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Evaluating the Effects of Clinical Characteristics and Therapeutic Regimens on Mortality in Hospitalized Patients with Severe COVID-19

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) is highly contagious and has turned into a global health problem. In this study, we investigated the role of clinical and laboratory characteristics along with administered therapeutic agents in patients with COVID-19, and identified some effective factors on the mortality of these individuals.

Methods: In this retrospective study, we evaluated the data from all the hospitalized patients who had been diagnosed with COVID-19 between February 23 and May 23, 2020. The data were obtained from medical records. Additionally, a checklist was used to record demographic, clinical, laboratory, imaging, and treatment data for each patient.

Results: Totally, 478 patients were involved in this study, and their median age was 58.5 years. Of these, 53.3% patients were male. The most common pre-existing underlying disease was hypertension (37.9%), and the mortality group had significantly more comorbidities (85.4%). Higher neutrophil lymphocyte ratio (NLR), lymphopenia, and reduced hemoglobin were more frequent in the mortality group ($p < 0.001$). Similarly, the need to be admitted to the intensive care unit was significantly greater in the mortality group ($p<0.001$). The most frequently administered therapeutic regimens included hydroxychloroquine and lopinavir/ritonavir, which did not have any correlation with survival outcome.

Conclusion: Older age, opioid addiction, cardiovascular disease, kidney disease, baseline NLR and hemoglobin, and ICU admission were independently associated with COVID-19 mortality. On the other hand, hydroxychloroquine and lopinavir/ritonavir indicated no beneficial effects on patients' outcome.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the new member of the human coronavirus family with 77.2% nucleotide similarity to SARS-CoV. The viral pneumonia caused by SARS-CoV-2 originated in China and has been affecting the world since its outbreak in December 2019. The World Health Organization (WHO) named the disease coronavirus disease 2019 (COVID-19) in February 2020 (1).

Everyone runs the risk of being infected with SARS-

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CoV-2 and catching its sever type, but studies have shown that advanced age and chronic medical conditions are independently associated with a higher risk of severe COVID-19 infection and mortality (2,3). There are some studies that confirm the effects of race and ethnicity on the severity and mortality of COVID-19, but the effects of racial and ethnic differences have not been accurately described yet (4,5).

Based on existing reports, the incubation period for COVID-19 is 4 to 5 days, and the severity of the disease is classified into 3 categories: approximately 80% of cases have been mild (no pneumonia or mild pneumonia), 15% have been moderate to severe (dyspnea, respiratory frequency ≥30 breaths/min, oxygen saturation (SpO2) ≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% have been critical (respiratory failure, septic shock, and/or multi-organ dysfunction or failure) (6).

The symptoms of the disease can vary: whereas a study in the United States found fever, cough, and shortness of breath followed by muscle pain and headache to be the most common symptoms (7), Wang et al., reported fever, fatigue, and dry cough as the most common symptoms in Wuhan, China (8).

COVID-19 is a respiratory disease. Although it usually affects the lungs, it could infect other organs in the body and lead to-among others-cardiac, hematological, hepatic, neurological, and renal complications.

In terms of the global spread of COVID-19, Iran was considered as one of the most affected countries. However, due to the wide incidence of the pandemic and the large number of infected patients, there are not adequate clinical trials on patients' prognosis. To address this gap, the present study aimed to evaluate the medical records of hospitalized patients with COVID-19 in the north of Iran in order to discover the possible demographic and clinical conditions that could affect COVID-19 mortality. We believed that these valuable data lead to a better understanding of potential prognostic factors of patients with COVID-19 and assist to develop proper preventive and therapeutic policies.

Methods

This retrospective cross-sectional study assessed the records of all patients with COVID-19 who had been admitted at Ibn Sina Hospital (Sari, north Iran) from February 23 to May 23, 2020. This research was approved by the Ethic Committee of Mazandaran University of Medical Sciences (No.: IRMAZUMS.REC.1399.715). Due to the retrospective design of the study and anonymity of the patients' data, the need for informed consent from patients or their guardians was waived.

According to the WHO interim guidance (10) and the Iranian National Committee on COVID-19, patients with positive reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal secretions or COVID-19 diagnosis based on chest CT imaging data were hospitalized if their peripheral oxygen saturation (SpO2) were less than 93% at ambient temperature.

Demographic characteristics such as age, sex, underlying diseases, laboratory tests, and clinical manifestations upon admission, course of symptoms during hospitalization, the need for oxygenation, the need for hospitalization in the intensive care unit (ICU), and the severity of the disease were determined using patients' medical records. Also, all the comorbidities were recorded. If the patient had a history of chronic kidney disease, proteinuria, and kidney transplants, they were assigned to the kidney disease category. Moreover, if the patient had a history of myocardial infarction, hypertension, valve replacement, and other cardiovascular diseases, they were sub-grouped within the cardiovascular disease category.

All treatment regimens including antivirals, corticosteroids, intravenous immunoglobulin (IVIG), vitamin C, antibiotics, analgesic agents, anti-nausea/vomiting agents, cardiovascular drugs, deep vein thrombosis, and stress ulcer prophylaxis were registered in the study checklist.

We used the Kidney Disease Improving Global Outcomes (KDIGO) criteria to determine acute kidney injury (AKI) (10). Acute cardiac injury (ACI) was considered as elevation (higher than 99th percentile of normal) in troponin serum level, irrespective of electrocardiography changes or abnormality in echocardiography. Liver dysfunction was defined in the case of noting an abnormal lab test, such as elevated hepatic enzyme levels > 3 times the upper limit of normal or serum total bilirubin above 2 mg/dl (11). The definition offered by WHO was adopted for anemia (12), the platelet count less than 100,000/μL was defined as thrombocytopenia, and electrolyte abnormality was confirmed when an abnormal concentration was observed in lab tests.

Mortality rate was considered the primary outcome, and hospitalization duration, ICU admission, and the need for mechanical ventilation were evaluated as secondary outcomes.

Statistical analysis was carried out in SPSS 24.0 (IBM Corp., Armonk, NY). Next, the frequency of each variable was determined. The Kolmogorov-Smirnov test was used to assess all interval variables in terms of normality of distribution. Sampled values with normal distributions were properly compared using Student's t-test. On the other hand, values lacking normal distributions were compared using the nonparametric Mann–Whitney U test. Furthermore, the qualitative variables were expressed in percentage and compared using the Chi-square test and Fisher's exact test. Mortality risk factors were predicted

using logistic regression model analysis. In case of observing data composed of several categorical responses together with categorical or continuous predictors, we used the multivariate logistic regression model to define a class that would be suitable for relating the joint distribution of the responses to predictors. The Kaplan-Meier cumulative survival plot was also drawn. P < 0.05 was regarded statistically significant.

Results

A total of 478 patients with moderate to severe COVID-19 were hospitalized in our setting during the study period; 103 (21.5%) of these individuals belonged to the mortality group, and 350 (78.5%) others were assigned to the recovery group. The median age of patients was 58.5 years. More specifically, it was 56 (41-69) years in the recovery group and 68 (57-78) years in the mortality group, indicating a significant difference between the two groups (p<0.001). In general, men were hospitalized more than women (53.3% vs 46.7%, respectively), but there was no significant difference between the two groups in this regard (p=0.647).

The most common underlying disease in patients was hypertension (37.9%), followed by diabetes mellitus (DM) (32%), and cardiovascular diseases (CVD) (19.2%). Although this trend was similar in both groups, there was a significant difference between them (54.4% vs 33.3% for hypertension; 44.7% vs 28.5% for DM; and 36.9% vs 14.4 for CVD in the mortality and recovery groups, respectively). The most common symptoms were fever (57.9%), cough (54.3%), and dyspnea (50.9%). The presented symptoms were statistically different between the two groups (P= 0.003, <0.001, and 0.004 for fever, cough, and dyspnea, respectively). However, in the mortality group, respiratory distress was the most common symptom (58.3%), followed by fever (43.7%), dyspnea (42%), confusion, cough (34.3%), and loss of consciousness (32.0%). On the other hand, fever (61.9%), cough (59.7%), and dyspnea (52.6%) were significantly more frequent in the recovery group. Other baseline demographics and characteristics of the patients are shown in Table 1.

Table 1. Baseline demographics and clinical characteristics of patients.

Variables	Survived	Death	Ttotal	P
Age, years, median (iqr)	56 (41-69)	68 (57-78)	58.5 (43-71)	<0.001
Age >40 years, n(%)	275(73.3)	100(97.1)	375(78.45)	<0.001
Gender, n (%)				0.647
Male	188 (52.8)	57(55.3)	225(53.3)	
Female	162(47.2)	46(44.7)	223(46.7)	
Comorbidity, n(%)				
Diabetes mellitus	103 (29.4)	46 (44.7)	149 (32)	0.003
Respiratory disease	12 (3.4)	7 (6.8)	19 (4.0)	0.114
Hypertension	122 (34.9)	56 (54.4)	178 (37.9)	<0.001
Ischemic heart disease	52 (14.9)	38 (36.9)	90 (19.2)	<0.001
Dyslipidemia	36(10.3)	30(29.1)	66(14)	<0.001
Renal disease	3 (0.8)	14 (13.6)	17 (3.6)	<0.001
Stroke	18 (4.8)	18 (17.5)	36 (7.5)	<0.001
Alzheimer	9 (2.55)	13 (12.6)	22 (5.8)	<0.001
Surgery	45(12)	24 (23.3)	69 (14.4)	0.004
BMI (kg/m^2), median (iqr)	27.11 (23.96-29.11)	25.00(23.89-28.62)	26.96	0.031
Weight status, n(%)				0.001
Under weight	12(3.4)	6(5.8)	18(4.7)	

Table 1. Continued

Normal	76 (21.7)	32 (31.1)	108(26.8)	
Over-weight	139(39.7)	21(20.4)	140 (45.1)	
Obesity	71 (20.3)	16 (15.5)	87 (23.4)	
Symptoms, n (%)				
Dyspnea	184(52.6)	42 (40.8)	226 (50.9)	0.003
Cough	224 (59.7)	35 (34.3)	259 (54.3)	<0.001
Fever	214 (61.9)	46 (43.7)	260 (57.9)	0.004
Chills	58 (15.5)	19 (18.4)	77 (16.1)	0277
Fatigue	11 (3.1)	33 (32)	44 (9.2)	<0.001
Vomiting	25(6.7)	14(13.6)	39(8.2)	0.023
Respiratory distress	6(1.7)	60(58.3)	66(14.2)	<0.001
Anorexia	33(8.8)	0	33(6.9)	0.002
Headache	33 (9.4)	3 (2.9)	39 (8.8)	0.017
Loss of consciousness	22(6.3)	33(32.0)	55(11.5)	<0.001
Confusion	8(2.1)	41(39.8)	49(10.3)	<0.001
Smoking	9(2.4)	3(2.9)	12(2.5)	0138
Opioid addiction	15(4)	22(21.4)	37(7.7)	<0.001
Symptoms onset, days, median (iqr)	5(2-7)	6.75(3.25-10)	4.25(2.75-7)	0.227
Vital signs and laboratory data at baseline				
Variables	Survived	Death	P	
Temperature, °c, median (iqr)	37.5(37.0-38.0)	37.0(36.8-38.0)	0174	
Heart rate, beats /minute, median (iqr)	83(79-94)	86(78-102)	0.189	
Respiratory rate, breaths /minute, median (iqr)	18(18-20)	18(18-21)	0.580	
Systolic blood pressure, mm hg, median (iqr)	120(105-130)	120(100-140)	0.027	
O2 sat (%)	94(91-96)	90(81-94)	<0.001	
Laboratory data: median (iqr)				
White blood cell; cells $\times 10^3$/ µl	6 (4.8-8.20)	9.19 (6.64-14.70)	<0.001	
Lymphocyte count; cells $\times 10^3$/ µl	22 (15-30)	22.6 (7.90-18)	<0.001	
Neutrophil; cells $\times 10^3$/ µl	71.5 (61-79.75)	83 (75-88)	<0.001	
NLR	3.36(2.02-5.14)	7.24(4.06-11.14)	<0.001	
Hemoglobin; g/dl	12.5 (11.20-13.90)	111.7 (9.87-13.40)	<0.001	

Table 1. Continued

HCT	36.3 (33-39.90)	35 (31.05-39)	0.121
Platelet count; cells $\times 10^3$/ µl	203.5 (156-266.75)	215 (161.75-262)	0.459
Blood urea nitrogen; mg/dl	26(21-35)	46 (30-82)	<0.001
Creatinine; mg/dl	1(.81-1.20)	1.2(1-1.9)	<0.001
Aspartate aminotransferase; unit/l	32(23-46)	44(30-58.5)	<0.001
Alanine aminotransferase; unit/l	22 (14.5-33)	20(15.25-33.75)	0.964
Alkaline phosphatase; unit/l	198(158-248)	218(165.75-303.25)	0.016
C-reactive protein; mg/dl	20 (1-120)	29(4-118)	<0.001
E	46(3.140)	67(4-956)	0.001
Lactate dehydrogenase; u/l	453(354.0-575.0)	665(440.0-938.0)	0.002
Blood sugar; mg/dl	108.0(90.0-154.0)	145(104.0-217.0)	0.004
INR	1(1-1.1)	1.1(1-1.3)	<0.001
PT	12.5(12.5-13.30)	13.4(12.5-14.6)	<0.001
PTT; sec	33(30-36)	33(30-38)	0.362
NEWS 2 baseline	3(2-5)	8(7-10)	<0.001
Positive lung CT; n (%)	338 (96.5)	103 (100)	0.164
Positive PCR; n (%)	35 (10.7)	15 (14.7)	0.01
Clinical symptoms at admission, n(%)			
Acute kidney injury	73(20.9)	43(41.7)	<0.001
Hepatic dysfunction	94(26.9)	37(35.9)	0.001>
Thrombocytopenia	65(18.6)	15(14.6)	0348
Anemia	135(38.6)	(53.4)55	0.001>
Hypokalemia	(3.2)11	12(11.7)	0.001>
Hyperkalemia	18(5.1)	21(20.4)	
Hypernatremia	2(0.6)	7(6.8)	0.001>
Hyponatremia	31(8.9)	15(14.6)	
Hypermagnesemia	29(8.3)	15(14.6)	0.077

BMI: Body Mass Index, ESR: Erythrocyte Sedimentation Rate, IQR: interquartile range, INR: international normalized ratio, PT: Prothrombin Time, PTT: Partial thromboplastin time, NEWS2: National Early Warning Score, CT: Computed Tomography, PCR: Polymerase chain reaction.

Baseline vital signs and laboratory data are also presented in Table 1. White blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophil count, neutrophil-lymphocyte ratio (NLR), blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alkaline phosphatase (ALP), lactate

dehydrogenase (LDH), and blood sugar were all significantly higher in the mortality group, but hemoglobin (Hgb) was significantly lower in this group ($p < 0.001$).

All hospitalized patients needed respiratory support with oxygen mask upon admission. On the basis of the national guidelines on COVID-19, Kaletra (lopinavir/ritonavir) and hydroxychloroquine were administrated for almost 70% of patients with no statistical difference between the two groups. Additionally, naproxen, interferon beta 1b, ribavirin, oseltamivir, vitamin C, and IVIG were administered for patients. In this regard, the two groups were similar except in terms of ribavirin and IVIG, which were more frequently administrated in the mortality group (Table 2). Corticosteroids, especially methylprednisolone, were used at statistically higher rates in the mortality group than the recovery group ($p<0.001$). Other findings are shown in Table 2.

Table 2. Medications during the hospitalization.

Variables	Survived	Death	P
Kaletra (lopinavir/ritonavir)	235(67.1)	76(73.8)	0.201
Interferon beta	78(23.3)	25(24.3)	0.485
Ribavirin	6(1.7)	13(12.6)	<0.001
Oseltamivir	125(35.7)	30(29.1)	0.135
Hydroxychloroquine	292(77.9)	72(69.9)	0.043
Corticosteroids	13(3.7)	19(18.4)	<0.001
IVIG	1(0.3)	4 (3.9)	0.002
Vitamin C	112(32.0)	32(31.1)	0.846
Antibiotics	160 (45.7)	94(91.3)	<0.001
Naproxen	210(60)	48(46.6)	0.016
PPIs	259 (74.0)	40 (38.8)	<0.001
Aspirin	51(13.9)	39 (37.9)	<0.001
VitaminD3	114(23.6)	10(9.7)	<0.001
Anticoagulants	(9.7)34	22(21.4)	0.002
ARBs	64(18.3)	37(35.9)	<0.001
Statins	87(24)	39(37.9)	0.003
Beta-blockers	32(9.1)	31(30.1)	<0.001
Insulin	69(19.7)	30(29.1)	0.042
Acetaminophen	188 (53.7)	54(52.4)	0.758

PPI: proton pump inhibitor, ARB: Angiotensin II Receptor Blocker, IVIG: intravenous immunoglobulin

Also, 22% of patients needed to be admitted to the intensive care unit (ICU). These individuals were mostly in the mortality group, and the difference between the two groups was significant in this regard ($p>0.001$). Among all patients, 3.8% required mechanical ventilation (MV), which was not significantly different between the two groups ($p=0.098$). As shown in Table 3, there were significantly more complications-including acute kidney injury, liver dysfunction, infection, anemia, and others-in the mortality group compared with the recovery group.

Table 3. Clinical and laboratory findings during hospitalization.

Variables	Survived	Death	P
Duration of hospital stay, days, median(IQR)	6(4-8)	5(2-9)	0.002
Required ICU care, n(%)	25 (7.1)	82 (79.6)	<0.001
Required MV, n(%)	12 (3.4)	6 (5.8)	0.098
Fever during hospital	84(24)	21(20.4)	0.562
Hypotension	131(37.4)	54(52.4)	<0.001
Hypertension	0	6(7.1)	
Tachycardia	30(8.6)	8(7.8)	<0.001
Bradycardia	1(0.3)	6(7.1)	
Reinfection	88(25.1)	59 (57.4)	<0.001
AKI	32(9.1)	41(39.8)	<0.001
Hepatic dysfunction	27(7.7)	16 (15.5)	<0.001
ACI	7(2.0)	6(5.8)	0.039
Thrombocytopenia	26(7.4)	17 (16.5)	<0.001
Anemia	120(34.3)	36(35)	<0.001
Hypokalemia	11(3.1)	7(6.8)	<0.001
Hyperkalemia	11(3.1)	30(29.1)	
Hypernatremia	5 (1.4)	17(16.5)	<0.001
Hypermagnesemia	8(2.3)	11(10.7)	<0.001

MV: mechanical ventilation, AKI: acute kidney injury, ARDS: acute respiratory distress syndrome, ACI: acute cardiac injury, ICU: intensive care unit

Multivariate logistic regression analysis showed that age (a demographic characteristic), opioid addiction, cardiovascular disease, kidney disease, and pulmonary disease (medical records) were independent predictors of mortality. Table 4 presents all of the factors affecting mortality rate of the study subjects.

The results of survival analysis with Kaplan-Meier estimator for all the above variables demonstrated that Age> 40 years and opioid addiction were correlated with COVID-19 mortality rate (HR:17.0 and 9.00, CI95%:10.184-23.816 and 1.512-6.036, p<0.001, respectively). Figure 1 shows that ICU admission also had a significant effect on mortality risk (HR:7.00 CI95%:4.956-9.044, p<0.001). Additionally, among underlying diseases, CVD (HR:11.0, CI95%:7.716-14.284, p<0.001) and kidney disease (HR:8.00, CI95%:4.121-11.879, p<0.001) were independently associated with COVID-19 mortality (Figure 1).

Table 4. Multivariate logistic regression analysis.

Variables	OR	95% C.I.	P
Age	0.955	0.932-0.980	≤0.001
Hospital duration	1.163	1.057-1.279	0.002
ICU admission	0.003	0.001-0.010	≤0.001
Opioid Addiction	0.120	0.043-0.336	≤0.001
Cardiovascular disease	0.258	0.120-0.553	0.001
Kidney disease	0.090	0.016-0.518	0.007
Respiratory distress	0.213	0.054-0.833	0.026
Cough	2.156	1.204-3.863	0.010
Fever	2.128	1.152-3.929	0.016
Fatigue	0.022	0.007-0.070	≤0.001
Loss of consciousness	0.198	0.094-0.417	≤0.001
Ribavirin	0.174	0.043-0.698	0.014
Corticosteroid	0.151	0.055-0.416	≤0.001
Aspirin	0.330	0.145-0.751	0.008
Beta-blockers	0.312	0.137-0.712	0.006
PPIs	9.163	4.712-17.819	≤0.001
Vitamin D3	6.233	2.720-14.283	≤0.001
NLR (at baseline)	1.181	1.053-1.324	0.005
Hemoglobin (at baseline)	0.500	0.290-0.860	0.012

ICU: Intensive Care Unit, PPI: Proton Pump Inhibitors, NLR: Neutrophil/lymphocyte rate

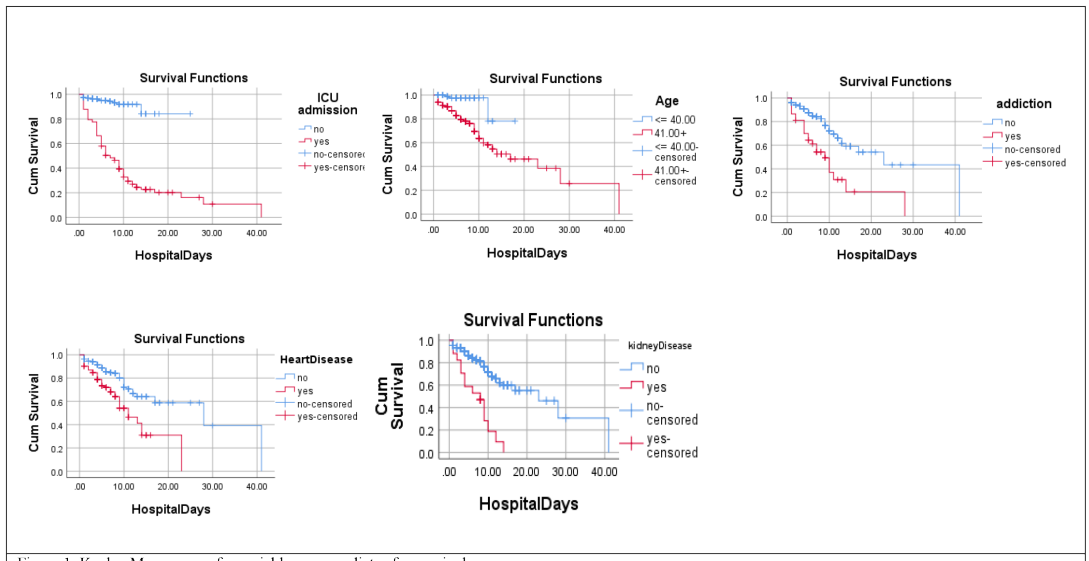

Figure 1. Kaplan Mayer curve for variables as a predictor for survival.

Discussion

During the COVID-19 outbreak, the diagnosis of the disease was difficult because of the variety of symptoms and the severity of the illness at the time of hospitalization. In fact, the detection of SARS-CoV-2 viral RNA or antigen in respiratory specimens was required for diagnosis of COVID-19 (CDC), but there were false-negative results and there could be a delay in observing the positive result after the initial symptoms (13). In this study, due to limited access to PCR, hospitalization was mainly based on clinical manifestations and a CT scan confirming COVID-19. Since there was a shortage of RT-PCR kits during the time of this study, only 28.1% of patients were tested for COVID-19, 41.6% of whom had a positive result.

The modified regression logistic model of our study demonstrated that hospital stay duration and ICU admission significantly affect death rate in patients with COVID-19 (OD: 1.163 and 0.003, respectively), such that ICU admission to ICU significantly decreases survival. Some other studies similarly confirm the effect of ICU admission and hospital stay duration on COVID-19 mortality (14-15). Regarding demographic characteristics, the findings showed that the greatest number of deaths occurred among the older population. Thus, the median age of patients was 58.5 years, and the median age of recovered patients was significantly lower than those who died. Most of the studies all over the world suggest that the mean age of COVID-19 patients is over 50 years and the survived cases are younger individuals (14-17).

In our study, older age (odd ratio: 0.955) was a prognostic factor for mortality, and survival analysis indicated that age over 40 independently contributes to a significant reduction in the survival of patients with COVID-19. The prevalence of COVID-19 along with its mortality rate was higher in males, but it was not a significant predictor for mortality, which is in line with a number of previous studies (14, 16, 17).

The most common baseline comorbidities in our patients were hypertension, DM, and CVD, which is in good agreement with the results of some other trials (17, 18). Meanwhile, multivariate logistic regression model of our data revealed that the odds of death increased with CVD and kidney disease-as common underlying diseases-in COVID-19 patients (OR: 0.258 and 0.090, IQR: [0.120-0.553 and 0.016-0.518], respectively). In addition, the results of survival analysis pointed to a significant reduction in survival rate for COVID-19 patients with CVD and kidney disease. Likewise, several foreign studies have indicated that DM, chronic kidney disease, hypertension, and CVD are associated with increased COVID-19 mortality and severity (18, 19).

We also noted that having a history of addiction could significantly affect mortality rate, as shown by the results of multivariate logistic regression model (OR:0.090, IQR [0.016-0.518]); besides, survival analysis showed addicted patients with COVID-19 had a lower survival rate compared with their non-addicted peers. These results are compatible with systematic reviews on the relationship between addiction and COVID-19 (19).

More than 65% of patients had BMI≥25, but the logistic regression model did not confirm weight as a significant prognostic factor for mortality. However, some studies have shown that obesity independently affects COVID-19 mortality (20). This incompatibility could be due the fact that our patients were more overweight than obese. Indeed, most of the epidemiologic findings have shown that although being overweight can be linked to a higher rate of COVID-19 hospitalization, it is obesity-especially its extreme type-that is more related to the risk of COVID-19 mortality (21). Moreover, the small percentage of obese people in our recruited patients with BMI closer to overweight state than obesity should be considered in interpreting the results of the logistic regression model.

The most common symptoms in our study were fever, cough, and dyspnea, which is similar to some other studies (18, 22). Dyspnea was frequently noted among the patients, which might be related to the national admission protocol that emphasized hospitalizing patients who required respiratory support. When the variables were adjusted in the logistic regression model, we found respiratory distress, fatigue, and LOC to be independently associated with mortality. In line with our findings, some studies have mentioned that impaired consciousness is a presenting feature of COVID-19 and it might be correlated with the severity of this disease (15, 23). Sobhani et al., observed that dyspnea was statistically more frequent in the non-survivor group, which is similar to our results; however, the authors suggested that dyspnea did not affect mortality prediction (14). In the same vein, Adham et al., reported that shortness of breath was the strongest prognostic factor for death due to COVID-19 (15).

The administration of aspirin and beta-blocker was significantly higher in the mortality group, and the analysis of multivariate logistic regression confirmed the significant effects of this medication on mortality. In this study, the administration of aspirin and beta-blocker was a means of treating patients' comorbidities, which were quite frequent in both groups (96.1% in the mortality group and 70% in the

recovery group). Therefore, it should not be assumed that this administration in itself increases the risk of mortality. Moreover, the correlation of CVD with increased mortality was significant, which might have affected the interpretation of results concerning the impact of beta-blocker and aspirin administration.

Comparatively, proton pump inhibitors (PPIs) and vitamin D3 had been administered more frequently in the survived patients of our study. Indeed, vitamin D3 with an odds ratio of 6.233 had a bearing on recovery following COVID-19 infection ($p<0.001$). Amrein et al., demonstrated vitamin D3 could decrease mortality rate among patients who had severe vitamin D deficiency (24). The retrospective study by Carpagnano et al., confirmed that severe vitamin D deficiency is correlated with higher mortality due to COVID-19 (25). However, there is controversy over the effect of vitamin D3 for COVID-19. Given the insufficient evidence, there is no definite opinion about the relationship between vitamin D administration and COVID-19 severity and mortality. In our study, most patients had received vitamin D3 irrespective of serum concentration. Therefore, its observed effects on survival should be interpreted cautiously.

In contrast, our results showed that PPIs with an odds ratio of 9.163 positively affected patients' survival ($P<0.001$), which could be due to the higher administration of PPI in the recovery group to treat the GI symptom during hospitalization. On the other hand, the mortality group did not receive antacid regularly except for stress ulcer prophylaxis.

About 20% of patients in our study who were in the late phase of the disease (admitted to ICU or needed MV) had received high-dose corticosteroids. Although the logistic model demonstrated that receiving high-dose corticosteroids (125- 500 mg methyl prednisolone) had an impact on mortality, it must be pointed out that a slight percentage of patients with moderate COVID-19 had managed to receive corticosteroids while most of the patients had received a high dosage at the time of ICU admission or disease progression. However, there is some evidence supporting that the use of high-dose corticosteroids is associated with higher rate of mortality in hospitalized patients (26, 27).

Although this study was not designed to evaluate or compare the therapeutic regimens such as Kaletra (lopinavir/ritonavir) and hydroxychloroquine administered for their possible antiviral effects on SARS-CoV-2, it is noteworthy that the rate of their administration did not differ between the two groups in this study. However, our analysis suggested that this medication does not affect the time of recovery and mortality rate, which is in line with the findings obtained in previous studies (22, 28). The same was true of Interferon beta 1b, which was another agent with a possible effect on SARS-CoV-2. We did not observe its beneficial effects on mortality, yet the time of interferon beta 1b administration was not the same among patients in the two groups. Indeed, previous studies that support the favorable results of interferon beta 1b have emphasized the need to start its administration at an early stage of the disease before the onset of the inflammatory phase (25).

According to our findings, reduction in lymphocyte count and Hgb level at baseline was significantly associated with mortality rate; however, the logistic regression analysis showed only Hgb reduction to be associated with mortality. Similarly, some studies have argued that the decline in hemoglobin levels upon admission is related to poor outcome and mortality (27, 29). In addition, the results of a meta-analysis of anemia in COVID-19 patients suggested that lower hemoglobin levels could increase the risk of mortality (31). Moreover, several studies have proposed that a decrease in Hgb level during hospitalization is associated with disease severity and mortality (27, 29). Nevertheless, while in our study anemia during hospitalization was more frequent in the mortality group, it was not a predictor for mortality.

NLR was a mortality predictor in our study, which is compatible with some other reports. Recent studies have highlighted the association between elevated CRP level and disease severity and mortality (14, 31). However, we could not find such a correlation with mortality, despite higher levels of CRP in the mortality group. Besides, some studies have proposed that elevated LDH levels could be a prognostic factor for COVID-19 severity (15, 32). Although our findings showed a higher LDH level in the mortality group, it was not a prognostic factor for mortality.

Our study has some limitations: first, the study population was from one region and one hospital; second, our database was limited to patients' admission data, and we did not have access to the exact time of symptom onset; third, some symptoms not initially recognized as presentations of COVID-19 (e.g., anosmia) were not included in this database from the beginning, and thus we did not have access to these data for all participants; finally, it was not feasible to actively follow up discharged patients to ascertain their vital status.

In conclusion, our retrospective cross-section study demonstrated that medical history and baseline clinical characteristics can play key roles in COVID-19 prognosis. Older age, underlying disease (including CVD and kidney

disease), and opioid addiction might be correlated with higher COVID-19 mortality. Besides, baseline hemoglobin levels and NLR were recognized as prognostic factors for mortality. Further trials with larger sample sizes and multiple settings can lead to more definite conclusions in this regard.

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