Original Article

Risk Factors for Mortality in Hospitalized Moderate-to-Severe COVID-19 Patients: A Single-center Retrospective Study

Leyla Bahadorizadeh[1,2], Soheil Rahmani Fard[1], Arman Karimi Behnagh[2,3], Seyed Ali Hashemi Kiapey[2,3], Seyed Hassan Saneii[4], Sara Minaeian[1]

[1]Antimicrobial Resistance Research Center, Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran, [2]Firoozabadi Clinical Research Development Unit (FACRDU), Iran University of Medical Sciences, Tehran, Iran, [3]Department of Internal Medicine, School of Medicine, Iran University of Medical sciences, Tehran, Iran, [4]Department of Basic Sciences of Rehabilitation, Rehabilitation Research Center, School of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran

ORCID:

Leyla Bahadorizadeh: 0000-0001-8143-4748

Sara Minaeian: 0000-0002-8787-5971

Downloaded from http://journals.lww.com/iahs by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Abstract

Aims: The aim of this study was to determine the mortality risk factors of hospitalized moderate-to-severe coronavirus disease 2019 (COVID-19) patients in Tehran. **Materials and Methods:** We retrospectively evaluated the baseline characteristics and clinical and paraclinical parameters of 223 deceased and discharged patients who were hospitalized in Firoozabadi General Hospital between March 1 and April 1, 2020. **Results:** According to our multiple logistic regression model, advanced age (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.02–1.09; $P < 0.01$), reduced oxygen saturation (OR, 0.92; 95% CI, 0.87–0.96; $P < 0.01$), and hypertension (OR, 2.59; 95% CI, 1.04–6.46; $P = 0.04$) can be perceived as independent risk factors for mortality. **Conclusion:** Our results suggest that patients with older age, lower oxygen saturation, and hypertension are predisposed to an increased risk of mortality. Thus, to lower the COVID-19 mortality rates, patients with these characteristics should be the primary targets for early treatment, vaccination, or monitoring strategies.

Keywords: Coronavirus disease 2019, mortality, risk factor, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19), which first emerged from China in December 2019,[1] has since grown to be one of the deadliest pandemics in recent history and as of February 21, 2021, has infected more than 110 million and caused more than 2.4 million deaths.[2] Despite rigorous worldwide efforts to contain the pandemic, it is still spreading throughout the world and no definitive treatment is available.

SARS-CoV-2, the virus responsible for COVID-19, is a member of coronavirus family (the same virus family responsible for SARS and MERS outbreaks) and uses angiotensin-converting enzyme 2 (ACE2) for cell entry.[3] General symptoms are fever, cough, and fatigue,[4] but because of the wide distribution of ACE2 throughout the body and the multifactorial nature of COVID-19 pathogenesis encompassing inflammation, endothelial function, and coagulation,[5] far more diverse clinical symptoms have been reported showcasing cardiac, kidney, liver, digestive tract, and nervous system injuries.[6]

Unfortunately, the current high COVID-19 mortality rates in Iran show that a lot of areas regarding screening, monitoring, treatment, and preventive strategies are in dire need of improvement. Analyzing the epidemiological, clinical, and laboratory characteristics of COVID-19 patients is crucial for screening and treatment strategy development and could be very helpful in early identification of patients who are predisposed to a higher risk of mortality. This ensures that

Address for correspondence: Dr. Sara Minaeian, Antimicrobial Resistance Research Center, Institute of Immunology and Infectious Diseases, Floor 3, Building no. 3, Hazrat-e Rasool General Hospital, Niyayesh St, Sattar Khan St, 1445613131, Tehran, Iran.
E-mail: sara.minaeian@gmail.com

Received: 07-Apr-2021 **Revised:** 24-Aug-2021
Accepted: 25-Aug-2021 **Published:** 30-Dec-2021

Access this article online

Quick Response Code:

Website: http://iahs.kaums.ac.ir

DOI: 10.4103/iahs.iahs_66_21

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Bahadorizadeh L, Fard SR, Behnagh AK, Hashemi Kiapey SA, Saneii SH, Minaeian S. Risk factors for mortality in hospitalized moderate-to-severe COVID-19 patients: A single-center retrospective study. Int Arch Health Sci 2021;8:267-73.

Downloaded from http://journals.lww.com/iahs by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

the medical and national resources are being used with utmost efficiency. Studies show that COVID-19 mortality risk factors include old age, hypertension, obesity, and decreased oxygen saturation.[7,8] As similar studies are scarce regarding the local population,[9,10] the current study was designed to evaluate the differences in epidemiological, comorbidities, clinical, and laboratory characteristics between deceased and discharged COVID-19 patients that were admitted to Firoozabadi General Hospital in Tehran between March and April of 2020.

Materials and Methods

The present study was a cross-sectional study that has been performed on 223 hospitalized cases of COVID-19 who were admitted to Firoozabadi General Hospital (Tehran, Iran) from March 1 to April 1, 2020. Patients' relevant data were extracted from the hospital digital records. For the purposes of this study, based on the clinical outcome, subjects were divided into two groups: (1) discharged and (2) deceased.

Patient inclusion criteria were based on national guidelines and were consisted of having three or more of the following symptoms: (1) cough, (2) weakness, (3) fever of ≥38.5°C, (4) intense fatigue, (5) myalgia, (6) sore throat, (7) dyspnea, (8) low appetite/diarrhea/nausea, and (9) decreased awareness or having one or more of the following disease characteristics: (1) oxygen saturation value of <93%, (2) disease confirmation based on chest imaging results, and (3) a respiratory rate >24 breaths per min.

Disease severity classification was also based on national guidelines. Moderate disease severity was designated as having one or more of the following: (1) presence of respiratory symptoms (dyspnea and feeling of pain or pressure in chest), (2) oxygen saturation value between 90% and 93%, and (3) lung involvement of <50%. Severe disease severity was designated as having one or more of the following: (1) rapid progression of respiratory symptoms (dyspnea in particular), (2) respiratory rate of more than 30 breaths per min, (3) oxygen saturation value of <90%, and (4) lung involvement of more than 50%.

All selected patients had a positive SARS-CoV-2-specific reverse transcription polymerase chain reaction test result, and patients with negative test results were excluded from the study.

This study was reviewed and approved by the Scientific Advisory and Ethical Committees of Iran University of Medical Sciences (registration number: IR.IUMS.REC.1399.013) and conforms to the principles of Helsinki declaration.

Clinical, laboratory, and epidemiological data of the patients were collected including age, gender, hospitalization period, blood pressure, respiratory rate, body temperature, peripheral oxygen saturation, erythrocyte sedimentation rate, C-reactive protein (CRP), complete blood count, prothrombin time, partial thromboplastin time, creatinine, potassium, magnesium, alanine transaminase (ALT), aspartate aminotransferase, and troponin. Cell counts and biochemical analysis were conducted using a Sysmex KX21N (Sysmex, Kobe, Japan) and Hitachi 912 Autoanalyzer (Roche Diagnostics GmbH, Germany), respectively.

Patient chest imaging results and baseline comorbidities, including hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular accident (CVA), lung diseases, and malignancies, were also collected. Chest imaging was conducted using a 16-row spiral computed tomography (CT) scanning device (Siemens AG). Any documented additional or necessary administered drugs and therapeutic procedures were also collected from the hospital digital database.

Descriptive statistics (e.g., mean and standard deviation or median and interquartile range [IQR] and simple proportions) were used to describe the data. The Kolmogorov–Smirnov test was used to assess the presence of normal distribution in data. According to the presence of normal distribution, the Student's *t*-test or Mann–Whitney U test were used to compare the mean scores between different subgroups. To compare proportions between different groups, the Chi-square or Fisher's exact test was used. Furthermore, the multiple logistic regression model was used to assess effective factors on the final status of COVID-19 cases after treatment (death, discharge). $P < 0.05$ was considered a statistical significance level. All analyses were performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA).

Results

Two hundred and twenty-three moderate-to-severe confirmed COVID-19 patients were enrolled in this study. The study population were predominantly male (132 [59.2%]), and the mean age was 58.52 ± 18.1 years. As this study was conducted in the early days of the pandemic, the mortality rates were quite high, and in our study population, 56 (25.1%) patients had perished. Analysis of basic characteristic data revealed that patients in the deceased group were significantly older than patients in the discharged group (68.96 ± 14.31 vs. 55.01 ± 17.91 years, $P = 0.01$). Furthermore, respiratory rate at admission date was also higher in the deceased group (19.11 ± 5.14 vs. 17.55 ± 3.70 breaths per min, $P = 0.02$) [Table 1].

In our study population, 57% of patients were suffering from one or more underlying condition including diabetes mellitus (32.7%), hypertension (31.8%), ischemic heart disease (20.2%), lung disease (8.5%), CVA (3.1%), and cancer (2.7%). Univariate analysis showed that hypertension (27 [48.2%] vs. 44 [26.3%], $P = 0.01$) and cancer (5 [8.9%] vs. 1 [0.6%], $P = 0.01$) were more frequent in the deceased group. In addition, a higher number of patients in the deceased group experienced dyspnea (49 [87.5%] vs. 119 [71.3%], $P = 0.01$) and neurological (15 [26.8%] vs. 23 [13.8%], $P = 0.02$) symptoms. Furthermore, weak myalgia (17 [30.4%] vs. 78 [46.7%], $P = 0.03$) and gastrointestinal symptoms (6 [10.7] vs. 38 [22.8], $P = 0.05$) were less frequent in the deceased group compared to the discharged group [Table 1].

Downloaded from http://journals.lww.com/iahs by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Table 1: Baseline characteristics, comorbidities, and admission symptoms of moderate-to-severe hospitalized coronavirus disease 2019 patients

	Discharged	Deceased	*P*
Gender (male)	103 (61.7)	29 (51.8)	0.19
Age[a]	55.01±17.91	68.96±14.31	0.01
Blood pressure[a]	124.54±18.30	125.70±26.20	0.72
Respiratory rate[a]	17.55±3.70	19.11±5.14	0.02
Temperature[a]	37.33±0.67	37.34±0.75	0.96
Hospitalization period[a]	5.67±3.95	5.21±3.39	0.47
Diabetes	53 (31.7)	20 (35.7)	0.58
Hypertension	44 (26.3)	27 (48.2)	0.01
CVA	4 (2.4)	3 (5.4)	0.27
IHD	33 (19.8)	12 (21.4)	0.79
Lung disease	12 (7.2)	7 (12.5)	0.22
Cancer	1 (0.6)	5 (8.9)	0.01
Dyspnea	119 (71.3)	49 (87.5)	0.01
Fever/chill	98 (58.7)	27 (48.2)	0.17
GI symptoms	38 (22.8)	6 (10.7)	0.05
Weak myalgia	78 (46.7)	17 (30.4)	0.03
URTI	12 (7.2)	4 (7.1)	0.99
Neurological symptoms	23 (13.8)	15 (26.8)	0.02
Chest paint	10 (6)	4 (7.1)	0.76
Cough			
No cough	58 (34.7)	24 (42.9)	0.29
Dry	97 (58.1)	26 (46.4)	
Productive	12 (7.2)	6 (10.7)	

[a]Data are presented as mean±SD. Data are presented as *n* (%).
CVA: Cerebrovascular Accident, IHD: Ischemic heart disease, GI: Gastrointestinal, URTI: Upper respiratory tract infection, SD: Standard deviation

Analysis of paraclinical test results revealed that in comparison to the discharged group, patients in the deceased group had higher neutrophil (8067.26 ± 4325.97 vs. 4983.43 ± 3090.20, $P = 0.01$), total white blood cell (9797.35 ± 4709.90 vs. 6882.38 ± 3230.75, $P = 0.01$), and neutrophil-to-lymphocyte ratio (9.86 ± 8.48 vs. 5.56 ± 6.82, $P = 0.01$). Despite that there was no significant difference in lymphocyte count between the study groups, lymphopenia (<1.1 × 10^9/L) was much more frequent in the deceased group (32 [65%] vs. 61 [43%], $P = 0.01$). These patients also had lower oxygen saturation (80.67 ± 14.23 vs. 90.69 ± 6.62, $P = 0.01$) on admission date and were more likely to have coagulation abnormalities ($P = 0.04$) [Table 2]. Furthermore, analysis of the existing laboratory test results revealed that patients in the deceased group were more likely to have higher CRP (65 median [IQR 86–31] vs. 35 median [IQR 63-14], $P = 0.01$), troponin (51.25 median [IQR 119.15–20.05] vs. 6.2 median [IQR 23-1.6], $P = 0.01$), and aspartate transaminase (AST) (53 median [IQR 99-37] vs. 32.5 median [IQR 64.75-25.25], $P = 0.01$) values. Although not reaching clinical significance, similar to AST, ALT was also generally higher in the deceased group (35 median [IQR 63-21] vs. 25 [IQR 43-15.25], $P = 0.06$), which is indicative of significant liver injury [Table 3]. In addition, no differences were observed in the frequency of chest imaging abnormalities between deceased and discharged groups [Table 2].

The results revealed that a higher number of deceased patients received corticosteroids (Cortone) (9 [16.1%] vs. 12 [7.1%], $P = 0.05$). Furthermore, the need for invasive oxygen support was much higher in the deceased group compared to the discharged group (49 [89.1%] vs. 15 [10.9%], $P = 0.01$) [Table 4].

In addition, the distribution of patients receiving no antibiotic treatment or receiving one, two, or three antibiotics was not significantly different between the study groups (three different types of antibiotics (56 patients [33.5%] vs. 27 patients [48.2%]) and no antibiotic treatment (26 patients [15.6%] vs. 5 patients [8.9%]) being the highest and lowest proportions for discharged and deceased groups respectively, $P = 0.08$). Similarly, no differences in the distribution of patients receiving no antiviral treatment and patients receiving single or combinational antiviral therapy were observed in the study groups (Kaletra/Tamiflu 91 [54.5%] vs. 31 [56.4%] and Kaletra/ribavirin [1 (0.6%) vs. 0] being the highest and lowest proportions for discharged and deceased groups respectively, $P = 0.28$) [Table 4].

Furthermore, the number and proportion of patients receiving intravenous immune globulin (0 vs. 2 [3.6%] for discharged and deceased groups, respectively, $P = 0.06$) and chloroquine (121 [72.5%] vs. 35 [62.5%], $P = 0.16$) were not statistically different between the study groups.

Based on initial symptoms and clinical characteristics of our study population, 86 patients matched the severe disease profile and 137 patients matched the moderate disease profile. Data analysis based on disease severity revealed that severe patients were older (62.65 ± 17.22 vs. 55.92 ± 18.21 years, $P = 0.01$), and a lower proportion of them suffered from CVA (0% vs. 5.1%, $P = 0.05$). Comparison of initial symptoms showed that more patients in the severe group suffered from dyspnea (86% vs. 68.6%, $P = 0.01$), and their respiratory rates were higher compared to the moderate group (19.36 ± 5.10 vs. 17.06 ± 3.14, $P = 0.01$) [Supplementary Table 1].

In addition, peripheral oxygen saturation was significantly lower in the severe group (79.84 ± 11.82 vs. 93.38 ± 2.51, $P = 0.01$), while white blood cell count, neutrophil count, and neutrophil-to-lymphocyte ratio (8952.44 ± 4700.93 vs. 6724.49 ± 2873.80, $P = 0.01$; 7209.49 ± 4556.96 vs. 4979.59 ± 2855.79, $P = 0.01$; and 8.77 ± 9.43 vs. 5.26 ± 5.50, $P = 0.01$, respectively) were found to be significantly higher compared to the moderate group. Moreover, abnormalities in coagulative processes were more frequent in the severe group ($P = 0.04$) [Supplementary Table 2]. Analysis of laboratory data revealed that patients in the severe group had higher troponin levels compared to the moderate group (27.65 median [IQR, 7.25–84] vs. 6.9 median [IQR, 1.75–27.45]) [Supplementary Table 3].

Furthermore, patients in the severe group were more likely to need invasive and noninvasive supplementary oxygen

Downloaded from http://journals.lww.com/ians by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Table 2: Paraclinical test results and chest imaging abnormalities of moderate-to-severe hospitalized coronavirus disease 2019 patients

	Discharged	Deceased	*P*
Lymphopenia (<1.1×10⁹/L)[a]	61 (43)	32 (65)	0.01
Neutrophilia (>7×10⁹/L)[a]	31 (22)	23 (47)	0.01
Lymphocyte	1348.05±764.06	1157.67±997.73	0.17
Neutrophil	4983.43±3090.20	8067.26±4325.97	0.01
PTT	41.44±21.87	41.29±12.02	0.11
PT	14.35±2.74	14.52±2.24	0.3
Oxygen saturation	90.69±6.62	80.67±14.23	0.01
WBC	6882.38±3230.75	9797.35±4709.90	0.01
Hb	13.73±2.033	13.46±2.123	0.42
Platelet	212.76±94.53	209.67±90.55	0.84
Neutrophil/lymphocyte ratio	5.56±6.82	9.86±8.48	0.01
Coagulopathy			
Negative[a]	50 (51.5)	15 (35.7)	0.04
PT[a]	32 (33)	14 (33.3)	
PTT[a]	7 (7.2)	2 (4.8)	
Both[a]	8 (8.2)	11 (26.2)	
Chest imaging abnormalities			
Negative[a]	63 (38)	21 (37)	0.37
GG[a]	25 (15)	12 (21)	
Consol[a]	4 (2)	2 (3)	
GG + consolidation[a]	74 (44)	20 (36)	
GG + reticular[a]	0	1 (2)	
GG + consolidation + reticular[a]	1 (0.5)	0	

[a]Data are presented as *n* (%). Data are presented as mean±SD. PTT: Partial thromboplastin time, PT: Prothrombin time, Hb: Hemoglobin, GG: Ground glass, SD: Standard deviation, WBC: White blood cell

support (P = 0.01) and succumb to the disease (46.5% vs. 11.7%, P = 0.01) [Supplementary Table 4].

The results of the multiple logistic regression model suggest that advanced age (odds ratio [OR], 1.06; 95% CI, 1.02–1.09; P = 0.01) and hypertension (OR, 2.59; 95% CI, 1.04–6.46; P = 0.04) can increase the chance of mortality in COVID-19 patients. Furthermore, we found that oxygen saturation has a reverse relationship with mortality as a higher oxygen saturation reduced the chance of mortality in our study population (OR, 0.92; 95% CI, 0.87–0.96; P = 0.01) [Table 5].

Discussion

Currently, countries all around the world are struggling to deal with the devastating effects of COVID-19 pandemic.[11,12] It has spread to more than 110 million people around the world with no sign of slowing down. There has been a great deal of concern regarding the high mortality rates of COVID-19 in Iran in the recent months, and identifying the risk factors in the local population can be very useful in early identification and treatment of patients whom are predisposed to a higher risk of mortality.

In the current study, out of the 223 moderate-to-severe COVID-19 patients that were included in the study, 56 have died. Analysis of epidemiological data revealed that patients in the deceased group were older and more frequently suffered from comorbidities such as hypertension and cancer. Furthermore, these patients more frequently experienced neurological symptoms and dyspnea and in contrast less likely to have gastrointestinal symptoms and myalgia upon admission. In addition, they had lower peripheral oxygen saturation and higher neutrophil-to-lymphocyte ratio and during the hospitalization period were more likely to need invasive supplementary oxygen support. Our Multiple Logistic Regression Model showed that age, peripheral oxygen saturation, and hypertension can act as independent risk factors for mortality.

Advanced age is probably the most well-known risk factor for COVID-19 mortality as it has been consistently reported as such in almost every risk assessment study.[7,8] Although the exact underlying mechanisms responsible for higher mortality rate in older population are still not fully understood, but it has been suggested that this might be the result of cumulative effects of multiple different phenomena such as endothelium and clotting functions, immunosenescence, inflammaging, comorbidities, and mitochondrial dysfunction in older patients.[13,14] A recent study conducted by Ho *et al*.[15] found that advanced age can increase the mortality risk by 13-fold. The authors further reported that even in older populations with no other underlying risk factors, the mortality rate is still 4 times higher than the general population. Our results also demonstrate that patients who have died due to COVID-19 complications were significantly older that patients who survived. These evidence

Downloaded from http://journals.lww.com/iahs by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Table 3: Paraclinical test results of moderate-to-severe hospitalized coronavirus disease 2019 patients

	Sample size	Median (IQR)	*P*
ESR			
Discharged	95	42 (29-58)	0.59
Deceased	40	43.5 (28.5-64)	
CRP (mg/L)			
Discharged	119	35 (14-63)	0.01
Deceased	41	65 (31-86)	
Cr (mg/dL)			
Discharged	137	1.1 (1-1.4)	0.09
Deceased	50	1.35 (1-1.8)	
K (mEq/L)			
Discharged	137	4.1 (3.8-4.5)	0.92
Deceased	50	4.15 (3.78-4.8)	
Mg (mg/dL)			
Discharged	90	2.1 (2-2.3)	0.94
Deceased	32	2.1 (2-2.3)	
ALT			
Discharged	96	25 (15.25-43)	0.06
Deceased	35	35 (21-63)	
AST			
Discharged	96	32.5 (25.25-64.75)	0.01
Deceased	35	53 (37-99)	
Troponin			
Discharged	59	6.2 (1.6-23)	0.01
Deceased	30	51.25 (20.05-119.15)	

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Cr: Creatinine, K: Potassium, Mg: Magnesium, ALT: Alanine transaminase, AST: Aspartate aminotransferase, IQR: Interquartile range

Table 4: Medications and supportive procedures administered during hospitalization period

	Discharged	Deceased	*P*
Cortone	12 (7.1)	9 (16.1)	0.05
IVIG	0	2 (3.6)	0.06
Chloroquine	121 (72.5)	35 (62.5)	0.16
Anti-biotic drugs			
Negative	26 (15.6)	5 (8.9)	0.08
One type	33 (19.8)	5 (8.9)	
Two types	52 (33.1)	19 (33.9)	
Three types	56 (33.5)	27 (48.2)	
Anti-viral drugs			
Negative	23 (13.8)	4 (7.3)	0.28
Kaletra	28 (16.8)	7 (12.7)	
Tamiflu	18 (10.8)	7 (12.7)	
Kaletra/Tamiflu	91 (54.5)	31 (56.4)	
Kaletra/ribavirin	1 (0.6)	0	
Kaletra/Tamiflu/ribavirin	6 (3.6)	6 (10.9)	
Oxygen support			
Noninvasive	123 (89.1)	6 (10.9)	0.01
Invasive	15 (10.9)	49 (89.1)	

Data are presented as *n* (%). IVIG: Intravenous immunoglobulin

corroborate the fact that older patients should be the priority in monitoring, therapeutic, or vaccination strategies.

Another well-documented characteristic for severe COVID-19 is reduced oxygen saturation. This is due to SARS-CoV-2 binding to ACE2 receptors in lungs and respiratory tract. Hypoxia progression can result in increased viral proliferation, cytokine storm, intravascular coagulation, and pulmonary hypoxic vasoconstriction, which are all characteristics of disease progression and are associated with higher rates of fatal outcome.[16] Comparably, patients in our study with reduced oxygen saturation were at a higher risk of mortality. In these patients, mitigating hypoxia through oxygen supplementation therapy may reduce the destructive consequences of hypoxia and consequently help reduce the mortality rates.

In the present study, mortality was much higher among patients suffering from hypertension. This is in line with several large-scale studies reporting a significantly higher mortality rate, intensive care unit admission, and severe disease course among patients with preexisting hypertension.[17-19] The exact mechanisms in which hypertension exacerbates the COVID-19 disease are not fully clear yet. Although renin–angiotensin–aldosterone system inhibitors were first thought to be the culprit by overexpressing the ACE2, it has since been proven by multiple studies that these drugs in fact reduce the mortality rate of COVID-19 patients with preexisting hypertension.[19,20] As older patients are more susceptible to hypertension and other comorbidities, timely identification and intervention is vital in controlling the disease severity.

Several other studies have found that neurological symptoms,[21-24] gastrointestinal symptoms,[25,26] cancer,[27,28] and changes in raw count and proportion of lymphocytes and neutrophils[29,30] could also act as predictors for COVID-19 severity and mortality; thus, based on these findings and our own univariate analysis results, we strongly recommend that these symptoms and conditions not be overlooked and should be thoroughly investigated in patients so that appropriate treatments can be administered in time.

This study has several limitations and they should be considered before any interpretations of our results. First, although some of the risk factors that were found to be clinically significant in our univariate analysis were dismissed as independent risk factors in multivariate analysis; this might be duo to our relatively small study population and their importance should not be disregarded. Second, some laboratory tests were not performed for the entirety of the study population and thus were forcefully discarded as they would have damaged the integrity of our statistical analysis. Third, patients in the current study all suffered from moderate-to-severe COVID-19; this has limited the capacity of our statistical models to also assess the mortality risk factors in patients with mild disease. Fourth, patient readmissions were not recorded which may have produced bias in our mortality rate analysis.

Conclusion

In this single-center retrospective cohort study, we found out that older age, decreased peripheral oxygen saturation, and hypertension are independent risk factor for COVID-19 mortality in moderate-to-severe patients. Early identification

Downloaded from http://journals.lww.com/ians by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Table 5: Multiple logistic regression model of risk factors for mortality in moderate-to-severe hospitalized coronavirus disease 2019 patients

	OR (95% CI)	SE	*P*
Age	1.06 (1.02-1.09)	0.02	0.01
Oxygen saturation	0.92 (0.87-0.96)	0.02	0.01
Hypertension			
No	1	-	-
Yes	2.59 (1.04-6.46)	0.47	0.04
Dyspnea			
No	1	-	-
Yes	2.56 (0.83-7.88)	0.57	0.10
GI symptoms			
No	1	-	-
Yes	0.54 (0.17-1.67)	0.58	0.28
Weak myalgia			
No	1	-	-
Yes	0.67 (0.28-1.62)	0.45	0.38
Neurological symptoms			
No	1	-	-
Yes	1.34 (0.44-4.1)	0.57	0.61
Neutrophil/lymphocyte ratio	1.04 (0.99-1.1)	0.03	0.11

GI: Gastrointestinal, OR: Odds ratio, CI: Confidence interval, SE: Standard error

and prioritizing treatments for these patients may help lower the COVID-19 mortality rates.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. World Health Organization. Weekly Epidemiological Update-15 December 2020. Available from: <https://www.who.int/publications/m/item/weekly-epidemiological-update---15-december-2020>. [Last accessed on 2020 Dec 15].
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a Clinically Proven protease inhibitor. Cell 2020;181:271-80.e8.
4. Pormohammad A, Ghorbani S, Baradaran B, Khatami A, J Turner R, Mansournia MA, *et al.* Clinical characteristics, laboratory findings, radiographic signs and outcomes of 61,742 patients with confirmed COVID-19 infection: A systematic review and meta-analysis. Microb Pathog 2020;147:104390.
5. Stein RA, Young LM. From ACE2 to COVID-19: A multiorgan endothelial disease. Int J Infect Dis 2020;100:425-30.
6. Dong M, Zhang J, Ma X, Tan J, Chen L, Liu S, *et al.* ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. Biomed Pharmacother 2020;131:110678.
7. Bertsimas D, Lukin G, Mingardi L, Nohadani O, Orfanoudaki A, Stellato B, *et al.* COVID-19 mortality risk assessment: An international multi-center study. PLoS One 2020;15:e0243262.
8. Núñez-Gil IJ, Fernández-Pérez C, Estrada V, Becerra-Muñoz VM, El-Battrawy I, Uribarri A, *et al.* Mortality risk assessment in Spain and Italy, insights of the HOPE COVID-19 registry. Intern Emerg Med 2021;16:957-66.
9. Zali A, Gholamzadeh S, Mohammadi G, Azizmohammad Looha M, Akrami F, Zarean E, *et al.* Baseline characteristics and associated factors of mortality in COVID-19 patients; an analysis of 16000 cases in Tehran, Iran. Arch Acad Emerg Med 2020;8:e70.
10. Homayounieh F, Zhang EW, Babaei R, Karimi Mobin H, Sharifian M, Mohseni I, *et al.* Clinical and imaging features predict mortality in COVID-19 infection in Iran. PLoS One 2020;15:e0239519.
11. Piltch-Loeb R, Merdjanoff A, Meltzer G. Anticipated mental health consequences of COVID-19 in a nationally-representative sample: Context, coverage, and economic consequences. Prev Med 2021;145:106441.
12. Morgan AK, Awafo BA, Quartey T. The effects of COVID-19 on global economic output and sustainability: Evidence from around the world and lessons for redress. Sustain Sci Pract Policy 2021;17:77-81.
13. Moreno Fernández-Ayala DJ, Navas P, López-Lluch G. Age-related mitochondrial dysfunction as a key factor in COVID-19 disease. Exp Gerontol 2020;142:111147.
14. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Child 2020;106:429-39.
15. Ho FK, Petermann-Rocha F, Gray SR, Jani BD, Katikireddi SV, Niedzwiedz CL, *et al.* Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. PLoS One 2020;15:e0241824.
16. Somers VK, Kara T, Xie J. Progressive hypoxia: A pivotal pathophysiologic mechanism of COVID-19 pneumonia. Mayo Clin Proc 2020;95:2339-42.
17. Barrera FJ, Shekhar S, Wurth R, Moreno-Pena PJ, Ponce OJ, Hajdenberg M, *et al.* Prevalence of diabetes and hypertension and their associated risks for poor outcomes in Covid-19 patients. J Endocr Soc 2020;4:bvaa102.
18. de Almeida-Pititto B, Dualib PM, Zajdenverg L, Dantas JR, de Souza FD, Rodacki M, *et al.* Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: A meta-analysis. Diabetol Metab Syndr 2020;12:75.
19. Rodilla E, Saura A, Jiménez I, Mendizábal A, Pineda-Cantero A, Lorenzo-Hernández E, *et al.* Association of hypertension with all-cause mortality among hospitalized patients with COVID-19. J Clin Med 2020;9:E3136.
20. Ssentongo AE, Ssentongo P, Heilbrunn ES, Lekoubou A, Du P, Liao D, *et al.* Renin-angiotensin-aldosterone system inhibitors and the risk of mortality in patients with hypertension hospitalised for COVID-19: Systematic review and meta-analysis. Open Heart 2020;7:e001353.
21. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series. Brain Behav Immun 2020;88:940-4.
22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, *et al.* Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ 2020;368:m1091.
23. Favas TT, Dev P, Chaurasia RN, Chakravarty K, Mishra R, Joshi D, *et al.* Neurological manifestations of COVID-19: A systematic review and meta-analysis of proportions. Neurol Sci 2020;41:3437-70.
24. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683-90.
25. Tariq R, Saha S, Furqan F, Hassett L, Pardi D, Khanna S. Prevalence and mortality of COVID-19 patients with gastrointestinal symptoms: A systematic review and meta-analysis. Mayo Clin Proc 2020;95:1632-48.
26. Renelus BD, Khoury N, Chandrasekaran K, Bekele E, Briggs WM, Jamorabo DS. Hospitalized coronavirus disease-2019 (COVID-19) patients with gastrointestinal symptoms have improved survival to discharge. Dig Liver Dis 2020;52:1403-6.
27. Crolley VE, Hanna D, Joharatnam-Hogan N, Chopra N, Bamac E, Desai M, *et al.* COVID-19 in cancer patients on systemic anti-cancer therapies: outcomes from the CAPITOL (COVID-19 cancer patient

outcomes in North London) cohort study. Ther Adv Med Oncol 2020;12:1758835920971147.
28. de Joode K, Dumoulin DW, Tol J, Westgeest HM, Beerepoot LV, van den Berkmortel FW, *et al.* Dutch oncology COVID-19 consortium: Outcome of COVID-19 in patients with cancer in a nationwide cohort study. Eur J Cancer 2020;141:171-84.
29. Lu Q, Wang Z, Yin Y, Zhao Y, Tao P, Zhong P. Association of peripheral lymphocyte and the subset levels with the progression and Mortality of COVID-19: A systematic review and meta-analysis. Front Med (Lausanne) 2020;7:558545.
30. Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, *et al.* Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: A systematic review and meta-analysis. Crit Care 2020;24:647.

Downloaded from http://journals.lww.com/ians by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Supplementary Table 1: Comparison of baseline characteristics, comorbidities, and admission symptoms of moderate and severe hospitalized coronavirus disease 2019 patients

	Moderate	Severe	*P*
Gender (male)	88 (64.2)	44 (51.2)	0.06
Age[a]	55.92±18.21	62.65±17.22	0.01
Blood pressure[a]	125.93±20.243	122.96±20.74	0.94
Respiratory rate[a]	17.06±3.14	19.36±5.10	0.01
Temperature[a]	37.34±0.67	37.32±0.72	0.76
Hospitalization period[a]	5.04±3.28	6.37±4.43	0.04
Diabetes	49 (35.8)	24 (27.9)	0.22
Hypertension	43 (31.4)	28 (32.6)	0.85
CVA	7 (5.1)	0	0.05
IHD	28 (20.4)	17 (19.8)	0.9
Lung disease	9 (6.6)	10 (11.6)	0.19
Cancer	5 (3.6)	1 (1.2)	0.41
Dyspnea	94 (68.6)	74 (86)	0.01
Fever/chill	83 (60.6)	42 (48.8)	0.09
GI symptoms	30 (21.9)	14 (16.3)	0.3
Weak myalgia	63 (46)	32 (37.2)	0.2
URTI	9 (6.6)	7 (8.1)	0.66
Neurological symptoms	20 (14.6)	18 (20.9)	0.22
Chest paint	9 (6.6)	5 (5.8)	0.82
Cough			
No cough	49 (35.8)	33 (38.4)	0.92
Dry	77 (56.2)	46 (53.5)	
Productive	11 (8)	7 (8.1)	

[a]Data are presented as mean±SD. Data are presented as *n* (%).
CVA: Cerebrovascular accident, IHD: Ischemic heart disease, GI: Gastrointestinal, URTI: Upper respiratory tract infection, SD: Standard deviation

Downloaded from http://journals.lww.com/ians by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Supplementary Table 2: Comparison of paraclinical test results and chest imaging abnormalities of moderate and severe hospitalized coronavirus disease 2019 patients

	Moderate	Severe	*P*
Lymphopenia (<1.1×10^9/L)[a]	53 (46.1)	40 (52.6)	0.38
Neutrophilia (>7×10^9/L)[a]	21 (18.4)	33 (43.4)	0.01
Lymphocyte	1304.90±664.20	1290.60±1039.97	0.09
Neutrophil	4979.59±2855.79	7209.49±4556.96	0.01
PTT	40.90±21.97	42.03±15.91	0.09
PT	14.16±2.36	14.69±2.80	0.06
Oxygen saturation	93.38±2.51	79.84±11.82	0.01
WBC	6724.49±2873.80	8952.44±4700.93	0.01
Hb	13.68±2.06	13.64±2.05	0.84
Platelet	218.91±99.00	201.78±83.86	0.32
Neutrophil/lymphocyte ratio	5.26±5.50	8.77±9.43	0.01
Coagulopathy			
Negative[a]	44 (57.1)	21 (33.9)	0.04
PT[a]	21 (27.3)	25 (40.3)	
PTT[a]	5 (6.5)	4 (6.5)	
Both[a]	7 (9.1)	12 (19.4)	
Chest imaging abnormalities			
Negative[a]	54 (39.4)	30 (34.9)	0.08
GG[a]	19 (13.9)	18 (20.9)	
Consol[a]	6 (4.4)	0	
GG + consolidation[a]	58 (42.3)	36 (41.9)	
GG + reticular[a]	0	1 (1.2)	
GG + consolidation + reticular[a]	0	1 (1.2)	

[a]Data are presented as *n* (%). Data are presented as mean±SD. PTT: Partial thromboplastin time, PT: Prothrombin time, Hb: Hemoglobin, GG: Ground glass, SD: Standard deviation, WBC: White blood cell

Downloaded from http://journals.lww.com/ians by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Downloaded from http://journals.lww.com/ians by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 06/14/2023

Supplementary Table 3: Comparison of paraclinical test results of moderate and severe hospitalized coronavirus disease 2019 patients

	Sample size	Median (IQR)	*P*
ESR			
Severe	57	40 (23.5-64.5)	0.75
Moderate	78	43 (30.75-75.25)	
CRP (mg/L)			
Severe	58	44 (24.75-72.75)	0.37
Moderate	102	39 (18-67)	
Cr (mg/dL)			
Severe	77	1.2 (1-1.65)	0.26
Moderate	110	1.1 (1-1.42)	
K (mEq/L)			
Severe	76	4.1 (3.8-4.68)	0.77
Moderate	111	4.1 (3.8-4.6)	
Mg (mg/dL)			
Severe	47	2.1 (2-2.3)	0.38
Moderate	75	2.1 (2-2.3)	
ALT			
Severe	54	25 (14-51)	0.86
Moderate	77	26 (18-45.5)	
AST			
Severe	54	42 (26.75-60.5)	0.19
Moderate	77	34 (26.5-52)	
Troponin			
Severe	36	27.65 (7.25-84)	0.01
Moderate	53	6.9 (1.75-27.45)	

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Cr: Creatinine, K: Potassium, Mg: Magnesium, ALT: Alanine transaminase, AST: Aspartate aminotransferase, IQR: Interquartile range

Supplementary Table 4: Comparison of medications and supportive procedures administered to moderate and severe patients during hospitalization

	Moderate	Severe	*P*
Cortone	10 (7.3)	11 (12.8)	0.17
IVIG	0	2 (2.3)	0.15
Chloroquine	92 (67.2)	64 (74.4)	0.25
Anti-biotic drugs			
Negative	23 (16.8)	8 (9.3)	0.17
One type	24 (17.5)	14 (16.3)	
Two types	46 (33.6)	25 (29.1)	
Three types	44 (32.1)	39 (45.3)	
Anti-viral drugs			
Negative	21 (15.4)	6 (7)	0.22
Kaletra	19 (14)	16 (18.6)	
Tamiflu	14 (10.3)	11 (12.8)	
Kaletra/Tamiflu	76 (55.9)	46 (53.5)	
Kaletra/ribavirin	1 (0.7)	0	
Kaletra/Tamiflu/ribavirin	5 (3.7)	7 (8.1)	
Oxygen support			
Noninvasive	94 (83.9)	35 (43.2)	0.01
Invasive	18 (16.1)	46 (56.8)	
Death	16 (11.7)	40 (46.5)	0.01

Data are presented as *n* (%). IVIG: Intravenous immunoglobulin