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 the severity of COVID-19 is useful in disease management. This study investigated the epidemiological and clinical features and factors related to severe COVID-19 in Iran's less-privileged area.

Methods

In a multicenter study, all patients admitted to Zahedan University of Medical Sciences hospitals located in southeastern Iran were investigated from February 29 to April 31, 2020. The demographic, epidemiological, and clinical data of patients were extracted from medical records. To explore the risk factors associated with the 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 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 the clinical management of COVID-19, especially in less privileged areas where fewer resources are available.

Background

The novel coronavirus has caused a global outbreak and is a significant public health issue worldwide. This virus has spread dramatically since the emergence in China at the end of 2019 (1). On February 11, 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, the Russian Federation, South Africa, Peru, Mexico, Colombia, Chile, and Iran, respectively (3). Until August 29, 2020, 21,249 (5.74%) deaths of all 369,911 confirmed patients in Iran occurred (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% required ICU admission,

8.3% invasive mechanical ventilation, and 3.2% extracorporeal membrane oxygenation for refractory hypoxemia (4-6). However, the ratio of severe COVID-19 patients is dissimilar in different countries (1, 7).

There is evidence that hypertension, respiratory disease, cardiovascular disease increase the risk of severe COVID-19 (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 the severity pattern of COVID-19 and its risk factors change soon. Morbidity to severe COVID-19 will increase death risk and consequently impose more expense to the health system. Therefore, it gives the impression that the estimation of risk factors for severe COVID-19 could help physicians 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, 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 are different in this area. Therefore, we aimed to determine the potential risk factors of severe COVID-19 patients and describe patients' epidemiological and clinical characteristics during hospitalization. As the first study of this region, this study results 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 29, 2020, and April 31, 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 the COVID-19 guideline, symptomatic patients without evidence of viral pneumonia or hypoxia were classified as a mild disease. Patients with clinical signs of pneumonia, but no signs of severe pneumonia were grouped as a 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.

Interviews with patients or their companions also collected the complementary data through two well-informed infectious disease residents, one anesthesia resident, two health workers during hospitalization, and referring patients to health centers at the early stage of the disease. Exposure to people with confirmed COVID-19 infection was defined as exposure history. All clinical data, symptoms, and signs were approved by special and sub-special physicians based on standard definitions. Two researchers checked all data.

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

Statistical analysis

The absolute frequency and percent were used to describe the categorical variables. The mean and standard deviation (SD) was used to summarize continuous variables. Independent samples T-test, χ^2 , or Fisher's exact test, compared the differences between severe 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 based on 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

Of 413 patients admitted to hospitals, 55.5% were male and 38.5% aged more than 50. The mean age of the patients was 45.05 ± 17.38 , ranging from 10 to 92 years. Regarding epidemiological characteristics, 9% and 3.9% of patients reported drug use and cigarette smoking, respectively. Patients who traveled to high-risk areas within 14 days before the onset of symptoms were 13.6%. Close contact with a respiratory patient in a medical center, in the family, and the workplace was 5.9%, 9.2%, and 2.7%, respectively. About 4% of patients reported a history of close contact with a COVID19 patient within 14 days before the onset of symptoms. Among patients, 41.4% used mask protection, and 54.7% went to a medical center personally. At admission, 145 (35.10%) patients were in severe and 268 (64.90%) in non-severe conditions. There was a significant relationship between age and severity of COVID-19. The odds of severe disease were 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 the hospital by ambulance (OR=3.53) were more likely to be in a severe condition of COVID-19 compared to those who went to the hospital personally. Although wearing a mask decreased the odds of severity (OR=0.38), there was no significant relationship between mask protection and the disease severity. There were 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 COVID-19 severe patients in the southeast of Iran

Demographics and epidemiological characteristics		Total N (%)	Severe N (%)	OR(95% CI)
Age (year)	Less/equal 50	254(61.5)	62 (24.4)	1.00
	More than 50	159(38.5)	83 (52.2)	3.38 (2.22,5.16) *
Gender	Female	184(44.5)	65 (35.3)	1.00
	Male	229(55.5)	80 (34.9)	0.98 (0.66,1.48) ^{NS}
Cigarette smoking	No	397(96.1)	138 (34.8)	1.00
	Yes	16(3.9)	7 (43.8)	1.46 (0.53,4.00) ^{NS}
Substance abuse	No	376(91)	126 (33.5)	1.00
	Yes	37(9)	19 (51.4)	2.09 (1.06,4.13) *
Travel to high-risk areas	No	357(86.4)	136 (38.1)	1.00
	Yes	56(13.6)	9 (16.1)	0.31 (0.14,0.65) *
Go to the medical care center within 14 days before the onset of symptoms	No	362(87.6)	122 (33.7)	1.00
	Yes	51(12.4)	23 (45.1)	1.62 (0.89,2.92) ^{NS}
Close contact with a respiratory patient within 14 days before the onset of symptoms	No	365(88.3)	127 (34.8)	1.00
	Yes	48(11.7)	18 (37.5)	1.12 (0.60,2.10) ^{NS}
Close contact with a respiratory patient within 14 days before the onset of symptoms in medical centers	No	389(94.1)	133 (34.2)	1.00
	Yes	24(5.9)	12 (50.0)	1.93 (0.84,4.40) ^{NS}
Close contact with a respiratory patient within 14 days before the onset of symptoms in the family	No	375(90.8)	130 (34.7)	1.00
	Yes	38(9.2)	15 (39.5)	1.23 (0.62,2.44) ^{NS}
Close contact with a respiratory patient within 14 days before the onset of symptoms in the workplace	No	402(97.3)	142 (35.3)	1.00
	Yes	11(2.7)	3 (27.3)	0.69 (0.18,2.63) ^{NS}
History of close contact with a COVID19 patient within 14 days before the onset of symptoms	No	397(96.1)	137 (34.5)	1.00
	Yes	16(3.9)	8 (50.0)	1.90 (0.70,5.17) ^{NS}
Using Mask protection	No	242(58.6)	106 (43.8)	1.00
	Yes	171(41.4)	39 (22.8)	0.38 (0.25,0.59) ^{NS}
How transferred to a medical center	Personally	223(54.4)	54	1.00

			(24.2)	
	By others	104(25.3)	44 (42.3)	2.30 (1.40,3.77) *
	By ambulance	83(20.3)	44 (53.0)	3.53 (2.08,5.99) *
Distance protection	No	404(97.8)	142 (35.1)	1.00
	Yes	9(2.2)	3 (33.3)	0.92 (0.23,3.74) ^{NS}
The duration between symptom onset and hospital admission (day)	More than 1	362(87.6)	121 (33.4)	1.00
	Less/equal 1	51(12.4)	24 (47.1)	1.77 (0.98,3.20) ^{NS}

√S: Not Significant, *Significant at the level of $P \leq 0.05$ -

Regarding clinical symptoms at admission, 37% of patients had a temperature of 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 the 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 no sign.

In univariate analysis, sepsis, respiratory failure, acute respiratory distress, heart failure, acute kidney, and liver injury were related to the 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 COVID-19 severe patients in the southeast of Iran

Clinical Characteristics at admission*		Total N (%)	Severe N(%)	OR (95% CI)
Temperature	Less/equal 37.5	257(63)	88 (34.2)	1.00
	37.5-38.5	107(26.2)	38 (35.5)	1.06 (0.66,1.70) ^{NS}
	More than 38.5	44(10.8)	17 (38.6)	1.21 (0.62,2.34) ^{NS}
Shiver	No	294(71)	106 (36.1)	1.00
	Yes	119(29)	39 (32.8)	0.86 (0.55,1.36) ^{NS}
Fever	No	280 (67.8)	22 (7.9)	1.00
	Yes	133 (32.2)	9 (6.7)	0.85 (0.35,1.73) ^{NS}
Cough	No	119(28.8)	54 (45.4)	1.00
	Yes	294(71.2)	91 (31.0)	0.54 (0.35,0.84) [*]
Shortness of breath	No	160(38.7)	42 (26.3)	1.00
	Yes	253(61.2)	103 (40.7)	1.93 (1.25,2.97) [*]
General weakness	No	348(84.22)	117 (33.6)	1.00
	Yes	65(15.8)	28 (43.1)	1.49 (0.87,2.56) ^{NS}
Bruising	No	296(71.6)	113 (38.2)	1.00
	Yes	117(28.4)	32 (27.4)	0.61 (0.38,1.08)
Sore throat	No	388(93.9)	140 (36.1)	1.00
	Yes	25(6.1)	5 (20.0)	0.44 (0.16,1.21) ^{NS}
Diarrhea	No	392(95)	142 (36.2)	1.00
	Yes	21(5)	3 (14.3)	0.29 (0.09,1.01) ^{NS}
Nausea	No	345(83.5)	123 (35.7)	1.00
	Yes	68(16.5)	22 (32.4)	0.86 (0.50,1.50) ^{NS}
Headache	No	344(83.3)	126 (36.6)	1.00
	Yes	69(16.7)	19 (27.5)	0.66 (0.37,1.16) ^{NS}
Chest pain	No	401(97)	141 (35.2)	1.00
	Yes	12(3)	4 (33.3)	0.92 (0.27,3.12) ^{NS}
Abdominal pain	No	403(97.5)	137 (34.0)	1.00
	Yes	10(2.5)	8 (80.0)	7.77 (1.63,37.08) [*]
Joint pain	No	393(95.1)	141 (35.9)	1.00
	Yes	20(4.9)	4 (20.0)	0.45 (0.15,1.36) ^{NS}
Tachypnea	No	408(98.8)	141 (34.6)	1.00
	Yes	5(1.2)	4 (80.0)	7.57 (0.84,68.41) ^{NS}
Abnormal lung sounds	No	369(89.3)	129 (35.0)	1.00
	Yes	44(10.7)	16 (36.4)	1.06 (0.56,2.04) ^{NS}
Abnormal CT	No	23(5.5)	6 (26.1)	1.00
	Yes	390(94.5)	139 (35.6)	1.57 (0.61,4.07) ^{NS}
Seizure	No	410(99.2)	143 (34.9)	1.00
	Yes	3(0.8)	2 (66.7)	3.73 (0.34,41.54) ^{NS}
Lack of appetite	No	361(87.4)	120 (33.2)	1.00
	Yes	52(12.6)	25 (48.1)	1.86 (1.04,3.34) [*]
Dizziness	No	395(95.6)	140 (35.4)	1.00
	Yes	18(4.4)	5 (27.8)	0.70 (0.24,2.01) ^{NS}
Loss of consciousness	No	386(93.4)	122 (31.6)	1.00
	Yes	27(6.6)	23 (85.2)	12.44 (4.21,36.76) [*]
complications created during treatment*		Total N (%)	Severe N(%)	OR (95% CI)
Sepsis	No	387(93.6)	121 (31.3)	1.00
	Yes	26(6.4)	24 (92.3)	26.38 (6.14,113.41) [*]

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

NS: Not Significant, *Significant at the 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 conditions, 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%) patients.

Table 3: Distribution of underlying condition among COVID-19 severe patients in the southeast of Iran

Underlying conditions		Total N (%)	Severe N(%)	OR (95% CI)
Dialysis	No	401(94.8)	140 (34.9)	1.00
	Yes	12(5.2)	5 (41.7)	1.33 (0.42,4.27) ^{NS}
Cardiovascular disease	No	359(86.9)	116 (32.3)	1.00
	Yes	54(13.1)	29 (53.7)	2.43 (1.36,4.34) *
Diabetes	No	342(82.8)	114 (33.3)	1.00
	Yes	71(17.2)	31 (43.7)	1.55 (0.92,2.61) ^{NS}
Liver disease	No	405(98)	139 (34.3)	1.00
	Yes	8(2)	6 (75.0)	5.74 (1.14,28.82) *
Chronic kidney disease	No	400(96.8)	138 (34.5)	1.00
	Yes	13(3.2)	7 (53.8)	2.22 (0.73,6.72) ^{NS}
Chronic neurological disease	No	404(97.8)	143 (35.4)	1.00
	Yes	9(2.2)	2 (22.2)	0.52 (0.11,2.54) ^{NS}
Chronic pulmonary disease	No	374(90.5)	121 (32.4)	1.00
	Yes	39(9.5)	24 (61.5)	3.34 (1.69,6.61) *
Malignant Disease	No	411(99.5)	144 (35.0)	1.00
	Yes	2(0.5)	1 (50.0)	1.85 (0.12,29.86) ^{NS}
Hypertension	No	316(76.5)	99 (31.3)	1.00
	Yes	97(23.5)	46 (47.4)	1.98 (1.24,3.14) *
Cerebrovascular disease	No	404(97.8)	140 (34.7)	1.00
	Yes	9(2.2)	5 (55.6)	2.36 (0.62,8.92) ^{NS}
Chronic blood disease	No	405(98)	142 (35.1)	1.00
	Yes	8(2)	3 (37.5)	1.11 (0.26,4.72) ^{NS}
Asthma	No	392(94.9)	136 (34.7)	1.00
	Yes	21(5.1)	9 (42.9)	1.41 (0.58,3.43) ^{NS}
Congestive heart disease	No	411(99.5)	143 (34.8)	
	Yes	2(0.5)	2 (100.0)	
Rheumatologic disease	No	401(97.1)	136 (33.9)	1.00
	Yes	12(2.9)	9 (75.0)	5.85 (1.56,21.95)*
Organ transplant	No	411(99.5)	143 (34.8)	
	Yes	2(0.5)	2 (100.0)	
Defect immune system	No	400(96.8)	140 (35.0)	1.00
	Yes	13(3.2)	5 (38.5)	1.16 (0.37,3.62) ^{NS}

NS: No Significant *Significant at the level of $P \leq 0.05$.

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. 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 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. 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 COVID-19 severe patients in the southeast of Iran

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

NS: No Significant, *Significant at the level of $P \leq 0.05$

Multivariate regression showed increased 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 the southeast of Iran*

Independent variables		B	SE 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, and acute respiratory distress syndrome were associated with severity in COVID-19 patients. Also, 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. Inadequate immune response in older patients leads to more complicated and critical situations 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, resulting from 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 the epidemic area is among the host risk factors for severe COVID-19 (22).

In terms of signs, this study showed that cough, shortness of breath, abdominal pain, losing appetite, heart rate, and the 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 a lack of appetite. The increased viral load and the spread of the virus in the gastrointestinal tract of COVID-19 patients can lead to the disease's severity (23). Other studies have shown that cough, shortness of breath, and abdominal pain are common in patients with severe COVID-19 (24-26). Furthermore, high respiratory and heart rates were the risk factors for the severity of COVID-19 patients (27).

The present study showed 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 was lower in severe patients. Also, unconsciousness, shortness of breath, oxygen therapy, invasive and non-invasive mechanical ventilation were ordinary in severe patients (28-31).

Regarding 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. Acute respiratory distress syndrome and acute cardiac injury are the most critical barriers to the treatment of COVID-19 patients (34). Cardiac injury is associated with the 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. 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, a risk factor for the severity of COVID-19 pneumonia (41, 42). Patients with established cardiovascular disease exhibited a greater expression of angiotensin-converting enzyme 2 (ACE2) and probably experienced 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 anti-hypertensive 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 at high risk for COVID-19 infection due to their immune conditions (51). Also, chronic inflammatory rheumatic patients with autoimmune or immune-mediated 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 the 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 health policymakers' attention to this area. Another strength of the study is the study's multicenter nature, which is representative of the population. This study had some limitations: one is the small sample size, leading 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 a large sample size. Second, in some cases, the information was collected as a self-report, leading 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; 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

The Research Ethics Committee of Zahedan University of Medical Sciences approved this study, 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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