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The Role of CHA_2DS_2-VASc Score in Predicting Intensive Care Unit Admission in Patients with COVID-19: Retrospective Study

CHA_2DS_2-VASc Skorunun COVID-19 Hastalarında Yoğun Bakım İhtiyacını Öngörmedeki Yeri: Retrospektif Çalışma

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This study was presented as orally at the 16th International Update in Cardiology and Cardiovascular Surgery Congress, 30 October-1 November 2020, İstanbul, Turkey.

ABSTRACT Objective: The CHA_2DS_2-VASc is a risk score used to determine the embolic risk in patients with atrial fibrillation. Also, its efficacy for prognosis has been demonstrated in other clinical situations. The coronavirus disease-2019 (COVID-19) disease is characterized by pneumonia, respiratory failure, venous and arterial thrombosis leading to multiorgan failure and mortality. Therefore, in this study, we aimed to show the predictive value of the CHA_2DS_2-VASc score to determine the need for intensive care unite admission in COVID-19 patients and its correlation with serum D-dimer levels. **Material and Methods:** Patients admitted to the hospital due to COVID-19 disease confirmed with a polymerase chain reaction test were evaluated, and those over 18 years of age were included in the study prospectively. Each patients' CHA_2DS_2-VASc score was calculated, also D-dimer and other laboratory parameters were recorded. Factors related to intensive care unit admission were evaluated. **Results:** Overall, 110 patients were included in the study. Among these, 16 patients needed intensive care unite admission. The CHA_2DS_2-VASc score was found to be an independent predictor of intensive care unite admission [Odds ratio: 1.94 (1.32-2.85 95% confidence interval), p=0.001]. Receiver operating characteristic analysis revealed that the 1.5 cut-off value predicted intensive care unit admission with a 75% sensitivity and specificity. There was also a significant correlation between the CHA_2DS_2-VASc risk score and serum D-dimer levels (p<0.001, r=0.34). **Conclusion:** The CHA_2DS_2-VASc risk score can be used to predict intensive care unit admission in COVID-19 patients, and it is correlated with serum D-dimer levels.

Keywords: COVID-19; CHA_2DS_2-VASc; D-dimer; thromboembolism, intensive care

ÖZET Amaç: CHA_2DS_2-VASc, atriyal fibrilasyon hastalarında embolik riskin belirlenmesi için kullanılan bir skordur. Ek olarak başka klinik olaylarda da prognostik açıdan değerli olduğu çalışmalarla gösterilmiştir. Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)], çoklu organ yetersizliği ve ölüme yol açabilen, pnömoni, solunum yetersizliği, arteriyel ve venöz trombozlar ile karakterize bir hastalıktır. Bu nedenle, bu çalışmada, CHA_2DS_2-VASc skorunun, COVID-19 hastalarında yoğun bakım ihtiyacını öngörmedeki yerini ve serum D-dimer düzeyleri ile arasındaki ilişkiyi ortaya koymayı amaçladık. **Gereç ve Yöntemler:** Bu retrospektif çalışmaya, COVID-19 nedeniyle hastaneye başvuran ve polimeraz zincir reaksiyonu testi ile tanısı doğrulanan, 18 yaş ve üzeri hastalar dâhil edildi. Tüm hastaların CHA_2DS_2-VASc skorları hesaplandı; D-dimer ve diğer laboratuvar tetkikleri kayıt edildi. Yoğun bakım ihtiyacı ile ilişkili olabilecek faktörler kaydedildi. **Bulgular:** Çalışmaya toplam 110 hasta dâhil edildi. Bu hastaların 16'sında yoğun bakım ihtiyacı gelişti. CHA_2DS_2-VASc skorunun, yoğun bakım ihtiyacının bağımsız bir öngörücüsü olduğu sonucu bulundu [Odds ratio: 1,94 (1,32-2,85 %95 güven aralığı), p=0,001]. Alıcı işletim karakteristiği analizi, 1,5 sınır değer ve üzerinde, bu skorun %75 duyarlılık ve özgüllük ile yoğun bakım ihtiyacını öngörebildiğini ortaya koydu. Ayrıca CHA_2DS_2-VASc skoru ile D-dimer düzeyleri arasında anlamlı korelasyon saptandı (p<0,001; r=0,34). **Sonuç:** CHA_2DS_2-VASc risk skoru, COVID-19 hastalarında yoğun bakım ihtiyacını öngörmede kullanılabilir ve D-dimer düzeyleri ile de koreledir.

Anahtar Kelimeler: COVID-19; CHA_2DS_2-VASc; D-dimer; tromboembolizm, yoğun bakım

The novel coronavirus is responsible for a worldwide outbreak of serious infection, termed coronavirus disease-2019 (COVID-19).[1] COVID-19 is often complicated with coagulation dysfunction. Cytokines regulate the effect of COVID-19 on coagulopathy.[2] COVID-19 is associated with venous and arterial thrombosis, and a recent study showed that venous thrombosis with pulmonary embolism is com-

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mon. Incidences of arterial thrombosis, including ischemic stroke and acute coronary syndrome, have also been noted.[3] Due to these inflammatory reactions, the entire microvascular system is affected, leading to abnormal coagulation, which pathologically manifests as vasculitis and micro thrombosis.[4,5]

The CHA_2DS_2-VASc score (C: Congestive heart failure, H: Hypertension, A: Age of ≥75, D: Diabetes mellitus, S: Prior stroke, V: Vascular disease, A: Age 65-74, Sc: Female) shows the embolic risk in atrial fibrillation (AF) patients with no valvulopathy, and thereby guide the anticoagulant treatment (A: Age of ≥75: 2 points, S: Previous stroke: 2 points, all others 1 point).[6] The CHA_2DS_2-VASc score is a better tool for determining low and intermediate-risk AF patients for cerebrovascular events. The CHA_2DS_2-VASc score is, therefore, well-validated in assessing the risk of thromboembolism associated with AF. The CHA_2DS_2-VASc score was also related to outcomes in patients with AF with pulmonary embolism, a chronic obstructive pulmonary disease (COPD), pulmonary embolism with right ventricle strain, decreased left ventricular ejection fraction, non-AF ischemic stroke, cardiovascular disease.[7-11]

The risk factors and pathways for thromboembolism and stroke associated with AF are described in various studies. As both conditions have a similar pathophysiologic basis of clot formation, one could infer that the risk factors for thrombosis occurrence could be similar.[12] In COVID-19 patients, the same thromboembolic pathway provoked by cytokines and procoagulants may cause vascular complications. An increased D-dimer is one of the most common laboratory findings noted in hospitalized COVID-19 patients. A previous study showed an elevated D-dimer level predicts the prognosis and death in COVID-19.[13]

A critical COVID-19 patient could be defined as respiratory failure due to lung infection and dysfunction of the kidney, liver, or peripheral blood components, increasing the risk of multiple organ failure. Respiration >30, saturation <92% in ambient air, PaO_2/FiO_2<300, pneumonic infiltration in computed tomography >50%, multiorgan failure, and shock accepted as the criteria of intensive care unit (ICU) requirement in patients with COVID-19.[14]

Remarkably, thrombotic complications have been described in severe COVID-19 patients. Prediction of thrombotic complications, determination of anticoagulant therapy initiation, and appropriate doses are critical for groups with very high thrombotic risk, such as ICU patients.[3] Therefore, the effective use of risk determinants in patients is crucial.

Our study aimed to show the predictive value of CHA_2DS_2-VASc score for ICU requirement in COVID-19 patients and its correlation to serum D-dimer levels to provide a fast and reliable scoring system that will guide therapy decisions.

MATERIAL AND METHODS

This retrospective study included 110 hospitalized COVID-19 patients consecutively who were 18 years or older and were diagnosed with a positive polymerase chain reaction (PCR) test between March 14, 2020, and May 20, 2020. Ethical approvals were obtained from the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (Date: 4.5.2020, No: 2020-10-19) and the Ministry of Health Ethics Committee. All participants' rights were protected according to the Helsinki Declaration (2013).

Patients with coagulation dysfunction, malignancy, chronic kidney disease (estimated glomerular filtration rate <60 mL/min), liver or lung disease, prosthetic valves, oral anticoagulant use and, haematological disease were excluded.

ICU REQUIREMENT CRITERIA

Respiratory rate >30/minute, oxygen saturation <92% despite oxygen support, partial oxygen pressure <60 mmHg, PaO_2/FiO_2<300, bilateral or multilobar infiltration on chest radiograph or computed tomography, and clinical deterioration. Sign of hypoperfusion in the skin, sequential organ failure assessment score >2 or lactate >2, blood pH<7.25 (arterial blood gas analysis), signs of shock (systolic pressure <90, or decrease >40, mean pressure <65 mmHg and vasopressor requirement), elevated cardiac enzymes, arrhythmia, kidney or liver enzyme elevation, acute bleeding diathesis, thrombocytopenia and development of macrophage activating syn-

drome, confusion or Glasgow Coma Scale <12, lactate dehydrogenase >389 U/L.[14] An attending physician observed the daily progress of all patients' physical findings and laboratory parameters. When there is any deterioration, the need for ICU was determined by making a bedside assessment with a consultant team consisting of an intensive care specialist, cardiologist, and neurologist. Any of the following criteria was deemed as an ICU admission requirement. Critical patients were also evaluated according to the benefits of extracorporeal membrane oxygenation support in ICU.[15]

Demographic data, medical history, and treatments of all patients were obtained from the database. The initial (admission) D-dimer, C-reactive protein (CRP), troponin, N-terminal brain natriuretic peptide (NT-pro BNP), procalcitonin values, and neutrophil-lymphocyte ratio (NLR) indicators of poor prognosis in COVID-19 patients were recorded. The CHA_2DS_2-VASc score of patients was calculated manually.

STATISTICAL ANALYSIS

SPSS 25.0 program was used in the analysis of variables. Normal distribution was tested using the Shapiro-Wilk. Continuous variables were given as mean±standard deviation, and categorical variables were presented as frequency (percent). The Mann-Whitney U tested comparison of two independent groups according to quantitative data. Spearman's rho tested the correlations of variables. Chi-square and Fisher's exact tests compared nominal variables. Sensitivity, specificity, and diagnostic accuracy rates for the CHA_2DS_2-VASc and D-dimer were analyzed and expressed by receiver operating characteristic (ROC) analysis. Logistic regression analysis examined the CHA_2DS_2-VASc score and D-dimer values in predicting clinical outcomes. Variables found significant in univariate analysis or with clinical relevance were added to the multivariate analysis. For all analyses, the statistical significance was set at two-tailed $p<0.05$.

RESULTS

Two hundred forty-one patients were diagnosed with COVID-19, according to the PCR result in our hospital. Among these, 107 opted for 14 days of home isolation, medical treatment, and PCR retesting after 14 days. They were discharged from the emergency department the same day. The remaining 134 patients were hospitalized, among whom 24 (10 with COPD, 7 with chronic renal failure, 2 with chronic liver disease, 4 with malignancy, and 1 with Factor V Leiden mutation) were not enrolled. Study cohort classified as ICU requiring and non-requiring group.

In total, 110 patients (ICU requiring: 16; non-requiring: 94) were included .The median age was 53, and 61.8% of patients were male. Baseline characteristics, clinical features, medications, laboratory findings, CHA_2DS_2-VASc score, and smoking are shown in Table 1.

Hypertension, diabetes, vascular diseases, heart failure, cerebrovascular events were recorded in 23 (20.9%), 12 (10.9%), 9 (8.2%), 5 (4.5%) and 2 (1.8%) patients, respectively. Sixteen (14.5%) patients required ICU admission of whom 6 (5.5%) died during the ICU stay. Twelve (10.9%) patients were using angiotensin converting enzyme inhibitors, 6 (5.45%) were taking angiotensin receptor blockers, 9 (8.18%) were taking calcium channel blockers and 2 (1.81%) were using alpha-blockers. Fourteen (12.7%) patients were using acetyl salicylic acid 100 mg. Six (5.45%) patients were using insulin and 12 (10.9%) patients were using oral antidiabetic drugs.

Hydroxychloroquine 200 mg twice/day and favipiravir 1,600 mg twice/day loading dose, and 600 mg twice/daily maintenance dose were administered to all 110 hospitalized patients. Enoxaparin 1 mg/kg twice/day subcutaneous was administered to 16 (14.5%) ICU patients and 0.4 mg/kg enoxaparin was administered to 94 (85.5%) non-ICU patients. A noradrenaline infusion was administered to 9 ICU patients and intravenous hydrocortisone to 13.

The mean D-dimer, CRP, troponin, procalcitonin, NT-pro BNP and NLR were 1.0±2.6 mg/L, 5.1±6.2 mg/dL, 0.1±0.4 ng/mL, 0.6±0.8 ng/mL 3.88±11.29 pg/mL and 4.4±3.3 respectively.

The median CHA_2DS_2-VASc score in ICU requiring and non-requiring patients was 1 (0-2) and 3 (1.25-3) respectively. The CHA_2DS_2-VASc score was

TABLE 1: Baseline clinical characteristics of the study patients.

	Total n=110	No ICU need (n=94, 85.5%)	ICU need (n=16, 14.5%)	p value
Age (years) *mean (SD)*	53 (17)	52 (17)	63 (13)	**0.004**
Gender (male) *n (%)*	68 (61.8)	59 (62.8)	9 (56.3)	0.62
Diabetes mellitus *n (%)*	12 (10.9)	8 (8.5)	4 (25)	0.051
Hypertension *n (%)*	23 (20.9)	15 (16.0)	8 (50.0)	**0.002**
CHF *n (%)*	5 (4.5)	3 (3.2)	2 (12.5)	0.15
Stroke *n (%)*	2 (1.8)	0	2 (12.5)	**0.02**
Vascular disease *n (%)*	9 (8.2)	5 (5.3)	4 (25.0)	**0.008**
Smoking *n (%)*	11 (10.0)	10 (10.6)	1 (6.3)	0.58
D-dimer, mg/L *median (IQR)*	0.54 (0.27-0.96)	0.48 (0.23-0.91)	0.92 (0.69-1.49)	**0.001**
C-reactive protein (mg/dL) *median (IQR)*	2.59 (0.78-7.79)	2.25 (0.58-6.86)	8.09 (1.91-12.89)	**0.01**
CHA_2DS_2-VASc *median* (IQR)	**1.0 (0-2.0)**	**1.0 (0-2.0)**	**3.0 (1.25-3.0)**	**0.001**
Troponin *mean* (ng/mL)	0.1±0.4	0.04±0,2	0.4±1.5	0.03
BNP *mean* (pg/mL)	3.88±11.29	0.71±10.8	22.5±14.1	**<0.01**
NLR *mean*	4.4±3.3	3.94±3.01	7.1±5.3	<0.01
Procalcitonin *mean* (ng/mL)	0.6±0.8	0.59±0.84	0.65±0.85	**0.79**
Mortality *mean n (%)*	6 (5.5)	0	6 (37.5)	<0.01

ICU: Intensive care unit; SD: Standard deviation; CHF: Congestive heart failure; IQR: Interquartile range; BNP: Brain natriuretic peptide; NLR: Neutrophil-lymphocyte ratio.

higher in ICU requiring group (p=0.001) (Table 1). D-dimer was found to be significantly higher in ICU-requiring patients (p=0.001). Age, hypertension, stroke and vascular disease, troponin, BNP, NLR and CRP were higher in ICU patients (p=0.004, p=0.002, p=0.02, p=0.008, p=0.03, p<0.01, p<0.01 and p=0.01, respectively) (Table 1).

A statistically significant correlation was found between the CHA_2DS_2-VASc score and D-dimer levels (p<0.001, r=0.35) (Table 2). A statistically significant correlation was also found between the CHA_2DS_2-VASc risk score and CRP level (p<0.044, r=0.19), troponin level (p=0.004, r=0.446), NT-pro BNP level (p=0.003, r=0.59), and the NLR (p=0.016, r=0.37). No correlation was found with procalcitonin levels (p<0.4) (Table 2).

In ROC analyses, area under the ROC curve for CHA_2DS_2-VASc score and D-dimer level was found 0.75 [95% confidence interval (CI), 0.61-0.89] p=0.001, 0.75 (95% CI 0.65-0.85) p=0.001 respectively (Figure 1, Figure 2). CHA_2DS_2-VASc score to predict ICU requirement with 75% sensitivity and 75% specificity at 1.5 points cut-off.

Logistic regression analysis was performed. On univariate analyses, CHA_2DS_2-VASc score, age and hypertension were found to be predictors of ICU requirement [Odds ratio (OR): 1.94 (1.32-2.85, 95% CI), p=0.001, 1.04 (1.00-1.076, 95% CI) p=0.01 and 5.26 (1.71-16.21, 95% CI) p=0.004 respectively].

TABLE 2: Correlation between CHA_2DS_2-VASc score and biochemical parameters.

	r value	p value
D-dimer	0.35	<0.001[s]
CRP	0.19	0.044[s]
Troponin	0.44	0.004[s]
NT-pro BNP	0.59	0.003[s]
Procalcitonin	0.15	0.406[s]
NLR	0.37	0.016[s]

[s]Spearman's rho test; r: Correlation; CRP: C-reactive protein; NT-pro BNP: N terminal brain natriuretic peptide; NLR: neutrophil-lymphocyte ratio.

The univariate and multivariate analyses were presented in Table 3. The CHA_2DS_2-VASc score was found to maintain its predictive ability even when adjusted for age and sex. To prevent over fitting, no further adjustments were attempted (OR: 2.19, 95% CI 1.16-4.13, p=0.01).

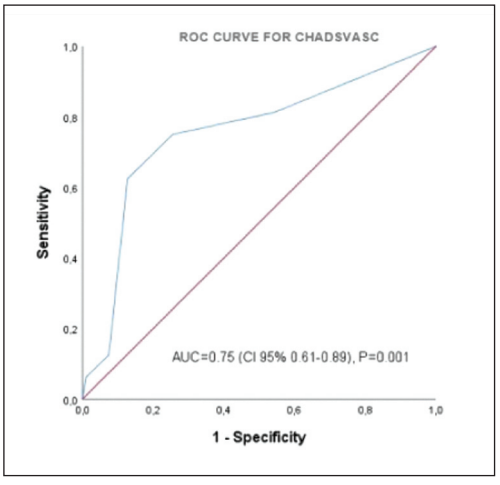

FIGURE 1: In receiver operating characteristic (ROC) analysis, area under the ROC curve for CHA_2DS_2-VASc score was found 0.75 (95% confidence interval, 0.61-0.89) p=0.001, 0.75 (95% confidence interval 0.61-0.89) p=0.001. ROC: Receiver operating characteristic; AUC: Area under the ROC curve; CI: Confidence interval.

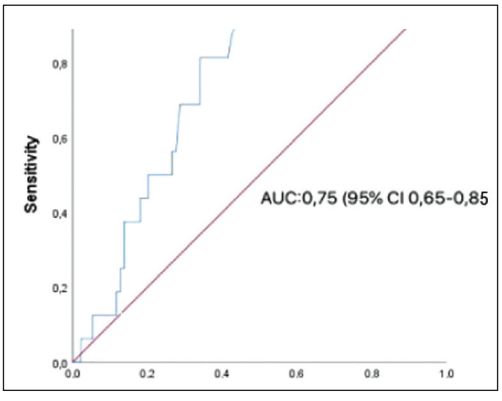

FIGURE 2: In receiver operating characteristic (ROC) analysis, area under the ROC curve for D-dimer was found 0.75 (95% confidence interval, 0.61-0.89) p=0.001, 0.75 (95% confidence interval 0.65-0.85) p=0.001. AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

DISCUSSION

In this study, the CHA_2DS_2-VASc risk score was found to be a predictor of ICU requirement in COVID-19 patients, also significantly correlated with D-dimer. The higher proportion of men with COVID-19 was similar to that seen in previous studies.[16,17] Hypertension was the most common chronic disease, as seen in previous studies. ICU requirement and mortality were also similar to the outcomes seen in some previous studies.[17-19] The CHA_2DS_2-VASc is a well-validated scoring that can be applied at the bedside on admission. It is shown that this score can be used for predicting mortality in patients with ST-segment elevation myocardial infarction (STEMI) who have performed primary revascularization and also no-reflow in non-STEMI.[19,20] The CHA_2DS_2-VASc score was found to have a significant correlation with patient outcomes in AF with pulmonary embolism, COPD with or without AF, right ventricle dysfunction with acute pulmonary embolism, decreased left ventricular ejection fraction, non-AF ischemic stroke, and cardiovascular disease.[7-11]

Previous trials revealed that the CHA_2DS_2-VASc has a close relationship with the risk of venous thromboembolism.[21] Onuk et al. examined the predictive ability of this score in acute pulmonary embolism, and the CHA_2DS_2-VASc score was found to be a predictor of mortality.[22]

The number of studies investigating the relation between the CHA_2DS_2-VASc and the need for ICU admission or the outcomes of ICU patients is limited. Karamchandani et al. investigated the CHA_2DS_2-VASc score's predictive value for mortality in ICU,

TABLE 3: Logistic regression analysis for intensive care unit requirement.

	Univariate		Multivariate	
	Odds ratio (95% confidence interval)	p value	Odds ratio (95% confidence interval)	p value
CHA2DS2-VASc score	1.94 (1.32-2.85)	**0.001**	2.19 (1.16-4.13)	**0.01**
Gender	0.76 (0.26-2.22)	0.62	1.42 (0.43-4.70)	0.56
Age	1.04 (1.008-1.076)	**0.01**	0.98 (0.93-1.04)	0.68
Diabetes mellitus	3.58 (0.93-13.73)	0.06		
Hypertension	5.26 (1.71-16.21)	**0.004**		
Vascular disease	5.93 (1.39-25.20)	0.01		
D-dimer	1.02 (0.86-1.22)	0.76		

and there was no correlation between the score and mortality. Different inclusion and exclusion criteria of study patients could partly explain these findings.[23] Contrarily, Gunduz et al. showed that CHA_2DS_2-VASc score and modified CHA_2DS_2-VASc score can predict mortality and ICU hospitalization in COVID-19 patients.[24] Our study finding is compatible with this study.

Shariff et al. reported in a review that the pathophysiology of AF-related embolism and venous thromboembolism were similar. The risk factors that make up CHA_2DS_2-VASc are also associated with venous thromboembolism development. This scoring system can, therefore, also be used to predict prognosis in venous thromboembolism.[12]

A recent study demonstrated that D-dimer predicts in-hospital mortality in COVID-19.[25] Huang et al. showed that the patients who needed critical care had higher D-dimer than those who did not require intensive care.[1] These results are compatible with those of our study. In a study with 1,099 patients, Guan et al. showed a significant relationship between a D-dimer level above 0.5 and ICU requirement, ventilation support requirement, and mortality.[18]

There was a mild to a moderate but significant relationship between the CHA_2DS_2-VASc score and D-dimer levels in our study. In You and Tang's study, D-dimer levels were also correlated with the CHA_2DS_2-VASc in stroke patients.[26]

Zhang et al. demonstrated that patients with a D-dimer 2 microns/mL were found to be higher in-hospital mortality.[25] An unexpected result in our study was that the D-dimer level was not found to be an independent predictor for ICU requirement with logistic regression analysis, although the ROC analysis being significant.

The onset of anticoagulant therapy and the drug and dose selection in COVID-19 patients is still a subject to be discussed and should be investigated further. Tang et al. found that heparinized patients had a lower mortality rate than that of non-users whose D-dimer values are high. As a result of this data, they suggested that anticoagulant treatment is beneficial for only selected patients, such as sepsis-induced coagulopathy or elevated D-dimer levels.[27]

This study may be novel to investigate whether the CHA_2DS_2-VASc score can predict intensive care requirements. A recent study with a large patient population showed that M (Modified)-CHA_2DS_2-VASc score (merely changing the gender female to male) predicted ICU admission and death in COVID-19.[28] Also, Quisi et al. showed that CHA_2DS_2-VASc score of ≥3 is an independent predictor of mortality in COVID-19 patients.[29] These two findings may support our results because most in-hospital mortality occurred in patients with COVID-19 and required ICU. Therefore, multi-center and extended studies are needed to demonstrate that this CHA_2DS_2-VASc score is valuable in predicting the need for ICU.

LIMITATIONS

The study's main limitations can be listed as its single-center, retrospective design, and small study population.

CONCLUSION

The CHA_2DS_2-VASc risk score predicts the ICU requirement in COVID-19 patients; the D-dimer level is also found to be correlated. We believe that this cost-free, quickly applied scoring system can be immediately applied to patient admission and provides additional benefits for predicting the prognosis and management strategies in patients with COVID-19.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Umut Karabulut;* ***Design:*** *Umut Karabulut;* ***Control/Supervision:*** *Umut Karabulut;* ***Data Collection and/or Processing:*** *Dilay Karabulut;* ***Analysis and/or Interpretation:*** *Dilay Karabulut;* ***Literature Review:*** *Dilay Karabulut;* ***Writing the Article:*** *Umut Karabulut;* ***Critical Review:*** *Dilay Karabulut.*

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