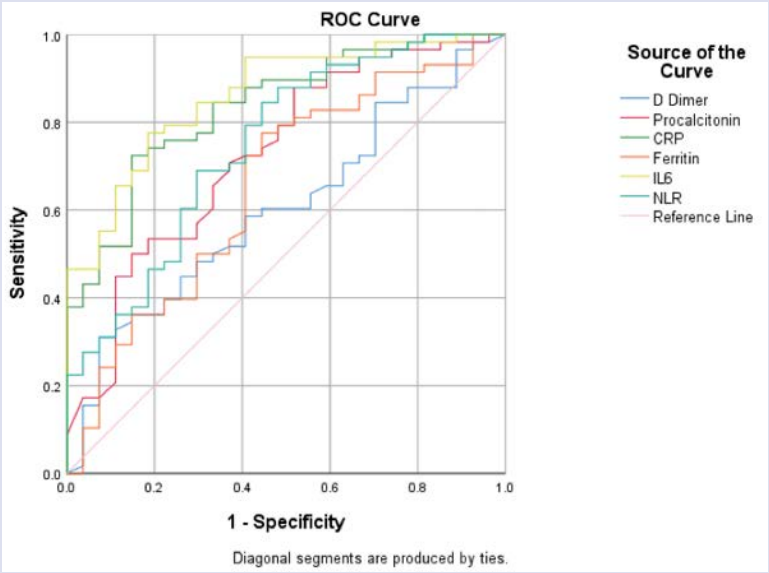

Figure 1. ROC curve analysis of biochemical markers in predicting mortality in COVID-19 infection.

of COVID-19 infections. Understanding these characteristics can help healthcare professionals better manage the disease and allocate resources accordingly. The mean age of patients has been observed to range from 42 to 57 years depending on the survival group. COVID-19 infections were more common in men more than women. According to this research, the male-to-female ratio is almost similar (4:5). Patients with pre-existing illnesses including diabetes, hypertension, and asthma are more prone to get severe COVID-19 infections and die as a result.

The results provide evidence that the biochemical markers of patients who did not survive after COVID-19 infection are distinct from the biochemical markers of survivors. CRP and IL6 were biomarkers with the most excellent discrimination. Although CRP is typically absent from viral infections, an adaptive immunity response seems necessary for the COVID-19 virus to be cleared, and macrophage activation may be responsible for the elevated blood CRP levels and the onset of sickness.[15] As a result of higher CRP levels at hospital admission, people with COVID-19 who are more severe than those who are not can be utilized as an independent biomarker for an early diagnosis of disease severity. In order to guide the severity of COVID-19 disease in clinical management, high CRP levels in patients are directly linked to the disease prognosis. Raising CRP levels are contributing factors for COVID-19 patient outcomes, which are highly correlated with ICU admission and death. Elevated CRP levels in COVID-19 infections are notably associated with mortality.[16,17]

Patients with COVID-19 have been found to have elevated cytokine levels, which suggests cytokine storm and exacerbates massive immune response to viral infection in COVID-19 infections, which is a major factor in COVID-19 severity.[18] Additionally, there were noticeable and persistent decreases in lymphocyte counts (CD4+cells and CD8+ cells), especially CD8+ T cells, when comparing patients with severe COVID-19 to those with lesser cases, but increases in neutrophil counts. An increase in inflammatory responses may result from T cell loss during SARS-CoV-2 infection, while a decrease in inflammatory responses may result from T cell restoration. Therefore, the neutrophil-to-lymphocyte ratio (NLR) may predict the outcome of COVID-19.[19]

Previous studies investigated D-dimer levels and found that elevated D-dimer were associated with increased in-hospital mortality. Increasing 1 µg/ml in D-dimer at hospital admission, there was a hazard ratio of 1.06 (95% CI 1.04–1.08, p<0.001) for all-cause mortality.[20,21] Another study demonstrated that excessive intracellular ferritin linked to tissue deterioration, coagulopathy (blood clotting), and ferroptosis (a type of cell death) are brought on by excessive intracellular ferritin.[22] The production of ferritin protein, which stores iron, has been related to both the severity and prognosis of COVID-19 by altering the immune system and inflammation. Similar to other biomarkers, associations between PCT and COVID-19 were reported in previous studies. PCT may be able to assist patients with COVID-19 in identifying bacterial coinfections in the lower respiratory tract.[23]

Similar results were also observed in a recent study that predicated COVID-19 outcomes on biochemical values. According to an analysis of the receiver operating characteristic (ROC) curve, the area under the curves for the NLR and CRP were, respectively, 0.737 and 0.734. NLR is the best indication of severe COVID-19, and severe COVID-19 can also be predicted by combining these three clinical markers. The threshold for CRP was ≥38.55 and NLR was ≥4,283 respectively.[24] While the optimum cut off for IL-6 was 27.3 pg/ml for distinguishing

mild to moderate and severe COVID-19.[25] In our analysis, cut off levels for CRP, IL-6, and NLR were notably lower than demonstrated by the previous report. These findings align with earlier observations. At admission, there were 140 patients, of whom 95 (679.9%), 91 (65.0%), and 8 (5.7%) exhibited increased levels of PCT, IL-6, and CRP, respectively. Compared to the mild manifestations of COVID-19, the severe group had a significantly higher number of patients with raised PCT, CRP, and IL-6 levels.[26,27]

The findings show possibility since they allow us to differentiate between low and high mortality risk. With more data, we hope to enhance our algorithm even further. Thus, prompt detection and treatment of COVID-19 infection are crucial to preventing adverse clinical outcomes. By considering these clinical laboratory biomarkers in regular testing, limited medical resources can be focused towards COVID-19 patients who need quick treatment, especially in areas where the virus is expanding.

CONCLUSION

This study clarifies how patient features, laboratory results, and biochemical results may affect COVID-19 prognosis and outcomes. Perhaps as a result of early diagnosis and treatment provided in the early stages of the illness, patients with elevated levels of biochemical markers at the early hospital treatment stage have considerably worse results than those with a low one. Because of high sensitivity and specificity, the use of the initial CRP and IL6 value from the blood sample as a predictive evaluation in COVID-19 prediction needs to be considered. The results of this study could improve our knowledge of the dynamics of the disease and provide insightful information for managing and preparing for outbreaks in the future.

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ETHICAL CONSIDERATION

The protocol of the study was approved by the Research Ethics Committee of Airlangga University Hospital (No.165/KEP/2021).

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

AUTHOR CONTRIBUTOR'S

All authors contributed to article preparation and paper revision and have collectively assumed responsibility for all aspects of this study.

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