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COVID19- in Iran: Clinical, Therapeutic, and Laboratory Findings Associated with Mortality

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ABSTRACT

Introduction: Currently, humankind is facing a COVID-19 pandemic that has spread worldwide. This is the first study conducted during the first phase of the COVID-19 outbreak in Mashhad, Iran, to describe the clinical, therapeutic, and laboratory findings of survivor and non-survivor patients with COVID-19.

Methods: This retrospective study included a total of 191 confirmed COVID19-patients aged ≥18 who were admitted to an intensive care unit in the northeast of Iran in 2020. Clinical, therapeutic, and laboratory findings were recruited. The data were analyzed using SPSS software (version 23) through the Mann-Whitney U test, Chi-Square test, independent sample t-test, as well as a single variable and multivariable logistic regression.

Results: Out of a total of 191 hospitalized patients, %71.7) 137) survived and 54 %28.2)) expired. The mean age of non-survived patients was 17 years higher than that of survived patients (P<0.0001). Hypertension, diabetes, and coronary and pulmonary diseases were significantly related to mortality (OR: 21.4 ,2.8 ,3, and 5.4, respectively; P<0.05). Respiratory rate >24/min, heart rate>125/min, platelet count <109*100/L, creatinine >133 µmol/L, LDH >245 U/L, WBC count >109*10/L, lymphocyte count <109*0.8/L and D-dimer >1 µg/mL were frequently observed in non-survivor patients (P<0.05). Most of the patients had an abnormality on chest radiographs, and bilateral pulmonary infiltration was the dominant chest radiograph abnormality in these patients. Moreover, consolidation and ground-glass opacification were observed more frequently in non-survived patients (P<0.05). More than %57 of severe cases required non-invasive and invasive mechanical ventilation before they died, while it was %1 in survived cases (P<0.05).

Conclusion: Older age, previous comorbidities such as diabetes, hypertension, coronary and pulmonary diseases, lymphopenia, leukocytosis, increased respiratory rate, creatinine, LDH, and D-dimer levels were related to a poor prognosis and mortality in patients with SARS-CoV2- infection.

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Introduction

On 31 December 2019, multiple cases of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) were recognized in Wuhan, China. World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) and named it coronavirus disease 2019 (COVID-19). This has been the first infectious pandemic disease in the 21st century (1).

This novel coronavirus disease is a highly contagious respiratory system infection, and epidemiological studies have shown that the virus can spread easily by droplets and aerosols (2,3). The clinical spectrum is wide, ranging from an asymptomatic state or a mild infection to pneumonia, respiratory failure, and death (4).

Since its emergence in China, COVID-19 has rapidly distributed worldwide and is now mutating into various and more contagious variants. Up until the performance of this manuscript (September 30th, 2021), a total of 233,136,147 patients have been reported to be positive for COVID-19 all over the world, including 4,771,408 deaths (5).

A total of 5,572,962 confirmed cases of COVID-19 and 120,160 deaths from Iran have been reported to WHO from January 3, 2020, to September 30, 2021. It is worth mentioning that a total of 51,950,783 vaccine doses have been administered in Iran since 26 September 2021 (6).This retrospective study aimed to describe the clinical, therapeutic, and laboratory features of survivor and non-survivor patients with COVID-19 during the first outbreak of the disease between February and December 2020 in Mashhad, northeast Iran.

Materials and Methods

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Research Department of Mashhad University of Medical Sciences (No: IR.MUMS.MEDICAL.REC.1399.336). No informed consent of the patients was required given the characteristics of the study design.

Patients

This retrospective study included 191 confirmed cases of COVID-19 aged ≥18 years who were admitted to the intensive care unit (ICU) of Imam-Reza Hospital, Mashhad, Iran, between February and November 2020. Following the WHO interim guidance, all enrolled patients were diagnosed with COVID-19 based on their clinical symptoms, laboratory findings, and chest computed tomography (CT) scans. All of these patients had a definite outcome (death or discharge) during the study period.

Data collection

Patients' information including demographic data, clinical characteristics, laboratory indexes, chest radiograph findings, and ventilator settings were extracted from the electronic medical records. The patients' outcome (death or discharge) was also recorded. The specimens for laboratory tests and chest radiographs were collected during the hospital stay.

Statistical analysis

Statistical analyses were carried out using SPSS software (IBM Corporation, New York, USA; version 23.0). Differences between survivor and non-survivor patients were assessed through independent sample t-test, Mann-Whitney U test, and $\chi 2$ test. Single variable and multivariable logistic regression were included in the multivariable analysis to determine risk factors with statistically significant differences in the single variable analysis. The level of significance was set at $P<0.05$.

Results

From February to November 2020, 191 confirmed COVID-19 patients aged ≥18 were hospitalized in the ICU of Imam-Reza Hospital, Mashhad, Iran, of whom 137 (71.7%) survived and were later discharged from the hospital, and 54 (28.2%) expired. The mean age of all patients was 56 years (ranging from 46 to 67 years), and the majority of them were male. The mean age of the expired patients was 17 years higher than that of the discharged patients ($P<0.0001$).

The most common presenting symptoms included fever (94.2%), weakness (89.5%), and dry cough (79%). Less common symptoms were myalgia (15.1%), diarrhea (4.7%), nausea, and vomiting (3.6%). The two groups of patients (survived and non-survived) had no significant difference in terms of their clinical presentations ($P>0.05$).

The clinical presentation of patients is listed in Table 1. The frequency of comorbidities such as hypertension, diabetes, coronary and pulmonary diseases, respiratory rate>24/min, and heart rate>125/min was significantly higher in non-survived rather than survived patients ($P<0.05$).

All enrolled patients underwent laboratory examinations on admission. The serum level of hemoglobin was within the normal range in both groups and no significant difference was observed between the two groups in terms of this variable

The increase in WBC count, creatinine, LDH, and D-dimer levels was more obvious in non-survived patients than in those who survived (46.2 vs. 11, $P<0.001$; 42.6 vs. 8.75, $P=0.045$; 98.1 vs. 51.1, $P<0.0001$; 81 vs.

Table 1: Demographic and clinical characteristics of non-survivor and survivor patients with COVID 19

Variables	Non-survivors N=54 n (%)	Survivors N=137 n (%)	Total N=191 n (%)	P-value*
Mean age (range)	69 (63-76)	52 (45-58)	56 (46-67)	<0.0001
Gender				
Male	38 (70.3)	81 (59.1)	119 (62.3)	0.15
Female	16 (29.6)	56 (40.8)	72 (37.6)	
Comorbidities				
Hypertension	26 (48.1)	32 (23.3)	58 (30.3)	0.0008
Diabetes	17 (31.4)	19 (13.8)	36 (18.8)	0.0051
Coronary disease	13 (24)	2 (1.4)	15 (7.8)	<0.0001
Pulmonary disease	4 (7.4)	2 (1.4)	6 (3.1)	0.047
Carcinoma	0	2 (1.4)	2(1)	0.37
Smoking	5 (9)	6 (4)	11(6)	0.21
Symptoms				
Fever	51 (94.4)	129 (94)	180 (94.2)	0.94
Dry cough	39 (72.2)	112 (81.7)	151 (79)	0.15
Sputum production	14 (26)	30 (21.8)	44 (23)	0.55
Myalgia	8 (14.8)	21 (15.3)	29 (15.1)	0.93
Weakness	48 (88.8)	123 (89.8)	171 (89.5)	0.33
Diarrhea	2 (3.7)	7 (5.1)	9 (4.7)	0.67
Nausea and vomiting	3 (5.5)	4 (3)	7 (3.6)	0.40
Heart rate >125/min	7(13)	5 (3.6)	12 (6.3)	0.024
Respiratory rate >24 /min	34 (63)	22 (16)	56 (29)	<0.0001
Systolic blood pressure <90 MmHg	6 (11.1)	18 (13.1)	24 (12.5)	0.53

*P-values are based on chi-square and independent sample t-test for qualitative and quantitative variables respectively

24, P<0.0001). The non-survivor patients had significantly lower counts of lymphocyte and platelet than the survivor patients (76 vs. 26.2, P<20.3 ;0.001 vs. 1.4, P<0.001). More details of the patient's clinical status are tabulated in Table 2.

Table 2: Laboratory features of non-survivor and survivor patients with COVID 19

Variables	Non-survivors N=54 n* (%)	Survivors N=137 n* (%)	Total N=191 n* (%)	P-value**
<4	5 (9.2)	27 (19.7)	32 (16.7)	<0.001
4-10	24 (44.4)	95 (69.3)	119 (62.3)	
>10	25(46.2)	15 (11)	40 (21)	<0.001
Median± SD	9.8 (2.1)	5.2 (3.6)	6.2 (2.8)	
Lymphocyte count (*109/l)				
<0.8	41 (76)	36 (26.2)	77 (40.3)	<0.001
>0.8	13 (24)	101 (73.7)	114 (59.6)	<0.001
Median± SD	0.6 (0.2)	1.1 (0.3)	1 (0.2)	

Hemoglobin (g/dl)				
Median± SD	12.6 (3.3)	12.8 (2.1)	12.8 (1.8)	0.30
Platelet count (*109/l)				
<100	11 (20.3)	2 (1.4)	13 (6.8)	<0.001
Median± SD	165.5 (21.2)	220 (19.8)	206 (20.1)	<0.001
Creatinine (µmol/l)				
>133	23 (42.6)	12 (8.75)	12 (8.75)	0.045
LDH (u/l)				
>245	53 (98.1)	70 (51.1)	123 (64.3)	<0.0001
Median± SD	521 (18.6)	253.5 (17.8)	300 (18.1)	<0.0001
D-dimer (µg/ml)				
<0.5	4 (7)	51 (43)	55 (32)	<0.0001
0.5-1	6 (11)	39 (33)	45 (26)	
>1	44 (81)	28 (24)	72 (42)	<0.0001
Median± SD	5.2 (0.8)	0.6 (0.6)	0.8 (0.4)	

** In some variables, it is median concentration± SD*
***P-values are based on chi-square and independent sample t-test for qualitative and quantitative variables respectively*

Most of the patients had an abnormality on the chest radiograph, presenting with consolidation, ground-glass opacification, and bilateral pulmonary infiltration. Bilateral pulmonary infiltration was the predominant (%75) abnormal chest radiograph finding. Consolidation and ground-glass opacification was observed more frequently in non-survivor patients than survivor patients (P≤0.049) (Table 3).

Table 3: Abnormal chest radiographic findings of non-survivor and survivor patients with COVID 19

	Non-survivors N=54 n (%)	Survivors N=137 n (%)	Total N=191 n (%)	P-value*
Consolidation	40 (74)	72 (53)	112 (59)	0.0065
Ground glass opacification	44 (81)	92 (67)	136 (71)	0.049
Bilateral pulmonary infiltration	45 (83)	98 (72)	143 (75)	0.090

*P-values are based on chi-square

More than %89 of all patients received supplemental oxygen, and invasive and non-invasive mechanical ventilation was highly provided to the expired patients (P<0.05) (Table 4).

Table 4: Respiratory settings of non-survivor and survivor patients with COVID19-

	Non-survivors N=54 n (%)	Survivors N=137 n (%)	Total N=191 n (%)	P-value*
Nasal O2 therapy	51 (94.4)	119 (86.9)	170 (89)	0.56
Non-invasive mechanical ventilation	24 (44)	2 (1)	26 (14)	<0.01
Invasive mechanical ventilation	31 (57)	1 (1)	32 (17)	<0.05

*P-values are based on chi-square

Based on univariate analysis, older age, hypertension, diabetes, coronary and pulmonary diseases, respiratory rate>24/min, WBC count>10*109/L, lymphocyte count<0.8*109/L, creatinine>133 µmol/L, LDH>245 U/L, and D-dimer>1µg/mL were risk factors associated with mortality in patients with COVID-19. Among these, LDH>245 u/l, D-dimer> 1µg/mL, and coronary disease with 45.4, 20, and 21.4-fold enhanced risk were the most noticeable risk factors related to death in patients with COVID-19 (Table 5).

Table 5: Risk factors associated with mortality among patients with COVID 19

Risk factors	Univariable		Multivariable	
	OR	P-value*	OR	P-value*
Mean age	1.1	<0.001	1.1	0.0043
Comorbidities				
Hypertension	3.0	0.010	-	-
Diabetes	2.8	0.0062	-	-
Coronary disease	21.4	<0.001	2.1	0.48
Pulmonary disease	5.4	0.056	-	
Respiratory rate				
>24/min	8.8	<0.001	-	
WBC				
>10*109/L	6.6	<0.001	-	
Lymphocyte				
<0.8*109/L	0.02	<0.001	0.1	0.13
Creatinine				
>133 µmol/L	4.3	0.048	-	-
LDH				
>245	45.4	0.002	-	-
D-dimer				
>1	20.0	<0.001	18.4	0.0033

* P-values are based on univariable and multivariable analyses; OR=Odds ratio

Discussion

This is the first study during the first COVID-19 outbreak in Mashhad, Iran, to describe clinical, therapeutic, and laboratory findings of patients with COVID 19. The majority of patients were relatively old and the mean age of the expired patients was 17 years higher than that of discharged patients (P<0.0001). Most of the patients had a mild disease presentation and were soon discharged from the hospital.

As presented in Table 5, patients with diabetes, hypertension, as well as coronary and pulmonary diseases were more in danger of COVID 19 severity and mortality than other individuals (OR: 2.8, 3, 21.4, and 5.4 respectively). Coronary disease with a 21.4-fold enhanced risk was the most severe comorbidity that can make patients highly prone to COVID-19 mortality. Some studies have demonstrated that myocardial injury among hospitalized patients with COVID-19 is associated with increased mortality (7, 8). According to a systematic review, there is also an increased risk of acute cardiac injury associated with COVID19 severity and mortality (9).

The results of a review study showed that patients with previous comorbidities such as chronic obstructive pulmonary disease (COPD) are at an increased risk of viral respiratory infections as well as COVID-19 susceptibility and severity (10).

In regard to hypertension, a systematic review reported a nearly 2.5-fold significantly enhanced risk of hypertension in cases with severe COVID-19 and mortality (OR: 2.49 [95%CI: 1.98-3.12] and OR: 2.42 [95%CI: 1.51-3.90], respectively) (11). In the current study, hypertension was found to be associated with a 3-fold higher risk of mortality and hence a poor outcome for COVID-19 patients.

The results of our study suggest that diabetes has a nearly 3-fold enhanced risk on clinical outcome (OR: 2.8, P=0.006). Similarly, Guan et al. reported a high prevalence of diabetes in the severe (16.2%) compared to non-severe patients (5.7%) (12). Consistently, Yang X et al. reported a high prevalence of diabetes in non-survivor patients (22%) compared to survivor patients (10%) with COVID-19 (13). The results of a systematic review also showed that diabetes was a risk factor contributing to COVID-19 severity and mortality (14). Therefore, COVID-19 patients with comorbidities are more likely than healthy people to develop poor outcomes.

The CT scan was widely used for COVID-19 diagnosis, prognosis, and treatment management (15). In the present study, most of the patients had abnormalities on chest radiographs. Consolidation, ground-glass opacification, and bilateral pulmonary infiltration were observed in 59%, 71%, and 75% of all patients, respectively.

Although bilateral pulmonary infiltration was the most common chest radiograph abnormality, there was no significant difference between survivor and non-survivor groups regarding this abnormality. On the contrary, consolidation and ground-glass opacification were observed more frequently among non-survived patients than survived patients (P≤0.049). It has been documented that ground-glass opacification presents during the early stages of the disease and consolidation presents at later stages (16). Shaher M. Samrah et al. reported that 17% of COVID-19 patients had infiltrates in chest radiographs that were significantly more common in symptomatic patients (17).

A systematic review and meta-analysis reported that the chest radiographs of most COVID-19 patients (76%) showed bilateral ground-glass appearances (18). The frequency of bilateral pulmonary involvement in these patients reached as high as 98% (19). Regarding the laboratory findings, there was no significant difference in hemoglobin median concentration between the two groups of patients. In contrast with this study, a meta-analysis reported that the patients with severe conditions were found to have a significantly lower hemoglobin level than patients with mild conditions (20).

Our findings showed a significantly increased level of leukocytes in patients who died compared to those who recovered (46.2% vs. 11%; P<0.001). Conversely, a significantly decreased level of leukocytes was found in survived patients compared to non-survived patients (19.7% vs. 9.2%; P<0.001). As a result, leukocytosis is indicative of clinical deterioration and contributes to a 6.6-fold higher risk of mortality. Increased neutrophils, decreased lymphocytes, eosinophils, and monocytes were also discovered in patients with COVID-19 (4).

Lymphopenia and LDH >245 were detected significantly in the non-survivor group compared to the survivor group (P<0.0001). The results of a random-effects meta-analysis showed that lymphopenia (47.9%, 95% CI 41.6–54.9%) and increased LDH (46.2%, 95% CI 37.9–54.7%) were two prevalent laboratory findings in patients with COVID-19. Zhang Z-L et al. showed that lymphopenia and increased LDH were associated with a higher risk in patients with severe presentations than those with non-severe presentations (21).

High LDH level in patients with severe symptoms is considered to be a potential marker indicating tissue damage and lung injury (22). In this study, a 45.4-fold enhanced risk of LDH>245 was found in clinical outcomes and was associated with mortality. In agreement with this study, Zhou et al. reported that the proportion of decreased lymphocyte and increased LDH levels in the non-survivor group was significantly higher than those in the survivor group (76% vs. 26%, P<0.001 and 98% vs. 54%, P<0.001, respectively) (23). These two findings were highly associated with severe conditions and mortality of patients with COVID-19. These results were also reported in several other studies (24-26).

Additionally, we found that the D-dimer median concentration was significantly higher in non-survived patients than in survived patients (5.2 vs. 0.6; P<0.0001). D-dimer level >1 lg/mL was observed to be 20-fold higher in non-survived patients (P<0.001). Therefore, D-dimer level is remarkably related to a worse prognosis for COVID-19 infection. In agreement with this result, Tang et al. reported approximately 3.5-fold higher D-dimer levels in patients with severe compared to non-severe disease. They also claimed that heparin treatment in cases with D-dimer levels>1 lg/mL can reduce the mortality rate (27).

Therefore, the anticoagulant treatment seems to be beneficial in patients with severe COVID-19 with a D-dimer level >1 lg/mL. Increased level of creatinine is another risk factor associated with mortality in patients with COVID-19 that can cause kidney damage. We found that creatinine>133 was 4.3-fold higher in non-survived patients than in survived patients (P=0.048). These results were confirmed by a study in which 28.8% of COVID-19 patients had an increased level of creatinine, indicating the virus's ability to induce kidney injury (28).

Thrombocytopenia is associated with an increased risk of severe conditions and mortality in patients with COVID-19 (29, 30). In this study, we found a significant correlation between platelet count and mortality (P<0.001). It was observed to be significantly low in non-survived patients who appeared to have severe symptoms. In a study conducted in China, 36.2% of patients presented with thrombocytopenia, and it occurred more frequently among patients with severe conditions (57.7%) (12). The results of a meta-analysis support this finding (31). Therefore, thrombocytopenia can be indicative of poor prognosis in COVID-19 patients.

The administration of supplemental oxygen is the first-line therapy for managing hypoxemic patients with COVID-19. In this study, almost all patients received supplemental oxygen, either through a nasal cannula or mechanical ventilation, as part of their treatment. Non-survived patients were in greater need of mechanical ventilation to maintain adequate saturation, and more than 57% of them required invasive and non-invasive mechanical ventilation before they died, while this rate was 1% in survived cases (P<0.05).

The mortality rate was higher in patients who received invasive mechanical ventilation compared to those with non-invasive mechanical ventilation (57% vs. 44%). It may be due to the fact that intubated patients with invasive mechanical ventilation might experience more severe respiratory failure leading to more death. Some studies, however, do not recommend using non-invasive mechanical ventilation for COVID-19 patients due to reasons such as the virus spreading through aerosolization (32, 33). Until the performance of this study, no validated treatment for COVID-19 has been issued by any medical or scientific entity. However, three more common modalities used for the treatment of COVID-19 include antiviral agents, antibiotics, and oxygen therapy (34).

This study had some limitations. First of all, we were not able to follow up the discharged patients. Secondly, the effects of other important laboratory indexes such as CRP, ASL, serum albumin, and ESR have not been evaluated on clinical outcomes. Finally, the efficacy of other treatment methods, such as antiviral agents and antibiotics on prognosis was not considered.

Conclusion

Factors such as older age, hypertension, diabetes, coronary and pulmonary diseases, leukocyte count >10 and <4*109/L, respiratory rate>24/min, heart rate>125/min, platelet count<100*109/L, creatinine>133 μmol/L, LDH>245 U/L, lymphocyte count >0.8 and <0.8*109/L, and D-dimer> 1μg/mL were significantly different between the survivor and non-survivors with COVID-19 and are associated with death in these patients.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Research Department of Mashhad University of Medical Sciences protocol number: IR.MUMS.MEDICAL.REC.1399.336.

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