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Coronavirus Pandemic

Clinical characteristics and risk factors associated with severe disease and outcome of patients with COVID-19

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Abstract

Introduction: Since the beginning of the pandemic, factors associated with mortality in patients with corona virus infection disease 2019 (COVID-19) have been investigated. Comorbidities and increased age have been frequently reported to be associated with mortality. We aimed to evaluate the factors associated with unfavorable outcome of patients with COVID-19 at an early period of the pandemic.

Methodology: This single center, retrospective, observational study was conducted among laboratory confirmed COVID-19 patients hospitalized between March 11 and May 5, 2020, at Umraniye Training and Research Hospital, Istanbul, Turkey. The effects of the severity of illness, comorbidities, symptoms, and laboratory findings on the clinical outcome were evaluated. Factors associated with unfavorable outcome (necessity of mechanical ventilation or death) were examined using Cox proportional hazards models.

Results: Out of a total of 728 patients, 53.8% were men and median age 54 years. The 30-day mortality rate was 4.9% among all hospitalized patients. A logistic regression model identified six predictors of unfavorable clinical outcome: age, severity of illness, the numbers of comorbidities, lymphopenia, high levels of C-reactive protein, and procalcitonin.

Conclusions: The mortality rate was lower among the patients with COVID-19, hospitalized during the early period of the pandemic. Older age, higher severity score on admission, the numbers of comorbidities, higher levels of C-reactive protein, procalcitonin, and lymphopenia were identified to be associated with unfavorable outcome of the hospitalized patients with COVID-19.

Key words: COVID-19; Mortality; Outcome.

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Introduction

In December 2019, a new severe respiratory syndrome was identified in Wuhan, China. At the beginning of 2020, a new Coronavirus was detected, and successively named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). On March 2021, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a major public health concern [1,2]. By May 3, 2021, 152,534,452 confirmed cases of COVID-19, including 3,198,528 deaths, were reported to the WHO resulting from this pandemic [3].

SARS-CoV-2 spreads through close face-to-face contact or inhalation of respiratory droplets and infects lung alveolar epithelial cells, causing first pneumonia and then acute respiratory distress syndrome (ARDS) [4]. The virus targets nasal, bronchial epithelial cells, pneumocytes and binds to the angiotensin-converting enzyme 2 (ACE2) receptor with the viral structural spike (S) protein [5]. SARS-CoV-2 infects pulmonary capillary endothelial cells, causes pulmonary interstitial edema, and clinically follows early phase of ARDS [5,6]. The most observed clinical features in hospitalized people are fever, non-productive cough, shortness of breath, myalgia, fatigue, and gastrointestinal symptoms such as diarrhea [4]. Most of COVID-19 cases have mild status. However, in a substantial percent of patients, illness progressed to a critical stage with hypoxemic respiratory failure requiring respiratory support [7]. COVID-19 has a considerable fatality rate among hospitalized patients [8]. It has been observed that patients with underlying comorbid diseases had a fatality rate as high as 14% [9].

Poor prognosis has been defined differently in each study, such as the need for intensive care, invasive mechanical ventilation, or death of the patients. Several studies and meta-analysis have revealed factors associated with poor prognosis to be older age and the presence of underlying comorbidities [8-14]. Researchers have also reported several other risk factors for poor prognosis such as lymphopenia, high level of procalcitonin (PCT), and C-reactive protein (CRP) [10,11,13,15-18].

For each country, the criteria of management, treatment, and hospitalization of patients with COVID-19 have been ever-changing, especially in the early period of the pandemic. In patients with COVID-19, it is important to identify the clinical stage, baseline laboratory values, and aggravating factors in order to identify and standardize steps to prioritize patients requiring hospitalization [14].

In this study, we evaluated the factors affecting poor prognosis of patients hospitalized with COVID-19.

Methodology

Study design and data collection

We conducted a retrospective, observational study among hospitalized patients diagnosed with COVID-19 between March 11 and May 05, 2020, in Istanbul, Umraniye Research and Training Hospital, Turkey. The real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 genome was conducted in the central public health laboratory using Coyote Bioscience Co., Ltd Kit (San Francisco, United States) according to the protocols provided by the manufacturer.

We collected the demographic characteristics, comorbidities, and clinical characteristics of the infection, as well as the outcomes from the medical records of the hospitalized patients in our hospital. The following clinical data were collected: age, gender, comorbidities (hypertension, diabetes mellitus, chronic obstructive lung disease, asthma, chronic renal failure, chronic hepatic disease, chronic cardiovascular disease [including coronary heart disease, congestive heart failure, and cerebrovascular disease], and immunosuppression). Immunosuppressive condition was defined as the presence of one or more of the following conditions: a rheumatic disease, inflammatory bowel disease, malignancy, transplantation, human immune deficiency virus, usage of steroids (> 20 mg prednisolone/day) for > 2 weeks, or the current use of anti-TNF drugs.

We recorded the symptoms of patients prior to their hospitalization, the baseline vital signs, and the laboratory values within the first 24 h of their hospital admission ((aspartate aminotransferase (AST) [mg/dL], CRP [mg/L], D-dimer, ferritin [ng/mL], fibrinogen [mg/mL], creatine kinase [U/L], creatinine [mg/dL], lactate dehydrogenase (LDH) [U/L], PCT [ng/mL], bilirubin [mg/dL], and lymphocyte counts)). With these data, the WHO progression scale was evaluated and used for clinical staging of the patients on hospital admission [19]. We obtained the patients' 30-day mortality data from the medical records of our hospital and then through direct phone interviews with the patients after discharge.

Only baseline characteristics were evaluated for the outcome of the patients. Although co-existing bacteremia and co-administered treatments of patients (such as supplemental oxygen, antiviral agents, tocilizumab, convalescent plasma, and antibacterial agents) were recorded, its relationship with the outcome was not evaluated.

Patients' definition

We included the patients aged ≥ 18 years with positive SARS-CoV-2 RT-PCR in nasopharyngeal swab samples in our study. The first admission of patients who were hospitalized more than once was included in the study. Exclusion criteria were patients who needed to be referred to an external center at the time of admission, transferred from an external intensive care unit (ICU) to our hospital, individuals aged <18 years, and COVID PCR-negative patients. Also, patients who died or intubated within the first 48 h of hospitalization were excluded to evaluate the effects of baseline parameters correctly on unfavorable outcome.

Outcome of Patients

Full recovery of the patients and discharge from hospital was considered as a favorable outcome. Unfavorable outcome was defined as death or need of mechanical ventilation of patients. Primary outcome was death and secondary outcome was intubation or need of mechanical ventilation of patients.

Statistical Analysis

The frequency and percent for categorical data and the median interquartile range (IQR) for continuous data were provided as descriptive values. Logistic Regression Analysis was applied to examine the factors that affected the occurrence of an unfavorable outcome. The variables that were observed to be significant ($p < 0.05$) in the univariate analysis were included in the multivariate analysis. Prior to multivariate analyses, the

best model was created with the Backward Wald method by adding the variable that best represented the model among the variables observed to be linear. The results were considered as statistically significant at $p < 0.05$. The mean imputation method was performed for missing data for variables with data loss of > 10% in multivariate analyses. All statistical analysis was performed using the IBM Statistical Package for the Social Sciences for Windows 21.0 package program.

Ethical issues

Table 1. Demographic and clinical characteristics of patients with SARS-CoV-2.

Characteristics (N = 728)	Total N = 728	Unfavorable Outcome N = 37	Favorable Outcome N = 691	*p* value
Sex, n (%)				
Male	392 (53.8)	26 (70.3)	366 (53.0)	0.043*
Female	336 (46.2)	11 (29.7)	325 (47.0)	
Age (y), median (IQR)	54 (44-65)	73 (61-81)	53 (43-64)	
< 60, n (%)	469 (64.4)	7 (18.9)	462 (66.9)	< 0.0001*
≥ 60, n (%)	259 (35.6)	30 (81.1)	229 (33.1)	
Severity of illness (WHO progression scale)				
≤ 3	631 (86.7)	22 (59.5)	609 (88.1)	< 0.0001*
> 3	97 (13.3)	15 (40.5)	82 (11.9)	< 0.0001*
Respiratory rate ≥ 24, n (%)	142 (19.5)	18 (50.0)	124 (17.9)	< 0.0001*
Oxygen saturation, n (%)				
≤ 93	103 (14.1)	16 (43.2)	87 (12.6)	< 0.0001*
> 93	625 (85.9)	21 (56.8)	604 (87.4)	
Fever > 38.0 °C, n (%)	71 (9.8)	6 (16.2)	65 (9.4)	0.162
Symptom duration before hospitalization, (median (IQR))	4 (3-7)	3 (1-6)	4 (3-7)	0.071
Hospitalization duration, (median (IQR))	6 (4-11)	14 (9-17)	6 (4-10)	< 0.0001*
Symptoms				
Cough, n (%)	477 (65.5)	18 (48.6)	459 (66.4)	0.033*
Fever, n (%)	290 (39.8)	13 (35.1)	277 (40.1)	0.608
Dyspnea, n (%)	201 (27.6)	12 (32.4)	189 (27.4)	0.571
Lassitude, n (%)	131 (18.0)	4 (10.8)	127 (18.4)	0.377
Myalgia, n (%)	82 (11.3)	3 (8.1)	79 (11.4)	0.789
Diarrhea, n (%)	50 (6.9)	4 (10.8)	46 (6.7)	0.311
Gastrointestinal symptoms, n (%)	50 (6.9)	3 (8.1)	47 (6.8)	0.735
Other Symptoms, n (%)	48 (6.6)	6 (16.2)	42 (6.1)	0.029*
Throat ache, n (%)	46 (6.3)	1 (2.7)	45 (6.5)	0.723
Headache, n (%)	45 (6.2)	1 (2.7)	44 (6.4)	0.721
Arthralgia, n (%)	34 (4.7)	1 (2.7)	33 (4.8)	0.474
Loss of taste and smell, n (%)	16 (2.2)	-	16 (2.3)	0.430
Chills, n (%)	16 (2.2)	-	16 (2.3)	0.430
Loss of appetite, n (%)	15 (2.1)	1 (2.7)	14 (2.0)	0.546
Comorbidities				
Hypertension, n (%)	234 (32.1)	20 (54.1)	214 (31)	0.006*
Diabetes mellitus, n (%)	181 (249)	13 (35.1)	168 (24.3)	0.170
Chronic respiratory disease	94 (12.9)	5 (13.5)	89 (12.9)	0.805
Chronic obstructive pulmonary disease (COPD), n (%)	25 (3.4)	3 (8.1)	22 (3.2)	0.129
Asthma, n (%)	69 (9.5)	2 (5.4)	67 (9.7)	0.567
Chronic cardiovascular disease, n (%)	85 (11.7)	7 (18.9)	78 (11.3)	0.183
Immunosuppressive disease, n (%)	36 (4.9)	3 (8.1)	33 (4.8)	0.420
Malignity	25 (69.4)	3 (100)	22 (66.7)	
Rheumatic or inflammatory bowel disease	10 (27.8)	-	10 (30.3)	
Human immunodeficiency virus (HIV)	1 (2.8)	-	1 (3.0)	
Chronic renal disease, n (%)	19 (2.6)	5 (13,5)	14 (2.0)	0.002*
Chronic hepatic disease, n (%)	5 (0.7)	1 (2.7)	4 (0.6)	0.230
Number of comorbidities, n (%)				
None	337 (46.3)	8 (21.6)	329 (47.6)	< 0.0001*
≥ 2	178 (24.5)	15 (40.5)	163 (23.6)	< 0.0001*
Oxygen need in follow-up (%)	172 (23.6)	37 (100)	135 (19.5)	< 0.0001*
Intubation in follow-up, n (%)	27 (3.7)	27 (73.0)	-	< 0.0001*
Invasive mechanical ventilation in follow-up, n (%)	19 (2.6)	19 (51.4)	-	< 0.0001*
Re-hospitalization after discharge, n (%)	22 (3.0)	-	22 (3.2)	0.621

* $p < 0.05$.

This study was approved by the Research Ethics Committee of the Health Sciences University of Umraniye Research and Training Hospital, Turkey (Ref. No:140).

Results

Clinical Findings

A total of 728 patients were included in the study. The median age of the participants was 54 years (IQR, 44–65) and 53.8% of them were men. Among the patients, 259 (35.6%) were aged ≥ 60 years. In the first 24 h of hospital admission, 19.5% of the patients had a respiratory rate > 24 breaths/min, 14.1% had oxygen saturation of ≤ 93, 9.8% were febrile. Seven patients (1%) were at stage 1, 147 (20.2%) were at stage 2, 477 (65.5%) were at stage 3, 93 (12.8%) were at stage 4 and 4 (0.5%) were at stage 5 according to the WHO classification (13.3% patients were at stage > 3).

The median duration from the onset of symptoms to hospital admission was 4 (IQR 3-7) days. The most common symptoms of the hospitalized patients were cough (477; 65.5%), fever (290; 39.8%), and dyspnea (201; 27.6%). The most common comorbidity was hypertension (234; 32.1%), followed by diabetes mellitus (181; 24.9%), chronic respiratory disease (94; 12.9%), and chronic cardiac disease (85; 11.7%) (Table 1).

Out of the 728 patients, 638 (87.6%) did not require supplemental oxygen on admission. Ninety patients (12.4%) needed oxygen therapy on admission and 8 (1%) were admitted to the ICU from emergency service. One hundred seventy seven (23.6%) patients needed oxygen therapy on hospital admission and during the follow-up period. Among these patients, 61 (8.4%) were followed up in the ICU. A total of 27 (3.7%) patients were intubated and 8 (29%) of them died after intubation without requiring any further mechanical ventilation. As of May 5, 18 of the 19 patients (94%) who were followed up with mechanical ventilation had died during a 30-day follow-up period (Table 1).

The overall mortality rate was 4.9%. The ICU mortality rate was 54%, and the mortality rate of patients on mechanical ventilation was 94%. Only 22 (3.0%) of patients among the survivors required re-hospitalization after discharge (Table 1).

Treatments

Fifty (6.9%) patients received hydroxychloroquine, 197 (27.2%) hydroxychloroquine plus azithromycin, 408 (56.3%) hydroxychloroquine plus azithromycin plus oseltamivir, 70 (9.7%) hydroxychloroquine plus oseltamivir, 177 (24.3%) favipiravir, and 21 (2.8%) lopinavir/ritonavir for the treatment of COVID-19. During the follow-up, tocilizumab was used in 33 (4.5%) patients, and COVID convalescent plasma was administered to 28 (3.8%) patients. Intravenous corticosteroid was used for 33 (% 4.5) patients. Antibiotics were administered to 185 (25.4%) of all patients due to a suspicion of secondary bacterial infections. In addition, 96 (13.2%) of these patients received ceftriaxone, 40 (5.5%) piperacillin tazobactam, 9 (1.3%) meropenem, and 4 (0.6%) teicoplanin.

Factors associated with poor prognosis

In the unfavorable outcome group, the proportion of men (70.3% versus 53.0%; $p < 0.043$) and the proportion of patients aged > 60 years (81.1% versus 33.1%; $p < 0.0001$) were higher as compared to the

Table 2. Baseline laboratory values with favorable and unfavorable outcome.

Characteristics N = 728	Total N = 728	Unfavorable Outcome N = 37	Favorable Outcome N = 691	*p* value
Laboratory				
Aspartate aminotransferase (AST) (U/L), median (IQR)	25 (20-35)	36 (29-54)	24 (19-34)	< 0.0001*
C-reactive protein (CRP) (mg/L), median (IQR)	1.4 (0.4-4.0)	6.8 (2.8-14)	1.3 (0.4-3.7)	< 0.0001*
D-dimer, median (IQR)	560 (380-943)	1098 (579-2409)	550 (375-894)	< 0.0001*
Ferritin (ng/mL), median (IQR)	201 (92-433)	473 (158-2238)	199 (88-410)	< 0.0001*
Fibrinogen (mg/mL), median (IQR)	442 (357-551)	510 (461-680)	437 (357-548)	0.005*
Creatine kinase (U/L), median (IQR)	76 (47-136)	185 (66-371)	74 (45-129)	< 0.0001*
Creatinine (mg/dL), median (IQR)	0.85 (0.74-1.01)	1.2 (1.0-1.89)	0.84 (0.74-1.0)	< 0.0001*
Lactate dehydrogenase (LDH) (U/L), median (IQR)	277 (214-347)	370 (262-487)	276 (212-340)	< 0.0001*
Procalcitonin (PCT) (ng/mL), median (IQR)	0.05 (0.05-0.06)	0.14 (0.07-0.56)	0.05 (0.05-0.06)	< 0.0001*
Total bilirubin (mg/dL), median (IQR)	0.49 (0.35-0.65)	0.56 (0.36-0.80)	0.49 (0.35-0.65)	0.190
≤ 0.50	604 (96.3)	27 (75.0)	577 (97.6)	< 0.0001*
> 0.50	23 (3.7)	9 (25.0)	14 (2.4)	
Lymphocyte count (U/L), median (IQR)	1430 (1050-1915)	920 (630-1360)	1450 (1070-1940)	< 0.0001*

* $p < 0.05$.

favorable outcome group. Except for coughing, which was more frequently noticed in the favorable outcome group than in the unfavorable outcome group (66.4% versus 48.6%; $p = 0.033$), the frequencies of other symptoms were similar in both the groups.

The patients with unfavorable outcome were more likely to have hypertension (54.1% versus 31%; $p = 0.006$) and chronic renal disease (13.2% versus 2%; $p < 0.002$). There was no difference noted in the incidence of diabetes mellitus (35.1% versus 24.3%; $p < 0.170$), chronic respiratory disease (13.5% versus 12.9%; $p < 0.805$), chronic cardiovascular disease (18.9% versus 11.3%; $p < 0.183$), immunosuppressive disease (8.1% versus 4.8%; $p < 0.420$) and chronic hepatic disease (2.7% versus 0.6%; $p < 0.230$) between the groups (Table 1).

A respiratory rate > 24 breaths/min (50% versus 17.9%; $p < 0.0001$), oxygen saturation level < 93% (43.2% versus 12.6%; $p < 0.0001$) and a WHO progression scale >3 (40.5% versus 11.9%; $p < 0.0001$) were significantly more common among patients in the unfavorable outcome group than in those in the favorable outcome group (Table 1).

High levels of AST, CRP, D-dimer, creatinine, ferritin, LDH, PCT, and total bilirubin (> 0.50 mg/dL) are associated with unfavorable outcome in univariate analysis ($p \leq 0.001$). Also the patients with unfavorable outcome group had higher levels of fibrinogen ($p = 0.05$) and creatine kinase ($p = 0.01$). We found that lower lymphocyte counts were associated with unfavorable outcome than favorable outcome patients ($p < 0.001$) (Table 2).

The number of patients treated with favipiravir ($p < 0.0001$), lopinavir ritonavir ($p < 0.018$) and tocilizumab ($p < 0.0001$) were more than in unfavorable outcome group univariate analysis (Table 3).

In multivariate analyses, missing data for variables other than PCT was < 10% and no imputation was performed. The mean imputation method was used for the missing PCT values. A logistic regression model identified six factors associated with unfavorable outcome; age (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.03 to 1.10), severity of illness (WHO severity score) (OR, 2.20; 95% CI, 1.76 to 3.15), the number of comorbidities (OR, 1.43; 95% CI, 1.13 to 2.47), CRP value (OR, 1.11; 95% CI, 1.04 to 1.18), PCT value (OR, 2.20; 95% CI, 1.45 to 3.55), and lymphocyte count (OR, 0.90; 95% CI, 0.79 to 0.99) (Table 4).

Discussion

A smaller proportion of patients with COVID-19 progressed to develop severe illness (8%-15%) such as respiratory failure, acute respiratory distress syndrome, multiple organ failure, and even death. The fatality rates of patients with COVID-19 reported in the literature range from 1% to 28% [20-22]. In our study, the 30-day mortality rate of patients who were hospitalized with COVID-19 was 4.9%.

In the literature, researchers have reported mortality rates as high as 36.4% and 45% among the hospitalized patients with COVID-19. These studies included more severe and older patients than in our study [13,23]. In Turkey, even at the early stage of pandemic, the patients with severe COVID-19 symptoms were hospitalized according to the recommendation of The Ministry of Health Turkey [24]. In our study, 86.7% of the patients had a WHO scale < 3 and their median age was 54 years, which was younger than in other studies. Therefore, the mortality rate was relatively lower. In a meta-analysis of 61,742 patients with a heterogeneous distribution of patients' mean age and hospitalization criteria, the overall mortality rate was 6% [25].

Table 3. Treatments given to patients with favorable and unfavorable outcome.

Treatment, n (%)	**Total N = 728**	**Unfavorable Outcome N = 37**	**Favorable Outcome N = 691**	***p* value**
Hydroxychloroquine	50 (6.9)	7 (18.9)	43 (6.3)	
Hydroxychloroquine + Azithromycin	197 (27.2)	6 (16.2)	191 (27.8)	0.014*
Hydroxychloroquine + Azithromycin + Oseltamivir	408 (56.3)	20 (54.1)	388 (56.4)	
Hydroxychloroquine + Oseltamivir	70 (9.7)	4 (10.8)	66 (9.6)	
Favipirevir, n (%)	177 (24.3)	31 (83.8)	146 (21.1)	< 0.0001*
Lopinavir Ritonavir, n (%)	21 (2.9)	4 (10.8)	17 (2.5)	0.018*
Antibiotherapy, n (%)	185 (25.4)	4 (10.8)	181 (26.2)	
Ceftriaxone	96 (13.2)	17 (45.9)	79 (11.4)	
Piperacillin tazobactam	40 (5.5)	14 (37.8)	26 (3.7)	
Meropenem	9 (1.3)	4 (10.8)	5 (0.7)	
Teicoplanin	4 (0.6)	2 (5.4)	2 (0.2)	
Tocilizumab, n (%)	33 (4.5)	13 (35.1)	20 (2.9)	< 0.0001*
Convalescent plasma, n (%)	28 (3.8)	3 (8.1)	25 (3.6)	0.165

* $p < 0.05$.

In our study, the 30-day mortality rate of patients followed up in ICU was 54%. The mortality rate of the patients who were followed up on mechanical ventilation was 94%. At the early phase of the pandemic, a study from China reported the fatality rate of patients with COVID-19 on invasive mechanical ventilation to be 97% [22]. Richardson *et al*. also reported a high mortality rate of 88% among invasively ventilated patients [26]. In another analysis from Italy, 88% of the patients in ICU were intubated and their mortality rate was 64% [27]. In a recent study, researchers from USA reported a comparatively lower mortality rate (36%) among invasively ventilated patients when compared to those from other countries during the early phase of the pandemic [28]. Higher death rates in the early phase of the pandemic may be attributed to the limited intensive care resources. Nevertheless, all patients, regardless of their advanced cancer or dementia status (who were referred to hospice care), who were followed up at ICU during the pandemic showed higher mortality rate in this study.

In this retrospective cohort study, we identified several factors associated with unfavorable outcome in adults hospitalized with COVID-19 during the early stage of COVID pandemic. First, we found that age > 60 years was associated with unfavorable outcome both at univariate and multivariate analyses, although male gender lost its significance in multivariate analysis. Older age was found to be associated with mortality in multivariate analysis conducted in almost all studies [10,12,15,29-31]. In a cohort study including 17,278,392 patients in the UK, advanced age and male gender were strongly associated with mortality in the logistic regression analysis [11]. The frequency of comorbid illness rises with age. Moreover, the infections manifest in a more severe form among the elderly because of their decreased efficiency of adaptive and innate immune system. In addition, drug usage is more common in older age, which suppresses the symptoms of COVID-19 and thus affects the outcome [32].

Hypertension, cardiovascular, or cerebrovascular diseases were reported to be closely related to severity of illness and mortality of patients in several studies [10,12,22,23]. These studies reported that two or more comorbid diseases is associated with poorer prognosis in patients with COVID-19 [33,34]. In our study, hypertension and chronic renal disease were more common among patients with unfavorable outcome in univariate analysis, as also reported by Melodina *et al.* [35]. The frequency of other comorbidities (such as DM, COPD, and immunosuppressive disease) was not different between the two groups in our study. Bommer *et al*. found that the patients with chronic comorbid diseases may have severe outcome risk, as high as 10-fold, when compared to individuals without any comorbidity [36]. In a systematic review, the fatality of patients showed an association with comorbidity [37]. Reliev *et al*. reported that the number of comorbidities were associated with higher mortality of COVID-19

Table 4. Factors associated with unfavorable outcome.

Characteristics	Univariate Model OR (95% CI)		Multivariate Model OR (95% CI)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Sex, n (%)				
Female	Ref		Ref	
Male	2.10 (1.02-4.31)	0.044	1.39 (0.60-3.22)	0.449
Age (y)	1.08 (1.06-1.11)	< 0.0001	1.06 (1.03-1.10)	< 0.0001*
Severity of illness (WHO progression scale)	4.51 (2.60-7.82)	< 0.0001	2.20 (1.76-3.15)	0.017*
Respiratory rate ≥ 24, n (%)	1.21 (1.11-1.32)	< 0.0001		
Oxygen Saturation ≤ 93, n (%)	0.85 (0.74-0.87)	< 0.0001		
Number of comorbidities, n (%)	1.58 (1.20-2.08)	0.001	1.43 (1.13-2.47)	0.018*
(AST) (U/L)	1.01 (1.00-1.02)	0.001		
(ALT) (U/L)	1.01 (1.00-1.02)	0.014		
CRP (mg/L)	1.18 (1.12-1.24)	< 0.0001	1.11 (1.04-1.18)	0.001*
D-dimer	1.00 (1.00-1.01)	< 0.0001		
Ferritin (ng/mL)	1.00 (1.00-1.01)	< 0.0001		
Fibrinogen (mg/mL)	1.00 (1.00-1.01)	< 0.0001		
Creatine kinase (U/L)	1.50 (1.15-1.93)	0.003		
Creatinine (mg/dL)	1.00 (1.00-1.01)	< 0.0001		
LDH (U/L)	1.01 (1.00-1.01)	< 0.0001		
Procalcitonin (ng/mL)	4.60 (2.18-9.71)	< 0.0001	2.20 (1.45-3.55)	0.045*
WBC (White blood cell count)	1.00 (0.99-1.01)	0.009		
Lymphocyte count (U/L)	1.00 (0.99-1.01)	< 0.0001	0.90 (0.79-0.99)	0.040*
Lymphocyte %	0.90 (0.86-0.94)	< 0.0001		

* $p < 0.05$.

[38]. Similarly, we found that each comorbid disease increased the unfavorable outcome in multivariate analysis ($p = 0.001$) (Table 4).

It has been reported that cough is the most common symptom of COVID-19, followed by fever and dyspnea [23,29]. Similarly, we found that the most common symptoms of hospitalized patients were cough (65.5%), followed by fever (39.8%) and dyspnea (27.6%). Patients do not always present with fever at the time of admission, and elderly patients may be afebrile in the early stage [7,39].

In this study, we found that patients with a disease severity scale of ≥ 3 on admission were associated with unfavorable outcome in multivariate analysis ($p \leq 0.001$).

Previously, several baseline acute phase reactants have been reported as important independent predictors of severe COVID-19 [20,22,25,34]. Some of the studies reported that lower lymphocyte counts and higher CRP levels were associated with severe COVID-19 status [16,18,40]. Moreover, in our study, multivariate analysis revealed that the higher level of CRP and lower lymphocyte count were associated with unfavorable outcome ($p \leq 0.001$; $p \leq 0.001$) (Table 4). In our study D-dimer, ferritin and LDH were associated with unfavorable outcome in univariate analysis, however lost their significance in multivariate analysis similar to observations by Zinellu *et al.* (Table 2, 4) [18]. Besides higher CRP levels and lymphopenia, higher level of PCT has also been associated with an unfavorable outcome in logistic regression analysis in our study ($p \leq 0.001$). PCT is normally synthesized and released by thyroid parafollicular C cells. However, it can also be synthesized in several extra thyroid tissues during bacterial infection [41]. Some studies have reported that the PCT levels > 0.5 ng/mL is associated with poor prognosis of patients with COVID-19 [10,42]. Recently, some authors have reported that elevated PCT is positively associated with the severity of COVID-19 [7,43]. Although it is difficult to demonstrate, higher levels of PCT may be due to bacterial coinfection on admission or it may be a prognostic factor for the severity of patients with COVID-19. Therefore, it is essential to rule out bacterial coinfection in patients with high PCT levels.

Male gender was reported to be associated with poor prognosis in COVID-19 in several studies [10,11,22,35]. In our study, while male gender was found to be associated with an unfavorable outcome in univariate analysis, it lost its significance in multivariate analysis.

Although there is no proven therapy for COVID-19, hydroxychloroquine, azithromycin, favipiravir, or lopinavir-ritonavir were used as repurposed drugs for COVID-19 treatment at the early stage of pandemic, according to the recommendation of The Ministry of Health, Turkey [24]. Since seasonal influenza could not be excluded in the early stage of the pandemic, oseltamivir treatment was also provided to some patients. Similarly, the patients received tocilizumab and convalescent (immune) plasma therapy according to The Ministry of Health Guidelines, and these drugs were administrated to seriously ill patients with COVID-19 [24]. The number of patients treated with favipiravir, lopinavir ritonavir and tocilizumab is higher than in unfavorable outcome patients in univariate analysis (Table 3). This may be related to the fact that treatments were given to more severe patients in the early period of the pandemic. The usage of these drugs may affect the outcome of patients. Since this was an observational study, the benefit of favipiravir, lopinavir/ritonavir, or tocilizumab could not be assessed.

This study has some limitations. Our study is retrospective, observational and monocentric. Most of the patients did not have high severity score and did not need oxygen therapy at hospital admission according to the recommendation of The Ministry of Health, Turkey. This may be the reason for the lower number of severe patients and the lower mortality rates. Also factors such as obesity or smoking history that could affect the outcome of the disease were not included in the study. Moreover, our study did not include the radiological staging of patients with COVID-19.

Conclusions

We recorded low mortality rate among all hospitalized patients and higher mortality rates among the intubated patients. In our study, most of the patients with WHO scale < 3 and younger age had relatively lower mortality rate.

We observed that older age, severity of illness, higher CRP values, and lymphopenia were some of the factors associated with unfavorable outcome. PCT testing on admission is a valuable parameter to aid early risk assessment of patients with COVID-19. Each comorbid disease was also associated with increased mortality among hospitalized patients. These baseline factors may facilitate the early recognition of patients at risk for unfavorable outcome and should be followed up more closely in a clinical setting.

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