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Clinical and Laboratory Predictors of Mortality in Hospitalized COVID-19 Patients

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Abstract

Background: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a variety of symptoms and laboratory and radiologic features whose identification can help diagnose and manage patients with COVID-19 more effectively.

Objectives: This study aimed to describe the epidemiological, clinical, and laboratory features of patients with COVID-19, compare clinical features of patients in the intensive care unit (ICU) with those of non-ICU admitted patients, and define mortality risk factors for this disease.

Methods: This cross-sectional study was carried out on 781 COVID-19 patients hospitalized in Rasool Akram Medical Complex, Tehran, Iran, from February to May 2020. Patients' epidemiological, demographic, clinical, laboratory findings were collected. Routine blood tests included complete blood count, coagulation profile, and serum biochemical tests. Confirmed infection was defined as positive reverse transcription-polymerase chain reaction (RT-PCR) to SARS-CoV-2 in their nasopharyngeal specimens or typical clinical, laboratory, and imaging findings of COVID-19 infection altogether. All data were analyzed using SPSS software (version 21).

Results: In this study, the majority of patients were male (n=470, 60.2%) and the remainder were female. The median age of the patients was 64 years. Hypertension (31.8%) and tuberculosis (1.4%) were the most common and the least common underlying condition among the patients, respectively. Moreover, cough and seizure were the most common (75.7%) and the least common (2.4%) symptoms in patients. The history of diabetes mellitus, the presence of dyspnea, loss of taste, and the occurrence of seizure were associated with a higher risk of ICU admission. On the other hand, advanced age, positive PCR, presence of dyspnea, myalgia, loss of taste, and elevated liver enzymes, and lactate dehydrogenase (LDH) were associated with a higher risk of mortality. Based on the results, smoking had a preventive effect on mortality (OR=0.292, P=0.048); however, it had no significant effect on ICU admission.

Conclusion: According to the obtained results, positive PCR and initial symptoms of dyspnea and myalgia were associated with increased odds of mortality by two times. In addition, elevated alanine aminotransferase and lactate dehydrogenase were associated with a higher rate of mortality. ICU admission was the main variable to increase the odds of mortality. Eventually, smoking might play a protective role against COVID-19 mortality.

Keywords: COVID-19, Epidemiology, Intensive care unit, Laboratory, Mortality

1. Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly recognized disease that has spread rapidly from Wuhan to other provinces in China and all around the world (1-2). Since the beginning of the new coronavirus pneumonia epidemic, this disease has spread widely throughout China and other countries in the world at a rapid pace, and the number of infected cases has increased especially in metropolises (1,3,4).

The rapid spread of Coronavirus Disease 2019 (COVID-19) has attracted worldwide attention, and the World Health Organization (WHO) has designated it as a Public Health Emergency of International Concern (5). COVID-19 can affect body organs such as the kidney, respiratory system, and liver (6-8). According to the World Health Organization, more than 74,879,038 people have been infected and 1,676,236 died worldwide due to COVID-19 by late December 2020 (9).

Clinical manifestations of the disease include fever, dry cough, shortness of breath, myalgia, fatigue, normal or decreased leukocyte count, and radiographic evidence of pneumonia. Organ failure, such as acute respiratory distress syndrome, heart, and renal failure, and even death may occur in severe

cases (10). In addition to the symptoms listed, patients with severe infections can also develop neurological manifestations, such as impaired consciousness as well as cerebrovascular diseases, and skeletal muscle injury (11). In addition, some patients may present with upper respiratory symptoms, such as sore throat, nasal congestion, rhinorrhea, and anosmia (12,13).

While most infected patients develop mild to moderate symptoms and recover without hospitalization, about 14% have severe symptoms that require hospital care, and one-third of hospitalized patients require invasive mechanical ventilation (14). At present, it is believed that some people including pregnant women and children are generally more susceptible to COVID-19. Most studies indicate that middle-aged people are more susceptible to COVID-19 (mean age at onset is about 55 years) (15). No specific drug or vaccine has been found yet to treat COVID-19; therefore, the management of patients with communicable diseases is similar to that of viral pneumonia and includes supportive therapy to control symptoms and protect multiple body functions (16).

2. Objectives

This study aimed to describe the epidemiological, clinical, laboratory, and radiological features, and outcomes of patients with COVID-19, define mortality risk factors, and compare clinical features of patients in the intensive care unit (ICU) with those of non-ICU admitted patients referred to Rasool Akram Medical Complex, Tehran, Iran.

3. Methods

3. 1. Study Population

This cross-sectional study was carried out on 781 COVID-19 patients hospitalized in Rasool Akram Medical Complex from February to May 2020. Epidemiological, demographic, clinical, and laboratory information was extracted from patients' medical records by a trained team using a data collection form. Routine blood tests included complete blood count, coagulation profile, and serum biochemical tests. The majority of clinical data used in this study were collected from the first day of patients' hospitalization. As the disease progressed, the secondary laboratory results (including the number and percentage of lymphocytes and eosinophils) were also collected during the hospital stay. Laboratory data for some patients were lost due to lack of testing or delayed results.

All data were reviewed by two physicians and a third researcher made the final decision in cases that the two main researchers had a disagreement. Patient confidentiality was protected by assigning an identified code, and the electronic data were stored on a locked computer with a protected password. This study has been approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran.

3.2. Definitions

Confirmed infection was defined as a positive real-time reverse transcription-polymerase chain reaction to SARS-CoV-2 in patients' nasopharyngeal specimens or typical clinical, laboratory, and imaging findings of COVID-19 infection altogether diagnosed by experts. Fever is defined as a body temperature ≥37.5 degrees Celsius. Lymphocytopenia and thrombocytopenia are defined as the number of lymphocytes count lower than 1500 cells per cubic millimeter and a platelet count of less than 150,000 per cubic millimeter, respectively.

3.3. Ethical issues

The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran. Accordingly, written informed consent was taken from all participants before any intervention.

3.4. Statistical analysis

All data were analyzed using SPSS software (version 21). Quantitative and qualitative data were reported as mean±SD as well as frequency and percentage, respectively. Paired t-test was used to compare the two means and a one-way ANOVA test was used to compare the means. Non-parametric tests were used in case the distribution of data was abnormal. A multivariate logistic regression model was used to investigate the relationship with confounding control. To prevent estimation bias, variables with a significance level less than 0.2 were entered in the logistic model. Link function was logit with significant fitting ($P<0.05$) and large goodness of fit ($P>0.05$). A p-value less than 0.05 was considered statistically significant.

4. Results

The present study was performed on 781 patients with COVID-19 who were admitted to Rasool Akram Medical Complex, Tehran, Iran from February to May 2020. The median age of the patients was 64 years (IQR 50–75, ranging from 10 to 98 years). Demographic characteristics of the patients and their underlying conditions were examined and the results showed that hypertension was the most common (31.8%) and tuberculosis was the least common (1.4%) underlying disease among patients. Table 1 presents the demographic characteristics and underlying conditions of the patients.

The initial symptoms of the patients were evaluated and the results showed that cough was the most common (75.7%) and seizure was the least

Table 1. Demographic characteristics and underlying diseases of the patients

Variable		Total (n=781)
Age (Mean±SD)		62.30±16.87
Gender	Female	311(39.8)
	Male	470(60.2)
HTN	No	533(68.2)
	Yes	248(31.8)
DM	No	537(68.8)
	Yes	244(31.2)
Malignancy	No	739(94.6)
	Yes	42(5.4)
TB	No	770(98.6)
	Yes	11(1.4)
Addiction	No	710(90.9)
	Yes	71(9.1)
Smoking	No	656(84.0)
	Yes	125(16.0)
Opium	No	747(95.6)
	Yes	34(4.4)
Kidney Disease	No	684()
	Yes	97(12.4)
Lung Disease	No	694(88.9)
	Yes	87(11.1)
Heart Disease	No	501(64.1)
	Yes	280(35.9)

common (2.4%) presenting symptoms. Table 2 tabulates the distribution of the patient's initial symptoms.

In this study, 214 patients (27.4%) were admitted to the ICU. The effects of demographic characteristics and the patient's initial symptoms were investigated on ICU admission. The results showed that the history of diabetes mellitus and the presence of dyspnea, seizure, and anosmia increased the odds of hospitalization in the ICU by 2.520 (95% CI: 1.376-4.615), 2.097 (95% CI: 1.057-4.158), 5.547 (95% CI: 1.461-21.067) and 2.202 (95% CI: 1.094-4.434) times, respectively. Other demographic characteristics and initial symptoms of patients had no significant effect on ICU admission (P>0.05). Table 3 presents the results of logistic regression for the correlation of demographic characteristics and the patient's initial symptoms on ICU admission.

Table 2. Distribution of initial symptoms of the patients

Variable		Total (n=781)
Fever	No	249(31.9)
	Yes	532(68.1)
Chills	No	232(29.7)
	Yes	549(70.3)
Cough	No	190(24.3)
	Yes	591(75.7)
Dyspnea	No	205(26.2)
	Yes	576(73.8)
Fatigue	No	227(29.1)
	Yes	554(70.9)
Anorexia	No	285(36.5)
	Yes	496(63.5)
Myalgia	No	296(37.9)
	Yes	485(62.1)
Sore throat	No	607(77.7)
	Yes	174(22.3)
Diarrhea	No	641(82.1)
	Yes	140(17.9)
Headache	No	507(64.9)
	Yes	274(35.1)
Vertigo	No	581(74.4)
	Yes	200(25.6)
Seizure	No	762(97.6)
	Yes	19(2.4)
Taste disorder	No	627(80.3)
	Yes	154(19.7)
Anosmia	No	611(78.2)
	Yes	170(21.8)

Table 3. Logistic regression results for the effect of demographic characteristics and initial symptoms on ICU admission

Characteristics	OR	95% CI for OR		P-value
		Lower	Upper	
Age	0.992	0.972	1.012	0.416
Gender	0.976	0.533	1.787	0.937
DM	2.520	1.376	4.615	0.003*
HTN	1.187	0.600	2.349	0.622
Malignancy	1.630	0.421	6.314	0.479
Addiction	0.629	0.154	2.575	0.519
Smoking	0.733	0.293	1.834	0.507
Opium	3.648	0.730	18.228	0.115
PCR	1.313	0.523	3.293	0.562
Fever	1.191	0.478	2.968	0.708
Chills	1.151	0.448	2.956	0.770
Cough	0.779	0.413	1.468	0.439
Dyspnea	2.097	1.057	4.158	0.034*
Anorexia	1.054	0.570	1.952	0.866
Myalgia	0.548	0.296	1.014	0.055
Sore throat	0.632	0.286	1.396	0.256
Vertigo	0.663	0.310	1.418	0.290
Seizure	5.547	1.461	21.067	0.012*
Ageusia	2.202	1.094	4.434	0.027*

The relationship between demographic characteristics, underlying conditions, and laboratory findings with the mortality of the hospitalized patients was investigated in this study. Based on the results, advanced age, positive PCR, dyspnea, myalgia, taste disorder, ICU admission, and increased lactate dehydrogenase (LDH) in hospitalized patients increased the chance of death by 1.053 (95% CI: 1.028-1.079), 4.237 (95% CI: 1.726-10.401), 2.925 (95% CI: 1.190-7.187), 2.540 (95% CI: 1.214-5.313), 10.262 (95% CI: 4.734-22.202), 1.021 (95% CI: 1.002-1.041), and 1.002 (95% CI: 1.001-1.004) times, respectively. Other factors had no significant relationship with the risk of death in hospitalized patients. Table 4 presents the relationship between demographic factors, underlying diseases, and laboratory findings with the risk of mortality in hospitalized patients.

5. Discussion

Nowadays, COVID-19 is a challenging health matter affecting all units of society. The performance of analytical studies with an adequate sample size is the key strategy to tackle this epidemic. In this regard, the present study described the epidemiological, clinical, laboratory features of patients with COVID-19 and compared clinical features of intensive care unit (ICU) and non-ICU

Table 4. Relationship between demographic factors, underlying diseases, and laboratory findings with the mortality of the hospitalized patients

Characteristics	OR	95% CI for OR		P-value
		Lower	Upper	
Age	1.053	1.028	1.079	<0.001*
Gender	1.888	0.894	3.986	0.096
PCR	4.237	1.726	10.401	0.002*
Fever	0.802	0.241	2.673	0.719
Chills	2.924	0.823	10.386	0.097
Cough	2.331	0.952	5.709	0.064
Dyspnea	2.925	1.190	7.187	0.019*
Fatigue	0.735	0.356	1.520	0.407
Myalgia	2.540	1.214	5.313	0.013*
Seizure	0.530	0.052	5.400	0.592
Taste	0.267	0.078	0.911	0.035*
Anosmia	0.684	0.244	1.916	0.470
HTN	1.129	0.550	2.318	0.742
Addiction	0.573	0.138	2.372	0.442
Smoking	0.292	0.086	0.989	0.048*
ICU[1]	10.262	4.743	22.202	<0.001*
WBC[2]	1.040	0.963	1.123	0.320
ESR[3]	0.994	0.982	1.006	0.300
AST[4]	1.021	1.002	1.041	0.032*
ALT[5]	0.969	0.947	0.991	0.007*
LDH[6]	1.002	1.001	1.004	0.002*

[1] Intensive care unit
[2] *White blood cells*
[3] The erythrocyte sedimentation rate
[4] Aspartate transaminase
[5] Alanine transaminase
[6] The *lactate dehydrogenase*

admitted patients referred to one of the largest educational hospitals in the capital city of Iran, Rasool Akram Medical Complex. Based on the results, positive PCR, dyspnea, and myalgia increased the rate of mortality in the patients admitted with COVID-19. Hospitalization in ICU was the main mortality risk factor and the relative mortality risk of hospitalized patients in the ICU was ten times higher than that of non-hospitalized patients. This can be justified by the fact that as the patient's status gets deteriorated, the more likely he will be admitted to ICU. In the same line, the results of a study conducted in Tehran, Iran, revealed that fever, cough, and shortness of breath were the main symptoms and multi-organ failure was notable in people aged over 60 years (17). The results of the present study revealed that aging, positive PCR, dyspnea, myalgia, elevated alanine transaminase (ALT), and LDH level were the most important factors related to the risk of death. The diagnostic milestones in the present study were re-checked by a pulmonologist, an infectious disease specialist, and a radiologist to get a definite diagnosis. Elevated ALT and LDH were signs of initiation of end-organ damage which could be a poor prognostic factor. In addition, these factors were a clue to severe myositis, a poor prognostic finding in COVID-19 patients, as myalgia was an important mortality risk factor. Dyspnea was an effective mortality risk factor. This was an expected result as well since most of the patients who died had severe respiratory involvement. The five most common symptoms at admission in the present study included cough, shortness of breath, fatigue, and chills, and fever, respectively, which was in line with the results of other studies in which cough and fever were the most common symptoms. Fever is not a constant symptom in all patients which may be due to routine application of antipyretics in out-patient visits or as an over-the-counter medicine.

The least common symptom in this study was seizure while it was an olfactory disorder in the study performed by Samimi et al. (17).

In a systematic review conducted by Rodriguez-Morales et al., ICU was required for 20.3% of patients with COVID-19 infection (18). In this review, 19 studies were assessed and the frequency of the symptoms related to COVID-19 was as following: fever (88.7%), cough (57.6%), and dyspnea (45.6%). Moreover, dyspnea and fever were present in 73.8% and 68.1% of patients, respectively. However, the rate of fever was lower in this study compared to the study performed by Rodriguez-Morales et al, according to the collected data. (19). Based on the results of a study conducted by Jin et al. paying attention to atypical patients with COVID-19 can increase the chance to protect health providers and improve health promotion interventions. Gastrointestinal (GI) symptoms were highlighted by Jin et al. and their study reported that 11.4% of the patients had at least one GI symptom such as nausea, vomiting, or diarrhea. The mean age of the patients in their study was 46.14 years and patients with GI symptoms had higher rates of fever >38.5°C, fatigue, shortness of breath, and headache, respectively. The results of the present study were inconsistent with those reported by Jin et al. in which anorexia was found in the majority (63.5%) of patients of and diarrhea was reported in 17.9% of the patients. The prevalence of GI symptoms was higher in the current study. In addition, the mean age of the patients in the present study was higher than the study conducted by Jin et al. (19). In a study performed by Besharat et al., the majority of the patients were overweight. It is worth mentioning that, in people aged more than 60 years, multi-organ failure was notable. Consistent with other studies, fever, cough, and shortness of breath were dominant symptoms in Besharat et al. study. There was no difference between males and females in terms of comorbidity symptoms and mortality rate (20). Their study was somewhat consistent with the current study in terms of symptoms. The least common symptom in the current study was seizure while it was meningoencephalitis in the study performed by Besharat et al. However, it should be noted that seizure was most probably a symptom of meningoencephalitis or hypoxia in the central nervous system of patients in the current study. The majority of the patients (60%) were male in the present study which was consistent with the study by

Besharat et al. in which 71% of patients were male (20). The age of more than 60 years was the effective risk factor for severe COVID-19 and death which was approved in both the present study and that of Besharat et al.

Many other studies are needed to identify this complex disease more comprehensively. Nowadays, many different treatments are proposed for COVID-19 (21); however, no definitive cure has been discovered up to now. Antiviral drugs used to treat COVID-19 can cause renal and liver complications and this complicates the process of symptom identification, prognosis, and treatment even more (22-23).

Regarding the smoking variable, it is worth mentioning that the results of this study revealed that smoking had a preventive effect on mortality which was indicated by OR less than 1 (OR=0.292). However, this had no significant effect on ICU admission. In a meta-analysis performed by Patanavanich and Glantz, smoking was found to be a risk factor for the progression of COVID-19 (24). The results of the current study were not consistent with a study conducted by Magfira and Heldain (25). Consistent with the present study, Wan et al. reported the protective effect of smoking on the COVID-19 progression with OR of 0.2 (26). Additionally, the results of the present study showed that being addicted is not a risk factor for ICU admission. During the COVID-19 pandemic, the use of opioids and substance abuse had an increasing trend (27). Volkow reported the vulnerability of COVID-19 patients who misused opioids, especially heroin, synthetic opioids, and methamphetamine (28). Regarding susceptibility to COVID-19, it should be noted that middle-aged people are more susceptible to COVID-19 (mean age at onset is about 55 years) (15). However, medical history can increase the mortality rate in such a way that COVID-19 patients with previous and active tuberculosis have prolonged recovery and high mortality rate as reported in a study conducted by Haw et al. (29). This is inconsistent with the results of the current study as patients with a history of tuberculosis were not at higher risk of mortality or ICU admission. The subject of "susceptible to COVID-19" needs further investigation to be clear.

6. Conclusion

Based on the obtained results, positive PCR, initial symptoms of dyspnea, and myalgia are associated with increased odds of mortality by two times. Elevated ALT and LDH are associated with a higher rate of mortality. The ICU admission is the main variable to increase the odds of mortality. Smoking may play a protective role against COVID-19 mortality. No association was observed between the history of tuberculosis and the risk of ICU admission or mortality in this study.

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Footnotes

Author's contributions: TR, SSh, SHRF were the principal investigators of the study. They prepared the study concept and design, revisited the manuscript, and critically evaluated the intellectual contents. All authors participated in the preparation of the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. Moreover, all authors have read and approved the content of the manuscript and confirmed the accuracy and integrity in every part of the study.

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Ethical considerations: Ethical issues including plagiarism, data fabrication, and double publication have been completely observed by the authors. The study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran.

Informed Consent: Informed consent was obtained from the patients.

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