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Original Article

Hemostatic and liver function parameters as COVID-19 severity markers

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a disease newly discovered in December 2019 which affects coagulation cascade and liver functions. The aim of this study was to investigate the potential of hemostatic and liver function parameters as severity markers in COVID-19 patients. This study was an observational analytic with cohort retrospective design using total sampling method. Data were retrieved from medical record of COVID-19 patients admitted to provincial hospital in Banda Aceh, Indonesia from March 2020 to March 2022. There were 1208 data eligible for the study after applying certain criteria. Mann–Whitney, logistic regression, and receiving operating characteristic (ROC) analyses were used to analysis the data. Thrombocyte count (p<0.001), prothrombin time (p<0.001), activated partial thromboplastin time (p<0.001), D-dimer (p<0.001), fibrinogen (p<0.001), aspartate aminotransferase (p<0.001), and alanine transaminase (p<0.001) significantly increased in severe compared to mild COVID-19 patients. After being adjusted, age (odds ratio (OR); 1.026 (95% confidence interval (CI): 1.016–1.037) was the most significant factor in predicting COVID-19 severity. Fibrinogen (cut-off 526.5 mg/L) was the best parameter associated with COVID-19 severity with 70% sensitivity and 66.4% specificity. Meanwhile, D-dimer (cut-off 805 ng/mL) had a sensitivity of 72.3% and specificity of 66.4%. Combining the parameters resulted in improved sensitivity to 82.0% with a slight decline of specificity to 65.5%. In conclusion, fibrinogen and D-dimer level on admission could be used as biomarkers in predicting COVID-19 prognosis. Routine monitoring and evaluation of laboratory testing especially D-dimer and fibrinogen could be implemented in order to reduce morbidity and mortality rate of COVID-19.

Keywords: COVID-19, hemostatic, liver function, severity, mortality

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been spread widely across countries since 2019 and it was declared as Public Health Emergency of International Concern in January 2020. World Health Organization (WHO) had reported more than 643 million cases with total death reaching 6.630.082 as of December 2022 [1]. The United States of America, India, and France are the highest country with COVID-19 positive confirmation cases [1]. SARS-CoV-2 could cause inflammatory response hence disturbing the mechanism of procoagulant and anticoagulant

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homeostatic system as the consequence from viremia or cytokine storm. Therefore, thrombotic complications might occur during these responses. Venous thromboembolism (VTE) and pulmonary embolism (PE) had also been detected in 22.5% and 10% non-intensive care unit (ICU) COVID-19 patients, respectively [2]. Hemostatic parameter abnormality and coagulation disorders are frequently identified in severe and critically ill COVID-19 patients [3]. Previously, it was found that certain laboratory parameters such as high D-dimer and fibrinogen concentration could be potential indicators for predicting the severity of COVID-19 [3-10].

Previously, studies have reported that patients with severe COVID-19 had significantly lower platelet count [11-15]. Prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) were also found to be significant in severe COVID-19 patients as compared with non-severe patients [13,16-18]. COVID-19 not only affects lungs, heart, kidney, nervous system, but also gastrointestinal and hepatobiliary system [19,20]. Recent study found that acute liver injury (ALI) was also significantly associated with severe COVID-19 and 76.3% patients had abnormal level of liver function tests [21,22]. Associations between the elevations of aminotransferase (AST) and alanine transaminase (ALT) levels and COVID-19 severity had been reported previously [23,24]. Taken altogether, PT, aPTT, AST, and ALT could be used as biomarkers for COVID-19 severity, which are useful for prognostication of the disease. Indeed, previous studies have reported these biomarkers but the contradiction in the results persists [23-29]. The aim of this study was to investigate the association between the foregoing parameters with COVID-19 severity.

Methods

Study design and participants

An analytical observational study with cohort retrospective approach was carried out to identify the association between hemostatic parameters and liver function tests with COVID-19 severity. This present study was conducted in April-August 2022 at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, which is the most established healthcare facility in Aceh province, Indonesia. As many as 3,803 hospitalized patients with positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) result of from nasal or oropharyngeal swab samples were initially included. However, only 1208 of them were eligible for this study. Cases with incomplete medical record, pregnancy, histories of anticoagulant therapy, blood abnormalities, liver disease, prior surgery/trauma within one months before the admission were excluded.

Study variables and data collection

The data upon admission to the hospital were retrieved from medical records, which included demographic characteristics (age, gender, and occupation) and clinical data (length of stay, ward and ventilation procedure, comorbidities, history of hypertension, diabetes mellitus, acute kidney injury, chronic kidney disease, coronary artery disease (CAD), congestive heart failure (CHF), stroke, tumor or cancer, chronic obstructive pulmonary disease (COPD), tuberculosis, and bronchial asthma, clinical symptoms, and vital signs). Laboratory results such as complete blood count-diftell (CBC-diff), random blood glucose, renal function, electrolyte serum, coagulation profile, and liver function parameters were also collected. In this study, explanatory variables were thrombocyte count, duration of PT and aPTT and concentration of D-dimer, fibrinogen, AST, and ALT, meanwhile the response variable was COVID-19 severity.

Severity assessment

The severity of COVID-19 case was defined in accordance with the WHO Clinical Management of COVID-19 Interim Guidance 2020 guideline. All cases were categorized into four types: mild, ordinary, severe, and critical cases. Mild cases were symptomatic patients without establishment of pneumonia or hypoxia and moderate cases were patients with pneumonia with SpO_2 ≥90% on room air. Severe cases were patients with clinical signs of pneumonia plus one of the following criteria: (1) including SpO_2 is less than 90% on room air; (2) respiratory rate >30 breaths/min; or (3) severe respiratory distress. Critical cases were identified with criteria of acute respiratory distress syndrome (ARDS), sepsis, and septic shock. In this study, mild and moderate cases were

considered as non-severe group meanwhile severe and critical cases were presented as severe group.

Laboratory measurement

The samples for coagulation profiles and liver function tests were collected within 24 hours and sent to the Clinical Pathology Laboratory of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia on the day of hospital admission. Thrombocyte count was determined by Sysmex XN-2000 or fluorescence flow cytometry method, while D-dimer was measured using immunoassay Stago, POCT photometer, or Cobas h232. PT and aPTT were measured using Stago Compact Max 3 or optical detection method. AST and ALT were measured by International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method without pyridoxal phosphate (p5p) or Indiko Plus.

Statistical analysis

Categorical variables were presented as frequency (n) and percentage (%). Normally distributed continuous variable was presented as mean±standard deviation (SD), while the data which were not normally distributed were expressed as median and interquartile range (IQR) (25–75th percentile). Distribution of the data were confirmed by the Kolmogorov-Smirnov normality test prior to further analysis. Binary logistic regression was performed to identify association among categorical variables. The Mann-Whitney non-parametric test for continuous variables was performed to compare the difference of continuous variable based on COVID-19 severity. During bivariate analysis, the odd ratios (ORs) and 95% CI were evaluated. Further, some variables were included for multivariate logistic regressions with backward stepwise method by calculating adjusted odd ratios (aORs). Variables to be included in regression models were selected based on statistical reasoning ($p \leq 0.05$) and pre-determined clinical justification. All statistical analysis were considered significant at $p \leq 0.05$ with 95% confidence interval (CI). All analyses were conducted on SPSS version 23.0 software (SPSS, IBM, New York, USA).

The accuracy of each hemostatic and liver function profile in predicting COVID-19 severity was measured using the receiver operator characteristic (ROC) curve. The area under the curve (AUC), 95%CI, cut-off point, sensitivity, specificity, positive predictive value, and negative predictive value of each parameter were determined based on ROC. The AUC, sensitivity, and specificity of combined parameter of variables were also determined using ROC analysis. The optimal cut-off value of each parameter was selected based on the point closest to the top-left of ROC curve graph.

Results

A total of 1208 hospitalized patients who were positive for SARS-CoV-2 on RT-PCTR were included in the study and their characteristics are presented in **Table 1**. There were 577 (47.8%) patients with severe and 631 (52.2%) patients with non-severe symptom. The associations between categorical variables with COVID-19 severity are summarized in **Table 1**. The age of patients ranged from 11 years to 92 years with median age of 56.0 (45.0–64.0). The median (IQR) age of the patients in the severe group was 59.0 (49.0–66.0) years compared to the non-severe group (53.0 (40.0–61.0)) with statistically significant results ($p<0.001$). Males (56.8%) were more impacted than females. Nevertheless, there was no association between gender and the severity of COVID-19 ($p<0.075$). The number of patients in the employed group were found higher compared to unemployed which were 745 (61.7%) and 463 (38.3%), respectively, but there was no association between occupation and COVID-19 severity. Co-morbidities were present in 908 (75.2%) patients. There was a significant difference between severe and non-severe patients in regard to the presence of comorbidities ($p<0.001$). Hypertension (42.1%), diabetes mellitus (34.4%), and chronic kidney disease (7.20%) were the most common comorbidities found in patients. Patients with hypertension, diabetes mellitus, and acute kidney injury had likelihood of 1.71, 1.65, and 1.69 times developing into severe stage, respectively. Cough (83.11%), fever (82.9%), and fatigue (65.14%) were the most often symptoms found in COVID-19 patients. Fever (OR: 1.72; 95%Cl: 1.26–2.35), cough (OR: 3.03; 95%Cl: 2.34–4.63), lack of appetite (OR: 1.41; 95%Cl: 1.12–1.79), and shortness of breath (OR: 24.28; 95%Cl: 17.35–33.98), were significantly

higher in severe cases compared to non-severe cases. Meanwhile, other symptoms such as headache (OR: 0.73; 95%Cl: 0.56–0.94), body-ache (OR: 95%Cl: 0.66 0.47–0.94), and vomiting (OR: 0.51; 95%Cl: 0.37–0.70) were significantly lower in severe compared with non-severe cases.

Table 1. Comparison of categorical variables between severe and non-severe COVID patients

Variable	Severe (%)	Non-severe (%)	Total (%)	Unadjusted OR (95% Cl)	*p*-value
Gender					
Woman	234 (40.6)	288 (45.6)	522 (43.2)	Ref.	
Man	343 (59.4)	343(54.4)	686 (56.8)	1.2 (1.0–1.6)	0.08
Occupation					
No	218 (37.8)	245 (38.8)	463 (38.3)	Ref.	
Yes	359 (62.2)	386 (61.2)	745 (61.7)	1.1 (0.8–1.3)	0.71
Ward and procedure					
Non-ICU+non-ventilator	268 (46.4)	581 (92.0)	849 (70.3)	Ref.	
ICU+non-ventilator	223 (38.6)	44 (7.0)	267 (22.1)	11.0 (7.7–15.7)	<0.01
ICU+ventilator	86 (14.9)	5 (0.8)	91 (7.5)	37.3 (15.0–93.0)	<0.01
Comorbidity					
No	97 (32.3	203 (67.7)	300 (24.8)	Ref.	
Yes	480 (83.2)	428 (67.8)	908 (75.2)	2.4 (1.8–3.0)	<0.01
Hypertension					
No	295 (51.1)	405 (64.2)	700 (57.9)	Ref.	
Yes	282 (48.9)	226 (35.8)	508 (42.1)	1.7 (1.4–2.2)	<0.01
Diabetes mellitus					
No	344 (59.6)	448 (71.0)	792 (65.6)	Ref.	
Yes	233 (40.4)	183 (29.0)	416 (34.4)	1.7 (1.3–2.1)	<0.01
Acute kidney injury					
No	529 (91.7)	599 (94.9)	1128 (93.4)	Ref.	
Yes	48 (8.3)	32 (5.1)	80 (6.6)	1.7 (1.1–2.7)	0.03
Chronic kidney disease					
No	541 (93.8)	580 (51.7)	1121 (92.8)	Ref.	
Yes	36 (6.2)	51 (8.1)	87 (7.2)	0.8 (0.5–1.2)	0.217
Coronary artery disease					
No	545 (94.5)	602 (95.4)	1147 (95.0)	Ref.	
Yes	32 (5.5)	29 (4.6)	61 (5.0)	1.2 (0.7–2.0)	0.452
Heart failure					
No	553 (95.8)	605 (95.9)	1158 (95.9)	Ref.	
Yes	24 (4.2)	26 (4.1)	50 (4.1)	1.0 (0.6–1.8)	0.973
Stroke					
No	557 (96.5)	615 (97.5)	1172 (97.0)	Ref.	
Yes	20 (3.5)	16 (44.4)	36 (3.0)	1.38 (0.7–2.7)	0.344
Tumor/cancer					
No	565 (97.9)	612 (97.0)	1177 (97.4)	Ref.	
Yes	12 (2.1)	19 (3.0)	31 (2.6)	0.7 (0.33–1.4)	0.309
Chronic obstructive pulmonary disease					
No	557 (96.5)	620 (98.3)	1177 (97.4)	Ref.	
Yes	20 (3.5)	11 (1.7)	31 (2.6)	2.0 (1.0–4.3)	0.063
Bronchial asthma					
No	568 (98.4)	627 (99.4)	1195 (98.9)	Ref.	
Yes	9 (1.6)	4 (0.6)	13 (1.1)	2.5 (0.8–8.1)	0.132
Tuberculosis					
No	572 (99.1)	622 (98.6)	1194 (98.8)	Ref.	
Yes	5 (0.9)	9 (1.4)	14 (1.2)	0.6 (0.2–1.8)	0.369
Fever					
No	76 (13.2)	131 (20.8)	207 (17.1)	Ref.	
Yes	501 (86.8)	500 (79.2)	1001 (82.9)	1.73 (1.3–2.4)	<0.01
Cough					
No	51 (8.8)	153 (24.2)	204 (16.9)	Ref.	
Yes	526 (91.2)	478 (75.8)	1004 (83.1)	3.3 (2.4–4.6)	<0.01
Sore throat					
No	511 (88.6)	547 (51.7)	1058 (87.6)	Ref.	
Yes	66 (11.4)	84 (13.3)	150 (12.4)	0.8 (0.6–1.2)	0.32
Headache					
No	437 (75.7)	439 (69.6)	876 (72.5)	Ref.	
Yes	140 (24.3)	192 (30.4)	332 (27.5)	0.7 (0.6–0.9)	0.02
Shortness of breath					

Variable	Severe (%)	Non-severe (%)	Total (%)	Unadjusted OR (95% Cl)	*p*-value
No	50 (8.7)	440 (69.7)	490 (40.6)	Ref.	
Yes	527 (91.3)	191 (30.3)	718 (59.4)	24.3 (17.4–34.0)	<0.01
Nausea					
No	352 (61.0)	352 (55.8)	704 (58.3)	Ref.	
Yes	225 (39.0)	279 (44.2)	504 (41.7)	0.8 (0.6–1.0)	0.07
Vomiting					
No	508 (88.0)	499 (79.1)	1007 (83.4)	Ref.	
Yes	69 (12.0)	132 (20.9)	201 (16.6)	0.5 (0.4–0.7)	<0.01
Diarrhea					
No	511 (88.6)	551 (87.3)	1062 (87.9)	Ref.	
Yes	66 (11.4)	80 (12.7)	146 (12.1)	0.9 (0.6–1.3)	0.51
Fatigue					
No	210 (49.9)	211 (50.1)	421 (34.9)	Ref.	
Yes	367 (63.6)	420 (53.4)	787 (65.1)	0.9(0.7–1.1)	0.28
Body ache					
No	518 (89.8)	539 (85.4)	1057 (87.5)	Ref.	
Yes	59 (10.2)	92 (14.6)	151 (12.5)	0.7 (0.5–0.9)	0.02
Chest pain					
No	530 (91.9)	590 (93.5)	1120 (92.7)	Ref.	
Yes	47 (8.1)	41 (6.5)	88 (7.3)	1.3 (0.8–2.0)	0.27
Smell disorder					
No	510 (88.4)	553 (87.6)	1063 (88.0)	Ref.	
Yes	67 (11.6)	78 (12.4)	145 (12.0)	0.93 (0.7–1.3)	0.69
Taste disorder					
No	552 (95.7)	613 (97.1)	1165 (96.4)	Ref.	
Yes	25 (4.3)	18 (2.9)	43 (3.6)	1.5 (0.8–2.9)	0.17
Lack of appetite					
No	336 (58.2)	419 (66.4)	755 (62.5)	Ref.	
Yes	241 (41.8)	212 (33.6)	453 (37.5)	1.4 (1.1–1.8)	<0.01

Median and IQR of age, length of hospitalization, systolic blood pressure, heart rate, respiratory rate, leucocyte, segment neutrophil, eosinophil, basophil, monocyte, random blood glucose, urea, creatinine, and kalium were significantly higher in severe than non-severe patients (**Table 2**). Meanwhile, oxygen saturation and lymphocyte count were found significantly lower in severe than non-severe patients. Median and IQR of thrombocyte, D-dimer, PT, aPTT, fibrinogen, AST, ALT were also found significantly higher in patients with severe than non-severe symptoms (**Table 2**). Based on the results of multivariate analysis using backward stepwise method, the variables associated with COVID-19 severity were age, PT, D-dimer, fibrinogen, and AST, respectively (**Table 3**).

After adjusted with age and the presence of comorbidities; thrombocyte count, aPTT, and ALT had no association with severity with p=0.086, p=0.239, and p=0.533, respectively. Meanwhile, PT (p<0.018), D-dimer (p<0.001), fibrinogen (p<0.001), and AST (p=0.001) were significant predictors of COVID-19 severity. Age on admission had the highest OR (1.026; 95%Cl: 1.016–1.037) compared to other variables; therefore, age was the most associated factor in predicting COVID-19 severity (**Table 3**).

ROC curve was generated to analyze whether these biomarkers could predict COVID-19 severity. The AUC for thrombocyte count, PT, aPTT, D-dimer, fibrinogen, AST and ALT values on admission against COVID-19 severity was 0.568 (95%CI: 0.535–0.600), 0.598 (95%CI: 0.567–0.630), 0.577 (95%CI: 0.545–0.610), 0.736 (95%CI: 0.709–0.764), 0.740 (95%CI: 0.712–0.768), 0.679 (95%CI: 0.649–0.709), 0.589 (95%CI: 0.557–0.621), respectively (**Table 4**). Amongst all parameters, fibrinogen, D-dimer, and AST yielded the best AUC which were 0.740, 0.736, and 0.679 respectively (**Figure 1A**). The optimal cut-off value of fibrinogen for predicting severity was 526.5 mg/dL, with a sensitivity of 70.0%, specificity of 66.4%, positive predictive value of 65.6% and negative predictive value of 70.8%. When all parameters combined, the AUC was 0.804 (95% CI: 0.779–0.829) with a sensitivity and specificity of 82.0% and 65.5%, respectively (p<0.001) (**Figure 1B**).

Table 2. Comparison of continuous variables between severe and non-severe COVID patients

Variable	Severe (median (IQR))	Non-severe (median (IQR))	Total (median (IQR))	*p*-value
Age (year)	59.0 (49.0–66.0)	53.0 (40.0–61.0)	56.0 (45.0–64.0)	<0.01
Hospitalization (day)	8.0 (5.0–12.0)	6.0 (4.0–9.0)	7.0 (5.0–11.0)	<0.01
Systolic blood pressure (SBP) (mmHg)	134.0 (121.0–150.0)	130.0 (118.0–147.0)	133.0 (120.0–149.0)	<0.01
Diastolic blood pressure (DBP) (mmHg)	80.0 (71.0–88.0)	79.0 (71.0–85.0)	79.0 (71.0–87.0)	0.24
Heart rate(x/minute)	96.0 (85.0–108.0)	91.0 (82.0-103.0)	93.0 (83.0–105.0)	<0.01
Respiratory rate (x/minute)	28.0 (25.0–30.0)	21.0 (20.0–24.0)	24.0 (20.0–28.0)	<0.01
Temperature (°C)	36.8 (36.5–37.0)	36.8 (36.5–37.0)	36.8 (36.5–37.0)	0.06
Oxygen saturation (%)	84.0 (74.0–89.0)	96.0 (93.0–98.0)	91.0 (84.0–96.0)	<0.01
Hemoglobin (mg/dL)	13.0 (12.0–15.0)	13.0 (12.0–14.0)	13.3 (11.9–14.5)	0.22
Hematocrit (%)	35.0 (38.0–42.0)	39.0 (34.0–42.0)	39.0 (34.0–42.0)	0.24
Erythrocyte (10^6/mm^3)	4.7 (4.2–5.2)	4.7 (4.2–5.2)	4.7 (4.2–5.2)	0.40
Leucocyte (10^3/mm^3)	10.0 (7.2–14.0)	6.9 (5.3–9.2)	8.0 (6.0–11.6)	<0.01
Band neutrophil (%)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.64
Segment neutrophil (%)	83.0 (76.0–88.0)	69.0 (61.0–78.0)	76.0 (66.0–85.0)	<0.01
Eosinophile (%)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	<0.01
Basophile (%)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.04
Monocyte (%)	5.0 (4.0–7.0)	8.0 (6.0–10.0)	7.0 (4.2–9.0)	<0.01
Lymphocyte (%)	11.0 (7.0–16.0)	21.0 (13.0–28.0)	15.0 (9.0–23.0)	<0.01
Blood glucose (mg/dL)	148.0 (113.0–231.5)	122.0 (103.0–189.0)	132.0 (107.0–216.0)	<0.01
Urea (mg/dL)	39.0 (25.0–70.0)	25.0 (18.0–41.0)	31.0 (20.0–54.0)	<0.01
Creatinine (mg/dL)	1.00 (0.80–1.40)	0.90 (0.80–1.30)	1.0 (0.8–1.3)	<0.01
Natrium (mmol/L)	139.0 (135.0–142.50)	140.0 (136.0–143.0)	4.2 (3.8–4.6)	0.05
Kalium (mmol/L)	3.80 (4.30–4.80)	4.10 (3.70–4.50)	4.20 (3.80–4.60)	<0.01
Chloride (mmol/L)	105.0 (101.0–109.0)	105.0 (101.0–108.0)	105.0 (101.0–108.0)	0.69
Thrombocyte (10^3/mm^3)	237.00 (176.00–318.50)	214.00 (161.00–285.00)	225.0 (166.0–301.0)	<0.01
D-dimer (ng/mL)	1410.00 (710.0–3360.0)	550.00 (350.00–1160.00)	860.0 (442.5–2067.5)	<0.01
Prothrombin time (PT) (second)	14.20 (13.20–15.75)	13.60 (12.80–14.80)	13.9 (13.0–15.3)	<0.01
Activated partial thromboplastin time (aPTT) (second)	35.00 (31.00–39.70)	33.00 (30.30–36.70)	33.8 (30.7–37.9)	<0.01
Fibrinogen (mg/dL)	606.0 (509.0–724.5)	468.0 (371.0–561.0)	532.0 (416.2–654.0)	<0.01
Aspartate aminotransferase (AST) (U/L)	60.0 (40.5–86.0)	40.0 (28.0–60.0)	48.0 (33.0–74.0)	<0.01
Alanine aminotransferase (ALT) (U/L)	42.0 (26.0–70.0)	33.0 (21.0–53.0)	38.0 (24.0–60.0)	<0.01

Table 3. Multivariate analysis showing factors associated with COVID-19 severity

Variable	Unadjusted		Adjusted	
	OR (95% Cl)	*p*-value	aOR (95% Cl)	*p*-value
Age (year)	Not applicable	<0.01	1.03 (1.02–1.04)	<0.01
Hypertension	1.7 (1.4–2.2)	<0.01	1.3 (1.0–1.7)	0.08
Diabetes mellitus	1.66 (1.3–2.1)	<0.01	1.0 (0.8–1.4)	0.83
Acute kidney injury	1.7 (1.1–2.7)	0.03	0.8 (0.5–1.4)	0.40
Thrombocyte (cell/mm^3)	Not applicable	<0.01	1.0 (1.0–1.0)	0.09
Prothrombin time (PT) (second)	Not applicable	<0.01	1.04 (1.0–1.1)	0.02
Activated partial thromboplastin time (aPTT) (second)	Not applicable	<0.01	1.01 (1.0–1.03)	0.24
D-dimer (ng/mL)	Not applicable	<0.01	1.0 (1.0–1.0)	<0.01
Fibrinogen (mg/dL)	Not applicable	<0.01	1.0 (1.004–1.006)	<0.01
Aspartate aminotransferase (AST) (U/L)	Not applicable	<0.01	1.004 (1.002–1.007)	<0.01
Alanine aminotransferase (ALT) (U/L)	Not applicable	<0.01	0.999 (0.997–1.002)	0.53

Table 4. Analysis of variables in COVID-19 patients with ROC curve

Variable	AUC	95% CI	Cut-off	Se (%)	Sp (%)	LR+	LR-	PPV (%)	NPV (%)
Thrombocyte (cell/mm^3)	0.568	0.535–0.600	223.5	57.2	55.0	1.3	0.8	53.7	58.4
D-dimer (ng/mL)	0.736	0.709–0.764	805	72.3	66.4	2.2	0.4	66.3	72.4
PT (second)	0.598	0.567–0.630	13.75	61.9	53.9	1.3	0.7	55.1	60.7
aPTT (second)	0.577	0.545–0.610	34.75	51.5	63.2	1.4	0.8	56.1	58.8
Fibrinogen (mg/dL)	0.740	0.712–0.768	526.5	70.0	66.4	2.1	0.5	65.6	70.8
AST (U/L)	0.679	0.649–0.709	48.5	65.2	64.7	1.8	0.5	62.8	67.0
ALT (U/L)	0.589	0.557–0.621	36.5	58.2	55.2	1.3	0.8	54.3	59.1

aPTT: activated partial thromboplastin time; AUC: area under the curve; LR+: likelihood ratio positive; LR-: likelihood ratio negative; NPV: negative predictive value; PPV: positive predictive value; PT: prothrombin time; Sp: specificity; Se: sensitivity

Discussion

In this study, age was the strongest predictor of COVID-19 severity. This result was consistent with some previous reports [30-32]. Age was also indicated as single risk factor for developing severe disease along with male gender and comorbidities, but their effects were on lesser extent when compared to age. Elderly and patients aged ≥60 years were more at risk of developing severe COVID-19 [33,34]. The present study showed no significant difference of gender based on severity. Nevertheless, the proportion of males (59.4%) having severe disease was higher than females (40.6%). This finding was contradicted with previous studies which stated male as significant predictor of severe cases [35-37]. Herein, the presence of comorbidities was associated with disease severity. In a previous meta-analysis, chronic respiratory disease (OR 3.56 (95% CI 2.87–4.41) was the strongest predictor among others [38]. Moreover, diabetes was suggested as the most consistent comorbidity that could predict COVID-19 severity [39].

The multivariate analysis herein revealed that thrombocyte count and aPTT were not significantly associated with COVID-19 severity and their AUCs were less than 0.60, respectively. These findings suggest that thrombocyte count and aPTT, as individual predictors, did not have good accuracies. These findings are in contradiction with previous studies which reported the association between thrombocytopenia and COVID-19 severity [40-44]. In a previous study, a series of thrombocyte count laboratory tests was performed three times during hospitalization (on 1st, 3rd, and 6th day of admission) [42]. They found that the non-survivors were likely to have decreasing or increasing-then-decreasing pattern of thrombocyte count compared to those who survived [42]. Moreover, APTT was previously reported having the predictive ability to differentiate mild from moderate and severe COVID-19 cases [17]. PT, however, was significantly associated with severe COVID-19 in this present study, where its AUC reached 0.598 (still below 0.60). Previous studies had reported significantly prolonged PT in severe compared to non-severe COVID-19 patients [45-49]. In different studies, prolonged PT was found to be capable of distinguishing different severity levels of COVID-19 [17,50].

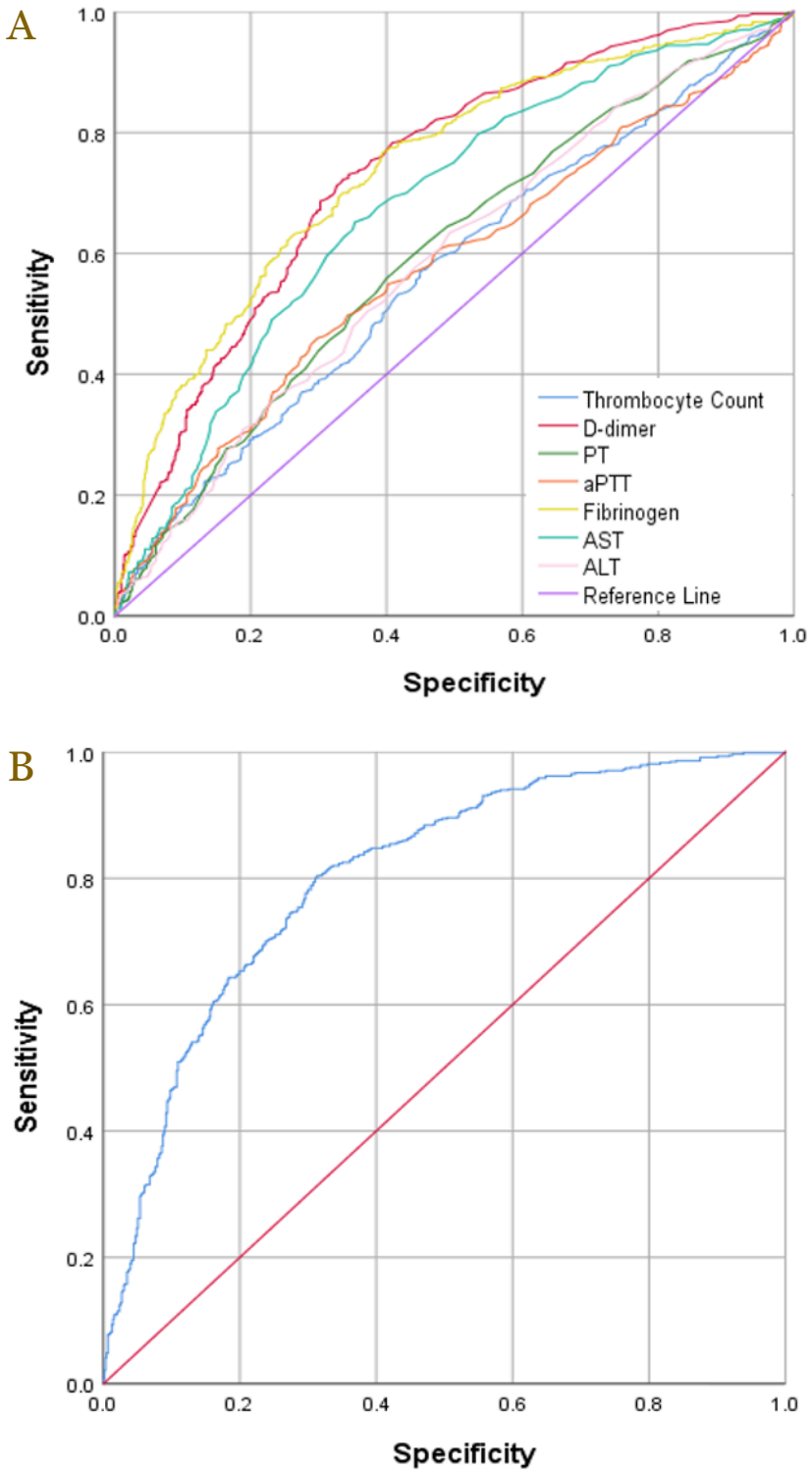

Figure 1. ROC curve for the ability of thrombocyte count, D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) to predict severity in COVID-19 (A) and combined parameters as predictors for COVID-19 severity (B).

In this present study, D-dimer was the best predictor for severe COVID-19 among others with AUC, sensitivity, and specificity of 0.736, 72.3% and 66.4%, respectively. The ability to predict severe cases among COVID-19 patients had been reported previously[51-54]. The predictive value of D-dimer in this present study is close with that reported previously [50,55]. In a previous study, it was also reported that AUC performed better than PT and TT as a COVID-19 severity predictor [56]. As for fibrinogen, it was found to be the second-best predictor after D-

dimer, where its AUC, sensitivity, and specificity reached 0.740, 70.0%, and 66.4%, respectively. In line with previous studies, they have reported significant association between fibrinogen and the disease severity [45,57]. Though fibrinogen on admission is higher among severe COVID-19 cases than that of non-severe cases, the level may decrease following the disease progression such as the disseminated intravascular coagulation (DIC) [50,58-62].

SARS CoV-2 infection can activate the coagulation pathway. The infection in blood vessel walls can damage their integrity and cause blood vessel cell death. The body responds to coagulation events by releasing fibrin and thrombus. It levels fibrin and D-dimer degradation products in severe COVID-19 patients [63]. The increment of D-dimer levels indicates hypercoagulability in patients. This condition might be caused by aggressive inflammatory response leading to the activation of fibrinolysis system in the alveoli. Formation of thrombin also increases due to endothelial cell dysfunction. Hypoxia could also trigger the formation of thrombosis due to the increased blood viscosity [64].

In the early phase, fibrinogen regulated the inflammatory response; the function of acute phase fibrinogen is associated with thrombus formation in this stage, which occurs at low levels and is characterized by a mild increase in D-dimer. Inflammation continues forming a large thrombus that limits the spread of microbes or proteins associated with damage. The formation of a thrombus is characterized by an increase in D-dimer, causing platelets to decline. Fibrinogen is no longer produced from platelets leading to the increase of D-dimer [65]. The increasing and decreasing phase of each parameter depends on the COVID-19 pathogenesis stage. Platelets, fibrinogen, PT, or aPTT are dependent to SARS-CoV-2 infection-related coagulopathy. Platelet count and fibrinogen could decline and PT or aPTT could be prolonged in DIC. Meanwhile, D-dimer increases significantly in both mild and severe COVID-19, and correlates with the mortality [66].

In the multivariate analysis herein, AST was associated with the worsening of COVID-19 but not the ALT. The ROC analysis in the present study yielded AST and ALT with AUCs of 0.679 and 0.589, respectively. According to a previous report, AST and ALT levels were significantly higher in patients with moderate-to-severe COVID-19 as compared to patients with asymptomatic-to-mild COVID-19 [67]. AST and AST/ALT elevation was also correlated with COVID-19 prognosis [68,69]. Liver damage caused by COVID-19 can be derived from various mechanisms, such as hypoxia related to pneumonia, drugs such as remdesivir or other antivirals, or due to critical phases of ICU treatment. Based on a study examining RNA sequencing in COVID-19 patients showed significantly higher expression of angiotensin converting enzyme-2 (ACE2) receptors in cholangiocytes (59.7%) than in hepatocytes (2.6%). This suggests that SARS-CoV-2 directly attacks the intrahepatic bile ducts and slightly attacks hepatocytes [70]. Hepatocellular or mixed injury were more likely to progress into severe disease. For patients with preexisting chronic liver disease, chronic hepatitis B, liver cirrhosis, certain medications such as antiviral, antibiotic, analgesic, antipyretics might also cause liver injury [22,71].

As predictors, thrombocyte, D-dimer, PT, aPTT, fibrinogen, AST, and ALT may decrease or increase depending on the infection stage, immune response, physiological changes, and underlying conditions of the patients. Therefore, the predictive ability of combined parameters was estimated in the present study yielding the AUC of 0.804. The value was higher than those yielded by the individual predictors themselves, suggesting an improvement in the accuracy of distinguishing severe from non-severe COVID-19 cases. To the best of our knowledge, this is the first study combining both hemostatic and liver function parameters to predict severe COVID-19.

The present study also has several limitations. First, it is a retrospective study which rather provides association, but incapable of finding causation and only relied on data retrieved from medical records. This study was also a single center study (involved only inpatients) which did not provide data with wide variability and probably reducing the ability to generalize this study. This study mostly retrieved data with moderate-severe symptoms (requiring hospitalization). Therefore, milder symptoms which only need house quarantine were found less frequent than other degrees. The lack of data regarding clinical follow-up and serial laboratory data during hospitalization adversely affected the analysis in this study. Stratifications of sensitivity, specificity, optimal cut-off value of hemostatic and liver functions parameters based on age, gender, and comorbidities were not carried out. In-depth multicenter prospective studies which

encompass all clinical and laboratory data on admission, during hospitalization, and when being discharged should be conducted in the future. Due to the difficulty of determining the causality of these hematological changes, further investigation using basic research with animal experiments is also suggested.

Conclusion

In conclusion, the results of this study showed that thrombocyte count, PT, D-dimer, fibrinogen, and AST on admission were significantly higher in severe than non-severe patients. Based on multivariate analysis, age was the strongest predictor associated with severity. Combining thrombocyte, D-dimer, PT, aPTT, fibrinogen, AST, and ALT increased the predictive value of individual predictors. By using combined variables, the severity can be predicted, and appropriate initial clinical management or treatment could be performed to reduce the risk of morbidity and mortality of COVID-19.

Ethics approval

Ethical clearance was approved by the Medical Ethics Review Board of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (No. 033/EA/FK-RSUDZA/2022). All information regarding study participants data were kept confidential.

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Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

All data underlying the results are available from the corresponding author upon reasonable request.

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