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ORIGINAL: Factors Associated with Mortality among Patients with COVID-19 in Intensive Care Units from Referral Heart Center in the North of Iran

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ABSTRACT

Introduction: The clinical spectrum of COVID-19 ranges from asymptomatic cases to severe viral pneumonia, leading to respiratory failure and death, with factors influencing mortality in severe cases being of paramount importance. This study aimed to identify risk factors associated with outcomes in severe COVID-19 patients admitted to the Intensive Care Units (ICU).

Material and Methods: A cross-sectional analysis was conducted on the clinical course of 99 hospitalized patients, aged 25 to 75, with confirmed COVID-19, admitted to the ICU at Fatemeh Zahra Hospital in Sari. Comprehensive medical records and clinical information were collected from admission throughout hospitalization until recovery or death, including the respective dates.

Results: The study revealed that Diabetes Mellitus (DM) and Hypertension (HTN) were significant risk factors in COVID-19 patients. Mortality rates were notably higher in patients who had a history of statin usage and exhibited low saturation in the ICU. Patients administered Chloroquine demonstrated significantly elevated mortality rates, whereas those treated with Oseltamivir in the ICU exhibited significantly lower mortality rates. Mortality was markedly higher in patients receiving interferon and Kaletra in the ICU. Groups with deceased patients experienced significantly higher incidences of cardiac, cardio-renal, and pulmonary complications. Mortality rates were notably higher in patients with abnormal final Electrocardiograms (ECG). Deceased patients also presented with abnormalities in laboratory tests.

Conclusion: The study concludes that Diabetes Mellitus, Hypertension, history of statin usage, specific treatment types, multi-organ complications, and abnormal ECG findings are associated with increased mortality in severe COVID-19 patients.

Introduction

Coronavirus Disease 2019 (COVID-19), caused by the novel beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is

an emerging infectious disease characterized by a spectrum of pneumonia symptoms(1). The initial cases were reported in Wuhan, Hubei, China, and subsequently, the disease swiftly spread across all continents. On March 12, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic(2,3). Globally, according to the latest WHO report, there have been 245,373,039 confirmed cases of COVID-19, resulting in 4,979,421 deaths, with a total of 6,838,727,352 vaccine doses administered(4). In the Islamic Republic of Iran, 5,899,509 confirmed cases have led to 125,875 deaths(5).

Recommended diagnostic tests for COVID-19 include RT-PCR and CT chest examinations(6). Typically, there is an incubation period of 5–6 days from infection to symptom onset(7). Common symptoms encompass fever, cough, myalgia, and fatigue, while less common manifestations include aches, sore throat, diarrhea, conjunctivitis, headache, and loss of taste or smell(1,8,9). The clinical spectrum of SARS-CoV-2 infection varies from asymptomatic or mild upper respiratory tract illness to severe viral pneumonia, resulting in respiratory failure and mortality, necessitating hospitalization in many cases(1,10,11).

Wu et al reported that older age and dysfunction in organs and coagulation were correlated with an increased risk of developing Acute Respiratory Distress Syndrome (ARDS) and death in COVID-19 pneumonia patients(2). Numerous clinical studies on hospitalized patients have indicated that older age, a high Sequential Organ Failure Assessment (SOFA) score, elevated white blood cell (WBC) count, decreased lymphocytes, neutrophilia, increased C-reactive protein (CRP) levels, and a d-dimer exceeding 1 µg/mL could aid clinicians in the early identification of patients with poor prognoses(10-12). Importantly, risk factors, clinical outcomes, and the association between COVID-19 and the risk of mortality exhibit regional and temporal variations. Thus, identifying high-risk groups is pivotal in reducing mortality rates. In this study, we comprehensively analyzed various factors, including clinical, para-clinical, and treatment statuses, in 99 hospitalized COVID-19 patients within the Intensive Care Units (ICU) of Fatemeh Zahra Hospital in Sari, Iran.

Methods

Study Design and Participants

This study is a cross-sectional analysis of 99 patients aged 25 to 75, diagnosed with confirmed COVID-19 pneumonia and hospitalized in the Intensive Care Unit (ICU) at Fatemeh Zahra Hospital in Sari. The study period spans from the onset of the epidemic to April 19, 2020. The diagnosis of COVID-19 aligns with the interim guidelines provided by the World Health Organization. Medical records and clinical data were gathered from admission through hospitalization, tracking patients' progress to either recovery or death. Ethical approval for the study was obtained from the regional ethical committee in the medical university, and patient informed consent was waived due to the retrospective nature of the study.

Data Collection

A total of 99 patients were included, diagnosed with COVID-19 based on pneumonia exclusion, clinical presentation, and characteristic chest CT images. Confirmation of the diagnosis relied on a positive Real-time reverse transcription polymerase chain reaction (RT-PCR) for COVID-19. Patient information, encompassing demographics, epidemiological data, medical history, smoking history, recent travel history, exposure details, onset of symptoms, admission date, disease confirmation date, chronic diseases, signs and symptoms, comorbidities, complications, laboratory examinations, Echocardiography and Electrocardiogram (ECG), CT scan, treatment modalities (antiviral, antibiotic, glucocorticoid therapies, immune gluco-corticoid therapy, and respiratory support), and outcomes, was meticulously collected and subjected to analysis.

Initial clinical laboratory investigations included a complete blood count, serum

biochemical tests (covering liver and kidney function, creatine kinase, lactate dehydrogenase, and electrolytes), a coagulation profile, lipid profile, and Venous Blood Gas (VBG) tests.

Outcome

The study recorded the date of death and recovery for each patient. Favorable outcomes, comprising death and recovery, were assessed, defining recovery as a positive change in the patient's clinical condition.

Statistical Analysis

All statistical analyses were conducted using SPSS Statistics 23.0 software, involving t-tests and Chi-square tests. Univariable and multivariable logistic regression models were employed to explore the role of various factors associated with outcomes. A significance level of $P < 0.05$ was adopted for statistical significance.

Results

General Characteristics

From the onset of the epidemic until April 19, 2020, a total of 99 patients with COVID-19 in the Intensive Care Unit (ICU) at Fatemeh Zahra Hospital in Sari were included in this study. Of these patients, 83 had died, and 16 had fully recovered and been discharged. The study comprised 48.5% females and 51.5% males, with no significant difference between sex and mortality rate (***Table1***). General characteristics of the death and recovered groups with COVID-19 are presented in ***Table1***.

In ***Table2***, the median age of deceased patients was 64.31 (SD=23.74), and recovered patients were 60.42 (SD=15.59), with no significant difference in age and weight concerning the mortality rate (***Table2***). Travel and smoking history also showed no significant difference in mortality rate (***Table1***).

Table 1. General Characteristics of the Death and Recovered Groups with COVID-19

Characteristics	Mortality			P-value
	No N (%)	Yes N (%)	Total N (%)	
Sex				
Female	43 (51.8)	5 (31.2)	48 (48.5)	0.175
Male	40 (48.2)	11 (68.8)	51 (51.5)	
Travel				
No	77 (96.2)	16 (100.0)	93 (96.9)	1.000
Yes	3 (3.8)	-	3 (3.1)	
Smoke				
No	71 (88.8)	14 (87.5)	85 (88.5)	1.000
Yes	9 (11.2)	2 (12.5)	11 (11.5)	
Diabetes mellitus				
No	61 (73.5)	7 (43.8)	68 (68.7)	0.036
Yes	22 (26.5)	9 (56.2)	31 (31.3)	
Lung diseases				
No	77 (92.8)	16 (100.0)	93 (93.9)	0.585
Yes	6 (7.2)	-	6 (6.1)	
Renal diseases				
No	73 (88.0)	12 (75.0)	85 (85.9)	0.234
Yes	10 (12.0)	4 (25.0)	14 (14.1)	
Heart diseases				
No	43 (51.8)	8 (50.0)	51 (51.5)	1.000
Yes	40 (48.2)	8 (50.0)	48 (48.5)	
Neurological diseases				
No	82 (98.8)	16 (100.0)	98 (99.0)	1.000
Yes	1 (1.2)	-	1 (1.0)	
HTN				
No	40 (48.2)	1 (6.2)	41 (41.4)	0.002
Yes	43 (51.8)	15 (93.8)	58 (58.6)	

Table1 Continue				
Immunodeficiency				
No	81 (97.6)	15 (93.8)	96 (97.0)	0.414
Yes	2 (2.4)	1 (6.2)	3 (3.0)	
Pregnancy				
No	82 (98.8)	16 (100.0)	98 (99.0)	1.000
Yes	1 (1.2)	-	1 (1.0)	
Drug history				
No	27 (32.5)	-	27 (27.3)	0.005
Yes	56 (67.5)	16 (100.0)	72 (72.7)	
Metoral or Indral				
No	53 (63.9)	9 (56.2)	62 (62.6)	0.583
Yes	30 (36.1)	7 (43.8)	37 (37.4)	
Captopril				
No	73 (88.0)	14 (87.5)	87 (87.9)	1.000
Yes	10 (12.0)	2 (12.5)	12 (12.1)	
ASA				
No	42 (50.6)	4 (25.0)	46 (46.5)	0.099
Yes	41 (49.4)	12 (75.0)	53 (53.5)	
Statins				
No	41 (49.4)	1 (6.2)	42 (42.4)	0.002
Yes	42 (50.6)	15 (93.8)	57 (57.6)	
Plavix				
No	70 (84.3)	12 (75.0)	82 (82.8)	0.467
Yes	13 (15.7)	4 (25.0)	17 (17.2)	
COVID-19 in family				
no	73 (88.0)	16 (100.0)	89 (89.9)	0.359
yes	10 (12.0)	-	10 (10.1)	
Close contact				
no	75 (90.4)	16 (100.0)	91 (91.9)	0.347
yes	8 (9.6)	-	8 (8.1)	

Table 2. Laboratory Test Abnormalities in the Death and Recovered Groups with COVID-19

	Mortality	N	Mean	SD	P-value
Age	No	83	60.42	15.59	0.407
	Yes	16	64.31	23.74	
Weight	No	78	74.08	12.04	0.308
	Yes	16	70.18	20.84	
WBC	No	82	6294.54	3208.88	0.004
	Yes	16	9089.37	4447.79	
RBC	No	82	8.86	42.72	0.619
	Yes	16	3.51	0.80	
PLT	No	83	216.21	73.99	0.017
	Yes	16	168.00	67.62	
Hb	No	83	13.68	16.54	0.335
	Yes	16	9.63	4.08	
AST	No	54	79.07	173.47	0.814
	Yes	10	92.50	103.05	
ALT	No	55	61.30	153.49	0.891
	Yes	10	68.10	56.09	
ALP	No	52	242.73	200.24	0.984
	Yes	9	241.33	89.87	
LDH	No	27	832.03	375.71	0.529
	Yes	8	736.62	362.24	
Ferritin	No	10	333.20	289.18	0.144
	Yes	1	818.00	.	
Trop	No	45	.71	3.47	0.476
	Yes	13	2.30	7.59	
BUN	No	83	24.13	18.72	0.013
	Yes	16	54.87	43.30	

Table2 Continue					
Cr	No	80	1.50	1.81	0.259
	Yes	16	8.30	23.21	
ESR	No	43	49.16	36.27	0.113
	Yes	8	71.62	35.63	
CRP	No	49	50.45	43.05	0.854
	Yes	7	53.71	48.35	
Na	No	80	129.69	29.28	0.399
	Yes	16	135.93	4.38	
K	No	79	4.48	1.25	0.533
	Yes	16	4.69	0.78	
Mg	No	60	3.21	5.23	0.499
	Yes	15	2.28	0.54	
INR	No	67	3.20	7.58	0.982
	Yes	16	3.25	5.28	
PT	No	67	19.19	21.51	0.395
	Yes	16	28.71	42.34	
PTT	No	66	44.75	27.22	0.686
	Yes	15	47.80	20.96	
Chol	No	41	133.63	49.55	0.976
	Yes	8	133.00	73.18	
HDL	No	40	42.67	28.44	0.796
	Yes	8	40.00	10.25	
TG	No	41	122.09	44.90	0.519
	Yes	8	149.37	112.28	
LDL	No	39	94.46	38.12	0.023
	Yes	7	59.71	14.16	
FBS	No	33	142.60	77.29	0.261
	Yes	9	179.11	111.00	
BS	No	58	186.90	117.88	0.446
	Yes	13	214.46	113.00	
Ca	No	20	11.14	13.41	0.579
	Yes	9	8.61	1.16	
PH	No	20	9.44	9.31	0.421
	Yes	13	7.32	0.15	
PCO2	No	20	40.45	14.05	0.234
	Yes	13	46.43	13.43	
PO2	No	20	71.05	55.73	0.906
	Yes	13	68.61	60.79	
HCO3	No	19	31.68	37.38	0.451
	Yes	13	23.68	4.85	
SO2	No	18	81.65	17.21	0.837
	Yes	13	80.32	18.31	

Comorbidities

Among the patients, 31.3% had diabetes mellitus (DM), and 68.7% had no history of DM. The DM rate was significantly higher (P=0.036) in deceased patients. Additionally, 58.6% had hypertension (HTN), and HTN disease was significantly higher (P=0.002) in deceased patients (***Table1***). There was no significant difference in mortality rate related to lung dysfunction history, renal dysfunction history, cardiovascular disease, neurology disease history, immunosuppressive positive history, and pregnancy (***Table1***).

Drug History

A positive drug history was noted in 72.7% of patients, and the mortality rate was significantly higher (P=0.005) in patients with a drug history. The mortality rate was also significantly higher (P=0.002) in patients with a positive history of using statin. No significant difference was observed in using metoprolol-propranolol, captopril, ASA (acetylsalicylic acid), and Clopidogrel in mortality rate (***Table1***).

Family and Exposure History

Ten percent had a positive COVID-19 family history, and 8.1% had an exposure history with COVID-19 patients, with no significant difference in mortality rate (***Table 1***).

Clinical Manifestations

Clinical manifestations, such as fever, sore throat, lethargy, myalgia, and dyspnea on admission, showed no significant difference in mortality rate. However, low oxygen saturation in the ICU was associated with a significantly higher mortality rate (P=0.013) (***Table3***).

Treatments and Complications

Various treatment regimens were employed, with Chloroquine associated with a significantly higher (P=0.049) mortality rate. Oseltamivir showed a significantly lower (P=0.003) mortality rate, while Kaletra and interferon were associated with significantly higher mortality rates (P=0.026 and P=0.000, respectively) (***Table4***). Complications such as cardiac, cardio-renal, and pulmonary were significantly associated with higher mortality rates (P=0.001, P=0.002, and P=0.001, respectively) (***Table5***).

Table 3. Clinical Manifestations in the Death and Recovered Groups with COVID-19

Characteristics	Mortality			P-value
	No N (%)	Yes N (%)	Total N (%)	
Fever				
No	6 (7.2)	-	6 (6.1)	0.585
Yes	77 (92.8)	16 (100.0)	93 (93.9)	
Sore throat				
No	33 (39.8)	10 (62.5)	43 (43.4)	0.106
Yes	50 (60.2)	6 (37.5)	56 (56.6)	
Lethargy				
No	53 (63.9)	9 (56.2)	62 (62.6)	0.583
Yes	30 (36.1)	7 (43.8)	37 (37.4)	
Dyspnea				
No	44 (53.0)	9 (56.2)	53 (53.5)	1.000
Yes	39 (47.0)	7 (43.8)	46 (46.5)	
Myalgia				
No	31 (37.3)	6 (37.5)	37 (37.4)	1.000
Yes	52 (62.7)	10 (62.5)	62 (62.6)	
Dyspnea in ICU admission				
No	22 (27.5)	6 (37.5)	28 (29.2)	0.547
Yes	58 (72.5)	10 (62.5)	68 (70.8)	
Low saturation in ICU admission				
No	48 (60.0)	4 (25.0)	52 (54.2)	0.013
Yes	32 (40.0)	12 (75.0)	44 (45.8)	

Table 4. Treatment Regimen of the Death and Recovered Groups with COVID-19

Treatment regimen	Mortality			P-value
	No N (%)	Yes N (%)	Total N (%)	
Chloroquine				
No	32 (38.6)	2 (12.5)	34 (34.3)	0.049
Yes	51 (61.4)	14 (87.5)	65 (65.7)	
Oseltamivir				
No	22 (26.5)	11 (68.8)	33 (33.3)	0.003
Yes	61 (73.5)	5 (31.2)	66 (66.7)	
Kaletra				
No	43 (51.8)	3 (18.8)	46 (46.5)	0.026
Yes	40 (48.2)	13 (81.2)	53 (53.5)	
Interferon				
No	72 (86.7)	7 (43.8)	79 (79.8)	0.000
Yes	11 (13.3)	9 (56.2)	20 (20.2)	

Table 5. Complications after Admission in the Death and Recovered Groups with COVID-19

Complications	Mortality			P-value
	No N (%)	Yes N (%)	Total N (%)	
Cardiac complications				
No	73 (89.0)	2 (13.3)	75 (77.3)	0.000
Yes	9 (11.0)	13 (86.7)	22 (22.7)	
Cardio-renal complications				
No	81 (98.8)	12 (75.0)	93 (94.9)	0.002
Yes	1 (1.2)	4 (25.0)	5 (5.1)	
Pulmonary complications				
No	60 (73.2)	1 (6.2)	61 (62.2)	0.000
Yes	22 (26.8)	15 (93.8)	37 (37.8)	

Table 6. Imaging Abnormalities of the Death and Recovered Groups with COVID-19

Imaging abnormalities	Mortality			P-value
	No N (%)	Yes N (%)	Total N (%)	
ground glass opacity in CT	83 (100.0)	16 (100.0)	99 (100.0)	-
Abnormal ejection fraction in echocardiography				
No	36 (45.0)	3 (30.0)	39 (43.3)	0.505
Yes	44 (55.0)	7 (70.0)	51 (56.7)	
ECG abnormal in hospital administration				
No	25 (30.5)	1 (7.7)	26 (27.4)	0.105
Yes	57 (69.5)	12 (92.3)	69 (72.6)	
ECG abnormal in ICU administration				
No	25 (30.5)	1 (7.7)	26 (27.4)	0.105
Yes	57 (69.5)	12 (92.3)	69 (72.6)	
ECG abnormal duration ICU administration				
No	75 (91.5)	1 (7.7)	76 (80.0)	0.000
Yes	7 (8.5)	12 (92.3)	19 (20.0)	

Imaging Abnormalities

CT abnormalities were universally present, with ground glass opacity (GGO) and infiltration in all patients. Abnormal Ejection Fraction (EF) in echocardiography showed no significant difference in mortality rate. However, abnormal ECG under mechanical ventilation was associated with a significantly higher mortality rate (P=0.001) (***Table6***).

Laboratory Test Abnormalities

As shown in ***Table2***, WBC counts (P=0.004) and BUN levels (P=0.013) were significantly higher in deceased patients, while PLT counts (P=0.017) and LDL level (P=0.023) were significantly lower. No significant differences were observed for other laboratory tests.

The provided text is well-written and does not require significant editing. The adjustments made for clarity are as follows:

Discussion

Coronavirus Disease 2019 (COVID-19), caused by the novel beta coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has emerged as a distinct infectious disease with a spectrum of pneumonia symptoms(1). The initial cases were reported in Wuhan, Hubei, China, leading to the World Health Organization (WHO) declaring COVID-19 a pandemic on March 12, 2020(2,3). Clinical studies have identified various risk factors associated with unfavorable outcomes in hospitalized patients with COVID-19. This study focuses on analyzing the clinical course of 99 patients admitted to the Intensive Care Unit (ICU) of Fatemeh Zahra Hospital in Sari to identify specific risk factors linked to clinical outcomes.

Age and smoking have been indicated as predictors of poor clinical outcomes in previous studies(13). Similarly, studies by Chen et al and Verity et al highlighted the association between older age and adverse outcomes(14,15). Obesity has been linked to prolonged hospital and ICU stays and is considered a risk factor for severe COVID-19(13,16,17). Contrary to these findings, our study revealed no significant differences in mortality rates based on sex, travel, or smoking history. Additionally, age and weight did not show a significant association with mortality.

Comorbidities play a crucial role in determining the severity of COVID-19. Our study demonstrated a significantly higher rate of diabetes mellitus (DM) and hypertension (HTN) in deceased patients. Previous research has also identified hypertension and cardiovascular comorbidities as contributors to mortality(7,14,18,19). However, the present study did not find significant differences in mortality related to lung dysfunction, renal dysfunction, cardiovascular disease, neurology disease history, immunosuppressive positive history, or pregnancy.

Patients' drug history emerged as a noteworthy factor, with a higher mortality rate observed in patients with a positive history of using statins. Studies have shown varied associations, such as the potential benefit of low-dose aspirin in reducing mortality(20,21). The mortality rate was notably higher in patients with low saturation in the ICU, aligning with findings that dyspnea and abnormal oxygen saturation are associated with poor outcomes(11,14).

Treatment regimens played a crucial role, with Chloroquine linked to higher mortality rates and Oseltamivir associated with lower mortality rates. The study also highlighted higher mortality rates in patients receiving interferon and Kaletra. Previous studies have provided mixed evidence on the efficacy of certain treatments, emphasizing the need for careful consideration in selecting treatment options(2,22,23,24,25).

Complications significantly impacted mortality rates, with cardiac, cardio-renal, and pulmonary complications contributing to higher mortality. Chen's study emphasized the prevalence of various complications in deceased patients, including acute respiratory distress syndrome, respiratory failure, sepsis, cardiac injury, heart failure, alkalosis, hyperkalemia, acute kidney injury, and hypoxic encephalopathy(14).

Imaging and paraclinical abnormalities demonstrated no significant differences in CT scan and echocardiography results, but the mortality rate was higher in patients with abnormal ECG. Laboratory test abnormalities, including elevated WBC counts and BUN levels and decreased PLT counts and LDL levels, were associated with increased mortality. These findings align with previous studies indicating the prognostic value of laboratory markers, including leukocytosis, neutrophilia, and elevated levels of various enzymes and biomarkers(13,14).

In conclusion, this study provides valuable insights into the clinical factors associated with poor outcomes in COVID-19 patients. The results emphasize the importance of considering age, comorbidities, drug history, treatment regimens, complications, and laboratory findings when assessing the prognosis of hospitalized patients. Further research and collaborative efforts are essential to refine our understanding and improve patient outcomes in the ongoing battle against COVID-19.

Conclusion

This study unveils key findings related to risk factors and outcomes in COVID-19 patients. The results are outlined as follows:

1. Risk Factors

- Diabetes Mellitus (DM) and Hypertension (HTN) were identified as significant risk factors in COVID-19 patients.

2. Statin Use

- Patients with a history of statin use exhibited a significantly higher mortality rate.

3. Oxygen Saturation

- Patients with low saturation in the Intensive

Care Unit (ICU) experienced a notably higher mortality rate.

4. Treatment Regimens

- Different treatment regimens showed varying mortality rates:
- Patients receiving Chloroquine in the ICU had significantly higher mortality rates.
- Patients receiving Oseltamivir in the ICU had significantly lower mortality rates.
- Higher mortality rates were observed in patients receiving interferon and Kaletra in the ICU.

5. Complications

- Cardiac, cardio-renal, and pulmonary complications were significantly more prevalent in patients who did not survive.

6. ECG Abnormalities

- Patients with a final abnormal ECG had a significantly higher mortality rate.

7. Laboratory Abnormalities

- Laboratory test abnormalities included:
- Higher White Blood Cell (WBC) counts and Blood Urea Nitrogen (BUN) levels in deceased patients.
- Lower Platelet (PLT) counts and Low-Density Lipoprotein (LDL) levels were significantly associated with increased mortality.

These findings emphasize the multifaceted nature of COVID-19 outcomes, highlighting the importance of considering various factors such as comorbidities, treatment responses, and complications. Further research is essential to deepen our understanding and enhance strategies for improving patient outcomes in the ongoing fight against COVID-19.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All authors were involved in the conception and design, analysis and interpretation of the data, drafting of the manuscript and revising it critically for intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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