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Padua Score and Coagulopathy Parameters on Survival of COVID-19 Patients at Prof Dr. R. D. Kandou General Hospital Manado

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Abstract

BACKGROUND: Coagulopathy in coronavirus disease 2019 (COVID-19) patients causes a prothrombotic state that increases the risk of thromboembolism. The Padua score and coagulopathy parameter including D-dimer values, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet counts are very important parameters to determine risk of thrombosis and mortality in hospitalized COVID-19 patients.

AIM: This study aimed to assess the prognosis of COVID-19 patients with Padua score and coagulopathy parameters.

METHODS: This retrospective cohort study was conducted in tertiary university hospital, Prof. Dr. R. D. Kandou Hospital Manado, Indonesia from October 2020 to July 2021. Patients admitted with final diagnosis of COVID-19 confirmed with positive reverse transcriptase-polymer chain reaction test were included in the study. The data were refined by excluding the patients under 18 years old and the patients with no blood test results, D-dimer values, fibrinogen values, PT values, aPTT values, and platelet counts. The association of Padua score and coagulopathy parameters with survival of COVID-19 patients was analyzed by multivariate cox regression and Kaplan–Meier analysis.

RESULTS: The probability of survival on day 14 in patients with Padua score <4, D-dimer <0.5 mg/dl, PT ≤16 s, aPTT ≤39 s, and platelets >150,000/μL was 100%, 100%, 84.6%, 81.5%, and 81.4%, respectively. COVID-19 survival was influenced by Padua score ≥4 (heart rate [HR] = 4.199; CI 95% 2.221–7.936), D-dimer ≥0.5 mg/L (HR = 4.772; CI 95% 2.244–10.147), PT >16 s (HR = 2.124; CI 95% 1.608–2.805), aPTT >39 s (HR = 1.449; CI 95% 1.080–1.943), and platelet count <150000/μL (HR = 2.056; CI 95% 1.489–2.840). Padua score has the highest probability of mortality compared to the other coagulopathy parameters ($p < 0.001$; HR = 3.655; CI 95% 1.927–6.932).

CONCLUSION: There was an association of Padua score, D-dimer value, PT value, aPTT value, and platelet count on survival of COVID-19 patients. Padua score being the most influential variable on survivals.

Introduction

Coronavirus disease 2019 (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed a significant threat to global heath [1]. Although initial infection is dominated by respiratory manifestations, many studies have shown that patients with severe COVID-19 developed coagulation disorders (coagulopathy) [2], [3]. A meta-analysis study by Zhang *et al*., in China, showed that from a total of 15 studies, it was found that coagulopathy was a risk factor that could aggravating the disease and causing death in COVID-19 patients [4]. This was associated with an increased mortality rate in the study of Zhou *et al*., in Wuhan, China who reported that the risk of death was 18 times higher in patients with coagulopathy [5].

Coagulopathy in COVID-19 patients that causes a prothrombotic state can increase the risk of thrombosis and thromboembolism [2], [6]. Study by Klok *et al*., in the Netherlands regarding the incidence of venous and arterial thrombosis in 184 severe COVID-19 patients admitted to the intensive care unit, reported that the cumulative incidence of venous and arterial thrombosis complications was 31%. Venous thromboembolism was the most common complication of thrombosis (28%) and the majority was pulmonary embolism (25%). Therefore, assessment of the risk of venous thromboembolism in coagulopathy in COVID-19 patients is important in reducing mortality [7].

The Padua score can be used to assess the risk of venous thromboembolism due to coagulopathy in hospitalized COVID-19 patients. A study by Wang *et al*., in china showed that patients with high Padua scores (Padua score ≥4) had a higher risk of venous thromboembolism, need for intensive care unit treatment, use of mechanical ventilation, and higher mortality, compared to patients with low Padua score (Padua score

<4) [8]. In addition to the Padua score, identification of laboratory blood tests related to coagulopathy in patients with confirmed COVID-19 is very important in determining the prognosis of diseases associated with complications due to thrombosis that contribute to increased mortality. The most common blood test parameters related to coagulopathy in COVID-19 patients is characterized by changes in D-dimer, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT) values, and platelet counts [3], [9]. Short *et al*., in the United States, in their study, concluded that higher D-dimer values were independently associated with a greater risk of death [10]. A retrospective study by Long *et al*., in China found that patients with fibrinogen values >4.2 g/L (heart rate [HR] 4.79, 95% CI: 1.14–20.20, p = 0.033) indicated a higher risk of death [11]. A study of 191 COVID-19 patients by Zhou et al. in Wuhan, China also reported that 50% of patients who died in hospital had prolonged PT and aPTT (p<0.001) [5]. A meta-analysis involving 24 studies in China and Singapore by Zong et al., found that trombocytopenia was significantly associated with the mortality of patients with severe disease (OR 7.37; 95% CI: 2.08-26.14) [12].

The mortality rate in COVID-19 has continued to increase since it was first announced in Indonesia. Data regarding coagulopathy on survival in COVID-19 patients in Indonesia are still not available. A better understanding of the thrombosis and thromboembolism risk in COVID-19 with an assessment of the Padua score and several coagulation parameters will determine the appropriate management and reduce mortality. This study aimed to assess the risk and prognosis of COVID-19 patients with Padua score and several coagulopathy parameters.

Methods

Research design, setting, and population

This retrospective cohort study was conducted from October 2021 to July 2022 in tertiary university hospital, Prof. Dr. R. D. Kandou Hospital Manado, Indonesia with 838 inpatient beds and an average occupancy rate of 79.8%. The data obtained from electronic medical record were retrospectively reviewed by doctors with four-eye-principle used in October 2021–July 2022. Patients admitted with final diagnosis of COVID-19 confirmed with positive reverse transcriptase-polymer chain reaction (RT-PCR) test were included in the study. The data were refined by excluding the patients under 18 years old and the patients with no blood test results, D-dimer values, fibrinogen values, PT values, aPTT values, and platelet counts. The estimated optimum sample size using the Lemeshow formula with the assumption of a 95% confidence level was 641 patients. This study was approved by ethics committee of Prof. Dr. R. D. Kandou Hospital (Reference No. 099/EC/UEPK-KANDOU/VI/2022) and the consent to participate was waived since the study was conducted using secondary data.

Study variables and data collection

The data collected from each patient including patient characteristics, Padua scores, several coagulopathy parameters, and death or survival time in patients confirmed positive for COVD-19. Patient characteristics consisted of demographic, comorbid, clinical, and laboratory characteristics. According to the World Health Organization, the definition of confirmed case is a person with a positive nucleic acid amplification test, such as RT-PCR, regardless of clinical criteria (acute onset of fever and cough; or acute onset of any three or more signs such as fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea,/diarrhea/anorexia), or epidemiological criteria (contact of a probable or confirmed case, or linked to a COVID-19 cluster. To assess the risk of developing venous thromboembolic complications, the Padua score consisting of 11 items was used where a total score of ≥4 indicates a low risk and a score <4 indicates a high risk of venous thromboembolism. Meanwhile, the coagulopathy parameters were measured on admission and consist of the value of D-dimer, Fibrinogen, PT, aPTT, and platelet count. Coagulopathy parameters were obtained by taking blood specimens.

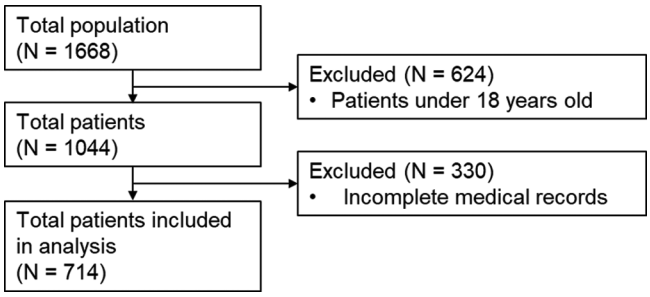

Figure 1: The flowchart of sample inclusion and exclusion

Statistical analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences program. Descriptive analysis was performed using univariate method. The numerical variables were described in frequency, percentage, median, minimum, and maximum. Meanwhile, categorical variables were described in frequency and percentage. The distribution of the data was assessed by Kolmogorov–Smirnov. The effect of Padua score with several coagulation parameters was analyzed using survival analysis and displayed in Kaplan–Meier curve. Multivariate analysis was carried out using Cox Regression to determine the most associated factors on survival in COVID-19. The Cox proportional hazard assumptions were used on significant covariates. Covariates with p < 0.25 in the hazard ratio analysis and met the proportional hazard assumption (based on the Kaplan–Meier curve)

were included in multivariate Cox regression. $p < 0.05$ were considered statistically significant.

Results

A total of 714 records of confirmed COVID-19 patients in Prof. Dr. R.D. Kandou Hospital were enrolled in this study (Figure 1). About 53.6% of patients was male and 60.1% of patients was <60 years old. In this study, 45.8% of confirmed COVID-19 patients had hypertension and 57.2% of them died and 25.5% of confirmed COVID-19 patients had type two diabetes mellitus with 36.5% of them died. The demographic and comorbid characteristics of patients are shown in Tables 1 and 2.

Table 1: Demographic characteristics of patients

Variables	n (%)
Age (years)	
≤ 60	429 (60.1)
> 60	285 (39.9)
Gender	
Male	383 (53.6)
Female	331 (46.4)

The results of this study showed that most of patients were hospitalized for >14 days (56%), had a body mass index <25 kg/m^2 (53.9%), had moderate COVID-19 (70%), and a Padua score ≥4 (80.8%). The moderate COVID-19 is patients with clinical signs of pneumonia (fever, cough, shortness of breath, and rapid breathing) but no sign of severe pneumonia including SpO_2 ≥90% on room air. Severe COVID-19 is patient with clinical signs of pneumonia (fever, cough, and dyspnea) plus one of the following: respiratory rate >30 breath/min, severe respiratory distress, and od SpO_2 <90% on room air. Mild and asymptomatic COVID-19 patients were not included since they did not meet the criteria for hospitalization. Most of the patients had hemoglobin values of ≥13 g/dL in males (64.5%) and ≥12 g/dL in females (52.9%), had a leukocyte count <5000/μL (8%), a platelet count ≤150,000/μL (14.7%), D-dimer level ≥0.5 mg/L (84.7%), fibrinogen level >400 mg/dL (74.8%), PT >16 s (26.8%), and aPTT >39 s (24.4%). The clinical and laboratory characteristics of patients are shown in Table 3.

Table 2: Comorbid characteristics of patients

Variable	Outcome		Total (n = 714)
	Survived (n = 506)	Died (n = 208)	
Hypertension, n (%)			
Yes	208 (41.1)	119 (57.2)	327 (45.8)
No	298 (58.9)	89 (42.8)	387 (54.2)
Type 2 DM, n (%)			
Yes	106 (20.9)	76 (36.5)	182 (25.5)
No	400 (79.1)	132 (63.5)	532 (74.5)
Kidney disease, n (%)			
Yes	45 (8.9)	56 (26.9)	101 (14.1)
No	461 (91.1)	152 (73.1)	613 (85.9)
Lung disease, n (%)			
Yes	16 (3.2)	20 (9.6)	36 (5.0)
No	490 (96.8)	188 (90.4)	678 (95.0)

DM: Diabetes mellitus.

Table 3: Clinical and laboratory characteristics of patients

Variables	Outcome		Total (n = 714) %	Normality
	Survived (n = 506) %	Died (n = 208) %		
BMI (kg/m^2)				< 0.001
< 25	291 (57.5)	94 (45.2)	385 (53.9)	
≥ 25	215 (42.5)	114 (54.8)	329 (46.1)	
COVID-19 severity				
Moderate	439 (86.8)	61 (29.3)	502 (70.3)	
Severe	67 (13.2)	147 (70.7)	212 (29.7)	
Hospitalized duration (days)				< 0.001
≤ 14	172 (34.0)	142 (68.3)	314 (44.0)	
> 14	334 (66.0)	66 (31.7)	400 (56.0)	
Padua Score				< 0.001
< 4	127 (25.1)	10 (4.8)	137 (19.2)	
≥ 4	379 (74.9)	198 (95.2)	198 (95.2)	
Hemoglobin (g/dL)				< 0.001
Male				
< 13			136 (35.5)	
≥ 13			247 (64.5)	
Female				
< 12			156 (47.1)	
≥ 12			175 (52.9)	
Leukocyte (10^3/μL)				< 0.001
< 5	51 (10.1)	6 (2.9)	57 (8.0)	
5–10	253 (50)	65 (31.3)	318 (44.5)	
> 10	202 (39.9)	137 (65.9)	339 (47.5)	
D-dimer (μg/mL)				< 0.001
< 0.5	102 (20.2)	7 (3.4)	109 (15.3)	
≥ 0.5	404 (79.8)	201 (96.6)	605 (84.7)	
Fibrinogen (mg/dL)				< 0.001
< 200	4 (0.8)	9 (4.3)	13 (1.8)	
200–400	126 (24.9)	41 (19.7)	167 (23.4)	
> 400	376 (74.3)	158 (76.0)	534 (74.8)	
PT (second)				< 0.001
< 12	20 (4.0)	2 (1.0)	22 (3.1)	
12–16	379 (74.9)	122 (58.7)	501 (70.2)	
> 16	107 (21.1)	84 (40.4)	191 (26.8)	
aPTT (second)				< 0.001
< 27	39 (7.7)	16 (7.7)	55 (7.7)	
27–39	358 (70.8)	127 (61)	485 (67.9)	
> 39	109 (21.5)	65 (31.3)	174 (24.4)	
Thrombocyte (10^3/μL)				< 0.001
< 150	57 (11.3)	48 (23.1)	105 (14.7)	
150–450	407 (80.4)	146 (70.2)	553 (77.5)	
≥ 150	42 (8.3)	14 (6.7)	56 (7.8)	

BMI: Body mass index, PT: Prothrombin time, aPTT: Activated partial thromboplastin time.

The Kaplan–Meier curve (Figure 2) was the survival curve of confirmed COVID-19 patients. This result showed most of patients survived in more than 14 days. The overall chance of survival for 714 COVID-19 patients was 78.8%. The survival rate of patients with Padua score <4 until day 14 and day 61 were 100% and 41.2%, while the survival rate of patients with a Padua score ≥4 until day 14 and day 61 were 74.2% and 35.7%, respectively. Based on coagulopathy parameters, the survival rate of patients with D-dimer value <0.5 mg/L until day 14 and day 61 observation (100% and 41.2%) was higher than patients with D-dimer value ≥ 0.5 mg/L (75.5% and 35.7%). In addition, the survival rate of patients with fibrinogen ≤400 mg/dL until day 14 and day 61 observation (76.2% and 25.2%) was lower than patients with fibrinogen >400 mg/dL (79.6% and 41.8%). According to PT levels, patients with PT ≤16 s in day 14 and day 61 observation (84.6% and 23%) had a higher survival rate than patients with PT value >16 s (62.4% and 40.4%). Similar to PT, patients with aPTT ≤39 s in day 14 and day 61 observation (81.5% and 50.4%) had a higher survival rate than patients with PT value >39 s (70.5% and 43.8%). Meanwhile, higher survival rate was obtained in patient with thrombocyte count >150,000/μL (81.4% and 36.9%) than patient with thrombocyte count ≤150,000/μL (63.2% and 30.9%) in day 14 and day 61 observation.Factors affected the survival rate based on the Kaplan–Meier curve were

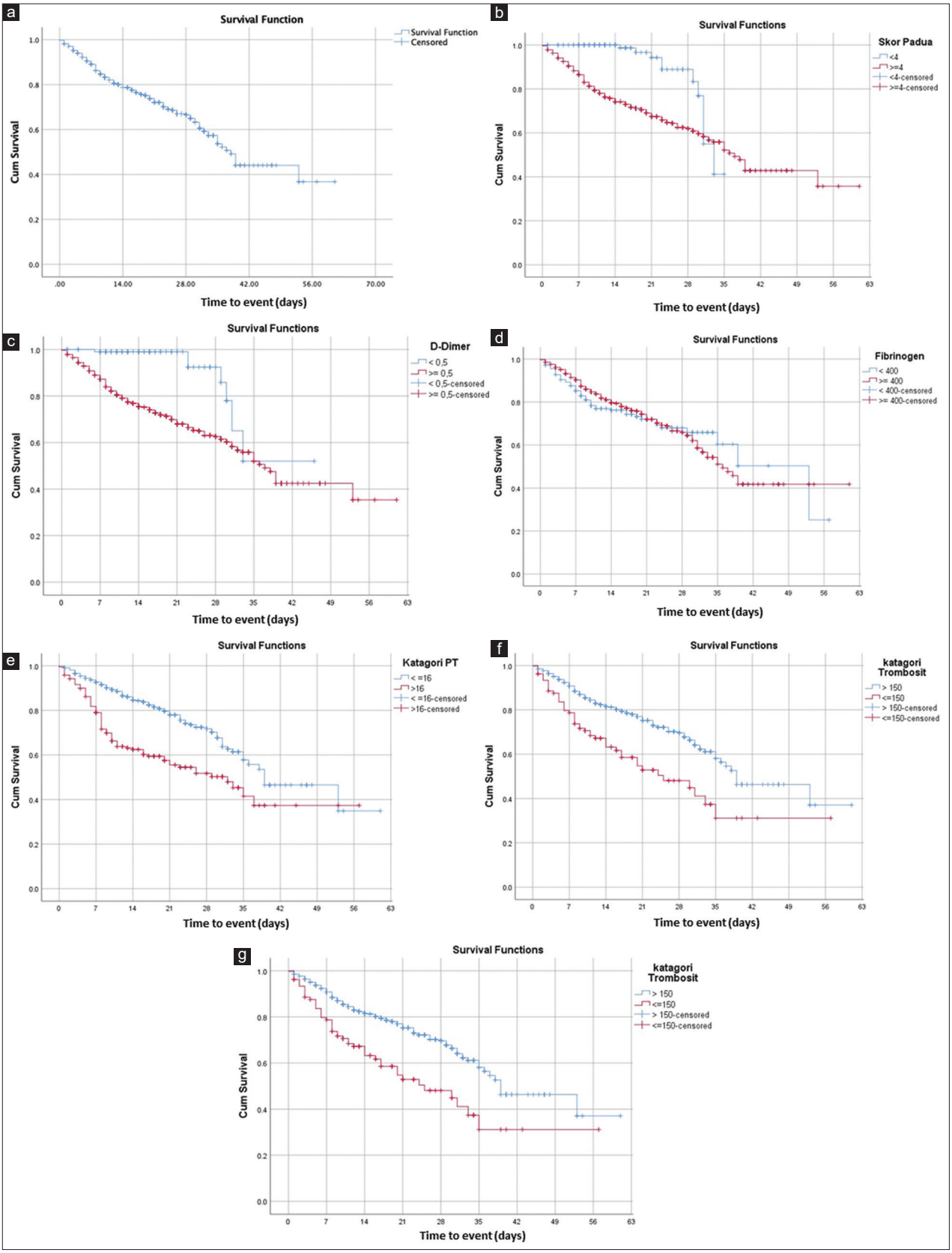

Figure 2: Overall survival rate of 714 COVID-19 patients (a) and survival based on Padua score (b), D-dimer (c), fibrinogen (d), prothrombin time (e), activated partial thromboplastin time (f), and thrombocytes count (g)

Padua score ≥4 (HR = 4.199; 95% CI 2.221–7.936), D-dimer value ≥0.5 mg/dL (HR = 4.772; 95% CI 2.244–10.147), PT value >16 s (HR = 2.124; 95% CI 1.6082.805), aPTT value >39 s (HR = 1.449; 95% CI 1.080–1.943), and platelet count ≤150,000/μL (HR = 2.056; CI 95% 1.489–2.840). The effect of Padua score and several coagulopathy parameters on survival in COVID-19 patients is shown in Table 4.

Table 4: Hazard ratio analysis of COVID-19 patients

Variables	Outcome		HR (CI 95%)	p-value
	Survived	Died		
Padua score, n (%)			4.199 (2.221–7.936)	< 0.001
≥ 4	379 (65.7)	198 (34.3)		
< 4	127 (92.7)	10 (7.3)		
D-dimer, n (%)			4.772 (2.244–10.147)	< 0.001
≥ 0.5	404 (66.8)	201 (33.2)		
< 0.5	102 (93.6)	7 (6.4)		
Fibrinogen, n (%)			0.970 (0.707–1.330)	0.849
> 400	377 (70.6)	157 (29.4)		
≤ 400	129 (71.7)	51 (28.3)		
PT, n (%)			2.124 (1.608–2.805)	< 0.001
> 16	107 (56.3)	83 (43.7)		
≤ 16	399 (76.1)	125 (23.9)		
aPTT, n (%)			1.449 (1.080–1.943)	0.013
> 39	109 (62.6)	65 (37.4)		
≤ 39	397 (73.5)	143 (26.5)		
Thrombocyte, n (%)			2.056 (1.489–2.840)	< 0.001
< 150,000	57 (54.3)	48 (45.7)		
≥ 150,000	449 (73.7)	160 (26.3)		

HR: Hazard Ratio, CI: Confidence Interval.

Variables with p < 0.25 in the hazard ratio analysis and met the proportional hazard assumption (based on the Kaplan–Meier curve) were included in the multivariate analysis. The variables included in the multivariate analysis were Padua score, D-dimer value, PT, aPTT, and platelet count. Multivariate analysis with Cox proportional hazard using regression model is carried out until p < 0.05 was obtained in the final model. The most influential variable on survival in COVID-19 patients in this study was the Padua score (p < 0.001; HR = 3.655; 95% CI 1.927–6.932). Cox regression on the survival of COVID-19 patients is shown in Table 5.

Table 5: Cox regression on the survival of COVID-19 patients

Step	Variables	p-value	HR (CI 95%)
Step 1	PT	< 0.001	1.776 (1.324–2.381)
	D-dimer	0.267	1.942 (0.601–6.274)
	aPTT	0.862	0.973 (0.710–1.332)
	Padua Score	0.102	2.285 (0.848–6.156)
	Thrombocyte	0.001	1.742 (1.244–2.439)
Step 2	PT	< 0.001	1.764 (1.328–2.344)
	D-dimer	0.269	1.938 (0.600–6.263)
	Padua Score	0.103	2.280 (0.846–6.141)
	Thrombocyte	0.001	1.731 (1.246–2.405)
Step 3	PT	< 0.001	1.775 (1.336–2.358)
	Padua score	< 0.001	3.655 (1.927–6.932)
	Thrombocyte	0.001	1.723 (1.240–2.393)

Discussion

The clinical symptoms of COVID-19 are vary from asymptomatic to acute respiratory distress syndrome (ARDS), coagulation disorders, and even multi-organ failure [13], [14]. The results of this study showed that the overall survival in 714 COVID-19 patients on the Kaplan–Meier curve was 78.8%. This result was supported by several the previous studies. A retrospective cohort study by Nlandu *et al*., in Congo, which analyzed the mortality predictors in COVID-19 patients, reported that the average survival of COVID-19 patients was 12 days with overall survival of 86.9% on day 5.65% on day 10 and 19.9% on day 20 [15]. Mortality in COVID-19 patients could be caused by acute respiratory distress syndrome, septic shock, hemorrhagic shock, and acute myocardial infarction. Multiple organ failures can also occur in COVID-19 patients which can lead to death. An overactive immune response together with the effects of virus on the host cell causes the ARDS state, septic shock, and multi-organ failure, which associated with mortality [16].

Coagulopathy in COVID-19 causes clinical manifestations of life-threatening arterial thrombosis and venous thromboembolism (VTE) [17]. The Padua score considers several risk factors and can be used to assess the risk of developing VTE in patients. The Padua score consisting of 11 items was used where a total score of ≥4 indicates a low risk and a score <4 indicates a high risk of venous thromboembolism. The variables included in Padua score was active cancer, previous history of venous thromboembolism, history of bed rest, thrombophilia, recent trauma and/or surgery, elderly age, heart and/respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity, and hormonal treatment [18]. The results of this study showed the survival of COVID-19 patients who had a Padua score of <4 (100%) was higher than the patients who had a Padua score of ≥4 (74.2%) on day 14. Study by Chen *et al*., in China, showed similar results where patients with a Padua score of <4 had a mortality rate of 2% with a survival rate of 98% and this mortality rate increased to 63% in patients with a Padua score of ≥4. This shows that a high Padua score is associated with high mortality [19]. The use of Padua scores for VTE risk assessment was associated with an adequate thromboprophylaxis administration and followed by a decrease in the incidence of VTE. Adequate administration of thromboprophylaxis in patients who are considered at high-risk during hospitalization results in long-term protection against thromboembolic events with a low risk of bleeding, thereby increasing survival in COVID-19 patients [20], [21].

D-dimer is a fibrin degradation product, widely used as a biomarker for thrombotic disorders. D-dimer values increase as the severity of COVID-19 increases [22]. The most common causes are viremia and cytokine storm syndrome, where there is an increase in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, and TNF-α) which are not sufficiently controlled by anti-inflammatory factors, thus inducing a coagulation cascade which predisposes to thrombosis and is associated with the high mortality of COVID-19 patients [23]. Thrombotic complications and coagulopathy in COVID-19 reflect the activation of coagulation cascades due to viremia or cytokine storms, or possibly due to superinfection and organ dysfunction [24]. Our results found that most patients had D-dimer values of ≥0.5 mg/L (84.7%). The high incidence of increased D-dimer values may be due to samples that we only assessed were moderate and severe COVID-19. The results of this study also showed a higher survival of COVID-19 patients who had a D-dimer value of <0.5 mg/L compared to patients who had a D-dimer value of ≥0.5 mg/L. The

previous study by Soni *et al*., in India, also showed that an increase in D-dimer levels ≥2.02 mg/L ($p < 0.01$; HR 3.165; 95% CI 2.013–4.977) was a significant predictor of the high mortality in COVID-19 patients based on the Kaplan–Meier curve [25].

Prolonged PT values, occurrence of thrombosis or bleeding, and disseminated intravascular coagulation complications have been observed in many COVID-19 patients [26]. The results of this study indicated that most patients have normal PT values and the survival for COVID-19 patients who have PT ≤16 s (84.6%) was higher than patients with PT >16 s (62.4%). These results are supported by Bintoro *et al*., in Surabaya, Indonesia, which examined risk factors for mortality, hematological, and coagulation parameters as predictors of survival in COVID-19 patients. The Kaplan–Meier curve in the results of their study showed a significant relationship between the mortality rate and the value of PT. Lower COVID-19 patient survival was significantly associated with prolonged PT values (>16 s) [27]. PT assesses the integrity of the extrinsic coagulation pathway and is influenced by the common pathway. Prolonged PT indicates a transition from coagulation activation to a fibrinolytic state due to consumption of coagulation factors [28].

Abnormalities in coagulopathy parameters have been widely reported especially in patients with COVID-19 and ARDS-related pneumonia, including prolonged aPTT and associated with COVID-19 mortality [23]. The results of this study showed that most patients had normal aPTT values and survival of COVID-19 patients on day 14 who had an aPTT value of ≤39 s (81.5%) was higher than patients with aPTT of >39 s (70.5%). These results were supported by Citu *et al*., in Romania, which showed that the aPTT value was significant predictor of mortality in COVID-19 patients [29]. Several factors contribute to hemostatic changes in COVID-19, including cytokine storms, neutrophil activation, endothelial function disorders, platelet activation, tissue factor expression, and coagulation induction. Pathogen-associated molecular pathway activation induced by SARS-CoV-2 infection can lead to activation of intrinsic and extrinsic coagulation cascades, which lead to an increase in aPTT and INR, respectively. This can induce biological cascade and severity of the disease [3].

Thrombocytopenia is a common manifestation and also an indicator of the poor prognosis of COVID-19 [30]. This study showed that a small percentage of patients had platelet counts of <150.000/μL (14.7%) and the probability of survival of COVID-19 patients who had platelet counts of >150.000/μL (81.4%) on day 14 observation was higher than patients who had platelet counts of ≤150.000/μL (63.2%). These results were supported by Zhu *et al*., in Wuhan, China which stated that patients with thrombocytopenia had significantly higher mortality rates not only in 28 days but also in 90 days and 180 days. Kaplan–Meier analysis of their study showed that patients with thrombocytopenia had a lower probability of survival ($p < 0.01$) [31]. When infection occurs, SARS-CoV-2 may directly infect hematopoietic stem cells or megakaryocyte through the enzyme ACE2, CD13, or CD66a, as in other coronavirus infections that cause thrombocytopenia [32]. In addition, platelets interact directly with viral pathogens through protease-activated receptor 4 and glycoprotein IIIa, and this interaction can lead to platelet activation, which is associated with lung inflammation as well as the severity of disease, lung injuries and death [33]. Thrombocytopenia induces the occurrence of organ disorders including kidney failure, acute lung injury, respiratory distress syndrome, vascular leakage syndrome, and septic shock which associated with increased mortality of COVID-19 patients [34].

The presence of various manifestations and complications of COVID-19, accurate, and widely available prognostic biomarkers is very useful in management that can affect the survival of COVID-19 [5]. This study results showed COVID-19 patients with higher Padua scores, higher D-dimer values and lower platelet counts had a higher probability of mortality within 14 days. This result was supported by several previous studies. The study by Liu *et al*., stated that platelets were predictors of the survival of COVID-19 patients where an increase in platelet counts of 50,000 was associated with a decrease in mortality by 40% [35]. Study by Zeng *et al*., found that a high Padua score (score of ≥4) was an independent predictor of mortality of COVID-19 patients in 28 days (HR = 7.35; 95% CI 3.08–16.01) [36]. Coagulation parameters not only reflect hemostatic but also related to inflammation and organ dysfunction [37]. Consumption which related to thrombin-mediated platelet activation and adhesion to endothelial cells as well as leukocytes may contribute to platelet reduction in critical COVID-19 patients [14]. In addition, high Padua scores indicate the presence of hypercoagulation that can be caused by the release of virus-induced pro-inflammatory cytokines, the presence of thrombogenic factors, and changes in ACE function in the vascular. This is associated with a high risk of VTE and increased mortality in COVID-19 patients [38].

The limitation of this study was using retrospective cohort design, so it depended on the completeness of the data from the medical record. The level of subjectivity in the filling of Padua scores can also influence the assessment on the patients of the study. Further studies should be conducted with randomized controlled trials or prospective cohort. In addition, the potential confounding factors such as comorbid or other clinical and laboratory factors can be controlled together with the parameters of this study.

Conclusion

There was an association of Padua score, D-dimer, PT, aPTT, and leukocyte count on survival in COVID-19 patients. The association between fibrinogen levels and survival of COVID-19 patients was not statistically significant. COVID-19 patients with Padua score <4, D-dimer <0.5 mg/L, PT ≤16, aPTT ≤39, and platelets >150.000/μL had a higher survival. The most influential factor on survival in COVID-19 patients was the Padua score.

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