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Predictors of critical COVID-19 in an Iranian population: Age and disabilities play a special role

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Abstract

Background: Ever since coronavirus disease 2019 (COVID-19) has emerged as a global public health problem, risk factors for severe disease have been reported in studies from Western countries. However, apart from studies of Chinese origin, few reports are available on COVID-19 severity among the Asian population. This study investigates potential risk factors for development of critical COVID-19 in an Iranian population.

Methods: In this retrospective cohort study, we included all adults with COVID-19 from 2 tertiary centers in Iran who had been diagnosed between February 20 and April 1, 2020, in either inpatient or outpatient settings. "Critical COVID-19" was proposed when a hospitalized patient was scheduled for admission to intensive care unit, assisted by mechanical ventilation, or pronounced dead. We used univariable and multivariable logistic and linear regression models to explore the potential risk factors associated with critical COVID-19, admission to hospital, and length of hospital stay.

Results: Of the 590 recruited patients, 427 (72.4%) were hospitalized, 186 (31.5%) had critical COVID-19, and 107 (18.2%) died. In the multivariable regression analysis, age >60 years and physical/mental disabilities were associated with critical COVID-19 (odds ratio (OR), 2.33 and 7.03; 95% CI, 1.51-3.60 and 2.88-17.13, respectively); and history of renal, heart, or liver failure was associated with both COVID-19 hospitalization (OR, 4.13; 95% CI 1.91-8.95; p<0.001) and length of hospital stay (Beta 1.90; 95% CI, 0.76-3.04; p=0.001).

Conclusion: Age >60 years and physical/mental disabilities can predict development of critical COVID-19 in the Iranian population. Also, the presence of renal, heart, or liver failure might predict both COVID-19 hospitalization and length of hospital stay.

Keywords: COVID-19, Prognosis, Risk Factor, Age, Disability, Iran

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Introduction

After first reports from China in December 2019 regarding a mysterious infection with a virus, subsequently des-

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↑*What is "already known" in this topic:*
Since COVID-19 was declared as a pandemic in 2020, various risk factors have been proposed for disease severity among Western populations. However, apart from Chinese studies, few reports are available on COVID-19 severity in the Asian population.

→*What this article adds:*
In this retrospective cohort study conducted on an Iranian population, older age (>60 years) and mental or physical disabilities were found as major predictors of critical COVID-19. In addition, preexisting renal, heart, or liver failure were proved as predictors of both COVID-19 hospitalization and length of stay in hospital.

ignated as “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2), it took <3 months for the disease—“coronavirus disease 2019” (COVID-19) — to be recognized as a “pandemic” by the w orld health organization when more than 118,000 people had already been infected worldwide (1). The rapid global spread of COVID-19 soon demonstrated that SARS-CoV-2 has an efficient person-to-person transmission (2). As a mounting number of cases were reported, the clinical spectrum of the disease became more evident, ranging from asymptomatic or mild upper respiratory illness to severe pneumonia and multiorgan failure requiring admission to intensive care unit (ICU) , and even death (3).

Although most COVID-19 patients have a self-limited course, the rate of progression to a fatal outcome was reported as about 2% in total and as high as 49% in critical cases (4). As there is no specific treatment for the disease and current therapeutic strategies are mainly supportive, it is crucial to timely identify patients at greater risk for critical illness.

According to the current literature, some demographic characteristics (male gender, older age, and Black ethnicity) as well as many preexisting conditions, such as obesity, cigarette smoking, diabetes, hypertension, and various other medical problems, have been proposed to be correlated with more severe COVID-19 and a higher mortality rate (5-9). However, apart from studies of Chinese origin, few reports are available on COVID-19 severity among the Asian population.

Therefore, this study was designed to determine risk factors for critical COVID-19 in an Iranian population.

Methods

Study Design

This was a historical cohort study in patients with COVID-19 who developed either critical or noncritical illness. The local limitation of medical resources made it impossible to perform real time reverse transcriptase polymerase chain reaction (RT-PCR) assay for all suspected cases of COVID-19. Therefore, we used an adapted case definition based on the WHO interim guidance (10). Accordingly, a patient was considered to have COVID-19 if each of the following criteria were met: (1) positive SARS-CoV-2 RT-PCR assay (PCR-based criterion) or (2) a typical appearance of COVID-19 pneumonia in chest CT scan, as described by the Radiological Society of North America (11), in a WHO suspect case (10), with no alternative diagnosis fully explaining the clinical presentation (CT-based criterion).

The “critical COVID-19” was proposed when one of the primary study endpoints was met as either a patient was scheduled for ICU admission, assisted by mechanical ventilation, and/or pronounced dead. In this definition, we used “being scheduled for ICU admission” instead of “ICU admission,” as many critical patients had been admitted to routine wards because of the shortage of ICU beds. The “noncritical COVID-19” group consisted of those who fulfilled the case definition criteria and were not categorized as critical.

Our secondary endpoint outcomes were admission to hospital during the study period and duration of hospitalization. The study protocol was approved by the ethics committees of Iran University of Medical Sciences (approval ID: IR.IUMS.REC.1399.232).

Study Participants

Eligible participants were those aged >18 years with a suspected diagnosis of COVID-19, visited between February 20, 2020 and April 1, 2020, at 2 tertiary clinical care centers, including Rasoul-E-Akram and Firouzabadi general hospitals, both located in Tehran, Iran.

Study Protocol: After preparing a list of eligible patients, an electronic data collection form (eDCF) was developed in detail for compiling data from each recruited participant. The eDCF included data on demographics, medical history (diabetes mellitus, hypertension, renal insufficiency, coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular accident (CVA), cirrhosis, chronic obstructive pulmonary disease (COPD), asthma, active cancer, disabling mental illness, disabling physical illness, the status of immune system), drug history (angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)), habitual history (cigarette, hookah), result of chest computed tomography (CT), result of RT-PCR assay for SARS-CoV-2, level of care assignment (inpatient, outpatient), hospital admission days, a set of prespecified clinical data (height, weight, hypoxemia at presentation, fever, being scheduled for ICU admission, mechanical ventilation support), and the patient’s outcome (survived or deceased).

Five data collectors, all among the authors (M.N., M.G., A.P., A.A., H.H.) were responsible to complete the eDCF for each study participant. They first extracted a part of the required data from hospital records of the patients; then, using the phone numbers registered in hospital files, they interviewed with the patients, or, if not possible, with their next of kin who were living at the same house to complete other parts of the eDCF. Several online meetings were held to confirm the interobserver agreement between the 5 data collectors.

At least 1 follow-up call was made 4 weeks after the last hospital visit for each participant to track possible readmission or late death and to complete eDCF. When at least 3 sets of phone calls on at least 2 different days were failed, it was considered as unsuccessful phone contact.

After primary enrollment, the patients were excluded if the phone contact was unsuccessful, the RT-PCR result was negative, or our case definition criteria for COVID-19 was not fulfilled.

Study Definitions

Operational definitions were set to establish uniformity in data gathering among the data collectors as follows: taking ACEIs/ARBs referred to taking either ACEIs or ARBs for at least 1 month lasting to the week prior to onset of the first related symptom, fever to the maximum recorded temperature of 37.7C° or higher, hypoxemia to the minimum recorded oxygen saturation of 93% or less measured by pulse oximetry, disabling mental or physical illness to the presence of any significant mental/physical condition that prevents the patient from performing daily activities, immunosuppression to any known congenital or acquired immunodeficiency, receiving immunosuppressive agents, chemotherapy during the last 6 months, or prior splenectomy.

Statistical Analysis

Descriptive statistics were performed to measure the proportions, means + SD, medians (with interquartile range (IQR)), and distribution of variables where appropriate. The independent samples t test and the chi-square test were used for between-group comparisons. The normality of data was evaluated by assessing the equality of variances, graphical visualization of data distribution in Q-Q plot, and using the Shapiro-Wilk test. We applied the nonparametric Mann-Whitney U test if the data were not normally distributed.

A univariable logistic regression model was used to examine the relation between potential demographic and clinical predictors and the risk of critical COVID-19 development, possibility of hospital admission, and duration of hospitalization. The multivariable logistic regression model and multiple linear regression analysis were employed to determine independent predictors of a more severe disease course and duration of hospitalization, respectively. In this regard, all potential variables with a P value < .2 were entered into the latter model. We used the variance inflation factor (VIF) to assess the statistical collinearity between study variables and VIF>1 was considered as significant collinearity. In addition, according to the literature, the mentioned potential predictors of critical COVID-19 have been reported to have statistical collinearity as well (5,12–14). To avoid overfitting and improve test sensitivity, the variables with similar clinical application were unified and entered as an inclusive variable. Hence, the presence of active cancer or history of chemotherapy during the last 6 months were unified as “cancerous state”; the history of renal insufficiency, CHF, or cirrhosis were unified as “organ failure”; the disabling physical illness or the disabling mental illness were unified as “disability state”; and the history of CVA or CAD were unified as “cardiovascular disease.” An age-adjusted OR with the associated 95% CI was also calculated for all variables.

All statistical tests were 2-tailed, and P values <0.05 were considered as statistically significant. SPSS 20.1 software (SPSS Inc) was used for all analyses.

Results

After the primary enrollment of 1393 patients (786 from Rasoul-E-Akram Hospital and 607 from Firouzabadi Hospital), 803 were excluded: 344 because of unsuccessful phone contact and 459 because of either negative SARS-CoV-2 RT-PCR or not fulfilling the case definition crite-

Table 1. Characteristics of the Study Patients According to Severity of COVID-19

Variable	Total Patients (N = 590)	Critical (n = 186)	Noncritical (n = 404)	p
Age > 60 yrs– no./total no. (%)	240/587 (40.9)	116/186 (62.4)	124/401 (30.9)	< 0.001
Male Gender – no./total no. (%)	342/587 (58.3)	117/185 (63.2)	225/402 (56.0)	0.105
Source of history– no./total no. (%)				< 0.001
Patient	182/588 (31.0)	22/186 (11.8)	160/402 (39.8)	-
First order relative	358/588 (60.9)	145/186 (78.0)	213/402 (53.0)	-
Others	48/588 (8.2)	19/186 (10.2)	29/402 (7.2)	-
Body Mass Index > 30 kg/m^2– no./total no. (%)	144/562 (25.6)	39/174 (22.4)	105/388 (27.1)	0.252
Preexisting Medical Condition– no./total no. (%)				
Diabetes	158/589 (26.8)	62/185 (33.5)	96/404 (23.8)	0.016
Hypertension	194/590 (32.9)	80/186 (43.0)	114/404 (28.2)	<0.001
Chronic Obstructive Pulmonary Disease / Asthma	49/587 (8.3)	22/184 (12.0)	27/403 (6.7)	0.033
Organ Failure	119/590 (20.2)	61/186 (32.8)	58/404 (14.4)	<0.001
Renal Insufficiency	43/590 (7.3)	22/186 (11.8)	21/404 (5.2)	0.006
Congestive Heart Failure	78/589 (13.2)	40/185 (21.6)	38/404 (9.4)	<0.001
Cirrhosis	8/588 (1.4)	6/185 (3.2)	2/403 (0.5)	0.014
Cardiovascular disease	120/590 (20.3)	62/186 (33.3)	58/404 (14.4)	<0.001
Coronary Artery Disease	101/589 (17.1)	50/186 (26.9)	51/403 (12.7)	<0.001
Cerebrovascular Accident	30/587 (5.1)	19/183 (10.4)	11/404 (2.7)	<0.001
The Cancerous State*	19/590 (3.2)	12/186 (6.5)	7/404 (1.7)	0.003
The Disability State	39/590 (6.6)	31/186 (16.7)	8/404 (2.0)	<0.001
Disabling Mental Illness	23/590 (3.9)	19/186 (10.2)	4/404 (1.0)	<0.001
Disabling Physical Illness	24/589 (4.1)	19/185 (10.3)	5/404 (1.2)	<0.001
Immunosuppression	34/590 (5.8)	11/186 (5.9)	23/404 (5.7)	0.915
Medications– no./total no. (%)				
Angiotensin Converting Enzyme Inhibitor (ACEI)	36/569 (6.3)	16/174 (9.2)	20/395 (5.1)	0.062
Angiotensin Receptor Blocker (ARB)	134/572 (23.4)	59/178 (33.1)	75/394 (19.0)	<0.001
ACEI or ARB	154/573 (26.9)	68/178 (38.2)	86/395 (21.8)	<0.001
Tobacco use– no./total no. (%)	41/590 (6.9)	11/186 (5.9)	30/402 (7.4)	0.502
Fever at presentation – no./total no. (%)	196/523 (37.5)	56/157 (35.7)	140/366 (38.3)	0.576
Hypoxemia at presentation – no./total no. (%)	237/534 (44.4)	121/171 (70.8)	116/363 (32.0)	<0.001
Admission to hospital – no./total no. (%)	427/590 (72.4)	186/186 (100)	241/404 (59.7)	< 0.001
Number of Days in Hospital – median (IQR)#	4 (0-8)	7 (4-10)	3 (0-6)	< 0.001
Scheduled for ICU admission – no./total no. (%)	162/590 (27.5)	162/186 (87.1)	0/404 (0.0)	<0.001
Mechanical Ventilatory Support – no./total no. (%)	93/585 (15.9)	93/186 (50.0)	0/399 (0.0)	<0.001
Deceaced – no./total no. (%)	107/588 (18.2)	107/186 (57.5)	0/402 (0.0)	<0.001

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ria. Very limited data were available for the 344 cases with unsuccessful phone calls; their mean age was 57.18 years, and 68% of them were men, while at least 49 patient died from the disease. Of the 590 finally recruited patients, 342 (58.3%) were men and 186 (31.5%) had critical COVID-19. The PCR-based and CT-based criteria were fulfilled for 20.5% and 92.4% of participants, respectively. The mean + SD of age was significantly higher in the critical COVID-19 group (68 + 15) compared to the noncritical group (55 + 17; p<0.001). Hypoxemia was present in 70.8% of critical versus 32% of the noncritical patients (p<0.001). The median (IQR) for the hospital admission days was 7 (4-10) and 3 (0-6) in the critical and noncritical groups, respectively (p<0.001). As seen in Table 1, nearly all of the preexisting medical conditions (except immunosuppression) were significantly more prevalent in the critical group. Death was the final outcome in 107 patients (18.2% of the total and 57.5% of the critical cases).

Table 2 shows the results of analyses on potential risk factors for development of critical COVID-19. In univariable analysis, patients older than 60 years had a higher odds for critical COVID-19. Taking ACEI or ARB, history of diabetes mellitus, hypertension, or COPD/asthma, history of CAD or CVA (both designated as the cardiovascular disease), history of CHF, renal insufficiency, or cirrhosis (collectively designated as the organ failure), cancer chemotherapy in the recent 6 months, or history of active cancer (both named as the cancerous state), and disabling physical or mental illness (both classified as the disability state) were also associated with critical COVID-19. After adjusting for age, the disability state had the highest odds for critical COVID-19 (6.92; 95% CI, 3.04-15.76), followed by cancerous state (3.50; 95% CI, 1.29-9.48), organ failure (2.22; 95% CI, 1.46-3.47), and cardiovascular disease (1.99; 95% CI, 1.28-3.10). In the multivariable logistic regression model, age >60 years (OR, 2.33; 95% CI, 1.51-3.60), cancerous state (OR=3.74; 95% CI, 1.31-10.65), and disability state (OR=7.03; 95% CI, 2.88-17.13) were found to be predictors of critical COVID-19.

Tables 3 and 4 summarize the results of analyses for assessing the association of study variables with hospitalization of the study population and their hospital admission

Table 2. Multiple Logistic Regression Analysis for Assessing Association Between the Study Variables and Severity of COVID-19*

Variables	Univariable OR (95%CI)	p	Age-adjusted OR (95%CI)	p	Multivariable OR (95%CI)	p
Age > 60 yrs	3.70 (2.57 – 5.33)	< 0.001	-	-	2.33 (1.51 – 3.60)	< 0.001
Male Gender	1.35 (0.95 - 1.94)	0.097	1.35 (0.93 – 1.96)	0.117	1.32 (0.87 – 1.99)	0.193
Body Mass Index > 30 kg/m^2	0.78 (0.51 – 1.19)	0.244	0.91 (0.59 – 1.42)	0.689	-	-
Diabetes	1.62 (1.10 – 2.37)	0.014	1.23 (0.82 – 1.84)	0.325	1.16 (0.71 – 1.82)	0.595
Hypertension	1.92 (1.34 – 2.76)	< 0.001	1.21 (0.81 – 1.81)	0.355	0.89 (0.46 – 1.71)	0.723
Chronic Obstructive Pulmonary Disease / Asthma	1.89 (1.05– 3.42)	0.035	1.52 (0.82 – 2.83)	0.188	1.19 (0.60 – 2.39)	0.620
Organ Failure#	2.91 (1.92 – 4.40)	< 0.001	2.22 (1.46 – 3.47)	< 0.001	1.57 (0.92 – 2.67)	0.094
Cardiovascular disease#	2.98 (1.97 – 4.51)	< 0.001	1.99 (1.28 – 3.10)	0.002	1.53 (0.90 – 2.61)	0.116
The Cancerous State#	3.91 (1.51 – 10.10)	0.005	3.50 (1.29 – 9.48)	0.014	3.74 (1.31 – 10.65)	0.013
The Disability State#	9.90 (4.45 – 22.01)	< 0.001	6.92 (3.04 – 15.76)	< 0.001	7.03 (2.88 – 17.13)	< 0.001
Immunosuppression	1.04 (0.50 – 2.18)	0.915	1.30 (0.60 – 2.82)	0.509	-	-
Taking ACEI or ARB	2.22 (1.51 – 3.26)	< 0.001	1.39 (0.91 – 2.13)	0.126	1.34 (0.68 – 1.62)	0.395
Tobacco use	0.78 (0.38 – 1.60)	0.503	0.99 (0.47 – 2.08)	0.974	-	-

* OR, odds ratio; CI, confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
** All variables with P value < .2 entered the model.
#Organ failure was defined as the presence of renal, heart, or liver failure; cardiovascular disease as the presence of either coronary artery disease or cerebrovascular accident; cancerous state as either receiving chemotherapy in the past 6 months or having active cancer; and disability state as the presence of any physical or mental disabilities.

Table 3. Multiple Logistic Regression Analysis for Assessing Association Between the Study Variables and Hospitalization of COVID-19 Patients*

Variables	Univariable OR (95% CI)	p	Age-adjusted OR (95% CI)	p	Multivariable OR** (95% CI)	p
Age > 60 yrs	5.48 (3.43 – 8.74)	< 0.001	-	-	4.54 (2.67 – 7.71)	< 0.001
Male Gender	0.93 (0.64 – 1.34)	0.704	0.88 (0.60 – 1.30)	0.516	-	-
Body Mass Index > 30 kg/m^2	1.00 (0.66 – 1.52)	0.999	1.20 (0.77 – 1.87)	0.413	-	-
Diabetes	1.90 (1.22 – 2.98)	0.005	1.73 (0.45 – 1.17)	0.191	1.00 (0.60 – 1.69)	0.993
Hypertension	2.63 (1.70 – 4.07)	< 0.001	1.59 (0.98 – 2.57)	0.058	1.59 (0.72 – 3.52)	0.249
Chronic Obstructive Pulmonary Disease / Asthma	2.45 (1.08 – 5.57)	0.033	1.89 (0.80 – 4.45)	0.146	1.80 (0.73 – 4.36)	0.195
Organ Failure#	5.24 (2.67 – 10.31)	< 0.001	3.87 (1.93 – 7.76)	< 0.001	4.13 (1.91 – 8.95)	< 0.001
Cardiovascular disease#	2.04 (1.22 – 3.40)	0.006	1.08 (0.61 – 1.89)	0.797	0.59 (0.31 – 1.13)	0.109
The Cancerous State#	1.45 (0.47 – 4.43)	0.517	1.10 (0.34 – 3.59)	0.878	-	-
The Disability State#	4.91 (1.49 – 16.18)	0.009	2.64 (0.77 – 9.08)	0.123	2.1 (0.60 – 7.58)	0.240
Immunosuppression	1.50 (0.64 – 3.52)	0.347	1.90 (0.79 – 4.57)	0.151	-	-
Taking ACEI or ARB	2.39 (1.50 – 3.82)	< 0.001	1.31 (0.783 – 2.20)	0.304	0.74 (0.32 – 1.73)	0.495
Tobacco use	0.81 (0.41 – 1.60)	0.545	1.01 (0.50 – 2.07)	0.970	-	-

* OR, odds ratio; CI, confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
** All variables with P value < .2 were entered into the model.
# Organ failure was defined as the presence of renal, heart, or liver failure; cardiovascular disease as the presence of either coronary artery disease or cerebrovascular accident; 'cancerous state as either receiving chemotherapy in the past 6 months or having active cancer; and 'disability state' as the presence of any physical or mental disabilities.

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Table 4. Multiple Linear Regression Analysis for Assessing Association Between the Study Variables and Duration of Hospitalization for COVID-19*

Variables	Univariable Beta (95% CI)	p	Age-adjusted Beta (95% CI)	p	Multivariable Beta** (95% CI)	p
Age > 60 yrs	0.17 (0.87 – 2.45)	< 0.001	-	-	0.89 (-0.02-1.80)	0.345
Male Gender	0.01 (-0.79 – 0.81)	0.980	-0.57 (-0.85-0.73)	0.887	-	-
Body Mass Index > 30 kg/m^2	0.44 (-0.48 – 1.36)	0.344	0.64 (-0.73-1.55)	0.173	-	-
Diabetes	0.13 (0.54 – 2.30)	0.002	1.05 (0.16-1.94)	0.021	0.69 (-0.28-1.66)	0.164
Hypertension	0.12 (0.43 – 2.09)	0.003	0.71 (-0.18-1.60)	0.116	0.06 (-1.297-1.42)	0.931
Chronic Obstructive Pulmonary Disease / Asthma	-0.00 (-1.50 – 1.36)	0.921	-0.42 (-1.84-0.99)	0.556	-	-
Organ Failure#	2.58 (1.63 – 3.53)	< 0.001	2.21 (1.24-3.18)	<0.001	1.90 (0.76-3.04)	0.001
Cardiovascular disease#	1.72 (0.75 – 2.68)	0.001	1.15 (0.14-2.16)	0.026	0.065 (-1.09-1.22)	0.911
The Cancerous State#	1.74 (-5.29 – 4.01)	0.133	1.46 (-0.78-3.71)	0.201	1.244 (-0.96-3.48)	0.276
The Disability State#	1.90 (0.32 – 3.49)	0.019	1.25 (-0.35-2.85)	0.126	1.110 (-0.56-2.78)	0.194
Immunosuppression	0.04 (-0.93 – 2.42)	0.384	0.97 (-0.69-2.63)	0.251	-	-
Taking ACEI or ARB	1.46 (0.56 – 2.36)	0.001	0.88 (-0.08-1.84)	0.073	0.274 (-1.15-1.70)	0.706
Tobacco use	-0.013 (-1.78 – 1.29)	0.753	0.02 (-1.51-1.54)	0.985	-	-

* OR: Odds Ratio; CI: Confidence Interval; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker
** All variables with P-value < 0.2 entered the model
#'Organ Failure' was defined as the presence of renal, heart or liver failure; 'Cardiovascular disease' as the presence of either coronary artery disease or cerebrovascular accident; 'The Cancerous State' as either receiving chemotherapy in recent 6 months or having active cancer; and 'The Disability State' as the presence of any physical or mental disabilities.

days, respectively. As noted, age >60 years and other clinical factors, except for the cancerous state, which had been found to be associated with critical COVID-19, were also associated with patients' hospitalization in univariable analysis. Excluding COPD/asthma, the same association was found for the hospital admission days. After age adjustment, the odds of hospitalization were highest in patients with organ failure (3.87, 95% CI, 1.93-7.76); likewise, the age-adjusted Beta statistics found the organ failure as the strongest predictor of hospital admission days (Beta, 2.21; 95% CI, 1.24-3.18), followed by cardiovascular disease (Beta, 1.15; 95% CI, 0.14-2.16) and diabetes mellitus (Beta, 1.05; 95% CI, 0.16-1.94). In the multivariable logistic regression model, age >60 years and organ failure were independent predictors of hospitalization (OR=4.54 (95% CI, 2.67-7.71) and 4.13 (95% CI, 1.91-8.95), respectively); whereas the latter was also related to the length of hospital stay (Beta=1.90; 95% CI, 0.76-3.04).

Discussion

Based on the results, patients with critical COVID-19 were older than those with noncritical disease. Based on the univariable analysis results, many preexisting medical conditions, including diabetes mellitus, hypertension, obstructive lung disease, cardiovascular disease, organ failure, physical or mental disability, and cancerous state were associated with critical disease. After age adjustment, however, only 4 of those conditions (cardiovascular disease, organ failure, disability, and cancerous states) retained their relation with the development of critical COVID-19; whereas, disability and cancerous states were the sole factors that remained associated after multivariable adjustment. Moreover, organ failure was the single factor that found to predict both COVID-19 hospitalization and hospital length of stay.

In line with our findings, older age has been previously reported as a risk factor for higher severity of and mortality due to COVID-19 in many other studies (5, 8, 15–19). With aging, the immune system undergoes changes that increase susceptibility to infections and various other diseases. These changes, namely, immunosenescence, include both a decline in some aspects of the immune function, especially adaptive immunity, and an inappropriate increase in some other aspects, especially innate immunity. The latter leads to an age-related chronic low grade inflammatory state, which is called "inflammaging" (20). In older COVID-19 patients, therefore, the combination of background inflammaging and poor antigen-specific, adaptive, immune reaction may contribute to the emergence of an excessive hyperinflammatory response and subsequent critical clinical consequences. We also found that the observed risk of diabetes, hypertension, and obstructive lung disease for development of a more severe COVID-19 is at least partially mediated by age, a fact that is not considered in many other investigations in the literature (4, 6, 8, 19, 21, 22). Furthermore, when the association of cardiovascular disease and end-organ failure with critical COVID-19 is eliminated by multivariable adjustment but remains unchanged after age-adjustment, the observed risk of those conditions for critical COVID-19 might be mediated by coexisting diabetes or hypertension, which are the well-known risk factors for both cardiovascular disease and the renal, hepatic, or heart failure. Here again, age could be considered as the main factor: the effects of cardiovascular disease and end-organ failure are mediated by diabetes and hypertension, which themselves have age-mediated effects.

Independent of age, cancerous state and disability state were both associated with critical COVID-19. Although this association is easily understood for the former state, more clarification is needed for the latter state. First, mental and physical disabilities are common among the population and more prevalent in the elderly. More than 1 billion people are living with disabilities worldwide, 80% of whom residing in the low- and middle-income countries. Also, as high as 46% of people over the age of 60 have one type of disability (23). Second, people with disabilities are disproportionately affected by COVID-19. They are more likely to be undereducated, unemployed, or live

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in poverty (24). Then, as one of the most socioeconomically marginalized population, they have usually unequal access to health services and may face barriers to timely receipt of public health information during the pandemics. They also have difficulties in adopting the recommended public health strategies. Many of them either need close care or are placed in the overcrowded nursing home facilities where physical distancing is not feasible. Necessity to touch things for physical support, physical difficulties in applying standard handwashing, and problems of amputees for observing their prostheses' hygiene are among other issues in this regard. Third, the observed association between disability state and critical COVID-19 could be attributed to some factors as follows: (1) Stigmatized information on public health against persons with disabilities (for example, prejudice about social irresponsibility of disabled persons in the pandemic and inadvertently associating a recent rise in transmission of COVID-19 with disabled people) makes them to deny early symptoms and to avoid seeking medical consult; (2) Disruption of support services during the pandemic prevents people with disabilities from accessing medical care in a timely manner. (3) Limitation of resources during the pandemic leads to health care prioritization, where persons with disabilities are less likely to be prioritized in resource allocation and rationing decisions, making them deprived of advanced therapeutic modalities. (4) Poor general health, sedentary lifestyle, and loss of physical fitness, which are common among people with disabilities (24), diminish the reserve of their respiratory system and make them more prone to respiratory complications of SARS-CoV-2 infection and severe COVID-19. Last, in general, as a multifactorial outcome, the consequences of pandemics are more likely to be worse among lower socioeconomic people and those living in care home facilities (25, 26), 2 settings in which people with disabilities are disproportionately represented worldwide (24). In this regard, according to international reports, care home residents account for 42% to 57% of all COVID-related deaths (27).

This was a retrospective cohort in which the patients were recruited from 2 main referral centers in the country's capital. Despite the problems inherent in the retrospective design, conducting at least 1 phone interview for each participant minimized our missing data. This way, we also revalidated our patients' outcome by taking into account the possibility of postdischarge complications. Another strength of this study, compared to similar investigations, is inclusion of many patients from outpatient setting. The relatively small sample size, however, limits the generalizability of our results. Using a CT-based criterion for COVID-19 case definition (without checking SARS-CoV-2 RT-PCR for many patients) is another limitation of this study. Inevitably, the cases not reachable by phone call were another limitation in this study. Although the comorbidity data of this group was not available, the lost to follow-up bias was minimalized considering age, which was found to be the main predictor of critical COVID-19 and was not significantly different in this group compared to the study population (p=0.48). Finally, such factors as more prepared health infrastructures, increased community awareness of COVID-19 (leading to modified behaviors), and improved COVID-19 management protocols may make the results of this study not be necessarily reproducible in upcoming COVID-19 peaks. Using RT-PCR-based case definition for COVID-19 in a larger population may help overcome these limitations in future studies.

Conclusion

In summary, in a retrospective evaluation of an Iranian population, we found that age >60 years and cancerous and disability states were the major predictors of critical COVID-19. Regarding clinical implications, our findings suggest a lower threshold for early initiation of advanced therapeutic interventions in older COVID-19 patients and those with a background disability or cancer. In addition, COVID-19 vaccination could be prioritized for those aged >60 years, residents of care home facilities, and others with a disability or cancerous state.

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Conflict of Interests

The authors declare that they have no competing interests.

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