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Comparison of Coagulation Parameters between Severe and Non-severe COVID-19 Patients Treated in a Tertiary Hospital in Indonesia

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Abstract

Objective: To determine the differences in coagulation features in patients with severe versus non-severe COVID-19.

Method: During the period of the study from July 2020 to June 2021, 371 COVID-19 patients were treated at Dr. Hasan Sadikin General Hospital Bandung, Indonesia. These patients were divided into two groups based on the WHO criteria into severe COVID-19 with clinical signs such as severe acute respiratory syndrome to respiratory failure and non-severe cases with no respiratory symptoms. Data analyzed were Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR), fibrinogen, D-dimer, and platelet count.

Results: Median INR was significantly higher in patients with severe cases than in non-severe cases (1.04 vs. 0.94, p<0.001), which was also true for median PT (12.3 vs. 12.0 sec, p=0.030) and median fibrinogen (522 vs. 428.5 mg/dL, p=0.004). Similarly, the median D-dimer was significantly higher in severe patients (1.91 vs. 0.75 mg/dl, p<0.001). Median aPTT and platelet count were in normal limits for both severe and non-severe COVID-19 patients (28.6 vs. 29.15 sec, p>0.652 and 246 vs. 242 $x10^3/mm^3$, p>0.924, respectively).

Conclusions: The INR, PT, fibrinogen, and D-dimer can be considered as features that can be used to predict the severity of the disease and to choose the proper treatment for COVID-19 patients.

Keywords: Coagulopathy disorders, COVID-19, severe acute respiratory syndrome, non-severe acute respiratory syndrome

Introduction

The Coronavirus Disease 2019 (COVID-19) is declared a global pandemic by the WHO in March 2020. Even though the pandemic status has ended, the disease is still a global problem, including Indonesia, especially because it leads to severe complications, deathd, and prolonged consequences. Findings from everal previous studies have demonstrated that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2)—which is widely expressed in various human tissues such as lungs, gastrointestinal tract, hearth, kidney, and blood vessel endothelium—as a receptor at the cellular level to facilitate the infection process. These tissues serve as the entry points for SARS-CoV-2 infection and replication through a direct cytopathic effect.[1-3] The clinical manifestations of this disease include a broad spectrum, starting from mild symptoms to severe symptoms such as Acute Respiratory Distress Syndrome (ARDS), multiple organ failure, COVID-19 Associated Coagulopathy

(CAC), and death.

COVID-19 Associated Coagulopathy or CAC is associated with disease morbidity and mortality. The most common manifestation of CAC is venous thromboembolism (VTE), such as deep vein thrombosis (DVT) or pulmonary embolism (PE). The high incidence of VTE in COVID-19 patients reveals the importance of coagulation parameter examinations to make a diagnosis and, eventually, treat the patient.[4-8] This coagulation parameter is a quantitative parameters used to assess the progression of COVID-19. These parameters consists of D-dimer, platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized number (INR), and fibrinogen.[8, 9] Understanding these parameters will enable the clinicians to differentiate between severe and non-severe COVID-19 that will lead to accurate and quick diagnosis and proper treatment. This study was conducted to determine the differences in coagulation parameters between severe and non-severe COVID-19 in patients treated in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Methods

This was a retrospective analytical descriptive study using the medical records of COVID-19 patients treated in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, during the period of June 2020 to July 2021. The sample of this study were medical records from 317 COVID-19 patients, divided into two groups of severe and non-severe COVID-19. The inclusion criteria were age over 18 years with severe and non-severe COVID-19. Patients with severe COVID-19 were defined as those having clinical signs of severe acute respiratory syndrome to respiratory failure. Meanwhile, non-severe patients were patients with no respiratory symptom COVID-19 according to the WHO criteria. Exclusion criteria are patient with previous anticoagulant treatment and those with hemostasis disorders, autoimmune disease, and neoplasm. Pregnant patients were also excluded. Data collected were analyzed using the Mann-Whitney test. This study has been approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General

Table 1 Subject Characteristics

Variable	Group		p-value
	Severe COVID-19 n=99	Non-severe COVID-19 n=218	
Age (years old), median (min-max)	57 (29–89)	52 (19–88)	<0.001[a]*
Gender, n (%)			
Female	43 (43.4)	109 (50.0)	0.278[b]
Male	56 (56.6)	109 (50.0)	
Comorbidities, n (%)			
Yes	75 (75.8)	112 (51.4)	<0.001[b]*
No	24 (24.2)	106 (48.6)	
Type of Comorbidity, n (%)			
Hypertension	45 (45.5)	61 (28.0)	0.002[b]*
Diabetes Mellitus	26 (26.3)	34 (15.6)	0.025[b]*
Cardiovascular Disease	17 (17.2)	14 (6.4)	0.003[b]*
Chronic Kidney Disease	6 (6.1)	6 (2.8)	0.202[c]
Chronic Pulmonary Disease	4 (4.0)	4 (1.8)	0.263[c]
Neurological Disease	3 (3.0)	3 (1.4)	0.381[c]
Liver Disease	2 (2.0)	1 (0.5)	0.231[c]
Rheumatic Disease	1 (1.0)	1 (0.5)	0.528[c]
HIV/AIDS	0 (0.0)	1 (0.5)	1.000[c]

[a]Mann Whitney test, [b]Chi Square test, [c]Fisher Exact test, * p<0.05

Table 2 Coagulation Parameters and the Clinical Outcomes

Variable	Groups		*P* value
	Severe COVID-19 n=99	Non-severe COVID-19 n=218	
Laboratory, median (min-max)			
Days of illness (th days)	8 (5–10)	6 (3–9)	0.001[a]*
INR	1.04 (0.93–1.14)	0.94 (0.89 –1.00)	<0.001[a]*
PT (seconds)	12.3 (11.0–14.2)	12.0 (10.5–13.6)	0.030[a]*
aPTT (seconds)	28.6 (24.3–34.7)	29.15 (24.8–33.0)	0.652[a]
Fibrinogen (mg/dL)	522 (350–680)	428.5 (329–564)	0.004[a]*
D-Dimer (mg/dL)	1.91 (0.80–9.57)	0.75 (0.40–1.82)	<0.001[a]*
Platelet (x10^3/mm^3)	246 (172–309)	242 (179–307)	0.924[a]
Outcome, n (%)			
Survival	62 (62.6)	203 (93.1)	<0.001[b]*
Death	37 (37.4)	15 (6.9)	

Median (IQR), [a]uji Mann Whitney, [b]uji Chi-Square, * p<0.05

Hospital, Bandung, Indonesia, under the ethical clearance No. LB.02.01/X.6.5/323/2021.

Results

Subject who met the inclusion and exclusion criteria were divided into two groups based on their severity of disease (99 patients with severe COVID-19 patients and 218 patients with non-severe COVID-19). The primary characteristics of the patients are described in Table 1.

Based on the data in Table 1, age, presence of comorbidities, as well as hypertension, diabetes mellitus, and cardiovascular disease as commorbidities are significantly different between the two groups (p<0.05). The median age of severe COVID-19 patients was 57 years old (range: 29–89 years old), while the median for non-severe COVID-19 patients were 52 years old(range: 19–88 years old). Severe COVID-19 patients had more comorbidities than non-severe COVID-19 patients (75.8% vs. 51.4%, p<0.001). Of all patients in severe COVID-19 group with comorbidities, 45.5% suffered from hypertension, 26.3% experienced diabetes mellitus (DM), and 17.2% had cardiovascular disease (CVD). In contrast, the majority of patients in the non-severe COVID-19 group with commorbidities had hypertension (28.0%), followed by DM (15.6%) and CVD (6.4%).

Table 2 presents the significant differences in days of illness, INR, PT, Fibrinogen, D-Dimer, and patient outcomes between the two groups (p<0.05). The median illness day of the severe COVID-19 group was higher than that of the non-severe COVID-19 group (p=0.001). The median INR and PT of the severe COVID-19 group were significantly higher than the non-severe COVID-19 group with p<0.001 and p=0.030, respectively. The severe COVID-19 group had median fibrinogen and D-dimer levels that were higher than in the non-severe COVID-19 group (p=0.004 and p<0.001, respectively). The mortality percentage in the severe COVID-19 group was higher than in the non-severe COVID-19 group (p<0.001).

Discussion

During the peak of the COVID-19 pandemic, the number of new cases increased sharply from day to day, accompanied by the identification of varying manifestations of disease. The basic pathogenesis of coagulopathy in COVID-19, as described in the Virchow's Triad theory, consists of three pathological processes of endothelial injury/damage, hypercoagulable state, and stasis. Endothelial damage occurs due to the direct invasion of the SARS-CoV-2 virus through the ACE2 receptor, the effects of pro-inflammatory cytokines, the release of various acute phase proteins, and the activation of the complement system, as well as the use of various intravascular catheters that stimulate

local inflammation. Stasis conditions, such as observed in patients with severe symptoms in the intensive care unit, prevents smooth blood flow in the blood vessels so that coagulation factors may concentrate in one location and then be activated, stimulating thrombosis.[10] In this study, clinically day off illness and survival date were significantly different in the two groups. All coagulation marker parameters increased in the severe group when compared to the non-severe Covid 19 group. These results aligned with previous studies.[11-14] Many patients infected with COVID-19 have mild or even no symptoms while some patients develop severe and critical cases that lead to multi-organ failures, including respiratory failure that will eventually lead to death if not treated properly. Inflammation, as well as immune system responses, play an important role in the pathophysiology of COVID-19, which is characterized by a significant increase in levels of pro-inflammatory cytokines.[10] In COVID-19, local and systemic inflammations cause a hypercoagulable state that eventually will lead to the disruption of the coagulation and fibrinolysis system balance. Hypercoagulation and hypofibrinolysis will trigger thrombosis in COVID-19 patients. Since a lot of ACE2 receptors are utilized by SARS-COV-2 to invade the human tissues, there is less ACE2 receptors available for angiotensin II (AT-II), and hence more AT-II is circulated. The virus and AT-II will together increase the production of plasminogen activator inhibitor 1 (PAI-1), which will establish a systemic pro-coagulant environment in the patients' circulation.[10] In COVID-19, the identification parameters or markers to predict disease progression is very important. Coagulation parameters are one of the markers to predict disease progression when the patient is admitted to the hospital. In this study, the median of aPTT in the two groups were not significantly different and was in a normal state. These results align with a past study in China which shows similar results.[15] On the other hand, PT and INR in severe COVID-19 patients are significantly higher than in the non-severe patients. Endothelial damages in COVID-19 exposes subendothelial tissue factor (TF) which will activate the extrinsic coagulation pathway. Furthermore, the tissue factor pathway inhibitor (TFPI), which inhibits the extrinsic coagulation pathway, is impaired by COVID-19. These mechanisms may explain why PT and INR, depicting the extrinsic coagulation pathway, are affected more significantly than aPTT which depicts the internal coagulation pathway.[12] The median of fibrinogen levels in the severe COVID-19 patients in this study was higher than in non-severe patients. Fibrinogen is one of acute-phase proteins synthesized by the liver as a response to stimulations from inflammatory cytokines and is involved in fibrin production of the final step of coagulation activity and its level increases in a hypercoagulable state.[13,14.] The median of D-dimer in the severe group was significantly higher than in the non-severe group. D-dimer is a specific cross-linked fibrin degradation product. D-dimer levels depict the process of fibrinolysis which will increase in a hypercoagulable state. D-dimer levels will increase as the severity of COVID-19 increases. D-dimer is one of the most established parameters used in monitoring hypercoagulable state in COVID-19.[12,14] The median platelet count of the two groups was still within normal limits. In contrast, several multicenter studies showed a higher incidence of thrombocytopenia in severe COVID-19 patients than in non-severe COVID-19 patients. The difference in the time when the platelet count is performed, in the beginning or middle of hospitalization, could cause this difference.[15, 16]

Some potential confounding factors in this study, such as liver and kidney diseases, were not analyzed, so parameter values do not fully depict coagulopathy merely due to COVID-19. In conclusion, INR, PT, fibrinogen, and D-dimer values increase significantly in severe COVID-19 cases and can be considered as a predictor of the severity of the disease and in choosing the appropriate treatment for COVID-19 patients. Thus, INR, PT, fibrinogen, and D-dimer measurements should be considered when predicting the severity of the disease and to choose the right treatment for COVID-19 patients.

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