

Epidemiological and Clinical Risk Factors Related to Severe COVID-19 in Iran: A multi-center study

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Abstract

Background Iran was one of the first countries to be affected by COVID-19. Identifying factors associated with severity of COVID-19 is effective in disease management. This study investigated the epidemiological and clinical features and factors associated with severity of COVID-19 in one of the less privileged areas in Iran.

Methods In a multi-center study, all patients admitted to hospitals of Zahedan University of Medical Sciences located in southeastern Iran were investigated from February 29 to April 31, 2020. Demographic, epidemiological and clinical data of patients were extracted from medical records. To explore the risk factors associated with severity of COVID-19, bivariate and multivariate logistic regression models were used.

Results Among the 413 patients, 55.5% were male and 145 (35.10%) were in a severe condition at admission time. Multivariate analysis showed that the adjusted odds of the disease severity increased in patients with older age (OR 3.51; 95% CI, 2.28-5.40), substance abuse (OR 2.22; 95% CI, 2.05-5.78) and at least one underlying disease (OR 3.45; 95% CI, 1.01-1.32).

Conclusions COVID-19 was more severe in older patients, patients with a history of substance abuse, and patients with at least one underlying disease. Understanding the factors affecting the disease severity can help for clinical management of COVID-19, especially in less privileged areas where fewer resources are available.

Background

The novel coronavirus has caused a large global outbreak and is a major public health issue around the world. This virus has spread dramatically since emergence in China at the end of 2019 (1). On 11 February 2020, the World Health Organization (WHO) announced a new name for the epidemic disease caused by novel coronavirus: COVID-19 (2). COVID-19 pandemic was declared by the WHO worldwide and it was most widespread in the United States of America, Brazil, India, Russian Federation, South Africa, Peru, Mexico, Colombia, Chile, and Iran, respectively (3). Until August 29th, 2020, there have been 21,249 (5.74%) death of all 369,911 confirmed patients in Iran (3). However, there is no comprehensive report regarding risk factors related to severe COVID-19 disease in Iran.

Regarding the risk factors for the severity of COVID-19, three pooled studies in China showed that, 20.1% of patients developed acute respiratory distress syndrome. Furthermore, 25.9%, 8.3%, and 3.2% required ICU admission, invasive mechanical ventilation, and extracorporeal membrane oxygenation for refractory

hypoxemia, respectively (4-6). However, the ration for sever COVID-19 patients is dissimilar in different countries (1, 7).

There is evidence that hypertension, respiratory disease, cardiovascular disease increase the risk of sever COVID-19 disease (8-10) and men are at higher risk (11). However, it seems that health records are often incomplete or inaccurate (12) and it is expected that probably the severity pattern of COVID-19 and its risk factors change in the near future. Morbidity to sever COVID-19 will increase the risk of death and consequently impose more expense to the health system. Therefore, it gives the impression that the estimation of risk factors for sever COVID-19 could be helpful for physicians to manage the patient treatment and effectively prioritize resources for patients with the highest risk (13), especially in deprived regions.

To our knowledge, no previous report has been published from patients with severe conditions and their characteristics in less privileged areas of Iran. Sistan and Baluchistan, which has known as a deprived region, is located in southeast Iran and has common borders with Pakistan and Afghanistan. It is hypothesized that the characteristics and risk factors for COVID-19 is different in this area. Therefore, we aimed to find out the potential risk factors of severe COVID-19 patients and describe the epidemiological and clinical characteristics of patients during hospitalization. The results of this study, as the first study of this region, could also provide the basis for comparison in future epidemiological studies.

Methods

Study design and population

This study was carried out on 413 COVID-19 patients in all hospitals under the supervision of Zahedan University of Medical Sciences, southeast of Iran. All patients diagnosed with COVID-19 according to WHO interim guidance (14), between February 29th, 2020 and April 31st 2020 were included in the study. These hospitals were referral for transfer of patients with COVID-19 from other medical centers in Zahedan. Therefore, the current study considered all adult inpatients hospitalized for COVID-19 during the mentioned epidemic time.

Evaluation of clinical results

According to the WHO clinical management of COVID-19 guideline, symptomatic patients without evidence of viral pneumonia or hypoxia were classified as mild disease. Patients with clinical signs of pneumonia but no signs of severe pneumonia were grouped as moderate disease. Patients with oxygen support were classified as a severe disease and those with further complications were classified as a critically ill disease (14).

Data collection

Epidemiological and demographic characteristics and clinical data (symptoms, underlying disease, treatments, complications after admission, and outcomes) were extracted from medical records. In addition, the complementary data were collected by interviewing with patients or their companions through two well-informed infectious disease residents and one anesthesia resident during hospitalization and also two health workers in cases of referring to health centers during the early stage of the disease. Exposure history was defined as exposure to people with confirmed COVID-19 infection. All clinical data, symptoms and signs were approved by special and sub-special physicians based on standard definitions. All data were checked by another two researchers.

COVID-19 detection in respiratory specimens by RT-PCR methods was supervised by the center for disease control and prevention at the ministry of health in Iran. At the commence of the epidemic, the throat-swab specimens obtained from COVID-19 suspects was sent to the reference laboratory at Tehran University of Medical Sciences (school of public health) and Pasteur Institute of Iran. From March 11th, 2020, the specimens were examined in launching laboratory for COVID-19 detection in Zahedan city. The throat-swab specimens were obtained from the patients with symptoms including fever, cough, and dyspnea. A confirmed case was defined as a suspected case with a positive test of RT-PCR assay on respiratory specimens.

Statistical analysis

The absolute frequency and percent was used to describe the categorical variables. The mean and standard deviation (SD) was used to summarize continues variables. Independent samples T-test, χ^2 or Fisher's exact test compared differences between sever and non-sever patients regarding epidemiological and clinical factors and underlying diseases. To explore the risk factors associated with disease severity, bivariate and multivariate logistic regression models were used. The logistic regression was chosen for multivariate analysis on the basis of previous findings and clinical constraints considering the collinearity before fitting the model. We excluded variables from the bivariate analysis if their between-group differences were not significant, their accuracy was unconfirmed, and the number of events was too small to calculate odds ratios. The data were analyzed in Stata.16 and the significance level was considered as 0.05.

Results

From a total of 413 patients admitted to hospitals, 55.5% were male and 38.5% aged more than 50 years. The mean age of the patients was 45.05 ± 17.38 , ranging from 10 to 92 years. Regarding epidemiological characteristics, the drug use and cigarette smoking were reported by 9% and 3.9% of patients, respectively. Patients who travelled to high-risk areas within 14 days before onset of symptoms were 13.6%. Close contact with a respiratory patient in a medical center, in the family, and in the workplace was 5.9%, 9.2%, and 2.7%, respectively. About 4% of patients reported the history of close contact with a COVID19 patient within 14 days before onset of symptoms. Among patients, 41.4% used mask protection and 54.7% went to a medical center personally. At admission, 145 (35.10%) of patients were in severe and 268 (64.90%) in non-severe condition. There was a significant relationship between age and severity of COVID-19. The odds of severe disease was 3.38 times greater in patients aged more than 50 years and it was 2.09 times greater in cases of substance abuse. Patients referred to hospital by ambulance (OR=3.53) was more likely to be in a severe condition of COVID-19 compared to those went to hospital personally. Although wearing a mask decreased the odds of severity (OR=0.38), there was not a significant relationship between the mask protection and the disease severity. There was 16 (3.9%) cigarette smokers and smoking was not the predictor of severity among COVID-19 patients (Table 1).

Table 1: Demographic and epidemiological characteristics of sever COVID-19 patients in southeast of Iran

OR(95% CI)	Severe N (%)	Total N (%)	Demographics and epidemiological characteristics	
1.00	62 (24.4)	254(61.5)	Less/equal 50	Age (year)
3.38 (2.22,5.16)*	83 (52.2)	159(38.5)	More than 50	
1.00	65 (35.3)	184(44.5)	Female	Gender
0.98 (0.66,1.48) ^{NS}	80 (34.9)	229(55.5)	Male	
1.00	138 (34.8)	397(96.1)	No	Cigarette smoking
1.46 (0.53,4.00) NS	7 (43.8)	16(3.9)	Yes	
1.00	126 (33.5)	376(91)	No	Substance abuse
2.09 (1.06,4.13) *	19 (51.4)	37(9)	Yes	
1.00	136 (38.1)	357(86.4)	No	Travel to high-risk areas
0.31 (0.14,0.65) *	9 (16.1)	56(13.6)	Yes	
1.00	122 (33.7)	362(87.6)	No	Go to medical care center within 14 days before onset of symptoms
1.62 (0.89,2.92) NS	23 (45.1)	51(12.4)	Yes	
1.00	127 (34.8)	365(88.3)	No	Close contact with a respiratory patient within 14 days before onset of symptoms
1.12 (0.60,2.10) NS	18 (37.5)	48(11.7)	Yes	
1.00	133 (34.2)	389(94.1)	No	Close contact with a respiratory patient within 14 days before onset of symptoms in medical centers
1.93 (0.84,4.40) NS	12 (50.0)	24(5.9)	Yes	

1.00	130 (34.7)	375(90.8)	No	Close contact with a respiratory patient within 14 days before onset of symptoms in the family
1.23 (0.62,2.44) NS	15 (39.5)	38(9.2)	Yes	
1.00	142 (35.3)	402(97.3)	No	Close contact with a respiratory patient within 14 days before onset of symptoms in the work place
0.69 (0.18,2.63) NS	3 (27.3)	11(2.7)	Yes	
1.00	137 (34.5)	397(96.1)	No	History of close contact with a COVID19 patient within 14 days before onset of symptoms
1.90 (0.70,5.17) NS	8 (50.0)	16(3.9)	Yes	
1.00	106 (43.8)	242(58.6)	No	Using Mask protection
0.38 (0.25,0.59) NS	39 (22.8)	171(41.4)	Yes	
1.00	54 (24.2)	223(54.4)	Personally	How transferred to a medical center
2.30 (1.40,3.77) *	44 (42.3)	104(25.3)	By others	
3.53 (2.08,5.99) *	44 (53.0)	83(20.3)	By ambulance	
1.00	142 (35.1)	404(97.8)	No	Distance protection
0.92 (0.23,3.74) NS	3 (33.3)	9(2.2)	Yes	
1.00	121 (33.4)	362(87.6)	More than 1	Duration between symptom onset and hospital admission (day)
1.77 (0.98,3.20) NS	24 (47.1)	51(12.4)	Less/equal 1	

NS: Not Significant, *Significant at level of $P < 0.05$

Regarding clinical symptoms at admission, 37% of patients had a temperature more than 37.5. The most prevalent symptoms were cough (71.2%), breath shortness (61.2%), fever (32.2%), shiver (29%) and

bruising (28.4%). An abnormal CT was found in 94.5%. In univariate analysis, cough, shortness of breath, abdominal pain, lack of appetite, and loss of consciousness were related to severity of disease among COVID-19 patients. Shortness of breath, increased the odds of severe COVID-19 (OR=1.93). The odds of severe COVID-19 was significantly greater in patients with abdominal pain (OR=7.7), seizure (OR=27.1), and loss of consciousness (OR=12.4) (Table 2). Among all patients, 1.4% had a runny nose and 1.7% had not sign.

In univariate analysis, sepsis, respiratory failure, acute respiratory distress, heart failure, acute kidney and liver injury were related to severity of disease among COVID-19 patients. The odds of severe COVID-19 was significantly greater in patients with sepsis (OR=26.3), respiratory failure (OR=39.1), acute respiratory distress syndrome (OR=30.81), heart failure (OR=24.2), acute heart injury (OR=11.5), acute kidney injury (OR=11.7), liver injury (OR=3.7) and acidosis (OR=11.5) (Table 2).

Table 2: Clinical characteristics and signs of sever COVID-19 patients in southeast of Iran

OR (95% CI)	Severe N(%)	Total N (%)	Clinical Characteristics at admission*	
1.00	88 (34.2)	257(63)	Less/equal 37.5	Temperature
1.06 (0.66,1.70) ^{NS}	38 (35.5)	107(26.2)	37.5-38.5	
1.21 (0.62,2.34) ^{NS}	17 (38.6)	44(10.8)	More than 38.5	
1.00	106 (36.1)	294(71)	No	Shiver
0.86 (0.55,1.36) ^{NS}	39 (32.8)	119(29)	Yes	
1.00	22 (7.9)	280 (67.8)	No	Fever
0.85 (0.35,1.73) ^{NS}	9 (6.7)	133 (32.2)	Yes	
1.00	54 (45.4)	119(28.8)	No	Cough
0.54 (0.35,0.84) [*]	91 (31.0)	294(71.2)	Yes	
1.00	42 (26.3)	160(38.7)	No	Shortness of breath
1.93 (1.25,2.97) [*]	103 (40.7)	253(61.2)	Yes	
1.00	117 (33.6)	348(84.22)	No	General weakness
1.49 (0.87,2.56) ^{NS}	28 (43.1)	65(15.8)	Yes	
1.00	113 (38.2)	296(71.6)	No	Bruising
0.61 (0.38,1.08)	32 (27.4)	117(28.4)	Yes	
1.00	140 (36.1)	388(93.9)	No	Sore throat
0.44 (0.16,1.21) ^{NS}	5 (20.0)	25(6.1)	Yes	
1.00	142 (36.2)	392(95)	No	Diarrhea
0.29 (0.09,1.01) ^{NS}	3 (14.3)	21(5)	Yes	
1.00	123 (35.7)	345(83.5)	No	Nausea
0.86 (0.50,1.50) ^{NS}	22 (32.4)	68(16.5)	Yes	
1.00	126	344(83.3)	No	Headache

	(36.6)			
0.66 (0.37,1.16) ^{NS}	19 (27.5)	69(16.7)	Yes	
1.00	141 (35.2)	401(97)	No	Chest pain
0.92 (0.27,3.12) ^{NS}	4 (33.3)	12(3)	Yes	
1.00	137 (34.0)	403(97.5)	No	Abdominal pain
7.77 (1.63,37.08)*	8 (80.0)	10(2.5)	Yes	
1.00	141 (35.9)	393(95.1)	No	Joint pain
0.45 (0.15,1.36) ^{NS}	4 (20.0)	20(4.9)	Yes	
1.00	141 (34.6)	408(98.8)	No	Tachypnea
7.57 (0.84,68.41) NS	4 (80.0)	5(1.2)	Yes	
1.00	129 (35.0)	369(89.3)	No	Abnormal lung sounds
1.06 (0.56,2.04) ^{NS}	16 (36.4)	44(10.7)	Yes	
1.00	6 (26.1)	23(5.5)	No	Abnormal CT
1.57 (0.61,4.07) ^{NS}	139 (35.6)	390(94.5)	Yes	
1.00	143 (34.9)	410(99.2)	No	Seizure
3.73 (0.34,41.54) NS	2 (66.7)	3(0.8)	Yes	
1.00	120 (33.2)	361(87.4)	No	Lack of appetite
1.86 (1.04,3.34)*	25 (48.1)	52(12.6)	Yes	
1.00	140 (35.4)	395(95.6)	No	Dizziness
0.70 (0.24,2.01) ^{NS}	5 (27.8)	18(4.4)	Yes	
1.00	122 (31.6)	386(93.4)	No	Loss of consciousness
12.44 (4.21,36.76)*	23 (85.2)	27(6.6)	Yes	

OR (95% CI)	Severe N(%)	Total N (%)	complications created during treatment*	
1.00	121 (31.3)	387(93.6)	No	Sepsis
26.38 (6.14,113.41) *	24 (92.3)	26(6.4)	Yes	
1.00	112 (29.6)	378 (91.5)	No	Respiratory failure
39.19 (9.24,166.10) *	33 (94.3)	35(8.5)	Yes	
1.00	142 (34.7)	409(99)	No	Coagulopathy
5.64 (0.58,54.73) ^{NS}	3 (75.0)	4(1)	Yes	
1.00	130 (32.7)	397(96.1)	No	Acute respiratory distress syndrome
30.81 (4.03,235.76) *	15 (93.8)	16(3.9)	Yes	
1.00	136 (33.7)	403(97.5)	No	Heart failure
24.2(3.33,249.09) *	9 (90.0)	10(2.5)	Yes	
1.00	139 (34.2)	406(98.3)	No	Acute heart injury
11.52 (1.37,96.68) *	6 (85.7)	7(1.7)	Yes	
1.00	128 (32.6)	393(95.1)	No	Acute kidney injury
11.73 (3.38,40.76) *	17 (85.0)	20(4.9)	Yes	
1.00	143 (34.9)	410(99.2)	No	Acute liver injury
3.73 (0.34,41.54) *	2 (66.7)	3(0.8)	Yes	
1.00	139 (34.2)	406(98.3)	No	Acidosis
11.52 (1.37,96.68) *	6 (85.7)	7(1.7)	Yes	

NS: Not Significant, *Significant at level of $P \leq 0.05$

The most prevalent underlying disease among COVID-19 patients were hypertension (23.5%), diabetes (17.2%), cardiovascular disease (13.1%), chronic pulmonary disease (9.5%), and asthma (5.1%). Underlying disease, including cardiovascular disease (OR=2.43), liver disease (OR=5.74), chronic lung disease (OR=3.34), hypertension (OR=1.98) and rheumatologic disease (OR=5.8) increased the odds of severity among COVID-19 patients (Table 3). Congestive heart disease, organ transplant and malignancy were reported in only 2 (0.5%) of the patients.

Table 3: Distribution of underlying disease among of sever COVID-19 patients in southeast of Iran

OR (95% CI)	Severe N(%)	Total N (%)	Underlying disease	
1.00	140 (34.9)	401(94.8)	No	Dialysis
1.33 (0.42,4.27) ^{NS}	5 (41.7)	12(5.2)	Yes	
1.00	116 (32.3)	359(86.9)	No	Cardiovascular disease
2.43 (1.36,4.34) *	29 (53.7)	54(13.1)	Yes	
1.00	114 (33.3)	342(82.8)	No	Diabetes
1.55 (0.92,2.61) ^{NS}	31 (43.7)	71(17.2)	Yes	
1.00	139 (34.3)	405(98)	No	Liver disease
5.74 (1.14,28.82) *	6 (75.0)	8(2)	Yes	
1.00	138 (34.5)	400(96.8)	No	Chronic kidney disease
2.22 (0.73,6.72) ^{NS}	7 (53.8)	13(3.2)	Yes	
1.00	143 (35.4)	404(97.8)	No	Chronic neurological disease
0.52 (0.11,2.54) ^{NS}	2 (22.2)	9(2.2)	Yes	
1.00	121 (32.4)	374(90.5)	No	Chronic pulmonary disease
3.34 (1.69,6.61) *	24 (61.5)	39(9.5)	Yes	
1.00	144 (35.0)	411(99.5)	No	Malignant Disease
1.85 (0.12,29.86) ^{NS}	1 (50.0)	2(0.5)	Yes	
1.00	99 (31.3)	316(76.5)	No	Hypertension
1.98 (1.24,3.14) *	46 (47.4)	97(23.5)	Yes	
1.00	140 (34.7)	404(97.8)	No	Cerebrovascular disease
2.36 (0.62,8.92) ^{NS}	5 (55.6)	9(2.2)	Yes	
1.00	142 (35.1)	405(98)	No	Chronic blood disease
1.11 (0.26,4.72) ^{NS}	3 (37.5)	8(2)	Yes	
1.00	136 (34.7)	392(94.9)	No	Asthma
1.41 (0.58,3.43) ^{NS}	9 (42.9)	21(5.1)	Yes	
	143 (34.8)	411(99.5)	No	Congestive heart disease

	2 (100.0)	2(0.5)	Yes	
1.00	136 (33.9)	401(97.1)	No	Rheumatologic disease
5.85 (1.56,21.95)*	9 (75.0)	12(2.9)	Yes	
	143 (34.8)	411(99.5)	No	Organ transplant
	2 (100.0)	2(0.5)	Yes	
1.00	140 (35.0)	400(96.8)	No	Defect immune system
1.16 (0.37,3.62) ^{NS}	5 (38.5)	13(3.2)	Yes	

NS: No Significant, *Significant at level of $P < 0.05$.

Among all patients, 37% had an oxygen saturation of more than 0.93, 11.4% were admitted to ICU eventually, and 8.7% received mechanical ventilation. According to oxygen therapy, 90.6% received high flow nasal cannula (HFNC) and 8.2% invasive mechanical ventilation (IMV). The odds of severe disease increased significantly in patients admitted to ICU (OR=27.8) and mechanically ventilated patients (OR=84.9). Oxygen saturation of more than 0.93 could prevent the disease severity by 70%. The mean of heart rate and respiratory rate were significantly different between the severe and non-severe patients ($P < 0.001$) (Table 4). About 36 (94.7%) of the severe patients were intubated. The most patients took antibiotics (91.5%) and antiviral drugs (97.3%), but their use was not related to severity among COVID-19 patients ($P > 0.05$).

Table 4: Distribution of oxygen therapy and vital sign among sever COVID-19 patients in southeast of Iran

OR (95% CI)	Severe N(%)	Total N (%)		
1.00	37 (94.9)	39(90.5)	No	High flow nasal cannula
0.02 (0.005,0.093)*	108 (28.9)	374(9.5)	Yes	
	137 (33.8)	405(98)	No	Non-Invasive mechanical ventilation
	8 (100.0)	8(2)	Yes	
1.00	112 (29.6)	379(91.7)	No	Invasive mechanical ventilation
78.67 (10.63,582.25) *	33 (97.1)	34(8.3)	Yes	
1.00	102 (27.9)	366(88.6)	No	ICU admission
27.82 (9.74,79.49) *	43 (91.5)	47(11.4)	Yes	
1.00	109 (29.1)	375(90.8)	No	Intubation
43.93 (10.40,185.63) *	36 (94.7)	38(9.2)	Yes	
1.00	110 (29.2)	377(91.3)	No	Mechanical ventilation
84.96 (11.50,627.82) *	35 (97.2)	36(8.7)	Yes	
1.00	30 (19.6)	153(37)	More than 0.93	Oxygen saturation
3.25 (2.03,5.18) *	114 (44.2)	258(63)	Less/equal 0.93	
P	Sever / Critically sever	Low / Moderate		Mean ± SD
0.002	97.75±18.57	92.33±12.94		Heart rate
<0.001	22.19±6.53	18.92±4.37		Respiratory rate
0.182 ^{NS}	118.36±19.21	115.95±16.35		Systolic blood pressure
0.234 ^{NS}	74.57±11.46	73.18±11.14		Diastolic blood pressure

NS: No Significant, *Significant at level of $P < 0.05$

Multivariate regression showed increasing odds of the severity for COVID-19 was associated with older age (OR=3.51), substance abuse (OR=2.22) and having at least one underlying disease (OR= 3.45) (Table

5).

Table 5: Multivariate logistic regression for predictors of severity among COVID-19 patients in southeast of Iran*

Independent variables		B	S.E of Beta	OR (95% CI)	P
Age	>50	1.25	.22	3.51(2.28, 5.4)	.0001
	≤50**	1			
Substance abuse	Yes	.78	.35	2.22(2.05, 5.78)	.0002
	No**	1			
Having underlying disease***	Yes	1.24	.26	3.45(1.01, 1.32)	.032
	No**	1			

* Variables for Table 4 not included in the model, ** Reference group, *** Having at least one underlying disease according to table 3.

Discussion

The current study investigated the clinical characteristics of patients with COVID-19 and potential risk factors for severity. Univariate analysis revealed that age, substance abuse, traveling to high-risk areas, means of transportation to a medical center, cough, shortness of breath, abdominal pain, lack of appetite, loss of consciousness, sepsis, respiratory failure, acute respiratory distress syndrome, heart failure, acute heart injury, acute kidney injury, acute liver injury, acidosis, cardiovascular disease, liver disease, chronic pulmonary disease, hypertension, rheumatologic disease, high flow nasal cannula oxygen therapy, invasive mechanical ventilation, ICU admission, intubation, mechanical ventilation, oxygen saturation, heart rate and respiratory rate were associated with severity in COVID-19 patients. Multivariate analysis revealed that age, substance abuse and underlying disease were predictors of severity in COVID-19 patients.

Among the 413 patients in this study, 145 (35.10%) were in severe condition and older patients were at higher risk of severe disease. Poor immune response in older patients leads to more severe and critical conditions such as ARDS, severe clinical manifestations, and longer disease duration (15, 16). Other studies have reported a lower prevalence of disease severity such as 17.6% and 25.6% (17, 18) which is expected based on various definitions.

Substance abuse was a risk factor for COVID-19 severity in the current study, which can be the result of direct damage to the respiratory system, modulating brain and immune functions (19). Severe disease was also associated with travel to high-risk areas. This finding highlights the importance of social distancing on viral inocula reduction (20) leading to less severe disease (21). Exposure to confirmed cases and recent travel to epidemic area are among host risk factor for severe COVID-19 (22).

In terms of signs, this study showed that cough, shortness of breath, abdominal pain, losing appetite, heart rate and number of breathing were associated with severity in COVID-19 patients. Gastrointestinal symptoms are more prevalent in severe COVID-19 patients, so that 100% of these patients experience lack of appetite. This may be due to the increased viral load and the spread of the virus in the gastrointestinal tract of COVID-19 patients, leading to the severity of the disease (23). Other studies have shown that cough, shortness of breath, and abdominal pain are more common in patients with severe COVID-19 (24-26). Furthermore, high respiratory and heart rate were the risk factors for the severity in COVID-19 patients (27).

The present study showed that a decreased level of consciousness, oxygen requirement at hospitalization, ICU admission, invasive mechanical ventilation, intubation and oxygen saturation were risk factors for severity in COVID-19 patients. Previous studies have shown that only severe patients need to be admitted to the ICU and oxygen saturation is lower in severe patients. In addition, unconsciousness, shortness of breath, use of oxygen therapy, invasive and non-invasive mechanical ventilation is also more common in severe patients (28-31).

Regarding the complications during treatment, sepsis, respiratory failure, acute respiratory distress syndrome, heart failure, acute heart injury, acute kidney injury and acidosis were risk factors for severity in COVID-19 patients in the current study. The cause of respiratory failure in patients with COVID-19 was impaired immune function (32). Uncontrolled viral infection causes macrophage penetration and further damage to the lungs (33). Serious complications such as acute respiratory distress syndrome, acute cardiac injury, acute kidney injury and shock can occur in patients with severe COVID-19 while acute respiratory distress syndrome and acute cardiac injury are the most important barriers to the treatment of COVID-19 patients (34). Cardiac injury is associated with severity of disease in patients with COVID-19 (35). The SARS-CoV-2 affects the cardiovascular system through angiotensin-converting enzyme 2 (ACE2) and causes complications such as myocardial injury and heart failure (36, 37). Acute kidney injury (AKI) is known as an indicator of disease severity and volume depletion may be the cause of acute kidney injury (38). The prevalence of liver dysfunction and liver injury is higher in patients with severe COVID-19. Liver impairment may be caused directly by a viral infection of the liver cells or by hepatotoxicity caused by drugs and immune-mediated inflammation (39).

In terms of underlying health conditions, cardiovascular disease, liver disease, chronic pulmonary disease, hypertension, and rheumatologic disease were risk factors for severe COVID-19 in this study. Underlying health conditions are responsible for 20% of severe COVID-19 worldwide (40). Severe COVID-19 patients experience a higher incidence of comorbidity, which is a risk factor for severity of COVID-19

pneumonia (41, 42). Patients with established cardiovascular disease exhibited a greater expression of angiotensin-converting enzyme 2 (ACE2) and probably experience a worse condition following SARS-CoV-2 infection (43, 44). Patients with a history of hypertension are more likely to develop severe COVID-19 as hypertension is a predictor of severe pneumonia (45, 46). There is evidence that antihypertensive drugs prevent patients with comorbid hypertension from severe pneumonia. Chronic respiratory conditions are also associated with the severity of COVID-19 (48). Elevated liver biochemical indicators are common in COVID-19 resulting in severe COVID-19 (49, 50). Patients with rheumatic diseases are high risk for COVID-19 infection due to their immune conditions (51). In addition, chronic inflammatory rheumatic patients with an autoimmune or immunomediated diseases are at risk of severe COVID-19 (52).

Conclusions

COVID-19 was more severe in older patients, patients with a history of substance abuse, and patients with at least one underlying disease. Understanding the factors affecting the disease severity can help for clinical management of COVID-19, especially in less privileged areas where fewer resources are available.

One of the strengths of the present study is that the patients were selected from a less privileged area which can draw the attention of health policy makers to this area. Another strength of the study is the multicenter nature of the study, which is representative of the population. This study had some limitations: one is the small sample size, which can lead to insignificant statistical results. Therefore, the results of this study should be interpreted with caution. Further studies are needed to investigate potential risk factors of severity in patients with COVID-19 with large sample size. Second, in some cases, the information was collected as self-report, which can lead to recall bias.

Abbreviations

COVID-19: Coronavirus disease; OR: *odds ratio*; WHO: World Health Organization; ICU: intensive care unit; RT-PCR: real-time reverse-transcription-polymerase-chain-reaction; SD: standard deviation; CT: *computed tomography*; HFNC: high flow nasal cannula; IMV: invasive mechanical ventilation; ARDS: *Acute respiratory distress syndrome*; AKI: Acute kidney injury; ACE2: angiotensin-converting enzyme 2

Declarations

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Authors' contributions

SMNT, AAM, SMHS, GMA, SSS, MZB, KS, MS, and HOA participated in designing the study.

TK, ASK, NT and **FAM** participated in data collection.

MM and **SMT** participated in data analysis.

HA, MA and **HOA** participated in preparing the manuscript.

All authors have read and approved the final version of the manuscript.

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Availability of data and materials

The data used in this study are available upon reasonable request from the corresponding author.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Zahedan University of Medical Sciences and the written informed consent was obtained from all patients or their relatives and companions.

Consent for publication

Not applicable.

Competing Interest

Non declare.

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