# Clustering of Deceased Patients with COVID-19 in Iran Based on Clinical Features in Hospitalization

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## Abstract

***Background:*** Effective clinical care and identifying susceptibility to COVID-19-related mortality requires rapid recognition of risk factors and their relations with disease outcomes. This study aimed to cluster and identify various subgroups of COVID-19 patients and examine the relationship between these subgroups and the causes of death.

***Methods:*** This retrospective study assessed the risk factors contributing to COVID-19 patients' death (n = 128) by evaluating deceased patients' demographic, clinical, and laboratory features and clustering various subgroups of individuals to investigate any correlation.

***Results:*** The mean age of deceived patients was 69.7 years, and the majority of them were male (65.6%). The levels of blood urea nitrogen, creatinine, alkaline phosphatase, erythrocyte sedimentation rate, lactate dehydrogenase, and C-reactive protein were high at admission and increased during the hospitalization. Shortness of breath (68%) and cough (62.5%) were the most common symptoms, and hypertension (50.8%) was the most common comorbidity among deceased patients. The clustering quality based on the underlying disease and symptoms was not acceptable. However, clustering based on vital signs showed significant differences in body temperature, pulse rate, respiratory rate and oxygen saturation (P<0.001). Furthermore, disseminated intravascular coagulation (DIC) was significantly higher in patients with weaker vital signs than those with better vital signs (15.36% vs. 0.0% P = 0.002).

***Conclusion:*** Older age, male sex, hypertension, and high inflammatory markers might be the risk factors for COVID-19-related mortality. Furthermore, considering that patients with poor vital signs were susceptible to develop DIC, prevention of these consequences might be helpful in COVID-19 management.

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**Keywords:** Cluster Analysis; COVID-19; Mortality; Risk Factors

## Introduction

Coronavirus disease 2019 (COVID-19) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has an extensive range of severity and clinical features (1). In symptomatic patients, considerable fractions show acute respiratory distress syndrome (ARDS) occasionally followed by systemic and immunological overresponses with several organ complications, including thrombotic events, cardiac failure, kidney dysfunction, and gastrointestinal and neurological injuries.

Studies have shown that a high mortality rate is linked to several parameters, such as concomitant diseases, older age, and particular laboratory factors (2,3). The features of deceased COVID-19 patients have been investigated in various studies worldwide to implement preventive measures (4-7). For example, in Badedi et al., study on patients who died of COVID-19, hypertension, diabetes, and smoking along with respiratory failure were reported in most of the patients (7). Another case series by Nouri-Vaskeh et al., showed that male gender, older age, low oxygen saturation, high levels of erythrocyte

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sedimentation rate (ESR), and lactate dehydrogenase (LDH) were the mostly observed features in deceased COVID-19 patients. Hypertension and diabetes also had a high rate among these patients (8). Despite numerous investigations worldwide, the detailed pathogenesis of the disease and the relation of its prognostic factors with the disease severity and survival rate remain to be uncovered precisely (8).

Predictive models based on clinical data can assist the risk stratification. Patients with COVID-19 may have different conditions in terms of vital signs during hospitalization. Therefore, clustering and identifying various subgroups of these individuals and examining the relationship between these subgroups and the causes of death can help to better management of patients during the hospitalization period and perform more effective clinical support to prevent inevitable deaths.

In the current research, we performed a retrospective study for clustering deceased patients with COVID-19. We performed a comprehensive risk assessment by evaluating deceased patients' demographic, clinical, and laboratory features and clustering and identifying various subgroups of these individuals to investigate any correlation.

## Methods

This retrospective observational study was performed at the Imam Reza hospital of Tabriz, Iran, a referral center for COVID-19 patients who need hospitalization and intensive care unit (ICU) management. Patients who died from laboratory-confirmed COVID-19 between February to May 2020 were included in the study. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (ID: IR.TBZMED.REC.1399.302). All study processes were in line with the Helsinki Declaration of 1975, as revised in 2008.

We obtained demographic characteristics and epidemiological information, including comorbidities, symptoms and vital signs, laboratory findings, course of the disease, and outcome data (cause of death) using standard case report forms and electronic records of deceased patients.

Clustering is a data mining technique that uses an unsupervised approach to analyze data (9). Data are clustered based on maximizing similarity within groups and minimizing similarity between groups. The clustering technique can reveal hidden relationships and patterns of extensive data by dividing the study subjects into more homogeneous subgroups. Its primary purpose is to reduce a big set of data into similar small groups according to the similarities between the objects.

In this study, deceased patients were clustered based on different characteristics. Clustering based on all demographics, disease symptoms, underlying diseases, and vital signs variables together did not lead to significant results in demonstrating the correlation of these indicators with each other. Therefore, cluster analysis was performed three times: patients were once clustered in terms of disease symptoms, once clustered based on underlying diseases, and once based on the patient's vital signs at hospital admission.

### *Statistical analysis*

Continuous variables were shown as mean ± standard deviation (SD), and categorical variables were presented as frequency (percentage). All statistical analyses were conducted using SPSS version 23 (SPSS Inc., Chicago IL, USA).

The Two-Step cluster analysis technique performed clustering (10). The Two-step cluster investigation method is an exploratory tool for detecting intrinsic groupings in a data set. The distance selected for clustering was LIKELIHOOD, and Bayesian Information Criterion (BIC) was considered the goodness of fit index. The data were also standardized before analysis to reduce the effect of outlier data. The silhouette index was reported as the index for clustering quality, ranging from −1 to +1, showing whether the object is well matched to a specific cluster.

The distance criterion calculates the distance between clusters. Two types of distance criteria are used: the log-likelihood index and the Euclidean index. The log-likelihood index considers the normal distribution for continuous variables and polynomial distributions for discrete. All variables are considered independent. Euclidean Measures is the "direct" distance between two clusters. This criterion can only be used when all variables are continuous.

## Results

This study included a total of 128 cases. The patient's demographic and baseline clinical characteristics, including underlying chronic diseases, symptoms, vital signs, laboratory findings, disease course, comorbidities, and outcomes, are presented in Tables 1 and 2. All markers distributed separately in men and women patients also are shown in the tables mentioned above. Overall, 34.4% (44 of 128 patients) were female, and 65.6% (84 of 128 patients) were male. The mean age ± SD was 69.73 ± 1.25 years. The mean time (day) ±SD from the onset of symptoms to hospital admission and admission to death were 7.73 ± 0.98 and 9.13 ± 0.91, respectively (Table 1).

**Table 1. Baseline characteristics, vital signs, blood gas, and laboratory findings of patients**

| | Total | Female | Male |
|---|---|---|---|
| **Baseline characteristics** | | | |
| **Sex** | 128 (100%) | 44 (34.4%) | 84 (65.6%) |
| **Age** | 69.73 ± 1.25 | 69.16 ± 1.64 | 70.02 ± 1.7 |
| **Duration of Symptoms to admission** | 7.73 ± 0.98 | 8.57 ± 1.79 | 7.3 ± 1.18 |
| **Duration of admission to Death** | 9.13 ± 0.91 | 9 ± 1.55 | 9.19 ± 1.14 |

**Table 1.** Continued

| | Total | Female | Male |
|---|---|---|---|
| **Vital signs** | | | |
| **$SpO_2$, (%)** | 79.36 ± 1.2 | 78.88 ± 2.3 | 79.61 ± 1.39 |
| **RR, (breath/min)** | 24.58 ± 0.63 | 24.66 ± 1.2 | 24.55 ± 0.75 |
| **PR, (beat/min)** | 94.98 ± 1.7 | 92.95 ± 0.05 | 96.02 ± 2.17 |
| **SBP, (mmHg)** | 115.39 ± 2.57 | 113.11 ± 4.57 | 116.61 ± 3.11 |
| **DBP, (mmHg)** | 77.55 ± 1.56 | 75.97 ± 2.3 | 78.38 ± 2.06 |
| **BT, (°C)** | 37.08 ± 0.07 | 37.02 ± 0.1 | 37.1 ± 0.09 |
| **Arterial blood gas characteristics** | | | |
| **PH 1** | 7.33 ± 0.00 | 7.33 ± 0.01 | 7.33 ± 0.01 |
| **PH 2** | 7.19 ± 0.01 | 7.21 ± 0.02 | 7.19 ± 0.02 |
| **$PO_2$ 1, (mmHg)** | 43.99 ± 2.36 | 47.58 ± 4.32 | 42.13 ± 2.79 |
| **$PO_2$ 2** | 51.37 ± 2.56 | 52.99 ± 5.21 | 50.52 ± 2.82 |
| **$PCO_2$ 1, (mmHg)** | 41.05 ± 1.04 | 41.58 ± 1.62 | 40.78 ± 1.34 |
| **$PCO_2$ 2** | 54.63 ± 2.66 | 51.6 ± 4.34 | 56.23 ± 3.36 |
| **$FiO_2$ 1, (%)** | 33.32 ±2.1 | 31.51 ± 3.61 | 34.28 ± 2.6 |
| **$FiO_2$ 2** | 42.33 ± 2.96 | 38.17 ± 4.63 | 44.52 ± 3.8 |
| **Blood pressure 1** | 680.31 ± 8.52 | 676.21 ± 18.06 | 682.46 ± 8.98 |
| **Blood pressure 2** | 671.06 ± 9.33 | 649.47 ± 25.64 | 682.29 ± 4.6 |
| **BEecf1, (mmol/l)** | -2.1 ± 0.62 | -2.8 ± 0.96 | -1.74 ± 0.81 |
| **BEecf2** | -3.2 ± 1 | -3.02 ± 1.77 | -3.3 ± 1.22 |
| **Base excess 1, (mmol/l)** | -1.3 ± 0.79 | -2.72 ± 0.82 | -0.56 ± 1.12 |
| **Base excess 2** | -3.95 ± 0.88 | -2.93 ± 1.71 | -4.5 ± 1 |
| **Total buffer base 1, (mmol/l)** | 42.59 ± 1.02 | 41.79 ± 1.69 | 43.03 ±1.29 |
| **Total buffer base 2** | 39.02 ± 1.24 | 40.03 ± 2.23 | 38.45 ± 1.48 |
| **$HCO_3$ 1, (mmol/l)** | 22.59 ± 051 | 22.62 ± 0.83 | 22.57 ± 0.65 |
| **$HCO_3$ 2** | 22.40 ± 1.13 | 24.01 ± 3 | 21.55 ± 0.7 |
| **Laboratory findings** | | | |
| **Leukocyte1, (count/µl)** | 9639 ± 471 | 10490 ± 848 | 9182 ±560 |
| **Leukocyte2** | 12611 ± 631 | 13259 ± 1120 | 12272 ± 764 |
| **Neutrophils 1, (%/µl)** | 80.35 ± 1.65 | 79.55 ± 3.48 | 80.81 ± 1.71 |
| **Neutrophils 2** | 86.24 ± 2.2 | 86.38 ± 1.79 | 86.15 ± 3.58 |
| **Lymphocyte 1, (%/µl)** | 11.9 ± 0.75 | 12.70 ± 1.61 | 11.4 ± 0.8 |
| **Lymphocyte 2** | 8.04 ± 0.8 | 10.18 ± 1.32 | 6.97 ± 1 |

**Table 1.** Continued

| | Total | Female | Male |
|---|---|---|---|
| **Hemoglobin 1, (g/dl)** | 12.68 ± 0.21 | 11.02 ± 0.28 | 13.55 ± 0.24 |
| **Hemoglobin 2** | 11.17 ± 0.24 | 9.97 ± 0.37 | 11.82 ± 0.28 |
| **Platelet 1, (count/µl)** | 191958 ± 9473 | 225827 ± 17768 | 173522 ± 10492 |
| **Platelet 2** | 199524 ± 12144 | 221973 ±21410 | 187487 ± 14616 |
| **Urea 1, (mg/dl)** | 71.15 ± 4.76 | 65.42 ± 6.78 | 74.12 ± 6.31 |
| **Urea 2** | 101.28 ± 6.05 | 86.07 ± 9.26 | 109.91 ± 7.75 |
| **Creatinine1, (mg/dl)** | 1.96 ± 0.18 | 2.1 ± 0.35 | 1.89 ± 0.2 |
| **Creatinine 2** | 2.09 ± 0.14 | 2.01 ± 0.23 | 2.14 ± 0.18 |
| **AST 1, (U/L)** | 120.69 ± 36.72 | 92.83 ± 47.8 | 136.76 ± 51.12 |
| **AST 2** | 58.93 ± 6.79 | 37.5 ± 4.88 | 71.30 ± 9.98 |
| **ALT 1, (U/L)** | 98.09 ± 30.87 | 94.23 ± 53.32 | 100.32 ± 38.14 |
| **ALT 2** | 53.64 ± 9.14 | 46.03 ± 19.3 | 58.03 ± 9.28 |
| **ALP 1, (U/L)** | 190.43 ± 8.96 | 190.4 ± 16.97 | 191.2 ± 10.67 |
| **ALP 2** | 227.7 ± 11.74 | 230.14 ± 24.15 | 223.95 ± 12.7 |
| **ESR 1, (mm/h)** | 45.26 ±3.69 | 58 ± 8.37 | 41.36 ± 3.98 |
| **ESR 2** | 62.45 ± 6.66 | 63.87 ± 10.1 | 61.64 ± 9 |
| **CRP 1 (qualitative)** | 1.9 ± 0.13 | 1.77 ± 0.27 | 1.95 ± 0.14 |
| **CRP 2** | 2.26 ± 0.34 | 2.8 ± 0.58 | 2 ± 0.42 |
| **LDH 1, (U/L)** | 824.1 ± 52.24 | 805.71 ± 87.79 | 711.85 ± 98.39 |
| **LDH 2** | 863.07 ± 62.48 | 837.41 ± 65.07 | 968.93 ± 76.37 |
| **Serum sodium 1, (mEq/L)** | 136.62 ± 0.45 | 136.34 ± 0.85 | 136.77 ± 0.52 |
| **Serum sodium 2** | 139.32 ± 0.59 | 137.43 ± 0.6 | 140.33 ± 0.83 |
| **Serum potassium 1, (mEq/L)** | 4.2 ± 0.06 | 4.2 ± 0.1 | 4.27 ± 0.07 |
| **Serum potassium 2** | 4.3 ± 0.69 | 4.21 ± 0.12 | 4.47 ± 0.07 |
| **Prothrombin time 1, (s)** | 16.96 ± 1.04 | 15.51 ± 1.22 | 17.83 ± 1.48 |
| **Prothrombin time 2** | 17.59 ± 0.87 | 16.23 ± 0.71 | 18.29 ± 1.31 |
| **INR1** | 1.33 ± 0.08 | 1.29 ± 0.08 | 1.37 ± 0.11 |
| **INR2** | 1.4 ± 0.08 | 1.3 ± 0.06 | 1.46 ± 0.13 |
| **aPTT 1, (s)** | 82.71 ± 2.19 | 88.52 ± 2.36 | 79.47 ± 3.02 |
| **aPTT 2** | 76.22 ± 2.33 | 84.9 ± 3.33 | 72.3 ± 2.92 |

Values are shown as number (%) for categorical data and mean ± SD for continuous data. For all variables, two values are expressed as 1 for admission time and 2 for the final test of patients.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BEecf, base excess in the extracellular fluid; CRP, C-reactive protein; $FiO_2$, the fraction of inspired oxygen; INR, international normalized ratio; SpO2, oxygen saturation; $PCO_2$, partial pressure of carbon dioxide; PO2, partial pressure of oxygen; Bicarbonate ($HCO_3$); LDH, lactate dehydrogenase

### *Vital signs*

For all patients, the vital signs of pulse rate (PR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature (BT), and saturation of oxygen (SpO2), were recorded at the time of admission. As it is presented in table 1, patients had lower SpO2 (79.36 ± 1.2) than the normal range (>90%) and a higher RR (24.58 ± 0.63 compared to the normal range of 12-18 beat/min).

### *Arterial blood gas characteristics*

The partial pressure of oxygen (PO2), the fraction of inspired oxygen (FiO2), partial pressure of carbon dioxide (PCO2), base excess in the extracellular fluid (BEecf), base excess (BEB), total buffer base (BB), and bicarbonate (HCO3) levels were collected in first (time of admission) and the last record of patients' blood gas characteristics. As shown in Table 1, the patient's condition changed to acidosis from the hospitalization process until death. There are changes in PH levels (7.19 to 7.33), BB (39.02 to 42.59), and BEB (-1.3 to -3.95) to lower than the normal values (PH: 7.35-7.45, BB: 48-49 mmol/L, BEB: -2 to +2 mEq/L) and an increase in PCO2 level (from 41.05 to 54.03) to higher than normal value (35 to 45 mmHg).

### *Laboratory findings*

The laboratory test results are presented in Table 1. Laboratory data were complete blood count (CBC), serum potassium (K), sodium (Na), ESR, C-reactive protein (CRP), LDH, blood urea nitrogen, creatinine, coagulation tests [international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT)], alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). In the course of the disease, patients showed leukocytosis and neutrophilia besides the lymphocytopenia. Furthermore, the downward trend in hemoglobin and liver enzymes of AST and ALT were recorded. In addition to the upward trend in ALP and inflammatory markers of LDH, ESR, and CRP, the initial amount of these factors was also high at admission. The kidney function indexes of blood urea nitrogen and creatinine also are higher than the normal range and increased during the hospitalization.

### *Symptoms at disease onset*

The symptoms that appeared from the onset of the disease till the admission time were presented in Table 2, which include: fever, cough, fatigue, anorexia, myalgia, shortness of breath, sputum production, hemoptysis, sore throat, diarrhea, nausea, abdominal pain, headache, weakness, and chills. The incidence of most commonly experienced symptoms was as follows: shortness of breath (68%), cough (62.5%), fever (45.5%), myalgia (27.3%), and weakness (25.8%). Less frequent symptoms were abdominal pain and sore throat (0.8%). There was no significant difference in the occurrence of the symptoms in both females and males except for headache, which was reported to be nearly four times higher ($P<0.05$) in males (16.7%) than in females (4.5%).

**Table 2. Symptoms, comorbidities, medical interventions, and complications of patients.**

| | Total 128 (100%) | Female 44 (34.4%) | Male 84 (65.6%) |
|---|---|---|---|
| **Symptoms at disease onset** | | | |
| **Fever** | 58 (45.3%) | 18 (40.9%) | 40 (47.6%) |
| **Cough** | 80 (62.5%) | 27 (61.4%) | 53 (63.1%) |
| **Anorexia** | 11 (8.65) | 4 (9.1%) | 7 (8.3%) |
| **Myalgia** | 35 (27.3%) | 8 (18.2%) | 27 (32.1%) |
| **shortness of breath** | 87 (68%) | 30 (68.2%) | 57 (67.9%) |
| **Sputum production** | 12 (9.4%) | 3 (6.8%) | 9 (10.7%) |
| **Hemoptysis** | 5 (3.9%) | 1 (2.3%) | 4 (4.8%) |
| **Sore throat** | 1 (0.8%) | 0 | 1 (1.2%) |
| **Diarrhea** | 3 (2.45) | 0 | 3 (3.6%) |
| **Nausea** | 16 (12.5%) | 8 (18.2%) | 8 (9.5%) |
| **Abdominal pain** | 1 (0.8%) | 0 | 1 (1.2%) |
| **Headache** | 16 (12.5%) | 2 (4.5%) | 14 (16.7%) |
| **Weakness** | 33 (25.8%) | 13 (29.5%) | 20 (23.8%) |
| **Chills** | 19 (14.8%) | 5 (11.4%) | 14 (16.7%) |

**Table 2.** Continued

| | Total 128 (100%) | Female 44 (34.4%) | Male 84 (65.6%) |
|---|---|---|---|
| **Comorbidities** | | | |
| **Hypertension** | 65 (50.8%) | 31 (70.5%) | 34 (40.5%) |
| **Diabetes** | 46 (35.9%) | 19 (43.2%) | 27 (32.1%) |
| **Cardiovascular disease** | 34 (26.6%) | 10 (22.7%) | 24 (28.6%) |
| **Hyperlipidemia** | 10 (7.8%) | 4 (9.1%) | 6 (7.1%) |
| **Chronic lung diseases** | 24 (18.8%) | 9 (20.5%) | 15 (17.9%) |
| **Malignancy** | 3 (2.4%) | 0 | 3 (3.6%) |
| **Cerebrovascular disease** | 5 (3.9%) | 2(4.7%) | 3 (3.6%) |
| **Hypothyroidism** | 4 (3.1%) | 2 (4.5%) | 2 (2.4%) |
| **Chronic kidney disease** | 6 (4.7%) | 5 (11.4%) | 1 (1.2%) |
| **Autoimmune disease** | 1 (0.8%) | 1 (2.3%) | 0 |
| **Medical interventions** | | | |
| **Dialysis** | 47 (36.7%) | 17 (38.6%) | 30 (35.7%) |
| **IV antibiotic** | 93 (72.7%) | 30 (68.2%) | 63 (75%) |
| **Complications** | | | |
| **Heart failure** | 7 (5.5%) | 3 (6.8%) | 4 (4.8%) |
| **Encephalopathy** | 6 (4.7%) | 2 (4.5%5) | 4 (4.8%) |
| **DIC** | 4 (3.1%) | 1 (2.3%) | 3 (3.6%) |
| **AKI** | 6 (4.7%) | 3 (6.8%) | 3 (3.6%) |
| **ARDS** | 71 (55.5%) | 21 (47.7%) | 36 (42.9%) |
| **Cardiac arrest** | 106 (83.5%) | 37 (84.1%) | 69 (83.1%) |

Values presented as number (%).

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; IV, intravenous

### *Comorbidities*

Hypertension (50.8%), diabetes (35.9%), cardiovascular disease (26.6%), and chronic lung diseases (18.8%) were the most common comorbidities. The incidence of comorbidities was similar in both sexes except for hypertension (70.5% versus 40.5%, P<0.01) and CKD (11.4% versus 1.2%, P<0.05), which were higher in women.

### *Medical intervention and complications*

Most patients received intravenous antibiotics (72.7%), and some needed dialysis during hospitalization (36.7%). The two leading causes of death in patients were cardiac arrest (83.5%) and ARDS (55.5%). Furthermore, patients presented multiple vital organ damages, including heart failure (HF, 5.5%), encephalopathy (4.7%), DIC (3.1%), and acute kidney injury (AKI, 4.7%).

### *Clustering of data*

According to the BIC index, models with 2 clusters were selected automatically by the two-step clustering method for all three cluster analyses.

Regarding the clustering based on disease symptoms, results showed that the first cluster had patients with more symptoms while the second cluster had a lower percentage of symptoms. Moreover, according to the rate of underlying disease, the clustering results indicated two groups. In general, according to the silhouette index, the quality of clustering based on the underlying disease and symptoms was not acceptable.

Eighty-eight patients entered the cluster analysis (the rest had missing observations). Results indicated that there were two hidden clusters among patients. The first cluster consisted of patients with weaker vital signs (29.5% of the sample), while the second cluster consisted

of patients with better vital signs (70.5% of the sample). Cluster quality with silhouette index was moderate: 0.45 (the closer one, the better the cluster quality).
After clustering, the results of the t-test showed a significant difference in most vital signs (except systolic and diastolic blood pressure) between the two clusters (Table 3).
Furthermore, we compared all recorded factors in these two subgroups. In addition to the indicated significant difference in vital signs, there were great differences in some indexes like lymphocyte, platelet, ALP, LDH, and incidence of DIC and AKI (Table 4).

**Table 3. Clustering of data based on vital signs**

| | Clusters (better or weaker vital signs) | N | Mean | Standard deviation | Minimum | Maximum | P-value |
|---|---|---|---|---|---|---|---|
| **SpO2** | Weak | 26 | 69.69 | 16.60 | 40.0 | 89.0 | <.001 |
| | Better | 62 | 85.18 | 6.73 | 69.0 | 99.0 | |
| | Total | 88 | 80.60 | 12.71 | 40.0 | 99.0 | |
| **RR** | Weak | 26 | 30.30 | 7.92 | 14.0 | 50.0 | <.001 |
| | Better | 62 | 22.06 | 4.83 | 14.0 | 33.0 | |
| | Total | 88 | 24.50 | 6.98 | 14.0 | 50.0 | |
| **PR** | Weak | 26 | 106.46 | 21.68 | 78.0 | 160.0 | .002 |
| | Better | 62 | 92.56 | 17.57 | 53.0 | 140.0 | |
| | Total | 88 | 96.67 | 19.80 | 53.0 | 160.0 | |
| **SBP** | Weak | 26 | 111.42 | 20.46 | 60.0 | 153.0 | .43 |
| | Better | 62 | 116.37 | 29.25 | 60.0 | 185.0 | |
| | Total | 88 | 114.90 | 26.93 | 60.0 | 185.0 | |
| **DBP** | Weak | 26 | 76.92 | 14.93 | 50.0 | 115.0 | .56 |
| | Better | 62 | 79.14 | 17.0 | 60.0 | 145.0 | |
| | Total | 88 | 78.48 | 16.36 | 50.0 | 145.0 | |
| **BT** | Weak | 26 | 37.60 | 1.04 | 35.5 | 39.3 | <.001 |
| | Better | 62 | 36.88 | .49 | 35.0 | 38.0 | |
| | Total | 88 | 37.09 | .77 | 35.0 | 39.3 | |

$P \leq 0.05$ is statistically significant analyzed by t-test.

BT, body temperature; DBP, diastolic blood pressure; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure; SpO2, oxygen saturation

**Table 4. The difference in clusters (patients with weaker vital signs and patients with better vital signs)**

| | Cluster, vital sign | N | Mean (standard error) | P-value |
|---|---|---|---|---|
| **Lymph1** | weak | 20 | 17.24 (2.8) | 0.61 |
| | better | 57 | 12.77 (0.98) | |
| **Lymph2** | weak | 18 | 12.45 (3.83) | 0.74 |
| | better | 52 | 7.83 (0.72) | |
| **Platelet1** | weak | 25 | 211344 (22029) | 0.99 |
| | better | 60 | 172888 (11707) | |
| **ALP1** | weak | 24 | 282.45 (66.49) | 0.79 |
| | better | 54 | 195.68 (14.08) | |
| **LDH2** | weak | 11 | 1046.27 (194.26) | 0.99 |
| | better | 30 | 795.13 (56.6) | |
| | Cluster, vital sign | N | Number (%) | P value |
| **AKI** | weak | 26 | 4 (15.36 %) | 0.4 |
| | better | 62 | 2 (3.22%) | |
| **DIC** | weak | 26 | 4 (15.36%) | 0.002 |
| | better | 62 | 0 | |

$P \leq 0.05$ is statistically significant analyzed by t-test. For all variables, two values are expressed as 1 for admission time and 2 for the final test of patients.
AKI, acute kidney injury; ALP, alkaline phosphatase; DIC, disseminated intravascular coagulation; LDH, lactate dehydrogenase

## Discussion

Despite the growing knowledge in COVID-19 pathophysiology, the precise causes of mortality remain unknown. Knowing potential factors that increase the mortality risk among COVID-19 patients is pivotal for better management of the disease. This study investigated the potentially influential factors in COVID-19 patients' death.

Similar to our results, Zhang et al., showed that most of the COVID-19 patients who have died had ages of more than 60 years (80.5%), male sex (66%), lymphopenia (73.7%), neutrophilia (100%), and hypertension (56%) (11). In this study, respiratory failure was responsible for the death of 69.5% of cases. We reported cardiac arrest as the leading cause of death in patients. Even though respiratory failure and cardiac arrest are distinct conditions, one can cause another if untreated.

In a retrospective cohort study, Chen et al., compared the clinical characteristics of deceased (n = 113) and recovered (116) COVID-19 patients. The results revealed that the median age of patients (68 versus 51 years), rate of male sex (73% versus 55%), and hypertension (48% versus 24%) were significantly higher among the deceased group.6 Several mechanisms were proposed for the sex-related differences in the COVID-19 severity Males express more transmembrane protease serine 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) receptors, which helps SARS-CoV-2 enter the host cells (12).

Similar to our results, several studies find hypertension the overwhelming risk factor for severe COVID-19 (3). In a meta-analysis of 24 observational studies on 99,918 COVID-19 patients, hypertension was associated with 2.17 times greater risk of death from COVID-19 (adjusted odds ratio: 2.17; 95% CI, 1.67-2.82; $P < 0.001$) (13).

Several studies suggested ACE inhibitors and angiotensin receptor blockers (ARBs) might facilitate viral cell entry by upregulating the ACE2 receptors (14,15). Conversely, in another view, SARS-CoV-2-induced ACE2 downregulation and subsequent rise in angiotensin II might be alleviated by ACE inhibitor and ARB use. Although the exact link is not fully understood, hypertension considerably increases the vulnerability to SARS-CoV-2 infection, serious disease, and death (16,17).

In the Open SAFELY trial on 17 million patients with COVID-19, male sex (hazard ratio 1.59, 95% CI 1.53-1.65), diabetes, older age, and severe asthma were the significant risk factors for COVID-19-related death (18). According to our results, chronic lung disease is fourth among the comorbidities observed in deceased COVID-19 patients. Inhalational corticosteroid use in patients with asthma and chronic obstructive pulmonary disease might have protective effects against severe COVID-19. However, further studies are required to confirm this hypothesis (19).

In our study, the mean age of deceased patients was 69.7 years, highlighting the importance of older age as a risk factor in COVID-19 mortality. Older patients are more likely to have other comorbidities, contributing to an increased rate of death in patients with COVID-19. However, in a cohort of 470,034 patients with COVID-19, older age was linked with a higher mortality rate independent of other risk factors such as hypertension, obesity, and smoking. In this study, patients over 75 years without other risk factors had a 4-times higher mortality risk compared to patients aged less than 65 years (95% CI 1.57–9.96, $P = 0.004$) (20).

According to the clustering results of this study, there were differences in some indexes like lymphocyte, platelet, ALP, LDH, and incidence of DIC and AKI in two clusters of patients with weaker vital signs and patients with better vital signs. The levels of lymphocyte, platelet, ALP, and LDH at admission can be interpreted as the risk factors for precipitating the patient's vital signs. Furthermore, patients with poor vital status might significantly have a higher rate of DIC, which can be very important in preventing these consequences.

Various studies reported a substantial correlation between vitals at baseline and COVID-19-related death rate. Older age, male gender, high BMI, hypertension, elevated D-dimer, and LDH were considerably associated with severe COVID-19 (21-23). A cross-sectional study was conducted in Mashhad city of Iran on inpatients with different severities of COVID-19. Their results indicated that the severity of the disease was highly correlated with the patient's age and malignant comorbidities. In this report, SpO2, nausea, vomiting, and the degree of lung involvement were considered independent predictors of severe disease (24).

This study might have some limitations. This work was a single-center study that was performed in a limited time. Also, several confounding factors might exist.

Identifying susceptibility to COVID-19-related mortality based on admission time risk factors might assist health care providers in performing timely and efficient care based on each patient's measures. Older age, male sex, hypertension, and high inflammatory markers can be interpreted as the risk factors for COVID-19-related mortality. Furthermore, considering that patients with poor vital signs were susceptible to develop DIC, prevention of these consequences might be helpful in COVID-19 management.

## Conflict of Interest:

The authors declare no conflict of interest.

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