

# Risk Factors for the Mortality in Hospitalized Patients with COVID-19: A Brief Report

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## What's Known

- The increasing growth of COVID-19-related mortality has highlighted the need to recognize the risk factors associated with severe COVID-19 infection.
- Recent epidemiological studies have investigated the relationship between various risk factors and the fatal risk of COVID-19.
- There is a lack of well-documented data regarding the association between impaired laboratory parameters and mortality risks related to COVID-19 infection.

## What's New

- We identified certain clinical risk factors, including a history of chronic obstructive pulmonary disease COPD, hypoxia during hospitalization, and initial computed tomography scan (CT) scores, which independently increase the odds of COVID-19-related mortality.
- We provided an independent COVID-19-related mortality prediction model based on the initial recorded laboratory tests on the data of multi-center hospitals.

## Abstract

The cumulative rate of death of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has necessitated better recognizing the risk factors of the disease and the COVID-19-induced mortality. This cross-sectional study aimed to determine the potential risk factors that predict COVID-19-related mortality concentrating on the initial recorded laboratory tests. We extracted admission's medical records of a total of 136 deaths related to COVID-19 and 272 discharged adult inpatients ( $\geq 18$  years old) related to four referral centers from February 24<sup>th</sup> to April 12<sup>th</sup>, 2020, in Isfahan, Iran, to figure out the relationship between the laboratory findings and mortality beyond demographic and clinical findings. We applied the independent sample *t* test and a chichi square test with SPSS software to compare the differences between the survivor and non-survivor patients. A P value of less than 0.05 was considered significant. Our results showed that greater length of hospitalization ( $P \leq 0.001$ ), pre-existing chronic obstructive pulmonary disease ( $P \leq 0.001$ ), high pulse rate, hypoxia ( $P \leq 0.001$ ), and high computed tomography scan score ( $P < 0.001$ ), in addition to high values of some laboratory parameters, increase the risk of mortality. Moreover, high neutrophil/lymphocyte ratio (OR, 1.890; 95% CI, 1.074-3.325,  $P = 0.027$ ), increased creatinine levels (OR, 15.488; 95% CI, 0.801-299.479,  $P = 0.07$ ), and elevated potassium levels (OR, 13.400; 95% CI, 1.084-165.618,  $P = 0.043$ ) independently predicted in-hospital death related to COVID-19 infection. These results emphasized the potential role of impaired laboratory parameters for the prognosis of fatal outcomes in adult inpatients.

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**Keywords** • COVID-19 • Risk factors • Mortality • Medical laboratory science

## Introduction

The outbreak of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a threat to global public health.<sup>1</sup> In general, due to the rapid spread of COVID-19 through human-to-human communication, the prevalence is currently on an increasing trend. In this regard, the WHO's latest global data recorded, as of 14 March 2021, just about 141.5 million confirmed cases of COVID-19.<sup>2</sup> Additionally, recent statistics determined that in the Middle East, a high death rate of COVID-19 cases was observed in Iran (58.61%) and Turkey (30.86%).<sup>3</sup> Furthermore, The COVID-19 epidemic model predicted mortality of 11.7% of in-hospital mortality in patients with COVID-19 using a case-control study in Isfahan.<sup>4, 5</sup> These outcomes highlighted the need

to better recognize the risk factors associated with severe COVID-19 infection.<sup>6</sup>

Recently, studies have specified that the average COVID-19-related deaths have been found in the older population and male gender.<sup>7</sup> Additionally, released epidemiological data by the Centers of Disease Control and Prevention (CDC) has revealed that several pre-existing comorbidities, including cardiovascular disease, hypertension, diabetes, respiratory disease, and cancers, are related to increased fatality risk.<sup>8</sup> In addition to the clinical and epidemiological characteristics, fluctuations in laboratory parameters are recently reported in COVID-19 to affect patients and have worse outcomes.<sup>9</sup> However, limited data are focusing on laboratory parameters beyond the epidemiology and clinical features of patients in the prognosis of COVID-19-related mortality.

This short report aimed to determine the potential risk factors that predict COVID-19-related mortality concentrating on the initial recorded laboratory tests based on the data of multi-center population-based cohort study.

## Methods

This cross-sectional study was conducted to determine the potential risk factors that predict COVID-19-related mortality. Therefore, we obtained the medical recorded information of 136 death cases caused by COVID-19 ( $\geq 18$  years old) related to four referral centers from February 24<sup>th</sup> to April 12<sup>th</sup>, 2020, in Isfahan, Iran. To determine the relationship between the demographic, clinical, and laboratory findings and mortality, we analyzed the medical information of 272 discharged inpatients and compared it

**Table 1:** Baseline demographic and clinical characteristics of survivor and non-survivor hospitalized COVID-19 patients

Patients characteristics			Total (n=408) N (%)	Survived (n=272) N (%)	Dead (n=136)	P value	
Demographics	Age	<35	39 (9.6)	36 (13.2)	3 (2.2)	<0.001	
		35-55	111 (27.2)	104 (38.2)	7 (5.1)		
		56-70	137 (33.6)	93 (34.2)	44 (32.4)		
		>70	121 (29.7)	39 (14.3)	82 (60.3)		
	Sex	Female	210 (51.5)	163 (59.9)	47 (34.6)	<0.001	
		Male	198 (48.53)	109 (40.07)	89 (65.44)		
	Hospital length of stay (days)		9.65 (5.17)	9.01 (5.22)	10.39 (5.04)	<0.001	
	Duration of symptom's onset to hospital admission (days)		6.99 (4.78)	7.47 (4.72)	5.99 (4.77)	0.004	
Comorbidities	Hypertension		158 (38.8)	82 (30.1)	76 (56.3)	<0.001	
	Heart failure		13 (3.2)	4 (1.5)	9 (6.6)	0.013	
	<i>Chronic obstructive pulmonary disease</i>		43 (10.5)	12 (4.4)	31 (22.8)	<0.001	
	Diabetes		130 (31.9)	68 (25.0)	62 (45.9)	<0.001	
	Cancer		12 (2.9)	5 (1.8)	7 (5.2)	0.069	
	<i>Chronic kidney disease</i>		25 (6.1)	10 (3.7)	15 (11.1)	0.007	
	Hyperlipoproteinemia		58 (14.3)	31 (11.4)	27 (20.0)	0.024	
	Vital Symptoms	Chest Pain		74 (20.7)	64 (29.0)	10 (7.4)	<0.001
Sore Throat		77 (21.0)	56 (24.2)	21 (15.4)	0.047		
Cough		324 (79.8)	218 (80.7)	106 (77.9)	0.515		
Shortness of Breath		299 (74.8)	179 (67.8)	120 (88.2)	<0.001		
Nausea		122 (32.2)	98 (40.3)	24 (17.6)	<0.001		
Vomiting		85 (22.3)	61 (24.9)	24 (17.6)	0.123		
Diarrhea		69 (18.4)	61 (25.6)	8 (5.9)	<0.001		
Headache		126 (34.4)	103 (44.8)	23 (16.9)	<0.001		
Chills		246 (62.3)	194 (74.9)	52 (38.2)	<0.001		
Weakness Fatigue		188 (52.1)	150 (66.7)	38 (27.9)	<0.001		
Fever Degree ( $^{\circ}$ C)		37.66 (0.99)	37.61 (0.99)	37.76 (1.01)	0.153		
Fever Degree $>38.5^{\circ}$ C		66 (16.5)	42 (15.8)	24 (17.9)	0.669		
Vital Signs (on triage)		Systolic blood pressure )mm Hg(		128.67(20.01)	129.72 (17.75)	126.44 (24.04)	0.173
		Diastolic blood pressure )mm Hg(		79.18 (34.69)	81.87 (40.73)	73.48 (13.84)	0.024
	Peripheral capillary oxygen saturation (SpO2)		87.48 (9.37)	90.70 (5.37)	80.98 (11.99)	<0.001	
	Pulse Rate $>100$		119 (29.3)	78 (28.9)	41 (30.1)	0.818	
Global CT Score (mean $\pm$ SD)			10.76 (5.44)	9.64 (4.84)	13.64 (5.87)	<0.001	

Data are presented as number (%), mean $\pm$ SD. Independent sample *t* test was used for continuous variables and Chi square test was used for categorical variables. Level of statistical significance=0.05. N: Number; CT: Computed tomography; SpO2: Peripheral capillary oxygen saturation

to the information of those, who experienced death in the hospital. Similar to previous studies, the diagnosis of COVID-19 relied on positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR).<sup>9, 10</sup> Investigators extracted demographic characteristics, medical history, pre-existing comorbidities, laboratory findings, and clinical outcomes on admission. Written informed consent was obtained from all the patients. This study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.680).

**Statistical Analysis**

We utilized an independent sample *t* test for continuous data and a Chi square test for categorical data to compare the differences between the survivor and non-survivor patients considering a *P* value<0.05 as statistically significant using SPSS (IBM SPSS Statistics 20.0). Continuous and categorical variables

were presented as mean±SD and number (%), respectively. Univariable and multivariable logistic regression models were employed to explore the potential risk factors associated with mortality. To analyze the association between the laboratory findings with mortality in patients affected by COVID-19, we categorized these according to previous studies.

**Results**

Table 1 represents the details of baseline characteristics of survivor (n=272) and non-survivor patients (n=136). A total of 408 cases (210 women and 198 men) were included in this study. Compared with the survived patients, those who experienced death were 55-70 years (*P*<0.001) and men (*P*<0.001). They also tended to have a higher mean length of patients' hospital stay (*P*<0.001) and a long duration of symptoms onset, the average duration of hospital admission until

**Table 2: Top variables of clinical, epidemiological, and laboratory findings in predicting in-hospital death of COVID-19 patients**

Patients characteristics			Univariate analysis		Multivariate analysis*	
			OR (95% CI)	P value	OR (95% CI)	P value
Demographics	Age	55-70	5.67 (1.658, 19.447)	0.006	-	-
	Sex	Female	0.35 (0.23, 0.54)	<0.001	-	-
		Male (Reference)				
	Hospital length of stay (days)		1.13 (1.08, 1.18)	<0.001	1.12 (1.07, 1.18)	<0.001
	Duration of symptom's onset to hospital admission (days)		0.92 (0.88, 0.97)	0.005	0.91 (0.86, 0.97)	0.004
Comorbidities	Hypertension		2.98 (1.94, 4.57)	<0.001	-	-
	Heart failure		4.74 (1.43, 15.71)	0.011	-	-
	Chronic obstructive pulmonary disease		6.07 (3.01, 12.26)	<0.001	5.36 (2.33, 12.30)	<0.001
	Diabetes		2.54 (1.64, 3.94)	<0.001	-	-
	Chronic kidney disease		3.27 (1.43, 7.502)	0.005	-	-
	Diastolic blood pressure (mm Hg)		0.96 (0.943, 0.979)	<0.001	0.98 (0.96, 1.00)	0.078
	SpO2		0.84 (0.812, 0.883)	<0.001	0.88 (0.84, 0.91)	<0.001
	SpO2 >90 (N, %)		217 (53.7%)	<0.001	114 (85.1%)	<0.001
	Pulse Rate >100		1.06 (0.67, 1.66)	0.793	2.05 (1.13, 3.71)	0.017
	Laboratory Findings	White blood cell <4×10 <sup>9</sup> (n/L)		2.70 (1.50, 4.85)	0.001	2.92 (1.42, 6.02)
Neutrophil/ Lymphocyte ratio			1.20 (1.13, 1.26)	<0.001	1.18 (1.11, 1.26)	<0.001
Hemoglobin <12 (g/dL)			2.72 (1.71, 4.34)	<0.001	1.63 (0.95, 2.81)	0.074
Platelet count			0.99 (0.99, 1.00)	0.066	0.99 (0.99, 1.00)	0.044
BUN >18 (mg/dL)			9.61 (5.82, 15.86)	<0.001	5.49 (3.06, 9.86)	<0.001
Creatinine >1.4 (mg/dL)			13.73 (7.72, 24.40)	0.011	6.39 (3.41, 11.96)	<0.001
Na (mmol/L)			1.15 (1.09, 1.22)	<0.001	1.18 (1.10, 1.27)	<0.001
Potassium (mmol/L)			3.03 (1.80, 5.10)	<0.001	2.17 (1.18, 3.98)	<0.012
ALT (U/L)			1.01 (1.00, 1.01)	0.003	1.01 (1.00, 1.02)	0.001
AST (U/L)			1.01 (1.00, 1.02)	<0.001	1.02 (1.01, 1.03)	<0.001
ALT /AST ratio			1.58 (1.22, 2.04)	<0.001	-	-
ALP (U/L)			1.00 (1.00, 1.01)	<0.001	1.00 (1.00, 1.01)	<0.001
Lactate dehydrogenase >800 (IU/L)			5.09 (1.79, 14.45)	0.011	4.77 (1.39, 16.33)	0.013
Calcium (mg/dL)			0.67 (0.49, 0.91)	0.012	0.69 (0.493, 0.98 )	0.042
Phosphorus (mg/dL)		2.17 (1.67, 2.82)	<0.001	1.97 (1.47, 2.63)	<0.001	
Global CT Score		1.15 (1.09, 1.22)	<0.001	1.19 (1.11, 1.27)	<0.001	

Univariate and multivariate logistic regression models, \*Adjusted by Sex and Age. Level of statistical significance=0.05. AST: Aspartate aminotransferase; ALT: Alanine transaminase; BUN: Blood urea nitrogen; ALP: Alkaline phosphatase; SpO2: Peripheral capillary oxygen saturation; CT: Computed Tomography

**Table 3: Univariable and multivariable laboratory findings models of mortality of hospitalized COVID-19 patients**

Clinical risk factors	Univariable laboratory findings model*		Multivariable laboratory findings model*	
	OR (95% CI)	P value	OR (95% CI)	P value
Neutrophil/Lymphocyte ratio	1.17 (1.10, 1.25)	<0.001	1.89 (1.07, 3.32)	0.027
Hemoglobin <12 (g/dL)	1.80 (1.01, 3.20)	0.044	-	-
White blood cell <4×10 <sup>9</sup> (n/L)	2.56 (1.25, 5.25)	0.010	-	-
Creatinine >1.4 (mg/dL)	6.72 (3.46, 13.04)	<0.001	15.48 (0.80, 299.47)	0.070
LDH >800 (IU/ml)	5.18 (1.37, 19.52)	0.015	-	-

Univariate and multivariate logistic regression models, \*Adjusted by Sex and Age, COPD, and Diastolic blood pressure. Level of statistical significance=0.05. BUN: Blood urea nitrogen; LDH: lactate dehydrogenase

the onset of symptoms, (P=0.005). Moreover, univariate analysis identified that comorbidities, including hypertension (P<0.001), diabetes (P<0.001), COPD (P<0.001), chronic kidney disease (P=0.007), heart failure (P=0.013), and hyperlipoproteinemia (P=0.024) were significantly different between the two groups. These results are in accordance with those derived from a previous study, which might be on account of the higher prevalence of medical problems in the mentioned disease.<sup>6</sup> Having dyspnea (P<0.001), diarrhea (P<0.001), and chills (P<0.001) were the main clinical death-related symptoms. Furthermore, some laboratory findings and global CT scores remained significantly different between the two groups. As presented in table 2, the logistic model indicated that a history of COPD, hypoxia, and CT scores increased the odds of COVID-19 mortality. In the multivariate analysis, we also observed that pre-existing pulmonary disease was associated with the risk of mortality.

Regarding laboratory data, we found the influential role of neutrophil/ lymphocyte ratio, serum blood urea nitrogen (BUN) creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), sodium, potassium, calcium, and phosphorus levels on the risk of mortality (table 3), in addition to other clinical characteristics. Furthermore, our investigation showed a significant relationship between low hemoglobin concentrations and mortality. The multivariate predictive model also indicated that high neutrophil/ lymphocyte ratio (OR, 1.890; 95% CI, 1.074-3.325, P=0.027), increased creatinine levels (OR, 15.488; 95% CI, 0.801-299.479, P=0.07), and elevated potassium levels (OR, 13.400; 95% CI, 1.084-165.618, P=0.043) are independent risk factors of the fatality of COVID-19 (table 3).

## Discussion

The present study initially identified that a history of COPD, hypoxia, and CT scores increase the odds of COVID-19 mortality

related to COVID-19 infection. However, unlike previous reports,<sup>11-13</sup> our multivariate analysis showed that only pre-existing pulmonary disease was associated with the risk of mortality. This result may be attributed to further adjustment for potential confounders.<sup>14</sup> We also indicated the risk of mortality accompanied by other clinical characteristics, similar to the previous papers.<sup>15-17</sup> As suggested by Chan and colleagues, patients with high creatinine, BUN, and potassium levels had a higher odds ratio (OR) of COVID-19 mortality.<sup>18</sup> Additionally, our investigation revealed the significant relationship between low hemoglobin concentrations and mortality for the first time. We assumed that this result might be owing to the critical role of hemoglobin in carrying oxygen.<sup>19</sup> Further analysis in our study indicated the raised neutrophil/ lymph ratio, creatinine, and elevated potassium levels as independent risk factors of the fatality of COVID-19 (table 2), due to neutrophils' role in the innate immune response and the dose-dependent relationship between acute kidney injury (AKI) stages and death.<sup>16, 20</sup>

Despite numerous strengths of our study, certain limitations should be noted; our comparison relied on inpatients' data. There were possibly some cases that were not hospitalized, and the information in our study was related to only those who required medically attended care. Therefore, the community-based study of patients infected with COVID-19 is needed to confirm our results.

## Conclusion

This report indicated that a high neutrophil/ lymphocyte ratio, increased creatinine levels, and elevated potassium levels could independently predict mortality induced by COVID-19. These results emphasized the potential role of impaired laboratory parameters for the prognosis of fatal outcomes and their practical benefits regarding their ability to be used for the prognosis of fatal outcomes in adults with COVID-19. Our findings could also assist clinicians to recognize patients with a poor prognosis.

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**Conflict of Interest:** None declared.

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