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Survival Study of D-dimer, Lactic Acid and BGA on COVID-19 Patients

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ABSTRACT

The value of D-dimer value, lactic acid levels, and the results of blood gas analysis (PaO2, PCO2, PH, and PaO2/FiO2) are prognostic factors for COVID-19 patients, although there is no agreement on the optimum cut-off point for specificity and sensitivity. The aim of this study is to examine D-dimer value, lactic acid levels, and the results of blood gas analysis as a prognosis for patients with severe or critical COVID-19. This was a retrospective study of the medical records of the UGM Academic Hospital. Overall survival was assessed by the Kaplan-Meier curve. Determination of the cut-off for D-dimer, lactic acid, and BGA variables was carried out using the ROC followed by calculating the Youden index. Then the hazard ratio was determined by Cox regression. The cut-off value to determine the group of patients on the D-dimer and lactic acid variable was 881 ng/mL (sensitivity 77.23%, specificity 32.31%) (p=0.040) and 21 ng/mL, patients with lactic acid values above the cut-off had a higher risk of death (p=0.391). The cut-off of pH, PaO2, and PaCO2 were 7.43, 72.2 mmHg, and 33.9, respectively. D-dimer levels, lactic acid, and PaCO2 values in blood gas analysis above the cut-off value had a worse survival rate, while patients also had a worse survival rate if the PaO2 and PH values were below the cut-off value.

Keywords: Blood gas analysis, COVID-19, D-dimer, lactic acid, prognostic factor

INTRODUCTION

COVID-19 caused by the SARS-CoV-2 virus is a terror for the whole world. It first appeared in the form of a pneumonia cluster in December 31st, 2019 in Wuhan, China. Then January 13th, 2020, officials confirmed the first case in Thailand, which was the first case outside China.[1,2] Based on the distribution of WHO data dated February 17th, 223 countries were affected by the pandemic. A total of 108,822,960 cases in the world were confirmed COVID-19 and 1,403,641 people died. The most confirmed cases according to the region were 48,457,101 cases in America, Europe with 36,806,380 cases, and Southeast Asia with 13,225,290 cases. Meanwhile, the most confirmed cases according to the country were in the United States 27,309,503 cases, India 10,925,710 cases, and in Brazil 9,834,513 cases.[3]

Based on data from the Committee for Handling COVID-19 and the Indonesian National Economic Recovery on February 17th, 2021, the total of confirmed patients was 1,233,959 people, 1,039,674 people recovered, 86,960 people were suspected, and 33,596 people dead. The highest number of confirmed cases were from DKI Jakarta 317,432 cases, West Java 175,950 cases, and Central Java 142,318 cases.[4]

Existing research states that D-dimer values, lactic acid levels, and Blood Gas Analysis (BGA) results (PaO2, PCO2, PH, and PaO2/FiO2) are prognostic factors in COVID-19 although there is no agreement on the best cut-off point value for specificity and sensitivity.[5,6] D-dimer describes the condition of hypercoagulability and lactic acid increases in severe sepsis. There has been no study evaluating these laboratory results as a determinant of the prognosis of COVID-19 in Indonesia. The aim of this study is needed to see the correlation between D-dimer values, lactic acid levels, BGA results (PaO2, PCO2, PH, and PaO2/FiO2), the prognosis of COVID-19, cases of sepsis, and hypercoagulability in ethnic groups in Indonesia.

METHODS

This study was a retrospective cohort analytic observational study. This research was conducted at the Academic Hospital of Gadjah Mada University from April 2021 to October 2021. This study's target population was patients diagnosed with PCR-confirmed COVID-19 with severe or critical severity.

Retrospective data was taken using secondary data in the form of medical records of COVID-19 patients who met the inclusion criteria namely: Patients with confirmed severe or critical COVID-19 based on the guidelines for the management of COVID-19 3rd edition; Patients with critically severe COVID-19 who were hospitalized at the Gadjah Mada University Academic Hospital; Patient's age >18 years old. The exclusion criteria were patients with a history of blood clotting disorder such as von Willebrand disease or hemophilia.

Data on the frequency of confirmed severe-critical COVID-19 patients were presented in proportions. Overall survival in this study was carried out by looking at the Kaplan-Meier curve to see the general survival of patients. Determination of the cut-off for the D-dimer, lactic acid, and BGA variables (pH, PaO2, PaCO2, PaO2/fiO2) was carried out using the Receiver Operating Curve (ROC) obtaining the sensitivity and specificity values. The Youden index was calculated, and the highest value was chosen to be the cut-off value. Survival analysis for each marker was performed using the Kaplan-Meier curve and the hazard ratio was determined by cox regression. The value that was considered significant had a p-value < 0.05.

All independent variables with p < 0.25 in bivariate analysis were entered into multivariate analysis using the Cox regression time-independent method. Statistical analysis in this study used SPSS version 26 software and Medcalc Statistical Software. To determine the strength of the study based on the hazard ratio value using the PS Power and Sample Size Calculation software version 3.1.2.

This research obtained ethical clearance from the Ethical Committee of the Faculty of Medicine, Gadjah Mada University with a number of KE/FK/0852/EC/2021.

RESULTS AND DISCUSSIONS

Based on Table 1, there was a total of 187 patients, and the median age of the patients was 62 years (95% CI 59-64 years). Based on the gender variable, 47 (40.9%) patients out of a total of 155 male patients survived, while 26 (36.1%) patients out of a total of 72 female patients survived. The total number of patients who had comorbidities was 127 people with 52 (40.9%) survivors. There were 60 patients without comorbidities and 21 (35%) survived.

This study involved 166 patients (166 of 187 patients) with severe and critical COVID-19 that was determined by D-dimer. Based on Table 1, the cut-off value to determine the patient group on the D-dimer variable was 881 ng/mL. Patients with D-dimer levels of 881 ng/mL were grouped into the low D-dimer group and >881 ng/mL into the high D-dimer group. In this study, the cut-off value was 881 ng/dL with a sensitivity of 77.23% and a specificity of 32.31% based on the ROC curve with a statistically significant p-value.

There were 44 patients with D-dimer values below the cut-off value and 122 D-dimers above the cut-off value. The median survival value for patients in the low D-dimer group was 29 days longer (95% CI

Table 1. Subject characteristics

Variables		Total Data Sets	N (%)	Median (95% CI)	Survival Status		p-value
					Survivor	Non-survivor	
Age		187		62 (59-64)	62 (58.65-65)	62 (58.00–64.00)	0.94
Gender	Male	187	155 (61.5)		47 (40.9)	68 (59.1)	0.517
	Female		72 (38.5)		26 (36.1)	46 (63.9)	
Comorbid	Yes	187	127 (67.9)		52 (40.9)	72 (59.1)	0.437
	No		60 32.1)		21 (35)	39 (65)	
Lactate[a] (mmol/L)		64		21.95 (17.40-24.96)	22.8 (13.172-26.130)	21.20 (16.58-24.77)	0.918
D-dimer[a] (ng/mL)		166		1475 (1209.10-1800.67)	120 (995.32-1952.31)	1545 (1183.27-2036.12)	0.699
pH[a]		187		7.43 (7.41- 7.44)	7.42 (7.41-7.45)	7.43 (7.40-7.44)	0.651
PaO2[a]		187		88.10 (84-96.67)	91.10 (83.10–100.40)	87.150 (81.64–98.48)	0.609
PaCO2[a]		187		228.60 (27.30–29.50)	29.30 (27.165-30.33)	28.35 (27.011-29.494)	0.484
HCO3[a]		187		19 (18-19)	19 (18-20)	18 (17-19)	0.363
BE[a]		187		-5.1 (-5.8 - -4.12)	-4.2 (-6.03 - -	-5.45 (-6.77 - -4.30)	

16-77 days) than in the group with high D-dimer values, which was 18 days (95% CI 14-22 days). Patients with D-dimer values above the cut-off had a higher risk of death than the group with D-dimer values below the cut-off (HR 1.60 vs. 0.62, 95% CI 1.02-2.40 vs. 0.41-0.98, p=0.04).

The results showed that the median D-dimer levels in non-survivor patients were higher than the median D-dimer levels in survivors (Fig. 1). A systematic review study conducted by Rostami *et al.* showed that the Relative Risk (RR) for death using a cut-off value of 500 ng/mL was 4.60 (95% CI 2.72-7.79).[7] However, there has been no agreement on the optimum cut-off value for D-dimer to determine the survival of COVID-19 patients. A lot of literature has shown the role of D-dimer in predicting the outcome and survival of COVID-19 patients.

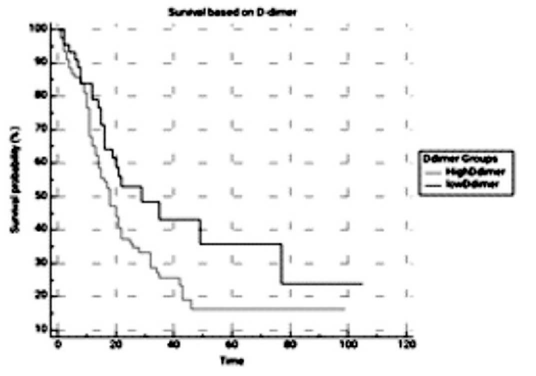

Figure 1. Kaplan Meier survival curve based on D-dimer

The cut-off value to determine the group of patients on the lactic acid variable was 21 ng/mL. Patients with lactic acid levels of 21 ng/mL were grouped into the low lactic acid group and > 21 ng/mL into the high lactic acid group (Fig.2). There were 30 patients with lactic acid values below the cut-off value and 34 lactic acid values above the cut-off value. The median survival value of patients in the low lactic acid group was 28 days (95% CI 20.43-39.272 days) compared to the group with high lactic acid values, which was 16 days (95% CI 10-25 days). Patients with lactic acid values above the cut-off had a higher risk of death than the group with lactic acid values below the cut-off (HR 1.27 vs. 0.782, 95% CI 0.709-2.403 vs. 0.416-1.409, p=0.391).

Acid-base disorders in ICU patients are a common finding with the majority of patients with metabolic acidosis with lactic acidosis as the main cause.[8] In the study of Wang *et al.* showed that more than 60% of critically ill COVID-19 patients had elevated levels of CRP, LDH, and lactic acid, which correlated with the infection-induced systemic immune response and initial hypoxic conditions.[9] There is two consensus regarding the causes of increased lactate concentrations, namely the presence of lactic acidosis due to O2-demand/DO2 mismatch and hyperlactatemia with blood pH approaching normal, which in advanced conditions will be associated with conditions of metabolic stress or hereditary diseases.[10]

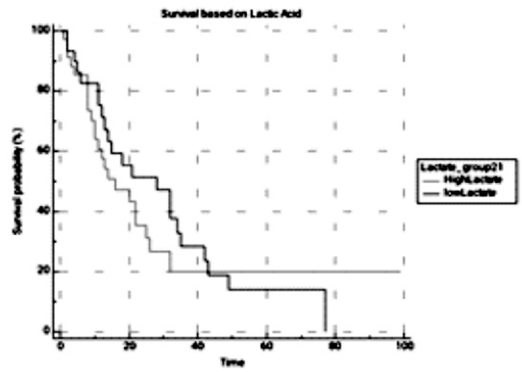

Figure 2. Kaplan Meier survival curve based on lactic acid

In Table 2, the cut-off pH value for grouping patients was 7.43. Patients with a pH of 7.43 were grouped below the median, while those >7.43 were above the median. There were 106 (56.7%) patients with pH below the cut-off value and 81 patients (43.3%) above the cut-off value. The median survival value with a pH below the cut-off value was 15 days (95% CI 13-22 days) compared to above the median

Table 2. Cut-off value, sensitivity, and specificity of laboratory examination

Variable	Cut-off	Sensitivity (%)	Specificity (%)	Group		P-value
				Low (%)	High (%)	
pH[a]	7.43			56.7	43.3	0.651
PaO2[a]	72.2	26.32	84.93	24.5	76.5	0.609
PaCO2[a]	33.9	85.1	25	80.7	19.3	0.484
HCO3[a]	19			59.4	40.6	0.363
BE[a]	-3.4	69.30	45.21	63.6	36.4	0.006

of 22 days (95% CI 18-32 days). Patients with a pH below the cut-off value had an increased risk of death compared with a pH above the cut-off value (HR 1.45 vs. 0.68, 95% CI 1.01-2.17 vs. 0.46-0.98, p=0.04).

Table 2 shows the cut-off value at PaO2 is 72.2 mmHg. Patients with PaO2 72.2 mmHg were classified as low PaO2, whereas >72.2 mmHg were high PaO2. The sensitivity of this cut-off value was 26.32%, while the specificity was 84.93% (AUC=0.522, p=0.031). From 187 ER examinations, 44 patients (24.5%) had PaO2 values below the cut-off value, and 143 patients (76.5%) were above the cut-off value. The median survival value in the low PaO2 group was 14 days (95% CI 11-20 days) compared to 21 days in the high PaO2 group (95% CI 18-32 days). Patients with a PaO2 value below the cut-off value had an increased risk of death compared to a PaO2 above the cut-off value (HR 1.53 vs. 0.64, 95% CI 1.04-2.62 vs. 0.38-0.95, p=0.03).

Table 2 also shows the cut-off value for PaCO2 at 33.9 mmHg. Patients with PaCO2 33.9 mmHg were classified as low PaCO2, while >33.9 mmHg were high PaCO2. The sensitivity of this cutoff value was 85.1%, while the specificity was 25% (AUC=0.5 p=0.150). From 187 ER examinations, 151 patients (80.7%) had PaCO2 values below the cut-off value and 36 patients (19.3%) above the cut-off value. The median survival value in the low PaCO2 group was 18 days (95% CI 15-21 days) compared to 28 days in the high PaCO2 group (95% CI 16-43 days). Patients with a PaCO2 value below the cut-off value had an increased risk of death compared to a PaCO2 above the cut-off value (HR 1.44 vs. 0.69, 95% CI 0.88-2.25 vs. 0.44-1.13, p=0.150).

Blood gas analysis examination is very crucial in determining the patient's prognosis. Hypoxemia on the patient's ER examination is the main marker in determining the severity of COVID-19 symptoms.[11] Other studies have also shown that hypoxemia can be used to determine patient mortality and is an indicator that patients require mechanical ventilation.[12,13] Often COVID-19 patients are found in a hypoxic condition too late but without symptoms, so the BGA examination can detect worsening more accurately.[14] Therefore, the PaO2 level in the ER examination is the key to determining what oxygen assistance should be given to the patient.

Changes in pH in critically ill patients admitted to the ICU are common. Several studies have shown that COVID-19 patients admitted to the intensive care unit often show an alkalotic pH.[15-17] However, the results of this study indicate that most patients with a pH below the cut-off value will increase mortality. This is in line with previous studies that acidosis is a marker of mortality in COVID-19 patients with critical symptoms.[18,19] Therefore, monitoring of BGA in critically symptomatic COVID-19 patients needs to be carried out routinely and more strictly to determine further medical action.

CONCLUSIONS AND SUGGESTIONS

From this study, it can be concluded that patients with D-dimer levels, lactic acid, and PaCO2 values above the cut-off value have worse survival, while patients with pH and PaO2 values below the cut-off have worse survival. Prospective studies are needed to assess D-dimer, lactic acid, and BGA results on the survival of COVID-19 patients with severe or critical degrees in the ICU COVID. A further study with a larger sample and multicenter is needed to validate the cut-off value of D-dimer, lactic acid, and BGA followed by their relationship with the survival prognosis of severe COVID-19 patients.

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