Acta Clin Croat 2025; 64:484-498
doi: 10.20471/acc.2025.64.03.09

Original Scientific Paper

COPD, AGE, LDH, TROPONIN, D-DIMER, AND CRP/ALBUMIN RATIO: A NEW PROGNOSTIC MODEL FOR COVID-19

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SUMMARY – The aim of this study was to determine the relationship between demographic characteristics, initial laboratory data and comorbidities with prognosis in inpatients followed up for coronavirus disease 2019 (COVID-19) and to create a new model for predicting mortality risk. In this multicenter, retrospective cohort study, patient demographic and clinical data were recorded at the first patient admission to the hospital. The primary outcome was to evaluate the relationship of demographic characteristics, laboratory parameters and comorbidities with mortality. Parameters found to be associated with mortality in univariate analyses were also evaluated with multivariate analyses and a final model was established. In the final model, the presence of chronic obstructive pulmonary disease (COPD) (OR: 3.177, 95% CI: 1.574-6.413), age (OR: 1.056, 95%CI: 1.034-1.078), lactate dehydrogenase (LDH) (OR: 1.002, 95%CI: 1.001-1.003), troponin (OR: 1.052, 95% CI: 1.007-1.099), D-dimer (OR: 1.012, 95%CI: 1.002-1.021), and C-reactive protein (CRP)/albumin ratio (OR: 1.278, 95%CI: 1.145-1.427) were found to be associated with mortality. The model accurately predicted mortality with a sensitivity of 82.6% and specificity of 77.7%. COPD, age, LDH, troponin, D-dimer, and CRP/albumin ratio were determined as factors associated with mortality. Assessment of these parameters at the time of admission of inpatients, classifying patients as high risk, and adopting early and appropriate treatment approaches may help in the management of patients.

Keywords: *COVID-19; Mortality; Prognosis; Chronic obstructive pulmonary disease; Lactate dehydrogenase*

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Received January 31, 2021, accepted April 12, 2022

Introduction

Coronavirus disease 2019 (COVID-19) is a disease with a broad clinical spectrum. Although there are asymptomatic cases, by causing up to severe acute respiratory illness, it can lead to the outcomes with a spectrum ranging from the need of invasive mechanical ventilation to death[1]. Differentiation of risk patients in terms of poor prognosis is important during hospital admission.

In some studies conducted in Wuhan, the rate of serious disease was found to be higher in those with high lactate dehydrogenase (LDH) and cardiac injury, and high D-dimer levels to predict mortality[2,3]. Neutrophil/lymphocyte ratio[4], troponin[5], increased C-reactive protein (CRP)[6], thrombocytopenia[7], and fibrinogen[8] are also among the parameters found to be associated with mortality. Despite all these studies, there still are uncertainties about which risk factors are important for adverse outcomes in COVID-19 patients with very high mortality and frequent unexpected deaths.

It has been stated in the literature that patients with asthma and chronic obstructive pulmonary disease (COPD) are at risk of severe COVID-19[9,10]. In a recent study, it was found that patients with asthma are more likely to receive critical care than those without pulmonary disease, while those with chronic pulmonary disease are less likely[11]. While there is an increased risk of mortality in patients with hypertension[12], it has not been identified as a risk factor independent of age and comorbidities[13]. Diabetes was found to be associated with worse outcomes in the study conducted by Seiglie *et al.*[14], while there was no difference in mortality between those with and without diabetes in the study of hospitalized patients performed by Ahmed *et al.*[15]. All these data show that the relationship between the severity of COVID-19 and comorbidities remains unclear.

Determining patients with a high mortality risk and initiating effective treatments in the early period can improve disease prognosis. We think that laboratory parameters at the time of admission to the hospital, demographic characteristics, and known comorbidities of the patients are important parameters in determining the prognosis. In addition, determining the high-risk groups will guide healthcare personnel in the triage practice.

The aim of this study was to determine the relationship between demographic characteristics, initial laboratory data, and comorbidities of patients hospitalized in Turkey due to COVID-19, with the length of hospital stay (LOS), intensive care unit (ICU) admission, and mortality, and to create a clinically interpretable model with good predictive performance in predicting mortality risk. Our hypothesis was that demographic characteristics, laboratory data, and comorbidities are associated with the LOS, ICU admission, and mortality, and mortality risk can be predicted with these clinical features. To predict the prognosis of the disease with clinical data of the patients will be useful in constituting triage, follow-up, and treatment algorithms for patients and determining priority groups.

Patients and Methods

Study design and participants

This multicenter, retrospective cohort study was conducted in İstanbul Sultan Abdülhamid Han Training and Research Hospital, and İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital. Patients hospitalized with the diagnosis of COVID-19 between March 1, 2020 and June 23, 2020 were included in the study, with data cut-off for the analyses on December 31, 2020. Inclusion criteria were age ≥18 years, having a diagnosis of COVID-19 with positive finding of real-time polymerase chain reaction (RT-PCR) in nasopharyngeal swab sample, and/or appearance of COVID-19 compatible radiological findings on computed tomography (CT) (ground glass view). Patients with negative SARS-CoV-2 PCR test, and having pneumonia on CT but not treated for COVID-19 because of not being considered to have COVID-19 were not included. Patients who were transferred from the hospital to another hospital were excluded because their outcome data could not be available; those who had hematologic malignancies were excluded because these could cause possible confusion in hematologic parameters; and those who were kept in the hospital during the isolation period despite recovering because they lived in collective places (military, etc.) were excluded as it may cause confusion in data on hospitalization time. Before starting the study, permission was obtained from the Ministry of Health of the Turkey

Republic (T.R.) and University of Health Sciences Hamidiye Ethics Committee (approval number: 20/307, approval date: 07/09/2020). The study was conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects of the Helsinki Declaration. The requirement for informed consent was waived because of the retrospective nature of the study. Permission was obtained from the hospital administration to access patient records. This study is registered with ClinicalTrials.gov, NCT04789460 (registration date: (03/04/2021). This cohort study was reported in adherence to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data collection

Patient sociodemographic information (age, gender), comorbidities (diabetes, heart failure, chronic kidney disease, hypertension, cardiovascular disease, hyperlipidemia, asthma, COPD, other lung diseases, cancer, hyperthyroidism, hypothyroidism, stroke, dementia, and others), and medicines they used for the treatment of COVID-19 were recorded. Also, the International Classification of Disease 10 (ICD-10) coded diagnoses and prescriptions registered in the Ministry of Health system were accessed and recorded. Patient results on LDH, hemoglobin, lymphocyte, eosinophil, leukocyte, neutrophil, platelet, troponin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, creatinine, albumin, CRP, fibrinogen and ferritin at the time of their first admission were recorded. If the examination was not performed at the first application to the hospital, the first test result obtained within 72 hours was acquired. Parameters were selected based on clinical aptitude and previously published studies. Data on the patient LOS, ICU admission, and state at discharge (recovery, exitus) were recorded. The epicrisis notes of COVID-19 patients were written in detail, and all records were independently checked by two separate internal medicine specialists to verify the data. In case of any discrepancy, two doctors came together to evaluate the data and a consensus was obtained.

All of the patients hospitalized were taking the recommended medicines in line with the treatment recommendations of the T.R. Ministry of Health at that time. These recommendations included hydroxychloroquine for most patients and lopinavir/ritonavir, favipravir, azithromycin, plasma therapy, tocilizumab, and corticosteroid treatments, depending on the disease state[16]. Corticosteroid therapy was less used in the early stages of the pandemic compared to current treatment approaches. In addition, there also were those who received various antibiotics and oseltamivir treatment in cases where influenza could not be excluded by the physician's decision. All patients received anticoagulant and antiaggregant treatment to avoid COVID-19 complications.

Outcomes

The primary outcome was to evaluate the relationship between demographic characteristics, potential predictive laboratory parameters, comorbidities, and mortality. Mortality was defined as mortality at the time of hospitalization and within the following 30 days. The secondary outcome was the relationship of the same parameters with the LOS and ICU admission. Parameters found to be associated with mortality on univariate analyses were also evaluated with multivariate analyses and a final model was established to estimate the probability of mortality in patients.

Statistical analysis

Descriptive statistics of the data obtained were calculated as median, interquartile range, count and percent frequencies. The conformity of the measured characteristics to the normal distribution was examined using the Shapiro-Wilk test. The relationships between total LOS and categorical characteristics were evaluated with an independent samples t-test. In addition, the relationships between total LOS and numerical characteristics were evaluated by correlation analysis. The categorical characteristics associated with ICU admission and mortality were examined using Pearson χ^2 analysis, one of the univariate tests, and their relationships with numerical features were evaluated using the independent samples t-test.

Risk factors for mortality with a statistically significant $p<0.05$ or $p<0.10$ were taken together with the multivariate logistic regression model. This model was named as full model. The reason why $p<0.10$ were also included in this model is that it may have biological/clinical significance and the p values are close to significance. After being taken to the multivariate

model, variables with a significant effect were left in the model with the stepwise variable selection method. Ultimately, the final model was obtained. The final model obtained was used to predict the probability of mortality in new patients. The model established to estimate the probability of mortality is as follows; the p value on the left side of the model is the probability of death, and *e* is the natural logarithm base:

$$P = \frac{e^{-7.701 + 1.156\,(KOAH\ VAR) - 1.254\,(INME\ VAR) + 0.054\,(YAŞ) + 0.002\,(LDH) + 0.051\,(TROPONIN) + 0.012\,(DDIMER) + 0.245\,(\frac{CRP}{ALB})}}{1 + e^{-7.701 + 1.156\,(KOAH\ VAR) - 1.254\,(INME\ VAR) + 0.054\,(YAŞ) + 0.002\,(LDH) + 0.051\,(TROPONIN) + 0.012\,(DDIMER) + 0.245\,(\frac{CRP}{ALB})}}$$

In addition, only one of the variables in the functional relationship was included in the model, so that they did not cause the multicollinearity problem. The variables that fall into this category are the neutrophil/lymphocyte ratio and a function of neutrophil count and lymphocyte count. These two properties and their ratio were found to be significant in the univariate test, but only the neutrophil/lymphocyte ratio was included in the model. Similarly, the CRP/albumin ratio is a function of albumin and CRP. These two properties and their ratio were found to be significant in the univariate test, but only the CRP/albumin ratio was included in the model.

The age comparison of the groups formed according to the presence of comorbidity associated with mortality in the final model was performed with independent samples t-test, and the comparison in terms of categorical variables was performed with Pearson χ^2 analysis.

The $p<0.05$ was accepted as the statistical significance level and SPSS (version 23) program was used for calculations. To determine the sample size, a power

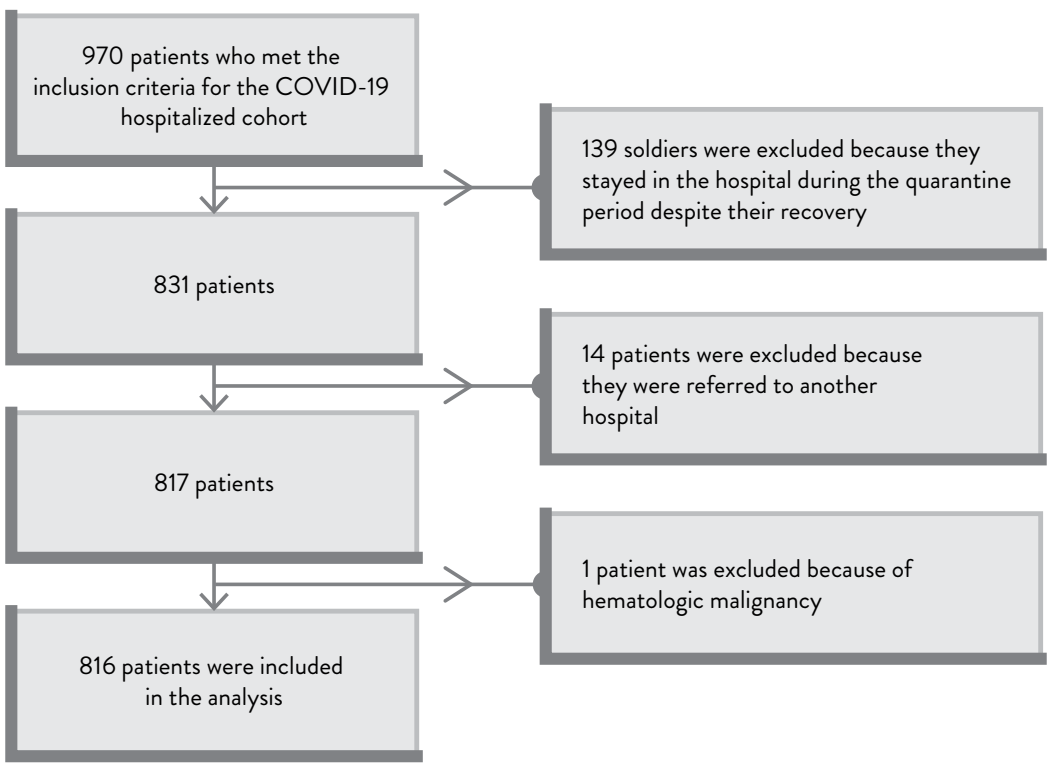

Fig. 1. Flow diagram for included patients.

analysis was calculated by taking into consideration the values of the data obtained from a similar study in the literature. In the calculation, the online calculation tool available on the website https://www.stat.ubc.ca/~rollin/stats/ssize/caco.html was used. The required sample size [alpha] at an effect size of 0.5 and error level of 0.05 was determined as 600. The strength of the analysis with this sample size was found to be 80%.

Results

A total of 970 patients who met the inclusion criteria for the COVID-19 hospitalized cohort identified and 816 patients were included in the analysis. The flow diagram for the included patients is illustrated in Figure 1. Comorbidities, demographic and clinical characteristics of all patients are shown in Table 1.

Table 1. Comorbidities, demographic and clinical characteristics of patients

		Median (IQR) n (%)
Gender	Male	461 (56.5)
	Female	355 (43.5)
Diabetes mellitus		187 (22.9)
Heart failure		45 (5.5)
Chronic kidney disease		30 (3.7)
Hypertension		306 (37.5)
Cardiovascular disease		29 (3.6)
Asthma		111 (13.6)
COPD		64 (7.8)
Cancer		11 (1.3)
Stroke		27 (3.3)
Age (years)		58.00 (45.25-70.00)
LDH (U/L)		413.50 (332.25-562.75)
Hemoglobin (g/dL)		12.90 (11.53-14.20)
Lymphocyte count (10^3/μL)		1.29 (0.94-1.78)
Eosinophil count (10^3/μL)		0.02 (0.01-0.09)
White cell count (10^9/L)		6.78 (5.01-9.23)
Neutrophil count (10^3/μL)		4.67 (3.17-7.05)
Neutrophil/lymphocyte		3.37 (2.05-6.11)
Platelet count (10^9/L)		205.00 (163.00-257.00)
Troponin (ng/mL)		4.60 (2.33-13.33)
AST (U/L)		24.00 (18.00-33.00)
ALT (U/L)		26.00 (17.00-40.00)
D-dimer (ng/mL)		472.00 (273.50-1100.00)
Creatinine (mg/dL)		1.01 (0.85-1.23)
Albumin (g/L)		37.00 (32.00-41.00)
C-reactive protein (mg/L)		31.00 (8.78-85.63)
C-reactive protein/albumin		0.82 (0.24-2.52)
Fibrinogen (mg/dL)		515.00 (417.00-629.00)
Ferritin (ng/mL)		199.16 (83.72-458.38)

IQR = interquartile range; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; COPD = chronic obstructive pulmonary disease

Table 2. Relationship of intensive care unit admission, mortality and demographic characteristics, laboratory data, comorbidities by univariate tests

		Non-ICU patients, median (IQR) n (%)	ICU patients, median (IQR) n (%)	p	Survivors, median (IQR) n (%)	Non-survivors, median (IQR) n (%)	p
N		673 (82.5)	143 (17.5)		724 (88.7)	92 (11.3)	
Gender	Male	375 (81.3)	86 (18.7)	[a]0.333	405 (87.9)	56 (12.1)	[a]0.369
	Female	298 (83.9)	57 (16.1)		319 (89.9)	36 (10.1)	
Diabetes mellitus		148 (79.1)	39 (20.9)	[a]0.172	162 (86.6)	25 (13.4)	[a]0.302
Heart failure		27 (60)	18 (40)	[a]0.001*	35 (77.8)	10 (22.2)	[a]0.017
Chronic kidney disease		18 (60)	12 (40)	[a]0.001*	22 (73.3)	8 (26.7)	[a]0.007
Hypertension		235 (76.8)	71 (23.2)	[a]0.001*	260 (85)	46 (15)	[a]0.009
Cardiovascular disease		76 (68.5)	35 (31.5)	[a]0.001	89 (80.2)	22 (19.8)	[a]0.002
Asthma		36 (87.8)	5 (12.2)	[a]0.357	38 (92.7)	3 (7.3)	[a]0.411
COPD		36 (56.3)	28 (43.8)	[a]0.001*	43 (67.2)	21 (32.8)	[a]0.001
Cancer		25 (65.8)	13 (34.2)	[a]0.006*	30 (78.9)	8 (21.1)	[a]0.050
Stroke		17 (63)	10 (37)	[a]0.007*	21 (77.8)	6 (22.2)	[a]0.067
Age (years)		56.00 (43.00-66.00)	71.00 (60.00-81.50)	[b]<0.001**	56.00 (44.00-67.00)	73.50 (64.25-82.00)	[b]<0.001**
LDH (U/L)		400.00 (326.00-542.00)	526.00 (395.50-765.00)	[b]<0.001**	407.00 (329.00-545.75)	544.00 (393.25-803.50)	[b]<0.001**
Hemoglobin (g/dL)		13.1 (11.80-14.30)	11.8 (10.15-13.7)	[b]<0.001**	13.00 (11.70-14.30)	11.80 (10.13-13.65)	[b]<0.001**
Lymphocyte count (10^3/μL)		1.34 (1.00-1.83)	1.06 (0.64-1.49)	[b]0.006*	1.32 (0.99-1.81)	1.03 (0.64-1.41)	[b]0.045*
Eosinophil count (10^3/μL)		0.02 (0.01-0.09)	0.02 (0.00-0.06)	[b]0.715	0.02 (0.01-0.09)	0.01 (0.00-0.06)	[b]0.760
White cell count (10^9/L)		6.43 (4.84-8.55)	9.75 (6.49-13.92)	[b]<0.001**	6.55 (4.90-8.75)	9.83 (6.48-13.97)	[b]0.010*
Neutrophil count (10^3/μL)		4.34 (2.97-6.13)	7.69 (4.64-11.13)	[b]<0.001**	4.48 (3.07-6.42)	7.68 (4.48-6.42)	[b]0.001*
Neutrophil/lymphocyte		3.03 (1.87-5.10)	7.30 (3.84-13.46)	[b]<0.001**	3.13 (1.94-5.34)	7.62 (3.74-12.74)	[b]<0.001**
Platelet count (10^9/L)		205.00 (165.00-254.00)	206.00 (146.00-292.50)	[b]0.438	205.00 (165.00-255.00)	205.00 (140.25-283.50)	[b]0.780
Troponin (ng/mL)		3.70 (2.00-8.20)	21.35 (7.55-92.83)	[b]0.073	4.00 (2.05-9.00)	27.00 (10.90-153.80)	[b]0.100
AST (U/L)		23.00 (18.00-31.00)	30.00 (20.00-47.00)	[b]0.049*	23.00 (18.00-31.75)	31.00 (19.25-49.00)	[b]0.065
ALT (U/L)		26.00 (17.00-40.00)	27.00 (17.50-45.50)	[b]0.137	26.00 (17.00-39.75)	2.00 (16.00-46.75)	[b]0.183
D-dimer (ng/mL)		395.00 (217.50-841.50	1400.00 (567.75-3500.00)	[b]<0.001**	436.50 (222.50-908.25)	1450.00 (540.00-3770.00)	[b]<0.001**
Creatinine (mg/dL)		0.98 (0.84-1.17)	1.24 (0.95-1.64)	[b]<0.001**	0.98 (0.85-1.19)	1.29 (0.95-1.67)	[b]<0.001**
Albumin (g/L)		38.00 (35.0-41.00)	30.00 (27.00-33.00)	[b]<0.001**	38.00 (34.00-41.00)	29.50 (26.00-33.00)	[b]<0.001**
C-reactive protein (mg/L)		24.00 (7.80-68.40)	89.00 (31.00-157.10)	[b]<0.001**	26.60 (8.40-71.55)	97.10 (30.28-172.35)	[b]<0.001**
C-reactive protein/albumin		0.66 (0.20-1.82)	3.02 (0.95-5.64)	[b]<0.001**	0.72 (0.21-2.16)	3.35 (0.92-6.15)	[b]<0.001**
Fibrinogen (mg/dL)		505.50 (409.50-614.75)	583.00 (465.50-712.50)	[b]<0.001**	510.50 (413.75-621.00)	583.00 (447.00-748.00)	[b]0.006*
Ferritin (ng/mL)		175.40 (73.75-384.04)	451.59 (140.99-1022.61)	[b]<0.001**	185.05 (76.57-411.00)	410.37 (122.22-1169.92)	[b]0.009*

IQR = interquartile range; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; COPD = chronic obstructive pulmonary disease; *p<0.05; **p<0.001; [a]Pearson χ^2-test; [b]independent samples t-test

Table 3. Relationship of total length of hospital stay and gender, and comorbidities by univariate tests

		n	Length of stay median (IQR)	p
All		816	6.00 (4.00-11.00)	
Gender	Male	461	7.00 (4.00-10.00)	0.859
	Female	355	6.00 (4.00-11.00)	
Diabetes mellitus	No	187	6.00 (4.00-10.00)	0.089
	Yes	629	7.00 (5.00-11.00)	
Heart failure	No	771	6.00 (4.00-10.00)	0.013*
	Yes	45	8.00 (5.50-17.00)	
Chronic kidney disease	No	786	6.00 (4.00-10.00)	0.197
	Yes	30	7.50 (5.00-11.25)	
Hypertension	No	510	6.00 (4.00-10.00)	0.074
	Yes	306	7.00 (4.75-12.00)	
Cardiovascular disease	No	705	6.00 (4.00-10.00)	0.022*
	Yes	111	8.00 (5.00-12.00)	
Asthma	No	775	6.00 (4.00-10.00)	0.254
	Yes	41	6.00 (4.00-9.50)	
COPD	No	752	6.00 (4.00-10.00)	0.041*
	Yes	64	7.50 (5.00-11.00)	
Cancer	No	778	6.00 (4.00-10.00)	0.181
	Yes	38	7.50 (6.00-11.25)	
Stroke	No	789	6.00 (4.00-10.00)	0.254
	Yes	27	8.00 (4.00-13.00)	

IQR = interquartile range; COPD = chronic obstructive pulmonary disease; *p<0.05; independent samples t-test was used

Table 4. Relationship of total length of hospital stay, age and laboratory data by univariate tests

	r	p
Age (years)	0.191	<0.001**
Lactate dehydrogenase (U/L)	0.030	0.396
Hemoglobin (g/dL)	-0.047	0.177
Lymphocyte count (10^3/μL)	-0.073	0.036*
Eosinophil count (10^3/μL)	0.079	0.024*
White cell count (10^9/L)	0.011	0.745
Neutrophil count (10^3/μL)	0.011	0.757
Neutrophil/lymphocyte	0.089	0.011*
Platelet count (10^9/L)	0.002	0.959
Troponin (ng/mL)	-0.012	0.748
Aspartate aminotransferase (U/L)	-0.035	0.315
Alanine aminotransferase (U/L)	-0.034	0.332
D-dimer (ng/mL)	0.101	0.005*
Creatinine (mg/dL)	0.073	0.036*
Albumin (g/L)	-0.273	<0.001**
C-reactive protein (mg/L)	0.090	0.012*
C-reactive protein/albumin	0.115	0.002*
Fibrinogen (mg/dL)	0.061	0.151
Ferritin (ng/mL)	0.055	0.130

*p<0.05; **p<0.001; correlation analysis was used

As a result of the evaluations with univariate tests, the relationships of demographic characteristics, laboratory data, and comorbidities with the mortality and the relationships of the same parameters with ICU admission are shown in Table 2.

The relationships of LOS and gender, and comorbidities with univariate tests are shown in Table 3, while the relationships of LOS and age, and laboratory data with univariate tests are displayed in Table 4.

When the multivariate logistic regression model was established by considering those variables with a clinically significant effect on mortality in Table 2, the results shown in Table 5 were obtained.

When nonsignificant variables were removed from the model, the final model was found as shown in Table 6.

The effect of stroke was not found to be significant at the 0.05 level. The risk of mortality was 3.177 times higher in those with COPD. The one-year increase in age significantly increased the risk of mortality by 1.056 times, while 1 unit increase in LDH (U/L) increased mortality 1.002 times. Mortality risk increased 1.052 times when troponin (ng/mL) increased by 0.01 units, while it increased 1.012 times when D-dimer increased by 0.01 units. It also increased 1.278 times when the CRP/albumin ratio increased by 1 unit. Except for these, no other variable was significantly associated with mortality.

The classification success of the model shown in Table 6 was as follows. It successfully classified 71 (82.6%) of 86 dead people and 426 (77.7%) of 522 discharged patients. In this classification, the cut-off

Table 5. Results of full model

Full model	**B**	**SE**	**p**	**OR**	**95% CI for OR**	
					Lower	**Upper**
Heart failure	-0.075	.606	0.902	0.928	0.283	3.041
Chronic kidney disease	0.103	.715	0.885	1.109	0.273	4.503
Hypertension	-0.343	.352	0.329	0.709	0.356	1.414
Cardiovascular disease	0.097	.384	0.801	1.102	0.520	2.336
Chronic obstructive pulmonary disease	1.327	.423	0.002	3.768	1.646	8.626
Cancer	0.201	.675	0.766	1.223	0.326	4.592
Stroke	-0.747	.811	0.357	0.474	0.097	2.322
Age (years)	0.057	.014	<0.001**	1.059	1.030	1.088
Lactate dehydrogenase (U/L)	0.002	.001	0.004*	1.002	1.001	1.004
Hemoglobin (g/dL)	0.051	.085	0.552	1.052	0.891	1.242
White cell count (10^9/L)	-0.003	.037	0.941	0.997	0.927	1.072
Neutrophil/lymphocyte	-0.008	.021	0.714	0.992	0.953	1.034
Troponin (ng/mL)	<0.001	<.001	0.044*	1.000	1.000	1.001
Aspartate aminotransferase (U/L)	<0.001	.005	0.969	1.000	0.991	1.009
D-dimer (ng/mL)	<0.001	<0.001	0.050	1.000	1.000	1.000
Creatinine (mg/dL)	-0.001	0.239	0.997	0.999	0.625	1.597
C-reactive protein/albumin	0.220	0.076	0.004*	1.247	1.073	1.448
Fibrinogen (mg/dL)	0.001	0.001	0.581	1.001	0.999	1.002
Ferritin (ng/mL)	<0.001	<0.001	0.352	1.000	1.000	1.000
Constant	-8.518	1.749	<0.001**	<0.001		

*p<0.05; **p<0.001; SE = standard error; OR = odds ratio; CI = confidence interval; multivariate logistic regression model was used

Table 6. Results of final model

Final model	B	SE	p	OR	95% CI for OR	
					Lower	Upper
Chronic obstructive pulmonary disease	1.156	0.358	0.001*	3.177	1.574	6.413
Stroke	-1.254	0.700	0.073	0.285	0.072	1.126
Age (years)	0.054	0.011	<0.001**	1.056	1.034	1.078
Lactate dehydrogenase (U/L)	0.002	0.001	<0.001**	1.002	1.001	1.003
Troponin (ng/mL)	0.051	0.022	0.022*	1.052	1.007	1.099
D-dimer (ng/mL)	0.012	0.005	0.016*	1.012	1.002	1.021
C-reactive protein/albumin	0.245	0.056	<0.001**	1.278	1.145	1.427
Constant	-7.701	0.883	<0.001**	<0.001		

*p<0.05; **p<0.001; SE = standard error; OR = odds ratio; CI = confidence interval; multivariate logistic regression model was used

Table 7. Comorbidities, demographic characteristics and treatments for COVID-19 in patients according to the presence of COPD

		Patient without COPD Mean ± SD n (%)	COPD patients Mean ± SD n (%)	p
Age (years)		56.20±17.74	74.10±11.51	[b]<0.001**
Gender	Male	418 (55.6)	43 (67.2)	[a]0.072
	Female	334 (44.4)	21 (32.8)	
Diabetes mellitus		170 (22.6)	17 (26.6)	[a]0.470
Heart failure		33 (4.4)	12 (18.8)	[a]<0.001**
Chronic kidney disease		25 (3.3)	5 (7.8)	[a]0.067
Hypertension		265 (35.2)	41 (64.1)	[a]<0.001**
Cardiovascular disease		92 (12.2)	19 (29.7)	[a]<0.001**
Cancer		35 (4.7)	3 (4.7)	[a]0.990
Stroke		22 (2.9)	5 (7.8)	[a]0.036*
Hydroxychloroquine		713 (94.8)	60 (93.8)	[a]0.715
Lopinavir/ritonavir		63 (8.4)	2 (3.1)	[a]0.136
Favipravir		218 (29.0)	34 (53.1)	[a]<0.001**
Azithromycin		601 (79.9)	50 (78.1)	[a]0.731
Plasma therapy		18 (2.4)	3 (4.7)	[a]0.266
Tocilizumab		20 (2.7)	4 (6.3)	[a]<0.103
Corticosteroid		39 (5.2)	15 (23.4)	[a]<0.001**

COPD = chronic obstructive pulmonary disease; SD = standard deviation; *p<0.05; **p<0.001; [a]Pearson χ^2-test; [b]independent samples t-test

value was taken as 13% for the probabilities estimated by the model, and this success was achieved when the patient was grouped as "low risk of mortality" if a patient's estimated probability value was lower than 13%, and "high risk of mortality" if it was greater.

On comparison of age, gender, comorbidity and treatment for COVID-19 by the groups formed according to the presence of COPD, comorbidity was found to be significantly associated with mortality in the model, as shown in Table 7.

Discussion

In our study, patients who were hospitalized with the diagnosis of COVID-19 in two tertiary level hospitals in Turkey were evaluated, and a prognostic model was established with age, COPD, LDH, troponin, D-dimer, and CRP/albumin ratio. This model has been shown to accurately predict mortality in COVID-19 patients with a sensitivity of 82.6% and specificity of 77.7%. We think that the regulation of treatment algorithms by creating risk determining models will improve clinical results.

Although the pathogenesis of the SARS-CoV-2 virus is widely understood, the patient-based approach in clinical practice may be inadequate in predicting severe disease and mortality. We think that risk prediction by evaluating demographic characteristics, comorbidities, and laboratory parameters of patients at the time of admission will enable effective inpatient management. We believe that determining all these parameters will guide establishment of treatment algorithms and triage of priority patients. Turkey is among the countries most affected by the COVID-19 pandemic. Despite all the measures taken and studies performed, the disease continues to spread and cause unexpected deaths. We believe that determining risk groups in hospitalized patients will alleviate the burden of hospitals. Identifying patients with a high risk of mortality probability and serious disease will provide convenience in clinical approach.

In our study, it was found that having a COPD increased the mortality risk more than 3 times. In a meta-analysis combining data from 16 countries, COPD was associated with more than 4-fold greater hospitalization, higher rate of ICU admissions, and a mortality rate of more than 2.5 times in COVID-19 patients[17]. Innate and adaptive immune response disorder is observed in COPD patients and respiratory tract viruses are cleared late[18]. In this study, LOS was found to be longer in COPD patients, and the presence of COPD was associated with ICU admission and mortality.

In our study, it was noteworthy that asthma was not associated with mortality, hospitalization, and LOS, unlike COPD. In previous studies, it has been stated that asthma and COPD increased COVID-19 mortality[9,10]. The fact that the expected increased mortality in asthma patients was not observed in our study may be attributed to the high rate of inhaled corticosteroid use in asthma patients. *In vitro* studies have shown that inhaled corticosteroids inhibit SARS-CoV-2 replication in infected epithelial cells[19]. Studies have shown decreased angiotensin-converting enzyme 2 (ACE2) levels in sputum with the use of inhaled corticosteroids in asthma and down-regulation of the gene and protein levels of ACE2 in COPD with the use of inhaled corticosteroids[20,21]. In the study of 75,463 COVID-19 patients by Bloom *et al.*, the use of inhaled corticosteroids in asthma patients aged 50 years and older was associated with lower mortality compared to patients without an underlying respiratory disease, whereas it was not found in COPD patients[11]. In our inpatient practice, inhaled corticosteroid treatment is one of the first medicines to be started in patients with pulmonary diseases. In addition, it has been stated in the literature that asthma patients do not have an increased risk of COVID-19 severity, contrary to common belief, and previous studies have high bias[22]. Decreased ACE2 receptor expression in patients with asthma is among the suggested mechanisms that the T helper 2 (Th2) immune response has a protective effect against inflammation caused by SARS-CoV-2 infection[23,24]. There was no difference in the LOS, rate of ICU admission, or mortality in COVID-19 patients diagnosed with asthma.

While heart failure, chronic kidney disease, hypertension, cardiovascular disease, cancer, and stroke were found to be associated with mortality in univariate analyses, this relationship was not observed in multivariate analyses. This result is different from previous studies. Since the beginning, these comorbidities have been identified as the most important factors associated with severe disease and mortality in COVID-19. In the report by the American College of Cardiology (ACC), mortality was 10.3% in patients with cardiovascular diseases, while this rate was 5.6% in patients with cancer, 7.3% in diabetes patients, 6% in hypertensive patients, and 6.4% in patients with chronic respiratory diseases, and all these rates are higher than those without chronic disease[12]. In the report organized by the China Center for Disease Control and Prevention, it was stated that aging, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer are associated with an increased risk of death[25]. Also, a meta-analysis of eight studies including patients with laboratory confirmed COVID-19 indicated that those

with the most severe disease were more likely to have hypertension (odds ratio 2.36 (95% CI 1.46-3.83)), respiratory disease (2.46 (1.76-3.44)), and cardiovascular disease (3.42 (1.88-6.22))[26]. However, these data are insufficient to state that comorbidities are associated with mortality independently from each other and from age, an important risk factor.

It is known that COPD is generally associated with increasing age and comorbidities[27]. In our study population, the mean age of COPD patients was higher than non-COPD patients, and a higher incidence of heart failure, hypertension, cardiovascular disease, and stroke was observed in COPD patients. It is not known whether the co-existence of all these risk factors has an additive effect on the course of the disease and which is the main responsible risk factor. In our study, all these factors were evaluated together and multivariate logistic regression analysis was performed to provide strong results; it was determined that only age and presence of COPD were associated with mortality, but not other comorbidities. In the study conducted by Atık *et al.*, similar to our study, hypertension, diabetes and asthma were not associated with the severity of COVID-19, while COPD was found to be more common in critically ill patients[28]. In our study, COPD patients were also evaluated in terms of the treatments they had received, and it was observed that corticosteroid and favipravir treatment were used at a higher rate in COPD patients. It is thought that the reason for this is the poor clinical course of COPD patients, and the Ministry of Health of the Republic of Turkey recommended favipravir and corticosteroid treatments as an advanced step treatment in severe COVID-19 patients at the time of the study[16].

In our study, there was a 1.056-fold increase in mortality with every 1-year increase in age. A relationship was found between age and LOS, ICU admission, and mortality. In a study in which data from six major countries from Europe and North America (United States of America, Germany, France, Italy, England and Wales, and Spain) were analyzed, although age groups differed from country to country, mortality rates in each country increased incrementally with age[29]. It is not surprising that age is also a risk factor in terms of COVID-19 severity and mortality in our country. However, our country has a higher rate of young population compared to these populations. It is noteworthy that the mean age of patients who are hospitalized in a tertiary hospital is 58 years. Since the beginning, being older than 65 years has been stated as an important risk factor for COVID-19 patients, but it is known that the disease is also severe in the 55-64 age group[30]. Still, there is a significant age difference between survivor and non-survivor groups with and without intensive care needs. This means that younger patients have a better prognosis despite the need of hospitalization. Male gender, which is known to be an important risk factor, has not emerged as a risk factor in our population. There was no difference between males and females in terms of LOS, ICU admission, or mortality. Although these results are important, their generalizability to the population in general is insufficient.

In our study, LDH was determined as an important risk factor for mortality. Higher levels of LDH were detected in ICU patients and in non-survivors. As in our study, high LDH has been determined as an important parameter in prognostic modelling studies conducted in various populations[2,31,32]. High LDH levels are observed in the most severe forms of SARS-CoV-2 infection, even a decrease in LDH levels has been associated with negative PCR and good prognosis[33]. Hypoxemia and pulmonary hypoxic vasoconstriction play an important role in the pathophysiology of COVID-19 related acute respiratory distress syndrome[34].When there is a decrease in tissue oxygenation, lactic acid formation increases so that micro-regional oxygen delivery is sufficient as an endothelial inflammatory response[35]. As a matter of fact, among the criteria defined for COVID-19-associated hyperinflammatory syndrome (CHIS), the presence of LDH >400 U/L was determined as an indicator of hepatic damage[36]. In CHIS, high D-dimer levels have also been defined as an important marker of coagulopathy. In our study, D-dimer elevation was determined as an important risk factor for mortality. It was also found to be associated with the LOS and ICU admission. Increased D-dimer due to sepsis and hypoxemia indicates hyperfibrinolysis or thrombotic disorders and is an important predictive indicator of venous thromboembolism or acute pulmonary embolism[37]. Microembolism in small branches of pulmonary artery causes hypoxemia and respiratory failure, while microembolism in coronary arteries causes acute cardiac damage[38]. The high D-dimer level in the patient at the

time of admission is an indicator of this whole process, and like many studies in the literature, it was found to be associated with mortality also in our study.

In our study, it was determined that the high troponin level, which is a marker of acute cardiac damage, was associated with mortality. In a meta-analysis by Toloui *et al.*, abnormal troponin elevation was found to be associated with a 19-fold higher risk of mortality in COVID-19 patients[39]. Early recognition of myocardial damage has been a common problem in the COVID-19 literature and practice. Considering the retrospective studies performed, it was seen that troponin was not examined in the first 24 hours in a significant portion of the cases with increased troponin[40]. This suggests that it may be too late for acute cardiac injury to be recognized. The presence of cardiovascular disease makes patients vulnerable to acute cardiac damage. However, it is remarkable that in our study, no relationship was found between cardiovascular disease and mortality in multivariate analyses. At the time of patient admission to the hospital, the level of troponin should particularly be considered.

In our study, it was found that when the CRP/albumin ratio increased by 1 unit, the mortality increased 1.3 times and was also associated with the LOS and the ICU admission. CRP induction is part of the acute phase response in which synthesis of many plasma proteins increases while albumin synthesis decreases. The CRP/albumin ratio is a biomarker of inflammation and nutritional condition and has been determined to predict prognosis in various diseases such as infection and cancer[41,42]. It has previously been shown that the CRP/albumin ratio is more accurate than CRP for predicting 28-day mortality in patients[43]. In our study with a larger patient population, results supporting previous studies were recorded.

Limitations

Our study had several limitations. Firstly, smoking status was not evaluated as an important factor in the pathogenicity of SARS-CoV-2 infection. Secondly, this retrospective study was based on data obtained from hospital records. Thirdly, the study was conducted in only two hospitals. The fourth one was that the information about how many days after the onset of symptoms patients were admitted to the hospital was not recorded because it was dependent on their history and would be subjective. For this reason, the time specified for recovery was calculated and recorded from the time of admission to the hospital. The fifth one was that chest radiography, which is an important parameter in predicting mortality, was not evaluated in this study. The sixth one was that the study was conducted only in Turkey, thus limiting the generalizability of the results to other country populations. Also, obesity, which is an important prognostic factor in COVID-19, was not evaluated in our study. Besides, patient comorbidities were recorded, but the medicines they were using for these comorbidities were not evaluated. The effects of various medicines used in diseases such as hypertension, hyperlipidemia, cancer, autoimmune disease, etc., on the pathogenesis of SARS-CoV-2 virus are still being investigated[44]. The effect of these medicines on the results is unknown and the fact that they were not evaluated in our study was an important limitation. Another one is that data of the patients who were referred to an external center were missing. Also, a prognostic model was established, but this model was not externally validated. Further studies are needed for validation of the prognostic model. Furthermore, we believe that even stronger results will be obtained by adding smoking status, radiological findings, and body mass index to this model in future studies.

Conclusion

In our study, patients who were hospitalized with the diagnosis of COVID-19 in two tertiary hospitals in Turkey were evaluated, and age, COPD, LDH, troponin, D-dimer, and CRP/albumin ratio were determined as factors associated with mortality. A prognostic model with high sensitivity and specificity was created by evaluating these six parameters together. Further studies are needed for external validation of this prognostic model. Assessment of age, presence of COPD, LDH, troponin, D-dimer levels, and CRP/albumin ratio at the time of inpatient admission, classifying patients as high risk, and adopting early and appropriate treatment approaches may help in the management of patients.

Acknowledgment

The authors would like to thank Aytekin Oğuz for his valuable support.

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Sažetak

KOPB, DOB, LDH, TROPONIN, D-DIMER I OMJER CRP/ALBUMIN: NOVI PROGNOSTIČKI MODEL ZA COVID-19

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Cilj ove studije bio je utvrditi odnos između demografskih karakteristika, početnih laboratorijskih podataka te komorbiditeta i prognoze stacionarnih bolesnika hospitaliziranih zbog koronavirusne bolesti 2019. (COVID-19) te stvoriti novi model za predviđanje rizika smrtnosti. U ovoj multicentričnoj, retrospektivnoj kohortnoj studiji demografski i klinički podaci bolesnika zabilježeni su pri prvom prijmu bolesnika u bolnicu. Primarni ishod bio je procijeniti odnos između demografskih karakteristika, laboratorijskih parametara, komorbiditeta i smrtnosti. Parametri za koje je univarijatnim analizama utvrđeno da su povezani sa smrtnošću također su ocijenjeni multivarijatnim analizama i uspostavljen je konačni model. U konačnom modelu su prisutnost kronične opstruktivne plućne bolesti (KOPB) (OR: 3,177, 95%CI: 1,574-6,413), dob (OR: 1,056, 95%CI: 1,034-1,078), laktat dehidrogenaza (LDH) (OR: 1,002, 95%CI: 1,001-1,003), troponin (OR: 1,052, 95%CI: 1,007-1,099), D-dimer (OR: 1,012, 95%CI: 1,002-1,021), omjer C-reaktivnog proteina (CRP) i albumina (OR: 1,278, 95%CI: 1,145-1,427) bili povezani sa smrtnošću. Model je točno predvidio smrtnost uz osjetljivost od 82,6% i specifičnost od 77,7%. KOPB, dob, LDH, troponin, D-dimer, omjer CRP/albumin određeni su kao čimbenici povezani sa smrtnošću. Procjena ovih parametara u vrijeme prijma u bolnicu, klasificiranje bolesnika kao visokorizične te usvajanje ranih i odgovarajućih pristupa liječenju mogu pomoći u liječenju bolesnika.

Ključne riječi: *COVID-19; Smrtnost; Prognoza; Kronična opstruktivna plućna bolest; Laktat dehidrogenaza*