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Risk Factors for In-hospital Mortality of Patients with COVID-19 in Iran: A Cross-sectional Study from Six Pandemic Waves

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Abstract

Background: Demographic factors, hospital status, and comorbidities affect the mortality of patients with coronavirus disease (COVID-19).

Aim: This cross-sectional study was performed with aim to evaluate the mortality predictors of hospitalized COVID-19 patients in northeastern Iran (Mashhad city).

Method: In this retrospective study, the electronic records (demographic data, clinical variables, and comorbid conditions) of survived and non-survived hospitalized COVID-19 patients were searched from March 2021 to March 2022 during six pandemic waves.

Results: Analysis of 59099 hospitalized COVID-19 patients showed the mean age of 54.4722.5 years (female: 46.92%). Binary logistic regression analysis showed that age, masculinity, respiratory distress, and loss of consciousness among demographic data and clinical variables significantly contributed to mortality (OR>1, P<0.05). Diabetes, cancer, respiratory diseases, kidney diseases, and immunodeficiency diseases increased the chance of death. High SpO_2 (>93) protected against death (OR<1, P<0.05).

Implications for Practice: The results of the present study revealed that the clinical outcome of COVID-19 infection is highly affected by demographic, clinical, and comorbidity factors. Several factors including age, masculinity, respiratory distress, loss of consciousness, diabetes, cancer, respiratory, kidney and immunodeficiency diseases had a risk effect on COVID-19 death during six pandemic waves. Also, high SpO_2 (>93) was detected as a protective factor for death followed by COVID-19 infection.

Keywords: COVID-19, Hospital mortality, Pandemics, Risk factors

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Introduction

Coronavirus disease (COVID-19), followed by acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has infected millions of people worldwide since the end of 2019 (1, 2). Initially, acute respiratory failure caused by SARS-CoV-2 and the rapid incidence of coronavirus disease (COVID-19) has emerged as a hot topic in medicine (3). However, the prevalence became widespread and mortality rate increased. Governments and health policymakers faced a serious crisis with COVID-19 death (4). To date, more than 6.5 million people have died from the severity of COVID-19-related symptoms (5). Also in Iran, since the definitive diagnosis of the first infected person on February 19, 2020 (6, 7), the number of infected cases and COVID-19 deaths peaked in six time periods (waves) from March 5, 2020 to March 6, 2022 (8).

One of the most common ways to control from the mortality rate of the disease and more effective health policies is to estimate the risk factors for death associated with the disease (9). Several risk factors for COVID-19 death are known, such as age (10, 11), gender (12, 13), respiratory problems (14, 15), diabetes (16-18), cardiovascular (19, 20), blood pressure (21, 22), kidney diseases (23), and other comorbidities (11, 24, 25). Parohan et al. (2020) analyzed 14 retrospective cohort studies and concluded that older age (>65 years), male gender, hypertension, cardiovascular diseases (CVDs), diabetes, and chronic obstructive pulmonary disease (COPD) were associated with a higher risk of death from COVID-19 (26). In another meta-analysis, 58 cohort studies were analyzed and the findings showed that older age, male gender, hospitalization in the intensive care unit (ICU), and comorbidities (older age, gender, obesity, hypertension, CVDs, cancer, and diabetes) were associated with mortality in hospitalized patients with COVID-19 (27). Also, a multi-center and cross-sectional study which was conducted in 19 public hospitals in Tehran (the capital and most populated city of Iran) reported that older age, male gender, hospitalization in the ICU or critical care unit (CCU) and underlying comorbidities (e.g. CVDs and diabetes) were associated with mortality rate in COVID-19 patients (28). Despite the importance of detection of risk factors for mortality in COVID-19 patients, there remains a paucity of evidence on COVID-19 death in different pandemic waves. The present study was performed with aim to investigate the risk and protective factors (i.e., demographics factors, hospital status, and comorbidities) associated with COVID-19 death in six pandemic waves in northeastern Iran.

Methods

This retrospective cross-sectional study was performed on the hospitalized COVID-19 patients from March 5, 2021 to March 6, 2022 in Mashhad city. Data were collected from medical care monitoring center (MCMC) database. Individuals with symptomatic COVID-19 and/or with quantitative positive reverse transcript polymerase chain reaction (qRT-PCR) SARS-CoV-2 test were included in this study. The number of patients for the first wave was 4634 patients (from March 5 to April 6, 2020), the second wave was 7647 (from June 27 to August 6, 2020), the third wave was 8429 (from October 8 to December 3, 2020), the fourth wave was 11841 (from April 1 to June 11, 2021), the fifth wave was 19307 (from June 22 to September 23, 2021), and the sixth wave was 7241 (from January 15 to March 21, 2022). Electronic records were compared between survivors and non-survivors, which survivors were discharged from hospital and non-survivors died at the hospital followed by COVID-19 infection.

Demographic data, such as age and gender were included in this study. Respiratory distress, loss of consciousness, and oxygen saturation levels (SpO_2) were also collected as hospital status parameters. Comorbidities, such as cancer, diabetes, respiratory diseases, kidney, liver, cardiovascular, blood, immunodeficiency (acquired immunodeficiency syndrome and other immunodeficiencies), neurological, and other diseases were included in this analysis.

Respiratory distress was defined as the acute onset of oedema and non-cardiogenic pulmonary hypoxemia (29). Loss of consciousness was defined as a temporary and transient period of inability to maintain posture and environmental awareness (30). SpO_2 (oxygen saturation levels) was defined as the change in intracellular oxygen pressure in millimeters of mercury (mm Hg), and less than 93 mmHg was considered the critical cut-off point (31). All comorbidities and disorders were diagnosed by specialist physicians based on valid medical guidelines and medical history.

Data were analyzed by SPSS (version 22.0). The continuous variables were presented as mean ± standard deviation, while the categorical data were expressed as numbers and percentages. The variables that presented significant differences in the univariate analysis were considered for analysis using binary logistic regression to verify the association between the independent demographic data, hospital status, and comorbidities risk factors and mortality as the dependent variable. The results were expressed as a 95% confidence interval (CI) and odds ratio (OR). P<0.05 was considered statistically significant.

Results

A total of 59099 patients (27728 women) in all waves were included in this study. The mean age of participants was 54.47±22.5 years (median age of 58 years). Table 1 shows descriptive information related to deceased and living patients separately for each wave according to the studied variables.

Table 1. Demographic data, hospital status and comorbidities of patients in different waves based on being alive and dead

Variable	First Wave			Second Wave			Third Wave			Fourth Wave			Fifth Wave			Sixth Wave		
	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Daed	Total	Alive	Dead	Total	Alive	Dead	Total
Demographic Data																		
Age (M±SD)	54.21± 19.53	67.13± 16.80	56.44± 19.70	56.50± 20.53	66.72± 16.26	58.98± 20.06	54.61± 22.28	67.26 ±17.39	57.07± 21.99	52.87± 21.94	66.46 ±17.10	54.46 ± 21.87	49.68 ± 22.33	62.66± 17.15	52.67 ± 21.94	49.24 ±27.76	69.28 ±18.76	50.36 ± 27.72
Gender (n (%))																		
Woman	1608 (34.7)	286 (6.2)	1894 (40.9)	2747 (35.9)	722 (9.4)	3469 (45.4)	3203 (38)	651 (7.7)	3854 (45.7)	5000 (42.2)	598 (5.1)	5598 (47.3)	7377 (38.2)	1994 (10.3)	9371 (48.5)	3369 (46.5)	173 (2.4)	3542 (48.9)
Man	2225 (48)	515 (11.1)	2740 (59.1)	3065 (40.1)	1113 (14.6)	4178 (54.6)	3602 (42.7)	973 (11.5)	4575 (54.3)	5481 (46.3)	762 (6.4)	6243 (52.7)	7480 (38.7)	2456 (12.7)	9936 (51.5)	3466 (47.9)	233 (6.3)	3699 (51.1)
Total	3833 (82.7)	801 (17.3)	4634 (100)	5812 (76)	1835 (24)	7647 (100)	6805 (80.7)	1624 (19.3)	8429 (100)	10481 (88.5)	1360 (11.5)	11841 (100)	14857 (77)	4450 (23)	19307 (100)	6835 (94.4)	406 (5.6)	7241 (100)
Hospital status (n (%))																		
Respiratory distress	2239 (79.3)	586 (20.7)	2825 (61)	3817 (72.1)	1480 (27.9)	5297 (69.3)	4276 (77)	1279 (23)	5555 (65.9)	6298 (85.7)	1050 (14.3)	7348 (62.1)	9877 (73.6)	3547 (26.4)	13424 (69.5)	3403 (92.2)	287 (7.8)	3690 (51)
Loss of consciousness	281 (52.1)	258 (47.9)	539 (11.6)	652 (56.9)	493 (43.1)	1145 (15)	358 (50.5)	351 (49.5)	709 (8.4)	350 (61.7)	217 (38.3)	567 (4.8)	416 (42.9)	553 (57.1)	969 (5)	293 (82.3)	63 (17.7)	356 (4.9)
Low SpO_2 (<93)	1844 (73)	681 (27)	2525 (54.5)	3648 (68.5)	1675 (31.5)	5323 (69.6)	3935 (73.9)	1390 (26.1)	5325 (63.2)	5319 (82.9)	1094 (17.1)	6413 (54.2)	9704 (71.2)	3931 (28.8)	13635 (70.6)	2866 (90.9)	288 (9.1)	3154 (43.6)
Comorbidities (n (%))																		
Diabetes	488 (76.5)	150 (23.5)	638 (13.8)	1123 (72.4)	428 (27.6)	1551 (20.3)	1297 (75.5)	422 (24.5)	1719 (20.4)	1294 (84.8)	232 (15.2)	1526 (12.9)	1441 (69.3)	638 (30.7)	2079 (10.8)	1083 (93.3)	78 (6.7)	1161 (16)
Cancer	96 (69.6)	42 (30.4)	138 (3)	149 (69.3)	66 (30.7)	215 (2.8)	237 (77.7)	68 (22.3)	305 (3.6)	222 (84.1)	42 (15.9)	264 (2.2)	243 (83.2)	49 (16.8)	292 (1.5)	298 (94)	19 (6)	317 (4.4)
Respiratory diseases	94 (73.4)	34 (26.6)	128 (2.8)	158 (65.3)	84 (34.7)	242 (3.2)	193 (73.4)	70 (26.6)	263 (3.1)	184 (81.8)	41 (18.2)	225 (1.9)	152 (68.2)	71 (31.8)	223 (1.2)	289 (88.4)	38 (11.6)	327 (4.5)
Blood pressures diseases	134 (87.6)	19 (12.4)	153 (4.2)	1210 (72.8)	451 (27.2)	1661 (2.7)	1462 (75.2)	481 (24.8)	1943 (23.1)	1519 (84.3)	283 (15.7)	1802 (15.2)	1641 (70.9)	672 (29.1)	2313 (12)	1375 (92.5)	111 (7.5)	1486 (20.5)
Kidney diseases	102 (73.4)	37 (26.6)	139 (3)	193 (69.9)	83 (30.1)	276 (3.6)	156 (81.3)	36 (18.8)	192 (2.3)	176 (86.7)	27 (13.3)	203 (1.7)	176 (75.2)	58 (24.8)	234 (1.2)	254 (924)	21 (7.6)	275 (3.8)
Neurological diseases	58 (72.5)	22 (27.5)	80 (1.7)	114 (68.3)	53 (31.7)	167 (2.2)	108 (74.5)	37 (25.5)	145 (1.7)	108 (78.3)	30 (21.7)	138 (1.2)	122 (78.2)	34 (21.8)	156 (0.8)	124 (94.7)	7 (5.3)	131 (1.8)
Cardiovascular diseases	452 (78.9)	121 (21.1)	573 (12.4)	732 (73.9)	259 (26.1)	991 (13)	875 (77.5)	254 (22.5)	1129 (13.4)	1033 (85.4)	176 (14.6)	1209 (10.2)	923 (71.7)	364 (28.3)	1287 (6.7)	878 (92.3)	73 (7.7)	951 (13.1)
Immunodeficiency	12 (63.2)	7 (36.8)	19 (0.4)	12 (75)	4 (25)	16 (0.2)	30 (93.8)	2 (6.3)	32 (0.4)	10 (71.4)	4 (28.6)	14 (0.1)	23 (85.2)	4 (14.8)	27 (0.1)	31 (100)	0 (0)	31 (0.4)
Liver diseases	25 (75.8)	8 (24.2)	33 (0.7)	50 (72.5)	19 (27.5)	69 (0.9)	54 (80.6)	13 (19.4)	67 (0.8)	70 (88.6)	9 (11.4)	79 (0.7)	68 (75.6)	22 (24.4)	90 (0.5)	69 (94.5)	4 (5.5)	73 (1)

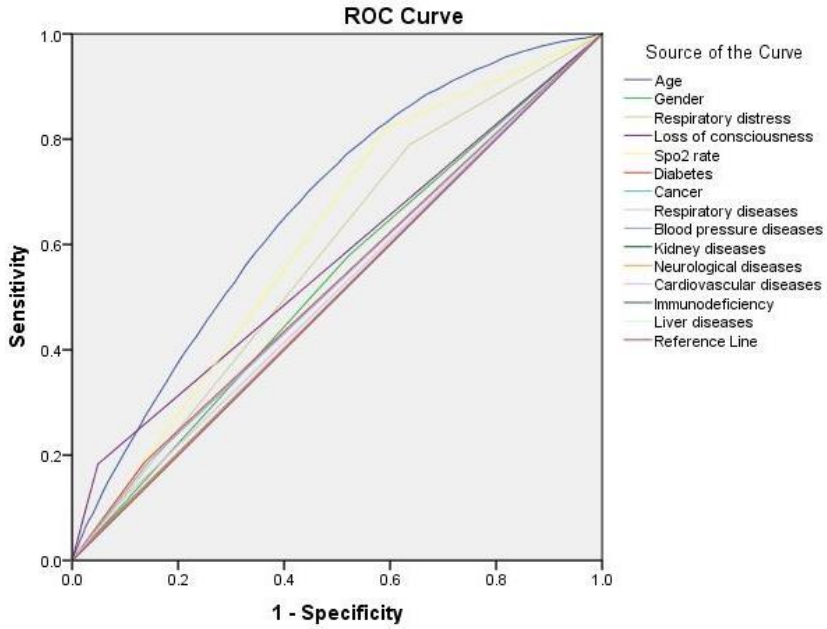

Figure 1. Sensitivity, specificity and accuracy of binary logistic regression

Table 2. Binary logistic regression results to investigate the role of demographic data, hospital status and comorbidities in the death of patients

Variable	First wave		Second wave		Third wave		Fourth wave		Fifth wave		Sixth wave	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Demographic data												
Age	1.033 (1.027-1.09)	<0.001	1.025 (1.021-1.028)	<0.001	1.026 (1.023-1.03)	<0.001	1.03 (1.027-1.034)	<0.001	1.029 (1.027-1.031)	<0.001	1.031 (1.025-1.037)	<0.001
Gender (Men to Women)	1.434 (1.182-1.739)	<0.001	1.298 (1.156-1.458)	<0.001	1.35 (1.157-1.473)	<0.001	1.14 (1.01-1.288)	0.034	1.198 (1.115-1.287)	<0.001	1.227 (0.995-1.513)	0.056
Hospital Status												
Respiratory distress	1.507 (1.228-1.85)	<0.001	1.76 (1.524-2.032)	<0.001	1.494 (1.289-1.732)	<0.001	1.417 (1.219-1.647)	<0.001	1.14 (1.038-1.253)	0.006	1.492 (1.173-1.899)	0.001
Loss of consciousness	4.661 (3.654-5.947)	<0.001	2.656 (2.295-3.075)	<0.001	4.407 (3.696-5.254)	<0.001	4.259 (3.497-5.188)	<0.001	4.088 (3.545-4.715)	<0.001	3.444 (2.52-4.707)	<0.001
High SpO_2 (>93)	0.198 (0.156-0.251)	<0.001	0.214 (0.179-0.255)	<0.001	0.334 (0.284-0.393)	<0.001	0.37 (0.317-0.432)	<0.001	0.348 (0.312-0.388)	<0.001	0.532 (0.419-0.676)	<0.001
Comorbidities												
Diabetes	1.247 (0.966-1.609)	0.091	1.023 (0.883-1.184)	0.765	1.167 (1.006-1.354)	0.041	1.116 (0.937-1.33)	0.218	1.212 (1.076-1.366)	0.002	0.846 (0.639-1.121)	0.244
Cancer	1.711 (1.031-2.839)	0.038	1.429 (1.023-1.997)	0.036	1.547 (1.134-2.111)	0.006	1.563 (1.084-2.254)	0.017	0.836 (0.594-1.177)	0.305	1.219 (0.745-1.996)	0.43
Respiratory diseases	0.922 (0.533-1.596)	0.772	1.158 (0.864-1.553)	0.325	1.16 (0.858-1.569)	0.335	1.067 (0.737-1.543)	0.732	1.028 (0.759-1.392)	0.859	1.524 (1.056-2.198)	0.024
Blood pressure diseases	N/A	-	N/A	-	1.023 (0.886-1.182)	0.755	0.97 (0.821-1.146)	0.721	0.898 (0.799-1.01)	0.072	0.873 (0.677-1.126)	0.295
Kidney diseases	1.209 (0.739-1.981)	0.45	1.446 (1.078-1.94)	0.014	0.997 (0.668-1.489)	0.989	1.207 (0.762-1.91)	0.422	1.089 (0.775-1.531)	0.624	1.592 (0.985-2.573)	0.058
Neurological diseases	0.648 (0.311-1.349)	0.246	1.398 (0.967-2.02)	0.075	0.753 (0.491-1.155)	0.194	1.263 (0.796-2.003)	0.321	0.686 (0.452-1.041)	0.077	0.633 (0.286-1.402)	0.26
Cardiovascular diseases	0.884 (0.673-1.161)	0.375	N/A	-	0.861 (0.727-1.019)	0.082	0.863 (0.713-1.044)	0.129	0.876 (0.76-1.01)	0.067	1.002 (0.758-1.326)	0.987
Immunodeficiency diseases	5.617 (1.506-20.95)	0.01	0.88 (0.248-3.12)	0.843	0.505 (0.111-2.292)	0.376	3.317 (0.99-11.113)	0.052	0.855 (0.277-2.638)	0.785	N/A	-
Liver diseases	1.027 (0.331-3.185)	0.963	0.977 (0.548-1.742)	0.937	1.106 (0.575-2.127)	0.762	0.995 (0.464-2.136)	0.99	0.86 (0.51-1.45)	0.86	0.785 (0.279-2.208)	0.647

N/A: Not applicable; Due to the large difference in the number of patients who survived and died in these statistics, the effect size was not significant

Before binary logistic regression analysis, sensitivity, specificity and accuracy of the model were measured by ROC curve (Figure 1) and the results showed that this model can be efficient for the purpose of this study.

The results of the binary logistic regression analysis are shown in Table 2. Accordingly in the demographic data, older age and masculinity (in the gender variable) were significant in almost all waves [the sixth wave is marginally significant] (OR>1, P<0.05). In hospital status, respiratory distress and loss of consciousness were detected as risk factors (OR>1, P<0.05), but high SpO_2 (>93) was identified as a protective factor (OR<1, P<0.05). In comorbidities, diabetes in the third and fifth waves, cancer in the first to fourth waves, respiratory diseases in the sixth wave, kidney diseases in the second wave, and immunodeficiency diseases in the first and fourth waves (marginally significant in the fourth wave) were the risk factors for death (OR>1, P<0.05). Blood pressure, neurological, cardiovascular, and liver diseases had no significant results to increased risk of death in the six waves (P>0.05).

Discussion

Finding out the risk factors associated with COVID-19 death in different sinus waves in Iran can help treat effectively and make preventive health policies for the next outbreaks. Accordingly, the findings of the present study showed that several factors including age, masculinity, respiratory distress, loss of consciousness, diabetes, cancer, respiratory, kidney and immunodeficiency diseases had a risk effect on COVID-19 death in different pandemic waves (i.e., six pandemic waves). On the other hand, high SpO_2 rate (>93) was detected as a protective factor for death followed by COVID-19 infection. Also, blood pressure, neurological disorders, cardiovascular, and liver diseases were included in the model of the present study; however, there was no significant result between these factors and COVID-19 death. As a result, the present retrospective study demonstrated that oxygen level is a main factor for reducing the mortality rate in COVID-19 patients. Furthermore, immunodeficiency was detected as a risk factor for COVID-19 death that this might be due to a prolonged viral phase in immunocompromised patients (32); therefore, managing these patients is a critical step for future viral pandemics. Among above-mentioned risk factors, policymakers and physicians should pay attention to diabetes because the prevalence of Diabetes Mellitus (DM) has risen rapidly in Iran (age-standardized prevalence: 8.3%) (33). Moreover, the prevalence of pre-diabetes was estimated about 25.8%, which is a serious warning for next pandemics. It is suggested that diabetes prevention program must be noticed as one of the main priorities for countries with the highest diabetes rates.

In accordance with the present results, previous studies have demonstrated that older age and masculinity were found as the risk factors for COVID-19 death (10-12). As an example, the risk of COVID-19 death was significantly increased by older age (over 70 years old) and masculinity as reported in Peru (Latin America), India, and Africa population (34, 35). Furthermore, a doubled mortality rate was observed for male patients and those over 90 years of age infected with COVID-19 (36, 37). Besides, in the present study, data from hospital status (e.g. consciousness, oxygen level, and respiratory status) seem to be consistent with other research which found hypoxia in COVID-19 patients over time can be exacerbated by leukocytosis and impair seriously the recovery process of patients (38). The present study confirms that SpO_2 is associated with recovery and survival. Thus, early detection and medication in terms of hypoxia are very important to prevent the worsening situation and death followed by COVID-19.

The most obvious finding emerged from the present study is that the impact of hospital status and comorbidities as risk factors on COVID-19 death were evaluated during different waves of pandemic in northeastern of Iran for the first time. The results of the present study revealed that cancer in four waves, diabetes and immunodeficiency diseases in two waves, as well as respiratory and chronic kidney diseases in one wave of pandemic were detected as a risk factor for COVID-19 death. However, other comorbidities including blood pressure, neurological, cardiovascular, and liver diseases had no significant correlation with death in COVID-19 patients. Based on data of the present study, it can be concluded that the diversity of comorbidities, mass vaccination, and increasing awareness of protecting against virus affected the behavior of disease that should be evaluated in future studies. Besides that, updated guidelines and specific care for patients with disability can improve the survival rate in COVID-19 patients. In the interpretation of the present data, the pathogenesis of SARS-CoV-2 plays important roles in different contexts. For example, the expression of the enzymes angiotensin converting enzyme 2 (ACE2) and dipeptidyl peptidase-IV (DPP4) have been changed in diabetes and the activity of these enzymes are associated with severity

of disease and outcomes (39, 40). However, more studies are needed to clarify the proportion of each risk factor in the pathogenesis and clinical outcomes of COVID-19.
The limitations of the present study include the missing data and recall biases. For this reason, the results of the present study should be carefully interpreted in claiming cause-effect relationship in data.
To sum up, different factors (i.e., demographic data, hospital status, and comorbidities) were analyzed on in-hospital mortality from COVID-19 infection during several pandemic waves in Iran. Data obtained from the present study showed that some parameters, such as age, masculinity, respiratory distress, loss of consciousness, diabetes, cancer, respiratory, chronic kidney disease and immunodeficiency disorders were associated with in-hospital mortality from COVID-19 in patients. Conversely, SpO2 was detected as a protective factor for COVID-19 death in all pandemic waves in Iran.

Implications for practice

The most obvious finding emerged from this study is that national prevention program and referral system in healthcare should be redesigned based on the most important risk factors for COVID-19 death to decrease in-hospital mortality rate. It is suggested that more researches be done to determine the relationship between risk factors and viral pandemics.

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Conflicts of interest

The authors declared no conflict of interest.

References

1. Rizkita LD, Astuti I. The potential of miRNA-based therapeutics in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A review. Journal of Pharmaceutical Analysis. 2021;11(3):265-71.
2. Welcome MO, Mastorakis NE. Neuropathophysiology of coronavirus disease 2019: Neuroinflammation and blood brain barrier disruption are critical pathophysiological processes that contribute to the clinical symptoms of SARS-CoV-2 infection. Inflammopharmacology. 2021;29(4):939-63.
3. De Maio A, Hightower LE. COVID-19, acute respiratory distress syndrome (ARDS), and hyperbaric oxygen therapy (HBOT): what is the link? Cell Stress and Chaperones. 2020;25(5):717-20.
4. Goodman JL, Borio L. Finding effective treatments for COVID-19: scientific integrity and public confidence in a time of crisis. Jama. 2020;323(19):1899-900.
5. Vargas-Rodriguez JR, Valdés Aguayo JJ, Garza-Veloz I, Martinez-Rendon J, del Refugio Rocha Pizaña M, Cabral-Pacheco GA, et al. Sustained Hyperglycemia and Its Relationship with the Outcome of Hospitalized Patients with Severe COVID-19: Potential Role of ACE2 Upregulation. Journal of Personalized Medicine. 2022;12(5):805.
6. Asadzadeh A, Mohammadzadeh Z, Fathifar Z, Jahangiri-Mirshekarlou S, Rezaei-Hachesu P. A framework for information technology-based management against COVID-19 in Iran. BMC Public Health. 2022;22(1):402.
7. Khoshnood Z, Mehdipour-Rabori R, Nazari Robati F, Helal Birjandi M, Bagherian S. Patients' experiences of living with coronavirus disease 2019: a qualitative study. Evidence Based Care. 2021;11(1):44-50.
8. World Health Organization (WHO). Available from: https://covid19.who.int/region/emro/country/ir

9. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. The Lancet. 2020;395(10226):795-808.
10. Ho FK, Petermann-Rocha F, Gray SR, Jani BD, Katikireddi SV, Niedzwiedz CL, et al. Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. PloS one. 2020;15(11):e0241824.
11. Alamdari NM, Afaghi S, Rahimi FS, Tarki FE, Tavana S, Zali A, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. The Tohoku journal of experimental medicine. 2020;252(1):73-84.
12. Nguyen NT, Chinn J, De Ferrante M, Kirby KA, Hohmann SF, Amin A. Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. PLoS One. 2021;16(7):e0254066.
13. Caramelo F, Ferreira N, Oliveiros B. Estimation of risk factors for COVID-19 mortality-preliminary results. MedRxiv. 2020; 2020-02.
14. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ. 2020;368:m1198.
15. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infectious Diseases. 2021;21(1):855.
16. McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LA, McAllister DA, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. The lancet diabetes & endocrinology. 2021;9(2):82-93.
17. Silverii GA, Monami M, Cernigliaro A, Vigneri E, Guarnotta V, Scondotto S, et al. Are diabetes and its medications risk factors for the development of COVID-19? Data from a population-based study in Sicily. Nutrition, Metabolism and Cardiovascular Diseases. 2021;31(2):396-8.
18. Khari S, Pazokian M. Perceived Stress and Preventive Behaviors in Patients with Diabetes during Outbreak of COVID-19. Evidence Based Care. 2021;11(3):53-9.
19. Silverio A, Di Maio M, Citro R, Esposito L, Iuliano G, Bellino M, et al. Cardiovascular risk factors and mortality in hospitalized patients with COVID-19: systematic review and meta-analysis of 45 studies and 18,300 patients. BMC cardiovascular disorders. 2021;21(1):23.
20. Leong DP, Banerjee A, Yusuf S. COVID-19 vaccination prioritization on the basis of cardiovascular risk factors and number needed to vaccinate to prevent death. Canadian Journal of Cardiology. 2021;37(7):1112-6.
21. Caillon A, Zhao K, Klein KO, Greenwood CM, Lu Z, Paradis P, et al. High systolic blood pressure at hospital admission is an important risk factor in models predicting outcome of COVID-19 patients. American journal of hypertension. 2021;34(3):282-90.
22. Leiva Sisnieguez CE,, Espeche WG, Salazar MR. Arterial hypertension and the risk of severity and mortality of COVID-19. European Respiratory Journal. 2020;55(6): 2001148.
23. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney international. 2020;97(5):829-38.
24. García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, Talavera B, et al. Neurological comorbidity is a predictor of death in Covid-19 disease: a cohort study on 576 patients. Frontiers in neurology. 2020:11; 781.
25. Hoffmann C, Casado JL, Härter G, Vizcarra P, Moreno A, Cattaneo D, et al. Immune deficiency is a risk factor for severe COVID-19 in people living with HIV. HIV medicine. 2021;22(5):372-8.
26. Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. The Aging Male. 2020;23(5):1416-24.
27. Noor FM, Islam MM. Prevalence and associated risk factors of mortality among COVID-19 patients: a meta-analysis. Journal of community health. 2020;45(6):1270-82.
28. Zali A, Gholamzadeh S, Mohammadi G, Looha MA, Akrami F, Zarean E, et al. Baseline characteristics and associated factors of mortality in COVID-19 patients; an analysis of 16000 cases in Tehran, Iran. Archives of academic emergency medicine. 2020;8(1); e70.

29. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. The Lancet Respiratory Medicine. 2018;6(9):691-8.
30. Fogarty AE, Guay CS, Simoneau G, Colorado BS, Segal GR, Werner Jr JK, et al. Head motion predicts transient loss of consciousness in human head trauma: a case-control study of mixed martial artists. American Journal of Physical Medicine & Rehabilitation. 2019;98(10):859-65.
31. Fakhri Y, Mouseli A, Azad MH, Mastaneh Z, Sarafraz M, Dadar M. Demographic and Clinical Characteristics Associated with COVID-19 Infection in Hormozgan Province, Iran Between January 24 to June 10, 2020. Hormozgan Medical Journal. 2020;24(4); e108254.
32. Cesaro S, Ljungman P, Mikulska M, Hirsch HH, von Lilienfeld-Toal M, Cordonnier C, et al. Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9). Leukemia. 2022;36(6):1467-80.
33. Mirzaei M, Rahmaninan M, Mirzaei M, Nadjarzadeh A. Epidemiology of diabetes mellitus, pre-diabetes, undiagnosed and uncontrolled diabetes in Central Iran: results from Yazd health study. BMC public health. 2020;20(1):1-9.
34. Munayco C, Chowell G, Tariq A, Undurraga EA, Mizumoto K. Risk of death by age and gender from CoVID-19 in Peru, March-May, 2020. Aging (Albany NY). 2020;12(14):13869-81.
35. Salyer SJ, Maeda J, Sembuche S, Kebede Y, Tshangela A, Moussif M, et al. The first and second waves of the COVID-19 pandemic in Africa: a cross-sectional study. The Lancet. 2021;397(10281):1265-75.
36. Guilmoto CZ. COVID-19 death rates by age and sex and the resulting mortality vulnerability of countries and regions in the world. MedRxiv. 2020.
37. Maestre-Muniz MM, Arias A, Arias-Gonzalez L, Angulo-Lara B, Lucendo AJ. Prognostic factors at admission for in-hospital mortality from COVID-19 infection in an older rural population in Central Spain. Journal of Clinical Medicine. 2021;10(2):318.
38. Grieb P, Swiatkiewicz M, Prus K, Rejdak K. Hypoxia may be a determinative factor in COVID-19 progression. Current Research in Pharmacology and Drug Discovery. 2021;2:100030.
39. Peric S, Stulnig TM. Diabetes and COVID-19: Disease-Management-People. Wiener Klinische Wochenschrift. 2020;132(13):356-61.
40. Bassendine MF, Bridge SH, McCaughan GW, Gorrell MD. COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity? Journal of diabetes. 2020;12(9):649-58.