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Survival and risk analysis of patients with COVID-19 in Iran

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ABSTRACT

Objective: To evaluate the risk factors of death caused by COVID-19 in Iran.

Methods: This study was a retrospective cohort study from February 20, 2020, to August 22, 2022, in the hospitals in Isfahan, Iran. The data were collected through a researcher-made checklist. To determine the risk factors of the death, logistic regression and Cox regression models were used. For each variable, the odds ratio and 95% confidence interval were also reported.

Results: 1 885 Patients were included. The age of deceased persons was significantly higher than that of the surviving persons. The risk of death for the age group above 60 years was about 14 times higher than that of people aged 19-35 years [95% *CI*: 14.41 (2.02-102.99), *P*<0.01]. Hypertension [95% *CI*: 1.92 (1.47-2.5), *P*<0.01], diabetes [95% *CI*: 1.62 (1.23-2.13), *P*<0.001], and chronic obstructive pulmonary disease [95% *CI*: 1.92 (1.47-2.50), *P*<0.01] were also risk factors of mortality.

Conclusions: This study reveals that the mortality rate due to COVID-19 is associated with old age, longer hospitalization in the ICU, increased length of stay, and comorbidities of high blood pressure, diabetes, and chronic pulmonary disease.

KEYWORDS: Cause; Death; Survival; COVID-19; Risk factors; Iran

1. Introduction

In March 2020, the World Health Organization officially announced COVID-19 as a pandemic[1,2]. With the spread of the epidemic, 231 countries started releasing reports on cases and deaths daily so over 700 million confirmed cases and nearly seven million deaths were reported worldwide by December 23, 2023[3]. According to the Worldometer, the reliable reference website

Significance

Considering the global epidemic of COVID-19, this study was conducted to identify the risk factors of survival. This study reveals that the mortality rate due to COVID-19 is associated with old age, longer hospitalization in the ICU, increased length of stay, and comorbidities of high blood pressure, diabetes, and chronic pulmonary disease.

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that publishes the updated statistics of the countries as per the reports issued by the Ministry of Health of each country, Iran has registered about 7 600 confirmed cases and roughly 146 000 deaths until December 23, 2023[3].

Based on the results of a meta-analysis of 141 papers, the estimated average incubation period of COVID-19 for all variants was 6.5 days; however, the incubation period varied by the virus variant, being 5, 4.5, 4.4, and 3.4 days for Alpha, Beta, Delta, and Omicron variants, respectively[4]. Numerous systematic reviews and meta-analyses focus on the effect of comorbidities on COVID-19 severity and mortality. These studies have illustrated that comorbidities are positively linked with an increased risk of severe disease and higher mortality in COVID-19 patients. Diseases such as high blood pressure, diabetes, cardiovascular disease, chronic kidney disease, obesity, cancer, chronic neurological disorders, dementia, and liver disease have been enumerated as important diseases contributing to the increased incidence of serious complications and mortality in people with COVID-19[5-7]. During the epidemic, some research has been undertaken in Iran to evaluate the COVID-19 mortality rate. These studies, some of which have utilized national data, were somehow successful in depicting the picture of the COVID-19 incidence and mortality rate in different periods[8,9]. Though the state of public emergency for COVID-19 has ended in Iran and other parts of the world, extracting and disseminating the data about the incidence rate and causes of death due to COVID-19 would not only be useful for health system policymakers and researchers but could also provide a basis for evidence-based decisions for the future pandemics.

Like many other cities of Iran, Isfahan as a metropolis experienced a large number of confirmed cases and deaths in the time of COVID-19, especially during the spread of the Delta variant. As a result, its hospitals have recorded valuable epidemiological data. Also, in the studies available to us, survival analysis was not performed and this is what distinguishes this study from other studies. Taking this fact into account, the present study was designed for survival analysis and risk analysis in patients with COVID-19 in Iran.

2. Subjects and methods

This is a retrospective cohort study. It included the data of COVID-19 patients admitted to COVID-19 referral hospitals located in Isfahan city, Iran, including Al-Zahra, Khorshid, Amin, and Isa Ibn Maryam hospitals from February 20, 2020, to August 21, 2022. The data were collected from records by a researcher-made checklist.

The present study was carried out after the approval of the research council and the ethics committee of Isfahan University of Medical Sciences with the code IR.MUI.NUREMA.REC.1401.050.

The sample size was according to the formula:

$$n=\frac{(Z_{(1-\alpha/2)}+Z_{(1-\beta)})^2}{(\log OR)^2\,\bar{\pi}(1-\bar{\pi})}$$

The sample size was calculated by considering the significance level of 5%, the power of 80%, the odds ratio 1.21 and the exposure ratio in the group of survivors equal to 73%. Including 30% drop in data (due to incomplete information), finally 1 900 people were considered.

The face and content validity of the designed checklist were evaluated. To report the quantitative and qualitative data, descriptive statistics were used. *t*-test and chi-square test were used. Likewise, to specify the link between the variables and death, the logistic regression models were applied. The odds ratio and 95% confidence intervals were also calculated for each variable. Finally, the survival analysis was executed with Cox regression to scrutinize the interaction between the factors and the time-to-event. All analyses were performed using SPSS 26 software and the statistical significance of the associations was assessed at α=5% level.

3. Results

Due to the incompleteness of the data, 15 patients were excluded and 1 885 patients were included in the final analysis (Figure 1).

3.1. Demographic characteristics

The mean age was (60±17) years with the mean age of the deceased persons being significantly higher than that of the surviving ones (P<0.01). In total, 223 patients with COVID-19 died, including 207 confirmed cases of COVID-19, 4 suspected cases, and 12 other cases (based on underlying cause of death).

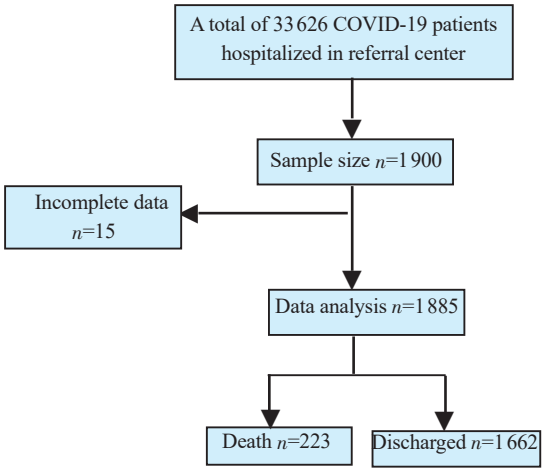

Figure 1. The study flowchart.

Acute respiratory distress syndrome has been referred to as the direct cause of death. The history of infection with COVID-19 in deceased persons was significantly higher than that of surviving persons (*i.e.* 5.4% *vs.* 1.4%) (P<0.01). Moreover, the history of hospitalization in the deceased cases was significantly higher than that of surviving cases (2.2% *vs.* 0.8%) (P=0.035). As Table 1 indicates there was no statistically significant difference between the deceased and surviving patients in terms of distribution of sex, place of residence, and smoking. In comparison with the surviving patients, the prevalence of ICU hospitalization among the deceased patients was significantly higher by 52%. The mean stay length was 6.5 days and it was significantly longer for the deceased cases compared to the surviving ones (P<0.01).

Table 1. Demographic characteristics (n=1 885).

Variables	Surviving (n=1 662)	Deceased (n=223)	t/χ^2	P
Age, years, mean±SD	58±17	73±14	11.95	<0.01
Age (Years, *n*, %)				
19-35	168 (10.1)	1 (0.4)	100.54	<0.01
36-60	716 (43.1)	39 (17.5)		
>60	778 (46.8)	183 (82.1)		
Sex (*n*, %)				
Female	805 (48.4)	95 (42.6)	2.68	0.101
Male	857 (51.6)	128 (57.4)		
Residence (*n*, %)				
Urban	1 596 (96.0)	215 (96.4)	0.08	0.782
Rural	66 (4.0)	8 (3.6)		
Smoking (*n*, %)				
Yes	63 (13.8)	6 (7.2)	2.75	0.970
No	392 (86.2)	77 (92.8)		
Hospitalization in ICU (*n*, %)				
Yes	111 (6.7)	133 (59.6)	489.42	<0.01
No	1 551 (93.3)	90 (40.4)		
History of hospitalization (*n*, %)				
Yes	13 (0.8)	5 (2.2)	4.43	0.035
No	1 649 (99.2)	218 (97.8)		
Length of stay (Day, median, Q1, Q3)	5 (3-7)	8 (3-14)	−6.25	<0.01

Table 2. Vital symptoms (n=1 885, mean±SD).

Vital symptoms	Surviving (n=1 662)	Deceased (n=223)	t	P
Respiratory rate (per minute)	20.77±6.86	22.83±7.97	1.25	<0.01
PO_2 level (mmHg)	90.78±6.16	81.44±13.04	17.08	<0.01
Heart rate (per minute)	84.80±14.14	91.79±20.66	−6.31	<0.01
Fever degree (°C)	36.99±3.17	36.97±1.13	0.11	0.911
Blood pressure (mmHg)				
SBP	119.65±15.87	122.70±20.93	−2.48	0.013
DBP	74.46±10.20	75.46±12.49	−1.26	0.204

SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3. Symptoms of patients with COVID-19 (n=1 885, n, %).

Symptoms	Surviving (n=1 662)	Deceased (n=223)	χ^2	P
Runny nose	76 (4.6)	14 (6.3)	1.250	0.262
Sneezing	29 (1.7)	6 (2.7)	0.965	0.326
Cough	915 (55.1)	117 (52.5)	0.531	0.466
Headache	350 (21.1)	27 (12.1)	9.840	0.002
Weakness & Lethargy	617 (37.1)	101 (45.3)	5.560	0.018
Nausea & Vomiting	314 (18.9)	33 (14.8)	2.190	0.138
Abdominal pain	72 (4.3)	11 (4.9)	0.168	0.681
Shortness of breath	941 (56.6)	165 (74.0)	24.470	<0.001
Fever	773 (46.5)	104 (46.6)	0.001	0.972
Muscle/body pain	497 (29.9)	57 (25.6)	1.780	0.181
Diarrhea	143 (8.6)	20 (9.0)	0.033	0.856
Smell/olfactory dysfunction	51 (3.1)	6 (2.7)	0.096	0.757
Taste/gustatory dysfunction	44 (2.6)	5 (2.2)	0.128	0.721

3.2. Vital symptoms

There was a statistically significant difference between the two groups as to the systolic blood pressure, PO_2 level, respiratory rate, and heart rate (Table 2).

3.3. Symptoms of patients

Table 3 lists the symptoms in the patients with COVID-19. The two groups exhibited no statistically significant difference concerning the symptoms except headache, weakness, lethargy, and shortness of breath.

3.4. Vaccination rate

The COVID-19 vaccination rate of the deceased patients was significantly lower than the surviving ones (20.2% *vs.* 80.3%, χ^2=361.46, P<0.01). The ratio of the zero dose and first dose of vaccine in patients with COVID-19 was significantly higher among the deceased (χ^2=384.82, P<0.01). While the vaccination rate of two doses and three doses was significantly lower in the deceased patients (χ^2=361.47, P<0.01) (Table 4).

Table 4. Vaccination status (n=1 885, n, %).

Dose	Surviving (n=1 662)	Deceased (n=223)
Zero dose	328 (19.7)	178 (79.8)
First dose	116 (7.0)	21 (9.4)
Second dose	491 (29.5)	18 (8.1)
Third dose	727 (43.7)	6 (2.7)

Table 5. Risk factors of mortality of patients with COVID-19 (n=1 885, n, %).

Variables	Odds ratio (95% *CI*)	Hazard ratio (95% *CI*)	*P*
Age (Years)			
19-35	1	1	<0.001
36-60	9.15 (1.25-67.08)	4.92 (0.68-35.89)	
>60	39.52 (5.50-284.04)	14.41 (2.02-102.99)	
Sex			
Female	1	1	0.292
Male	1.27 (0.96-1.68)	1.15 (0.89-1.51)	
Residence			
Urban	1	1	0.361
Rural	0.90 (0.43-1.9)	1.39 (0.68-2.82)	
Hospitalization in ICU			
Yes	20.65 (14.86-28.72)	3.76 (2.84-4.1)	<0.001
No	1	1	
Hypertension			
Yes	3.07 (2.31-4.08)	1.92 (1.47-2.5)	<0.001
No	1	1	
Diabetes			
Yes	2.17 (1.61-2.92)	1.62 (1.23-2.13)	<0.001
No	1	1	
Coronary artery disease			
Yes	0.68 (0.09-5.27)	0.63 (0.09-4.45)	0.632
No	1	1	
Chronic kidney disease			
Yes	2.85 (1.11-7.35)	1.46 (0.65-3.28)	0.359
No	1	1	
Chronic liver disease			
Yes	-	-	0.786
No	1	1	
Chronic obstructive pulmonary disease			
Yes	3.07 (2.31-4.08)	1.92 (1.47-2.50)	<0.001
No	1	1	
Immunodeficiency			
Yes	-	-	0.818
No	1	1	
Prostate cancer			
Yes	2.50 (0.26-24.06)	2.27 (0.32-16.2)	0.399
No	1	1	
Lung cancer			
Yes	7.52 (1.06-53.6)	2.93 (0.73-11.81)	0.111
No	1	1	

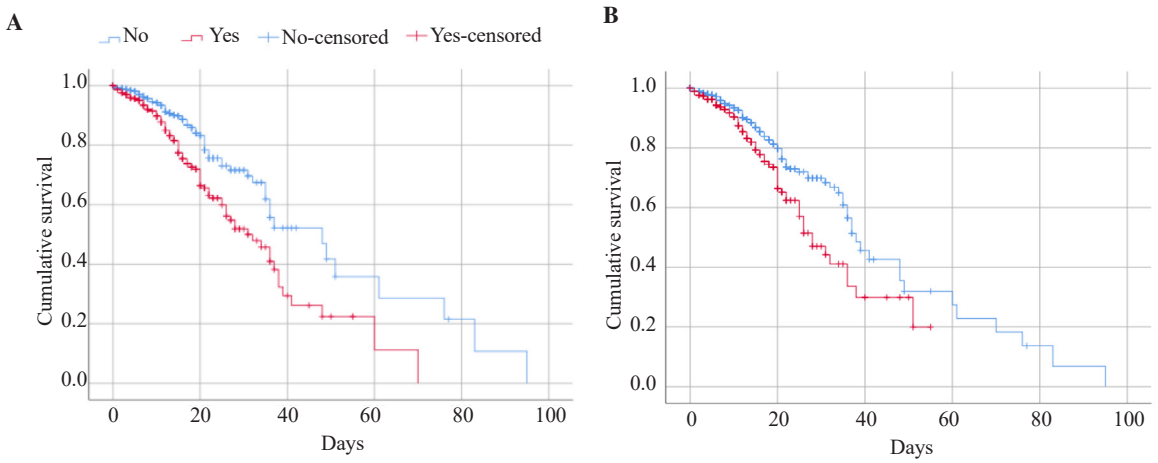

Figure 2. Survival analysis of high blood pressure (A) and diabetes (B) in patients with COVID-19.

3.5. Results of logistic regression analysis and survival analysis

Logistic regression analysis showed that the odds of death for people aged 36-60 and over 60 years old were about 9 times and nearly 40 times greater than the people aged 19-35. Survival analysis showed that the risks of death for the age group of 36-60 and over 60 years old were about 5 times and 14 times that of people aged 19-35 years. Additionally, sex and place of residence were not significantly associated with mortality. The odds ratio of death for people with high blood pressure and diabetes was about 3 times and 2 times higher than people without these diseases, respectively. Following the survival analysis, the risk of death for people with high blood pressure and diabetes was about twice compared of other people without these comorbidities. However, advanced survival analysis did not reveal any significant relationship between coronary heart disease, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, immunodeficiency, prostate cancer, and lung cancer in patients with COVID-19 and the risk of death (Table 5, Figure 2).

4. Discussion

In the present study, the risk factors associated with the death of COVID-19 were investigated. A total of 1 885 cases admitted to the hospitals situated in Isfahan City, Iran were included. The findings showed that the age, hospitalization in ICU, and length of stay were greater in the deceased patients. The two groups exhibited no statistically significant difference concerning the symptoms except headache, weakness, lethargy, and shortness of breath. Hypertension, diabetes, and chronic obstructive pulmonary disease were risk factors for mortality.

In the present study, 82.1% of deceased patients with COVID-19 were over 60 years old, which is in line with the study by Diop *et al*[10]. Age is significantly associated with death in patients with COVID-19. In this study, logistic regression analysis showed that the odds of death for people aged 36-60 and over 60 years old were about 9 times and nearly 40 times greater than the people aged 19-35. Survival analysis showed that the risks of death for the age group of 36-60 and over 60 years old were about 5 times and 14 times that of people aged 19-35 years. The mortality increases with age. Age over 60 years acts as an influential factor in mortality of COVID-19, a finding which substantiates that reported in similar studies by Ali Mahmoud in Somalia[11], Pontes in Paraná, Brazil[12], Garbin in Espirito Santo, Brazil[13], Muyinda in Uganda[14], and Setianegari in Indonesia[15]. Some studies reported higher mortality in men[16-20]. This finding can be attributed to a higher probability of kidney failure disease[21] as well as a higher smoking rate in men. These studies consider sex as a risk factor[21-24]. But in our study, there is no significant difference between males and females, which is consistent with the research conducted in Spain and Brazil[12,25].

In this study, 12.9% of cases of COVID-19 were admitted to the ICU, out of whom 59.6% died. In one study by Soto *et al*., out of 3.9% of ICU patients, 67.4% died[26]. In the same vein, in Rafati *et al*.'s study, of 12.2% of cases admitted to ICU, as many as 56.92% lost their life[27]. In the present study, the odds ratio and risk of death for ICU COVID patients were 21 and around 4 times higher than that of non-ICU patients, respectively. These findings were consistent with the studies by Ghelmani *et al*. and Cueto-Manzano *et al*. wherein ICU hospitalization was identified as a risk factor for the mortality of patients with COVID-19[28,29].

The results of this study show that risky comorbidities in patients with COVID-19 included high blood pressure, diabetes, and chronic pulmonary disease, which is consistent with other studies[30,31]. This

study indicates that high blood pressure and diabetes are positively linked with the risk of death. Logistic regression analysis shows the odds of death from COVID-19 are 3 times and 2 times higher than that of patients without high blood pressure, respectively. Survival analysis shows that comparing the diabetic and non-diabetic patients, the risk of death from COVID-19 is 2 times and 1.6 times higher, respectively. These findings are similar to Rafati *et al*.'s study, which concluded that diabetic patients had a 1.62 times increased risk of mortality than the non-diabetic cases[27].

Given the findings of this study, as the age of patients increases- especially the patients diagnosed with comorbidities, such as high blood pressure, diabetes, and chronic pulmonary disease- they tend to become more vulnerable to infectious diseases and acute respiratory syndrome and have higher mortality from COVID-19. This may be mainly due to their poorer physical condition and weaker immune system. Accordingly, it is important to prevent infection among individuals at high risk to reduce COVID-19-related mortality. Further, as was observed in this study, the most frequent clinical symptoms were fever, shortness of breath, weakness and lethargy, cough, high breathing rate, hypoxemia, high heart rate, and high systolic blood pressure. These findings can be helpful in the identification and prognosis of patients with COVID-19 during the initial examinations or upon their arrival at the hospital.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

FM wrote the manuscript, acquired data, created the dataset, and revised the final version of the manuscript. SSI and RS wrote the manuscript. SSI analyzed and interpreted data, designed the study, and revised the final version of the manuscript. ZH performed statistical analyses and revised the article. HM acquired data.

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