Evaluation of COVID-19 Patients According to the Survival Time

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ABSTRACT

Background: *Coronavirus disease 2019 (COVID-19) was first detected as a form of atypical pneumonia. COVID-19 is a highly contagious virus, and some patients may experience acute respiratory distress syndrome (ARDS) and acute respiratory failure leading to death. We aim to evaluate the clinical, imaging, and laboratory parameters according to survival time to predict mortality in fatal COVID-19 patients.* ***Methods****: Fatal 350 and survived 150 COVID-19 patients were included in the study. Fatal patients were divided into three groups according to the median value of the survival days. Demographic characteristics and in-hospital complications were obtained from medical databases.* ***Results****: Of the non-survived patients, 30% (104) died within three days, 32% (110) died within 4-10 days, and 39% (136) died within over ten days. Pneumonia on computational tomography (CT), symptom duration before hospital admission (SDBHA), intensive care unit (ICU), hypertension (HT), C-reactive protein (CRP), D-dimer, multi-organ dysfunction syndrome (MODS), cardiac and acute kidney injury, left ventricular ejection fraction (LVEF), right ventricular fractional area change (RV-FAC), and Tocilizumab/Steroid therapy were independent predictors of mortality within three days compared to between 4-10 days and over ten days mortality. A combined diagnosis model was evaluated for the age, CT score, SDBHA, hs-TnI, and D-dimer. The combined model had a higher area under the ROC curve (0.913).* ***Conclusion****: This study showed that age, pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, cardiac injury, MODS, acute kidney injury, LVEF, and RV-FAC were independently associated with short-term mortality in non-surviving COVID-19 patients in the Turkish population. Moreover, Tocilizumab/Steroid therapy was a protective and independent predictor of mortality within three days.*

Keywords*: COVID-19, mortality, acute respiratory distress syndrome, echocardiography.*

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus disease 2019 (COVID-19) was first detected as a form of atypical pneumonia in Wuhan, China, in December 2019.[1] COVID-19 was an unprecedented epidemic, and the World Health Organization (WHO) declared it a pandemic.[2] According to the WHO report, about 243 million people were diagnosed with COVID-19 in 219 countries by 24 October 2021. COVID-19 is a highly contagious virus and killed approximately 4.9 million people worldwide.[3]

Mild acute respiratory infection symptoms such as fever, dry cough, and tiredness are common in the early stages of COVID-19. Some COVID-19 patients may experience ARDS and acute respiratory failure leading to death. Although pulmonary complications were the leading cause of death, multiple organ dysfunction syndrome (MODS), myocardial, kidney, and liver injuries could lead to death in COVID-19 patients.[1,4-6] About two-thirds of severe COVID-19 patients have a fatal outcome.[7-9] Therefore, many clinical features and laboratory parameters were evaluated to predict mortality in COVID-19 patients. It was reported that age, gender, comorbidities, smoking history, and many biomarkers including d-dimer and troponin were a predictor of mortality.[10-13] Although there is no specific treatment for COVID-19 so far, corticosteroids and some anti-inflammatory agents have been shown to be effective in treatment.[14] In addition, supportive care and early detection are beneficial.[15,16] Therefore, the determination of simple and reliable predictors of survival in severe COVID-19 patients is necessary. Due to the limited number of intensive care unit beds and the financial burden of the COVID-19 disease in some countries, adequate supportive therapy and correct triage are essential in the survival period.

This study aimed to compare clinical, imaging, and laboratory parameters according to the day of death of patients who died from COVID-19 and determine independent predictors according to the day of death.

METHODS

The study was planned with a retrospective, cross-sectional, multicenter and observational design. Three hundred and fifty deceased and 150 surviving COVID-19 patients were included in the research for 28 March 2020 and 15 January 2021. The presence of SARS-CoV-2 RNA was detected by real-time reverse transcription-polymerase chain reaction (RT-PCR) in the Ministry of Health Public Health Microbiology Reference Laboratory after obtaining oropharyngeal and nasal specimens by using the same swab and placing the swab on the same transport medium. The guidelines for COVID-19, which the Ministry of Health prepared, were implemented, and the patients used the suggested medications. The anticoagulant, steroid, antibiotic therapy, antiviral therapy, invasive and non-invasive mechanical ventilation was performed according to these guidelines. COVID-19 RT-PCR (+), surviving COVID-19 patients, and deceased COVID-19 patients were included in the study. Patients with the following conditions were excluded from the study: age < 18 years, pregnancy, ST-elevation myocardial infarction, advanced malignancy, severe valvular heart disease, and negative PCR tests.

Demographic characteristics and in-hospital complications were obtained from medical databases. Patient age, gender, smoking status, hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), hyperlipidemia (HLD), malignancy, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) history were recorded. Also, laboratory parameters such as urea, creatinine, sodium, potassium, glucose, high-sensitivity troponin I (hs-TnI), d-dimer, hemoglobin, white blood cell (WBC), procalcitonin, and C-reactive protein (CRP) were obtained from hospital admission records. In all cases, a semi-quantitative computational tomography (CT) severity scoring proposed by Pan et al. was calculated for each of the five lobes considering the extent of anatomic involvement.[17] Deceased patients were divided into three groups according to the median value of the survival days. The study was conducted under the Helsinki

Declaration, and the study protocol was approved by the local ethics committee and the Ministry of Health (approval number: 2020/0623).

Definitions

Myocardial injury was defined as a troponin value exceeding the upper reference limit (URL, 99%) according to the Fourth Universal Definition of Myocardial Infarction (MI).[18] Acute kidney injury (AKI) was defined based on the kidney disease: Improving Global Outcomes (KDIGO) definition.[19] CAD was diagnosed in patients with a history of previous percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). MODS is defined as the concurrent dysfunction of two or more organs or systems, including hematological, gastrointestinal, cardiovascular, neurological, respiratory, hepatic, and renal.[9]

Transthoracic Two-dimensional Echocardiography

Two-dimensional echocardiography (2DE) studies were performed by a cardiologist using an X5 transducer (Philips Epiq7; Philips Healthcare, Inc., Andover, MA, USA) to evaluate the parasternal and apical images (2D, M-mode, Doppler echocardiography). The echocardiographic examination was performed within the first 24 hours after admission, and the data were recorded. In the echocardiographic examination, three cycles were recorded and analyzed during any phase of respiration. After the 2DE images were recorded, the analysis was performed by two independent, experienced cardiologists blinded by the clinical data of the patients. Echocardiographic images were obtained in all four standard views (long-axis parasternal, short-axis parasternal, two-chamber apical, and four-chamber apical) using the techniques recommended by the American Society of Echocardiography (ASE) guidelines.[20]

Electrocardiographic Evaluation

12-lead admission electrocardiography (ECG) was obtained from each patient on admission before any treatment was started. All standard 12-lead electrocardiograms were recorded on digitized 12-lead ECG recordings using the on-screen digital caliper software (Cardio Calipers version 3.3, Iconico, Inc., New York, NY). All ECGs (filter range 0.5-150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV) were analyzed by two independent cardiologists blinded to the clinical data of the patients according to the modified Minnesota criteria, and the findings were recorded on sheets.[21] Corrected QT interval (QTc); the QT interval measured in either lead II or V5-6, QTc was calculated using Bazett's formula ($QTc = QT / (\sqrt{RR})$.[22] QRS fragmentation (fQRS) was defined as a notch in the R wave or S wave in two consecutive leads associated with the myocardial region, or multiple R' waves and QRS<120 ms.[23]

Statistical Analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze the normality of the data. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median with interquartile range (IQR). The categorical variables are presented as percentages. A Chi-square test was used to assess differences in categorical variables between groups. The primary analysis used ANOVA to compare all reported data for parametric variables, whereas the Kruskal–Wallis test was used to compare nonparametric variables between the median value of the survival days. The univariate effects of type of age, gender, pneumonia on CT, symptom duration before hospital admission (SDBHA), intensive care unit (ICU), HT, CAD, CRP, d-dimer, cardiac injury, MODS, Acute kidney injury, LVEF, RV-FAC and Tocilizumab/ Steroid on death of patients was investigated using the log rank test. The possible factors identified with univariate analyses were further entered into the Cox regression analysis, with backward selection, to determine independent predictors of death. The proportional hazards assumption and model fit was assessed by means of residual (Schoenfeld and Martingale) analysis. Multinomial logistic regression analysis was used to identify independent predictors of mortality in three days. Receiver operating characteristic (ROC) curves were obtained, and the optimal values with the greatest total

sensitivity and specificity in the prediction of mortality in three days were selected. All the parameters in the ROC curve analysis were included in the binary logistic regression analysis. Combined model was created with the obtained probability value. A combined model, which was created with mortality predictors, was analyzed by ROC curves. Finally, 20 patients were assigned randomly to test the intra-observer and interobserver variability expressed as the intra-class correlation coefficient for the CT score, echocardiographic and electrocardiographic measurements, respectively. Significance was assumed at a 2-sided p <0.05.

RESULTS

Three hundred and fifty non-surviving patients were divided into three groups according to the day of the death. Of the non-surviving patients, 30% (104) died within three days, 32% (110) died within 4–10 days, and 39% (136) died after ten days. The patients' clinical and demographic characteristics are shown in **Table 1**. The patients who died within three days were older than the others (p<0.001). While the body mass index (BMI), gender, and smoking were similar between study groups (p>0.05), heart rate (HR), respiratory rate (RR), pneumonia on CT, CT score, and SDBHA were statistically different between the study groups (p <0.001). Moreover, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), ICU admission and body temperature values were different in study groups (p<0.001). In patients' past medical histories, DM, HLD, and malignancy were similar in the study population. Also, HT, CAD, COPD, and CKD were significantly higher in patients who died within three days (p<0.05). The hemoglobin, sodium, potassium, and glucose levels were similar among the three groups. WBC, creatinine, CRP, hs-TnI, d-dimer, procalcitonin, and oxygen saturation (sO2) levels were significantly different in patients who died three days compared to other groups (p<0.05). The previous medication was similar between the study groups (p>0.05). While the used drugs were compared between the groups during the disease, steroid and tocilizumab were significantly higher in the survival group than the non-survival group. Invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIMV), high-flow oxygen (HFO), vasopressor, and renal replacement therapy (RTT) rates were higher in the non-surviving patients compared to surviving patients (p<0.05). MODS, cardiac, and kidney injury rates were significantly higher in patients who died three days than in other groups (p<0.05).

Table 1. The Demographic and Clinical Data of COVID-19 Patients.

	Survivor (n=150)	Non-survivor ≤3 days (n=104)	Non-survivor 4-10 days (n = 110)	Non-survivor >10 days (n = 136)	p
Clinical characteristics					
Age (years)	54.6±8.5$^{\#\&@}$	67.8±9.1$^{\#*a}$	64.0 ± 8.1$^{\&*}$	63.4 ± 7.7$^{@a}$	<0.001
Male, n (%)	93(62)	69(66)	74(67)	77(56)	0.187
BMI (kg/m^2)	23.9±3.3	23.4±2.3	24.2 ± 3.4	24.4 ±3.8	0.108
HR, beats/min	82.0±10.7$^{\#\&}$	91.3±12.3$^{\#*a}$	86.4±14.9$^{\&*e}$	81.3±12.0^{ae}	<0.001
RR, times/min	21.3±6.5$^{\#\&}$	28.0±8.5$^{\#*a}$	24.0±4.8$^{\&*e}$	21.7±4.2^{ae}	<0.001
SAP, mmHg	107.6±14.8$^{\#}$	98.514.4$^{\#*a}$	104.2±13.7*	106.9±15.0^{a}	<0.001
DAP, mmHg	66.1±11.1$^{\#}$	60.5±11.3$^{\#a}$	63.9±10.4	65.6±11.1^{a}	<0.001
Smoker, n (%)	65(43)	49(47)	54(49)	50(36)	0.125
Pneumonia on CT, n (%)	98(65)$^{\#\&}$	96(92)$^{\#*a}$	90(81)$^{\&*e}$	96(70)^{ae}	<0.001
CT score	2(0-4)$^{\#\&}$	6(3-11)$^{\#*a}$	2(2-7)$^{\&*e}$	2(1-5)^{ae}	<0.001
SDBHA (days)	4.1±2.0$^{\#\&@}$	7.23.1$^{\#*a}$	5.9±2.5$^{\&*e}$	4.9±2.1$^{@ae}$	<0.001
Hospital stay (days)	13(7-17)$^{\#\&}$	2(2-2)$^{\#*a}$	5(4-8)$^{\&*e}$	15(12-18)^{ae}	<0.001
ICU admission, n (%)	40(27)$^{\#\&}$	75(72)$^{\#*a}$	48(43)$^{\&*}$	43(31)^{a}	<0.001
Body Temperature (°C)	36.9±1.2$^{\#}$	37.71.9$^{\#*a}$	37.0±0.8*	36.9±0.6^{a}	<0.001
Chronic medical illness					
HT, n (%)	68(45)$^{\#}$	71(68)$^{\#*a}$	57(51)*	65(47)^{a}	0.012
DM, n (%)	36(24)	33(31)	25(22)	32(23)	0.301

CAD, n (%)	30(20)[#]	37(35)[#*a]	24(21)[*]	29(21)[a]	0.034
HLD, n (%)	38(25)	28(26)	31(28)	38(27)	0.875
Malignite, n (%)	9(6)	13(12)	9(8)	7(5)	0.203
COPD, n (%)	18(12)[#]	26(25)[#*a]	14(12)[*]	18(12)[a]	0.037
CKD, n (%)	15(10)[#]	24(23)[#*a]	14(12)[*]	16(11)[a]	0.039
Laboratory findings					
Haemoglobin(g/dl)	11.02.3	11.2±2.4	11.7 ± 1.8	11.5 ± 2.0	0.167
WBC (10^3 /µl)	8.0(5.0-14.0)[#]	9.3(7.0-19.7)[#*a]	8.3(5.1-13.1)[*]	8.3(5.9-13.0)[a]	0.009
Creatinine (mg/dl)	1.2(0.9-2.0)[#]	1.7(1.1-2.6)[#*a]	1.4(0.9-2.1)[*]	1.3(0.9-2.2)[a]	0.021
Sodium (mmol/L)	140.0±6.4	141.7±9.2	139.9 ± 9.3	141.4 ± 9.7	0.346
Potassium (mmol/L)	4.3±0.6	4.5±0.8	4.3 ± 0.8	4.3 ± 0.8	0.512
Glucose (mg/dL)	135(99-199)	141(105-205)	136(102-205)	149(112-237)	0.462
CRP (mg/dL)	110(80-165)[#]	131(111-185)[#*a]	114(89-171)[*]	113(70-172)[a]	<0.001
hs-TnI (NR<14pg/ml)	30(13-44)[#&@]	60(32-152)[#*a]	47(20-93)[&*e]	34(14-58)[@ae]	<0.001
D-dimer (ng/mL)	1460(757-2920)[#&@]	3490(1395-4080)[#*a]	2525(1120-4100)[&*e]	1465(925-3655)[@ae]	<0.001
Procalcitonin (ng/mL)	0.7(0.2-1.3)[#&]	1.8(0.4-11.7)[#a]	1.7(0.4-3.2)[&e]	0.9(0.3-2.7)[ae]	0.006
sO2	95.8±5.0[#&]	90.5±5.3[#*a]	92.9±5.1[&*e]	94.4±3.9[ae]	<0.001
Treatments					
ACEİ/ARB, n (%)	60(40)	50(48)	60(54)	58(42)	0.238
BB, n (%)	60(40)	51(49)	51(46)	52(38)	0.221
CCB, n (%)	38(25)	32(30)	35(31)	37(27)	0.665
ASA, n (%)	45(30)	37(35)	39(35)	38(27)	0.341
Statin, n (%)	38(25)	34(32)	32(29)	34(25)	0.421
OAD, n (%)	48(32)	36(34)	38(34)	41(30)	0.688
Steroid, n(%)	109(73)[#&@]	40(39)[#*a]	60(55)[&*]	78(58)[@a]	<0.001
Tocilizumab, n(%)	24(16)[#&@]	1(1)[#]	6(6)[&]	7(5)[@]	0.033
IMV, n(%)	33(22)[#&]	72(70)[#*a]	39(36)[&*]	38(28)[a]	0.004
NIMV, n(%)	21(14)[#&@]	28(27)[#*a]	58(53)[&*]	66(49)[@a]	<0.001
HFO, n(%)	37(25)[#&]	3(3)[#a]	12(11)[&e]	31(23)[ae]	0.007
Vasopressor, n(%)	24(16)[#&@]	70(68)[#*a]	35(32)[&*]	40(30)[@a]	<0.001
RRT, n(%)	0(0)[#&@]	27(26)[#]	20(19)[&]	28(21)[@]	0.031
Organ Injury					
Cardiac injury, n (%)	33(22)[#&@]	62(59)[#*a]	42(38)[&*]	44(32)[@a]	<0.001
MODS, n (%)	23(15)[#]	37(35)[#*a]	25(22)[*]	25(18)[a]	0.014
Acute kidney injury, n (%)	26(17)[#]	38(36)[#*a]	25(22)[*]	33(24)[a]	0.042

[#] *P*<0.05 Between surviver and ≤3 days groups, [&]*P*<0.05 Between surviver and 4-10 days groups, [@]*P*<0.05 Between surviver and >10 days groups, [*]*P*<0.05 Between ≤3 days and 4-10 days groups, [a]*P*<0.05 between 3 days and >10 days groups, [e]*P*<0.05 between 4-10 days and >10 days groups. **Abbreviations:** BMI, body mass index; HR, heart rate; RR, respiratory rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; CT, computed tomography; SDBHA, symptom duration before hospital admission; ICU, intensive care unit; HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HLD, hyperlipidemia; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; WBC, white blood cell, CRP, C-reactive protein; hs-TnI, high sensitive-Troponin I; NR, normal range; CK, creatinine kinase; sO2, oxygen saturation ; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; ASA, acetylsalicylic acid; OAD, oral antidiabetic; IMV, invasive mechanical ventilation; NIMV, non-invasive mechanical ventilation; HFO, high-flow oxygen; RRT, renal replacement therapy; MODS, multiple organ dysfunction syndrome.

The patients' echocardiography and ECG parameters are shown in **Table 2**. The LVEF and tricuspid annular plane systolic excursion (TAPSE) values were statistically different among the study groups (p<0.001). Left ventricular diastolic functions were lower in non-surviving patients than in patients who survived, and it was lowest in patients who died within the first three days. Left atrium (LA), right ventricular diameter, RV-FAC, systolic pulmonary artery pressure (sPAP), and pericardial effusion values were significantly higher in patients who died three days compared to other patients (p<0.001). While the left ventricular end-diastolic diameter (LVEDD) was similar between study groups, left ventricular end-systolic diameter (LVESD) was significantly higher in patients who died within three days. While there was no statistically significant difference between the groups in terms of the

Table 2. Comparison of Conventional Echocardiographic and Electrocardiographic Parameters of COVID-19 Patients.

Variables	Survive (n=150)	Non-survive 3 days (n=104)	Non-survive 4-10 days (n = 110)	Non-survive >10 days (n = 136)	p
Left heart findings					
LVEF (%)	59.9±7.1$^{\#\&}$	53.1±9.9$^{\#*a}$	57.3 ± 7.4$^{\&*e}$	59.6 ± 5.7^{ae}	<0.001
LVEDD (mm)	44.9±3.5	45.7±4.1	44.6±3.4	44.7±3.4	0.091
LVESD (mm)	28.8±3.7$^{\#}$	30.7±4.0$^{\#a}$	29.9 ± 3.9	28.9 ±3.3^{a}	0.013
LA (mm)	36.7±4.1$^{\#}$	42.3±4.5$^{\#*a}$	36.5±3.3*	37.3±5.1 ^{a}	<0.001
E/A ratio	1.2±0.4$^{\#\&@}$	0.7±0.2$^{\#*a}$	0.9±0.3$^{\&*}$	1.0±0.4$^{@a}$	<0.001
RV diamater(mm)	33.1±4.8$^{\#\&@}$	39.5±4.7$^{\#*a}$	36.5±4.1$^{\&*}$	36.1±4.4$^{@a}$	<0.001
RV-FAC (%)	45.5±5.5$^{\#\&}$	39.7±6.7$^{\#*a}$	42.9±5.3$^{\&*}$	43.9±4.8^{a}	<0.001
TAPSE (mm)	21.4±3.4$^{\#\&}$	18.2±3.2$^{\#*a}$	19.9±3.1$^{\&*e}$	21.5±3.0 ^{ae}	<0.001
sPAP, mmHg	30.1±5.1$^{\#}$	34.8±7.8$^{\#*a}$	31.6±8.0*	30.6±7.9^{a}	<0.001
ACP, n(%)	0(0)	7(7)	3(3)	3(2)	0.129
Pericardial effusion, n(%)	8(5)$^{\#\&@}$	31(30)$^{\#*a}$	16(17)$^{\&*}$	21(16)$^{@a}$	0.005
Sinus Rhythm, n (%)	139(93)$^{\#}$	82(78)$^{\#*a}$	97(88)*	125(91)^{a}	0.008
HR, beats/min	78.9±12.7$^{\#\&}$	91.3±12.3$^{\#*a}$	86.4±14.9$^{\&*e}$	81.3±12.0^{ae}	<0.001
RBBB, n(%)	12(8)	16(15)	10(9)	10(7)	0.182
LBBB, n(%)	9(6)	11(10)	7(6)	6(4)	0.328
ST depression,, n(%)	30(20)$^{\#}$	48(46)$^{\#*a}$	31(28)*	30(22)^{a}	<0.001
fQRS, n(%)	18(12)	15(14)	19(17)	19(14)	0.716
QTc	428.9±22.1	432.4±26.3	429.2±22.0	430.5±21.3	0.394

$^{\#}$ *P*<0.05 Between surviver and ≤3 days groups, $^{\&}$*P*<0.05 Between surviver and 4-10 days groups, $^{@}$*P*<0.05 Between surviver and >10 days groups, **P*<0.05 Between 3 days and 4-10 days groups, ^{a}*P*<0.05 between 3 days and >10 days groups, ^{e}*P*<0.05 between 4-10 days and >10 days groups. **Abbreviations:** LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESV, left ventricular end systolic diameter; LA, left atrial; RV-FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; ACP, acute cor pulmonale; HR, heart rate; RBBB, right bundle branch block; LBBB, left bundle branch block; fQRS, fragmante QRS; QTc, corrected QT.

frequency of acute corrected QT values, it was highest in patients who died within the first three days. In the electrocardiographic analysis, right bundle branch block (RBBB), left bundle branch block (LBBB), fQRS, and QTc values were similar among the study groups. However, HR, ST-depression, and non-sinus rhythm ratios were higher in patients who died within three days compared to other patients.

Parameters affecting mortality were evaluated by univariate and multivariate analyzes using Cox regression analysis. Age, Pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, cardiac injury, MODS, acute kidney injury, LVEF, RV-FAC, and Tocilizumab/Steroid parameters, which were statistically significant in the univariate analysis, were included in the multivariate analysis. These parameters were determined as independent predictors of mortality (**Table 3**).

Table 4 shows the independent predictors of mortality within three days. First, a regression model was used to elicit mortality predictors in regression analyses. Age, gender, pneumonia on CT, SDBHA, ICU, HT, CAD, CRP, d-dimer, MODS, cardiac and acute kidney injury, LVEF, RV-FAC, and Tocilizumab/Steroid were included in the regression analyses. Gender and CAD were not independent predictors of mortality within three days. However, age, pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, MODS, cardiac and acute kidney injury, LVEF, RV-FAC, and Tocilizumab/Steroid were independent predictors of mortality within three days compared to the 4–10 days and more than ten days mortality and the surviving patients.

ROC curve analysis was used to evaluate the values for age, CT score, SDBHA, hs-TnI, and d-dimer to predict mortality within three days (**Figure 1**). Areas under the curve (AUC) for Age, CT score, SDBHA, hs-TnI, and d-dimer were determined (0.755 / 0.734 / 0.766 / 0.639 / 0.620, respectively). **Table 5** shows the sensitivity, specificity, and cut-off values of age, CT score, SDBHA, hs-TnI, and d-dimer. The age, CT score, SDBHA, hs-TnI, and d-dimer were evaluated by binary logistic regression

Table 3. Cox Regression Analysis on the Risk Factors Associated With Mortality in PatientsWith COVID-19.

Variable	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Age	2.295	1.488-5.142	<0.001	1.110	1.033-1.254	0.001
Gender	1.601	0.771-4.976	0.450			
Pneumonia on CT	5.245	2.101-10.431	<0.001	6.513	2.266-12.765	<0.001
SDBHA	1.421	1.091-2.822	0.009	1.102	1.017-1.273	0.011
ICU	3.003	1.641-8.499	<0.001	4.653	1.989-9.762	<0.001
HT	1.932	1.081-4.989	0.002	2.010	1.256-5.665	0.008
CAD	1.210	0.991-1.909	0.231			
CRP	3.141	1.754-8.249	<0.001	1.975	1.168-4.052	0.005
D-dimer	1.215	1.084-1.413	<0.001	1.022	1.006-1.049	0.003
Cardiac injury	3.165	1.622-8.555	<0.001	1.952	1.075-3.405	0.010
MODS	3.972	1.255-7.973	<0.001	3.080	1.753-7.231	<0.001
Acute kidney injury	1.563	1.107-3.882	<0.001	1.217	1.029-3.918	0.014
LVEF	0.894	0.710-0.994	<0.001	0.924	0.886-0.981	<0.001
RV-FAC	0.855	0.612-0.949	<0.001	0.875	0.811-0.951	<0.001
Tocilizumab/Steroid	0.377	0.218-0.689	<0.001	0.410	0.261-0.732	0.001

Abbreviations: CT, computed tomography; SDBHA, symptom duration before hospital admission; ICU, intensive care unit; HT, hypertension; CAD, coronary artery disease; CRP, C-reactive protein; MODS, multiple organ dysfunction syndrome; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change.

analysis to determine the combined diagnosis model. Then the combined diagnosis model was analyzed by the ROC curve. In **Figure 2**, the red line represents the combined diagnosis model, and the AUC was 0.913.

Reproducibility

CT score, and echocardiography and electrocardiography values of 20 patients were randomly selected to assess intra-observer and interobserver reliability. The intra-observer and interobserver variabilities for CT score were 0.93 and 0.90, respectively. The intra-observer and interobserver variabilities for echocardiography were 0.91 and 0.88, respectively, and the intra-observer and interobserver variabilities for electrocardiography were 0.94 and 0.91, respectively.

DISCUSSION

This study has investigated short- and long-term mortality predictors in surviving and non-surviving COVID-19 patients. First, we showed that age, pneumonia on CT, SDBHA, ICU admission, HT, CRP, d-dimer, MODS, cardiac and acute kidney injury, LVEF, RV-FAC and Tocilizumab/Steroid therapy were independent predictors of mortality within three days. Second, the AUC values of the age, CT score, SDBHA, hs-TnI, and d-dimer were statistically significant in showing mortality within three days. Finally, the combined diagnosis model had a strong predictive value for mortality within three days in COVID-19 patients who died.

The rapid spread of COVID-19 infection worldwide has put the health systems in a difficult situation that has never been experienced before. The exact cause of patient death has not been fully elucidated against the hyperinflammatory reaction and hypercoagulopathy that is the primary pathophysiological mechanism of COVID-19.[24,25] Unlike classical ARDS, COVID-19 ARDS is characterized by early pulmonary endothelial damage using Ang 2 and ICAM-1 pathological pathways.[26] It is known that ICU patients have higher mortality rates than non-ICU patients (30–70%).[27]

Due to the high mortality rates in severe COVID-19 patients, many previous studies tried to find the best model for predicting mortality. As in our research, the data presented in the literature indicate that age was an independent predictor of mortality.[12,28,29] A recent study comparing patients according to age group showed that mortality increased with age.[30] Pulmonary infiltrates

Table 4. Multinomial Logistic Regression analysis on the risk factors associated with short-term mortality in patients with COVID-19.

Survive	OR	95% CI	p	Variable (4-10 days)	OR	OR	95% CI	p	Variable (>10 days)	OR	95% CI	p
Age	2.113	1.301-3.443	0.009	Age	1.654	1.654	1.064-2.741	0.017	Age	1.865	1.094-3.362	0.011
Gender	1.421	0.824-4.432	0.321	Gender	1.326	1.326	0.899-4.141	0.341	Gender	1.532	0.872-4.172	0.512
Pneumonia on CT	7.653	2.534-12.856	<0.001	Pneumonia on CT	3.031	3.031	1.754-6.10	0.001	Pneumonia on CT	6.012	2.210-13.978	<0.001
SDBHA	1.432	1.141-2.465	0.014	SDBHA	1.231	1.231	1.092-2.876	0.022	SDBHA	1.302	1.099-1.600	0.018
ICU	3.441	1.580-8.745	<0.001	ICU	3.352	3.352	1.243-8.683	<0.001	ICU	3.212	1.431-8.435	<0.001
HT	1.876	1.053-4.126	0.013	HT	1.142	1.142	1.020-2.637	0.020	HT	1.212	1.078-4.031	0.016
CAD	1.154	0.853-2.798	0.372	CAD	1.021	1.021	0.984-1.072	0.672	CAD	1.142	0.831-3.579	0.597
CRP	1.957	1.069-5.132	0.004	CRP	1.474	1.474	1.091-2.982	0.009	CRP	1.531	1.103-2.985	0.007
D-dimer	1.053	1.011-1.163	<0.001	D-dimer	1.012	1.012	1.003-1.028	0.003	D-dimer	1.021	1.006-1.039	0.001
Cardiac injury	4.765	1.949-11.423	<0.001	Cardiac injury	4.231	4.231	1.463-10.856	<0.001	Cardiac injury	4.972	1.342-9.187	<0.001
MODS	3.965	1.451-8.763	<0.001	MODS	3.442	3.442	1.474-7.345	<0.001	MODS	3.902	1.792-8.945	<0.001
Acute kidney injury	1.721	1.068-4.173	0.012	Acute kidney injury	1.451	1.451	1.143-3.373	0.026	Acute kidney injury	1.605	1.101-3.869	0.016
LVEF	0.821	0.713-0.951	<0.001	LVEF	0.912	0.912	0.887-0.972	0.005	LVEF	0.889	0.798-0.973	<0.001
RV-FAC	0.817	0.699-0.948	<0.001	RV-FAC	0.902	0.902	0.859-0.949	0.001	RV-FAC	0.873	0.727-0.956	<0.001
Tocilizumab/ Steroid	0.310	0.198-0.632	<0.001	Tocilizumab/ Steroid	0.409	0.409	0.238-0.825	<0.001	Tocilizumab/ Steroid	0.369	0.220-0.701	<0.001

Abbreviations: CT, computed tomography; SDBHA, symptom duration before hospital admission; ICU, intensive care unit; HT, hypertension; CAD, coronary artery disease; CRP, C-reactive protein; MODS, multiple organ dysfunction syndrome; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change.

Table 5. Parameter Values Predicting Early Mortality as a Result of ROC Analysis in Patients with Death due to COVID-19.

Variable	AUC	p	95%CI	Sensitivity	Specificity	Cut-off value
Age	0.755	<0.001	0.701-0.810	65	66	³ 64.5
CT score	0.734	<0.001	0.678-797	74	60	³ 3.5
SDBHA	0.766	<0.001	0.717-0.815	79	63	³ 5.5
hs-TnI	0.639	<0.001	0.576-0.701	59	57	40.5
D-dimer	0.620	<0.001	0.560-0.681	61	61	³ 2705
CDM	0.913	<0.001	0.883-0.942	84	80	³ 0.25

Abbreviation: CT, computed tomography; SDBHA, symptom duration before hospital admission hs-TnI, high sensitive-Troponin I; CDM, Combined diagnosis model

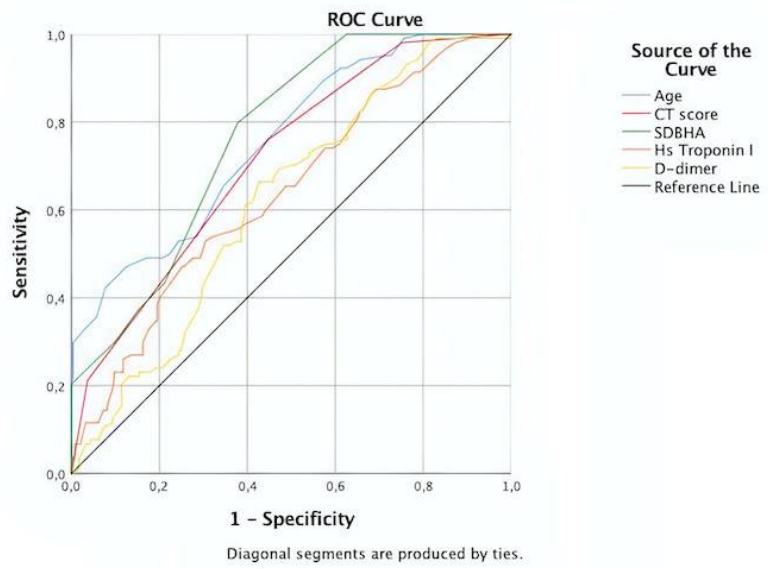

Figure 1. In ROC curve analyses, areas under the curve (AUC) for Age, computed tomography (CT) score, symptom duration before hospital admission (SDBHA), high sensitive-Troponin I (hs-TnI), and D-dimer were determined (0.755 / 0.734 / 0.766 / 0.639 / 0.620 respectively).

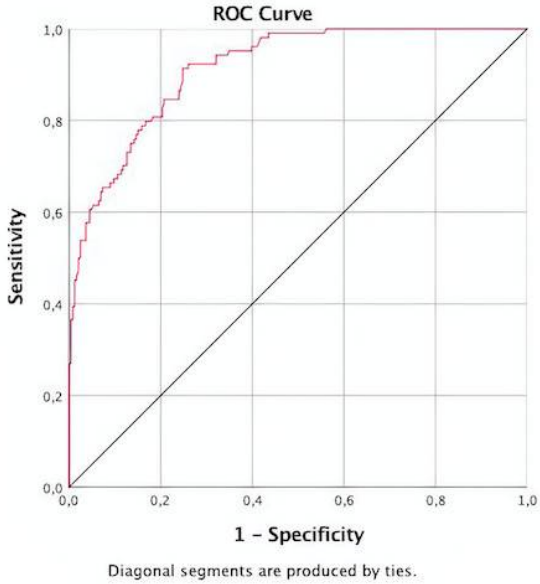

Figure 2. The combined diagnosis model of the age, computed tomography (CT) score, symptom duration before hospital admission (SDBHA), high sensitive-Troponin I (hs-TnI), and D-dimer was analyzed by the ROC curve. The red line represents the combined diagnosis model, and the area under the curve (AUC) was 0.913.

on CT are also an independent predictor of mortality over time. This study presented that COVID-19 patients with pulmonary infiltration have a poor prognosis, consistent with other literature reports.[30,31] Unlike previous studies,[11,32] we indicated SDBHA was an independent predictor of mortality. Possible mechanisms that affect SDBHA as an independent predictor were advanced disease due to delayed diagnosis and thrombotic complications. Given the importance of the early treatment of COVID-19, it seems logical that delayed hospital admissions are related to short-term mortality. The current study presented that ICU admission, HT, CRP, and d-dimer were short-term mortality predictors, which has been proven many times in previous studies.[33]

COVID-19 has adverse effects on the cardiovascular system, and the myocardial injury rate was 14%–19% in these patients.[1,34] High platelet activation has been shown to correlate with disease severity, myocardial damage, and mortality.[35] The current study showed that COVID-19 associated myocardial injury was an independent predictor of short-term mortality, consistent with the literature report.[29,36,37] Therefore, it seems logical that decreased LVEF and RV-FAC values were independent predictors of short-term mortality in COVID-19 patients with cardiac injury. Barman et al. demonstrated that decreased LVEF and RV-FAC were associated with disease severity in COVID-19 patients.[38] Similar to our study results, a previous investigation showed that decreased left and right ventricular function were related to mortality in COVID-19 patients.[39] It is known that myocardial injury is associated with worse prognosis in COVID-19 patients.[12,40] It seems that cardiac functions are affected by many mechanisms and mortality significantly increased in these patients. The mechanisms that affect cardiac functions, such as: (I) cytokine storm and multi-organ failure due to acute systemic inflammatory response, (II) an imbalance between myocardial oxygen supply and demand which secondary to severe hypoxia due to acute respiratory failure, (III) medications related to cardiotoxicity, (IIII) increased coronary thrombosis and embolic complications due to systemic inflammation, (V) the heart inflammation caused by COVID-19 can directly cause myocarditis. Considering these mechanisms, decreased left and right ventricular functions affect early mortality in COVID-19 patients. Moreover, in the regression analyses, we determined MODS was an independent predictor of short-term mortality. Our study results showed the COVID-19 adverse effect is not limited to lung injury but also renal insufficiency and cardiac injury.[41,42] Clinicians should be aware of and manage the potential systemic complications of COVID-19, such as MODS. COVID-19 associated mortality predictors provide potential clinical benefit to improve characterization and comprehensive evaluation of these patients who have an inadequate response to conventional therapy.

This study also determined that age, CT score, SDBHA, hs-TnI, and d-dimer were independently associated with short-term mortality in non-survived COVID-19 patients. Moreover, these parameters' diagnostic value was compatible with previous studies.[31,43-45] To determine the best-fitting model, we analyzed various variables in binary logistic regressions. Then we used a combined model to find the best predictor of short-term mortality in COVID-19 patients who died. The current study indicated the combined diagnosis model was a strong predictor of short-term mortality (AUC value 0.91 (95% CI, 0.88–0.94)). Because of the high mortality rate in critically ill COVID-19 patients (49%), it is crucial to identify patients with a bad prognosis in the early stages.[46] Therefore, we assumed the combined diagnosis model might help physicians predict the prognosis of COVID-19 patients earlier and guide their treatment methods. Thus, severe COVID-19 patients can be monitored closely for mortality and might be treated in the early stages of the disease.

Even though COVID-19 patients may have a good or poor clinical prognosis, the course of the disease is not entirely predictable. The current study was designed to partially fill this critical gap. Therefore, we have evaluated the effects of various clinical factors on mortality by days.

The current study is unique and has specific strengths compared to previous studies.

COVID-19 patients who died were categorized according to their survival time rather than other factors used in earlier reports. Another advantage of our study is that the combined diagnosis model was created by clinical, laboratory, and imaging parameters. The combined model was a predictor of short-term mortality in non-surviving COVID-19 patients, which is a strength of our study compared with literature data. Another essential difference in our study is that we tried to find a more accurate definition of patients who died within the first 72 hours. If we can identify the acute phase, and then we can raise awareness to diagnose these patients earlier.

On February 24, 2022, about 25 months since the first reported case of COVID-19 and after a global estimated 426 million cases and 5.8 million deaths was reported.[47] On 25 November 2021, the world health organization listed Omicron as a new variant of concern. Omicron has some deletions and more than 30 mutations.[48] Moreover, Omicron has 15 mutations in the receptor-binding domain of spike. These mutations are increased transmissibility, higher viral binding affinity, and higher antibody escape.[49,50] The Omicron variant is more infectious than the previous variants.[51] Also, an increased risk of reinfection related to Omicron.[52] Omicron variant is related to lower risk of COVID-19 hospitalization.[53] Vaccinated people have a much lower risk of severe disease from omicron infection. Cough, runny/stuffy nose, fatigue/lethargy, sore throat, headache, and fever were the most prevalent symptoms.[54] The current COVID-19 vaccines associated with lower immunity to the omicron variant. Moreover, a new booster dose will increase the efficacy against omicron infection.[55]

By March 2021, thirteen vaccines have been authorized for use in many countries. These vaccines have been demonstrated to be effective in preventing the infection of COVID-19 at varying efficacy. COVID-19 vaccines have essentially focused on prevention of infection and hospitalizations.[56,57] SARS-CoV-2 infection in vaccinated persons is expected to trigger memory antibody and cellular responses owing to prior vaccination; these immune responses could mitigate disease progression, possibly preventing life-threatening organ failure and death.[58,59] Tenforde et al. evaluated the association between vaccination and COVID-19 hospitalization and disease severity. They presented that COVID-19 hospitalization was strongly associated with lower likelihood of vaccination for previous variants. And vaccinated cases less commonly received invasive mechanical ventilation. Moreover, COVID-19 hospitalization was strongly related to a lower likelihood of vaccination. Among patients hospitalized with COVID-19, the outcome of death or invasive mechanical ventilation was associated with a lower likelihood of vaccination.[60] We have designed our research in March 2020 and January 2021. And our patients had not got omicron variant at that time. We know that patients with omicron have lower hospitality and mortality. Also, our patients were not vaccinated, so they have higher mortality rates than vaccinated patients.

This study has limitations, including the retrospective study design, and the number of patients was relatively low. Another limitation is that we did not include the complaints of the patients on admission. A subgroup analysis of MODS was not performed due to the limited number of patients. Also, the study's design did not allow the accurate retrieval of data to include underlying diseases, potentially up or down-scoring the net effect of each comorbidity. As criteria for hospitalization of COVID–19 patients are different across different institutions, an inclusion bias cannot be excluded. Finally, as this is an observational study, residual confounding may exist.

CONCLUSION

In conclusion, this study discovered that age, pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, cardiac injury, MODS, acute kidney injury, LVEF, and RV-FAC were all independently associated with short-term mortality in COVID-19 patients in the Turkish population. Moreover, Tocilizumab/Steroid therapy was a protective and independent predictor of mortality within three days. The combined diagnosis model was a strong predictor of short-term mortality in non-

surviving COVID-19 patients. Because of the increased mortality risk in severe COVID-19 patients, it is essential to identify poor prognosis markers at an early stage. More prospective randomized studies are needed to confirm our findings.

COMPETING INTERESTS

All authors have no declarations of interest to report.

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AUTHORS' CONTRİBUTİONS

Atici A, Asoglu R, Barman HA and Aciksari G contributed to the conception and design of the study; Baycan OF, Tatlisu MA and Ozcan FB collected data; Atici A, and Yilmaz Y analysed the data; Atici A, and Caliskan M wrote and revised the manuscript.

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