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Coagulation Profile and Outcomes of COVID-19 Patients at Wahidin Sudirohusodo Hospital, Makassar, Indonesia

Soraya Wildhani Jamil[1]*, Muhammad Ilyas[1], Nur Ahmad[2], Syakib Bakri[3], Tutik Hardjianti[4], Muhammad Lutfi Parewangi[5], Arifin Seweng[6]

[1]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [2]Department of Internal Medicine, Division of Pulmonology and Respiratory, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [3]Department of Internal Medicine, Division of Nephrology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [4]Department of Internal Medicine, Division of Hematology Oncology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [5]Department of Internal Medicine, Division of Gastroentero Hepatology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [6]Department of Biostatistics, Public Health Faculty, Hasanuddin University, Makassar, Indonesia

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***Correspondence:** Soraya Wildhani Jamil, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.
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Abstract

BACKGROUND: Coronavirus disease 2019 (COVID-19) is a viral pneumonia that spreads rapidly globally and was designated a pandemic by the World Health Organization (WHO). The number of cases has exceeded 15,000,000 worldwide, and the disease carries a mortality rate of ± 4%. One of the complications of COVID-19 is the incidence of coagulopathy and thromboembolism. The coronavirus (SARS-CoV-2) activates inflammatory and thrombotic processes, and the presence of coagulopathy and abnormal coagulation parameters is among the most significant biomarkers for poor prognosis in COVID-19 patients. COVID-19-associated coagulopathy is characterized by a decreased platelet count and the presence of a cytokine storm, indicating an extreme hypercoagulable state.

AIM: This study aims to determine the coagulation profile and outcomes of patients with moderate-severe COVID-19.

METHODS: This study was conducted in Wahidin Sudirohusodo Hospital. Medical record data were included for all inpatients diagnosed with COVID-19 using the RT-PCR test, from January 2021 to August 2021. The Kolmogorov–Smirnov normality test, Chi-squared test, odds ratio (OR), Mann–Whitney U-test, and independent t-test were used for statistical analysis. Multivariate analysis was carried out using the multiple logistic regression – backward Wald method. $p < 0.05$ was taken as statistically significant.

RESULTS: A total of 231 patients with confirmed COVID-19 were included in this study. The mean prothrombin time (PT), D-dimer, and fibrinogen were higher in severe COVID-19 patients than in moderate patients and had significant results. Platelet (PLT) levels were not found to be significant in moderate-severe COVID-19. The relationship between groups of coagulation marker variables was found to be significantly associated with moderate-severe COVID-19. All coagulation markers were significantly related to patient outcome ($p < 0.05$). The mean value of each variable was found to be higher in patients who died than in those with better outcomes.

CONCLUSION: An increase in PT, activated partial thromboplastin time (APTT), and fibrinogen is associated with mortality in patients with moderate COVID-19. In patients with severe COVID-19, mortality is associated with increased PT. PT is, therefore, a coagulation marker that is significantly related to COVID-19 outcome.

Introduction

Coronavirus disease 2019 (COVID-19) is a viral pneumonia that has recently spread rapidly globally [1], [2] and was declared a pandemic on March 11, 2020, by the World Health Organization (WHO) [3]. The first case of COVID-19 in Indonesia was announced on March 2, 2020, approximately 4 months after the first case in China [4].

Various clinical manifestations of COVID-19 have been reported, including fever, cough, shortness of breath, muscle aches, headache, painful swallowing, rhinorrhea, chest pain, diarrhea, and nausea/vomiting. Approximately 8–19% of cases progress to acute respiratory distress syndrome (ARDS), particularly in elderly patients and those with multiple comorbidities [5], [6], [7].

One of the complications of COVID-19 is the incidence of coagulopathy and thromboembolism, as SARS-CoV-2 activates inflammatory and thrombotic processes. Mononuclear cells interact with activated platelets and the coagulation cascade, which activates inflammatory cells by binding to thrombin and tissue factor (TF) with the protease-activated receptor (PAR), and to fibrin at toll-like receptor 4 (TLR4). Activation of inflammatory cells results in the release of pro-inflammatory cytokines, which leads to the breakdown of natural coagulation pathways and cessation of fibrinolysis [8], [9].

Coagulopathy and abnormal coagulation parameters are the most significant biomarkers for poor

prognosis in COVID-19 patients [10], [11]; in particular, D-dimer and prothrombin time (PT) are notable indicators of COVID-19 severity [12], [13]. Coagulopathy associated with COVID-19 is characterized by thrombocytopenia, prolonged PT, and raised D-dimer, fibrinogen, factor VIII, and von Willebrand factor. A reduced platelet (PLT) count and the presence of a cytokine storm indicate an extreme hypercoagulable state [10], [14], [15].

This study aims to determine the coagulation profile outcomes of patients with moderate-severe COVID-19.

Methods

This study was performed retrospectively using secondary data from patients' medical records. The research was carried out at Wahidin Sudirohusodo Hospital, Makassar, Indonesia, over a period from January to August 2021. Our Institutional Review Board approved all protocols used in this study (number 7039/UN4.6.8/TP.02.02/2021).

Sample

The patients in this study were all hospitalized at Wahidin Hospital, Makassar (Indonesia), with COVID-19, which was confirmed using an RT-PCR test. The information used for this study was secondary data from patients' medical records. The total sampling technique was performed for subjects who met the inclusion criteria of this study. The inclusion criteria were as follows: Age >18 years, confirmed COVID-19 (positive RT-PCR results), and complete laboratory data available (PLT, PT, D-dimer, and fibrinogen). The exclusion criteria for this study were cancer, pregnancy, chronic liver disease, hematologic malignancy, surgery or trauma within 30 days, acute coronary syndrome, and patients without PLT, PT, D-dimer, and fibrinogen testing on admission.

Sampling methods

Samples were collected from patients at Wahidin Sudirohusodo Hospital using purposive sampling based on the established research criteria and PCR results. Information was collected on PLT (normal range 150 × 10^3–400 × 10^3/μl), PT (normal value 10–14 s), D-dimer (normal value < 0.5 μg/ml), and fibrinogen (normal value 150–375 mg/dL).

Data analysis

Data analysis was performed using SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). The statistical analysis performed was descriptive statistical calculation and frequency distribution. Data distribution was evaluated using the Kolmogorov–Smirnov test. Mean differences were determined using the Chi-squared, Mann–Whitney, and Kruskal–Wallis tests. The results of the statistical analysis were deemed significant at $p < 0.05$.

Results

Data characteristics

This study was conducted using patients aged >18 years who were diagnosed with COVID-19 using RT-PCR at the Infection Center of Wahidin Sudirohusodo Hospital from January 2021 to August 2021. A total of 231 subjects met the inclusion criteria for this study. The distribution of variable categories in the patient population (including sex, age, PT, D-dimer, and levels of PLT and fibrinogen) is shown in Tables 1 and 2.

Table 1: Coagulation parameters in patients with COVID-19

Variable	Min	Max	Median	Mean	SD
PLT counts (×10^3) (/μl)	4.0	814.0	271.00	284.95	142.56
PT (s)	9.40	109.00	11.40	12.94	9.02
D-dimer (μg/ml)	0.05	82.50	1.92	5.91	13.02
Fibrinogen (mg/dl)	129.3	864.0	430.20	461.49	147.75

Table 3 shows the relationship between coagulation variables in moderately severe COVID-19 and patient outcome. A prolonged PT (>14 s) and activated partial thromboplastin time (APTT) (>30 sec) were found to be significantly associated with patient death, while PLT, D-dimer, and fibrinogen were not ($p > 0.05$).

Table 2: Patients characteristic

Variable	n	%
Sex		
Male	126	54.5
Female	105	45.5
Age* (years)		
<45	69	29.9
45–59	92	39.8
≥60	70	30.3
PLT		
Normal	195	84.4
Decreased	36	15.6
PT		
Normal	203	87.9
Prolonged	28	12.1
D-dimer		
Normal	38	16.5
Elevated	193	83.5
Fibrinogen		
Normal	61	26.4
Elevated	170	73.6

*As categorized by the WHO.

From the information in Table 3, a multivariate test was performed to determine the variables with the strongest influence on the outcomes of patients with moderate COVID-19 and found that a prolonged PT increased their risk of death by 15.067 times (Table 4).

Table 5 shows the relationship between coagulation variables and outcomes for patients

Table 3: Correlation between coagulation variables and outcomes in patients with moderate COVID-19

	Outcome		p-value*
	Alive	Died	
PLT			
Normal			
n	111	84	0.370
%	56.9	43.1	
Decreased			
n	12	24	
%	33.3	66.7	
PT			
Normal			
n	113	5	0.017
%	95.8	4.2	
Prolonged			
n	3	2	
%	60.0	40.0	
APTT			
Normal			
n	89	3	0.045
%	96.7	3.3	
Prolonged			
n	27	4	
%	87.1	12.9	
D-dimer			
Normal			
n	26	1	0.614
%	96.3	3.7	
Elevated			
n	90	6	
%	93.8	6.3	
Fibrinogen			
Normal			
n	38	4	0.186
%	90.5	9.5	
Elevated			
n	78	3	
%	96.3	3.7	

*Chi-squared test.

with severe COVID-19. The variables PT, APTT, and fibrinogen were found to be significantly associated with severe COVID-19 patient outcome ($p < 0.05$), while PLT and D-dimer were not associated ($p > 0.05$).

Table 4: Results of multivariate analysis of variables with mortality in patients with moderate COVID-19

Step	Variable	B	S.E.	Wald	p-value	OR	95% C.I	
							Lower	Upper
Step 1	PT	2.079	1.173	3.145	0.076	8.000	0.803	79.655
	APTT	0.905	0.941	0.924	0.336	2.472	0.391	15.646
Step 2	PT	2.712	1.021	7.060	0.008	15.067	2.037	111.426

Multiple logistic regression – backward Wald method, R^2=0.144.

From the information in Table 5, a multivariate test was performed to determine the variables with the strongest influence on severe COVID-19 patient outcome. The results of this analysis showed that PT, APTT, and fibrinogen remained influential, with a risk of 6.312 (95% CI 1.451–27.466), 3.127 (95% CI 1.148–8.516), and 7.909 (95% CI 1.510–41.416), respectively (Table 6).

Discussion

The results of this study show that coagulation markers are significantly related to COVID-19 patient outcome ($p < 0.05$). The mean value of each coagulation marker was found to be greater in patients with severe outcomes than in those with moderate outcomes. This is consistent with the results of a study conducted by Long *et al.* using 115 patients with confirmed COVID-19, which found that 23 patients who died had an elevated D-dimer, while 18 others had a prolonged PT [13]. Another study by Sayad *et al*. in Iran found the overall mortality rate in 74 patients with severe COVID-19 to be 52.7% [16].

Table 5: Relationship between coagulation variables and patient outcome in patients with severe COVID-19

	Outcome		p-value*
	Alive	Death	
PLT			
Normal			
n	50	34	0.121
%	59.5	40.5	
Decreased			
n	10	14	
%	41.7	58.3	
PT			
Normal			
n	56	29	0.001
%	65.9	34.1	
Prolonged			
n	4	19	
%	17.4	82.6	
APTT			
Normal			
n	48	18	<0.001
%	72.7	27.3	
Prolonged			
n	12	30	
%	28.6	71.4	
D-dimer			
Normal			
n	9	2	0.064
%	81.8	18.2	
Elevated			
n	51	46	
%	52.6	47.4	
Fibrinogen			
Normal			
n	16	3	0.012
%	84.2	15.8	
Elevated			
n	44	45	
%	49.4	50.6	

Our study shows that coagulation factor most strongly associated with mortality in COVID-19 patients is PT, and our results show that a prolonged PT increases the risk of death from moderate COVID-19 by 15.067 times. PT prolongation indicates activation of the coagulation cascade and the consumption of coagulation factors in COVID-19.

Table 6: Results of multivariate analysis of variables with mortality in patients with severe COVID-19

Step/variable		B	S.E.	Wald	p-value	OR	95% C.I	
							Lower	Upper
Step 1	PT	1.842	0.750	6.031	0.014	6.312	1.451	27.466
	APTT	1.140	0.511	4.976	0.026	3.127	1.148	8.516
	Fibrinogen	2.068	0.845	5.994	0.014	7.909	1.510	41.416

Multiple logistic regression – backward Wald method, R^2=0.357.

A study by Yao *et al.* [17] also found that D-dimer levels >2.14 mg/L could predict mortality with a sensitivity of 88.2% and a specificity of 71.3%. In contrast, Poudel *et al.* [18] reported a lower D-dimer value for predicting mortality, with a cutoff point of 1.5 mg/L, 70.6% sensitivity, and 78.4% specificity. It should be noted that some underlying conditions or diseases, such as diabetes, cancer, stroke, and pregnancy, can trigger an unrelated increase in D-dimer in COVID-19 patients, and D-dimer is, therefore, one of the most commonly elevated coagulation factors. D-dimer may also be used to indicate prognosis and mortality in COVID-19 patients [17], [19].

Fibrinogen is one of the coagulation parameters that are often found to be elevated in COVID-19 patients [10], [20], [21]. Several systematic reviews and meta-analyses have shown that fibrinogen

can be used as an indicator of COVID-19 disease progression. Fibrinogen has been found to be increased in patients with severe COVID-19 compared to those with mild disease. A cohort study by Micco *et al.* [22] reported that fibrinogen was significantly increased in a cohort of COVID-19 patients with ARDS, compared to patients without ARDS. Micco *et al.* also found that an increase in serum fibrinogen level of 617 mg/dl on initial hospital admission could help to identify patients at risk of ARDS with a sensitivity of 76% and a specificity of 79%. Long *et al.* [23] also conducted a retrospective cohort study with 1643 patients to determine the role of fibrinogen levels in the prognosis of COVID-19 patients. Their results found that patients with fibrinogen levels of < 2.2 g/L and > 4.2 g/L had a higher risk of mortality compared to patients with fibrinogen levels between 2.2 and 4.2 g/L. In addition, abnormal fibrinogen levels have been associated with increased risk of severe disease progression. This suggests that fibrinogen may serve as a prognostic indicator in hospitalized COVID-19 patients. Increased fibrinogen in COVID-19 patients is correlated with increased levels of IL-6 (a biomarker of inflammation) and with lung injury due to inflammation or viral effects on lung tissue [20], [24].

This study found significant mean differences in PT, APTT, and fibrinogen levels in patients with moderate and severe COVID-19, with higher levels in severe cases than in moderate ($p < 0.05$). However, PLT levels were not significantly associated with moderate or severe COVID-19. This is consistent with the results of a meta-analysis by Zhang *et al.* [25] which found that the levels of PT, D-dimer, and fibrinogen were higher in severe COVID-19 compared to mild, but that PLT levels were lower in severe cases than in mild cases. A retrospective study conducted by Xu *et al.* [26] on 1131 patients found that patients with mild COVID-19 had a slightly higher PT, INR, and APTT levels, while D-dimer was significantly higher in patients with severe COVID-19. A study by Zou *et al.* [27] also reported that the median D-dimer in patients with severe COVID-19 was higher compared to those with mild disease (1.04 compared to 0.43, $p < 0.05$).

In patients with severe COVID-19, PT, APTT, and fibrinogen are significantly associated with patient outcome ($p < 0.05$), but PLT and D-dimer are not ($p > 0.05$). A multivariate analysis showed that PT, APTT, and fibrinogen levels influence the outcomes of patients with severe COVID-19, with ORs of 6.312 (95% CI 1.451–27.466), 3.127 (CI 95% 1.148–8.516), and 7.909 (95% CI 1.510–41.416), respectively.

In terms of the limitations of this study, it should be noted that no assessment was performed of the risk factors that can affect the severity of COVID-19 in patients. Based on the results of this study, we would recommend that intervention be carried out immediately in COVID-19 patients who experience coagulation disorders, and that vital signs be monitored stringently.

Conclusion

An increase in PT, APTT, and fibrinogen is associated with mortality in patients with moderately severe COVID-19, and an increase in PT is associated with mortality in patients with severe COVID-19. PT is a coagulation marker significantly related to patient outcome.

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