



Risk Factors for Mortality in Hospitalized Patients with COVID-19: A Cross-Sectional Study in Southwestern Iran

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Received 2021 June 12; Revised 2021 August 07; Accepted 2021 August 29.

Abstract

Background: Coronavirus disease 2019 (COVID-19) has become a global health challenge with high transmission and mortality rates.

Objectives: This study aimed to identify the risk factors for mortality in hospitalized patients with COVID-19 in Behbahan, Southwestern of Iran.

Methods: In this cross-sectional study, information of 800 patients with COVID-19 admitted to Shahidzadeh Hospital in Behbahan, Southwest of Iran, were investigated from March 20, 2020, to January 20, 2021. Subsequently, the demographic characteristics, clinical symptoms, vital signs, pharmacotherapy, laboratory findings, and the patients' underlying diseases were extracted from their medical records. Multivariable Cox regression with proportional hazard assumption was used to investigate the risk factors of death.

Results: The present study included 800 patients with COVID-19 with a mean age of 57.51±16.83 years at the time of diagnosis. Overall, 447 (55.8%) male and 353 (44.1%) female patients were included in this study, respectively. Among the total patients, 116 (14.5%) and 684 (85.5%) cases died and recovered, respectively. Based on the multivariable Cox regression analysis, age (HR=1.04; 95% CI: 1.03-1.05; P<0.001), cardiovascular diseases (HR=2.46; 95% CI: 1.63- 3.70; P<0.001), and renal failure (HR=2.77; 95% CI: 1.43- 5.34; P<0.001) were found to be associated with the death hazard in patients with COVID-19.

Conclusion: According to the findings of this study, the patient's age at the time of diagnosis, cardiovascular diseases, and renal failure were indicated to be the risk factors of high mortality rate in patients with COVID-19. Identification of these risk factors can be helpful in the timely intervention of patients at high risk of death for health care providers.

Keywords: COVID-19, Iran, Mortality, Risk factors, Prognostic factors

1. Background

In December 2019, a new variant of coronavirus from the coronavirus family emerged in Wuhan, China. Afterward, this disease rapidly spread around the world, and on February 11, 2020, it was announced as an epidemic (1,2). The recently discovered coronavirus is the cause of coronavirus disease 2019 (COVID-19). Most people infected with COVID-19 mostly experience mild to moderate respiratory disease and recover with performing no special treatment (3). Older people and those with underlying diseases, such as chronic respiratory disease, cardiovascular diseases, diabetes, and cancer are more at the risk of severe illness and death, compared to normal people (3,4). The results of recently performed meta-analyses in this regard have shown that underlying diseases, such as diabetes, coronary heart disease, and hypertension are the main prognostic factors of high mortality in patients with COVID-19 (5,6). Some studies conducted in Iran and the United States also confirmed age, gender, and underlying diseases as the main prognostic factors responsible for death

risk (4,7-9). Another meta-analysis indicated a relationship between tobacco use and high mortality rate among patients with COVID-19 (10). Strong knowledge of prognostic factors and predictors that may be involved in the death of patients with COVID-19 is essential because by identifying these factors, the chance of treatment of high-risk patients is higher through early and intensive interventions (11). On the other hand, due to the demographic characteristics of different regions, the risk factors associated with mortality in patients with COVID-19 may be different. Studies in different areas can better find the risk factors associated with mortality in different populations, and based on this, appropriate interventions can be performed.

2. Objectives

The present study aimed to identify the prognosis factors of the risk of death among the hospitalized patients with COVID-19 in Behbahan, Southwest of Iran.

3. Methods

3.1. Sample Collection

This cross-sectional study investigated the data of 800 patients with a definitive diagnosis of COVID-19 (positive RT-PCR test) who were hospitalized in Shahidzadeh Hospital in Behbahan, Southwestern Iran, from March 20, 2020, to January 20, 2021. All patients' information (demographic characteristics, clinical signs, vital signs, and underlying diseases) was extracted from their medical records and recorded. Patients whose files were incomplete or voluntarily discharged from the hospital were excluded from the study. In this study, demographic characteristics included age and gender. Clinical signs upon admission included chills, pain and bruising, weakness and lethargy, dry mouth, loss of smell, headache, sore throat, runny nose, cough, chest pain, dyspnea, loss of taste, anorexia, abdominal pain, nausea and vomiting, diarrhea, loss of consciousness, vertigo and orthopnea. Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate, and oxygen saturation. Furthermore, underlying diseases included hypertension, diabetes, renal failure, cardiovascular diseases, hypothyroidism, hyperlipidemia, cancer, rheumatism, osteoporosis, and peptic ulcer. Information on the history of heart disease and stroke, as well as smoking, was also extracted. Laboratory and biochemical tests included white blood cell count (WBC), red blood cell count (RBC), platelet count (PLT), blood urea nitrogen (BUN), and creatinine (CR). Patients' therapeutic medications during hospitalization included Ribavirin, Kaletra, Hydroxychloroquine, Atazanavir/Ritonavir, Oseltamivir, Favipiravir, Remdesiver, Seroflo, Atrovent, Sofosbuvir, Corticosteroids, Antibiotic, and Naproxen. The time (by day) from hospital admission to death or recovery was considered the response variable.

3.2. Statistical Analysis

The obtained data were analyzed in SPSS (version 26) and R (version 3.5.1) software along with the survival package. Quantitative and qualitative data were described as mean±SD, as well as frequency and percentage, respectively. Mann-Whitney test was used for detecting differences in the mean values of continuous variables between the two groups (survival and death). Chi-square test or Fisher's exact test as appropriate were employed for classification of data, and survival times between groups were compared using Kaplan-Meier curve and log-rank test. Furthermore, Cox regression with the assumption of proportional hazard (PH) was employed to investigate the prognosis factors associated with mortality in COVID-19 patients. Initially, variables with a p-value less than 0.2 were identified using univariate Cox regression and

entered into multivariable Cox regression. In Cox regression, multivariable variables were identified using the backward method ($P<0.05$) on the hazard (risk) of death of COVID-19 patients.

4. Results

The present study included 800 patients with COVID-19 with a mean age of 57.51 ± 16.83 years (age range: 13-96 years) at the time of diagnosis. The study sample consisted of 447 (55.8%) male and 353 (44.1%) female patients. Among the total patients, 116 (14.5%) and 684 (85.5%) cases died and recovered, respectively. The most common clinical symptoms at the time of admission were dyspnea (61.4%), cough (43.4%), chills (40.8%), as well as weakness and lethargy (29.9%). Moreover, underlying diseases, including hypertension ($n=198$; 24.8%), diabetes ($n=199$; 24.9%), and cardiovascular diseases ($n=87$; 10.9%) obtained the highest frequency. Table 2 tabulates the laboratory findings of the patients upon admission, which show that the WBC was significantly higher in the group who died, compared to the group that survived ($P<0.05$).

On the other hand, RBC, PLT, and HGB were significantly lower in those who died, compared to those who survived ($P<0.05$). In addition, the results of biochemical and coagulation tests of BUN and Cr in the group who died were significantly higher, compared to the other group (recovered or survived) ($P<0.05$).

In the univariate model, age, cardiovascular diseases, diabetes, renal failure, hyperlipidemia, as well as a history of stroke and heart attack with a p-value less than 0.2 entered the final model. Analysis of the final model (multivariable Cox regression) showed that age, cardiovascular diseases, and renal failure were associated with mortality in COVID-19 patients. As the age of each year increases, the hazard of death increases by 4%, ($HR=1.04$; 95% CI: 1.03-1.05; $P<0.001$). Moreover, the hazard of death in cardiovascular patients was 2.46 times higher than those without cardiovascular diseases ($HR=2.46$; 95% CI: 1.63-3.70; $P<0.001$). In addition, patients with renal failure had a 2.77 times higher hazard of death than those without renal failure ($HR=2.77$; 95% CI: 1.43- 534; $P<0.001$) (Table 3).

Based on the Kaplan-Meier survival curve and Log-rank test survival curve, it was observed that the survival rate among patients with cardiovascular, diabetes, and renal failure diseases were significantly lower than that of other patients ($P<0.05$). In fact, these groups of patients experienced more severe disease stages (Figure 1; Table 3). On the other hand, evidence showed (Table 2) that mortality in patients with cardiovascular and renal failure diseases was higher than that in other patients. Other variables, such as cancer and gender showed no statistically significant difference in this regard.

Table 1. Demographic characteristics and symptoms of patients with COVID-19 (n=800)

Variables	Total	Survival	Death	P-value
Overall	800	684 (85.5%)	116 (14.5%)	-
Demographic characteristics				
Age (mean±SD)	57.51±16.83	55.56±16.23	69.4±15.72	<0.001
Gender				0.411
Female	353 (44.1 %)	306 (86.7%)	47 (13.3%)	
Male	447 (55.9 %)	378 (84.6%)	69 (15.4%)	
Clinical manifestations upon admission				
Chills	326 (40.8 %)	276 (84.7%)	50 (15.3%)	0.582
Pain and bruising	152 (19.0 %)	143 (94.1%)	9 (5.9%)	0.012
Weakness and lethargy	239 (29.9 %)	196 (82.1%)	43 (17.9%)	0.673
Loss of smell	33 (4.1 %)	30 (90.9%)	3 (9.1%)	0.388
Headache	78 (9.8 %)	73 (93.6%)	5 (6.4%)	0.031
Sore throat	24 (3.0 %)	23 (95.8%)	1 (4.2%)	0.142
Runny nose	6 (0.8 %)	6 (100%)	0 (0)	0.312
Cough	347 (43.4 %)	314 (90.5%)	33 (9.5%)	<0.001
Chest pain	39 (4.9 %)	35 (89.7%)	4 (10.3%)	0.441
Dyspnea	491 (61.4 %)	416 (84.7%)	75 (15.3%)	0.434
Anorexia	107 (13.4 %)	97 (90.7%)	10 (9.3%)	0.121
Abdominal pain	25 (3.1 %)	23 (92%)	2 (8%)	0.354
Nausea and vomiting	80 (10 %)	75 (93.8%)	5 (6.2%)	0.036
Diarrhea	31 (3.9 %)	29 (93.5%)	2 (6.5%)	0.224
Loss of consciousness	38 (4.8 %)	13 (34.2%)	25 (65.8%)	<0.001
Vertigo	31 (3.9 %)	27 (87.1%)	4 (12.9%)	0.831
Orthopnea	36 (4.5 %)	34 (94.4%)	2 (5.6%)	0.126
Vital signs upon admission				
Fever (T> 37,5 C)	256 (32 %)	213 (83.2%)	43 (16.8%)	0.215
Spo2<93	436 (57.9 %)	403 (92.4%)	33 (7.6%)	<0.001
Respiratory rate (mean±SD)	21.15±2.88	21±2.51	22±4.38	0.014
Systolic blood pressure (mean±SD)	116.45±19.73	116.01±18.70	119.04±25.10	0.384
Diastolic blood pressure (mean±SD)	73.02±27.95	73.10±29.75	73.13±13.12	0.548
Heart rate (mean±SD)	91.83±17.48	91.54±17.11	93.56±19.51	0.331
Underlying diseases				
Hypertension	198 (24.8%)	162 (81.8%)	36 (18.2%)	0.090
Diabetes	199 (24.9%)	159 (79.9%)	40 (20.1%)	0.012
Renal failure	25 (3.1%)	15 (60%)	10 (40%)	<0.001
Cardiovascular disease	87 (10.9%)	55 (63.2%)	32 (36.8%)	<0.001
Hypothyroidism	15 (1.9%)	14 (93.3%)	1 (6.7%)	0.386
Hyperlipidemia	35 (4.4%)	34 (97.1%)	2 (2.9%)	0.040
Cancer	10 (1.3%)	9 (90%)	1 (10%)	0.684
Rheumatism	10 (1.3%)	8 (80%)	2 (20%)	0.627
Osteoporosis	9 (1.13%)	7 (77.8%)	2 (22.2%)	0.519
Peptic ulcer	16 (2%)	13 (81.3%)	3 (18.7%)	0.634
History of stroke	30 (3.8%)	22 (73.3%)	8 (26.7%)	0.051
History of myocardial infarction	20 (2.5%)	15 (75%)	5 (15%)	0.182
Smoking	71 (2.5%)	55 (77.5%)	16 (22.5%)	0.050
Length of hospital stay	6.65±4.67	6.36±4.32	8.35±6.12	-

Table 2. Laboratory test results of patients with COVID-19

Demographic features	Total Mean±SD	Survival Mean±SD	Death Mean±SD	P-value
Overall	800	684	116	-
WBC, × 10⁹/L	7.85±5.83	7.53±4.76	10.85±11.52	0.007
RBC, ×10¹²/L	4.59±0.78	4.63±0.73	4.32±0.82	<0.001
PLT, ×10⁹/L	218.73±89.49	221.49±88.40	192.64±96.21	0.003
HGB, g/L	12.76±2.13	12.86±2.05	11.73±2.54	<0.001
BUN mmol/L	20.43±17.67	18.39±12.10	39.32±38.40	<0.001
Cr, mg/dL	1.32±1.26	1.22±0.85	2.21±3.01	<0.001

WBC: White blood cell count;

RBC: Red blood cell count;

PLT: Platelet count;

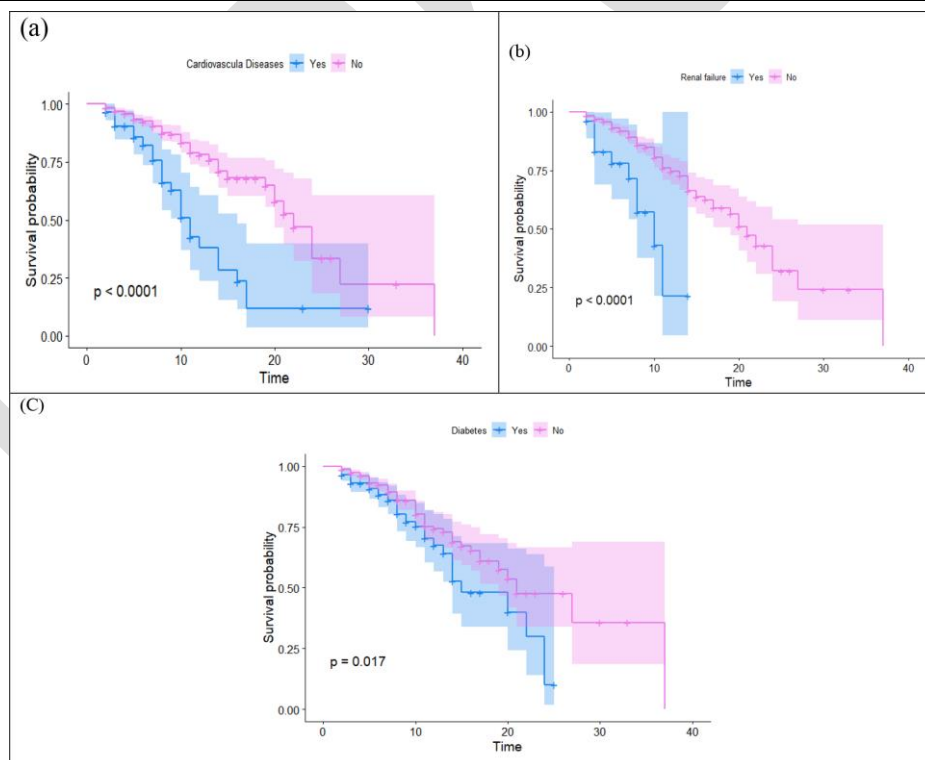
HGB: Hemoglobin;

BUN: Blood urea nitrogen;

Cr: Creatinine

Table 3. Result of univariate and multivariable Cox proportional hazard survival analysis in patients with COVID-19

Variables	Univariate Hazard Ratio (95%CI)	P-value	Multivariable Hazard Ratio (95%CI)	P-value
Age	1.03 (1.02- 1.06)	<0.001	1.04 (1.03- 1.06)	<0.001
(Gender) (ref: Male)	1.11 (0.77- 1.62)	0.577		
Cardiovascular disease(ref: No)	3.44 (1.59- 7.43)	0.002	2.77 (1.43- 5.34)	<0.001
Hypertension (ref: No)	0.99 (0.66- 1.48)	0.961	-	-
Renal failure (ref: No)	3.61 (1.87- 6.95)	<0.001	2.46 (1.63- 3.7)	<0.001
Diabetes (ref: No)	1.60 (1.09- 2.35)	0.021	-	-
Hypothyroidism (ref: No)	0.34 (0.04- 2.42)	0.282	-	-
Hyperlipidemia (ref: No)	0.23 (0.03- 1.68)	0.151	-	-
History of Stroke (ref: No)	2.25 (1.09- 4.64)	0.030	-	-
History of Myocardial Infarction (ref: No)	1.91 (0.78- 4.69)	0.161	-	-
Rheumatism (ref: No)	1.8 (0.44- 7.31)	0.413	-	-
Osteoporosis (ref: No)	0.95 (0.23- 3.84)	0.942	-	-
Peptic ulcer (ref: No)	1.54 (0.49- 4.84)	0.467	-	-
Cancer (ref: No)	0.69 (0.1- 4.95)	0.715	-	-
Smoking (ref: No)	1.12 (0.65- 1.93)	0.692	-	-

**Figure 1.** Kaplan-Meier curve for the clinical variables in the COVID-19 patients in Behbahan, Iran. (a) Cardiovascular disease patients with COVID-19; (b) Renal failure patients with COVID-19; (c) Diabetic patients with COVID-19

5. Discussion

This study aimed to identify the prognosis factors of the risk of death among the hospitalized

patients with COVID-19 in Behbahan, Southwest of Iran, using the proportional Cox risk model. The results of the present study showed a significant relationship of the risk of death of patients with

COVID-19 with aging, cardiovascular diseases, and renal failure. In the current study, the patients' age at the time of diagnosis was found as an important prognostic factor in the risk of death among those with COVID-19 and for every 1 year of age, the risk of death increases by 4%. Recently, the results of a study conducted on patients with COVID-19 in Iran have demonstrated that with increasing age every year, the risk of death of patients with COVID-19 increases by 2% (12). Another study performed in Italy reported age as one of the strongest predictors of mortality in COVID-19 patients (10). Moreover, the results of a study in China indicated a relationship between age and risk of death among patients with COVID-19 (13). Notably, with aging, the immune response to infectious agents becomes weaker, especially in the elderly, who are more susceptible to infection at its severe stage. Furthermore, underlying diseases, especially in older people, put them at more risk of developing COVID-19 associated with worse outcomes, such as death (4,14).

Based on the results of this study, cardiovascular diseases were identified as an important factor effective in increasing the risk of death among COVID-19 patients. Patients with cardiovascular diseases due to their weakness and sensitivity to cardiac involvement are at special risk of death caused by COVID-19 (15). Recently, the results of studies performed in Iran and China have indicated that coronary heart disease is a risk factor for death in COVID-19 patients (16,17).

A British study also found that patients with both COVID-19 and heart failure were more likely to be at the risk of death (18).

The results of a study conducted in Spain also showed the increased number of deaths in patients with both COVID-19 and acute heart failure (19). Moreover, in the current study, it was found that patients with kidney failure were at greater risk of death resulted from COVID-19. Additionally, diffuse alveolar damage was found as the main feature of COVID-19. However, the involvement of other organs is important; therefore, it should be considered. After lung infection, the penetrated virus may enter the circulation, be accumulated in the kidney, and damage the residual cells of the kidney. On the other hand, patients with a history of chronic kidney disease have a pro-inflammatory environment and functional defects in innate and adaptive immune cells, which may make them more vulnerable. Recently, a study in Iran showed high mortality rates in COVID-19 patients with kidney disease (4). On the other hand, the results of a study conducted on hemodialysis patients with COVID-19 in Romania showed a high mortality rate. In fact, lower serum albumin, anemia, and low basal oxygen saturation when entering the hospital were reported as factors associated with poor prognosis (20).

Limitation

One of the limitations of the present study was the lack of complete results of computed tomography findings and the percentage of lung involvement in patients since it was not performed in many patients, which might have affected the results of the study. On the other hand, the present study was conducted in a specific geographical area in Iran, which may be socio-economically different from other regions with different populations. Moreover, there may even be some unknown genetic or environmental factors that affect the results of the study; therefore, the findings of this study may not be generalized to other populations.

Strengths

Despite the limitations of this study, complete information on clinical and vital signs, pharmacotherapy, and underlying diseases of patients were collected through their medical records and recorded. The results of this information led to the recognition of the effects of prognostic factors, such as age, cardiovascular diseases, and renal failure on the risk of death in COVID-19 patients.

6. Conclusion

The findings of this study showed that age, history of cardiovascular diseases, and renal failure were critical prognostic factors effective in the risk of mortality in COVID-19 patients. Identification of these risk factors is necessary for health care providers, which can be effective in the timely intervention of patients at high risk of death.

Acknowledgments

This study was supported by Behbahan Faculty of Medical Sciences, Behbahan, Iran. The authors are grateful to Behbahan Shahidzadeh Hospital Archive personnel for their helpful corporation.

Footnotes

Authors' contribution: T N M and K A A: Study design, data analysis, and writing of the first draft of the manuscript. A A, S A, V R N, and A P: Data collection under the supervision of T N M. J F A, J Z, and M S: Manuscript review and interpretation of the study results. J F A, J Z, and M S: Clinical review and interpretation of the results, and help collect and control data quality.

Conflicts of Interest: The authors have no conflicts of interest to report.

Ethical Approval: The study protocol was approved by the Ethics Committee of Behbahan Faculty of Medical Sciences, Behbahan, Iran (IR.BHN.REC.1399.062).

Funding/Support: This study was supported by Behbahan Faculty of Medical Sciences, Behbahan, Iran.

Financial Disclosure: None

Informed consent: Not applicable.

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