Comorbidities and Mortality Risk in COVID-19 Infected Patients: A Cross-Sectional Study in North-Eastern Iran

COVID-19 Enfekte Hastalarda Eşzamanlı Hastalık ve Ölüm Riski: Kuzeydoğu İran'da Kesitsel Bir Çalışma

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ABSTRACT Objective: The coronavirus disease-2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2, started in Wuhan, China, and was recognized as a pandemic by the World Health Organization. In Iran, the first confirmed COVID-19 case was officially reported on February 19. The aim of this study was to investigate the epidemiological and clinical characteristics, and comorbid conditions, and determine risk factors for the mortality of COVID-19 patients as well as provide a comparison of the epidemiological features between the 3 waves of COVID-19 in the North-East of Iran from January 21, 2020, to March 20, 2021. **Material and Methods:** The current retrospective epidemiological population-based study was conducted on COVID-19 patients who were admitted to the hospitals affiliated to the Mashhad University of Medical Sciences in Razavi-Khorasan province, Iran. The data were extracted from the Medical Care Monitoring System of the Mashhad University of Medical Sciences. **Results:** In total, 43.6% of subjects had at least one coexisting underlying medical condition. The most common comorbidities were hypertension, diabetes, and cardiovascular diseases with the prevalence of 19.7, 15.1, and 13.3%; respectively. The overall case fatality rate was 15.0%, following a median of 4 days [interquartile range (IQR) 1-10] of hospitalization. The mean±SD and the median (IQR) of age in expired subjects were 67.40±18.27 and 70 (59-81) years; respectively. **Conclusion:** Our results demonstrated that age >60, male sex, loss of consciousness, respiratory distress, having at least one comorbidity, and diabetes were mortality risk factors among COVID-19 patients.

Keywords: COVID-19; comorbidity; mortality; Iran

ÖZET Amaç: Koronavirüs hastalığı-2019 (COVID-19)'a, yeni şiddetli akut solunum sendromu koronavirüs 2 sebep olmuş, Wuhan, Çin'de başlamış ve Dünya Sağlık Örgütü tarafından pandemi olarak tanınmıştır. İran'da, onaylanmış ilk COVID-19 vakası resmi olarak 19 Şubat'ta bildirilmiştir. Bu çalışmanın amacı; COVID-19'un epidemiyolojik ve klinik özelliklerini, eşzamanlı hastalık koşullarını ve COVID-19 hastalarının ölüm risk faktörlerini belirlemenin yanı sıra Kuzeydoğu İran'da 21 Ocak 2020'den 20 Mart 2021'e kadar olan 3 COVID-19 dalgasının epidemiyolojik özelliklerini karşılaştırmaktır. **Gereç ve Yöntemler:** Mevcut retrospektif epidemiyolojik popülasyon bazlı çalışma, İran, Khorasan İli'nde Mashhad Üniversitesi Tıbbi Bilimle'e bağlı hastanelere başvuran COVID-19 hastaları üzerinden yürütülmüştür. Veriler, Mashhad Üniversitesi Tıbbi Bilimler, Tıbbi Bakım İzleme Sistemi'nden alınmıştır. **Bulgular:** Toplamda, hastaların %43,6'sının aynı zamanda altta yatan en az bir tıbbi durumu mevcuttu. En yaygın eşzamanlı hastalıklar, hipertansiyon, diyabet ve kardiyovasküler hastalıklar olup yaygınlık oranları sırasıyla %19,7, 15,1 ve 13,3'tü. Ortalama 4 günlük [çeyrekler arası aralık (ÇAA) 1-10] hastaneye yatışın ardından toplam vaka ölüm oranı %15,0'dı. Ölen hastaların yaş ortalaması±SS 67,40±18,27 ve medyanı (ÇAA) 70 (59-81) idi. **Sonuç:** Sonuçlarımız, COVID-19 hastalarının ölüm risk faktörleri arasında yaşın 60'tan ileri olması, cinsiyetin erkek olması, bilinç kaybı, solunum problemleri, en az bir eşzamanlı hastalık ve diyabet olduğunu göstermiştir.

Anahtar Kelimeler: COVID-19; eşzamanlı hastalık; ölüm; İran

In late December 2019, the coronavirus disease-2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), started in Wuhan, China, and was recognized as a pandemic by the World Health Organization on March 11, 2020.[1,2] SARS-CoV-2, a member of the Coronaviridae family, is a single-stranded positive-sense RNA virus that can cause respiratory tract infections. SARS-CoV-2 transmits through contact droplets and fomites from infected individuals.[3,4] In

recent decades, 2 other significant human infections by the Coronaviridae family viruses were reported: SARS-CoV (severe acute respiratory syndrome) and Middle East respiratory syndrome-Cov.[3,5]

As of 20th February 2022, 422 million confirmed COVID-19 cases, including 5.8 million deaths, have been reported worldwide.[6]

In Iran, the first confirmed COVID-19 case was officially reported on February 19.[7] To date, more than 6 million confirmed COVID-19 cases and more than 130,000 deaths have been identified in Iran.[6] Three nationwide outbreaks have occurred in Iran including the first outbreak (February 2020-May 2020), 2nd outbreak (August 2020-November 2020), and 3rd outbreak (November 2020-January 2021).

The clinical presentation of COVID-19 ranges from asymptomatic to mild or severe symptoms. Common clinical symptoms include fever, headache, dyspnea, cough, myalgia, loss of smell, gustatory dysfunction, and sore throat.[8,9] In severe COVID-19 cases, acute respiratory distress syndrome, sepsis, and multi-system organ failure can occur, which require hospitalization and may lead to death.[8,9] At-risk individuals for critical outcomes include the elderly, male gender, and individuals with underlying conditions, such as diabetes mellitus, hypertension, obesity, cancer, and chronic cardiovascular and respiratory diseases.[10-12] However, severe outcomes can also occur in individuals from all age groups and with no underlying conditions.[11,13]

Identifying the epidemiological features and clinical characteristics, and mortality risk factors of COVID-19 can improve our current understanding of the disease and can contribute to the early diagnosis of COVID-19 cases and identification of the at-risk patients. In addition, comparing the epidemiologic and clinical features between the 3 outbreaks of COVID-19 in this region can be helpful in the decision-making of the health policies for the control and prevention of future epidemics. The aim of this study was to investigate the epidemiological and clinical characteristics, and comorbid conditions, and determine risk factors for the mortality of COVID-19 patients as well as provide a comparison of the epidemiological features between the 3 waves of

COVID-19 in the North-East of Iran from January 21, 2020, to March 20, 2021.

MATERIAL AND METHODS

STUDY DESIGN

The current retrospective epidemiological population-based study was conducted from January 21, 2020 (first wave) to March 20, 2021 (third wave) to determine the characteristics of COVID-19 patients, clinical presentations of COVID-19, and COVID-19 associated factors with mortality during the first, 2nd, and 3rd wave in the COVID-19 patients who were admitted to the hospitals affiliated to the Mashhad University of Medical Sciences in Razavi-Khorasan province, Iran. The study was performed according to the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (date: November 13, 2021, no: IR.MUMS.REC.1400.247).

DATA SOURCE AND STUDY POPULATION

The data were extracted from the Medical Care Monitoring System (MCMC) of the Mashhad University of Medical Sciences. This system was created from the beginning of the COVID-19 pandemic in Iran to monitor COVID-19 inpatients in the country. The data of the MCMC in Razavi-Khorasan province is collected from 6 medical universities/faculties of the province and is being updated continuously 24 hours a day. Moreover, the recorded information in the MCMC is going to be matched with the patients' information in the disease management portal in the deputy of health and Hospital Information System of the medical universities/faculties.

Hospitalized patients with a definitive diagnosis of coronavirus infection by reverse transcriptase-polymerase chain reaction method or through clinical evaluations and admission to public hospitals affiliated to Mashhad University of Medical Sciences in the Razavi-Khorasan province whose information was recorded through MCMC from January 21, 2020, to March 20, 2021, were included in this study. After extraction of the patients' reports from the MCMC system and before statistical analysis of demographics and clinical presentations of patients, data quality

control was performed by researchers and all duplicate reports were excluded.

OUTCOMES

The information and outcomes gathered from the MCMC archive and assessed in this study are as follows: 1) demographic data including gender, age, hospitalization date and duration, comorbidities (such as hypertension, diabetes, cardiovascular disease, pulmonary diseases, kidney disease, cancer, neurologic disease, liver disease, hematologic disease), and patients status (expired or not); 2) clinical presentations of COVID-19 at admission, including respiratory distress, fever, cough, myalgia, neurologic symptoms (headache, loss of consciousness, seizure, paresis, plegia), anorexia, nausea, vomiting, diarrhea, chest pain, abdominal pain, and anosmia/ageusia.

SAMPLING METHOD

With the purpose of reaching more exact results, we sampled a stratified random sample from the patients of first three waves COVID-19 epidemics in Iran from January 21, 2020 to March 20, 2021. Based on Krejcie-Morgan's table of sample size, 383 persons randomly selected from our total population to generate an suitable representative population.

STATISTICAL ANALYSIS

We performed the analyses based on non-missing data, and missing data were not imputed. To check the normal distribution of variables, we used Kolmogorov-Smirnov test. The age, sex and disease presentations were analyzed in overall and over all of the 3 waves of COVID-19 epidemics. The male-to-female ration (sex ratio) and the case fatality rate (CFR) were calculated. We presented continuous and categorical data as mean±SD, median [interquartile range (IQR)], and absolute number (percentage); as appropriate. To compare proportions, we employed the chi-square (χ^2) and Fisher's exact test. A multiple logistic binary regression model evaluated the effect of multiple variables comprised of age, gender, disease early presentations, and comorbidities on the COVID-19 mortality. All of the data were interpreted using IBM SPSS v.26 (SPSS Inc. Chicago, USA). Statistical significance was set at $p \leq 0.05$.

■ RESULTS

ALL PATIENTS

Demographic Data

A total of 80,499 patients were admitted to all hospitals of Mashhad University of Medical Sciences with laboratory/clinical COVID-19 confirmed disease, between January 21, 2020 and March 20, 2021. Of the subjects, 52.4% were male (male-to-female ratio=1.10:1). The mean age of our COVID-19 individuals was 55.67±23.27 with a median of 60 years (IQR 40-74). The most (50,708, 63.0%) of population were >50 years of age. The patients were hospitalized with a median of 3 days (IQR 1-7). In total, 43.6% of subjects had at least one coexisting underlying medical condition. The most common comorbidities were hypertension, diabetes, and cardiovascular diseases (CVD) with the prevalence of 19.7, 15.1, and 13.3%; respectively. The different comorbidities that patients presented before contracting COVID-19, as well as the demographic data are shown in Table 1.

Clinical Presentations

In terms of the pattern of COVID-19 presentation, the most frequently reported presenting symptoms in histories provided at the admission time (emergency room) were respiratory distress (58.2%), fever (36.7%), cough (34.9%), and myalgia (16.3%), loss of conciseness (10.2%); while the less common ones were ageusia (0.5%), paresis (0.5%), plegia (0.2%), and dermatitis (0.2%). Table 2 included the rest of presentations data.

As shown in Table 3, the top 5 most frequent presentations were significantly more prevalent in males than females. Among different age groups, respiratory distress, fever, cough, and myalgia were more reported in patients aged between 61-70; while loss of conciseness was more common in 71-80 years old subjects. The most prevalent presentation in individuals age between 21-30 and older than 31 was respiratory distress, and cough; respectively. On the other hand, fever was the most common reported symptom in patients younger than 20.

TABLE 1: Demographic characteristics of COVID-19 patients.*				
	Wave			
Variable	First wave (n=17,231)	2nd wave (n=25,286)	3rd wave (n=37,982)	Total (n=80,499)
Sex-male	9333 (54.2)	13031 (51.5)	19845 (52.2)	42209 (52.4)
Age	58 (39-72)	61 (42-75)	60 (40-74)	60 (40-74)
Hospitalization duration	3 (1-7)	4 (1-7)	4 (1-7)	3 (1-7)
Age group				
<10	434 (2.5)	1129 (4.5)	3385 (8.9)	4948 (6.1)
11-20	486 (2.8)	647 (2.6)	929 (2.4)	2062 (2.6)
21-30	1460 (8.5)	1572 (6.2)	2007 (5.3)	5039 (6.3)
31-40	2274 (13.2)	2612 (10.3)	3558 (9.4)	8444 (10.5)
41-50	2043 (11.9)	2792 (11)	3910 (10.3)	8745 (10.9)
51-60	2691 (15.6)	3636 (14.4)	5271 (13.9)	11598 (14.4)
61-70	2984 (17.3)	4803 (19)	7285 (19.2)	15072 (18.7)
71-80	2446 (14.2)	4128 (16.3)	6396 (16.8)	12970 (16.1)
81-90	1909 (11.1)	3091 (12.2)	4549 (12)	9549 (11.9)
91<	315 (1.8)	512 (2)	692 (1.8)	1519 (1.9)
Comorbidity				
At least one				
Hypertension	1962 (11.4)	5368 (21.2)	8550 (22.5)	15880 (19.7)
Diabetes	2099 (12.2)	4106 (16.2)	5972 (15.7)	12177 (15.1)
Cardiovascular disease	2112 (12.3)	3314 (13.1)	5301 (14)	10727 (13.3)
Pulmonary diseases (except asthma)	752 (4.4)	977 (3.9)	1272 (3.3)	3001 (3.7)
Asthma	602 (3.5)	658 (2.6)	1060 (2.8)	2320 (2.9)
Kidney disease	517 (3.0)	792 (3.1)	852 (2.2)	2161 (2.7)
Cancer	464 (2.7)	648 (2.6)	923 (2.4)	2035 (2.5)
Neurologic disease	365 (2.1)	579 (2.3)	651 (1.7)	1595 (2.0)
Liver disease	138 (0.8)	236 (0.9)	269 (0.7)	643 (0.8)
Hematologic disease	135 (0.8)	193 (0.8)	239 (0.6)	567 (0.7)
Expired	2154 (12.5)	4192 (16.6)	5773 (15.2)	12119 (15.1)

*Data expressed as n (%), mean (SD) and median (IQR); as appropriate; COVID-19: Coronavirus disease-2019.

TABLE 2: Initial clinical presentations of COVID-19 at admission.*					
	Frequency (%)				
Presentation	First wave (n=17,231)	2nd wave (n=25,286)	3rd wave (n=37,982)	Total (n=80,499)	p value
Respiratory distress	9340 (54.2)	15199 (60.1)	22340 (58.8)	46879 (58.2)	<0.001
Fever	6449 (37.4)	10356 (41)	12717 (33.5)	29522 (36.7)	<0.001
Cough	7398 (42.9)	8604 (34.0)	12124 (31.9)	28126 (34.9)	<0.001
Myalgia	2260 (13.1)	4354 (17.2)	6528 (17.2)	13142 (16.3)	<0.001
Loss of conciseness	1703 (9.9)	3150 (12.5)	3335 (8.8)	8188 (10.2)	<0.001
Chest pain	120 (0.7)	895 (3.5)	1593 (4.2)	2608 (3.2)	<0.001
Headache	149 (0.9)	1132 (4.5)	732 (1.9)	2013 (2.5)	<0.001
Dizziness	71 (0.4)	666 (2.6)	877 (2.3)	1614 (2.0)	<0.001
Anosmia	51 (0.3)	179 (0.7)	324 (0.9)	554 (0.7)	<0.001
Seizure	55 (0.3)	166 (0.7)	323 (0.9)	544 (0.7)	<0.001
Ageusia	25 (0.1)	131 (0.5)	280 (0.7)	436 (0.5)	<0.001
Paresis	16 (0.1)	117 (0.5)	286 (0.8)	419 (0.5)	<0.001
Plegia	10 (0.1)	54 (0.2)	116 (0.3)	180 (0.2)	0.002
Dermatitis	10 (0.1)	39 (0.2)	106 (0.3)	155 (0.2)	<0.001

*Data expressed as n (% within the wave); COVID-19: Coronavirus disease-2019.

| | Respiratory distress | | Fever | | Cough | | Myalgia | | Loss of conciseness | |
Variable	(n=46,879)	p-value	(n=29,522)	p-value	(n=28,126)	p-value	(n=13,142)	p-value	(n=8,188)	p-value
Sex										
Male	24970 (53.3)	HS	15808 (53.5)	HS	14786 (52.6)	NS	6719 (51.1)	HS	4636 (56.6)	HS
Female	21909 (46.7)		13714 (46.5)		13340 (47.4)		6423 (48.9)		3552 (43.4)	
Age group										
<10	1640 (3.5)	HS	2999 (10.2)	HS	1206 (4.3)	HS	223 (1.7)	HS	295 (3.6)	HS
11-20	705 (1.5)		941 (3.2)		671 (2.4)		318 (2.4)		191 (2.3)	
21-30	1883 (4.0)		2027 (6.9)		2100 (7.5)		1069 (8.1)		266 (3.3)	
31-40	4214 (9.0)		3356 (11.4)		3653 (13)		1774 (13.5)		453 (5.6)	
41-50	5037 (10.8)		3269 (11.1)		3691 (13.2)		1753 (13.3)		517 (6.3)	
51-60	7320 (15.7)		4038 (13.8)		4445 (15.9)		2087 (15.9)		966 (11.8)	
61-70	9898 (21.3)		5030 (17.1)		5068 (18.1)		2423 (18.4)		1641 (20.1)	
71-80	8505 (18.3)		4177 (14.2)		3993 (14.3)		1983 (15.1)		1822 (22.3)	
81-90	6385 (13.7)		3027 (10.3)		2761 (9.9)		1334 (10.2)		1645 (20.2)	
91<	986 (2.1)		472 (1.6)		425 (1.5)		174 (1.3)		357 (4.4)	
Comorbidity										
At least 1	22446 (47.9)	HS	12199 (41.3)	HS	11520 (41)	HS	5052 (38.4)	HS	4876 (59.6)	HS
HT	10386 (22.2)	HS	5468 (18.5)	HS	5368 (19.1)	HS	2427 (18.5)	HS	2178 (26.6)	HS
Diabetes	7863 (16.8)	HS	4333 (14.7)	VS	4221 (15.0)	NS	1870 (14.2)	VS	1744 (21.3)	HS
CVD	7131 (15.2)	HS	3315 (11.2)	HS	3304 (11.7)	HS	1531 (11.6)	HS	1433 (17.5)	HS
PD	2340 (5.0)	HS	911 (3.1)	HS	1039 (3.7)	NS	328 (2.5)	HS	494 (6.0)	HS
Cancer	1190 (2.5)	NS	780 (2.6)	NS	534 (1.9)	HS	239 (1.8)	HS	444 (5.4)	HS
Asthma	1819 (3.9)	HS	757 (2.6)	HS	852 (3.0)	NS	317 (2.4)	HS	212 (2.6)	NS
KD	1261 (2.7)	NS	758 (2.6)	NS	586 (2.1)	HS	302 (2.3)	VS	379 (4.6)	HS
ND	922 (2.0)	NS	582 (2.0)	NS	432 (1.5)	HS	190 (1.4)	HS	469 (5.7)	HS
Dialysis	735 (2.3)	S	405 (1.9)	VS	319 (1.6)	HS	153 (1.6)	HS	211 (3.4)	HS
LD	365 (0.8)	NS	227 (0.8)	NS	196 (0.7)	S	94 (0.7)	NS	120 (1.5)	HS
HD	324 (0.7)	NS	260 (0.9)	HS	182 (0.6)	NS	80 (0.6)	NS	73 (0.9)	S
KT	174 (31.6)	NS	118 (32.2)	NS	78 (29.2)	NS	34 (29.1)	NS	60 (31.1)	NS

TABLE 3: Relationship between initial presentations of COVID-19 at admission and demographic data.*

*Data expressed as n (% within category; for sex and age), and n (% within gastrointestinal presentations; for comorbidities); HS: Highly significant (p<0.001); VS: Very significant (p<0.01); S: Significant (p<0.05); NS: Not significant (p>0.05); COVID-19: Coronavirus disease-2019; HT: Hypertension; CVD: Cardiovascular diseases; PD: Pulmonary diseases (except asthma); KD: Kidney diseases; ND: Neurology diseases; LD: Liver diseases; HD: Hematologic diseases; KT: Chemotherapy.

Of people with loss of conciseness, 59.6% had at least one comorbidity. This proportion for respiratory distress, fever, cough, and myalgia was in this order; 47.9%, 41.3%, 41.0%, and 38.4%. Hypertension, diabetes and CVD was the most common comorbidities among the all of presentations.

DISEASE MORTALITY

In all, 12,119 had deceased in our study, as of April 21, 2021. The overall CFR was 15.0%, following a median of 4 days (IQR 1-10) of hospitalization. The mean±SD and the median (IQR) of age in expired subjects were 67.40±18.27 and 70 (59-81) years; respectively.

The gender-based CFR specified that men had a significant higher rate of mortality [16.6% vs 13.4%, p<0.001; odds ratio (OR) 1.29, 95% confidence interval (CI) 1.24-1.34, p<0.001]. The highest age-based CFR were observed in the patients aged over 90 with rate of 31.3% (30.7% vs 32.1%; males vs females). Instead, patients in age group of 21-30 years had the lowest rate of mortality (3.4%).

Age, being male sex, and wave of COVID-19 epidemics, as well as cough, myalgia, respiratory distress, loss of consciousness, dizziness, chest pain, having at least one comorbidity, diabetes, and hypertension were independently associated with the mortality of COVID-19, based on the multivariable binary logistic regression model.

Age >60 was an important predictor of disease mortality (OR 2.51 95% CI 2.39-2.63; p<0.001). Male had a 31% higher probability of death, com-

pared to females. Among the initial reported presentations of COVID-19, loss of consciousness was a prominent predictor of death (OR 3.90 95% CI 3.69-4.13; p<0.05). Furthermore, patients who admitted with reported respiratory distress, experienced higher rates of death (OR 2.11 95% CI 2.01-2.22; p<0.001). The presence of cough, myalgia, dizziness, and chest pain were associated, on the other hand, with a lower risk of mortality. However, fever, alterations of smell and taste (anosmia and ageusia), seizure, paresis, plegia, and dermatitis were accompanied with a lower risk of death, but not significantly.

Of 12,119 deceased subjects, 57.1% had at least one comorbidity, 26.0% hypertension, 21.1% diabetes, and 18.5% CVD. On the other hand, patients with and without at least 1 comorbidity had mortality rate of 19.7% and 11.5%; respectively. In addition, having at least 1 comorbidity increases the rates of mortality (OR 1.39 95% CI 1.31-1.47; p<0.001). Diabetes was associated with an increase in mortality (OR 1.11 95% CI 1.05-1.18; p<0.001), as the diabetic patients had higher rate of mortality, compared to non-diabetic subjects (21.0% vs 13.9%). Mortality of COVID-19 patients with co-existing CVD was higher compared to the healthy ones, but the difference was not statistically significant (20.9% vs 14.2, OR 1.01 95% CI 0.95-1.07; p=0.776). Although hypertensive patients significantly died much more frequently (19.8% vs 13.9%) than normotensive subjects, but according to the binary logistic regression hypertension was associated with lower risk of death (OR 0.86 95% CI 0.81-0.91; p<0.001) (Table 4, Figure 1).

STRATIFIED SAMPLE

Demographic Data

In a stratified random sample consisted of 383 patients; including 196 (male-to-female ratio 1.05:1) men, the most (201, 53.2%) of population were ≤60 years of age. This investigation indicated that the patients had a mean age of 52.5±20.2 and a median of 59.5 (38-72) years. The hospitalization duration had a median of 4 (1-7) days. Among all cases of the sample, 154 (40.2%) had at least 1 chronic underlying medical condition. Hypertension, diabetes, and CVD were the most common with the prevalence of 20.4, 16.2, and 13.1%, respectively (Table 5).

CLINICAL PRESENTATIONS

Respiratory distress (52.2%), fever (40.2%), cough (33.9%), and myalgia (16.7%) were the most prevalent presentations of disease at the time of admission; while the less common were anosmia (0.3%), and paresis (0.8%). The pattern of headache prevalence was significantly different among the waves of COVID-19 epidemic (p=0.008). Excluding the headache, we were unable to find significance differences in the other presentations during the 3 waves of epidemic (Table 6).

DISCUSSION

This study was conducted on 80,499 patients, admitted to all the hospitals of Mashhad University of Medical Sciences with laboratory or clinical COVID-19 confirmed disease, between January 21, 2020, and March 20, 2021, during the 3 outbreaks of the disease in this region. We evaluated the epidemiological and clinical characteristics, and comorbid conditions of these patients, and determined the mortality risk factors of the disease.

In the present study, the mean age of our subjects was 55.67±23.27 with a male-to-female ratio of 1.10:1. The mean age of COVID-19 patients has been previously reported to be between 34 to 63.[10,14,15] This difference can be due to study samples with a different number of participants and different demographics. Similar to our findings, most studies have shown a male predominance among COVID-19 patients.[10,11,15,16] However, there are some reports of female predominance.[14,17,18]

The median of hospitalization of our patients was 3 (IQR 1-7) days and 43.6% of our subjects, had at least one coexisting underlying medical condition. The most common comorbidities were hypertension (19.7%), diabetes (15.1%), and CVD (13.3%), which are in line with previous studies.[10,11,16] A meta-analysis of 12,149 COVID-19 patients reported 31% patients to have comorbidities. Similar to our results, hypertension was the most common (20.93%), followed by heart failure (10.5%), diabetes mellitus (10.4%), and coronary heart disease (8.5%).[16]

Among our subjects, the most common clinical symptoms at the admission time (emergency room)

TABLE 4: Independent predictors associated with mortality: Multivariable binary logistic regression analysis.*					
Subject characteristics	Alive (n=68,380)	Deceased (n=12,119)	Comparison	OR (95% CI)	p value
Age					
<60 years	37979 (55.6)	3390 (28.0)	>60 vs <60	2.51 (2.39-2.63)	<0.001
>60 years	30368 (44.4)	8729 (72.0)			
Mean±SD	53.58±23.44	67.40±18.27	Alive vs Expire	-	<0.001
Median [IQR]	57 [37-72]	70 [59-81]	Alive vs Expire		<0.001
Sex					
Male	35191 (51.5)	6998 (57.7)	M vs F	1.31 (1.26-1.37)	<0.001
Female	33156 (48.5)	5121 (42.3)			
Wave of epidemics					
1st wave of epidemics	15077 (22.1)	2154 (17.8)	-	-	<0.001
2nd wave of epidemics	21091 (30.9)	4192 (34.6)	W2 vs W1	1.15 (1.09-1.20)	
3rd wave of epidemics	32179 (47.1)	5773 (47.6)	W3 vs W1	0.90 (0.86-0.94)	
Early presentations					
Fever					
No	42769 (62.6)	8176 (67.5)	Y vs N	1.00 (0.95-1.04)	0.852
Yes	25577 (37.4)	3943 (32.5)			
Cough					
No	43663 (63.9)	8678 (71.6)	Y vs N	0.94 (0.89-0.98)	0.007
Yes	24683 (36.1)	3441 (28.4)			
Myalgia					
No	56640 (82.9)	10683 (88.2)	Y vs N	0.86 (0.81-0.92)	<0.001
Yes	11706 (17.1)	1436 (11.8)			
Respiratory distress					
No	30431 (44.5)	3176 (26.2)	Y vs N	2.11 (2.01-2.22)	<0.001
Yes	37915 (55.5)	8943 (73.8)			
Loss of consciousness					
No	63397 (92.8)	8897 (73.4)	Y vs N	3.90 (3.69-4.13)	<0.05
Yes	4949 (7.2)	3222 (26.6)			
Anosmia					
No	66086 (99.2)	11965 (99.6)	Y vs N	0.95 (0.66-1.38)	0.796
Yes	505 (0.8)	49 (0.4)			
Seizure					
No	65425 (99.3)	11898 (99.4)	Y vs N	0.88 (0.66-1.17)	0.388
Yes	477 (0.7)	66 (0.6)			
Ageusia					
No	65510 (99.4)	11920 (99.6)	Y vs N	0.85 (0.57-1.26)	0.419
Yes	392 (0.6)	44 (0.4)			
Dizziness					
No	59436 (97.6)	10971 (98.5)	Y vs N	0.69 (0.59-0.82)	<0.001
Yes	1445 (2.4)	169 (1.5)			
Paresis					
No	60529 (99.4)	11073 (99.4)	Y vs N	0.79 (0.60-1.05)	0.101
Yes	352 (0.6)	67 (0.6)			
Plegia					
No	60739 (99.8)	11102 (99.7)	Y vs N	0.90 (0.61-1.33)	0.599
Yes	142 (0.2)	38 (0.3)			
Chest pain					
No	58529 (96.1)	10884 (97.7)	Y vs N	0.60 (0.53-0.69)	<0.001
Yes	2352 (3.9)	256 (2.3)			
Dermatitis					
No	60734 (99.8)	11132 (99.9)	Y vs N	0.54 (0.26-1.12)	0.096
Yes	147 (0.2)	8 (0.1)			
Comorbidities					
Having at least one					
No	40169 (58.8)	5200 (42.9)	Y vs N	1.39 (1.31-1.47)	<0.001
Yes	28178 (41.2)	6919 (57.1)			
Diabetes					
No	58730 (85.9)	9560 (78.9)	Y vs N	1.11 (1.05-1.18)	0.001
Yes	9617 (14.1)	2559 (21.1)			
Hypertension					
No	55616 (81.4)	8970 (74.0)	Y vs N	0.86 (0.81-0.91)	<0.001
Yes	12731 (18.6)	3149 (26.0)			
Cardiovascular disease					
No	59858 (87.6)	9882 (81.5)	Y vs N	1.01 (0.95-1.07)	0.776
Yes	8489 (12.4)	2237 (18.5)			

*Data are expressed as n (% within alive/deceased group, as appropriate). Sum of each category percents can be greater than 100, due the round numbers; OR: Odds ratio; CI: Confidence interval; SD: Standard deviation; IQR: Interquartile range. **Model:** Age, sex, wave of epidemics, fever, cough, myalgia, respiratory distress, loss of consciousness, anosmia, seizure, ageusia, dizziness, paresis, plegia, chest pain, dermatitis, comorbidities, having at least one comorbidity, diabetes, hypertension, cardiovascular disease.
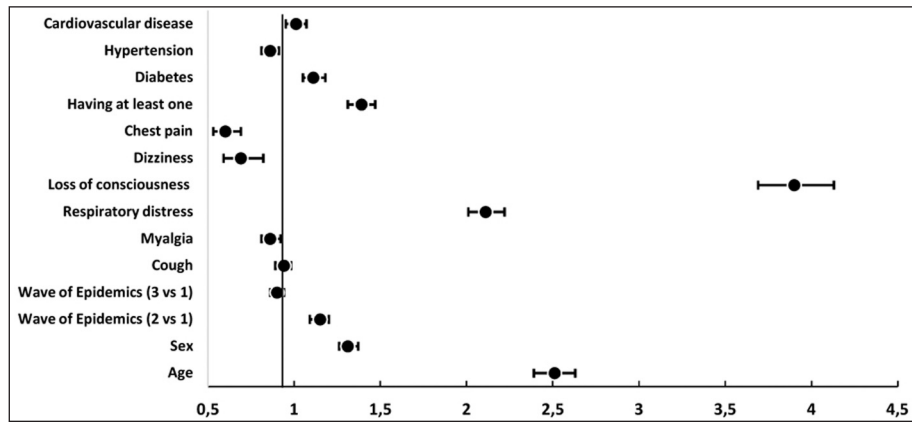
FIGURE 1: Independent predictors associated with mortality: Multivariable binary logistic regression analysis.

	Wave			
TABLE 5: Demographic characteristics of COVID-19 in-patients (based on stratified random sample).*				
Variable	First wave (n=82)	2ⁿᵈ wave (n=120)	3ʳᵈ wave (n=181)	Total (n=383)
Sex-male	41 (50)	63 (52.5)	92 (50.8)	196 (51.2)
Age	55 [36-68]	60 [40-74]	60 [38-74]	59.5 [38-72]
Hospitalization duration	5 [1-8]	4 [0.5-6]	3 [1-6.5]	4 [1-7]
Age group				
<10	2 (2.4)	7 (5.8)	22 (12.2)	31 (8.1)
11-20	2 (2.4)	1 (0.8)	4 (2.2)	7 (1.8)
21-30	7 (8.5)	6 (5)	7 (3.9)	20 (5.2)
31-40	16 (19.5)	17 (14.2)	17 (9.4)	50 (13.1)
41-50	7 (8.5)	13 (10.8)	18 (9.9)	38 (9.9)
51-60	14 (17.1)	16 (13.3)	25 (13.8)	55 (14.4)
61-70	18 (22)	21 (17.5)	36 (19.9)	75 (19.6)
71-80	10 (12.2)	19 (15.8)	34 (18.8)	63 (16.4)
81-90	4 (4.9)	14 (11.7)	16 (8.8)	34 (8.9)
91<	1 (1.2)	2 (1.7)	2 (1.1)	5 (1.3)
Comorbidity				
Hypertension	7 (8.5)	31 (25.8)	40 (22.1)	78 (20.4)
Diabetes	12 (14.6)	18 (15)	32 (17.7)	62 (16.2)
Cardiovascular disease	7 (8.5)	15 (12.5)	28 (15.5)	50 (13.1)
Expired	15 (18.3)	21 (17.5)	25 (13.8)	61 (15.9)

*Data expressed as n (%), and median [IQR]; as appropriate; IQR: Interquartile range; COVID-19: Coronavirus disease-2019.

were respiratory distress (58.2%), fever (36.7%), cough (34.9%), and myalgia (16.3%), loss of conciseness (10.2%); while the less common ones were anosmia (0.7%), ageusia (0.5%), paresis (0.5%), plegia (0.2%), and dermatitis (0.2%). Interestingly, the top 5 frequent presentations were more prevalent in male subjects than females. Previous studies have also found respiratory distress, fever, and cough to be among the most commonly reported symptoms.[10,11,16,19] A meta-analysis of 281,461 COVID-19

patients showed the most common symptom to be fever (78.8%), followed by cough (53.9%) and malaise 37.9%.[20] In our study anosmia and ageusia were much less prevalent than previous reports, which reported anosmia and ageusia to be between 5-48%, and 5-24% respectively.[19,21,22]

In terms of age patterns, respiratory distress, fever, cough, and myalgia were more reported in patients aged between 61-70; while loss of conciseness was more common in 71-80 years old subjects. The

TABLE 6: Initial clinical presentations of COVID-19 at admission (based on stratified random sample).*					
	Frequency (%)				
Presentation	First wave (n=82)	2nd wave (n=120)	3rd wave (n=181)	Total (n=383)	p value
Respiratory distress	38 (46.3)	72 (60)	90 (49.7)	200 (52.2)	0.11
Fever	34 (41.5)	57 (47.5)	63 (34.8)	154 (40.2)	0.09
Cough	32 (39)	44 (36.7)	54 (29.8)	130 (33.9)	0.26
Myalgia	11 (13.4)	24 (20)	29 (16)	64 (16.7)	0.44
Loss of conciseness	10 (12.2)	14 (11.7)	17 (9.4)	41 (10.7)	0.73
Chest pain	0 (0)	7 (5.8)	4 (2.2)	11 (2.9)	0.11
Headache	0 (0)	0 (0)	4 (2.2)	4 (1)	<0.01
Dizziness	0 (0)	0 (0)	4 (2.2)	4 (1)	0.19
Paresis	0 (0)	2 (1.7)	1 (0.6)	3 (0.8)	0.71
Anosmia	0 (0)	1 (0.8)	0 (0)	1 (0.3)	0.52

*Data expressed as n (%); COVID-19: Coronavirus disease-2019.

most prevalent presentation in individuals aged between 21-30 and older than 31 was respiratory distress, and cough; respectively. On the other hand, fever was the most common reported symptom in patients younger than 20. These results are in line with several studies reporting a difference in COVID-19 symptoms according to different age groups.[11,23]

Overall, 12,119 of our subjects had deceased, as of April 21, 2021, resulting in an overall CFR of 15.0%, following a median of 4 (IQR 1-10) days of hospitalization. Previous studies in Iran reported a mortality rate of 1.8-10.8%.[10,23] Studies from around the world reported a mortality rate of 2.5-18%.[13,24,25] The difference in the reported mortality rate might be due to health care systems and the difference in the demographics of the evaluated subjects. The mean age of the expired subjects was 67.40±18.27, with the highest and lowest age-based CFR of 31.3% in patients aged over 90 years and 3.4% in patients aged 21-30 years. These results are in line with previous reports, which show increasing age increases the fatality of the disease.[11,19,25-28] Gender-based CFR demonstrated a higher mortality rate in men as compared to women. Most studies show a higher mortality rate in men than women.[26,28] However, a study among 500 hospitalized patients in Tehran, Iran reported women to be at a higher risk of mortality.[19]

In terms of mortality predictors, age >60, male sex, loss of consciousness, respiratory distress, were associated with a higher risk of death whereas cough, myalgia, dizziness, and chest pain were associated with a lower risk of mortality. A study conducted on 162,045 COVID-19 patients in Brazil showed older age, male gender, respiratory distress, and dyspnea to be associated with poor prognosis.[29] In contrast with our findings, a meta-analysis showed no significant differences between the nonsurvivor and survivor groups in terms of presenting symptoms.[20]

Of the deceased subjects, 57.1% had at least one comorbidity, 26.0% hypertension, 21.1% diabetes, and 18.5% CVD. In support of previous reports, our results indicated that having at least one comorbidity increases the rates of mortality.[11,26] Among the comorbidities, diabetes was a significant mortality predictor in our study. In support of our findings, diabetes has been widely suggested by previous studies as a mortality and poor outcome predictor among COVID-19 patients.[30-32] Moreover, mortality of COVID-19 patients with co-existing CVD was higher compared to the healthy ones, but we did not find a statistically significant difference. Similar to our findings, three studies conducted in Georgia, Brazil, and Italy, reported CVD patients to have a higher mortality rate, but they did not detect CVD as a significant mortality predictor.[25,29,33] CDC states that diabetes and cardiovascular diseases increase the risk of severe disease among COVID-19 patients.[34] In addition, CDC describes hypertension to have "mixed evidence" as a risk factor for severe disease.[34] In our study, although hypertensive patients significantly died much more frequently (19.8% vs 13.9%) than

normotensive subjects, but according to the binary logistic regression, hypertension was associated with a lower risk of death. A meta-analysis evaluating the mortality predictors among COVID-19 patients showed age ≥50, male gender, kidney disease, cerebrovascular disease, CVD, respiratory disease, diabetes, hypertension, and cancer to increase the risk of mortality.[35]

Our study was limited by the absence of biochemical tests and imaging studies of our subjects, which may have limited the factors shown to be associated with the disease mortality. In addition, the vaccination status of the participants was not included. However, the large sample size and multicentric approach of our study were among its strong points.

CONCLUSION

In conclusion, our study provides an overview of the epidemiological and clinical characteristics, and co-morbid conditions of COVID-19 patients in Mashhad, Iran, during the 3 outbreaks of the disease. Our results demonstrated that age >60, male sex, loss of consciousness, respiratory distress, having at least 1 comorbidity, and diabetes were mortality risk factors among COVID-19 patients. Assessment of these findings in practice can aid physicians in the diagnosis process of the disease and help identify the at-risk patients at an early stage. Hopefully, earlier management and support of these patients can minimize the severe outcomes of the disease and reduce the mortality rate of COVID-19 patients.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mohammadtaghi Shakeri, Maryam Salari; Design: Mohammadtaghi Shakeri, Maryam Salari; Control/Supervision: Mohammadtaghi Shakeri, Maryam Salari; Data Collection and/or Processing: Mohammadtaghi Shakeri, Maryam Salari, Parham Ahmadi, Ghazahel Ghorbannezhad, Amirreza Nasirzadeh, Sayed Masoud Sadati; Analysis and/or Interpretation: Maryam Salari, Sayed Masoud Sadati, Mohammedtaghi Shakeri; Literature Review: Maryam Salari, Parham Ahmadi, Ghazahel Ghorbonnezhad, Amirreza Nasirzadeh; Writing the Article: Parham Ahmadi, Ghazadel Ghorbonnezhad, Samaneh Abolbashari, Amirreza Nasirzadeh; Critical Review: Mohammadtaghi Shakeri, Matyam Salari, Samaneh Abolbashari; References and Fundings: Mohammadtaghi Shakeri, Sayed Masoud Sadati; Materials: Mohammadtaghi Shakeri, Sayed Masoud Sadati, Maryam Salari.

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