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Original Article

Predictors of Intensive Care Unit Admission in Patients with Confirmed Coronavirus Disease 2019: A Cross-Sectional Study

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What's Known

- Despite widespread vaccination against COVID-19, the disease still poses a major challenge to clinicians worldwide.
- Several studies have addressed factors that contribute to intensive care unit (ICU) admission and affect mortality. However, risk factors must be identified and managed to ameliorate prognosis and survival rates.

What's New

- Predictors of ICU admission for COVID-19 patients in Iran are determined.
- The main risk factors for ICU admission are comorbidity (primarily stroke, chronic obstructive pulmonary disease, and autoimmune diseases) and a surge in white blood cell count, cardiac troponin concentrations, lactate dehydrogenase levels, erythrocyte sedimentation rates, and blood urea nitrogen levels.

Abstract

Background: The coronavirus disease 2019 (COVID-19) has become the leading source of pneumonia outbreaks in the world. The present study aimed to compare the condition of intensive care unit (ICU) and non-ICU COVID-19 patients in terms of epidemiological and clinical features, laboratory findings, and outcomes in three cities across Iran.

Methods: In a cross-sectional study, 195 COVID-19 patients admitted to five hospitals across Iran during March-April 2020 were recruited. Collected information included demographic data, laboratory findings, symptoms, medical history, and outcomes. Data were analyzed using SPSS software with *t* test or Mann-Whitney U test (continuous data) and Chi square test or Fisher's exact test (categorical variables). $P<0.05$ was considered statistically significant.

Results: Of the 195 patients, 57.4% were men, and 67.7% had at least one comorbidity. The prevalence of stroke, chronic obstructive pulmonary disease, and autoimmune diseases was higher in ICU than in non-ICU patients (P=0.042, P=0.020, and P=0.002, respectively). Compared with non-ICU, ICU patients had significantly higher white blood cell (WBC) count (P=0.008), cardiac troponin concentrations (P=0.040), lactate dehydrogenase levels (P=0.027), erythrocyte sedimentation rates (P=0.008), and blood urea nitrogen (BUN) (P=0.029), but lower hematocrit levels (P=0.001). The mortality rate in ICU and non-ICU patients was 48.1% and 6.1%, respectively. The risk factors for mortality included age>40 years, body mass index<18 Kg/m^2, hypertension, coronary artery disease, fever, cough, dyspnea, ST-segment changes, pericardial effusion, and a surge in WBC and C-reactive protein, aspartate aminotransferase, and BUN.

Conclusion: A high index of suspicion for ICU admission should be maintained in patients with positive clinical and laboratory predictive factors.

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Keywords ● COVID-19 ● SARS-CoV-2 ● Dyspnea ● Pneumonia ● Intensive care unit

Introduction

The coronavirus disease 2019 (COVID-19), which initially emerged in Wuhan (China), is a viral respiratory disease caused by the severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) infection. Currently, the disease has become the leading source of pneumonia outbreaks in the world. The rapid spread of the virus through infected patients and its outbreak over a wide geographical area is a major concern and poses a global threat to public health.[1, 2] It is confirmed that the virus is primarily transmitted through respiratory droplets, close contact with an infected person, and fecal-oral route.[3, 4]

The clinical features of COVID-19 are non-specific, and patients can be asymptomatic or exhibit a variety of symptoms ranging from mild to severe pneumonia, which may lead to death.[2] Those with mild symptoms should self-isolate and, if necessary, receive symptomatic treatments, mainly to control fever. However, patients with severe pneumonia require pharmacological intervention, hospitalization, and even intensive care unit (ICU) admission in case of the need for assisted mechanical ventilation.[3] Early identification of COVID-19 patients is essential to prevent disease progression and respiratory failure, and ultimately reduce mortality.[1]

The surge of COVID-19 has put immense pressure on the Iranian healthcare system and the available ICU capacity. The present study aimed to compare the condition of ICU and non-ICU COVID-19 patients, in three cities spread across Iran, based on epidemiological and clinical features, laboratory findings, and outcomes. The findings of the study can be utilized by healthcare providers to better manage COVID-19 and allow hospital managers to efficiently allocate the limited ICU capacity.

Patients and Methods

A cross-sectional study was conducted in March-April 2020 at five hospitals located in the North, South, and Southwest of Iran. The target hospitals were the Ali-Asghar and Chamran Hospitals affiliated with Shiraz University of Medical Sciences (Shiraz, Iran), Razi Hospital affiliated with Jundishapur University of Medical Sciences (Ahvaz, Iran), and Razi and Golestan Hospitals affiliated with Gilan University of Medical Sciences (Rasht, Iran). The study was performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.018). Written informed consent was obtained from all the patients.

A total of 195 laboratory-confirmed COVID-19 patients, using a real-time polymerase chain reaction (PCR) test, who were referred to one of the above-mentioned hospitals, were recruited into the study. The data for each patient were collected in accordance with a pre-defined list of questions by health professionals not involved with patient care. The data were encrypted with an identification number and entered into a password-protected database. The collected data were reviewed and refined by the authors, after which the anonymized data were analyzed by a statistician. The anonymity of patients' data was ensured throughout the study.

The obtained information included demographic data, laboratory findings, symptoms, medical history of cardiovascular diseases (CVD), exposure history, underlying diseases, treatments, systolic and diastolic blood pressure, heart rate, hospital stay, days from illness to the onset of dyspnea, and outcomes. Laboratory test data included levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), creatine phosphokinase (CPK), creatinine phosphokinase-myocardial band (CPK-MB), erythrocyte sedimentation rates (ESR), white blood cell (WBC) count, and troponin concentrations. Information related to COVID-19 symptoms included fever, cough, myalgia, fatigue, sputum production, headache, hemoptysis, diarrhea, nausea/vomiting, and dyspnea. Information related to the pharmacological interventions included the kind of drugs used such as acetylsalicylic acid (ASA), statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARB), diuretics, estrogen antagonists, warfarin, non-vitamin K antagonist oral anticoagulants (NOAC), and enoxaparin. The documented medical history of CVD included supraventricular arrhythmia, QT prolongation, bundle branch block, ST-segment changes, pericardial effusion, and left ventricular ejection fraction. Patient outcomes were defined as cured or dead.

Based on the severity of the disease, a variety of therapeutic approaches were utilized, including general supportive therapy, symptomatic treatment to control fever, antiviral treatment, monitoring of the lung, heart, liver, and kidney functions, and oxygen therapy, especially in critically ill patients. The criteria for ICU admission included respiratory failure requiring non-invasive or invasive mechanical ventilation despite optimized oxygen therapy, decreased level of consciousness, and CVD. ICU discharge criteria included recovery from organ failure, oxygen saturation >92% using standard face masks for at least 24 hours, and a normal level of consciousness. Conditions for discharge included fever-free for at least three days, significant improvement in respiratory function, and negative PCR test results.

Statistical Analysis

The data were analyzed using SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous data were compared using Student's *t* test or Mann-Whitney U test; expressed as mean±SD or medians with interquartile range (IQR). Categorical variables were compared using Chi square test or Fisher's exact test; expressed as numbers and percentages. To report the odds ratio (OR), binary logistic regression was used. P values less than 0.05 were considered statistically significant.

Results

Demographic data: The study population included 195 hospitalized patients (Shiraz: 130 patients, Ahvaz: 21 patients, Rasht: 44 patients) with confirmed COVID-19. Of those, 112 (57.4%) were male which was significantly higher than the number of female patients (P=0.045). The number of patients admitted to isolation wards and ICU were 114 (58.5%) and 81 (41.5%), respectively. Body mass index (BMI) was significantly higher in non-ICU patients (P=0.011) (table 1).

Table 1: Baseline characteristics of ICU and non-ICU patients with confirmed COVID-19

Variable	Total (n=195)	ICU care (n=81)	Non-ICU care (n=114)	P value
Demographics				
Age (years)[D]	57.0±18.63	61.18±18.08	54.03±18.54	0.008*
Male patients[¨]	112 (57.4)	47 (58)	65 (57)	0.889#
BMI (Kg/m^2)[D]	26.08±4.82	24.71±5.40	26.90±4.25	0.011*
Source of infection[¨]				
Hospital	17 (8.72)	14 (17.28)	3 (2.63)	0.001#
Family	41 (21.02)	21 (25.92)	20 (17.54)	0.216#
Travel	10 (5.13)	4 (4.94)	6 (5.26)	0.930#
Others	127 (65.13)	42 (51.85)	85 (74.56)	0.002#
Comorbidities[¨]	132 (67.70)	62 (76.50)	70 (61.40)	0.026#
Smoking	18 (9.20)	11 (13.60)	7 (6.10)	0.077#
Hypertension	81 (41.50)	39 (48.10)	42 (36.80)	0.114#
Cardiovascular disease	43 (22.10)	23 (28.40)	20 (17.50)	0.072#
Congestive heart failure	9 (4.60)	4 (4.90)	5 (4.40)	0.856#
Coronary artery disease	33 (16.90)	11 (13.60)	22 (19.30)	0.294#
Stroke	17 (8.70)	11 (13.60)	6 (5.30)	0.042#
Diabetes	56 (28.70)	23 (28.40)	33 (28.90)	0.933#
Chronic obstructive pulmonary disease	31 (15.90)	7 (8.60)	24 (21.10)	0.020#
Chronic kidney disease	9 (4.60)	4 (4.90)	5 (4.40)	0.856#
Malignancy	4 (2.10)	1 (1.20)	3 (2.60)	0.643#
Chronic liver disease	4 (2.10)	2 (2.50)	2 (1.80)	>0.999#
Hyperlipidemia	44 (22.60)	16 (19.80)	28 (24.60)	0.429#
Sleep apnea	5 (2.60)	1 (1.20)	4 (3.50)	0.322#
Autoimmune disease	10 (5.10)	9 (11.10)	1 (0.90)	0.002#
Cancer therapy	14 (7.18)	8 (9.88)	6 (5.26)	0.343#
Signs and symptoms[¨]				
Dyspnea	149 (76.40)	70 (86.40)	79 (69.30)	0.006#
Fever	138 (70.80)	66 (81.50)	72 (63.20)	0.006#
Cough	140 (71.80)	63 (77.80)	77 (67.50)	0.118#
Myalgia or fatigue	124 (63.60)	49 (60.50)	75 (65.80)	0.449#
Headache	83 (42.60)	34 (42.00)	49 (43.00)	0.889#
Chills	81 (41.50)	20 (24.70)	61 (53.50)	<0.001#
Diarrhea	39 (20.10)	6 (7.50)	33 (28.90)	<0.001#
Sputum production	20 (10.30)	11 (13.60)	9 (7.90)	0.197#
Nausea and vomiting	20 (10.30)	2 (2.50)	18 (15.80)	0.003#
Hemoptysis	2 (1.00)	1 (1.20)	1 (0.90)	>0.999#
Vital signs				
Systolic blood pressure[·] (mmHg)	120 (110-130)	114 (100-130)	112 (110-130.50)	0.002**
Diastolic blood pressure[·] (mmHg)	72 (70-80)	70 (70-80)	75 (70-80)	0.232**
Mean arterial pressure[·] (mmHg)	90 (83.30-96.70)	89.67 (83.30-96.70)	90 (83.30-96.70)	0.443**
Respiratory rate (>24 BPM)[¨]	64 (32.80)	31 (38.30)	33 (28.90)	0.399#
Oxygen saturation (%)[·]	88 (75.50-92.75)	82 (69-90)	88 (84-94)	0.001**

Data presented as [¨]Number (%); [D]Mean±SD; [·]Median and interquartile range (IQR); *Independent sample *t* test; **Mann-Whitney U test; #Chi square or Fisher's exact test; BMI: Body mass index; ICU: Intensive care unit

Source of Infection: Patients were infected with SARS-CoV-2 due to close contact with infected family members (n=41, 21.02%), during travel (n=10, 5.13%), hospitalization (n=17, 8.72%), or other activities such as shopping, attending mosques, and so on (n=127, 65.13%). Among these, a significant number of patients with hospital-acquired infections were admitted to the ICU (P=0.001) (table 1).

Comorbidities: Of the 195 patients, 132 (67.7%) had at least one coexisting medical condition. Compared with non-ICU patients, comorbidity was significantly higher among patients admitted to the ICU, especially those with a history of stroke (P=0.042), chronic obstructive pulmonary disease (COPD) (P=0.020), and autoimmune diseases (P<0.001) (table 1).

Signs and Symptoms: The most common signs and symptoms were dyspnea (76.4%), cough (71.8%), fever (70.8%), myalgia or fatigue (63.6%), headache (42.6%), and chills (41.5%). Fever and dyspnea were significantly higher in patients admitted to the ICU than non-ICU patients (P=0.006 for both). However, chills, diarrhea, nausea, and vomiting were more common in non-ICU patients (P<0.001 for chills and diarrhea, and P=0.003 for nausea and vomiting). High systolic blood pressure was statistically significant in patients, who required ICU care (median: 114) compared with non-ICU patients (median: 112, P=0.002). In total, 32.8% of the patients had respiratory rate >24 bpm, of which 38.3% and 28.9% were ICU and non-ICU patients, respectively; the difference was not statistically significant. Oxygen saturation was lower in the ICU patients (median: 82) than the non-ICU patients (median: 88, P=0.001) (table 1).

Cardiovascular Diseases: More ICU patients had a prior history of supraventricular arrhythmia (19.8%) compared with non-ICU patients (4.4%) (P=0.001). This was also the case for pericardial effusion (17.3% vs.1.8%, P<0.001). The maximum and minimum IQR for the left ventricular ejection fraction were 35 and 55 with a median of 50 (table 2).

Patient Outcome and Related Factors: Of the 195 patients, 46 (23.6%) died due to COVID-19. The mortality rate among ICU patients was significantly higher than the non-ICU patients (48.1% vs. 6.1%, P<0.001). Moreover, the ICU patients had a longer hospital stay than the non-ICU patients (14.24±8.22 vs. 7.93±6.13 days, P<0.001). The median of days from illness onset to dyspnea was 5 (table 3).

Medication History: The most common medications used by the patients were statins (31.8%), ASA (31.3%), diuretics (20.5%), ARB (20%), and beta-blockers (14.9%). Of all drugs, the use of ASA, diuretic, thiazide, and warfarin was the highest in patients admitted to the ICU (table 4).

Laboratory Data: The results showed that some parameters in ICU patients were significantly higher than the non-ICU patients, namely WBC count (median: 7.40 vs. 6.35, P=0.008), cardiac troponin concentrations (median: 10 vs. 4, P=0.040), LDH (median: 692 vs. 502, P=0.027), ESR (median: 68.5 vs. 49, P=0.008), BUN (median: 16 vs. 12, P=0.029). However, the median for neutrophil levels and lymphocyte counts did not differ between the two groups (P=0.347 and P=0.109, respectively). The hematocrit levels in ICU patients were significantly lower than in the non-ICU patients (median: 34.7 vs. 42.8, P=0.001). Other laboratory data were not significantly different between the two groups (table 5).

Table 2: Medical history of cardiovascular disorders in ICU and non-ICU patients with confirmed COVID-19

Cardiovascular disorders	Total (n=195)	ICU care (n=81)	Non-ICU care (n=114)	P value
Supraventricular arrhythmia¯	21 (10.80)	16 (19.80)	5 (4.40)	0.001#
QT prolongation¯	35 (17.90)	13 (16)	22 (19.30)	0.560#
Bundle branch block¯	7 (3.60)	2 (2.50)	5 (4.40)	0.702#
ST segment change¯	15 (7.70)	5 (6.20)	10 (8.80)	0.502#
Pericardial effusion¯	16 (8.20)	14 (17.30)	2 (1.80)	<0.001#
Left ventricular ejection fraction¸	50 (35-55)	55 (50-55)	50 (25-55)	0.145**

Data are presented as ¯Number (%), ¸Median and interquartile range (IQR); **Mann-Whitney U test; #Chi square or Fisher's exact test

Table 3: Patients' outcome and related factors in ICU and non-ICU patients with confirmed COVID-19

	Total (n=195)	ICU care (n=81)	Non-ICU care (n=114)	P value
Dead¯	46 (23.60)	39 (48.10)	7 (6.10)	<0.001#
Length of hospital stay (days)ᴰ	10.13±7.54	14.24±8.22	7.93±6.13	<0.001*
Days from illness onset to dyspnea¸	5 (4-7)	5 (4-7)	5 (4-8)	0.767**

Data presented as ¯Number (%), ᴰMean±SD, ¸Median and interquartile range (IQR); *Independent sample *t* test; **Mann-Whitney U test; #Chi square or Fisher's exact test

Table 4: Medication history in ICU and non-ICU patients with confirmed COVID-19

Treatments	Total (n=195)	ICU care (n=81)	Non-ICU care (n=114)	P value#
Statin	62 (31.80)	24 (29.60)	38 (33.30)	0.584
ASA	61 (31.30)	33 (40.70)	28 (24.60)	0.016
Diuretic	40 (20.50)	24 (29.60)	16 (14.00)	0.008
ARB	39 (20.00)	16 (19.80)	23 (20.20)	0.942
Beta-blockers	29 (14.90)	16 (19.80)	13 (11.40)	0.106
Aldosterone antagonist	11 (5.60)	2 (2.50)	9 (7.90)	0.126
Thiazide	8 (4.10)	8 (9.90)	0 (0)	0.001
NOAC	6 (3.10)	2 (2.50)	4 (3.50)	>0.999
ACEIs	7 (3.60)	3 (3.70)	4 (3.50)	>0.999
Warfarin	4 (2.10)	4 (4.90)	0 (0)	0.028

Data presented as numbers and percentages. #Chi square or Fisher's exact test; ASA: Acetylsalicylic acid; ARB: Angiotensin II receptor blockers; NOAC: Novel oral anticoagulants; ACEIs: Angiotensin-converting enzyme inhibitors

Table 5: Laboratory test results of ICU and non-ICU patients with confirmed COVID-19

	Normal range	Total (n=195)	ICU care (n=81)	Non-ICU care (n=114)	P value
White blood cell count, $\times10^9$/L	3.5-9.5	6.80 (5.30-6.90)	7.40 (5.75-14.85)	6.35 (5.20-8.00)	0.008
Neutrophil count, $\times10^9$/L	1.8-6.3	68.25 (55.20-77.00)	70 (55.50-83.40)	68 (55.20-76.20)	0.347
Lymphocyte count, $\times10^9$/L	1.1-3.2	23.30 (13.20-31.70)	20.65 (7.10-23.50)	20.5 (14.70-34.60)	0.109
Hematocrit (HCT)	35-45	40.3 (35.00-44.20)	34.7 (30.10-41.20)	42.8 (38.00-45.50)	0.001
Platelet count, $\times10^9$/L	125-350	230 (158-302)	237 (194-298)	226 (157-310)	0.583
Prothrombin time, s	9.4-12.5	16 (14-17)	17 (14.00-18.50)	15 (14-17)	0.256
Partial thromboplastin time, s	25.1-36.5	34 (30.75-42.50)	32.5 (26.00-41.75)	35 (32.50-43.00)	0.282
The international normalized ratio	<2	1.37 (1.10-1.50)	1.5 (1.10-1.70)	1.2 (1.10-1.40)	0.296
Cardiac troponin, ng/mL	<0.05	14 (7.18)	10 (12.35)	4 (3.51)	0.04#
Creatine phosphokinase, units/L	<200	101 (56.50-233.50)	110 (58.50-362.50)	89 (56.00-194.25)	0.259
Creatine phosphokinase – myocardial band, units/L	<24	34 (23-61)	34 (25.50-54.00)	29.5 (19.75-76.50)	0.694
Lactate dehydrogenase, U/L	<250	547 (388-801)	692 (440.25-882.00)	502 (382-689)	0.027
C-reactive protein, mg/L	<12	35.2 (12.75-71.75)	36 (12.75-79.00)	35 (12.50-67.00)	0.311
Erythrocyte sedimentation rate, mL/h	<20	57.5 (33-76)	68.5 (36.50-86.25)	49 (32.00-67.50)	0.008
Glucose, mg/dl	70-100	100 (84-120)	112 (84-184)	98 (84.00-118.50)	0.287
ALT, U/L	9-50	25 (16-45)	31 (13.20-52.20)	23 (18-36)	0.916
AST, U/L	15-40	28 (18-41)	35.5 (18.20-52)	23 (18-36)	0.098
ALP, U/L	30-120	199 (149.00-262.50)	180 (146.50-276.00)	204 (152-233)	0.827
Total bilirubin, mmol/L	5-21		0.7 (0.50-0.90)	0.7 (0.50-1.20)	0.467
Na, mEq/L	135-145	139 (135-141)	138 (135-142)	139 (136-141)	0.486
K, mEq/L	3.6-5.0	4.2 (3.90-4.55)	4.2 (3.90-4.80)	4.2 (3.90-4.50)	0.339
BUN, mmol/L	2.8-7.6	13 (9.40-18.25)	16 (11.00-23.50)	12 (8.60-17.00)	0.029
Cr, mg/dL	0.6-1.3	1 (0.80-1.20)	1 (0.80-1.30)	1 (0.80-1.20)	0.822
$PaCo_2$, mmHg	35-45	42 (34.40-45)	43 (36.65-45.10)	39.4 (34.20-44.70)	0.436
Be, mmHg	-2 to +2	-1.5 (-30 to -0.50)	-1.90 (-3.75 to -0.30)	-1.2 (-30 to -0.60)	0.808
Hco_3, mmHg	22-26	23.7 (22.20-24.30)	23.80 (23.00-24.70)	23.7 (22.00-24.10)	0.539
PH	7.35-7.45	7.36 (7.35-7.41)	7.36 (7.32-7.41)	7.37 (7.35-7.41)	0.530

Unless stated, data are presented as the median and interquartile range (IQR), using the Mann-Whiney U test. Data expressed as numbers and percentages, using Chi square test; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; BUN: Blood urea nitrogen; Cr: Creatinine; Be: Base excess

Factors Associated with Mortality

The results showed an association between underlying conditions and mortality. The odds ratio of some conditions indicated an increase in mortality, namely the presence of at least one comorbid disease (OR: 3.43, P=0.006), hypertension (OR: 2.60, P=0.007), coronary artery disease (OR: 2.32, P=0.040), age>40 years (OR: 4.82, P=0.012), and underweight (OR: 5.82, P=0.047). In contrast, overweight and obesity showed a decrease in the mortality rate (table 6). The presence of some symptoms was considered a risk factor for the mortality rate, namely fever (OR: 2.48, P=0.034), cough (OR: 2.40, P=0.042), dyspnea (OR: 4.29, P=0.009), ST-segment changes (OR: 3.72, P=0.017), and pericardial effusion (OR: 22.76, P<0.001). However, symptoms such as diarrhea

Table 6: Factors associated with mortality in patients with confirmed COVID-19

	OR*	95% CI	P value
Underlying condition			
Presence of at least one comorbid disease	3.439	1.429-8.278	0.006
Smoking	2.172	0.774-6.090	0.140
Age>40 years	4.827	1.404-16.597	0.012
Male sex	1.061	0.537-2.097	0.865
Obesity and overweight (BMI>25 Kg/m^2)	0.415	0.193-0.896	0.025
Underweight (BMI<18 Kg/m^2)	5.824	1.021-33.229	0.047
Hypertension	2.603	1.306-5.189	0.007
Congestive heart failure	3.872	0.993-15.103	0.051
Coronary artery disease	2.322	1.038-5.195	0.040
Chronic obstructive pulmonary disease	1.058	0.413-2.709	0.906
Signs and symptoms			
Fever	2.485	1.069-5.777	0.034
Chills	0.143	0.057-0.361	<0.001
Cough	2.403	1.033-5.588	0.042
Dyspnea	4.290	1.438-12.796	0.009
Diarrhea	0.133	0.030-0.577	0.007
ST segment change	3.729	1.270-10.954	0.017
Pericardial effusion	22.765	4.861-106.602	<0.001
O2 saturation<90%	3.807	1.354-10.707	0.011
O2 saturation<85%	4.290	1.917-9.600	<0.001
O2 saturation<80%	5.10	2.279-11.412	<0.001
Laboratory results			
WBC>10×10^9/L	5.087	2.367-10.931	<0.001
CRP>12 mg/L	9.187	1.189-71.014	0.034
AST>35 U/L	8.842	1.713-45.651	0.009
BUN>20 mmol/L	13.490	3.244-56.104	<0.001
Length of hospital stay >8 days	2.491	1.116-5.563	0.026

*Unadjusted odds ratio; WBC: White blood cell; CRP: C-reactive protein; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen

and chills were not considered mortality risk factors (table 6). The surge in some blood serum levels significantly increased risk of death, namely WBC>10×10^9/L (OR: 5.08, P<0.001), CRP>12 mg/L (OR: 9.18, P=0.034), aspartate aminotransferase (AST)>35 U/L (OR: 8.84, P=0.009), and BUN>20 mmol/L (OR: 13.49, P<0.001) (table 6).

Discussion

The data obtained from 195 patients with confirmed COVID-19 showed that 132 (67.7%) patients had at least one underlying disease. The prevalence of stroke, COPD, and autoimmune diseases was higher in ICU patients. Although WBC count, cardiac troponin concentrations, lactate dehydrogenase levels, erythrocyte sedimentation rates, and BUN were significantly higher in ICU patients, they had lower hematocrit levels than the non-ICU patients. The mortality rate in ICU and non-ICU patients was 48.1% and 6.1%, respectively. The risk factors for mortality rate included age>40 years, BMI<18 Kg/m^2, hypertension, coronary artery disease, fever, cough, dyspnea, ST-segment changes, pericardial effusion, and a surge in WBC, CRP, AST, and BUN.

In line with previous studies, we also found that male COVID-19 patients significantly outnumbered female patients.[5-7] It is suggested that women are less prone to viral infections due to protection by the X chromosome and sex hormones, which play a major role in innate and adaptive immunity.[5] Moreover, women tend to adopt a healthier lifestyle and behavior than men.[8]

A high prevalence of COVID-19 patients with at least one comorbidity was also reported in several studies. Compared to 67.7% in our study, Chen and colleagues reported that 51% of SARS-CoV-2 infected patients had chronic diseases.[5] However, some other studies reported a lower prevalence in the range of 30-37%.[9, 10] In line with a study by Wang and colleagues, the most prevalent comorbidity among our patients included hypertension, diabetes, CVD, COPD, and hyperlipidemia.[6] A study conducted in Italy on 1,591 COVID-19 patients showed hypertension as the most common comorbid disease followed by CVD, hypercholesterolemia, and diabetes.[7] A meta-analysis study also reported hypertension, diabetes, and CVD as the

most common comorbidities, however, COPD was less common.[10] It has been suggested that comorbidity in COVID-19 patients is associated with poor outcomes,[1] especially in severe cases.[1] However, it is still not clear which of the comorbidities most exacerbates the course of the disease. COPD is shown to increase the risk of disease progression by 5.9-fold.[1] Hypertension, diabetes, CVD, and cerebrovascular diseases are among the leading candidates for disease exacerbation. Whereas, the role of liver disease, malignant tumors, and kidney disease has not been confirmed yet.[11] In comparison with non-ICU patients, we found that the prevalence of coexisting medical conditions (e.g., stroke, COPD, and autoimmune diseases) was higher in those who required ICU care (61.4% vs. 76.5%). Wang and colleagues reported that hypertension, CVD, cerebrovascular diseases, and diabetes were significantly higher in patients admitted to ICU.[6]

The results of the present study showed that the main clinical features of COVID-19 patients were dyspnea, cough, fever, myalgia, fatigue, headache, and chills; to a lesser extent diarrhea, sputum production, nausea and vomiting, and hemoptysis. Similar findings were also reported in some other studies.[6, 9, 11] However, as confirmed in a previous study,[10] it seems that intestine-associated symptoms (e.g., diarrhea) are less common in COVID-19 patients. In line with another study, we found that the prevalence of fever and dyspnea were significantly higher in ICU than the non-ICU patients. Whereas chills, diarrhea, nausea, and vomiting were more common in non-ICU patients.[6]

QT prolongation and supraventricular arrhythmia were the most common types of arrhythmias in patients with COVID-19. Cardiac arrhythmias are reported as the primary complications in COVID-19 patients during hospitalization, with 44.4% prevalence in the ICU.[1,9] In our study, the prevalence of supraventricular arrhythmias and pericardial effusion was higher in ICU patients than the non-ICU patients. To the best of our knowledge, no other study has reported a comparison between ICU and non-ICU patients in terms of cardiac arrhythmias.

Data on mortality rates due to COVID-19 differ in various countries and time points. Our results showed a total mortality rate of 23.6% from March to April 2020, of which 48.1% were ICU patients, and 6.1% were non-ICU patients. Huang and colleagues reported a mortality rate of 15% from December 2019 to January 2020, of which 38% were ICU patients, and 4% were non-ICU patients.[12] Other studies reported a mortality rate of 78% among critical COVID-19 patients (China),[13] a rate of 16.9% among non-ICU and 18.9% among ICU patients in Brazil,[14] and a rate of 26% among ICU patients in Italy during two-month period.[7]

In terms of blood test results, we found higher levels of WBC, cardiac troponin, LDH, ESR, and BUN in ICU patients compared with those not in the ICU, whereas hematocrit levels were lower. In line with our results, Wang and colleagues also reported higher levels of WBC, LDH, and BUN in ICU patients, but creatine kinase (CK) levels were not significantly different from those not in ICU. They also reported significantly higher levels of CK-MB, neutrophil, lymphocyte, ALT, AST, bilirubin, Cr, and troponin I in ICU patients.[6]

In line with previous studies, we found that age was a risk factor for mortality in COVID-19 patients (age>40 years, OR: 4.82).[13, 14] It is reported that older age is associated with reduced T-cell and B-cell production impairing innate immunity function, resulting in type 2 cytokine storm leading to poor prognosis and adverse outcome.[14, 15] This is the reason for higher morbidity and increased risk of mortality in older adults.[14]

Previous studies have shown that obesity in COVID-19 patients is associated with severe pneumonia,[16] hospitalizations,[17] and assisted invasive mechanical ventilation.[17] In contrast, our results showed that mortality was 5.82-fold higher in underweight patients (BMI<18 Kg/m^2), whereas obesity and overweight (BMI>25 Kg/m^2) reduced the risk of mortality (OR: 0.41). Other studies also reported that despite a higher risk of mortality in obese patients with COVID-19 due to comorbidities such as diabetes and CVD, increased BMI was not associated with poor prognosis and severity of the disease.[17, 18] Therefore, it is possible that the reported association of obesity and overweight with the severity of COVID-19 is due to other independent risk factors than BMI.[17] There are controversies about the effect of smoking and COPD, as an underlying condition in COVID-19 patients, on disease progression and mortality. Despite the reported association between COPD in COVID-19 patients and increased mortality rate,[19, 20] our results do not support this. It is suggested that high mortality in patients with severe stages of COPD, requiring ICU intervention, is mainly due to the lack of respiratory support facilities, limited critical care unit capacity, and acute shortage of clinicians.[21] In terms of smoking and its effect on COVID-19, most studies have reported higher mortality among smokers,[11, 22] and that it increases the risk of disease severity by two-fold,[23] due to its toxicity, inflammatory, and oxidative properties.[24] It is also suggested

that inhalation of tobacco smoke may increase the transmission of the virus.[21] This last study also hypothesizes that smoking upregulates the expression of angiotensin-converting enzyme 2 receptors (ACE2), leading to increased disease severity and higher mortality. In contrast, other studies have reported a low number of smokers among hospitalized COVID-19 patients and suggested the potential inhibitory effect of nicotine on the inflammatory response.[25, 26]

Our results showed that the presence of some COVID-19 symptoms, such as fever (OR: 2.48), cough (OR: 2.40), and dyspnea (OR: 4.29) were risk factors for mortality. In line with our findings, Zhang and colleagues reported that fever and dyspnea were correlated with improvement during follow-up (OR: 1.74 and 2.36, respectively).[27] On the other hand, it is reported that the presence of dyspnea in COVID-19 patients can significantly increase the mortality rate by 2.2-fold.[19] It is proposed that a cytokine storm (a prominent feature of COVID-19) triggers over-activation of the immune system, leading to the proliferation of immune cells throughout the body and multi-organ failure. In the lungs, this leads to a build-up of fluid in its air sacs (the alveoli) resulting in lung dysfunction, dyspnea, and acute respiratory failure.[19] In terms of cardiac arrhythmias, ST-segment changes, and pericardial effusion increased the mortality rate (OR: 3.72 and 22.76, respectively). Diarrhea was found to be a protective factor against mortality (OR: 0.13), probably due to the IgA and $CD19^{+}$ B-cells production, which enhances mucosal immunity in the gut, lungs, and urogenital system.[28]

Our laboratory test results showed that BUN>20 mmol/L increased the mortality rate by 13.49-fold. It is reported that COVID-19 can cause multiple organ damage (e.g., liver, gastrointestinal tract, and kidneys) due to systemic inflammation induced by a cytokine storm.[29, 30] Renal involvement is associated with a higher mortality rate.[31] Moreover, elevated serum creatinine and BUN levels are shown as independent risk factors for mortality.[30] ACE2 is strongly expressed in epithelial cells of urinary organs (about 100 times higher than in the lungs). Therefore, SARS-CoV-2 can infect ACE2 causing damage to renal cells by depleting Ang 1-7 and Ang 1-9 levels, resulting in an inflammatory cascade. The virus-induced cytokine production might indirectly exert a negative effect on renal function, resulting in hypoxia, shock, and rhabdomyolysis.[29, 30] Our results showed that CRP>12 mg/L had a major effect on the mortality rate in COVID-19 patients (OR: 9.18). Other studies supported the association of elevated CRP with immune dysfunction in COVID-19 patients,[32] higher risk of mortality, and the need for mechanical ventilation.[33]

The laboratory results showed that AST>35 U/L increased the risk of mortality by 8.84-fold. Liver function is reported as a prognostic factor for mortality in COVID-19 patients. Abnormalities in liver enzymes might be attributed to medications used by these patients, as well as a cytokine storm-induced inflammatory response.[32] Our results also showed that WBC>10×10^{9}/L increased the risk of mortality by five-fold. In line with our results, a previous study reported the effect of high-sensitivity CRP on increasing mortality (OR: 1.04) followed by neutrophil and glomerular filtration rate (GFR). However, AST did not cause a significant increase in mortality.[32] Another study reported the effect of CRP>27 mg/L and WBC>10×10^{9}/L (hazard ratios 28.8 and 2.5, respectively) as well as neutrophil >6×10^{9}/L on the increased risk of mortality.[34] Zhang and colleagues evaluated risk factors associated with the lack of improvement during follow-up of COVID-19 patients and reported poor outcomes in patients with increased CRP (OR: 4.69), AST (OR: 2.08), and kidney function damage (OR: 5.95). Moreover, ALT and LDH had similar effects.[27] In line with our result, another study reported that CRP>8 mg/L and BUN >20 mmol/L significantly increased mortality by 27.95-fold and 6.77-fold, respectively.[20] In our study, neutrophil levels and some other laboratory data did not seem to have a significant association with mortality. This could be due to insufficient sample size or differences in the socio-demographic composition of our patients.

There is an inverse relationship between oxygen saturation and mortality. In line with previous studies, our results showed that oxygen saturation <90%, <85%, and <80% increased the OR by 3.8-, 4.29-, and 5.1-fold, respectively.[19, 20, 34] Low levels of oxygen saturation in COVID-19 patients is indicative of severe illness.[32] It is suggested that the virus-induced inflammatory response may cause lung injury and hypoxemia. Therefore, reducing inflammation in the early stages of the disease would improve oxygenation, i.e., reduce mortality.[34]

The main limitations of the study were the unavailability of some laboratory and clinical data from participating COVID-19 patients, and the evaluation of results based on short-term patient outcomes. Further studies using long-term patient outcomes are recommended.

Conclusion

Predictors of mortality outcome in COVID-19 patients include underlying diseases (hypertension

and CVD), age>40 years, BMI<18 Kg/m^2, cardiac arrhythmias, fever, cough, dyspnea, oxygen saturation <90%, abnormal laboratory test results (WBC, CRP, BUN, and AST levels), and prolonged hospitalization. Overall, COVID-19 patients in the ICU have poor prognoses compared with non-ICU patients. The findings of the study can be utilized by healthcare providers to better manage COVID-19 and allow hospital managers to efficiently allocate the limited ICU capacity.

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Conflict of Interest

Farid Zand, Editor-in-Chief, was not involved in the peer-review and decision-making processes for this manuscript. The non-author, Chairperson, oversaw the peer review process for this paper. Naeimehossadat Asmarian, as the Editorial Board Member, was not involved in any stage of handling this manuscript. A team of independent experts were formed by the Editorial Board to review the editor's article without her knowledge.

Authors' Contribution

N.A, F.Z, G.S, P.D, Z.E, Y.M, and M.S: Study concept and design, literature search, Acquisition, and interpretation of data; V.K, F.J, F.S, F.Y, E.H.S, M.H, A.D.M, F.D.M, and S.G: Literature search, Acquisition of data. All authors contribute in drafting and revision of the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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