D-dimer levels at admission to predict mortality of ICU patients with COVID-19

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Abstract

Background: The coronavirus disease (COVID-19) was first found in Wuhan, China, on the 31st of December 2019. The spread has imposed changes in the world. Preceding studies have reported myriad laboratory values that may predict mortality in COVID-19 patients. Hence, this research aims to analyze routine laboratory testing results that can be used as a predictor of COVID-19 mortality to reduce complications, further disease progression, and in-hospital mortality
Method: This is an analytical observational retrospective study conducted at Universitas Airlangga Hospital, Surabaya, that analyzed patients' demographic and laboratory results with the mortality of COVID-19 patients in the ICU from January to June 2021. Total consecutive sampling was conducted on patients aged 18 and above with a confirmed COVID-19 diagnosis.
Results: From a total of 116 patients included in this study, 71 were deceased, with a mortality rate of 61.2%. Univariate logistic regression reveals that D-dimer levels on admission with a cut-off point of > 2000 ng/mL were associated with mortality and positively correlated with COVID-19 mortality (OR [95%]: 2.684 [1.177-6.122]; p= 0.019).
Conclusion: Elevated D-dimer at admission (>2000 ng/mL) should be used as a predictor of COVID-19 mortality to decrease the risk of complications and decrease in-hospital mortality.

Keywords: COVID-19; D-dimer; Predictor; Mortality

1. Introduction

The current coronavirus disease 2019 (COVID-19) was first found in Wuhan, China, on the 31st of December 2019. The World Health Organization (WHO) declared a COVID-19 global pandemic on the 15th of March 2020 [1]. The spread of COVID-19 has caused changes in the world, such as nationwide lockdowns, socioeconomic, political, and psychosocial, and the healthcare system with its increased burden and pressure [2]. One of the efforts in the health sector is to reduce complications and the number of deaths by knowing what factors predict COVID-19 mortality.

COVID-19 is caused by the infection of the SARS-CoV-2 virus that gains entry to the host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptors. A study conducted by Huang et al., 2020, in China reported that out of 41 patients, leukopenia (white blood cell count less than 4 x 10^9 /L) and lymphopenia (lymphocyte count <1.0 x 10^9 /L) was found during admission with a percentage of 25 and 63 respectively [3]. A study in Indonesia also revealed that lymphopenia and eosinopenia were observed in dying patients [4]. Another study in China conducted by Qu et al., 2020 discovered that the lymphocyte level at admission was related to the patient's prognosis in which patients with a lower lymphocyte and platelet count suffered a

much more severe disease and stayed longer in the hospital [5]. In addition, the platelets-to-lymphocyte ratio (PLR) was an excellent marker for determining the severity and mortality of COVID-19. PLR elevation suggests an overactive inflammatory response, resulting in a poorer patient prognosis. It was reported that high PLR values were associated with severe COVID-19, which reflects a higher degree of cytokine storm [6]. Moreover, a study by Ma et al., 2020, discovered that the neutrophil-to-lymphocyte ratio (NLR), a simple biomarker of inflammation that can be measured by routine blood workup, is associated with clinical deterioration and mortality in COVID- 19 patients. Patients with high NLR (NLR >9.8) showed a higher incidence of acute respiratory distress syndrome (ARDS) (p-value: 0.002) and a higher rate of non-invasive (p-value: 0.002) and invasive (p-value: 0.048) mechanical ventilation [7]. A study in Indonesia also reported that NLR values above 5.8 increase the likelihood of mortality by three times [8].

COVID-19 also has a close relationship with venous thromboembolism (VTE). VTE is generally observed more frequently in ICU patients and patients with a critical illness [9]. Factors that contribute to the development of VTE include hypoxia, immobilization, diffuse intravascular coagulation, and excessive inflammation [10]. D-dimer is highly predictive of increased thrombotic risk and poorer outcomes for hospitalized patients with COVID-19. Patients in the intensive care unit (ICU) reported higher D-dimer levels [11]. Elevated D-dimers were also reported with decreased survival and increased treatment requirements [12].

Currently, there is no data regarding which laboratory results are predictors of mortality in Indonesia. There also needs to be data regarding the cut-off point used in clinical settings to predict COVID-19 mortality. This situation puts clinicians in a predicament as numerous laboratory tests can be ordered for a patient. Hence, this research aims to analyze routine laboratory testing results that can be used as a predictor of COVID-19 mortality to reduce complications, further disease progression, and in-hospital mortality.

2. Method

This is an analytical observational retrospective study conducted at Universitas Airlangga Hospital in Surabaya from January to June 2021. Total consecutive sampling was conducted on patients admitted with a confirmed COVID-19 diagnosis in the ICU. Confirmation of COVID-19 diagnosis was based on the reverse transcriptase-polymerase chain reaction (RT-PCR) results. All patients aged 18 years and above were included in this study. Patients discharged upon request who died with a negative RT-PCR result and were pregnant or in the post-partum period were excluded from the study. The study collected demographic and laboratory data from patients in the ICU and compared it with the outcome of the patients. Medical records that did not meet the eligibility criteria were excluded from the study. Due to the retrospective design, no informed consent was required throughout the study.

This study obtained the association of the demographic and laboratory data by conducting the chi-square test. This study conducted a single phase of statistical analysis using SPSS Statistics Version 26. The statistical analysis was performed using the univariate logistic regression with enter method to obtain the crudes odds ratio. Variables with a p-value <0.05 are considered statistically significant.

3. Results

Out of 116 patients, 71 were deceased, with a mortality rate of 61.2%. COVID-19 patients in the ICU of Universitas Airlangga Hospital from January to June 2021 were predominated by the male gender and patients aged 18 to 60 years old, with a percentage of 62.2 and 66.7, respectively. The majority of the patients had a normal BMI. Twenty-five patients were obese, of which 68% were deceased, while only three were

malnourished, of which 33.3% were discharged. Based on the patient demographic data, there was no significant association between age, sex, and BMI towards the mortality of COVID-19 patients.

Based on the laboratory results, most deceased patients presented with lymphopenia (93%) and an increased neutrophil-to-lymphocyte ratio (NLR) (90.1%). Laboratory results showed that patients who presented with an elevated d-dimer were significantly associated with mortality (p= 0.017). Further details about the characteristics of the study are shown in table 1.

Table 1. Characteristics of the study

	Discharged (%)	Deceased (%)	P value
Patient Demography			
Age			
18-60 years old	30 (66.7)	43 (60.6)	0.641
> 60 years old	15 (33.3)	28 (39.4)	
Sex			
Male	28 (62.2)	40 (56.3)	0.665
Female	17 (37.8)	31 (43.7)	
BMI			
> 30.0 kg/m^2	8 (17.8)	17 (23.9)	0.579
< 18.5 kg/m^2	2 (4.4)	1 (1.4)	0.687
Laboratory Results			
Leukopenia	11 (24.4)	11 (15.5)	0.339
Lymphopenia	39 (86.7)	66 (93.0)	0.423
PLR (>180)	29 (64.4)	49 (69.0)	0.758
NLR (≥ 3.13)	37 (82.2)	64 (90.1)	0.340
D-dimer (> 2000 ng/mL)	11 (24.4)	33 (46.5)	0.017

Description: BMI: Body Mass Index; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio

A single-phase statistical analysis using univariate logistic regression was conducted to obtain the crudes odds ratio. No patient demography showed a statistically significant correlation with mortality. Patients who presented with obesity upon hospital admission were positively associated with mortality (OR [95%]: 1.456 [0.570-3.722]; p= 0.433). Based on the laboratory results, only patients who presented with an elevated d-dimer upon hospital admission were statistically associated with mortality (OR [95%]: 2.684 [1.177-6.122]; p= 0.019). Further details about the result of the univariate logistic regression analysis on the mortality of ICU patients with COVID-19 are shown in table 2.

Table 2. Univariate logistic regression analysis on the mortality of ICU patients with COVID-19

	Crudes OR	P value	95% C.I.	
			Lower	Upper
Patient Demography				
Age				
18-60 years old	0.768	0.508	0.351	1.678
> 60 years old	Ref	Ref	Ref	Ref
Sex				
Male	0.783	0.531	0.365	1.681

Female	Ref	Ref	Ref	Ref
BMI				
> 30.0 kg/m^2	1.456	0.433	0.570	3.722
< 18.5 kg/m^2	0.307	0.341	0.027	3.490
Laboratory Results				
Leukopenia	0.567	0.234	0.222	1.444
Lymphopenia	2.031	0.267	0.581	7.096
PLR (>180)	1.229	0.610	0.557	2.710
NLR (≥ 3.13)	1.977	0.221	0.663	5.892
D-dimer (> 2000 ng/mL)	2.684	0.019	1.177	6.122

Description: BMI: Body Mass Index; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds Ratio

4. Discussion

The main finding of this study is that D-dimer levels greater than 2000 ng/mL at admission were a predictor of mortality in ICU patients with COVID-19 at Universitas Airlangga Hospital, Surabaya. This finding provides substantial information as to how patients with a potentially poor prognosis could be identified as early as possible to prevent in-hospital mortality. Although other laboratory results were not statistically significant to be correlated with mortality, lymphopenia had the second-largest odds ratio following the D-dimer level. SARS-CoV-2 infection may lead to profound lymphopenia in patients as it causes a defect in antiviral and immune regulatory immunity by killing the T-lymphocyte cells. The viral inflammatory response comprising of innate and adaptive immunity also impairs lymphopoiesis and increases lymphocyte apoptosis hence giving rise to lymphopenia in COVID-19 patients [13, 14].

This study uses a cut-off point of D-dimer >2000 ng/mL. This was in line with the suggestion made by Zhang et al., 2020, in which d-dimers >2000 ng/mL at admission might be the optimum cut-off point that may predict COVID-19 in-hospital mortality [15]. Although only 44 patients presented with an elevated D-dimer level at admission, the in-hospital mortality of patients with elevated d-dimers is 46.5%. However, in the present study, only D-dimer levels at admission were significantly correlated with mortality. This may be due to the greater percentage of severe and critically ill patients in our hospital due to the number of patients being referred to our hospital.

D-dimers are plasmin-derived degradation products of cross-linked fibrin. It serves as a valuable marker of activation of coagulation and fibrinolysis. Before the emergence of COVID-19, D-dimers were extensively used for the diagnosis of VTE, disseminated intravascular coagulation, and to identify patients at high risk of venous thromboembolism [16]. However, since then, elevated D-dimers and thrombotic complications have been widely reported among COVID-19 patients [17].

D-dimers were one of the commonest laboratory findings in COVID-19 patients [17]. Elevated D-dimers occur due to an inflammatory response and even the cytokine storm due to the SARS-CoV-2 infection. This causes a rise in pro-inflammatory cytokines (IL2, IL6, TNF-a) due to the imbalance control by the anti-inflammatory cytokines, hence, overwhelming the coagulation cascade. The hyperinflammatory state in the body may induce dysfunction and damage to the endothelial cells resulting in excess D-dimer levels and excess thrombin generation [17,18,19].

D-dimers cause mortality in COVID-19 patients by disrupting the coagulation and anticoagulation cascade, which results in worsening COVID-19 lung pathology. COVID-19 patients in the ICU were also commonly

reported with thrombotic complications. Thrombosis may be stimulated by increasing blood viscosity and activating hypoxia-inducible transcription factor-dependent signaling pathways as a result of organ damage and hypoxemia due to SARS-CoV-2 infection [19].

5. Conclusion

In conclusion, elevated D-dimers at admission with a value of greater than 2000 ng/mL should be used as a predictor of COVID-19 mortality. Hence, immediate measurement and monitoring by clinicians are required to prevent disease complications and reduce in-hospital mortality.

Conflict of Interest
None to declare

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Ethical Considerations
This research has completed the requirements and cleared the ethical clearance from the ethical committee of Universitas Airlangga Hospital, Surabaya (UA-02-2179).

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