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Research Article

Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen, and D-dimer in Coronavirus Disease 2019 Outcome

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Abstract: COVID-19, caused by SARS-CoV-2 has been reported to be associated with coagulopathy and DIC. This study aimed to investigate the profiles and differences of PT, APTT, fibrinogen, and D-dimer in COVID- 19 outcome. This retrospective cohort was conducted at Central Laboratory Clinical Pathology Department of dr. Cipto Mangunkusumo Hospital from July – December 2020. Demographic, clinical, and laboratory data were extracted from EHR and compared between poor and good outcome. Ninety-seven subjects were confirmed positive COVID-19, 45 of whom (46.4%) were in poor outcome group, while 52 subjects (53.6%) were in good outcome group. Median of PT 11.0″ (9.7-28.3), APTT 38.4″ (23.9-121), fibrinogen 484.8 mg/dL (51.2-940.9), and D-dimer 1,800 μg/L (190-35,200). Longer PT, APTT, and higher D-dimer ($p < 0.05$), while lower fibrinogen ($p > 0.05$) was found in poor outcome group. There were significant differences of PT, APTT and D-dimer in COVID-19 outcome.

Keywords: APTT; Covid-19; D-dimer; fibrinogen; outcome; PT

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1. Introduction

An outbreak of pneumonia of unknown origin from Wuhan, China has expanded globally, infecting many individuals and became known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus Disease 2019 (COVID-19). This virus causes respiratory, gastrointestinal and hepatic Neurological illnesses have various clinical presentations and spectrums. Patients who are infected with coronavirus may present with symptoms of upper respiratory tract infection, including rhinorrhea and sore throat [1]. The most common clinical signs are fever, cough, and shortness of breath, which can progress to acute respiratory distress syndrome (ARDS), abrupt heart damage, and even death [2]. The most prevalent general symptoms at the onset of the disease were fever (98.6%), dry cough (59.4%), lethargy (69.6%), dyspnea (31.2%), and myalgia (34.8%) in 138 hospitalized patients in the study. Headache, abdominal pain, vertigo, nausea, vomiting, and diarrhea are among the less prevalent symptoms of SARS-CoV-2 infection [3].

Despite the broad definition of the clinical characteristics of COVID-19, an outline of the most representative laboratory abnormalities found in patients with COVID-19

infection is still lacking, to the best of our knowledge. COVID-19 can cause abnormalities in many laboratory parameters including hematology, clinical chemistry, immunology, and hemostasis which might affect its outcome. Some studies related COVID-19 stated that COVID-19 could cause organ disfunction, coagulopathy, and disseminated intravascular coagulation (DIC) which may lead to death. Higher D-dimer and fibrinogen levels, as well as longer PT (Prothrombin Time) and APTT (Activated Partial Thromboplastin Time), have been linked to more severe COVID-19 [3,4].

According to Wang et al. (2020) prolonged PT (45.7%), APTT (42.6%), fibrinogen (45.7%), and D-dimer (88.6%) were associated with deteriorating COVID-19 or even mortality.[5] In contrast, there have been little studies in Indonesia on the variations in PT, APTT, fibrinogen, and D-dimer in COVID-19 outcomes. The purpose of this study was to look into the profiles and differences of PT, APTT, fibrinogen, and D-dimer in COVID-19 outcomes.

2. Results

As shown in Table 1, there were 97 subjects enrolled, 45 of whom (46.4%) were in poor outcome, while 52 subjects (53.6%) were in good outcome Forty-nine subjects (50.5%) were female, while majority of subjects (51.1%) in poor outcome group were male. Median age of subjects in poor outcome group was 56 years old, older than median age of all subjects. Most subjects (58.8%) were moderate COVID-19 cases, followed by severe COVID-19 cases (18.5%) of 97 subjects, 74 subjects had many different comorbidities such as hypertension, DM, obesity, and others (kidney, cardiovascular, liver, autoimmune diseases, malignancies, major surgeries, asthma, stroke, polycythemia, and burns) as the most dominant comorbidities (50.5%). Median PT, APTT, fibrinogen, and D-dimer of all subjects were 11 seconds, 38.4 seconds, 484.8 mg/dL, and 1800 μg/L respectively.

Table 1. Characteristics of Subjects

Characteristic	Outcome		Total (n=97)
	Poor (n=45)	Good (n=52)	
Gender, n (%)			
Male	23 (51.1)	25 (48.1)	48 (49.5)
Female	22 (48.9)	27 (51.9)	49 (50.5)
Age (years old)	56 (18-82)	47.5 (18-84)	54 (18-84)
Clinical spectrum, n (%)			
Mild	1 (2.2)	15 (28.8)	16 (16.5)
Moderate	23 (51.1)	34 (65.4)	57 (58.8)
Severe	15 (33.3)	3 (5.8)	18 (18.5)
Critical	6 (13.3)	0	6 (6.2)
Comorbidity, n (%)			
Hypertension	15 (33.3)	15 (28.8)	30 (30.9)
DM	19 (42.2)	10 (19.2)	29 (29.9)
Obesity	2 (4.4)	4 (7.7)	6 (6.2)
Others	30 (66.7)	19 (36.5)	49 (50.5)
Laboratory			
PT (second)	11.9 (9.8-28.3)	11.1 (SD 1.1)	11.0 (9.7-28.3)
APTT (second)	44.4 (28.2-121)	34.7 (23.9-93.4)	38.4 (23.9-121)
Fibrinogen (mg/dL)	483.9 (51.2-940.9)	495 (160.2-900)	484.8 (51.2-940.9)
D-dimer (μg/L)	3900 (420-35200)	1055 (190-35200)	1800 (190-35200)

Bivariate analysis was done among PT, APTT, fibrinogen, and D-dimer between poor and good outcome group as shown in Table 2. Longer PT, APTT, and higher D-dimer were found in poor outcome group, while fibrinogen was found lower in poor outcome group. There was no significant difference in fibrinogen between groups (Mann-Whitney U test, $p>0.05$). However, there were significant differences (Mann-Whitney U test, $p<0.05$) in PT, APTT, and D-dimer across groups.

Table 2. Differences of PT, APTT, Fibrinogen, and D-dimer in COVID-19 Outcome

Parameter	Outcome		P value
	Poor	Good	
PT (second)	11.9 (9.8-28.3)	11.1 (SD 1.1)	0.000[m]
APTT (second)	44.4 (28.2-121)	34.7 (23.9-93.4)	0.000[m]
Fibrinogen (mg/dL)	483.9 (51.2-940.9)	495 (160.2-900)	0.948[m]
D-dimer (μg/L)	3900 (420-35200)	1055 (190-35200)	0.000[m]

[m)]Mann-Whitney U test

3. Discussion

In our analysis, there was a little female predominance over male COVID-19 instances (50.5%), while more male participants had poor outcomes. Jin et al. (2020), found that men and women were equally susceptible to COVID-19, but men were more likely to die. Jin et al. (2020), found that there were 2.4 times more men than women among deceased patients. Not only are circulating ACE2 levels higher in males than in women, but the X chromosome and estrogen hormones have a protective role in adaptive immune processes [10,11].

The median age of participants in the bad outcome group was 56 years old, which was higher than the median age of both all and excellent outcome subjects. Similar to this study, Karyono et al. (2020), stated that subjects in the productive age (18-59 years old) dominated COVID-19 incidence in Indonesia; additionally, the aging process may cause a lack of immune system, and most elderly subjects contracted multimorbidities, making them more vulnerable to the worsening of COVID-19 [11].

Clinical spectrum of subjects with poor outcome was dominated by moderate, severe, and critical cases respectively. This finding was different from previous study. Terwangne, et al. (2020), discovered that the proportion of death and worsening were highest in critical case, followed by severe and moderate cases respectively [12]. This might be due to the difference of total subjects enrolled and characteristics.

Most subjects had comorbid diseases. The most dominant was others, followed by hypertension, and DM. This finding was consistent with Karyono, et al. (2020). Chronic diseases share proinflammatory state which may aggravate COVID-19 infection, People with unstable blood pressure frequently had more renin angiotensin aldosterone system (RAAS) inhibitors such as ACE2, which are connected to COVID-19 susceptibility, and poor glycemic management was related to the poor prognosis of patients with severe COVID-19 [11,13]. Sattar et al. (2020), further suggested that obesity could be a risk factor for severe COVID-19 infection due to its effects on immunological dysregulation, metabolic impairments, and thrombotic risk [14].

The prothrombin time was substantially longer in the poor outcome group compared to the excellent outcome group. This finding was consistent with Huang et al. (2020), finding that PT was longer in COVID-19 patients in the ICU versus non-ICU patients [2]. This conclusion was likewise similar to Zhou et al, who showed prolonged PT in non-survivor COVID-19 [15].

Activated Partial Thromboplastin Time was also found to be longer in poor than good outcome group and significantly different. This result was similar to Wang, et al that discovered APTT was longer in death than survival group. Prolongation of PT and APTT

occur due to coagulation cascade activation and consumptive coagulopathy [5]. Prolongation of PT >3 seconds or APTT >5 seconds is a marker of coagulopathy and a predictor of thrombotic complication in COVID-19 [16].

Higher D-dimer was found in poor than good outcome group and significantly different. Tang et al found that D-dimer in non-survivor was almost 3 [5]. times as high as survivor COVID-19 [4]. This study was similar to previous studies, as D-dimer in poor outcome group was almost four times as high as good outcome group. Elevation of D-dimer occurs as a result of coagulation cascade activation and secondary hyperfibrinolysis due to monocyte and endothelial activation, proinflammatory cytokines release, tissue factor expression, and von Willebrand Factor (vWF) secretion [4].

Fibrinogen in poor outcome group was found to be lower than good outcome group, but was not significantly different. This finding was consistent with Wang, et al 2020, that discovered fibrinogen was lower in death than survival group, but was not significantly different [5]. This result was different from Zhai, et al. (2021), that reported fibrinogen was found higher in COVID-19 moderate cases than mild ones and significantly different.[18] This difference might be due to the distinction in subjects' clinical spectrum. Fibrinogen in mild and moderate COVID-19 cases is found to be increasing, otherwise decreasing in more severe COVID-19 cases [19]. The increasing of fibrinogen might occur due to hypercoagulable state, besides fibrinogen also has a role as an acute phase reactant correlates with inflammation,[16] but fibrinogen might also be decreasing as a result of worsening coagulopathy. This might explain the possibility of insignificant difference in fibrinogen.

This study had some limitations because comorbid diseases was not detailed into each disease, the design of this study was not prospective cohort, and analysis of the variables was not continued to multivariate analysis, meanwhile there were not many publications about differences of PT, APTT, fibrinogen, and D-dimer in COVID- 19 outcome in Indonesia.

4. Materials and Methods

This study was approved by The Ethics Committee of Faculty of Medicine, Universitas Indonesia (KET- 549/UN2.F1/ETIK/PPM.00.02/2020). This retrospective cohort study was conducted at the Central Laboratory Clinical Pathology Department of dr. Cipto Mangunkusumo Hospital from July to December 2020. The study involved analyzing secondary data of PT, APTT, fibrinogen, and D-dimer levels, as well as the outcomes of COVID-19 patients who were admitted to dr. Cipto Mangunkusumo Hospital and were 18 years of age or older. The data was collected consecutively. We excluded patients with history of hemostasis disorders and history of prior anticoagulants use. Outcome was extracted up to 14 days after PT, APTT, fibrinogen, and D-dimer were examined, and consisted of poor and good outcome which defined in Table 3.

Table 3. Patients Outcome

Poor	Good
Patients were admitted to the High Care Unit (HCU) or Intensive Care Unit (ICU)	Patients improved clinically
Addition of diagnosis that aggravated patients' condition	Patients were fully recovered
Patients died	Patients were discharged from hospital

Clinical spectrums of SARS-CoV-2 infection were defined according to Pedoman Tatalaksana COVID-19 edisi 3 [6]. Hypertension was defined using Konsensus Penatalaksanaan Hipertensi 2019 [7] diabetes mellitus (DM) was defined according to Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia 2019,

[8] obesity was defined using WHO classification,9 and others for diseases other than hypertension, DM, and obesity. Each subject may have many comorbidities.

The data was analyzed using the Statistical Product and Service Solution (SPSS) 26.0. Numeric data was checked for normalcy using the coefficient of variation. For regularly distributed data, mean and standard deviation were utilized, whereas for non-normally distributed data, median with minimum and maximum values were used. Categorical data were reported as n (percentage). Bivariate analysis was carried out using the Mann-Whitney U test. A 95% confidence interval, 80% power, and a p-value of <0.05 were considered significant.

5. Conclusions

The profiles of PT, APTT, fibrinogen, and D-dimer in COVID-19 patients were respectively 11 seconds, 38.4 seconds, 484.8 mg/dL, and 1800 μg/L. There were differences in PT, APTT, and D-dimer between COVID-19 poor and good outcome group, while no difference was found in fibrinogen between the two groups.

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