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In-hospital mortality prediction using dual antiplatelet therapy score in coronavirus disease 2019

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Abstract

Aim: Mortality rates are high in cases of coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) despite the advances in treatment regimens. The Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score, an up-to-date scoring system, is frequently used in cardiology practice after stent implantation.
This study aimed to investigate the use of the PRECISE-DAPT score to predict in-hospital mortality in patients with COVID-19.
Material and Methods: A total of 264 consecutive patients with positive COVID-19 polymerase chain reaction (PCR) tests were enrolled in this study. Patients were divided into three groups according to PRECISE-DAPT scores: low-, intermediate-, and high-score groups (PRECISE-DAPT scores of <17, 17–24, and ≥25; n=170, 57, and 37, respectively). Those who died in the hospital and those discharged after recovery were noted.
Results: Among 120 women and 144 men with positive PCR test results, a total of 40 patients (low-score, n=16; intermediate-score, n=11; and high-score, n=13) died in the hospital. Prolonged hospital stay was observed in the high-score group compared with the low-score group (p=0.011). In multivariate analysis, the PRECISE-DAPT score (hazard ratio: 0.962, 95% confidence interval: 0.943–0.982, p<0.001) significantly correlated with in-hospital mortality.
Discussion: PRECISE-DAPT scores are associated with mortality in patients with COVID-19. The PRECISE-DAPT scoring system may be useful for predicting in-hospital mortality.

Keywords
COVID-19, Mortality, Survival, Poor Prognosis

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Introduction

In the last year, a factor of unknown origin in Wuhan of Hubei Province in the People's Republic of China caused severe respiratory failure and affected the entire world in a short time with a serious increase in deaths [1]. The factor that left all humanity desperate was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) on February 11, 2020, and the disease that emerged was added to the medical literature as coronavirus disease 2019 (COVID-19) [2].

The disease became better known; however, it continued to spread across the continents. In addition to pulmonary involvement, COVID-19 presents with cardiac, renal, and central nervous system involvements, and it can cause increased mortality and morbidity [3]. There is no simple and widely accepted scoring system that can be used to reduce the short-term and long-term mortality associated with the disease, but studies have shown that low platelet counts and acute renal failure during hospitalization are associated with increased mortality [4,5]. In one study, older age and female gender were associated with more arrhythmic events [6].

The Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score, which has recently been used especially in cardiology practice, is useful in patients with ST-elevation myocardial infarction (STEMI) in terms of determining for which individuals and how long dual antiplatelet therapy should continue after the invasive procedure [7]. The PRECISE-DAPT score is simply calculated by using five components (age, hemoglobin level, white blood cell count, creatinine clearance, and bleeding history of the patient) [8]. In addition to the information provided about the optimal duration of dual antiaggregant therapy in patients with STEMI, recent studies have shown that it can be a useful score in predicting the short-term and long-term mortality of patients with STEMI. Furthermore, another study showed that it can be used to predict contrast nephropathy that may develop after coronary angiography in patients with STEMI [9]. Although studies have been conducted to evaluate individual risk factors in COVID-19, the use of a scoring system to be obtained with a combination of various parameters remains unclear. The aim of our study was to investigate the use of the PRECISE-DAPT score, which plays a role in the understanding of various issues from the treatment process to mortality studies in cardiology practice, in predicting in-hospital deaths in patients diagnosed with COVID-19.

Material and Methods

Patient group and study protocol

This single-center retrospective observational study comprised 264 consecutive patients whose polymerase chain reaction (PCR) tests were positive for COVID-19 according to the diagnostic guidance of the WHO. Patients who applied to our tertiary university hospital between April and December 2020 and were found to have RNA for SARS-CoV-2 in samples taken from combined throat and nasal swabs were included in the study.

Patient data such as demographic characteristics, comorbidities, and laboratory results were obtained from electronic medical records. The background information of the patients was collected from medical records for comorbidities including hypertension, diabetes, cardiovascular disease, chronic kidney disease, and malignancy. Laboratory values and PCR test results obtained from peripheral venous blood samples taken during hospitalization were recorded.

The PRECISE-DAPT score for all patients was calculated using the website of the PRECISE-DAPT Score Working Group Executive Committee (http://www.precisedaptscore.com). This score evaluates age, hemoglobin level, white blood cell count, creatinine clearance, and bleeding history [10]. The patients were divided into three groups according to their scores as low-, intermediate-, and high-score groups (PRECISE-DAPT scores of <17, 17–24, and ≥25; n=170, 57, and 37, respectively) as defined in the literature. Those who died in the hospital and those discharged after recovery were noted (Figure 1).

The following patients were excluded from the study: those who underwent an intervention in the hospital due to newly diagnosed coronary artery disease, stage 5 chronic kidney disease or dialysis, or an active infection other than COVID-19; those with an acute cerebrovascular disease or active bleeding that may cause anemia; those receiving plasma therapy, those with a history of bleeding diathesis or known coagulopathy, and those receiving immunosuppressive therapy; and all patients younger than 18 years of age. The study was approved by the COVID-19 Science Committee of the Ministry of Health and our university's ethics committee and was conducted in accordance with the Declaration of Helsinki (Decision No: 23-2011-KAEK-27/2020-E.200018129).

Definitions

Hypertension was defined as systolic blood pressure of >140 mmHg and/or diastolic blood pressure of >90 mmHg or the use of antihypertensive drugs. Diabetes mellitus was defined as fasting blood glucose of >126 mg/dL or the use of antidiabetic medication. Chronic kidney disease was defined as a glomerular filtration rate of <60 mL/min/1.73 cm2. Anemia was defined as the presence of hemoglobin values of <12.0 g/dL in women and <13.0 g/dL in men. Bleeding history was defined as active pathological bleeding or major bleeding within the previous 3 months.

Statistical analysis

Statistical data were analyzed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to evaluate the distribution of continuous variables. Data that did not conform to normal distribution are expressed as median

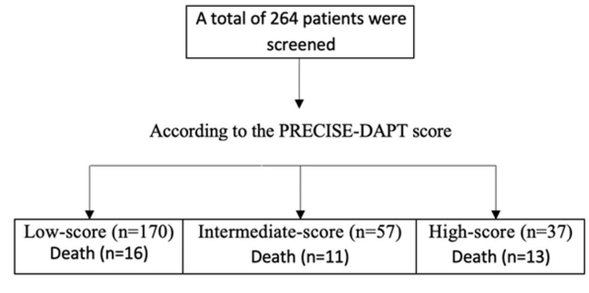

Figure 1. The study's flow chart

and interquartile range. Categorical variables are expressed as percentages and numbers. The chi-square test was used when comparing the probability ratios of categorical variables. For the comparison of continuous variables between groups, the Kruskal–Wallis test was used. In addition, Bonferroni's post hoc test was used. Univariate and multivariate Cox proportional hazard analyses were performed to determine the relation of the PRECISE-DAPT score and its components with mortality. Receiver operating characteristic (ROC) curves were used for in-hospital mortality predictions of the PRECISE-DAPT score and its components in patients with COVID-19. Values of $p<0.05$ were considered statistically significant.

Results

Clinical features

The demographic results of the patients are shown in Table 1. We included 264 PCR-positive patients with COVID-19 (144 men and 120 women). There were 170 (103 men and 67 women), 57 (30 men and 27 women), and 37 (11 men and 26 women) patients in the low-, intermediate-, and high-score groups, respectively. The high-score group comprised older patients. There was no difference between the groups in terms of diabetes mellitus, previous cardiovascular disease, heart failure, chronic kidney disease, or previous malignancy.

At the time of first diagnosis, oxygen therapy in room air was begun by looking at oxygen saturation and respiratory support. Considering the length of hospitalization between the groups, longer hospitalization was observed in patients with high

Table 1. Baseline characteristics of COVID-19 patients

	Low score (n=170)	Intermediate score (n=57)	High score (n=37)	p
PRECISE-DAPT score**	9; 7 (0-16)	19; 3 (17-24)	27; 4 (25-38)	<0.001*† 0.011‡
Age (years)**	51; 25 (18-82)	76; 18 (20-96)	80; 17 (43-93)	<0.001*† 0.616‡
Female, n (%)	67 (39.4)	27 (47.4)	26 (70.3)	0.003
Comorbidities, n (%)				
HT	41 (24.1)	25 (43.9)	18 (48.6)	0.001
DM	24 (14.1)	11 (19.3)	5 (13.5)	0.612
Anemia	57 (33.5)	27 (47.4)	30 (81.1)	<0.001
Previous CVD	6 (3.5)	3 (5.3)	2 (5.4)	0.784
Heart failure	13 (7.6)	1(1.8)	3 (8.1)	0.265
Chronic kidney disease	8 (4.7)	2 (3.5)	3 (8.1)	0.588
Previous malignancy	6 (3.5)	1(1.8)	1 (2.7)	0.789
In-hospital medications, n (%)				
Hydroxychloroquine	146 (85.9)	50 (87.7)	33 (89.2)	0.840
Oseltamivir	114 (67.1)	42 (73.7)	26 (70.3)	0.634
Azithromycin	121 (71.2)	40 (70.2)	26 (70.3)	0.986
Favipiravir	11 (6.5)	2 (3.5)	5 (13.5)	0.163
Clinical outcomes				
Length of hospital stay (days)**	9; 5 (2-15)	9; 6.5 (3-14)	11; 7.5 (1-22)	0.011†
Death, n (%)	16 (9.4)	11 (19.3)	13 (35.1)	0.196* <0.001†

PRECISE-DAPT: Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy, HT: Hypertension, DM: Diabetes mellitus, CVD: Cardiovascular diseases *Low-score vs. Intermediate-score, †Low-score vs. High-score, ‡Intermediate-score vs. High-score **: Data presented as median (Med) with interquartile range (IQR), minimum (Min), and maximum (Max) [(Med; IQR (Min-Max)]

Table 2. Comparisons of laboratory features of patients according to PRECISE-DAPT score

Variables**	Low score (n=170)	Intermediate score (n=57)	High score (n=37)	p
Glucose (mg/dL)	111.5; 36 (43-331)	101; 32 (76-212)	111; 43 (77-828)	0.038
Creatinine (mg/dL)	0.85; 0 (1-1)	0.87; 0 (1-1)	0.88; 0 (1-1)	0.344
Creatinine clearance (mL/min)	93; 26 (57-132)	83; 21 (52-149)	68; 26 (52-128)	<0.001† 0.005*
White blood cells (×103 µL)	7.6; 4.5 (0.8-44.3)	9; 8.4 (3.4-44.3)	10.7; 7.8 (3.1-18.7)	0.022*
Hemoglobin (g/dL)	13.5; 2.7 (5.5-17)	12.3; 3.4 (4.6-17)	10; 2.3 (5.3-16)	0.004‡ <0.001† 0.001*
Thrombocyte count (×103 µL)	216; 126.8 (16.9-1235)	232; 165 (62-809)	259; 137 (78-693)	0.274
Neutrophil count (×103 /L)	5.2; 4 (0-86.8)	6.2; 6.9 (2-40.4)	8.8; 8.1 (2.1-17.6)	0.041†
Lymphocyte count (×103 /L)	1.5; 1.1 (0.1-23.9)	1.2; 0.8 (0.1-9)	1.1; 1.2 (0.2-2.9)	0.038*
CRP (mg/dL)	2.0; 8.1 (0-37.7)	6; 11.8 (0.1-37.5)	8.5; 19.6 (0-46.6)	0.002†
D-dimer (ng/mL)	402; 252 (46-1154)	442; 287 (316-1160)	464; 500 (318-2000)	0.548
Hs-TnT (ng/L)	66; 126 (13-432)	76; 143.5 (13-435)	87; 250 (14-567)	0.685

CRP: C-reactive protein, Hs-TnT: High-sensitive troponin T, *Low-score vs. Intermediate-score, †Low-score vs. High-score, ‡Intermediate score vs. High-score, **: Data presented as median (Med) with interquartile range (IQR), minimum (Min), and maximum (Max) [(Med; IQR (Min-Max)]

Table 3. Univariate and multivariate regression analyses of predictors of mortality

	Univariable			Multivariable		
Variables	HR	95% CI	p	HR	95% CI	p
Female gender	1.052	0.807-1.373	0.707			
Hypertension	1.508	1.129-2.013	0.005	1.303	0.964-1.761	0.085
Diabetes	1.135	0.794-1.622	0.489			
WBC count	0.971	0.947-0.996	0.022	0.987	0.963-1.011	0.286
Hemoglobin	1.085	1.026-1.146	0.004	1.009	0.943-1.079	0.797
Creatinine clearance	1.003	0.996-1.010	0.395			
Hs-TnT	0.999	0.998-1.000	0.227			
D-dimer	1.000	0.999-1.000	0.190			
PRECISE-DAPT score	0.962	0.947-0.978	<0.001	0.962	0.943-0.982	<0.001

CI: Confidence interval, HR: Hazard ratio; Other abbreviations in Table 2

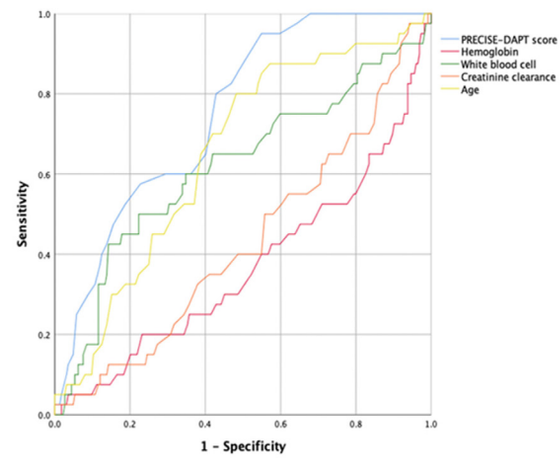

Figure 1. Receiver operating characteristic (ROC) curves to predict mortality in patients with COVID-19

scores. When the groups were compared in terms of mortality and complications related to COVID-19 pneumonia, 16 patients in the low-, 11 in the intermediate-, and 13 patients in the high-score groups died during the in-hospital period. The laboratory results of the patients are shown in Table 2.

Regression analyses

In univariate and multivariate Cox proportional hazard analyses, in-hospital mortality, diabetes mellitus, hypertension, age, and the PRECISE-DAPT score and its components were analyzed. In univariate analysis, hypertension, white blood cell count, hemoglobin, and PRECISE-DAPT score were associated with mortality (p=0.005, p<0.022, p=0.004, and p<0.001, respectively). In multivariate analysis, there was a relationship between the PRECISE-DAPT score and mortality (hazard ratio [HR]: 0.962, 95% confidence interval [CI]: 0.943–0.982, p<0.001; Table 3).

ROC analysis

The area under the curve value of the PRECISE-DAPT score and its components (hemoglobin, white blood cell count, creatinine clearance, and age) was 0.752 (95% CI: 0.681–0.823, p<0.001) for all-cause mortality (Figure 2). The predictive value of the PRECISE-DAPT score for in-hospital death in patients with COVID-19 was superior to that of three components of the score (white blood cell count 0.618, 95% CI: 0.514–0.722, p=0.018; hemoglobin 0.368, 95% CI: 0.267–0.469, p=0.008; age 0.651, 95% CI: 0.564–0.738, p=0.002). No statistical difference was observed when it was compared with creatinine clearance (0.429, 95% CI: 0.333–0.525, p=0.155).

Discussion

To the best of our knowledge, there are no simple scoring algorithms that can be used routinely to predict in-hospital mortality according to the current guidelines for patients with COVID-19. This is the first study to show the relationship between the PRECISE-DAPT scoring system and in-hospital mortality in patients with COVID-19.

Advanced age, diabetes, hypertension, congestive heart failure, and chronic renal failure are well-known prognostic factors in patients with COVID-19. Systemic diseases were observed at varying rates between patient groups, and the effects of hypertension on mortality in univariate regression analysis were similar to the results in the literature [11].

Our present information about the PRECISE-DAPT score comes from patients with coronary artery disease. It is a useful score to obtain information about the duration of the use of antiplatelet drugs following invasive procedures, especially in patients with STEMI [12]. In addition to its routine use, in a study in which Tanik et al. examined the PRECISE-DAPT score in two groups of patients with STEMI with scores of ≥25 and <25, they demonstrated the use of the score to predict in-hospital mortality [13]. In addition to such studies, as seen in our study, both prolonged hospitalization and mortality rate were associated with increased scores in patients with COVID-19, which were examined here among three groups according to PRECISE-DAPT scores.

Disruptions in oxygen and carbon dioxide exchange as a result of secretion and infiltration in the lungs in patients with COVID-19 cause hypoxia. Changes in iron metabolism because of hypoxia result in a decrease in hemoglobin levels. The decrease in hemoglobin, which is the main determinant of blood oxygen concentration, may cause adverse events that can result in multiple organ failure and death by worsening the clinical picture [14]. Recent studies have shown that comorbid conditions such as cardiovascular diseases and chronic obstructive diseases are associated with increased mortality in patients with advanced age hospitalized for COVID-19; however, there were no differences in hemoglobin levels between survivors and nonsurvivors [15,16]. Another study showed that decreased hemoglobin levels were associated with increased mortality in individuals aged <60 years [17]. In our study, decreased hemoglobin levels were associated with increased mortality in univariate regression analysis. Despite this, hemoglobin was not associated with mortality in multivariate regression analysis, and in our ROC analysis, the PRECISE-DAPT score was superior to the hemoglobin variable.

Inflammatory markers may vary in blood serum levels depending on the severity of the disease and other accompanying comorbid conditions. According to the information obtained from studies conducted among patients with COVID-19, inflammatory markers vary according to the course of the disease [18]. White blood cell count was analyzed in our study; however, it was not statistically useful for predicting mortality and it was not superior to the PRECISE-DAPT score.

In recent studies, in addition to many clinical conditions such as acute coronary syndrome and pulmonary embolism, troponin and D-dimer values have been found useful as prognostic tools in patients with COVID-19 [19]. In our study, high-sensitivity troponin T and D-dimer values could not be shown to be associated with mortality, but the PRECISE-DAPT score was superior to D-dimer and troponin T for mortality.

When the results of the studies in the literature are evaluated, it seems more logical to use combinations instead of single parameters in various clinical situations. As seen in our study, the PRECISE-DAPT score can be used to predict in-hospital mortality in patients with COVID-19.

Limitations

Our study had some limitations. First, the study comprised a single center and a small number of patients. Second, the use of the PRECISE-DAPT score was examined in the in-hospital period and we could not obtain data about its usability after discharge. Considering the study dates, the score should be reconsidered with patients who have received the full vaccination protocol. Therefore, larger multicenter studies are needed.

Conclusion

The PRECISE-DAPT score is a simple scoring system that uses the patient's clinical and complete blood count parameters, and increased PRECISE-DAPT scores are associated with mortality in patients with COVID-19. Therefore, we think that the PRECISE-DAPT score can be useful in various applications beyond patients with STEMI.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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References
1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020; 382(13): 1199-207.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395(10224): 565574.
3. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020; 5(7): 831-40.
4. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost. 2020; 18(6): 1469-72.
5. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020; 97(5): 829-38.
6. Nabors C, Sridhar A, Hooda U, Lobo SA, Levine A, Frishman WH, et al. Characteristics and Outcomes of Patients 80 Years and Older Hospitalized With Coronavirus Disease 2019 (COVID-19). Cardiol Rev. 2021; 29(1): 39-42.
7. Choi KH, Song YB, Lee JM, Park TK, Yang JH, Choi JH, et al. Clinical Usefulness of PRECISE-DAPT Score for Predicting Bleeding Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: An Analysis From the SMART-DATE Randomized Trial. Circ Cardiovasc Interv. 2020; 13(5): e008530.
8. Morici N, Tavecchia GA, Antolini L, Caporale MR, Cantoni S, Bertuccio P, et al. Use of PRECISE-DAPT Score and Admission Platelet Count to Predict Mortality Risk in Patients With Acute Coronary Syndrome. Angiology. 2019; 70(9): 867-77.
9. Çınar T, Tanık VO, Aruğaslan E, Karabağ Y, Çağdaş M, Rencüzoğulları İ, et al. The association of PRECISE-DAPT score with development of contrast-induced nephropathy in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Cardiovasc Interv Ther. 2019; 34(3): 207-15.
10. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389(10073): 1025-34.
11. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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(10229): 1054-62.
12. Sharma R, Kumar P, Prashanth SP, Belagali Y. Dual Antiplatelet Therapy in Coronary Artery Disease. Cardiol Ther. 2020; 9(2): 349-61.
13. Tanik VO, Cinar T, Arugaslan E, Karabag Y, Hayiroglu MI, Cagdas M, et al. The Predictive Value of PRECISE-DAPT Score for In-Hospital Mortality in Patients With ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Angiology. 2019; 70(5): 440-47.
14. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. Eur J Epidemiol. 2020; 35(8): 763-73.
15. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13): 1239-42.
16. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020; 81(1) :e6–12.
17. Sayad B, Afshar ZM, Mansouri F, Rahimi Z. Leukocytosis and alteration of hemoglobin level in patients with severe COVID-19: Association of leukocytosis with mortality. Health Sci Rep. 2020; 3(4): e194.
18. Guan X, Zhang B, Fu M, Li M, Yuan X, Zhu Y, et al. Clinical and inflammatory features based machine learning model for fatal risk prediction of hospitalized COVID-19 patients: results from a retrospective cohort study. Ann Med. 2021; 53(1): 257-66.
19. Hachim MY, Hachim IY, Naeem KB, Hannawi H, Salmi IA, Hannawi S. D-dimer, Troponin, and Urea Level at Presentation With COVID-19 can Predict ICU Admission: A Single Centered Study. Front Med (Lausanne). 2020; 7: 585003.

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