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Novel COVID Model to Help Early Diagnosis of COVID-19 and Prediction of Disease Severity: A Multicenter Study

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ABSTRACT

Early identification of patients with coronavirus disease-2019 (COVID-19) particularly those who develop critical illness is of great importance and aids in delivering proper treatment and optimizing the use of resources. This work aimed to develop a clinical score at hospital admission for COVID-19 diagnosis and predicting severe disease. This is a multicenter case-control study including 2793 PCR-confirmed consecutive COVID-19 patients and 251 patients without COVID-19 presented to 6 hospitals affiliated to the General Organization for Teaching Hospitals, Egypt (1st-May-2020 to 31st-July-2020). There was no difference among groups regarding age and gender distribution. Patients with COVID-19 had significantly higher white blood cell count, platelet count, ALT, AST, total serum bilirubin, serum creatinine, CRP, Ferritin, D-dimer, and fibrinogen and lower serum albumin and more prolonged INR. ALT, ferritin, D-dimer, and Fibrinogen were significantly higher and oxygen saturation was significantly lower, in patients with severe COVID-19. Multivariate regression analysis revealed Oxygen saturation, ferritin, D-dimer and CRP are the independent factors associated with severity. We developed a novel COVID model which enabled the correct diagnosis of COVID-19 at cutoff point (0.1) with an AUC=0.99, (P-value<0.0001), sensitivity 99%, and specificity 89%. At this point, COVID-19 severity could be diagnosed with AUC of 0.88, sensitivity 87%, specificity 71%.

Keywords

COVID-19, SARS-CoV-2, Pandemic, Egypt, COVID model.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection has spread to over 200 countries worldwide since January 2020 [1]. Most individuals with COVID-19 infection (about 80%) have been reported to present with mild uncomplicated disease, and only a subset develops severe disease requiring hospitalization [2]. the mean duration from onset of symptoms to death was estimated to be 17.8 days and to hospital discharge to be 24.7 days [3]. The pandemic has led to the loss

of livelihoods due to long shutdowns, which have harmed the global economy. Consequential progress in COVID-19 related clinical research and practice has led to a better understanding of the disease and its management. On the other hand, there is a big concern about the continued spread of the virus, as SARS-CoV-2 continues to wreak havoc across the world, with many countries enduring the third wave of outbreaks that is mainly attributed to the emergence of mutant variants [2]. This continued spread is due to the easy viral transmission by patients with only mild illness or asymptomatic carriers [4].

This large number of infected patients resulted in overwhelming unmet medical needs. Huang and his colleagues [5] first reported clinical manifestations of 41 patients with COVID-19 and observed that patients admitted to the intensive care units showed higher cytokine levels in the plasma compared with patients in the wards. Older males with comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, and cerebrovascular disease are more likely affected with COVID-19 [6].

This study aimed to clarifying the independent high-risk factors with multivariate analysis and establishing an accurate prediction of progression of COVID-19 become desirable. In the present study, we stepwise multivariate discriminant analysis to provide an accurate risk estimation model to help clinicians to identify severe cases with COVID-19.

Materials and Methods

This is a multicenter case-control study that included consecutive patients with and without COVID-19 disease presented 6 hospitals affiliated to the General Organization for Teaching Hospitals and Institutes (GOTHI) during the period from 1st of May 2020 to 31st of July 2020 who agreed to participate in the study and provide blood samples. We included patients with severe and non-severe COVID-19 disease. The included hospitals are Al-Sahel hospital, Al-Matareya hospital, Al-Ahrar hospital, Ahmed Maher Teaching Hospital, Al-Gomhoreya hospital, and the National Hepatology and Tropical Medicine Research Institute (NHTMRI). The diagnosis of COVID-19 was based on a positive reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal swabs. Patients with negative RT-PCR results or those who did not undergo the swab were excluded.

Ethics Statement

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the ethical committee of the General Organization for Teaching Hospitals and Institutions (GOTHI), Number HAM00117, 22/7/2020. Written informed consent was obtained from all patients before they participated in the study.

Subjects

This study included adults above 18 years, male and female genders. Patients with a confirmed diagnosis of SARS-CoV-2 virus infection (defined as a positive result of real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for nasal and pharyngeal swab specimens) were recruited. Written informed consent was obtained from all patients before they participated in the study. We included patients with severe and non-severe COVID-19 disease at hospital admission. The severity of COVID-19 was categorized according to the management protocol of the Egyptian Ministry of Health and Population into mild, moderate, and severe cases. Mild cases are defined as symptomatic cases with lymphopenia or leucopenia with no radiological lung affection by pneumonia. Moderate cases are symptomatic patients with radiological features of pneumonia with or without leucopenia and lymphopenia. Severe and critical cases are defined by the presence of any of the following: respiratory rate: above 30 per minute, SaO2 less than 92 at room air, PaO_2/FiO_2 ratio less than 300, chest radiology showing more than 50% lung affection or progressive lung affection within 24 to 48 hours, critically ill if SaO2 less than 92, or respiratory rate above 30 per minute, or PaO2/FiO2 ratio < 200 despite oxygen therapy. Severe and critical cases are indicated for intensive care unit (ICU) admission. Treatments were applied according to the protocol [7]. Baseline data were collected in the form of Demographic data e.g. Age, Gender, cigarette smoking, comorbidities in addition to all the presenting symptoms of the included patients.

Routine laboratory investigations were done including

Complete blood picture (CBC), Erythrocyte sedimentation rate (ESR), Liver function tests: (serum Bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Kidney function tests: (blood urea nitrogen, serum creatinine), lactate dehydrogenase (LDH), and D-dimer. Inflammation biomarkers: (Serum ferritin (determined using the chemiluminescence immunoassay (CLIA)), C-reactive protein (CRP), Pro-calcitonin (measured by Chemiluminescence), Tumor necrosis factor-alpha (TNF-Alpha) (measured by TNF-Alpha ELISA Assay Kit, Immundiagnostik, Germany, normal value is <20 pg/ml), Interleukin-6 IIL-6 (Roche Cobas e411 (Roche Diagnostics GmbH, Mannheim, Germany. The upper limit of normal is 7 pg/ml)) were assessed according to manufacture instructions. Regression analysis was performed to detect the independent markers involved in COVID-19 diagnosis.

Statistical analysis

Data collection and cleaning were done using Microsoft excel 365©, while for Statistical analysis IBM SPSS 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) was used. Descriptive statistics were done in order to explore, summarize and present the data. For hypothesis testing, we used Mann whitney tests and Chi square tests with significance level of 5%. The independent discriminative value of variables for the diagnosis of COVID 19 and severity were then assessed by ROC curves and stepwise multivariate discriminant analysis. The score was constructed by combination of the independent factors. The best score for discrimination was the logistic regression function that combined the most discriminatory

independent factors. The best cutoff values for optimal diagnosis of COVID19 and severity were determined from the ROC curves. Common indicators of the variables and the score performances were calculated.

Results

This case-control study included 2793 PCR-confirmed COVID-19 patients and 251 patients with NON-COVID-19 diagnoses from hospitals affiliated to GOTHI. Demographic features of the studied patients are shown in table 1. There was no difference among the studied groups regarding age and gender distribution (P-value >0.05). Patients with COVID-19 had significantly higher white blood cell count, platelet count, ALT, AST, total serum bilirubin, serum creatinine, CRP, Ferritin, D-dimer, and fibrinogen and lower serum albumin and more prolonged INR.

For the differentiation of patients with and without severe COVID-19, Univariate analysis revealed that ALT, ferritin, D-dimer, and Fibrinogen were significantly higher and oxygen saturation was significantly lower in patients with severe COVID-19 infection. Multivariate regression analysis was performed to detect the independent factors associated with severity and revealed Oxygen saturation, ferritin, D-dimer, and CRP, table 2. The best overall model that could best diagnose COVID-19 was then constructed by entering four significant variables into the regression model. We developed a novel model for COVID 19 diagnosis named the COVID model. It can be represented as: (0.88 + CRP * 0.002 + Ferritin * 0.001 + D dimer * 0.0001) – (Oxygen saturation * 0.01). The levels (median; IR) of COVID model in healthy participants and patients with COVID-19 were – 0.007 (-0.04- - 0.048) and 0.63 (0.2-1.2), respectively (P-value < 0.0001). The levels (median; IR) of COVID model in patients with non-severe and severe COVID-19 were 0.59 0.26-1.1) and 1.8 (1.6-2.1), respectively (P-value < 0.0001) Figureure 1 (A-B).

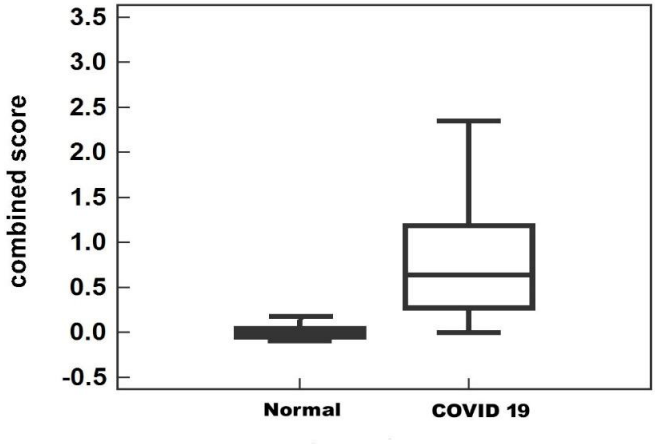


Figure 1a: COVID model in normal and patients with COVID-19.

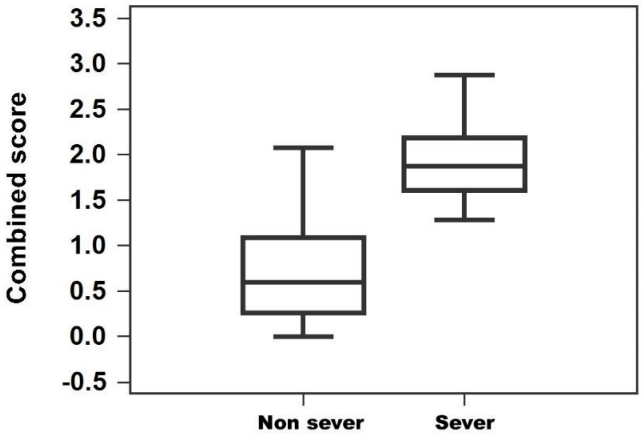


Figure 1b: COVID model in severe and non-severe patients with COVID-19.

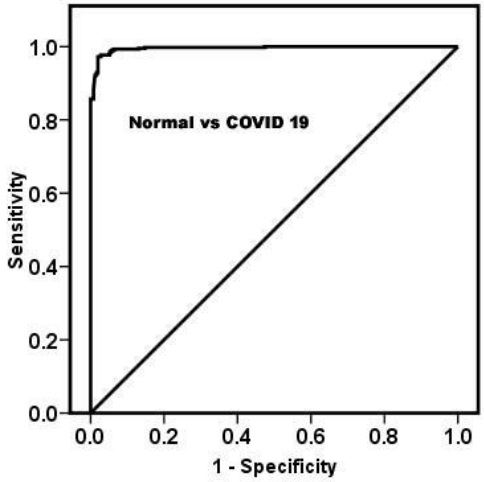
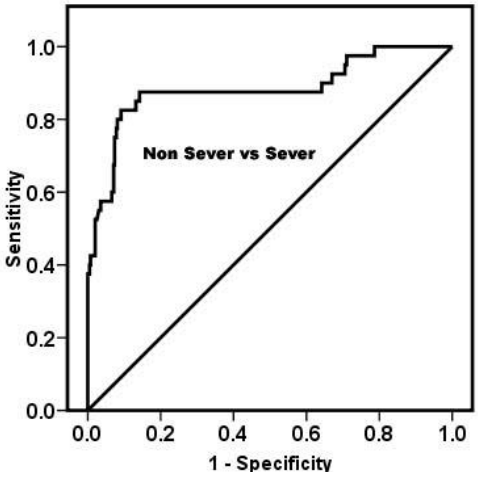


Figure 1c: ROC curve for the use of COVID model in COVID-19 diagnosis.

Figure 1d: ROC curve for the use of COVID model in the diagnosis of severe COVID-19.



COVID model enabled the correct diagnosis of patients with

Table 1: Demographic and laboratory features of the studied groups.

Variables	Healthy (n= 251)	All COVID (n=2793)	P value
Female No (%)	145 (57.7 %)	1619 (58%)	0.12
Male No (%)	106 (42.3%)	1174 (42%)	
Age (Years)	52.6±14.5	52.4±17.9	0.86
Haemoglobin (gm /dl)	13.6±1.4	13.1±9.2	0.37
White blood cells (10^9/L)	6.2 (5.0-7.7)	8.0 (6.0-11.0)	< 0.0001
Platelet count (10^9/L)	253.6±64.5	328.7±113.9	< 0.0001
ALT (U/L)	19.9±9.7	46.7±11.9	< 0.0001
AST (U/L)	25.9±4.2	51.6±14.3	< 0.0001
Albumin (gm/L)	42.2±6.1	39.3± 11	< 0.0001
Total bilirubin (mg/dl)	0.83±0.3	0.83±0.5	0.7
Direct bilirubin (mg/dl)	0.25±0.12	0.36±0.29	0.8
Creatinine (mg/dl)	0.8±0.4	1.3±0.81	< 0.0001
Sodium (mEq/L)	135.5±3.4	136.5±20.8	0.7
Potassium (mEq/L)	4.5±2.1	4.5±4.0	0.9
INR	1.0± .0.2	1.3± .0.5	< 0.0001
Temperature	36.1±0.2	38.2±0.45	< 0.0001
Respiratory rate	-	22.4±5.3	-
Oxygen saturation (mmHg)	99±0.82	94.9±5.8	< 0.0001
coma scale	-	14.9±0.4	-
CRP (mg/L)	1.6 (1.0-2.7)	16.0 (6.0-48.0)	< 0.0001
Ferritin (ng/ml)	68 (30-121)	550 (250-1000)	< 0.0001
D dimer (ng/ml)	300 (200- 400)	900 (500-1500)	< 0.0001
Fibrinogen	10.0 (9.0-10)	20 (10-100)	< 0.0001

Table 2: Univariate and Multivariate Regression analysis for prediction of severe COVID-19 disease.

Variables	Univariate analysis			Multivariate analysis	
	Non severe (n= 2404)	Severe (n= 389)	P value [a]	Odd ratio	P value [b]
Female					
Male	914 (38.0 %)				
1490 (61.9%)	133 (34.2%)				
256 (65.8 %)	0.13	-	-		
Age (years)	51.2±16.2	52.4±17.9	0.73	-	-
Hb (gm /dl)	13.2±9.7	13.2±1.9	0.93	-	-
TLC(10^9/L)	8.0 (6.0- 11.0)	9.0 (7.0- 12.0)	.0.07	-	-
Platelet count (10^9/L)	328.6±111.9	330.4±133.5	0.92	-	-
ALT (U/L)	46.7±11.9	46.7±11.8	0.01	0.95 (0.91-1.0)	0.78
AST (U/L)	51.1±14.2	55.6±15.1	0.06	-	-
Albumin (gm/dl)	38±1.16	4.0±0.85	0.09	-	-
Total bilirubin (mg/dl)	0.82±0.30	0.93±0.28	0.07	-	-
Direct bilirubin (mg/dl)	0.35±0.29	0.45±0.28	0.08	-	-
Creatinine (mg/dl)	1.3±0.8	1.3±0.3	0.95	-	-
Sodium (mEq/L)	136.1±21.8	140.1±5.7	0.25	-	-
Potassium (mEq/L)	4.5±4.2	4.2±0.9	0.61	-	-
INR	1.2±0.3	1.2±0.37	0.83	-	-
Temperature	38.1±0.97	38.2±1.1	0.42	-	-
Respiratory rate	22.1±5.2	24.5±5.7	-	-	-
Oxygen saturation (mmHg)	95.5±5.4	89.1±7.2	< 0.0001	1.6 (1.3-2.5)	0.003

Glasgow coma scale	14.9±37	14.8±0.6	0.07	-	-
CRP (mg/L)	12 (6-48)	36 (12-96)	< 0.0001	1.8 (1.4-2.9)	0.001
Ferritin (ng/ml)	550 (250 -1000)	1000 (500-1500)	< 0.0001	2.8 (1.5-4.3)	< 0.0001
D-dimer (ng/ml)	850 (500-1500)	1500 (750- 2000)	0.009	1.3 (1.1-2.0)	0.05
Fibrinogen	20 (10- 100)	100 (20-200)	0.02	0.96 (0.92-1.0)	0.79

Table 3: Diagnostic power of candidate variables and score.

Markers	AUC (95% Cl)	Cut-off	Sensitivity	Specificity	PPV	NPV
Normal vs. all COVID 19						
CRP	0.99 (0.99-1.0)	6	98	100	99	99
D-Dimer	0.93 (0.91-0.95)	400	85	90	94	78
Oxygen saturation	0.77 (0.73-0.81)	98	66	67	77	53
Ferritin	0.98 (0.97-0.99)	250	71	98	98	66
Score	0.99 (0.99-1.0)	0.1	99	89	94	99
Non severe vs. severe COVID-19						
CRP	0.82 (0.72-0.91)	50	78	81	30	97
Oxygen saturation	0.76 (0.68-0.85)	85	28	93	30	93
D-Dimer	0.69 (0.61-0.77)	1000	65	69	20	95
Ferritin	0.84 (0.76-0.92)	1000	73	84	32	97
Score	0.88 (0.81-0.95)	1.0	87	71	35	98

COVID-19 with an AUC of 0.99 (Figure 1C). Based on the ROC curve, the optimal cutoff point (0.1) was chosen for COVID diagnosis. Using this cutoff, the COVID model had a sensitivity of 99% and specificity of 89%. At this point, the severity of COVID-19 can be diagnosed with an AUC of 0.88 (table 3 and Figure 1C-1D).

Discussion

The rapidly increasing number of new COVID-19 cases worldwide daily has put a heavy burden on the medical resources in countries with large outbreaks. Therefore, identifying risk factors at the presentation that help guiding the diagnosis and predict the likelihood of disease progression would help the physicians to decide which group of patients can be managed safely at outpatient clinics and hospitals and who needs early transfer to tertiary centers [8]. In this study, oxygen saturation, ferritin, D-dimer, and CRP were associated with the diagnosis of COVID-19 and the development of severe disease in Egyptian patients with COVID-19.

A study by Guan et al. [9] that recruited 1,099 patients with COVID-19 revealed that Oxygen saturation, respiratory rate, leukocyte/lymphocyte count, and chest X-ray/CT manifestations predicted poor outcomes. In their study, older ages and the presence of comorbidities were associated with COVID-19. Severe presentations were associated with distinguished laboratory abnormalities (leukopenia, lymphopenia, thrombocytopenia, elevated CRP) as compared with non-severe cases. Another study by Zhou et al. [10] showed that increasing age, worse SOFA score, and d-dimer above 1 µg/L are potential predicting factors that could help physicians to identify patients with poor prognoses at an early disease stage. Zhang and his colleagues reported the clinical manifestations of 140 patients with COVID-19. They found no gender difference between severe and non-severe illnesses. On admission laboratory results revealed normal total leukocyte count with decreased lymphocyte and eosinophil counts in the majority of patients. Follow-up laboratory testing revealed a progressive reduction in lymphocyte and eosinophil counts, and these changes had a positive correlation with disease severity. Similar to our study, they found that D-dimer levels above 0.4 µg/mL, CRP levels above 4.76 mg/dL, and procalcitonin (above 0.01 µg/dL) were associated with a severe COVID-19 presentation [11]. They also found that patients with older age, chronic medical illnesses, and prominent abnormal laboratory results were also associated with severe disease [11]. Several studies have displayed an association of COVID-19 severity, progression, and unfavorable outcome with male elderly individuals (over 60 years) with chronic medical illnesses e,g, Diabetes mellitus, cardiovascular and cerebrovascular diseases [12,13].

Coagulation indices were studied in SARS-CoV-2–infected patients with different disease severities, and compared to healthy individuals in several studies [14]. A retrospective study of 94 patients with SARS-CoV-2 infection found that Levels of D-dimer (10.36 ± 25.31 µg/mL), fibrinogen (502 ± 153 mg/dL), and FDP (33.83 ± 82.28 µg/mL) were significantly higher in all patients with COVID-19 compared to healthy individuals. Furthermore, D-dimer (19.1 ± 35.5 µg/mL versus 2.1 ± 2.9 µg/mL) and FDP (60 ± 10.9 µg/mL versus 7.9 ± 11.4 µg/mL) values were higher in severe cases compared with mild cases [15]. Abnormal coagulation factors and overt widespread intravascular coagulation is an early indicator of increased mortality in patients with COVID-19. D-dimer appears in the blood after coagulation is established. D-dimer is a strong independent predictor of severe

disease and mortality in COVID-19 [16]. During the early stages of COVID-19 disease, the D-dimer level is frequently normal or slightly elevated [17].

A systematic review that reviewed and critically appraised prediction models for diagnosing COVID-19 in patients with suspected infection revealed that the most common reported predictors of SARS-CoV-2 infection are age, gender, body temperature, clinical manifestations, blood pressure, and serum creatinine. The most common reported predictors of severe COVID-19 presentation are age and features derived from chest computed tomography (CT) examinations [18].

In conclusion, Prediction models for SARS-CoV-2 infection are progressively used in COVID-19 related scientific research to support medical decision-making when urgently needed. Oxygen saturation, ferritin, D-dimer, and CRP, and the built COVID model were associated with the diagnosis of COVID-19 and severe COVID-19 presentation among our Egyptian patients with COVID-19.

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References

1. https://www.who.int/docs/default-source/coronaviruse/situationreports/20200229-sitrep-40-covid-19.pdf
2. Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19). In: StatPearls. 2021.
3. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020; 20: 669-677.
4. Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. N Engl J Med. 2020; 382: 1278-1280.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395: 507-513.
7. https://www.elwatannews.com/data/iframe/pdf/17175200761591035127.pdf
8. Shang Y, Liu T, Wei Y, et al. Scoring systems for predicting mortality for severe patients with COVID-19. EClinical Medicine. 2020; 24: 100426.
9. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382: 1708-1720.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-1062.
11. Zhang J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75: 1730-1741.
12. Shi Q, Zhao K, Yu J, et al. Clinical characteristics of 101 non-survivors hospitalized with COVID-19 - a single center, retrospective study. medRxiv. 2020.
13. Xu L, Mao Y, Chen G. Risk factors for 2019 novel coronavirus disease (COVID-19) patients progressing to critical illness: a systematic review and meta-analysis. Aging (Albany NY). 2020; 12: 12410-12421.
14. Tjendra Y, Al Mana AF, Espejo AP, et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med. 2020; 144: 1465-1474.
15. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020; 58: 1116-1120.
16. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis. 2020; 95: 304-307.
17. Grobler C, Maphumulo SC, Grobbelaar LM, et al. Covid-19: The Rollercoaster of Fibrin (Ogen), D-Dimer, Von Willebrand Factor, P-Selectin and Their Interactions with Endothelial Cells, Platelets and Erythrocytes. Int J Mol Sci. 2020; 21: 5168.
18. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of COVID-19: systematic review and critical appraisal. BMJ. 2020; 369: m1328.