






Is It Possible to Have a Risk Scoring System that Provides Early Warning of the Poor Prognosis in COVID-19?

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ABSTRACT

Objective: In our study, we aimed to determine the factors associated with poor outcome by evaluating the data of possible/definite Coronavirus 2019 (COVID-19) cases coming to the emergency department in two centers and to establish a risk scoring system.

Methods: This study has been designed as a retrospective study performed on COVID-19 cases. Patients' sociodemographic data, complaints, vital signs, laboratory parameters, service/intensive care admission status, and the presence of death were analyzed.

Results: A total of 436 patients were included in the study. We divided the cases into two groups in terms of poor outcome. The factors associated with poor outcome such as the presence of comorbid disease ($p=0.001$), being 50 years and older ($p<0.001$), symptoms of shortness of breath ($p<0.001$), saturation value $<95\%$ ($p<0.001$), neutrophil count $>7 \times 10^9 L^{-1}$ ($p=0.006$), lymphocyte count $<1.1 \times 10^9 L^{-1}$ ($p=0.020$), procalcitonin value ≥ 0.015 ng/mL ($p=0.001$), D-dimer value ≥ 500 mg/L ($p=0.009$) were found to be statistically significant.

Conclusion: The scoring system we have created is considered to be a comprehensive, easily applicable, and reliable method in determining the prognosis and the treatment strategy.

INTRODUCTION

Coronavirus 2019 (COVID-19) pandemic caused by severe respiratory syndrome coronavirus-2 (SARS-CoV-2) was first detected in Wuhan, China.^[1] In late December 2019, it was reported that the origin of unknown pneumonia in some hospitalized patients was the seafood and wet animal market in Wuhan, China.^[2] Afterward, this infection spread to 180 countries around the world.^[3] Coronavirus is an enveloped RNA virus that causes multiple diseases.^[2]

Full genome sequence and phylogenetic analysis showed that SARS-CoV-2 is one of the sarbecovirus subtypes of the

beta coronavirus subfamily, but showed differences with beta coronaviruses such as MERS-CoV and SARS-CoV.^[4] The severity of the clinical presentation of COVID-19 infection varies.^[5] Some patients present with asymptomatic or mild upper respiratory tract symptoms, while some experience severe fever, cough, shortness of breath, and severe respiratory failure symptoms with bilateral infiltrates. Approximately, 20% of patients experience severe respiratory tract infections. Nevertheless, the mortality rate is around 2.3%.^[6]

In the highly variable clinical course of COVID-19 infection, the risk factors are important in determining prognosis and treatment options. There are a few studies on this

subject in the literature.^[4,5,7-10] In our study, we aimed to create a simple and easy scoring system that can be used to predict the clinical severity of COVID-19 infection in emergency medicine departments.

MATERIALS AND METHODS

Study design

This study was planned as a retrospective cohort study. Patients' data between May 1, 2020, and May 31, 2020, were obtained from the hospital data system of the centers where the study was conducted. The ethics committee approval for the study has been made by the ethics committee of the Erzurum Atatürk University, Ministry of Health Scientific Research Platform.

Patient population and data collection

The study was organized in two different centers. Patients above 18 years of age, who have applied to hospitals with a probable/definite diagnosis of COVID-19 infection, have been included in the study according to the Republic of Türkiye Ministry of Health algorithm.^[11] In Erzurum Atatürk University Hospital, patients who suspected COVID-19 were determined according to the algorithm. In Manisa Merkezefendi State Hospital was announced as a quarantine hospital and only accepted probable/definite COVID-19 cases. Furthermore, those who have been suspected as probable/definite cases but discharged from the emergency department were not included in this study.

Demographic data of patients, comorbidity, application and contact information, complaints, vital signs, laboratory parameters (leukocyte, lymphocyte, neutrophil and platelet counts, percentages, C-reactive protein, procalcitonin, and D-dimer), chest computed tomography (CT) scans reported by radiologists, and real-time polymerase chain reaction (RT-PCR) test results have been retrospectively evaluated. Hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF), and malignancy were questioned as comorbid diseases. RT-PCR test samples were obtained by the combined throat and nose swab method and were studied in the laboratories of Manisa Celal Bayar University Faculty of Medicine and Erzurum Atatürk University Faculty of Medicine. Patients were divided into two groups according to disease severity as "good outcome" and "poor outcome." Poor outcome criteria were defined as having at least one of the following two conditions: death and intensive care stay during hospital follow-up. The rest of the cases were classified under the good outcome group. We aimed to establish our own poor prognosis scoring system with the data of patients and their relationship with risk factors. All data were collected by two researchers, and they were checked for differences based on interpretation by the third researcher.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (version 20.0, Chicago, IL, USA). The percentages and frequencies for the categorical variables and the mean values for the continuous variables were determined. The normal distribution of continuous variables was assessed by the Shapiro–Wilk test. Comparisons between treatment groups were performed with unpaired t-tests and Mann–Whitney tests. For categorical variables, the Chi-squared test was used. The patient's data that could affect the poor outcome were examined with logistic regression analysis. As a result of this analysis, it was planned to use independent patient factors, which were found to have an effect on the poor outcome, in risk scoring. Receiver operating characteristic (ROC) curve analysis was used to evaluate the cutoff values of specific laboratory results in detecting poor patient outcome. The confidence interval (CI) was determined as 95%, and a value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Clinical characteristics of patients

The study included 436 patients of whom 176 (40.4%) were females and 260 (59.6%) were males. The mean age was 47 ± 19 years. The detailed distribution of the data of the two patient groups is shown in Table 1. Of the total patients, 128 (29.4%) had a positive contact history. Among the positive contact history patients, 73 (57.0%) had a family contact history, 36 (28.1%) had friends and workplace contact history, and 19 patients (14.8%) had patient contact history. Of the 128 people with positive contact history, 24 (18.8%) were healthcare workers among whom 15 (62.5%) were females and 9 (37.5%) were males, and this difference between gender ratios was statistically significant ($p < 0.023$). There was no significant difference in age between the patients who were healthcare workers and those who were not ($p < 0.059$). RT-PCR positive detection rate in healthcare workers was 58.3%, which was significantly higher than the other patients ($p < 0.0001$). On the other hand, CT findings were completely opposite. The rate of positive CT findings was higher in other patients who were not healthcare workers ($p < 0.014$).

The mean age of those with a negative contact history was significantly higher than those with a positive contact history (mean difference: 9.9, 95% CI: 6.9–13.6) ($p < 0.001$). RT-PCR positivity rate was found to be significantly higher in those with positive contact history ($p < 0.001$). In terms of CT findings, the situation was the opposite. The frequency of CT positivity was found to be significantly higher in patients without positive contact history ($p < 0.001$).

When the comorbidity status was evaluated, 181 (41.5%) out of 436 patients had at least one comorbid disease. The most common comorbid disease was HT, and it was present in 32.3% of the patients. This was followed by

Table 1. Clinical characteristics and symptoms of patients by good and poor outcome groups

Parameters	Good outcome (n=382)	Poor outcome (n=54)	p
Gender, n (%)			
Male	234 (61.3)	26 (48.1)	0.066
Female	148 (38.7)	28 (51.9)	
Age	44.1±17.3	68.0±16.7	<0.001
Positive exposure history, n (%)	122 (31.9)	6 (11.1)	0.002
Healthcare workers, n (%)	22 (5.8)	2 (3.7)	0.535
Comorbidities, n (%)			
Any	136 (35.6)	45 (83.3)	<0.001
Hypertension	110 (28.8)	31 (57.4)	<0.001
Cardiovascular disease	38 (9.9)	18 (33.3)	<0.001
Chronic respiratory disease	33 (8.6)	12 (22.2)	0.002
Diabetes mellitus	29 (7.6)	14 (25.9)	<0.001
Malignancy	5 (1.3)	8 (14.8)	<0.001
Chronic kidney disease	6 (1.6)	5 (9.3)	0.001
Duration of symptom (days)	2.1±1.2	2.8±1.1	<0.001
Symptoms, n (%)			
Any	322 (84.3)	51 (94.4)	0.050
Fever	213 (55.8)	36 (66.7)	0.130
Cough	163 (42.7)	25 (46.3)	0.615
Dyspnea	62 (16.2)	39 (72.2)	0.955
Fatigue	73 (19.1)	6 (11.1)	0.153
Chest pain	24 (6.3)	4 (7.4)	0.752
Vital signs			
Body temperature (°C)	37.2±0.9	37.4±1.1	0.178
Oxygen saturation (%)	97.2±2.3	93.8±4.7	<0.001
Laboratory results			
Leukocyte count ($\times 10^9$ L ⁻¹ ; normal range 3.5–9.5)	8.1±3.5	12.6±6.2	<0.001
Neutrophil count ($\times 10^9$ L ⁻¹ ; normal range 2.1–7)	5.6±3.3	10.6±6.3	<0.001
Lymphocyte count ($\times 10^9$ L ⁻¹ ; normal range 1.1–3.6)	1.8±0.8	1.5±1.0	0.019
Platelet count ($\times 10^9$ L ⁻¹ ; normal range 125–350)	225.14±75.09	233.28±58.49	0.509
Hemoglobin level (g/L; normal range 11.2–15.7)	13.4±2.2	12.8±2.1	0.086
Procalcitonin (ng/mL; normal range 0–0.1)	0.01 (IQR: 0.1)	0.1 (IQR: 0.7)	<0.001
D-dimer (mg/L; normal range 0–500)	150 (IQR: 129)	530 (IQR: 745)	<0.001
CRP (mg/L; normal range 0–3)	35.27±57.62	97.89±82.78	<0.001
Positive RT-PCR results, n (%)	140 (36.6)	13 (24.1)	0.070
Positive CT findings, n (%)	239 (62.6)	44 (81.5)	0.006

Chronic respiratory disease includes chronic obstructive pulmonary disease and asthma. IQR: Interquartile range; RT-PCR: Real-time polymerase chain reaction; CRP: C-reactive protein; CT: Computed tomography.

CAD (12.8%), COPD (10.3%), DM (9.9%), malignancy (3%), and CRF (2.5%).

Symptoms

In patients with negative contact history, the mean fever measured at presentation was significantly higher than those with positive contact history (mean difference: 0.28, 95% CI: 0.11–0.47) ($p < 0.002$). At least one symptom was present in 373 patients (85.6%) and the most common symptom was high fever (presented in 249 patients, 66.8% of those with symptoms applied with high fever). In patients with poor outcomes, mean saturation values at presentation were significantly lower (mean difference: 3.4, 95% CI:

2.1–4.7) ($p < 0.001$). Regarding the rate of RT-PCR samples, 153 patients (35.1%) were RT-PCR positive and 283 patients (64.9%) were RT-PCR negative. CT results were positive in 283 patients (64.9%). The number of patients who were positive for both RT-PCR and CT was 91 (20.9%).

High-risk factors for mortality

We performed logistic regression analysis to determine the factors that may have an impact on the poor outcome. When the groups were examined in terms of poor outcome, the difference between the genders was not statistically significant ($p = 0.066$). The patients were examined in two groups as over 50 and under 50 years of age. The in-

cidence of poor outcome was significantly higher in those aged 50 years and over ($p<0.001$). There was an inverse relationship between the presence of contact history and poor outcome. Poor outcome was observed less frequently in patients with positive contact history ($p=0.002$). There was no relationship between being a healthcare worker and clinical patient outcomes ($p=0.535$). The incidence of poor outcome was significantly higher in patients with at least one comorbid disease ($p<0.001$). HT is the most common comorbid disease, and the incidence of poor outcome was significantly higher in patients with comorbid HT ($p<0.001$). Again, there was a significant relationship between the presence of malignancy and the frequency of poor outcome ($p<0.001$).

When admission symptoms are evaluated, poor outcomes were higher in those with shortness of breath ($p<0.001$). No significant relationship was found with poor outcomes when other symptoms were examined. Nevertheless, among the cases with a saturation value below 95%, the frequency of poor outcome was significantly higher ($p<0.001$).

Neutrophil count was significantly higher in the poor outcome patient group (mean difference: 4.94, 95% CI: 3.18–6.69) ($p<0.001$). There was a significant correlation between having a neutrophil count of $7 \times 10^9 \text{ L}^{-1}$ and above and poor outcome ($p<0.001$). (Our normal reference range is $2\text{--}7 \times 10^9 \text{ L}^{-1}$.) Low lymphocyte count was found to be associated with poor outcome (mean difference: 0.35, 95% CI: 0.06–0.65) ($p=0.019$). (Our normal reference range is $1.1\text{--}3.6 \times 10^9 \text{ L}^{-1}$.) There was a significant relationship between lymphocyte count below $1.1 \times 10^9 \text{ L}^{-1}$ and poor outcome ($p<0.001$). C-reactive protein (CRP) value was significantly higher in the poor outcome patient group (mean difference: 62.6, 95% CI: 39.3–85.9) ($p<0.001$). Looking at the ROC curve analysis, when 30 mg/L value was accepted as a cutoff value for predicting poor patient outcomes, sensitivity was 70% and specificity was 72%. The incidence of poor outcome was significantly higher in patients with a CRP value of 30 mg/L and above ($p<0.001$). Furthermore, procalcitonin was significantly higher in this patient group ($p<0.001$). When we analyzed it with ROC curve analysis, if we considered the cutoff value of 0.015 ng/mL for predicting poor patient outcomes, sensitivity was 80% and specificity was 65%. The incidence of poor outcome was significantly higher in patients with procalcitonin values of 0.015 ng/mL and above ($p<0.001$). D-dimer values were significantly higher in the poor outcome patient group ($p<0.001$). When 500 mg/L value was accepted as the cutoff value in the ROC curve analysis, sensitivity for predicting poor patient outcome was found to be 77.8% and specificity 84.9%. Based on this, the incidence of poor outcome was significantly higher in patients with D-dimer values of 500 mg/L and above ($p<0.001$).

The relationship between poor outcome and conditions such as RT-PCR positivity, CT positivity, and both RT-PCR and CT positivity was examined. There was only a significant relationship between the positivity of CT and the percentage of patients with poor outcome ($p=0.006$).

When the factors that may be associated with poor outcome are examined in the logistic regression analysis, the presence of any comorbid disease (odds ratio: 0.26; 95% CI: 0.12–0.59, $p=0.001$), being 50 years and older (odds ratio: 0.24; 95% CI: 0.11–0.52, $p<0.001$), symptom of shortness of breath (odds ratio: 0.15; 95% CI: 0.07–0.31, $p<0.001$), below 95% of the saturation value measured at the time of admission (odds ratio: 0.23; 95% CI: 0.11–0.47, $p<0.001$), a neutrophil count $7 \times 10^9 \text{ L}^{-1}$ and above (odds ratio: 0.36; 95% CI: 0.17–0.75, $p=0.006$), a lymphocyte count less than $1.1 \times 10^9 \text{ L}^{-1}$ (odds ratio: 2.27; 95% CI: 1.14–4.51, $p=0.020$), a procalcitonin value 0.015 ng/mL and above (odds ratio: 0.27; 95% CI: 0.13–0.58, $p=0.001$), and a D-dimer value 500 mg/L and above (odds ratio: 2.85; 95% CI: 1.30–6.29, $p=0.009$) were statistically significant.

Risk scoring system

After evaluating the relationship between the patients' data and poor outcome, we created our own scoring system for poor clinical outcomes of COVID-19 infection (Table 2). The mean risk score of all patients in our study was 2.4 ± 2.1 . The mean score for patients with poor outcome was 5.3 ± 1.8 . The mean score of the patients with poor outcome was significantly higher than the other patients (mean difference: 3.34, 95% CI: 2.82–3.86, $p<0.001$). The area under the curve for predicting "poor prognosis" was 0.89 (95% CI: 0.85–0.93, $p<0.001$) for the calculated risk score (Fig. 1). When the score was above 2, sensitivity was 94.4%, specificity 69.8%, PPV 30.7%, and NPV 98.8% in terms of predicting poor patient outcome. When the score was above 3, sensitivity was 81.5%, specificity 79.6%, PPV 36.1%, and NPV 96.8%.

DISCUSSION

COVID-19 infection has emerged as a global epidemic with a rapid increase and variable clinical diversity. This

Table 2. Risk scoring system associated with poor outcome

Risk factor	Points
Age <50 years	0
Age \geq 50 years	1
Comorbid disease (any)	1
Dyspnea	1
Saturation \geq 95%	0
Saturation <95%	1
Neutrophil $\leq 7 \times 10^9 \text{ L}^{-1}$	0
Neutrophil $> 7 \times 10^9 \text{ L}^{-1}$	1
Lymphocyte $\geq 1.1 \times 10^9 \text{ L}^{-1}$	0
Lymphocyte $< 1.1 \times 10^9 \text{ L}^{-1}$	1
Procalcitonin <0.015 ng/mL	0
Procalcitonin \geq 0.015 ng/mL	1
D-dimer <500 mg/L	0
D-dimer \geq 500 mg/L	1

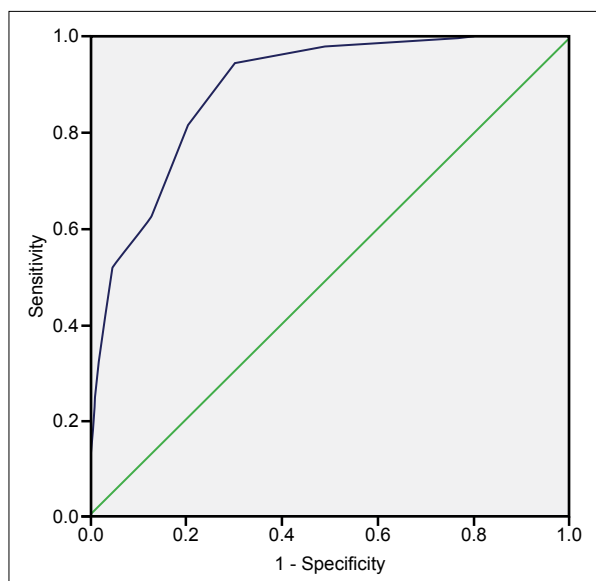


Figure 1. Receiver operating characteristics curve analysis of calculated risk score for predicting the “poor outcome.” The area under the curve was 0.89 (95% CI: 0.85–0.93, $p < 0.001$).

makes it difficult to determine patient diagnosis and treatment methods and prognosis. Many factors are effective in this sense. It is necessary to determine the patient’s risk factors from the admission to predict the clinical course of the disease and whether the patients will need intensive care. Likewise, the World Health Organization states that risk factors must be determined to decide on the severity of this infectious disease.^[12]

In our study, when sociodemographic characteristics were examined, healthcare workers and RT-PCR and CT positivity were found to be correlated. Approximately half of the healthcare workers were found to be RT-PCR positive, and this rate was significantly higher than those who were not healthcare workers. On the other hand, the CT positivity rate was found to be higher in patients who were not healthcare workers. Consistent with the literature, these results made us think that COVID-19 infection in healthcare workers showed a less symptomatic clinical presentation than other patients.^[13] In addition, this indicates that symptom follow-up is better in healthcare workers, and early diagnosis can be made through the ease of access to resources.

In our study, the mean age of patients with negative contact history was significantly higher than those with positive contact history. This finding suggests that the younger age group does not comply with the isolation rules adequately.

In comorbidities, nearly half of the patients had at least one comorbid disease. Considering the frequency of comorbidities, the most common comorbid disease was HT. In similar studies in the literature, HT was found to be the most common comorbid disease.^[4,10,14] In clinical presentations, most of the patients had at least one symptom and the most common symptom was high fever.^[10,15] Likewise, in a study conducted in the pediatric age group, fever was among the most common symptoms.^[16]

There was an inverse relationship between positive contact history and poor outcome in our study. Poor outcome was less common in patients with positive contact history. This finding suggests that knowing positive contact history provides early diagnosis and isolation. In our study, our primary goal was to develop a risk scoring system that provides early warning of poor prognoses, such as death and intensive care follow-up. There are several studies in the literature examining variable risk factors associated with poor prognosis.^[5,9] In the review of 17 studies by Rod et al.,^[17] 60 risk factors were determined and divided into three categories: high, moderate, and low consistency. With this review, it is seen that the determination of risk factors occupies a large place in the literature. In the study conducted by Zhou et al.,^[10] 191 patients were recruited and the risk factors among the patients who died and who were discharged were evaluated. According to this evaluation, age, high SOFA score, and D-dimer > 1 $\mu\text{g/mL}$ were determined as poor prognosis indicators. In the other study, age, comorbid disease, and number of positive contact history were associated with disease severity.^[18] In addition, advanced age was found to be associated with mortality in a study in similar literature. HT was found as a risk factor in other studies.^[7,19] The heterogeneity of the risk factors reported in the studies indicates the need for standard risk scoring systems. In addition, these studies mostly examined China and the Far East. It may be insufficient to directly reflect risk factors globally.

After evaluating the effects of all the patient data, we created our own scoring system for poor clinical outcomes. There are very few studies in the literature in which a standard risk scoring system has been developed. In a multicenter retrospective study by Ji et al.,^[3] a new scoring model called the CALL score was used. Comorbidity, low lymphocyte counts, and lactate dehydrogenase values were examined in the CALL score. In another study by Shi et al.,^[18] 487 cases were examined in two groups, mild and moderate. Age > 50 years, male gender, and HT were used as risk factors.

The fact that there are few studies in the literature on the risk scoring system and the variable risk factors indicates the need for similar studies to be further performed. We created our own risk scoring system that is more comprehensive than the literature. Our model consists of eight parameters: age, comorbidity, dyspnea, oxygen saturation, neutrophil, lymphocyte, procalcitonin, and D-dimer. In our study, the mean score of the patients with poor outcome was significantly higher than the other patients.

Limitations

First, our sample size was small because patients were included from two centers only. Examining a larger number of patients may increase the reliability of the scoring system. Second, in our study, the changes in scores during follow-up could not be examined. The data of patients who were referred to intensive care units or outpatients could not be evaluated.

CONCLUSION

As a result, our scoring system is considered to be a comprehensive, easy, applicable, and reliable method. Using this scoring system is useful in determining early diagnosis and treatment strategies and the requirement for intensive care of patients at the time of the first admission to the emergency department. Therefore, it is expected to reduce the mortality of the patients.

Ethics Committee Approval

This study approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 23.01.2020, Decision No: 01/76).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: S.Ö.; Design: S.Ö., S.D.; Supervision: S.Ö.; Fundings: S.D., A.O.K.; Materials: A.O.K., İ.A.; Data: B.A., S.Ö.; Analysis: S.D.; Literature search: S.Ö., S.D.; Writing: S.Ö.; Critical revision: B.A., A.O.K.

Conflict of Interest

None declared.

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COVID-19 Hastalarında Kötü Prognoz İçin Erken Uyarıcı Bir Risk Puanlama Sistemine Sahip Olmak Mümkün Müdür?

Amaç: Çalışmamızda iki merkezin acil servisine başvuran olası/kesin COVID-19 olgularının verilerini değerlendirerek kötü prognoz ilişkili faktörleri belirlemeyi ve risk skorlama sistemi oluşturmayı amaçladık.

Gereç ve Yöntem: Bu çalışma, COVID-19 olgularında geriye dönük olarak tasarlandı. Hastaların sosyodemografik verileri, şikayetleri, vital bulguları, laboratuvar bulguları, servis/yoğun bakım yatış durumu, ve ölüm varlığı analiz edilmiştir.

Bulgular: Çalışmaya 436 hasta dahil edildi. Olguları kötü prognoz açısından iki gruba ayırdık kötü prognoza ilişkili faktörler değerlendirildiğinde; komorbidite varlığı ($p=0.001$), 50 yaş ve üzeri olmak ($p<0.001$), nefes darlığı semptomunun olması ($p<0.001$), oksijen satürasyon değerinin %95 altında olması ($p<0.001$), nötrofil sayısının $7 \times 10^9/L^{-1}$ üzerinde olması ($p=0.006$), lenfosit sayısının $1.1 \times 10^9/L^{-1}$ altında olması ($p=0.020$), Prokalsitonin düzeyinin 0.015 ng/mL ve üzerinde olması ($p=0.001$), D dimer değerinin 500 mg/L ve üzerinde olması ($p=0.009$) istatistiksel olarak anlamlı bulundu.

Sonuç: Kapsamlı risk skorlama sistemimizi oluşturduk. Modelimiz sekiz parametreden oluşmaktadır. Kötü prognoza sahip hastaların puan ortalamaları diğer hastalara göre anlamlı derecede yüksekti. Oluşturduğumuz skorlama sisteminin prognoz ve tedavi stratejisinin belirlenmesinde kapsamlı, kolay uygulanabilir ve güvenilir bir yöntem olduğu düşünülmektedir.

Anahtar Sözcükler: COVID-19; kötü prognoz; mortalite; skorlama sistemi.