Clinical Research

Coagulation factors as potential predictors of COVID-19 patient outcomes

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ABSTRACT

BACKGROUND Causes of death and length of hospitalization in patients with COVID-19 have been associated with coagulopathy. The coagulopathy mechanism involves the process of coagulation and endothelial damage triggered by an inflammatory response of the SARS-CoV-2 infection due to excessive release of proinflammatory cytokines. This study aimed to determine the association of coagulation factors as potential predictors of COVID-19 patient outcomes.

METHODS This retrospective study was performed on 595 patients at Wahidin Sudirohusodo Hospital, Makassar, from June 2020 to June 2021. Participants were recruited using total sampling and assessed for COVID-19 severity using the World Health Organization classification and coagulation factors (D-dimer, fibrinogen, thrombocyte, and prothrombin time [PT]). Patient outcome assessments were survival and length of hospitalization.

RESULTS We found a significant sex-based disparity, with a higher COVID-19 incidence in males. Severe cases were more common among those aged >50 years, with prolonged hospitalization (>10 days) linked to higher severity (odds ratio [OR] = 2.22, 95% confidence interval [CI] = 1.31–3.77, $p<0.001$). Elevated fibrinogen and D-dimer levels, as well as prolonged PT, predicted severe cases. However, D-dimer had the highest influence compared to other coagulation factors (OR = 14.50, 95% CI = 5.85–35.95, $p<0.001$), while prolonged PT influenced mortality rates (OR = 4.02, 95% CI = 1.35–12.00, $p = 0.01$).

CONCLUSIONS Coagulation factors, such as elevated D-dimer and fibrinogen levels and prolonged PT, predicted the severity of COVID-19 patients leading to death.

KEYWORDS blood coagulation factors, COVID-19, patient outcome assessment

The World Health Organization (WHO) has reported more than 583 million confirmed coronavirus disease 2019 (COVID-19) cases and more than six million deaths by August 2022. The prevalence of COVID-19 demonstrates how effectively it spreads through droplet respiration in local populations. Although symptom variability exists among individuals, the average incubation period of COVID-19 is predicted to be 6.57 days.[1–3] COVID-19 symptoms include fever, chills, cough, runny nose, sore throat, breathing difficulties, myalgia, nausea, vomiting, and diarrhea. Although some patients remain asymptomatic, others may experience severe respiratory conditions such as acute respiratory distress syndrome or systemic infections, leading to multiorgan failure and death.[4–6] The inflammatory reaction in patients with COVID-19 releases proinflammatory cytokines that activate the coagulation system and host defense mechanisms, leading to disseminated intravascular coagulation. The cytokine storm enabled by the excessive inflammatory

response also causes increased coagulation factors and D-dimer levels, called COVID-19-associated coagulopathy.[7,8]

Coagulation abnormalities are also associated with severe cases of COVID-19. Several studies have agreed that coagulation factors strongly influence the outcomes of patients with COVID-19, such as prolonged prothrombin time (PT), elevated D-dimer and fibrinogen levels, and thrombocytopenia.[9–15] However, other studies have found standard coagulation factors, such as platelets and fibrinogen. These factors are influenced by various individual and population factors related to race and ethnicity.[16,17] Few studies exist, especially in Indonesia, that examine the relationship between coagulation factors and outcomes in patients with COVID-19, with a variable focus on confounding factors. Therefore, this study aimed to determine the influence of coagulation factors as potential predictors of the outcomes in patients with COVID-19 based on disease severity, survival, and length of hospitalization.

METHODS

Research design and patient selection

This retrospective study used the medical records of all patients with COVID-19 at Wahidin Sudirohusodo Hospital, Makassar, from June 2020 to June 2021. Participants who met the inclusion and exclusion criteria were selected using total sampling. The inclusion criteria were patients who tested positive for the virus that causes COVID-19, at least 18 years of age, and had complete laboratory data on D-dimer, fibrinogen, platelets, and PT levels, as well as data on the length of hospitalization and discharge status. Patients who requested hospital discharge were excluded. Additionally, we included data on comorbidities that contributed to the development of COVID-19, including active smoking, pulmonary tuberculosis, chronic liver disease, malignancy, diabetes mellitus, hypertension, cardiovascular diseases (coronary artery disease, hypertensive heart disease, and congestive heart failure), chronic kidney disease, autoimmune disease, and HIV infection.

Severity classification and measurement of patient outcomes

The severity of COVID-19 was evaluated using the WHO severity classification. Severe illness was defined as oxygen saturation below 90% with room air, signs of pneumonia, respiratory distress characterized using accessory respiratory muscles, inability to complete a sentence, and respiratory rate >30 breaths per min. Non-severe illness classification was based on the absence of signs of a severe illness. Coagulation factors that were measured during hospitalization, but not limited to hospital admission, such as platelet/thrombocyte (normal range 150×10^3–400×10^3/µl), PT (normal value 10–14 sec), D-dimer (normal value <0.5 µg/ml), and fibrinogen (normal value 150–375 mg/dl) were obtained through medical records. Additionally, patient outcomes such as survival status and length of hospitalization were obtained from medical records. Based on Lucijanic et al,[18] a median of 10 days was the cut-off for determining the length of hospitalization.

Statistical analysis

The collected data samples were grouped according to their purpose and were not normally distributed. Statistical analyses were performed using Microsoft Excel 2020 (Microsoft Corp., USA) and SPSS software version 26 (IBM Corp., USA). Univariate analysis was used to describe the general characteristics, and bivariate analysis using the chi-square test was used to determine the correlation between categorical data. Multivariate binary logistic regression analysis was performed to determine the influence of variables on COVID-19 severity and patient survival. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (No: 38/UN4.6.4.5.31/PP36/2023).

RESULTS

The review of medical records was conducted from January to April 2023, with a total sample of 595 patients screened based on the inclusion and exclusion criteria. We efficiently assessed the severity of COVID-19, coagulation factors, and patient outcomes, all at a relatively low cost. The participant selection flowchart is shown in Figure 1.

Furthermore, we reported the distribution of baseline demographic characteristics (age and sex), comorbidities, independent variables of coagulation factors (thrombocytes, fibrinogen, D-dimer, and PT), patient outcomes (survival, non-survival, and length of hospitalization), and COVID-19 severity (severe and non-severe) as dependent variables (Table 1).

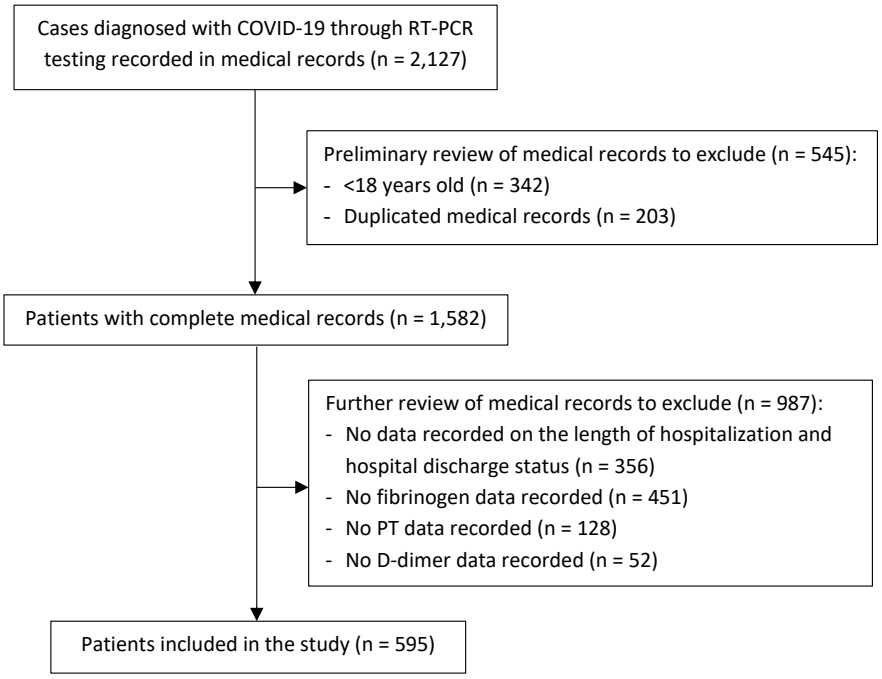

Figure 1. Patient selection diagram. COVID-19=coronavirus disease 2019; PT=prothrombin time; RT-PCR=real time-polymerase chain reaction

Table 1. Patient characteristics

Characteristics	N = 595
Male sex, n (%)	291 (48.9)
Age (years), n (%)	
≤50	362 (60.8)
>50	233 (39.2)
Comorbidities, n (%)	
Smoker	78 (13.1)
Lung tuberculosis	14 (2.4)
Liver disease	40 (6.7)
Malignancies	65 (10.9)
Diabetes mellitus	106 (17.8)
Hypertension	138 (23.2)
Cardiovascular disease	104 (17.5)
Chronic kidney disease	53 (8.9)
Autoimmune	5 (0.8)
HIV	3 (0.5)
Length of stay (days), mean (SD)	10 (6)
Survive, n (%)	520 (87.4)
Severe COVID-19, n (%)	75 (12.6)
Coagulation factors, mean (SD)	
Thrombocyte (/µl)	286.078 (121.347)
Fibrinogen (mg/dl)	360.61 (158.44)
D-dimer (mg/l)	3.90 (11.14)
PT (sec)	11.23 (1.64)

COVID-19=coronavirus disease 2019; PT=prothrombin time; SD=standard deviation

Subsequently, bivariate and multivariate analyses were performed to ascertain the interplay between the variables and their impact on the severity of COVID-19 (Table 2) and survival groups (survivor and non-survivor) (Table 3). Analyses of these two dependent variables revealed a notable sex-based disparity with a higher incidence in males. A distinct distribution pattern in age stratification was observed; most patients with COVID-19 aged >50 years had severe disease and high mortality rates. Exploring the impact of the length of hospitalization on severity, the severe group generally required a significantly extended hospitalization of more than 10 days (odds ratio [OR] = 2.22, 95% confidence interval [CI] = 1.31–3.77, $p<0.001$). The survivor group had an average stay within 10 days, but there was no statistically significant effect (OR = 0.77, 95% CI = 0.46–1.29, $p = 0.32$). In terms of coagulation factors, elevated D-dimer levels (OR = 14.50, 95% CI = 5.85–35.95, $p<0.001$) had the highest statistically significant OR to predict severe COVID-19 cases. Among all variables examined, only prolonged PT significantly influenced the mortality rate of patients with COVID-19.

DISCUSSION

This study found a statistically significant relationship between the severity of COVID-19, coagulation factors, and patient outcomes. Several previous studies

Table 2. Variables associated with COVID-19 severity

Variables	Severe (N = 138)	Non-severe (N = 457)	Bivariate analysis*		Multivariate analysis†	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Sex, n (%)				**<0.001**		**0.004**
Male	90 (65.2)	201 (44.0)	1.00		1.00	
Female	48 (34.8)	256 (56.0)	0.42 (0.28–0.62)		0.44 (0.25–0.77)	
Age (years), n (%)				**<0.001**		**<0.001**
≤50	47 (34.1)	315 (68.9)	4.23 (2.87–6.43)		2.97 (1.66–5.32)	
>50	91 (65.9)	142 (31.1)	1.00		1.00	
Length of stay (days), mean (SD)	11.78 (7.59)	9.83 (5.99)				
>10, n (%)	68 (49.3)	167 (36.5)	1.68 (1.15–2.47)	**<0.001**	2.22 (1.31–3.77)	**<0.001**
Platelets (/µl), mean (SD)	265,442.03 (118,680.95)	292,309.19 (121,580.27)				
<150,000, n (%)	21 (15.2)	36 (7.9)	2.09 (1.18–3.73)	0.10	0.80 (0.34–1.85)	0.60
Fibrinogen (mg/dl), mean (SD)	405.54 (195.14)	347.05 (143.05)				
>375, n (%)	73 (52.9)	153 (33.5)	2.23 (1.51–3.28)	**<0.001**	1.52 (0.88–2.61)	**0.02**
D-dimer (µg/ml), mean (SD)	9.85 (18.61)	2.10 (6.61)				
≥0.5, n (%)	131 (94.9)	217 (47.5)	20.69 (9.46–45.25)	**<0.001**	14.50 (5.85–35.95)	**<0.001**
PT (sec), mean (SD)	12.25 (2.28)	10.93 (1.25)				
≥14	19 (13.8)	12 (2.6)	5.92 (2.79–12.54)	**<0.001**	2.16 (0.77–6.03)	**0.01**

CI=confidence interval; COVID-19=coronavirus disease 2019; OR=odds ratio; PT=prothrombin time; SD=standard deviation
*Chi-square test, significant if $p<0.05$; †binary logistic regression test, significant if $p<0.05$

have been conducted on the relationship between fibrinogen levels and COVID-19 severity,[19–23] showing significant fibrinogen values in severe COVID-19 cases compared to non-severe cases. Plasma fibrinogen levels exhibit rapid escalation in pathological states such as injury, infection, and inflammation, which are crucial in facilitating fibrinolysis, resulting in damage to vascular endothelial cells. In patients with COVID-19, inflammation can directly target vascular endothelial cells and initiate coagulation. Consequently, a salient hallmark of COVID-19 resides in its acute-phase procoagulant response, whereby acute-phase reactants are associated with an elevated risk of thrombosis and are intrinsically linked to increased fibrinogen levels.[20,24]

D-dimer, a product of fibrin breakdown triggered by endothelial damage, inflammation, or insufficient oxygen in the blood (hypoxemia), can increase owing to intensified inflammation as COVID-19 severity escalates, prompting increased fibrin degradation and, consequently, elevated D-dimer levels.[19] These elevated D-dimer levels are frequently associated with the severity of COVID-19 and are linked to unfavorable outcomes. Higher D-dimer concentrations can worsen conditions by promoting clot formation within the pulmonary veins, leading to venous thromboembolism.[24] Elevated D-dimer levels may indicate a severe viral infection. Viral infections progressing to sepsis can disturb coagulation, which is common in severe disease progression, especially for COVID-19. In addition, elevated D-dimer levels are indirectly associated with inflammatory reactions, as inflammatory cytokine responses can disrupt the coagulation-fibrinolysis balance in pulmonary alveoli, leading to activation of the fibrinolysis system and increased D-dimer levels.[25]

Prolonged PT is another coagulation factor contributing to elevated fibrinogen and D-dimer levels. In the present study, prolonged PT in both dependent groups was associated with COVID-19 severity. While previous research generally concurs about the significance of fibrinogen and D-dimer levels, studies on the relationship between PT and disease severity have yielded conflicting results. Di Minno et al[21] and Zhang et al[22] observed significant PT prolongation in patients with severe COVID-19 compared with non-severe cases. The viral presence in COVID-19 incites the extrinsic coagulation pathway via prothrombin-to-thrombin transformation, which is characterized

Table 3. Variables associated with survival

Variables	Survive (N = 522)	Non-survive (N = 73)	Bivariate analysis*		Multivariate analysis†	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Sex, n (%)				**0.02**		0.55
Male	246 (47.1)	45 (61.6)	1.00		1.00	
Female	276 (52.9)	28 (38.4)	0.55 (0.33–0.91)		0.49 (0.24–1.01)	
Age (years), n (%)				**<0.001**		0.05
≤50	330 (63.2)	32 (43.8)	2.20 (1.34–3.61)		0.50 (0.25–1.01)	
>50	192 (36.8)	41 (56.2)	1.00		1.00	
Length of stay (days), mean (SD)	10.40 (6.30)	9.48 (7.36)				
>10, n (%)	210 (40.2)	25 (34.2)	0.77 (0.46–1.29)	0.32	-	-
Thrombocyte (/µl), mean (SD)	288,544.64 (118,862.11)	268,438.36 (137,435.74)				
<150,000, n (%)	43 (8.2)	14 (19.2)	2.64 (1.36–5.12)	**<0.001**	2.19 (0.82–5.85)	0.11
Fibrinogen (mg/dl), mean (SD)	351.96 (148.88)	422.52 (205.63)				
>375, n (%)	184 (35.2)	42 (57.5)	2.49 (1.51–4.09)	**<0.001**	1.99 (0.99–3.98)	0.05
D-dimer (µg/ml), mean (SD)	2.58 (7.61)	13.34 (22.43)				
≥0.5, n (%)	279 (53.4)	69 (94.5)	15.02 (5.40–41.77)	**<0.001**	1.76 (0.50–6.24)	0.37
PT (sec), mean (SD)	11.04 (1.34)	12.62 (2.68)				
≥14, n (%)	17 (3.3)	14 (19.2)	7.05 (3.30–15.02)	**<0.001**	4.02 (1.35–12.00)	**0.01**
COVID-19 severity, n (%)			87.81 (34.22–225.35)	**<0.001**	92.08 (33.86–250.43)	**<0.001**
Severe	70 (13.4)	68 (93.2)				
Non-severe	452 (86.6)	5 (6.8)				

CI=confidence interval; COVID-19=coronavirus disease 2019; OR=odds ratio; PT=prothrombin time; SD=standard deviation
*Chi-square test, significant if $p<0.05$; †binary logistic regression test, significant if $p<0.05$

by prolonged PT. Prolonged PT signifies inflammation-induced coagulation in infection-driven conditions and is associated with increased disease severity.

In patients with COVID-19, the mechanism underlying thrombocytopenia is likely multifactorial. The combination of viral infection and mechanical ventilation causes endothelial damage that triggers platelet activation, aggregation, and microthrombi formation to overcome the damage in the lung, leading to excessive platelet consumption and decreased platelets in the blood.[26] Coronavirus can also directly infect bone marrow cells, resulting in abnormal hematopoiesis or triggering an autoimmune response to blood cells.[13] High values of fibrinogen and D-dimer levels accompanied by prolonged PT and decreased platelet levels indicate a high coagulopathy process in patients with severe COVID-19, which is one of the factors often associated with disease prognosis.[9,14,27] However, in the present study, thrombocytopenia did not significantly influence the severity of COVID-19 or patient survival. Therefore, thrombocytopenia was not a primary contributing factor to COVID-19 progression, although this condition persisted in some patients.

Several studies have reported that patients with severe COVID-19 have higher mortality rates than those with less severe COVID-19. In addition, patients with non-severe COVID-19 showed a higher probability of recovery than those who died of COVID-19.[28–33] This is consistent with the results of our study. Wang et al[29] observed that individuals subjected to high-flow oxygen therapy and mechanical ventilation had decreased survival rates compared to those without mechanical ventilation who survived COVID-19. The utilization of high-flow oxygen therapy and mechanical ventilation was more prevalent in patients with severe COVID-19, thereby indirectly supporting the notion that higher degrees of severity are associated with a higher susceptibility to unfavorable outcomes. Consequently,

the present study also found an association between disease severity and duration of hospitalization. Severe cases were more associated with longer hospitalization than non-severe cases.

Low platelet levels were not significantly associated with coagulation factors and patient outcomes. The lack of statistical significance in the results of the present study could be due to significant differences in the number of survivors and non-survivors. Although the platelet counts tended to be lower in the non-survivor group owing to the difference in numbers between the two groups, the mean platelet counts were not statistically significant. A meta-analysis by Di Minno et al[21] showed a significant increase in D-dimer levels in 1,149 non-survivors compared with 4,407 survivors. In addition, 15 studies showed a significant prolongation of PT in 840 non-survivors compared to 3,287 COVID-19 survivors.[21] Furthermore, Zhang et al[22] found increased D-dimer levels and a significant prolongation of PT in the non-survivor group compared to the survivor group. In the present study, only prolonged PT was significantly associated with patient survival among the various coagulation factors. This lack of significance can be caused by comorbidities in patients with COVID-19, which may affect the severity and length of hospitalization. These findings deepen our understanding of the complex interactions among sex, age, length of hospitalization, and coagulation variables affecting patient outcomes in determining the survival dynamics of patients with COVID-19.

This study had several limitations. This investigation was conducted retrospectively over a short period to meet the essential requirements for short-term mortality predictors and to establish appropriate management methods. Using secondary data from medical records introduced potential biases, including selection, recall, and misclassification biases. Furthermore, the study design precluded the establishment of causal relationships. The cohort of examined patients underwent multidisciplinary care, which increased the potential bias when defining each comorbidity based on individual interpretations. Consequently, a comprehensive analysis of the comorbidities may have been more feasible.

In conclusion, coagulation factors such as elevated D-dimer and fibrinogen levels and prolonged PT predicted the severity of COVID-19 in patients, leading to death. These markers are promising predictors of disease severity and individual outcomes in patients with COVID-19. As a future direction, we suggest additional prospective clinical investigations that carefully explore the interaction between coagulation factors and patient outcomes to predict disease severity and mortality in critically ill patients with COVID-19.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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