

RESEARCH
ARTICLE

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Is It Possible To Predict Mortality Using Initial Data Of Adult Patients Hospitalized with COVID-19? A Mortality Prediction Model in the Early Phase of COVID-19

ABSTRACT

Objective: In this study, we aimed to determine the factors that contribute to the early determination of mortality risk in patients hospitalized with COVID-19.

Methods: We included 941 adult inpatients (474 male [50.4%], mean age, 53.5±17.0. The patients were divided into two groups: the discharge group and the death group. Epidemiological data, medical history, underlying comorbidities, laboratory findings, chest computed tomographic scans, real-time reverse transcription polymerase chain reaction detection results, and survival data were obtained with retrospective recordings on admission and follow-up. The statistical relationship between survival data and parameters was analyzed. A mathematical model was created from the data of both groups.

Results: While 863 patients survived, 78 were non-survivors. During the study period, the preliminary case fatality rate of the inpatients was 8.3%. The mean age of the non-survivors was 71.7±11.2 SD (P <0.001). Laboratory findings showed that mortality was high in those with high D-dimer, sodium, lactate dehydrogenase (LDH), troponin, creatine kinase-myocardial band (CK-MB), ferritin, blood lactate, activated partial thromboplastin time, and high blood glucose levels (P <0.05). Furthermore, mortality was high in patients with low albumin, lymphocyte, and platelet levels (P <0.05). The logistic regression model showed that advanced age, hypertension, high D-Dimer (>1000 ng/ml), high C-reactive protein (CRP), CK-MB, and LDH, and low lymphocyte count were associated with poor prognosis.

Conclusions: According to week 1 data of patients with COVID-19, advanced age, hypertension, D-Dimer, CRP, CK-MB, high LDH, and low lymphocyte were associated with poor prognosis. We believe that this model will be useful in predicting patient mortality.

Keywords: COVID-19, Mortality, Predictive Factors

COVID-19 Tanısıyla Hastaneye Yatırılan Yetişkin Hastaların İlk Verilerini Kullanarak Ölüm Oranını Tahmin Etmek Mümkün Müdür? COVID-19'un Erken Evresinde Bir Ölüm Tahmin Modeli

ÖZET

Amaç: Bu çalışmada COVID-19 tanısıyla hastaneye yatırılan hastalarda mortalite riskinin erken dönemde belirlenmesine katkıda bulunan faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Hastanede yatan 941 COVID-19 tanılı erişkin hasta (474 erkek [% 50.4], yaş ortalaması 53.5 ± 17 çalışmaya dahil edildi. Hastalar taburcu edilenler ve mortal seyredenler olarak iki gruba ayrıldı. Epidemiyolojik veriler, tıbbi öykü, alta yatan komorbiditeler, laboratuvar sonuçları, akciğer bilgisayarlı tomografi görüntüleri, PCR sonuçları, sağkalım verileri, başvuru ve takipte geriye dönük olarak kaydedildi. Sağkalım verileri ile parametreler arasındaki istatistiksel ilişki incelendi. Her iki grup verilerinden matematiksel bir model oluşturuldu.

Bulgular: 863 hasta hayatta kalırken, 78 hasta mortal seyretti. Çalışma süresi boyunca, yatan hastaların ilk vaka ölüm oranı % 8.3 idi. Mortal grupta hastaların ortalama yaşı 71.7 ± 11.2 SD idi (P <0.001). Laboratuvar bulgularında, D-Dimer, sodyum, laktat dehidrojenaz (LDH), troponin, kreatin kinaz-miyokardiyal bant (CK-MB), ferritin, kan laktat, aktive parsiyel tromboplastin zamanı ve kan şekeri düzeyleri yüksek olanlarda ölüm oranının yüksek olduğu tespit edilmiştir (P <0.05). Ayrıca; albümin, lenfosit ve trombosit düzeyi düşük hastalarda da mortalite yüksek saptandı (P <0.05). Lojistik regresyon modeli, ileri yaş, hipertansiyon, yüksek D-Dimer (> 1000 ng / ml), yüksek C-reaktif protein (CRP), CK-MB ve LDH ve düşük lenfosit sayısının kötü prognozla ilişkili olduğunu gösterdi.

Sonuç: COVID-19 hastalarının 1. hafta verilerine göre ileri yaş, hipertansiyon, yüksek D-Dimer, CRP, CK-MB, LDH ve düşük lenfosit kötü prognozla ilişkilendirildi. Bu modelin hasta ölümlerini tahmin etmede faydalı olacağına inanıyoruz.

Anahtar Kelimeler: COVID-19, mortalite, prediktif faktörler

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak, first detected in Wuhan, China in December 2019, has become a pandemic with millions of cases and thousands of deaths reported (1). The case fatality rate (CFR) is calculated by dividing the number of deaths from an illness/disease by the number of people diagnosed with the disease. CFR is used to identify outbreak measures and evaluate the success of treatment. Mortality in patients with COVID-19 varies across countries, regions, and hospitals. For example, while mortality at the age of 30–39 is 0.3%, it is 1.3% at 50–59 years, 2.5% at 60–69 years, and 9.7% at 70–79 years (2-4). Hence, the chances of survival are related to the country's health system and medical facilities, as well as age-related. Recent studies reported a 3.2% CFR, ranging between 2% and 4% with strong heterogeneity between studies (5), and it differs between mortality rates calculated at the beginning of an epidemic. In the later stages of the epidemic, the CFR varies with the deaths that occur in patients presumed to survive (6).

Many factors or a combination of factors affect mortality and morbidity. Various factors associated with poor prognosis in COVID-19 have been identified. Advanced age, male gender, hypertension, high blood clotting factors, fibrin degradation products, D-dimer, and acute phase reactants were the main defined factors. Identifying these factors is extremely crucial for developing measures needed in new outbreaks. Could the serious course of patients with COVID-19 be predicted by considering the clinical and laboratory findings at the beginning of the disease? This study aims to analyze the initial data of patients hospitalized with COVID-19 and to reveal the model that can rapidly identify those with serious disease risk.

MATERIALS AND METHODS

Hospital and Patients: Sakarya city is a province in Turkey, located in the Eastern Marmara Region, with approximately 1 million inhabitants and gained the status of Metropolitan Municipality. This study was conducted in Sakarya University Training and Research Hospital, which is the only tertiary health care service hospital in Sakarya city. This hospital was commissioned by the Ministry of Health as a reference hospital to serve patients with COVID-19 and had served the most patients in the city during this pandemic. We included 941 adult inpatients (474 male [50.4%], 467 female [49.6%]; mean age, 53.5 ± 17.0 SD [median 54]).

Case Definition: The Republic of Turkey Ministry of Health Covidien-19 met the case definition criteria and verified that a polymerase chain reaction (PCR) test (nasal swab or farineal [nasopharyngeal] sample in the presence of severe acute respiratory syndrome coronavirus 2 [SARS-

CoV-2] RNA), which enrolled patients. Treatment and care were given to patients in line with this guide.

PCR Samples: Oro/nasopharyngeal samples were collected by Dacron-flocked swabs, using a single swab. First, the swab was inserted into the oropharynx and then into the nasopharynx. Oropharyngeal swabs were collected by inserting the swab into the posterior oropharynx and swabbed for 2–3 seconds. The swab was then inserted through the nostril using a rotating movement until it reaches the nasopharynx and the sample was obtained by gently rotating the swab for 2–3 seconds. The swab was placed into a 5-ml tube containing 2 ml viral transport medium.

After the samples were accepted in the microbiology laboratory, they were taken to level 3 biosafe negative pressure laboratory. Bio-Speedy® Viral Nucleic Acid Isolation Kit for the isolation of total nucleic acid from samples (bioeks, Turkey) was used. Reverse transcription (RT)-PCR Bio-Speedy® COVID-19 RT-qPCR Detection Kit (bioeks, Turkey) was used. Isolation, PCR amplification, and evaluation of the results were carried out in line with the recommendations of the manufacturer.

Treatment: Hydroxychloroquine (HDC) was given to hospitalized patients for five days, and favipiravir was given to patients who did not respond to HDC treatment for five days. Patients who did not respond to favipiravir were evaluated for plasma treatment or intensive care monitoring or both. Enoxaparin was given to all patients with high D-dimer and ferritin or at risk for coagulability.

Serious Disease Criteria: Patients with the severe course were followed up in the intensive care unit. The disease was considered severe if a patient had any of the following:

- respiratory distress and/or respiratory rate >30 minutes
- oxygen saturation $<93\%$
- resting and partial arterial oxygen pressure/inspiratory oxygen fraction ratio of ≤ 300 mmHg
- respiratory failure requiring mechanical ventilation
- shock
- other organ failures requiring ICU treatment

Laboratory Tests: Blood samples were obtained within 24 hours of admission to the hospital. All measurements were made within 3 hours after the blood was sent to the laboratory.

Discharge Criteria: For a hospitalized patient, no fever in the last 48 hours or disappearing respiratory symptoms or negative test result for the SARS-CoV-2 RT-PCR test at a 24-hour interval after the treatment were evaluated as discharge criteria.

Data Collection: The data were collected by authors O.K. and E.G. at the infectious diseases clinic. Epidemiological data, medical history,

underlying comorbidities, admission, laboratory findings, chest computed tomographic scans, real-time RT-PCR detection results, and survival data were obtained from the retrospective records of patients. These data were examined by two doctors from the public health department.

Statistical Methods: In descriptive statistics, frequencies and percentages were determined. Chi-square test of independence and Fisher’s exact test was calculated, comparing the frequency of independent variables in survivors and non-survivors. A p-value <0.05 was considered statistically significant. Phi and Cramer’s V values were used in effect size calculations.

A multivariate binary logistic regression model was used to determine the independent effects on the association between mortality and independent variables, estimating odds ratio, and confidence interval (CI, 95%). The variables with statistically significant associations ($P < 0.05$) with mortality were kept in the final model.

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the model were calculated with 95% CI. When calculating CI for sensitivity, specificity, and accuracy, Clopper–Pearson CI were used and for CI of the predictive values, the standard logit CI stated in Mercaldo et al. 2007 publications were based.

The receiver operating characteristic (ROC) curve was plotted for the regression model and the

area under the curve (AUC) was calculated. Analyses were performed using Statistical Package for the Social Sciences version 20.0 (IBM SPSS Statistics; Armonk, NY, USA).

Approvals: This research was carried out with permission from the local hospital management and the Turkish Ministry of Health. All data have been approved by the local ethics committee. In this retrospective cohort type study, the first-week data of adult patients diagnosed with COVID-19 who were hospitalized between 21 March and 30 April 2020 in Sakarya University Training and Research Hospital were included. An ethics committee approval from Sakarya University Medical Faculty was provided for this study (approval number: 71522473/050.01.04./310).

RESULTS

While 863 patients survived, 78 were non-survivors. During the study period, the preliminary CFR of the inpatients was 8.3%. However, the age range at which most deaths were detected was >70 years old. The number of cases >80 years old was small (Figure 1). The mean age of the survivors was 51.9 ± 16.5 SD (median, 51) and the mean age of the non-survivors was 71.7 ± 11.2 SD (median, 72) ($P < 0.001$). The demographic, clinical history, and laboratory findings of the patients are summarized in Table 1.

Table 1. Comparisons of demographics, clinical history and laboratory findings of Covid-19 inpatients in Sakarya University Training and Research Hospital (SUTRH).

Parameters	Survivors	Non-survivors	Statistic
	N (%)	N (%)	Test score p value Effect size
Gender			$X^2 (1, N = 941) = 1.24$
Female	433 (92.7)	34 (7.3)	$p = 0.265$
Male	430 (90.7)	44 (9.3)	$\Phi = 0.036$
Age group			$X^2 (1, N = 941) = 80.38$
< 60 years of age	567 (98.1)	11 (1.9)	$p < 0.001$
≥ 60 years of age	296 (81.5)	67 (18.5)	$\Phi = 0.292$
Having at least one underlying disease			$X^2 (1, N = 941) = 101.52$
No	693 (96.8)	23 (3.2)	$p < 0.001$
Yes	170 (75.6)	55 (24.4)	$\Phi = 0.328$
Hypertension			$X^2 (1, N = 941) = 32.33$
No	775 (93.6)	53 (6.4)	$p < 0.001$
Yes	88 (77.9)	25 (22.1)	$\Phi = 0.185$
Diabetes Mellitus			$X^2 (1, N = 941) = 150.27$
No	797 (95.7)	36 (4.3)	$p < 0.001$
Yes	66 (61.1)	42 (38.9)	$\Phi = 0.400$
Chronic Renal Disease			$N = 941$
No	851 (92.0)	74 (8.0)	$p = 0.037^*$
Yes	12 (75.0)	4 (25.0)	$\Phi = 0.080$
Chronic obstructive pulmoner disease or Asthma			$X^2 (1, N = 941) = 0.20$
No	818 (91.8)	73 (8.2)	$p = 0.652$ $\Phi = 0.015$

Yes	45 (90.0)	5 (10.0)	
D-dimer			$X^2 (1, N = 940) = 155.99$
< 1000 ng/mL	647 (99.2)	5 (0.8)	$p < 0.001$
≥ 1000 ng/mL	216 (75.0)	72 (25.0)	$Phi = 0.407$
CRP			$X^2 (1, N = 918) = 207.73$
< 100 mg/L	689 (99.0)	7 (1.0)	$p < 0.001$
≥ 100 mg/L	151 (68.0)	71 (32.0)	$Phi = 0.476$
Troponin			$X^2 (1, N = 320) = 60.67$
< 50 ng/mL	223 (86.8)	34 (13.2)	$p < 0.001$
≥ 50 ng/mL	26 (41.3)	37 (58.7)	$Phi = 0.435$
CK-MB			$X^2 (1, N = 885) = 97.68$
< 25 ng/mL	710 (96.1)	29 (3.9)	$p < 0.001$
≥ 25 ng/mL	105 (71.9)	41 (28.1)	$Phi = 0.332$
Albumin			$X^2 (1, N = 684) = 200.70$
≥ 30 g/L	508 (98.6)	7 (1.4)	$p < 0.001$
< 30 g/L	100 (59.2)	69 (40.8)	$Phi = 0.542$
Creatinine			$X^2 (1, N = 920) = 162.01$
< 1.5 mg/dL	799 (95.6)	37 (4.4)	$p < 0.001$
≥ 1.5 mg/dL	47 (56.0)	37 (44.0)	$Phi = 0.420$
Sodium			$X^2 (1, N = 736) = 7.83$
< 140 mmol/L	437 (92.0)	38 (8.0)	$p = 0.005$
≥ 140 mmol/L	223 (85.4)	38 (14.6)	$Phi = 0.103$
Ferritin			$X^2 (1, N = 892) = 125.61$
< 1000 µg/l	711 (96.7)	24 (3.3)	$p < 0.001$
≥ 1000 µg/l	110 (70.1)	47 (29.9)	$Phi = 0.375$
LDH			$X^2 (1, N = 887) = 125.61$
< 500 U/L	725 (96.7)	25 (3.3)	$p < 0.001$
≥ 500 U/L	85 (62.0)	52 (38.0)	$Phi = 0.444$
Fibrinogen			$N = 260$
< 200 mg/dL	5 (83.3)	1 (16.7)	$p = 0.505^*$
≥ 200 mg/dL	187 (73.6)	67 (26.4)	$Phi = 0.033$
Blood Lactate			$X^2 (2, N = 568) = 6.74$
< 2 mmol/L	256 (92.1)	22 (7.9)	$p = 0.034$
2 – 3.9 mmol/L	225 (86.5)	35 (13.5)	$Cramer's V = 0.109$
≥ 4 mmol/L	24 (80.0)	6 (20.0)	
Active partial thromboplastin time			$X^2 (1, N = 695) = 87.70$
< 33.5 sec	596 (92.4)	49 (7.6)	$p < 0.001$
≥ 33.5 sec	25 (50.0)	25 (50.0)	$Phi = 0.355$
Glucose			$X^2 (1, N = 754) = 117.09$
< 200 mg/dL	613 (94.7)	34 (5.3)	$p < 0.001$
≥ 200 mg/dL	65 (60.7)	42 (39.3)	$Phi = 0.394$
Hematuria			$X^2 (1, N = 634) = 0.09$
< 3 RBC in urine	337 (95.2)	17 (4.8)	$p = 0.757$
≥ 3 RBC in urine	268 (95.7)	12 (4.3)	$Phi = 0.012$
Proteinuria			$X^2 (1, N = 636) = 31.82$
Negative	442 (98.2)	8 (1.8)	$p < 0.001$
Positive	163 (87.6)	23 (12.4)	$Phi = 0.224$
Lymphocyte Count in CBC			$X^2 (1, N = 898) = 163.81$
≥ 1000 /mm ³	569 (99.0)	6 (1.0)	$p < 0.001$
800 – 999 /mm ³	104 (92.9)	8 (7.1)	$Cramer's V = 0.427$
< 800 /mm ³	148 (70.1)	63 (29.9)	
Platelet Count in CBC			$X^2 (1, N = 898) = 19.22$
≥ 150,000/mm ³	584 (93.4)	41 (6.6)	$p < 0.001$
100,000 – 149,999/mm ³	220 (88.4)	29 (11.6)	$Cramer's V = 0.146$
< 100,000/mm ³	17 (70.8)	7 (29.2)	

*Fisher's Exact Test

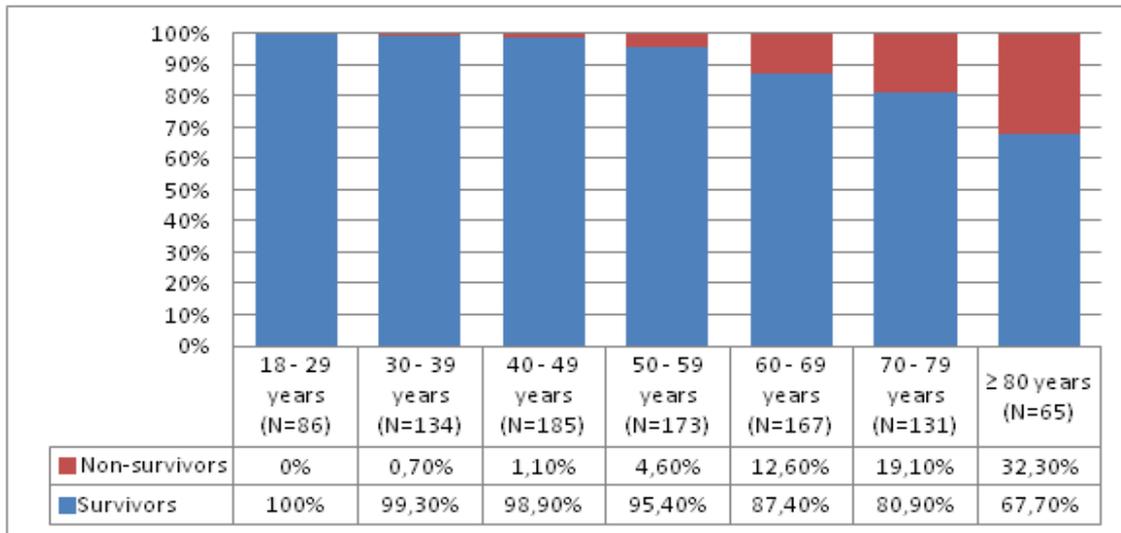


Figure 1. Death prevalence of study group according to age

Using one-way statistical analysis, >60 years of age, hypertension, chronic renal failure, and diabetes mellitus were associated with poor prognosis ($P < 0.05$). In laboratory findings, D-dimer, sodium, lactate dehydrogenase (LDH), troponin, creatinin kinase myocardial band (CK-MB), ferritin, blood lactate level, high blood glucose, and presence of blood and protein in urine were associated with mortality ($P < 0.05$). In addition, low albumin, lymphocyte, and platelet levels were associated with mortality ($P < 0.05$) (Table 1).

According to the data obtained using the logistic regression model, advanced age, hypertension, high d-dimer, elevated C-reactive protein (CRP), CK-MB, and LDH, and lymphocyte deficiency were associated with poor prognosis (Table 2). The ROC curve of the model created for

the prediction of mortality outcome in Covid-19 patients (Figure 2).

In one-way statistical analysis; over the age of 60, hypertension, chronic renal failure and diabetes mellitus showed poor prognosis ($P < 0.05$). In laboratory findings; D-dimer, sodium, LDH, troponin, CK-MB, ferritin, blood lactate level, high blood glucose, presence of blood and protein in urine were associated with mortality ($P < 0.05$). In addition, low albumin, lymphocyte and platelet levels were associated with mortality ($P < 0.05$) (Table 1).

According to the data obtained using the logistic regression model; advanced age, presence of hypertension, high d-dimer, elevated CRP, creatinin kinase myocardial band (CK-MB) and LDH, lymphocyte deficiency were associated with poor prognosis (Table 2).

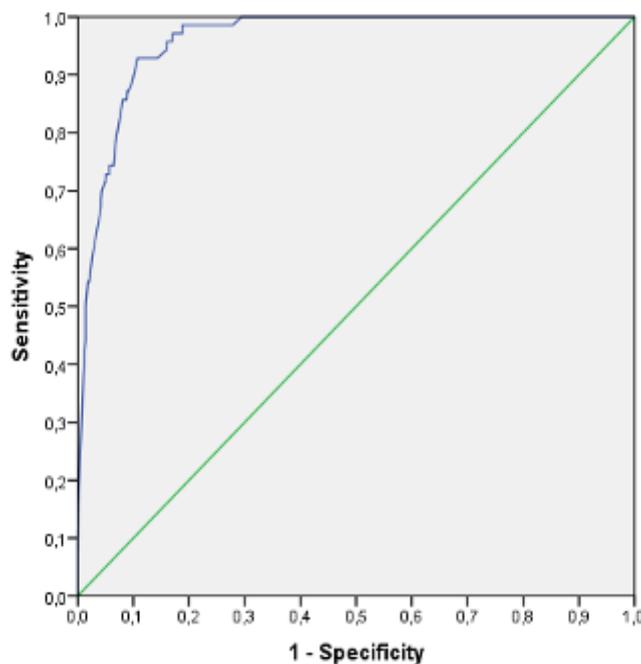


Figure 2. The ROC curve of the model created for the prediction of mortality outcome in Covid-19 patients

Table 2. Multivariate binary logistic regression model predicting likelihood of mortality of Covid-19 inpatients in Sakarya University Training and Research Hospital (SUTRH) based on age group, hypertension history, lymphocyte count, D-dimer, CRP, LDH and CK-MB levels.

Parameters	B	SE	Wald	df	p	Odds Ratio	95 % Confidence Interval for Odds Ratio
Age group < 60 years of age (0*) ≥ 60 years of age (1)	0.96	0.44	4.80	1	0.028	2.62	1.11 – 6.18
Hypertension No (0) Yes (1)	1.29	0.42	9.36	1	0.002	3.63	1.59 – 8.29
D-dimer < 1000 ng/mL (0) ≥ 1000 ng/mL (1)	2.05	0.57	13.15	1	< 0.001	7.77	2.57 – 23.53
CRP < 100 mg/L (0) ≥ 100 mg/L (1)	1.95	0.51	14.66	1	< 0.001	7.05	2.59 – 19.16
CK-MB < 25 ng/mL (0) ≥ 25 ng/mL (1)	1.36	0.37	13.61	1	< 0.001	3.88	1.89 – 7.96
LDH < 500 U/L (0) ≥ 500 U/L (1)	1.07	0.39	7.27	1	0.007	2.91	1.34 – 6.31
Lymphocyte Count ≥ 800 /mm ³ (0) < 800 /mm ³ (1)	0.84	0.41	4.19	1	0.041	2.31	1.04 – 5.13
Constant	- 7.17	0.72	98.55	1	< 0.001	0.001	

*0 = Reference Group

The model $X^2 (7, N = 831) = 258.27$ $p = < 0.001$ indicates that the model is significant. For goodness of fit of the model Hosmer Lemeshow test was conducted and p value was found to be 0.86. It suggests the model is a good fit to the data. Nagelkerke R^2 was found to be 0.61. The model can predict 61% of variance in mortality outcome. The predicted correction percentage increased from 91.6 % to 94.5 % with the model. Sensitivity was 54.3% (95% CI 41.9 – 66.3 %), specificity was 98.2% (95% CI 96.9 – 98.9 %), positive predictive value was 73.1% (95% CI 60.8 – 82.6 %), negative predictive value was 95.9% (95% CI 94.8 – 96.8 %), and accuracy was 94.5 (95% CI 92.7 – 95.9 %).

Regression Model Formula = (Age group × 0.961) + (Hypertension × 1.29) + (D-dimer × 2.05) + (CRP × 1.953) + (CKMB × 1.355) + (LDH × 1.067) + (Lymphocyte count × 0.836) - 7.165. The area under the ROC curve was 0.960 (95% CI 0.945 to 0.975), which is an outstanding level of discrimination (7). When these seven

parameters (age, hypertension, D-dimer, CRP, CKMB, LDH, Lymphocyte count) in the regression model are given 1 and 0 according to the intervals determined, the total result obtained from the formula is below 0, when the patient is close to death, below 0. those who survived were more likely to survive (Table 2).

DISCUSSION

In this study, we examined the data of 941 patients who were hospitalized and monitored. The severity criteria were investigated according to the initial laboratory and clinical findings of the patients with COVID-19. We compared the data of 77 patients (8.1%) with mortality to those with no mortality. According to the data obtained using the logistic regression model, >60 years old, hypertension, high d-dimer, CRP, CK-MB, and LDH, and low lymphocyte count were associated with poor prognosis.

Furthermore, advanced age (>60 years old) and accompanying comorbidity were associated with poor prognosis. In many different studies,

these factors have already been identified as risk factors for serious illness (8). The mortality rate in patients >60 years of age was higher compared to younger patients. Here, it was found that deaths were concentrated especially in the older population, which could be attributed to the weakened immune systems in the older population to fight off viral infections. Furthermore, patients >60 years old had the highest risk of severe disease and death. As of May 2020, Turkey was among the 10 most-affected countries with COVID-19. However, the mortality rate in Turkey (2.2%) was lower compared to other countries. In this case, it is also effective that the hospital bed capacity is not exceeded and the age structure of our population is relatively younger. While 65+ population was created 9% of the population in Turkey, this ratio is around 20% in many other countries. In some countries, the median age is >80 years. Thus, it would be more accurate to compare age-specific speeds (9,10).

Comorbidity increases with increasing age. Patients with underlying conditions, such as diabetes, cardiovascular disease, hypertension, chronic lung disease, and cancer, have been identified as risk factors for COVID-19. The SARS-CoV-2 binds to the human receptor angiotensin-converting enzyme 2 (ACE2) proteins and enters the target cell. ACE2 protein is found on the surface of many cells. Most importantly, the receptor of ACE2 increases with increasing age (11). Typically, hypertension increases the amount of ACE2 receptors (12). However, most of the severe cases of COVID-19 have been associated with overactivity of the immune system.

COVID-19 is a systemic disease that affects both the bleeding and coagulation system. According to our findings, the mortality rate in patients with lymphopenia is 2.31 times higher. A meta-analysis conducted showed that a lymphocyte count of less than $1.5 \times 10^9/L$ was the criteria for severe disease and adverse prognosis (13). In this study, a lymphocyte count $<800/mm^3$ was found to be associated with poor prognosis. Why is the disease more serious in those with lymphopenia? There are some hypotheses on this subject. First, the virus can directly infect lymphocytes, causing immune-mediated lymphocyte death (14). Second, some studies have confirmed that tumor necrosis factor α , interleukin (IL)-6, IL-1, and other proinflammatory cytokines can induce lymphocytopenia (15). According to these findings, lymphopenia should be followed closely from the beginning of the disease.

Based on our analysis, patients with severe COVID-19 have high blood lactic acid levels. Lactic acid can suppress the proliferation of lymphocytes. In addition, the findings of our study suggest that high lactic acid was a risk factor for severe disease (16). In patients with severe COVID-19, elevated lactic acid levels may trigger

lymphopenia. However, the number of research on this subject is limited. We believe that further research is needed to examine the relationships between high lactic acid levels and lymphopenia (17). A study reported that lactic acid produced from tumor cells have shown to block T cell production (18).

We found that high D-dimer was associated with the severity of COVID-19 infection. D-dimer is a plasmin-derived fibrin degradation product. Severe COVID-19 infection causes extensive damage to the endothelium. Furthermore, endothelial damage triggers the coagulation cascade. Studies have shown that high D-dimer is associated with mortality in COVID-19. COVID-19 was associated with hemostatic abnormalities, and significantly higher D-dimer levels have been reported in severe cases (19,20). A severe pro-inflammatory response in COVID-19 viremia and this lack of control causes dysfunction of the endothelial cells in the same case. This causes excess thrombin release and D-dimer elevation (21). In addition, postmortem lung organ dissection of critically ill patients with serious COVID-19 showed occlusion and micro thrombosis of small pulmonary vessels (21,22). Considering the hematological clinical findings in COVID-19, we believe that one of the most important issues is coagulopathy, thrombosis, and anticoagulation management. Reportedly, many patients with severe course experienced significant thrombosis (23,24). Some studies and the results obtained in this study suggested that the risk of embolic events was high for these patients and that prophylactic thrombosis-relieving drugs (e.g., enoxaparin) should be used early in these patients.

CRP is a nonspecific marker of infection, inflammation, and tissue damage. In this study, we found that patients with severe prognosis had high CRP (>100 mg/L) values in the early days. This is related to the disease-related inflammatory reaction and destruction of tissues. Studies have shown that a high CRP level is due to lung damage and poor prognosis (25). Our findings showed that CRP can be used as a marker in monitoring the activation of the disease. However, it should be remembered that the half-life of CRP is approximately 18 hours (26). A study in China indicated that CRP could be a valuable marker to estimate the probability of serious progression of COVID-19 (27).

In this study, LDH was associated with severe disease. As previously mentioned, according to our values on day 1, we found a worse course in patients with high LDH levels. LDH has different isomers (LDH-1 in the heart, red blood cells, and brain; LDH-2 in the reticuloendothelial system; LDH-3 in the lungs; LDH-4 in the kidneys and pancreas; and LDH-5 in the liver and striated muscle). Therefore, we believe that high LDH is especially related to widespread damage to the muscles, including the lungs, erythrocytes, and

heart. Many studies reported that high LDH indicated a poor prognosis (28,29).

We analyzed the items found meaningful in this research with modeling. When data from this research were calculated with statistical modeling, we obtained a regression model formula. According to this formula, by applying certain coefficients to the variables, such as age group, history of hypertension, D-dimer, CRP, CK-MB, LDH, and lymphocyte count, the disease will show a severe course compared to this formula and a severe clinical picture when <0 . This is not expected. Furthermore, according to the data obtained within the first 7 days after hospitalization, we believe that the application of this formula will help determine the number of patients who need intensive care and those who need specialized treatments (e.g., plasma treatment). According to the ROC curve of this formula, we predicted a value of 0.960 curves, which showed a clear distinction.

Although the sensitivity of this model is low, its specificity is quite good and will, therefore, enable successful prediction of cases that may not

be severe. However, we believe that the model we obtained should be validated by evaluating the studies to be conducted in different COVID-19 groups. In addition, we believe that the study design will be planned prospectively (longitudinal) and will establish stronger causal relationships.

As a result, in this study, the data of the first week of approximately 1000 confirmed COVID-19 patients were examined and age, hypertension, d-dimer, CRP, CK-MB, LDH elevation, and low lymphocytes were associated with serious prognosis. We believe that the modeling we have developed for these patients will be beneficial for possible pandemics.

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REFERENCES

1. Kobayashi T, Jung S-M, Linton NM, Kinoshita R, Hayashi K, Miyama T, et al. Communicating the Risk of Death from Novel Coronavirus Disease (COVID-19). *J Clin Med Res* 2020;9. <https://doi.org/10.3390/jcm9020580>.
2. Jin H, Liu J, Cui M, Lu L. Novel coronavirus pneumonia emergency in Zhuhai: impact and challenges. *Journal of Hospital Infection* 2020;104:452–3. <https://doi.org/10.1016/j.jhin.2020.02.005>.
3. Website n.d. https://www.epicentro.iss.it/coronavirus/bollettino/Bollettinosorveglianza-integrata-COVID-19_16-aprile-2020.pdf. (accessed May 19, 2020).
4. Website n.d. <https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaR ENAVE/EnfermedadesTransmisibles/Documents/INFORMES/Informes%20COVID-19/Informe%20n%C2%BA%2023.%20Situaci%C3%B3n%20de%20COVID-19%20en%20Espana%20B1a%20a%2016%20de%20abril%20de%202020.pdf> (accessed May 19, 2020).
5. Giorgi Rossi P, Emilia-Romagna COVID-19 working group, Broccoli S, Angelini P. Case fatality rate in patients with COVID-19 infection and its relationship with length of follow up. *J Clin Virol* 2020;128:104415.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
7. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. Wiley Series in Probability and Statistics 2013. <https://doi.org/10.1002/9781118548387>.
8. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020. [https://doi.org/10.1016/S1473-3099\(20\)30243-7](https://doi.org/10.1016/S1473-3099(20)30243-7).
9. Volpato S, Landi F, Incalzi RA. A Frail Health Care System for an Old Population: Lesson form the COVID-19 Outbreak in Italy. *The Journals of Gerontology: Series A* 2020. <https://doi.org/10.1093/gerona/glaa087>.
10. Nguyen NP, Vinh-Hung V, Baumert B, Zamagni A, Arenas M, Motta M, et al. Older Cancer Patients during the COVID-19 Epidemic: Practice Proposal of the International Geriatric Radiotherapy Group. *Cancers* 2020;12. <https://doi.org/10.3390/cancers12051287>.
11. Magrone T, Magrone M, Jirillo E. Focus on Receptors for Coronaviruses with Special Reference to Angiotensin-converting Enzyme 2 as a Potential Drug Target - A Perspective. *Endocr Metab Immune Disord Drug Targets* 2020. <https://doi.org/10.2174/1871530320666200427112902>.
12. Bourgonje AR, Abdulle AE, Timens W, Hillebrands J-L, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme-2 (ACE2), SARS-CoV-2 and pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol* 2020. <https://doi.org/10.1002/path.5471>.

13. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Deng Y, et al. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. *Int J Infect Dis* 2020;96:131–5.
14. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine* 2020;382:727–33. <https://doi.org/10.1056/nejmoa2001017>.
15. Conti P, Ronconi G, Caraffa A, Gallenga C, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 2020;34. <https://doi.org/10.23812/CONTI-E>.
16. Liao Y-C, Liang W-G, Chen F-W, Hsu J-H, Yang J-J, Chang M-S. IL-19 Induces Production of IL-6 and TNF- α and Results in Cell Apoptosis Through TNF- α . *The Journal of Immunology* 2002;169:4288–97. <https://doi.org/10.4049/jimmunol.169.8.4288>.
17. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020;5:33.
18. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood* 2007;109:3812–9. <https://doi.org/10.1182/blood-2006-07-035972>.
19. Arachchillage DRJ, Laffan M. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:1233–4.
20. Lee KS. Pneumonia Associated with 2019 Novel Coronavirus: Can Computed Tomographic Findings Help Predict the Prognosis of the Disease? *Korean Journal of Radiology* 2020;21:257. <https://doi.org/10.3348/kjr.2020.0096>.
21. Wong JP, Viswanathan S, Wang M, Sun L-Q, Clark GC, D'Elia RV. Current and future developments in the treatment of virus-induced hypercytokinemia. *Future Med Chem* 2017;9:169–78.
22. Fakültesi ZÜT. COVID-19 Önleme ve Tedavi El Kitabı. Sistematik; 2020.
23. Porfidia A, Pola R. Venous thromboembolism in COVID-19 patients. *J Thromb Haemost* 2020. <https://doi.org/10.1111/jth.14842>.
24. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res* 2020. <https://doi.org/10.1016/j.thromres.2020.04.041>.
25. Deng Y, Liu W, Liu K, Fang Y-Y, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. *Chin Med J* 2020. <https://doi.org/10.1097/CM9.0000000000000824>.
26. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *Journal of Clinical Investigation* 2003;111:1805–12. <https://doi.org/10.1172/jci200318921>.
27. Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation. *Open Forum Infect Dis* 2020;7:ofaa153.
28. Bolten MP. C. Janzing, A. van den Berg en F. Kruisdijk (2003). *Handboek voor milieutherapie. Theorie en praktijk van de klinische psychotherapie (deel 2)*. Assen: Van Gorcum. 244 pp., € 36,-. *Tijdschrift Voor Psychotherapie* 2005;31:93–6. <https://doi.org/10.1007/bf03062133>.
29. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. *Am J Hematol* 2020. <https://doi.org/10.1002/ajh.25829>.