Risk factors for COVID-19 severity and mortality among inpatients in Southern Iran

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Summary

Introduction. *COVID-19 is a highly contagious respiratory disease and many factors can affect its severity and mortality. This study aimed to investigate the risk factors associated with the severity and mortality of COVID-19.*

Methods. *In this cross-sectional study, 311 cases with COVID-19 approved by the CORONALAB database in the Center for Disease Control and Prevention (CDC) in southern Iran were selected using systematic random sampling from 15 May to 13 June 2020. The data were collected through interviews and phone calls using a researcher-made questionnaire.*

Results. *The mean age of the participants was 45.82 ± 17.92 years, and the male to female ratio was 1.57:1. In addition, the Case Fatality Rate (CFR) was 4.50%, and the disease was severe in 47.5% of the cases. The most common clinical symptoms were cough (39.22%), fever (31.83%), and dyspnea (24.76%). The*

severity of COVID-19 was significantly associated with age and history of Cardiovascular Disease (CVD). Besides, the mortality of COVID-19 was significantly related to age, gender, hypertension, CVD, and Chronic Kidney Disease (CKD). The mean interval between the onset of the first symptom and referral to a health center was 3.02 ± 2.82 days. Additionally, the mean interval between the referral to health centers and testing was 0.88 ± 2.20 days.

Conclusion. *Older patients, males, and those who had CVD, CKD, and hypertension required accurate healthcare and early intervention to prevent the exacerbation of COVID-19. Furthermore, the interval between the onset of the first symptom and testing was relatively long. Overall, early diagnosis, isolation, and treatment of patients were found to be essential to control COVID-19.*

Introduction

Coronavirus 2019 (COVID-19) is highly contagious and spreads rapidly from one individual to another [1]. This disease has become a global concern and an important health problem, as the number of infected people and affected countries has been increasing rapidly [2]. The dramatic increase in the number of severe infections in Acute Coronavirus Respiratory Syndrome 2 (SARS-CoV-2) has led to "an urgent need to expand public health activities to clarify the epidemiological characteristics of this new virus and to identify its potential effects" [3]. Given the fact that the mortality rate of COVID-19 is about 3% and more than 20% of patients develop a severe disease, COVID-19 has been considered a global health emergency [4].

This disease is highly contagious and each infected person can infect at least three other people on the average [5]. Most cases have mild symptoms such as fever, cough, sore throat, and myalgia. However, some cases experience severe conditions such as multiple organ involvement, acute respiratory syndrome, pulmonary edema, and pneumonia [6-8]. Due to the transmission of COVID-19 from person to person, the virus can be transmitted to

other susceptible people from the cases who have not been undiagnosed or were not diagnosed soon, which increases the risk of the transmission of COVID-19 infection.

There is currently no evidence of Randomized Controlled Trials (RCTs) recommending any specific anti-SARS-CoV-2 treatment for patients with COVID-19 infection. Hence, rapid and accurate diagnosis of COVID-19 is very important to control its prevalence in the community and hospitals [9]. Yet, it is not easy to diagnose COVID-19 and the delay between the onset of symptoms and accurate diagnosis has been frequently observed. Except for confirmed cases of pneumonia, there are still many undiagnosed infections and delayed diagnoses due to the lack of diagnostic reagents as well as long waiting times for diagnosis [10]. Therefore, it is very important to be able to diagnose and treat the infection in a timely manner. Different studies have shown that the progression or mortality of COVID-19 could be affected by various factors including old age, male gender, history of diabetes, hypertension, CVD, and kidney disease [11-13]. Moreover, the mortality rate of COVID-19 varied between the patients admitted in Intensive Care Units (ICU) and non-ICU patients as well as between severe and non-severe cases. Accordingly, the mortality rate was

higher among the patients admitted to ICUs and severe cases compared to non-ICU and non-severe ones [14, 15]. Since the severity and mortality of COVID-19 disease can be affected by various factors, the present study aims to investigate the risk factors associated with the severity and mortality of COVID-19 with regard to the time interval between the onset of the first symptom and referring to health centers for testing.

Methods

STUDY DESIGN AND DATA COLLECTION

The Center for Disease Control and Prevention (CDC) for COVID-19 was established in Fars province on February 20, 2020 to monitor the spread of COVID-19. Fars province is the fourth most populous province in Iran, with Shiraz as its capital, that is located in south of the country. In this study, 311 COVID-19 cases approved by the CORONALAB database at the CDC of Shiraz University of Medical Sciences were selected using systematic random sampling from 15 May to 13 June 2020. Diagnosis of COVID-19 for the suspected cases was confirmed using throat and nose samples and Real-Time Polymerase Chain Reaction (RT-PCR) test.

The data were collected using a researcher-made questionnaire. The reliability of the questionnaire was evaluated among 25 individuals via the test-retest method with a two-week interval. The intra-cluster correlation coefficient was 0.79, revealing the acceptable reliability of the questionnaire.

During active care, the patients received a phone call at home or were visited in the hospital. Then, their information was collected and completed via interviews. The history of diseases and medical records were checked for hospitalized patients. The patients who were isolated at home were called, as well. In case they mentioned the history of diseases, they were asked to refer to the health centers with their medical records for further examinations after the isolation period.

The demographic characteristics of all the cases were recorded, which included age, gender, occupation, disease severity, patient care status, symptoms (fever, cough, shortness of breath, cyanosis, gastrointestinal problems, sore throat, and runny nose), comorbidities (diabetes, hypertension, cancer, CVD, and CKD), history of physical contact with patients, time of onset of the first symptom, and time of referring to health centers and testing. The patients were divided into severe and non-severe groups according to the severity of their disease and the American Thoracic Society guidelines for community-acquired pneumonia [16, 17].

STATISTICAL ANALYSIS

Relative and absolute frequencies were calculated for grouping the variables. Mean and standard deviation were calculated for quantitative variables. The relationships between the qualitative variables were determined by chi-square test. In addition, the interval between the onset of the first symptom and referral to health centers, the interval between referral to health centers and testing, and the interval between the onset of the first symptom and testing were calculated and their relationships with gender, disease severity, and mortality were assessed using t-test. The significance level was set at 0.05.

Results

The mean age of the cases was 45.82 ± 17.92 years. The youngest case was one year old and the oldest case was 87 years old. Most cases (49.02%) belonged to ≤ 45 age group. In addition, 61.09% of the cases were male, with the male to female ratio of 1.57:1.98. Besides, 39% of the cases were Iranian, and 9.65% were healthcare personnel. Moreover, 47.5% of the cases had severe disease and were admitted to the ICU. The most common clinical symptoms included cough (39.23%), fever (31.83%), and dyspnea (24.76%). The mortality rate was 4.50%. Furthermore, 15.76% of the patients had a history of physical contact with an infected person, 7.72% had diabetes, 6.75% had CVD, and 5.47% had hypertension.

The results showed a statistically significant relationship between the severity of COVID-19 and age ($p = 0.017$) and CVD ($p = 0.021$). There was also a statistically significant relationship between the mortality of COVID-19 and gender ($p = 0.046$), age ($p = 0.001$), hypertension ($p = 0.034$), CVD ($p = 0.01$), and CKD ($p = 0.002$). Cough was the prognostic factor for the severity of COVID-19, but had no significant relationship with mortality. The results also revealed no statistically significant relationship between nationality and occupation and COVID-19 severity and mortality ($p > 0.05$) (Tab. I).

The interval between the onset of the first symptom and referral to health centers and testing based on gender, disease severity, and mortality of COVID-19 has been presented in Table II. Accordingly, the mean interval between the onset of the first symptom and referral to health centers was 3.02 ± 2.82 days (range: 0-12 days), the mean interval between referral to health centers and testing was 0.88 ± 2.20 days (range: 0-12 days), and the mean interval between the onset of the first symptom and testing was 3.90 ± 3.55 days (range: 0-18 days). The results indicated a statistically significant relationship between the interval between the onset of the first symptom and testing and the mortality of COVID-19 ($p < 0.001$). The mean interval between the onset of the first symptom and testing was longer in the cases who were still alive than in the dead cases (3.99 ± 3.55 *vs* 0.63 ± 1.18).

Discussion

This study was conducted on 311 cases with COVID-19 approved by the CORONA database in southern Iran in order to determine the risk factors of COVID-19 severity and mortality. The results showed a statistically significant relationship between the severity of COVID-19 and age

Tab. I. Demographic and clinical characteristics of the COVID-19 cases.

Variables	Total n = 311	Disease severity Non-severe n = 294	Severe n = 17	P-value*	Disease mortality Alive n = 297	Dead n = 14	P-value*
Gender							
Male	190 (61.09)	179 (94.21)	11 (5.79)	0.753	185 (97.37)	5 (2.63)	0.046
Female	121 (38.91)	115 (95.04)	6 (4.96)		112 (92.56)	9 (7.44)	
Age (years)							
< 25	26 (8.36)	25 (96.15)	1 (3.85)		26 (100)	0 (0)	
25-44	132 (42.44)	130 (98.48)	2 (1.52)	0.017	132 (100)	0 (0)	0.001
≥ 45	153 (49.20)	139 (90.85)	14 (9.15)		139 (90.85)	14 (9.15)	
Occupation							
Healthcare worker	30 (9.65)	30 (100)	0 (0)	0.388	29 (96.67)	1 (3.33)	1
Non-healthcare worker	281 (90.35)	264 (93.95)	17 (6.05)		268 (95.37)	13 (4.63)	
Nationality							
Iranian	306 (98.39)	289 (94.44)	17 (5.56)	1	292 (95.42)	14 (4.58)	1
Non-Iranian	5 (1.61)	5 (100)	0 (0)		5 (100)	0 (0)	
Signs and ** **symptoms**							
Cough	122 (39.23)	111 (90.98)	11 (9.02)	0.027	116 (95.08)	6 (4.92)	0.776
Fever > 38	99 (31.83)	95 (95.96)	4 (4.04)	0.450	96 (96.97)	3 (3.03)	0.560
Sore throat	61 (19.61)	60 (98.36)	1 (1.64)	0.211	59 (96.72)	2 (3.28)	1
Dyspnea	77 (24.76)	70 (90.91)	7 (9.09)	0.144	74 (96.10)	3 (3.90)	1
Gastrointestinal problems	37 (11.90)	35 (94.59)	2 (5.41)	1	37 (100)	0 (0)	0.388
Rhinorrhea	18 (5.79)	17 (94.44)	1 (5.56)	1	18 (100)	0 (0)	1
Cyanosis	4 (1.29)	4 (100)	0 (0)	1	4 (100)	0 (0)	1
Other	7 (2.25)	7 (100)	0 (0)	1	7 (100)	0 (0)	1
History of contact with infected cases (yes)	49 (15.76)	48 (97.96)	1 (2.04)	0.684	48 (97.96)	1 (2.04)	0.293
Medical history							
Diabetes	24 (7.72)	22 (91.67)	2 (8.33)	0.630	21 (87.50)	3 (12.50)	0.084
Hypertension	17 (5.47)	15 (88.24)	2 (11.76)	0.236	14 (82.35)	3 (17.65)	0.034
Cardiovascular disease	21 (6.75)	17 (80.95)	4 (19.05)	0.021	17 (80.95)	4 (19.05)	0.010
Chronic kidney disease	7 (2.25)	5 (71.43)	2 (28.57)	0.050	4 (57.14)	3 (42.86)	0.002
Cancer	3 (0.96)	3 (100)	0 (0)	1	3 (100)	0 (0)	1
Other diseases**	12 (3.86)	8 (66.67)	4 (33.33)	0.002	8 (66.67)	4 (33.33)	0.001

* Chi-square test; ** Other diseases included psychiatric diseases, cerebral palsy, rheumatoid arthritis, neurodegenerative diseases, stroke, etc.

Tab. II. The interval between the onset of the first symptom and testing for COVID-19 detection.

Interval (day)	Total	Gender Male	Female	P-value*	Disease severity Non-severe	Severe	P-value*	Disease mortality Alive	Dead	P-value*
The first symptom to admission (μ ± SD)	3.02 ± 2.82	2.99 ± 2.81	3.06 ± 2.83	0.845	3.03 ± 2.79	2.73 ± 3.52	0.726	3.02 ± 2.83	3 ± 2.20	0.984
Admission to testing (μ ± SD)	0.88 ± 2.20	0.87 ± 2.24	0.90 ± 2.16	0.923	0.90 ± 2.23	0.36 ± 1.21	0.429	0.84 ± 2.18	2.63 ± 2.44	0.078
The first symptom to testing (μ ± SD)	3.90 ± 3.55	3.88 ± 3.49	3.93 ± 3.65	0.897	3.93 ± 3.55	3.09 ± 3.65	0.443	3.99 ± 3.55	0.63 ± 1.18	< 0.001

* T-test.

and CVD. In addition, the mortality of COVID-19 was significantly related to gender, age, hypertension, CVD, and CKD. The interval between the onset of symptoms and referral to health centers and testing was also assessed in the present study. The results demonstrated that COVID-19 mortality was significantly related to the interval between the onset of the first symptom and testing.

In the present study, the mean age of the cases was 45.82 ± 17.92 years. In another study, the mean age of the cases was 55.50 ± 15.15 years [18], which was higher

compared to the present study. In addition, the male to female ratio was 1.57:1, but this measure was found to be 1.93:1 and 1.6:1 in the studies conducted in Tehran and Shiraz, respectively [17, 18].

In the current investigation, 5.47% of the cases had the severe form of the disease. In another study, approximately 14% of the people infected with COVID-19 had severe disease and 6% had very severe disease [19]. In the current study, severe cases included those admitted to the ICU. Furthermore, 9.65% of the cases were healthcare personnel, while this measure was found to be 2.8% in another research [17].

The current study findings revealed that the Case Fatality Rate (CFR) was 4.50% in all the cases and 35.29% in severe ones. The results of a systematic review and meta-analysis indicated that CFR was 13% in hospitalized cases [6]. In other studies conducted in Iran, CFR was reported to be 8.06 and 55.6% in hospitalized patients [17, 18]. This measure was found to be 15 and 11% in China [7, 20]. Overall, the CFR was lower in the present study than in other studies, which might be due to the prompt and timely treatment of severe COVID-19 cases.

The present study findings revealed a significant relationship between age and COVID-19 severity and mortality. Accordingly, COVID-19 was more severe and resulted in higher mortality in older ages. Other studies have also shown a higher risk of mortality in older ages [18, 21]. The reasons for the higher severity and mortality of COVID-19 at older ages could be the higher prevalence of comorbidities in this age group. It has also been stated that old age was associated with the decreased immune system capacity [22].

The present study findings demonstrated a significant relationship between gender and COVID-19 mortality (p = 0.046). Based on the results, nearly 35% of the severe cases and 63% of the dead ones were female. However, other studies indicated that the mortality rate was higher in males than in females [17, 18, 23]. In a prior research, estrogen protected against such pathogens as HIV, hepatitis C virus, Ebola, and human cytomegalovirus in females [24]. Estrogen receptor signaling also played an essential role in coronavirus infection and mortality [25]. Another study demonstrated that estrogen signaling could be one of the reasons for the rapid recuperation and low mortality due to COVID-19 amongst females [26]. The discrepancy between the results might be associated with the comorbidities or higher age of the females suffering from COVID-19 in the present study.

The current study results showed that the severity of COVID-19 was significantly associated with CVD and its mortality was correlated to hypertension, CVD, and CKD. The results of a meta-analysis also revealed that the mortality of COVID-19 was higher in patients with CVD and CKD [27]. Countries with the highest mortality rates such as the United States, Europe, and China have been shown to have the highest incidence of these chronic diseases [28]. The results of another study proved that hypertension increased the risk of severity or mortality of COVID-19 by almost 2.5 times [29]. Moreover, the risk of developing severe COVID-19 was three times higher

in the CKD patients than in those without CKD. The suppressed immune system might significantly predispose CKD patients to infectious complications. Likewise, having a chronic systemic inflammation could increase their mortality [30]. In addition to the explored variables, a high genetic burden was strongly related to the severity and hospitalization risk of COVID-19, particularly amongst people with few recognized risk factors [31].

In the present study, cough (39.23%) was the most common clinical symptom as well as a prognostic factor for the disease severity (p = 0.027). Similarly, other studies indicated that cough was a common clinical symptom of COVID-19 [8, 32, 33]. Another research also revealed that cough was associated with the severity of COVID-19 [32, 34], which was in agreement with the current study findings [8, 33].

The results of the present investigation showed that the mean interval between the onset of the first symptom and referral to health centers was 3.02 ± 2.82 days, the mean interval between referral to the health centers and testing was 0.88 ± 2.20 days, and the mean interval between the onset of the first symptom and testing was 3.90 ± 3.55 days. There was a statistically significant relationship between the interval between the onset of the first symptom and testing and the mortality of COVID-19 (p < 0.001). Accordingly, the mean interval between the onset of the first symptom and testing was longer in the alive cases than in the dead ones (3.99 ± 3.55 *vs* 0.63 ± 1.18 days). In fact, the patients who died had more severe symptoms at the onset of the disease and, consequently, they had referred to health centers for treatment earlier, while it took longer to take the test from the patients who did not have severe symptoms. Since the people who are asymptomatic or have mild symptoms are still able to transmit the disease, it is necessary to examine all the patients immediately after their referral to health centers. Due to the fact that the mean interval between the onset of the first symptom and referral to health centers and testing was relatively long, there is a need for public education and raising public awareness about the symptoms of COVID-19 and referral to health centers for testing as soon as possible.

One of the strong points of the present research was that it evaluated the relationship between the severity and mortality of COVID-19 and the interval between the onset of the first symptom and referral to health centers, interval between referral to health centers and testing, and interval between the onset of the first symptom and testing. However, one of the limitations of the study was that the patients' biochemical test results and lung CT scans were not available. Therefore, further studies are required to consider other risk factors such as laboratory and radiological markers in addition to demographic and clinical factors. Moreover, the researchers did not have access to the patients' complete information about the history of diseases such as diabetes (HbA1c, controlled or not), cancer status (current or past, type of cancer, stage, and course of therapy), and CKD stages. Another study limitation was related to the interview method. In fact, the history of diseases and medical records were checked for the hospitalized patients, while phone calls

were made to contact the patients who were isolated at home. In case they mentioned the history of diseases, they were asked to refer to the health centers with their medical records for further examinations.

Conclusions

Old age and CVD were associated with the severity of the disease in patients with COVID-19. Therefore, these patients required accurate healthcare as well as early intervention to prevent the exacerbation of the disease. Moreover, older age, female gender, and having a history of hypertension, CVD, and CKD might increase the risk of COVID-19 mortality. Since the interval between the onset of the first symptom and testing was relatively long, it is essential to make a timely diagnosis, stay in quarantine, and treat the patients as soon as possible to control COVID-19. Future studies are suggested to evaluate the predictors of COVID-19 severity and mortality based on the risk factors revealed in the present research.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the study conception and design. AMA and HG participated in the design of the study. MGG and FR performed data collection, wrote the manuscript, helped with statistical analysis, and prepared the illustrations. AH and FR edited the manuscript. All authors read and approved the final manuscript.

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