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Relationship of D-dimer, PT, APTT, and albumin with severity and mortality rate in covid-19 positive patients

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Abstract: COVID-19 is a global health problem that is divided into mild, moderate, and severe degrees of severity and a high mortality rate. The coagulopathy system has value in COVID-19 patients. This study aims to determine the relationship and predictive value of d-dimer, PT, aPTT, and albumin with severity and mortality in COVID-19 positive patients. The type of research used is retrospective with a cross-sectional approach. The research data were taken using a simple random sampling technique from the Medical Record Installation of Husada Utama Hospital, Surabaya in August-September 2021. Bivariate relationship data analysis used the Chi-Square test followed by a multivariate logistic regression test with cut-off values of D-dimer, PT, aPTT, and albumin each 0.5 g/mL, 14.0 sec. 36.0 seconds and 3.5 g/dL. The results of the chi-square test ($\alpha < 0.05$) showed the sig value of D-Dimer, PT, aPTT albumin with a severity level of 0.000; 0.000; 0.001; 0.001 while the value of Sig. with a mortality of 0.000; 0.047; 0.239; 0.022. The results of the multivariate logistic regression test with the degree of severity obtained the value of Sig. 0.000; 0.000; 0.021; 0.000 with a [PR] value of 16.7; 4.4; 2.7; 14.4. The results of the multivariate logistic regression test with mortality obtained the value of Sig. 0.000; 0.020; 0.273 with a [PR] value of 26.9; 2.8;1.6. There is a relationship between D-Dimer, PT, aPTT, and albumin with severity and mortality and can be used as a predictor of severity and mortality in COVID-19 patients.

Keywords: D-dimer**;** PT (*prothrombin time);* aPTT (Activated Partial *thromboplastin time);* Albumin; Severity and Mortality Rate

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) or better known as Corona Disease (COVID-19) is known to infect humans and cause severe respiratory disease (1). The number of confirmed cases of COVID-19 infection until March 28, 2020, reached 571,678 cases, Indonesia reported the first case on March 2, 2020, and continued to grow, until September 28, 2020, there had been 498,000 cases with deaths reaching 15,884 (2).

COVID-19 is manifested by several symptoms, namely fever, cough, fatigue, mild shortness of breath, sore throat, headache, conjunctivitis, and gastrointestinal problems. The infection is transmitted and spread through the respiratory tract, through human-to-human aerosol transmission, and through contact with a contaminated environment (2,3,4). COVID-19 disease has three stages of severity according to clinical findings, namely stage 1 (mild), stage II

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(moderate), and stage III (severe) (3). Laboratory examinations, especially hematology and biochemistry, have the potential to help diagnose quickly, practically, and economically as well as to assist in disease prognosis and optimization of clinical monitoring (4, 2, 5).

D-Dimer is an important prognostic factor that was found to be higher in patients with SARS CoV-2 cases (5). Overproduction of proinflammatory cytokines, systemic inflammation, and vascular endothelial damage due to COVID-19 are the main causes of coagulation disorders and hypoalbuminemia (5). The coagulation system has significant value in COVID-19 patients because most patients have coagulopathy. Dynamic monitoring of the coagulation system parameters D-dimer, PT, and aPTT can be the key to controlling COVID-19 death to prevent thrombus or disseminated intravascular coagulation (DIC) in COVID-19 patients (6).

Low serum albumin levels are important predictors of disease morbidity and mortality (7). The mechanism of albumin reduction is caused by several factors, one of which is the presence of systemic inflammation and hypercoagulability. The liver where albumin is synthesized is also involved in the clearance of clotting factors activated by fibrinolytic products; therefore, decreased albumin may be associated with coagulopathy (9, 10). Routine hemostasis tests and albumin liver function tests can be used as additional tests for early diagnosis and monitoring the gradual progression of disease severity to prevent disease progression to death (9).

MATERIAL AND METHOD

Research Design

This study is a retrospective study with a cross-sectional approach. The study was conducted by recording medical record data of COVID-19 patients to determine the relationship between the parameters D-Dimer, PT, aPTT, albumin with mortality and severity in COVID-19 positive patients.

Population and sample research

The population of this study is medical record data from October 2020 - January 2021, positive patients for COVID-19 who were hospitalized and died at Husada Utama Hospital Surabaya. The sample size of 233 patient data was obtained from the calculation of the Isaac & Michael formula.

Research Stages

Samples of patient data that met the inclusion criteria were taken using a simple random sampling technique of 233 patient data. The data taken include patient code, gender, the value of D-dimer, PT, aPTT, albumin, and comorbid. Further stages were performing data analysis and reporting the results.

Data analysis

Data analysis was carried out using the SPSS program statistically with the Chi-Square test followed by the Logistics Multivariate Regression test and analysis of the prediction model.

Ethics Statement

This research was approved by the ethics committee of the Faculty of Medicine and Health, Universitas Airlangga Surabaya, Indonesia Number 340/HRECC.FODM/VI/2021.

RESULTS AND DISCUSSION

Based on the characteristics of 233 study subjects with positive RT-PCR results (100%) divided into moderate and severe severity groups 115 patients (49%) and 118 patients (51%) respectively and the living and dead groups were

202 (87%) and 31 (13%) respectively. Patients infected with SARS-CoV-2 will experience variable disease progression. Most COVID-19 patients are asymptomatic, experiencing mild symptoms and some will progress to severe degrees. Risk factors for disease progression that are more severe in individuals with advanced age, female sex, comorbidities, and severe pneumonia can increase mortality in COVID-19-positive patients because metabolic disorders can cause decreased immunity by impairing macrophage and lymphocyte function (12, 13). Statistical analysis for D-Dimer, PT, aPTT, and albumin with severity and mortality in COVID-19 positive patients is presented in Table 1-5.

Table 1. Characteristics of D-Dimer, PT, aPTT, and Albumin in COVID-19 positive patients

Examination Parameters	**Result Characteristics**		
	Minimum	Maximum	Average ±SD
D-Dimer (µg/mL)	0.02	180.9	3.1
PT (second)	9.6	66.2	14.6
aPTT (second)	20.8	271.2	36.1
Albumin (g/dL)	2.3	5.2	3.9

Table 2. Relationship of D-Dimer with severity and mortality

		Severity		***p-value***
		Moderate	**Severe**	
D-Dimer (µg/mL)	≤ 0.5	78	6	
	> 0.5	37	112	0. 000
Total		115	118	
		Mortality		***P-values***
		Living	**Died**	
D-Dimer (µg/mL)	≤ 0.5	83	1	
	> 0.5	118	31	0. 000
Total		201	32	

Table 3. Relationship between PT and Severity and Mortality in COVID-19 Positive Patients

		Severity		***p-value***
		Moderate	**Severe**	
PT (second)	≤ 14	74	44	
	> 14	41	74	0.000
Total		115	118	
		Mortality		***p-value***
		Living	**Died**	
PT (second)	≤ 14	107	11	
	> 14	94	21	0.047
Total		201	32	

Table 4. Relationship of aPTT with Severity and Mortality in COVID-19 Positive Patients

	Severity		***p-value***
	Moderate	**Severe**	

aPTT (second)	≤ 36	93	73	
	> 36	22	45	0.001
Tota		115	118	
		Mortality		***p-value***
		Living	**Died**	
aPTT (second)	≤ 36	146	20	
	> 36	55	12	0.239
Total		201	32	

P: Uji Chi-Square

Table 5. Relationship of Albumin with Severity and Mortality in COVID-19 Positive Patients

		Severity		***p-value***
		Moderate	**Severe**	
Albumin (g/dL)	>3.5	108	68	
	≤ 3.5	7	50	0.001
Total		115	118	
		Mortality		***p-value***
		Living	**Died**	
Albumin (g/dL)	> 3.5	157	19	
	≤ 3.5	44	13	0.022
Total		201	32	

Statistical analysis of bivariate logistic regression of D-Dimer, PT, aPTT and albumin with severity and mortality using the chi-square test in this study can be seen in table 6.

Table 6. Bivariate logistic regression test of D-dimer, PT, aPTT and Albumin with severity and mortality

Parameter	***P-value***	
	Severity	Mortality
D-Dimer	0.000	0.000
PT	0.000	0.047
aPTT	0.001	0.239
Albumin	0.001	0.022

Statistical analysis using multivariate logistic regression test D-Dimer, PT, aPTT and albumin with degrees of severity and mortality in the study can be seen in Tables 7 and 8.

Table 7. Multivariate logistic regression test of D-Dimer, PT, aPTT and Albumin with severity

	Sig.	**Exp(B)**	**95% C.I. for EXP(B)**	
			Lower	**Upper**
D-Dimer	0.000	16.720	7.418	37.689

Albumin	0.000	14.487	5.057	41.504
PT	0.000	4.398	1.989	9.726
aPTT	0.021	2.699	1.161	6.272
Constant	0.000	0.065		

Table 8. Multivariate logistic regression test of D-Dimer, PT and Albumin with mortality

			95% C.I. for EXP(B)	
	Sig.	**Exp(B)**	**Lower**	**Upper**
D-Dimer	0.000	26.797	6.118	117.374
PT	0.034	2.659	1.076	6.57
albumin	0.280	1.616	0.676	3.864
aPTT	0.789	1.135	0.447	2.882
Constant	0.000	0.007		

The PR value for risk factors or the predicted value of D-dimer > 0.5 g/mL in COVID-19 patients will have a 16-fold risk of increasing the severity and a 30-fold risk of increased mortality in Covid-19 positive patients. PT values > 14 seconds will have a 4-fold increased risk of severity and a 3-fold risk of increased mortality in COVID-19 positive patients. APTT values > 36 will have a 3-fold risk of increasing the severity of COVID-19-positive patients. Albumin values <3.5 g/dL will have a 14-fold risk of increasing the severity of COVID-19 positive patients.

Increasing D-dimer and thrombotic complications have been widely reported in COVID-19 patients. Several studies have been conducted to investigate the relationship between D-dimer measurements and disease severity (11). High levels of D-dimer are an indication of the occurrence of thrombosis due to pulmonary capillary endothelial injury that contributes to the death of severe COVID-19 patients (12). Prolongation of PT >3 seconds or aPTT >5 seconds from the reference value is a marker of coagulopathy and a predictor of thrombotic complications in COVID-19 patients (13). Albumin is a protein that exerts an important homeostatic effect which is a predictive marker for risk in critically ill patients with COVID-19 (14). Hypoalbuminemia in inflammation due to SARS-CoV-2 virus infection is associated with thrombosis and poor disease prognosis (15). The coagulation pathogenesis of COVID-19 is a coagulopathy leading to intravascular coagulation (DIC) which is considered a major contributing factor to death (16).

Severe inflammatory conditions due to COVID-19 infection cause severe disruption of coagulation system hemostasis, decreased platelet count, prolonged prothrombin and activated partial thromboplastin time (PT/aPTT), increased fibrin degradation products such as D-Dimer and decreased albumin (17). COVID-19 patients with severe severity show blood clotting disorders which are characterized by increased D-dimer, prolonged PT and aPTT so that monitoring of blood clotting function in COVID-19 patients can be used as a predictor of severity and mortality and is useful for early diagnosis, prevention. and treatment in COVID-19 positive patients (14).

The limitation of this study is that this study is a retrospective one. The secondary data collection was carried out due to the high risk of COVID-19 so data collection for D-dimer, PT, aPTT, and albumin was not evenly distributed on a

regular basis in COVID-19 patients. Data were taken from only one data of D-dimer, PT, aPTT and albumin at the onset of an increase.

CONCLUSION

There is a significant relationship between D-dimer, PT, aPTT, and albumin with the severity and mortality of COVID-19 patients. Parameters D-dimer, PT, aPTT, and albumin can be used as predictors of severity and mortality in COVID-19 patients. Suggestions for further research need to do a serial examination of D-dimer, PT, aPTT, and albumin in order to find out how the pattern of increase and decrease in D-dimer, PT, aPTT and Albumin values in COVID-19 positive patients.

AUTHORS' CONTRIBUTIONS

Budi Santosa: concept and design, writing original and revising manuscript, analysis and interpretation of data, supervision and final approval of the version to be published.
Amellya Octifani: concept and design, methodology, laboratory analysis, administration, and research permission.
Junaedi Wibawa: concept and design, writing original and revising manuscript, analysis and interpretation of data, supervision and final approval of the version to be published.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute in this research are available from the corresponding author on reasonable request

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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