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ASSOCIATION BETWEEN HEMOSTATIC MARKERS WITH THE SEVERITY OF COVID-19 IN MEDAN, INDONESIA

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ABSTRACT

The Coronavirus disease of 2019 (COVID-19) has resulted in significant morbidity and mortality worldwide. Doctors may use several laboratory tests, such as the biomarkers for hemostasis alteration, to assess the severity and prognosis of COVID-19 patients. This study aims to determine the association between hemostatic markers [including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), D-dimer, fibrinogen, platelet] and the clinical spectrum of SARS-CoV-2 infected patients (including moderate and severe COVID-19, and the non-survivors). This retrospective cohort analyzed the hospital medical records of 120 COVID-19 inpatients from January to December 2021 in Medan city, Indonesia. This study revealed a significant association between increasing values of PT/INR, APTT, fibrinogen, D-dimer, and the clinical spectrum of COVID-19 patients.

1. Introduction

COVID-19 is a highly contagious viral infection caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which has caused a global pandemic and dramatic loss of human life worldwide [1]. The clinical spectrum of COVID-19 varies from asymptomatic or presymptomatic infection to various degrees of symptomatic illness (mild, moderate, severe, and critical) [2]. COVID-19 was characterized by a triad of fever, cough, and shortness of breath, then the Centers for Disease Control and Prevention (CDC) added chills, muscle aches, headaches, sore throats, and anosmia or ageusia [3].

The diagnosis of COVID-19 can be reviewed from clinical characteristics and supporting examinations. Several laboratory tests may help doctors to predict the severity and prognosis of COVID-19 patients.

A meta-analysis study of COVID-19 patients in Asian populations showed significant differences in the results of complete blood count tests, liver and kidney function tests, inflammatory markers, serum electrolytes, and glucose between COVID-19 patients with high and low severity of illness [4]. Coagulation system disorders are more likely to occur in severe and critical COVID-19 patients [5].

D-dimer and prothrombin time (PT) were indicators predicting the risk of death from COVID-19 [6].

In a retrospective cohort study conducted in Madrid, Spain, patients who did not survive COVID-19 had abnormal coagulation parameters such as PT, Activated Partial Thromboplastin Time (APTT), elevated D-dimer, and high level of fibrinogen compared to the survivors [7]. In this study, we analyze the association between the abnormal value of PT, international normalized ratio (INR), APTT, D-dimer, fibrinogen, platelet and moderate illness, severe illness, and mortality in COVID-19 patients hospitalized in Medan, Indonesia.

2. Material and methods

Study design

This retrospective cohort study used medical records of COVID-19 patients hospitalized in teaching hospitals (Haji Adam Malik General Hospital and Prof. Chairuddin P. Lubis Hospital) in Medan, Indonesia, from January to December 2021. SARS-CoV-2 RNA amplification from throat swab samples was the laboratory method used to confirm the COVID-19 diagnosis of each patient in both hospitals.

Patients aged ≥ 18 years, patients with moderate illness, patients with severe illness, and patients who died due to COVID-19 were the inclusion criteria of this study.

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Classification of age was based on the American Medical Associations' destinations for adults and older adults [8]. Determination of COVID-19 severity followed the World Health Organization (WHO) guidelines [9]. The term "death due to COVID-19" (or "death" or "non-survivors") was adopted from WHO guidelines.

WHO guidelines define "death due to COVID-19" as death of a patient who did not survive the critical illness of confirmed COVID-19 where no other unrelated cause of death could be identified (e.g. trauma) [10]. We excluded patients without complete laboratory analysis results, patients with a history of taking drugs that may affect the value of hemostasis function (such as anticoagulants), patients with prolonged use of broad-spectrum antibiotics, patients with liver dysfunction, and pregnant patients.

We collected the laboratory examination results for PT, INR, APTT, D-dimer, fibrinogen, and platelet upon hospital admission from each patient. The INR levels were calculated as mentioned in the reference [11]. Each marker was considered as prolonged or increasing by the following values: >15.3 seconds for PT, >1.1 for INR, >38.9 seconds for APTT, >500 ng/mL for D-dimer, and >400 mg/dL for fibrinogen. We rated platelets between 150-450 x 10^9/L as normal.

The Research Ethics Committee at the Faculty of Medicine, Universitas Sumatera Utara, approved the ethical clearance with reference number 725/KEPK/USU/2022 in agreement with the official Declaration of Helsinki.

Data processing and analysis

The statistical analysis included Chi-square test using Statistics Package for Social Science (SPSS) 26 and one-way analysis of variance (ANOVA) using GraphPad Prism 9. The result was considered significant when the *P* value was less than 0.05.

3. Results

Demographics of the study population

There were 120 eligible inpatient medical records, collected from January to December 2021 (Table 1). The majority of the COVID-19 patients were female 62/120 (51.7%), yet severe illness and death were more frequent in males (19.2%, respectively) than in females (14.2%, respectively). Female patients mostly suffered from moderate illness 28/120 (23.3%). Adults (18-64 years), median age 55 years, dominated COVID-19 incidents among hospitalized patients 98/120 (81.7%). The median age of male and female patients was 55 and 51 years, respectively.

Based on Chi-square analysis ($P < 0.05$), patients' gender is associated with moderate and severe illness and death due to COVID-19 ($p = 0.018$) (Table 2). In contrast, there is no association between age and COVID-19 clinical spectrum and death ($p = 0.626$).

Table 1. Characteristics of COVID-19 patients

Characteristics	Frequency ($N = 120$)	Percentage (%)
Gender		
Male	58	48.3
Female	62	51.7
Age		
Adults (18 – 64)	98	81.7
Older adults (≥ 65)	22	18.3
Moderate illness		
Male	12	10
Female	28	23.3
Severe illness		
Male	23	19.2
Female	17	14.2
Non-survivors		
Male	23	19.2
Female	17	14.2

Table 2. Association between patients' demographics and COVID-19 clinical spectrum and death

Demographics ($N = 120$)	COVID-19 Clinical Spectrum		Non-survivors	p-Value*
	Moderate	Severe		
Age				
Adults (18-64 years)	34 (28.3%)	31 (25.8%)	32 (26.7%)	0.626
Older adults (≥ 65 years)	6 (5%)	9 (7.5%)	8 (6.7%)	
Gender				
Male	12 (10.0%)	23 (19.2%)	23 (19.2%)	0.018
Female	28 (23.3%)	17 (14.2%)	17 (14.2%)	

The data were analyzed using the Chi-square test, P < 0.05.

Relationships between hemostatic markers and COVID-19 clinical spectrum and death

Table 3 showed statistical analyses (Chi-square, $P < 0.05$) of some hemostatic markers (PT, INR, APTT, D-dimer, fibrinogen, and platelet) and their association with moderate and severe COVID-19 and death. We found significant associations between PT, INR, APTT, D-dimer, and fibrinogen with moderate and severe COVID-19 and death. Prolonged PT and INR were found in 34/120 (28.3%) and 12/120 (10%) patients, respectively.

Table 3. Association between the hemostatic markers and COVID-19 clinical spectrum and death

Variables ($N = 120$)	COVID-19 Clinical Spectrum				Non-survivors		p-Value*
	Moderate		Severe				
	Normal	Increased/ decreased	Normal	Increased/ decreased	Normal	Increased/ decreased	
PT	37 (92.5%)	3 (7.5%)	22 (55%)	18 (45%)	27 (67.5%)	13 (32.5%)	0.001
INR	38 (95%)	2 (5%)	36 (90%)	4 (10%)	34 (85%)	6 (15%)	0.047
APTT	36 (90%)	4 (10%)	26 (65%)	14 (35%)	19 (47.5%)	21 (52.5%)	< 0.001
D-dimer	21 (52.5%)	19 (47.5%)	7 (17.5%)	33 (82.5%)	3 (7.5%)	37 (92.5%)	< 0.001
Fibrinogen	17 (42.5%)	23 (57.5%)	4 (10%)	36 (90%)	7 (17.5%)	33 (82.5%)	0.002
Platelet	36 (90%)	2 (5%)/ 2 (5%)	33 (82.5%)	3 (7.5%)/ 4 (10%)	35 (87.5%)	3 (7.5%)/ 2 (5%)	0.855

PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time. Chi-square test, P < 0.05.

APTT was prolonged in 39/120 (32.5%) patients. D-dimer was increased in 89/120 (74.2%) patients. Fibrinogen was elevated in 92/120 (76.6%) patients. We found an equal number of patients with abnormal (increasing/decreasing) platelets, each in 8/120 (6.6%) patients.

Further, we analyzed the relationship between PT, INR, APTT, D-dimer, fibrinogen, and platelet with COVID-19 clinical spectrum and death.

Using the one-way ANOVA, we found that elevated D-dimer was significantly related to COVID-19 severity and death ($P < 0.05$) (Figure 1).

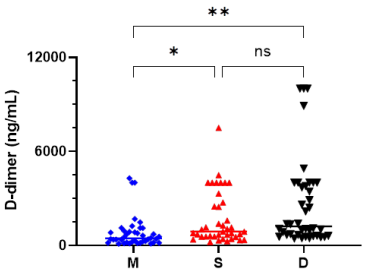

Figure 1. Relationship between D-dimer and COVID-19 severity and death. One-way ANOVA showed D-dimer values in the moderate (M), severe (S), and dead (D) COVID-19 patients. Tukey's multiple comparisons tests showed a significant difference in D-dimer level between M and S (* p = 0.018) and between M and D (p = 0.002). ns: not significant.**

There was a significant difference in D-dimer value between the moderate and severe COVID-19 patients (p = 0.018) and between the moderate COVID-19 patients and the non-survivors (p = 0.002).

Conversely, the prolonged PT/INR/APTT, the increase of fibrinogen, and the increased/decreased value of platelets were not significantly related to COVID-19 severity and death (data not shown).

4. Discussion

We found more COVID-19 incidents in females than males, yet more frequent severe illness and deaths in male than female hospitalized patients. Our results correspond with published data from several countries [12, 13, 14]. The hypothesis of gender susceptibility to SARS-CoV-2 infection is perhaps the most rational explanation for low COVID-19 severity in females. Theoretically, angiotensin-converting enzyme 2 (ACE-2) expression could be higher in females than males caused either by estrogen or the inactive X chromosome that subsequently supply ACE-2, the cell surface receptor for SARS-CoV-2 [15].

However, estrogen may regulate human immune cells (macrophage, natural killer cells, T- and B-lymphocytes) as they possess estrogen receptors, as well as promote antibodies (Immunoglobulin G and Immunoglobulin M) [16, 17]. Males, in contrast, tend to have androgens that may increase transmembrane protease serine 2 (TMPRSS2) expression that allows COVID-19 progression [15, 18]. Further, due to the difference in sex hormones, males have lower immune responses (humoral and cell-mediated) compared to females and therefore tend to suffer from the harmful outcome of SARS-CoV-2 infection [17, 18]. Other factors may play a part in COVID-19 severity, such as gender-specific behaviors (cigarette smoking, alcohol consumption), co-morbidities (such as cardiovascular disease, chronic obstructive pulmonary disease) and aging [18].

According to the Indonesian COVID-19 Handling Task Force, the age group of 19-30 years (27.4%), followed by the age group of 31-45 years (26.8%) and the age group of 46-59 years (17%), dominated hospitalized cases in Indonesia [19]. The hospitalized patients in this study are predominantly adults (age group of 18 to 64 years), which means our data correspond with the national data reported by COVID-19 Handling Task Force. Adults (18-64 years) consist of people who are actively working or at their productive age, so adults are considered the most mobile in a population. Consequently, adults have a higher risk of exposing themself to SARS-CoV-2 in the environment and contracting the disease than the other age group. A study of COVID-19 incidence in China found peak morbidity in the 50-59 years age group (~22.5%), while data from the Korean Republic showed the highest morbidity in 20-29 years (30%) and 50-59 years (19%) age groups [14]. The authors mentioned a lack of compliance with social distancing and self-quarantine to explain the high COVID-19 morbidity among those age groups [14].

Another explanation for the high incidence of COVID-19 and hospitalization in adults could be the emergence of the SARS-CoV-2 Delta variant in Indonesia around May 2021, which contributed to the second (and highest) peak of COVID-19 on July 2021 [19]. In the meantime, Indonesian obtained COVID-19 vaccination started in mid-January 2021, which prioritized healthcare workers, followed by the first doses for the elderly in February 2021. By mid-August 2021, only 10% of the Indonesian population had been fully vaccinated. Besides the low herd immunity against COVID-19 in 2021, the Indonesian population faced the nature of the Delta variant which can escape immune response [20]. Therefore, the very contagious Delta variant was possibly responsible for most COVID-19 cases in the Indonesian population during 2021, especially in productive age people.

Previous studies showed a relationship between aging and COVID-19 morbidity and mortality [14, 21, 22]. Similarly, COVID-19 Handling Task Force data revealed the highest mortality (47.6%) in the Indonesian population at age ≥ 60 years [19]. Elderly patients are often associated with a decreased physiological function (including the immune system) and increased co-morbidities (such as hypertension, diabetes, cardiovascular disease, and respiratory disease) that may worsen the COVID-19 outcome [22, 23]. Therefore, most studies found the highest COVID-19 mortality rate in the elderly [14, 21, 22, 23].

Most patients in this study are 18-64-year-old adults resulting in a higher percentage (bias) of morbidity and mortality rate in adults than the ≥ 65 years older adults. We consequently found no association between aging and COVID-19 severity and death. A future study involving a larger population than the current study would be able to analyze the correlation between the elderly and COVID-19 mortality in our region.

Coagulation disorders in COVID-19 patients, known as COVID-19-associated coagulopathy (CAC), often involve various tissues and organs [24]. As part of systemic inflammatory response, CAC is a common feature of severe illness, and approximately 20%-55% of COVID-19 inpatients have hematologic changes in coagulation tests, including

prolonged PT, elevated D-dimer, mild thrombocytopenia, and low fibrinogen levels) [25]. Moreover, COVID-19 non-survivors frequently suffer from disseminated intravascular coagulation (DIC) [26]. Hence, monitoring the hemostatic biomarkers is crucial to screen for the degree of coagulation activity [27, 28] and DIC outcome in COVID-19 patients [27, 28, 29].

This study showed a higher proportion of COVID-19 patients with PT prolongation in the severe illness and non-survivor groups compared to the moderate illness group (Table 3). APTT prolongation was higher in the COVID-19 non-survivors compared to patients in the other groups. Patients with D-dimer elevation were higher in the non-survivor group than in the other groups. Most patients from each group showed increasing fibrinogen. Finally, we found normal platelets and INR in most patients, with a notable increase of INR in the non-survivors. Previous studies described more PT and APTT prolongation in patients who died compared to the surviving patients [26, 30], which presumably indicates the hyperactivation of coagulation and consumption of coagulation factors by the non-survivors [26, 27, 29].

The D-dimer elevation is one of the most common laboratory findings in COVID-19 inpatients [28, 31]. D-dimer elevation was significant in patients with severe COVID-19 compared to moderate COVID-19, and in patients who died, compared to moderate COVID-19 (Figure 1). Previous studies found significantly high D-dimer in severe COVID-19 [31, 32, 33] and the non-survivors [26, 30]. The elevation of D-dimer in COVID-19 patients represents an increased inflammation response to SARS-CoV-2 infection and indicates coagulopathy [30, 31]. Besides, a high level of D-dimer (≥1500 ng/mL) on admission to the intensive care units could be an indicator of organ dysfunction as a response to SARS-CoV-2 infection [34]. The evidence of multiple organ dysfunction in COVID-19 non-survivors based on the autopsy result [35] supports the speculation of the importance of monitoring D-dimer levels to predict the prognosis of patients with severe illness [34].

In the screening for classic DIC, such as the DIC caused by bacterial sepsis or trauma, checking INR value is not recommended and should be monitored only when the patient uses an oral anticoagulant [29]. There are findings of mild prolongation of PT in COVID-19 survivors [25, 37], which is similar to our results. Thus, there is speculation of non-significant prolongation of INR value in COVID-19 patients. In contrast, some studies revealed significant INR prolongation in severe COVID-19 [36] and the non-survivors [26, 30, 36], thus suggesting the association between INR prolongation and COVID-19 morbidity and mortality. Nonetheless, INR prolongation is one of the parameters of coagulopathy in COVID-19 patients, and it might still be worth monitoring INR for the screening of CAC.

One of the SARS-CoV-2 acute phase infection features is an increased risk of thrombosis, which is related to the elevation of fibrinogen [38]. In addition, fibrinogen is possibly involved in leukocyte adhesion via integrin to the endothelium and the migration of the adherent cells to the inflammation sites [39]. Previous studies found fibrinogen elevation at hospital admission of severe COVID-19 patients [26, 32], which corresponds to our results. Fibrinogen elevation may reflect the viremia following SARS-CoV-2 infection, pro-inflammatory cytokines abundance in circulations, and thrombin formation [24, 27].

Conversely, studies found a significant reduction of fibrinogen in COVID-19 non-survivors [26, 30]. The authors revealed a range of 1-12 days from admission to DIC, and fibrinogen decreased in the non-survivors at days 10-14 [26]. Nonetheless, abnormality in fibrinogen levels may predict COVID-19 severity [26, 30]. Future study to reveal the underlying mechanism of uncommon switches in fibrinogen levels concerning CAC is necessary.

Normal platelets at admission are dominant in moderate, severe, and deceased COVID-19 patients in this study. In consequence, we found no association between platelets and COVID-19 severity and death (Chi-square analysis, $p = 0.855$). Thrombocytopenia could be prognostic for DIC and death in sepsis [27, 28], yet it is not prominent at hospital admission of COVID-19 patients [30, 38, 40]. The proportion of thrombocytopenia in COVID-19 non-survivors is higher than in the survivors [30, 40], which corresponds with our findings. Despite its low specificity, we support the role of platelets as a coagulation marker to predict mortality in COVID-19 patients [40]. The limited knowledge of a detailed mechanism for low platelet counts during SARS-CoV-2 infection and CAC requires further investigation.

Based on Chi-square analysis ($P < 0.05$), we found an association between the hemostatic biomarkers (PT, APTT, INR, D-dimer, fibrinogen) and COVID-19 severity and death. D-dimer elevation was the most notable marker related to severe COVID-19 and death. However, there is no association between platelets and COVID-19 severity and death. The latter is possible due to the data collection in this cohort targeting only laboratory examination results of the patients at admission. Future studies with different methods and considerable samples may provide more reliable results.

5. Conclusions

Susceptibility to COVID-19 severity resulted in more frequent severe illness and deaths in male than female hospitalized patients. Adults from the age group of 18 to 64 years dominated the hospitalized COVID-19 cases in Indonesia. Abnormal levels of hemostatic markers, especially PT/INR and APTT prolongation, high levels of D-dimer, and fibrinogen elevation, may have prognostic value for COVID-19 severity and death. Our results support D-dimer as a dominant marker for CAC incidents in COVID-19 patients.

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