



Risk Factors Associated with Severity and Death from COVID-19 in Iran: A Systematic Review and Meta-Analysis Study

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Abstract

Objectives: This study aims to investigate the risk factors associated with severity and death from COVID-19 through a systematic review and meta-analysis of the published documents in Iran. **Methods:** A systematic search was performed based on all articles indexed in Scopus, Embase, Web of Science (WOS), PubMed, and Google Scholar in English and Scientific Information Database (SID) and Iranian Research Institute for Information Science and Technology (IRA)NDOC indexes in Persian. To assess quality, we used the Newcastle Ottawa Scale. Publication bias was assessed using Egger's tests. Forest plots were used for a graphical description of the results. We used HRs, and ORs reported for the association between risk factors and COVID-19 severity and death. **Results:** Sixty-nine studies were included in the meta-analysis, of which 62 and 13 had assessed risk factors for death and severity, respectively. The results showed a significant association between death from COVID-19 and age, male gender, diabetes, hypertension, cardiovascular disease (CVD), cerebrovascular disease, chronic kidney disease (CKD), Headache, and Dyspnea. We observed a significant association between increased white blood cell (WBC), decreased Lymphocyte, increased blood urea nitrogen (BUN), increased creatinine, vitamin D deficiency, and death from COVID-19. There was only a significant relationship between CVD and disease severity. **Conclusion:** It is recommended that the predictive risk factors of COVID-19 severity and death mentioned in this study to be used for therapeutic and health interventions, to update clinical guidelines and determine patients' prognoses.

Keywords

COVID-19, severity, mortality, death, risk factor

Introduction

The COVID-19 disease spread rapidly to all other countries after being detected in China in 2019, and the World Health Organization declared COVID-19 pandemics.^{1,2} Although it was initially thought that this disease was no different from other diseases such as SARS and influenza in terms of mortality, hospitalization, and death,³ with increasing evidence and over time, it was shown that in addition to various health, economic and social consequences it also has many psychological effects on human societies.^{4,5} As of July 22, 2022, this pandemic has affected about 551 million people and killed 6.5 million people worldwide.⁶ In Iran, until Jun 22, 2022, six waves of epidemics have been repeated. About 7.5 million cases of COVID-19 disease have been tested positive for PCR, and with 141 300 deaths reported, the death rate from the disease is 1.88 per 100 000 general population.⁷ These numbers can vary depending on the disease's underestimation and lack of testing. Based on the estimated excess death related to COVID-19, the actual death will be twice as many as reported in Iran.⁸

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Although interventions such as vaccination have been able to reduce the incidence of death and COVID-19 worldwide, the long-term problems with COVID have added to the concerns of human societies.^{9,10} Evidence suggests that COVID-19 has long-term consequences for the heart, brain, and other organs.¹¹ Globally, about 53.2 million major depressive disorder cases have been reported due to the COVID-19 pandemic, and the pooled prevalence is 3152.9 cases per 100 000 population. As a result, the side effects of COVID-19 can be serious and manifest themselves in the long run.¹² The risk of cardiovascular disorders in people with COVID-19 is significantly higher than in those without the disease.¹³ It is estimated that the countries will face many challenges with long-COVID in the next years. As a result, it is possible to reduce the long-term and short-term effects of COVID-19 infection by performing evidence-based interventions, identifying the relevant, effective factors, and finally preventing infection, death, and hospitalization.¹⁴

From the beginning of the COVID-19 pandemic, countries have adopted different policies and interventions to reduce the burden of COVID-19 in terms of death, hospitalization, and even social, psychological, and economic effects.¹⁵ Some countries, such as China, have followed the zero-COVID-19 approach,¹⁶ while others have imposed restrictions, mass vaccinations, contact tracing, and other non-pharmacological interventions.¹⁷ Although social and public interventions in countries reduce the adverse effects of COVID-19, recognizing the risk factors associated with COVID-19 severity and death in communities can help the health system identify high-risk groups and implement appropriate risk-reduction interventions.^{18,19} In Iran, several social and non-pharmacological interventions have been performed to reduce the COVID-19 adverse effects, but recognizing the factors associated with the incidence of death and severity can provide comprehensive information on high-risk and low-risk groups. To our knowledge, separate studies have shown the relationship between some factors, but systematically, related risk factors have not been studied. Current meta-analysis studies have also been conducted with limited articles in the past, and the findings of newer meta-analyses can help to show better the clinical, epidemiological, and diagnostic aspects of this disease. This study aims to investigate the risk factors associated with severity and death from COVID-19 through a systematic review and meta-analysis of the published documents in Iran.

Materials and Methods

Setting

This study is in line with the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁰ We have investigated the risk factors associated with severity and death from COVID-19 in Iran from the beginning of the COVID-19 epidemic to March 20, 2022.

Search Strategy

A systematic searching was performed based on all articles indexed in Scopus, Embase, Web of Science (WOS), PubMed, and Google Scholar in English and Scientific Information Database (SID) and IRANDOC indexes using the keywords (“Iran”[Mesh Terms] OR “Iran”[All Fields]) AND (“COVID-19”[Title/Abstract] OR “Corona”[Title/Abstract] OR “2019 novel coronavirus”[Title/Abstract] OR “severe acute respiratory syndrome coronavirus 2”[Title/Abstract] OR “corona virus disease 2019”[Title/Abstract] OR “SARS-COV-2”[Title/Abstract] OR “Coronavirus”[Title/Abstract]) OR “COVID”[Mesh]) AND (“infection”[Title/Abstract] OR “incidence”[Title/Abstract] OR “morbidity”[Title/Abstract] OR “sick*”[Title/Abstract] OR “death”[Title/Abstract] OR “mortality”[Title/Abstract] OR “fatal*”[Title/Abstract] OR “severity”[Title/Abstract] OR “ICU”[Title/Abstract] OR “hospital*”[Title/Abstract] OR “Dying”[Title/Abstract] OR “intensit*”[Title/Abstract]) AND (“related factor*”[All Fields] OR “factor associated”[All Fields] OR “associated factor”[All Fields] OR “risk factor”[All Fields] OR “factor*”[All Fields] OR “factor related”[All Fields]).”

Inclusion Criteria

All studies were included by identifying observational studies conducted in Iran. Other review studies, case studies, and laboratory studies that did not meet the inclusion criteria were excluded. Two researchers evaluated the search results independently. We also did snowballing with searching the references of the included articles to explore our search strategy. Based on COVID-19 Treatment Guidelines Panel and Coronavirus Disease 2019 (COVID-19) Treatment Guidelines,²¹ severity disease due to COVID-19 mentioned in studies was defined: “Individuals who have SpO₂ < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50% and Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.” Disease severity in our study was defined as a form of the disease that requires hospitalization, oxygen therapy, and/or mechanical ventilation in ICU or Hospital.²² Cardiovascular diseases were defined to any cardiovascular disorder related to the heart and blood vessels.²³ Cerebrovascular disease was included all disorders in which an area of the brain is temporarily or permanently affected by ischemia or hemorrhage, and one or more blood vessels of the brain are involved in the pathological process.²⁴ chronic liver disease was determined” Chronic liver disease (CLD) is a progressive deterioration of liver functions for more than six months, which includes synthesis of clotting factors, other proteins, detoxification of harmful products of metabolism, and excretion of bile.”²⁵ ARDS also was defined “as syndrome of inflammation and increased permeability” leading to acute onset of bilateral infiltrates on chest radiograph with PaO₂/FiO₂ ≤ 200 that cannot be explained by left heart dysfunction.”²⁶ Any study that introduced these conditions as inclusion criteria were included.

Selection Process

Two independent researchers initially screened the search strategy results based on abstracts and titles. Then the full texts of related articles were evaluated based on inclusion and exclusion criteria. A third researcher reviewed studies in which individuals did not reach a decision. Finally, observational studies that reported death and severity-related factors related to COVID-19 were included in the meta-analysis.

Data Collection Process

Two researchers also independently extracted the required data from the studies. The third researcher reviewed the list of articles and extracted the data to ensure that there were no duplicate articles and resolved disputes over the study's inclusion.

Assessment of Methodological Quality, Risk of Bias, and Publication Bias

We used the Newcastle Ottawa Scale for cohort, evidence-based, and cross-sectional studies to assess quality. According to these checklists, studies can be divided into three groups (good, acceptable, and poor quality).²⁷

Statistical Approach

The "metan" command performed a random-effects meta-analysis in STATA. Forest plots were used for a graphical description of the results. We used HRs and ORs reported for the association between risk factors and COVID-19 severity and death to calculate ln HRs, ln ORs, and their standard errors (SE). Finally, publication bias was assessed by the Egger test. The data were analyzed using Stata version 11.0. Pooled estimates in meta-analyses were estimated with a 95% confidence interval. *P*-values were considered significant at the level of $<.05$.

Results

Search Results and Quality Assessment

After deleting duplicates, we identified 2463 studies from four databases and then screened articles by title and full text according to the study's objectives. Finally, 69 studies were included in the meta-analysis (Figure 1), of which 62 studies had assessed risk factors for death from COVID²⁸⁻⁸⁹; 13 studies determined risk factors for severity ((^{41,50,53-55,65,90-96}), out of which six studies reported both outcomes ((35, 44, 47-49, 59)). Out of 69 studies, 33 were cohort studies, eight were case-control studies, and 28 were cross-sectional studies. The mean sample size was 2742 (Range: 35-40 957) (Table 1).

When we assess the quality of included studies, the Newcastle Ottawa scale showed that 10 studies (14.49%) scored 9, 18 studies (26.09%) scored 8, and 27 studies (39.13%) scored 7, and 14 studies (20.29%) scored six points.

Therefore, all studies scored above five and had high quality (Table 1).

Demographic Characteristics and Risk of Death from COVID-19

In a meta-analysis, 35 studies examined the effect of age on Death from COVID-19, and 35 effect sizes were obtained. The meta-analysis results showed a significant association between older age and Death from COVID-19, and the pooled OR and HR were 1.04 (95% CI=1.03 to 1.06) and 1.03 (95% CI=1.02 to 1.04) for each one-year increase in age respectively. Twenty-seven studies assessed the risk of Death from COVID-19 for gender and showed that the male gender significantly affects death, and the pooled OR was 1.21 (95% CI=1.05 to 1.38) (Table 2 and Figure 2).

Comorbidities and Risk of Death from COVID-19

Twenty-three studies evaluated the association between diabetes and Death from COVID-19 and showed a significant association between diabetes and coronaviruses mortality (pOR = 1.76; 95%CI=1.48 to 2.09; pHR = 1.77; 95%CI=1.46 to 2.14). In addition, we found a significant positive association between hypertension (pOR = 1.64; 95% CI=1.20, 2.25; pHR = 1.42; 95% CI 1.05 to 1.93), cardiovascular disease (CVD) (pOR = 1.74; 95% CI=1.45 to 2.08; pHR=2.01; 95% CI=1.63 to 2.47), cerebrovascular disease (pOR=3.29; 95% CI=1.49 to 7.27), pulmonary diseases (pOR = 1.71; 95% CI=1.20 to 2.43), chronic kidney disease (CKD) (pOR = 2.27; 95% CI=1.47 to 3.50; pHR = 2.24; 95% CI=1.39 to 3.61), cancer (pOR = 2.40; 95% CI=1.44 to 3.98; pHR = 2.78; 95% CI=1.85 to 4.18), and Death from COVID-19 (Table 2 and Figure 3).

Symptoms and Risk of Death from COVID-19

Death from COVID-19 risk was significantly associated with a negative direction with Headache (pOR = 0.67; 95%CI=0.46 to 0.98). In addition, the combined nine effect sizes from 9 studies showed a significant association between Dyspnea and Death from COVID-19 (pOR = 1.75; 95%CI = 1.31 to 2.35) (Table 2).

Laboratory Parameters and Risk of Death from COVID-19

Six studies have investigated the effect of the increased WBC on Death from COVID-19. The results showed a significant association between increased WBC and coronaviruses mortality (pOR = 1.42; 95%CI=1.05 to 1.91). In addition, we found a significant association between decreased Lymphocyte (pOR = 1.68; 95% CI 1.32, 2.14), increased blood urea nitrogen (BUN) (pOR = 1.05; 95% CI 1.00 to 1.10), increased creatinine (pOR = 1.82; 95% CI 1.29 to 2.56), vitamin D deficiency (pOR = 2.64; 95% CI = 1.86 to 3.76; pHR = 1.86; 95% CI = 1.38 to 2.51), and Death from COVID-19 (Table 2).

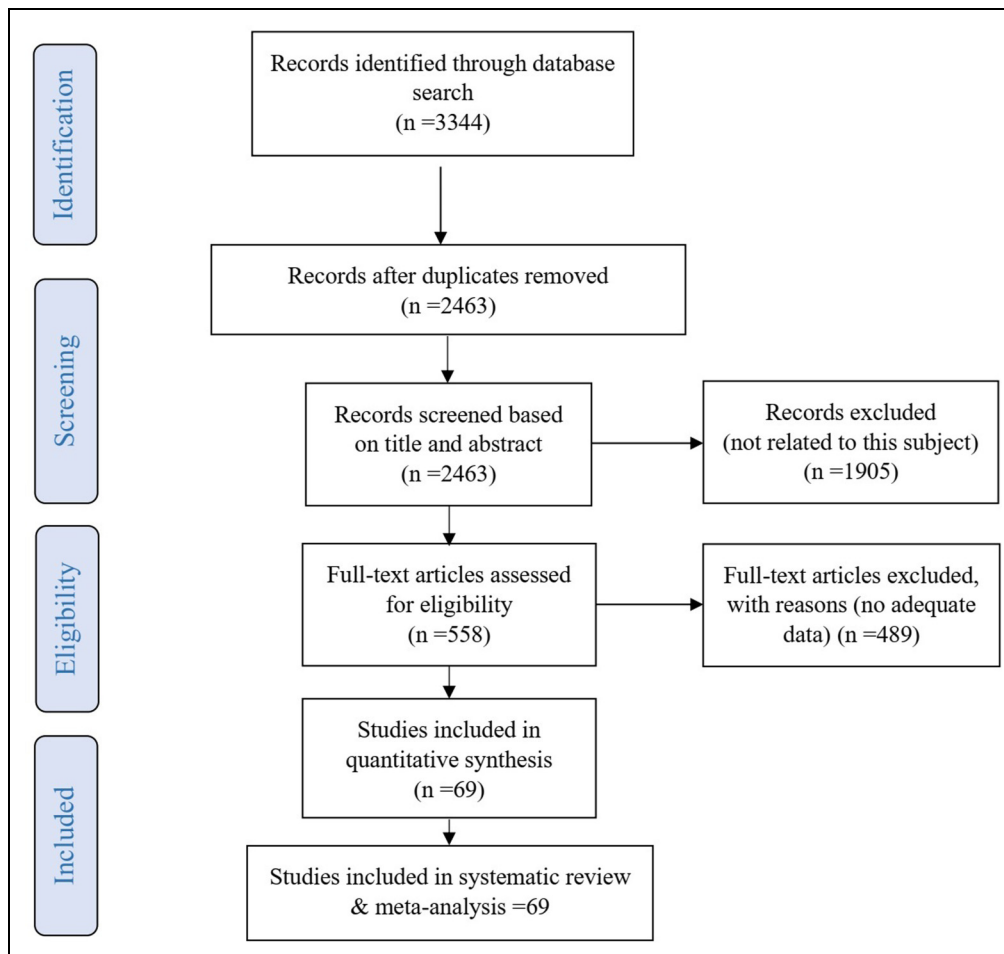


Figure 1. Flow diagram of the study selection process.

Disease Severity-Related Risk Factors

In a meta-analysis of 18 effect sizes, demographic and clinical features were obtained from 13 studies. The results of the meta-analysis showed that there was only a significant relationship between CVD and disease severity (pOR = 2.42; 95% CI = 2.27 to 2.59) (Table 3).

Publication Bias

Based on the results of the Egger's test (age: $P = .087$, gender: $P = .070$, smoking: $P = .216$, diabetes: $P = .221$, hypertension: $P = .589$, CVD: $P = .284$, CVA: $P = .602$, pulmonary diseases: $P = .881$, CKD: $P = .210$, chronic liver disease: $P = .624$, cancer: $P = .938$, fever: $P = .230$, cough: $P = .327$, dyspnea: $P = .667$, chest pain: $P = .174$, headache: $P = 1.000$, WBC: $P = .142$, lymphocyte: $P = .573$, neutrophil: $P = .624$, platelet: $P = .055$, HB: $P = .498$, BUN: $P = .621$, creatinine: $P = 1.000$, CRP: $P = .573$, LDH: $P = .176$, vitamin D: $P = .142$), there was no evidence of publication bias among articles assessing risk factors for Death from COVID-19. In addition, there was

no evidence of publication bias among articles assessing disease severity risk factors (age: $P = .624$, gender: $P = .065$, diabetes: $P = .117$, CVD: $P = .602$, CKD: $P = .602$).

Meta-Regression Analysis

Meta-regression showed that the sample size is an important source of heterogeneity when examining the potential predictive effect of hypertension (Original $I^2 = 91.5$, I^2 residual = 64.8, $P = .002$) and creatinine (Original $I^2 = 71.7$, I^2 residual = 0.0, $P = .039$). Also, the mean age of patients is an important source of heterogeneity when examining the potential predictive effect of lymphocyte (Original $I^2 = 97.2$, I^2 residual = 77.7, $P = .045$) (Table 4).

Discussion

This study aimed to assess risk factors associated with COVID-19 severity and death in Iran. Based on this meta-analysis study, some factors related to the dimensions of the

Table 1. Characteristics of Included Studies and Quality of Assessment.

First Author	Year	Sample Size	Age	Gender	Study Type	Score of Quality Assessment
Abdollahi A	2020	397	NA	F/M	Cross-sectional	*****
Abdollahpour I	2021	513	1-97 range	F/M	Case-control	*****
Abkhoo A	2021	121	62.2 ± 14	F/M	Retrospective	*****
Abrishami A	2021	73	55.18 ± 17.6	F/M	Retrospective	*****
Abrishami A	2021	80	54.29 ± 15.21	F/M	Cohort	*****
Aghajani MH	2021	893	62 ± 17.2	F/M	Cohort	*****
Aghajani MH	2021	893	62.3 ± 19.3	F/M	Cohort	*****
Aghajani MH	2022	649	64.30 ± 17.8	F/M	Cohort	*****
Asgari A	2021	98	64.45 ± 15.67	F/M	Cross-sectional	*****
Adham D	2021	5586	52.25 ± 20.21	F/M	Retrospective	*****
Afaghi S	2021	646	53.7 ± 15.8	F/M	Retrospective	*****
Ahmadi A	2021	800	57.51 ± 16.83	F/M	Cross-sectional	*****
Aliasgarzade S	2021	106	58.99 ± 15.94	F/M	Cross-sectional	*****
Azarkar Z	2021	364	54.28 ± 18.81	F/M	Retrospective	*****
Borzouei S	2021	1680	NA	F/M	Case-control	*****
Davarpanah AH	2020	228	56.1 ± 15.9	F/M	Retrospective	*****
Derakhshanian H	2021	290	61.6 ± 16.9	F/M	Retrospective	*****
Esfahanian F	2021	493	NA	F/M	Cross-sectional	*****
Emami A	2021	458	61.3	F/M	Cross-sectional	*****
Fatemi A	2021	248	59.30 ± 22.37	F/M	Cross-sectional	*****
Faraji N	2021	522	72.5 ± 8.4	F/M	Retrospective	*****
Fathi M	2022	3732	77.9 ± 9.2	F/M	Cohort	*****
Faghih Dinevari M	2021	1274	64.43 ± 17.16	F/M	Prospective	*****
Ghadamgahi F	2021	2000	65.77 ± 12.2	F/M	Case-control	*****
Ghafari M	2021	361	62 ± 16.76	F/M	Cross-sectional	*****
Ghamari A	2022	474	61 ± 16	F/M	Cross-sectional	*****
Goshayeshi L	2021	1278	56.9 ± 18.7	F/M	Cross-sectional	*****
Hajjahmadi S	2021	192	57.5 ± 1.11	F/M	Cross-sectional	*****
Hashemi SA	2021	611	57.51 ± 17.6	F/M	Case-control	*****
Hashemi-Shahri SM	2022	413	45.05 ± 17.38	F/M	Cross-sectional	*****
Homayounieh F	2020	90	59.4 ± 16.6	F/M	Cross-sectional	*****
Honarvar MR	2021	2835	54 ± 19.3	F/M	Cohort	*****
Hosseinzadeh R	2021	598	58.21 ± 22.5	F/M	Cross-sectional	*****
Izadi A	2021	107	63.36 ± 16.43	F/M	Cross-sectional	*****
Jalili E	2021	512	68.32 ± 14.72	F/M	Cross-sectional	*****
Javani M	2021	557	60.2 ± 15.3	F/M	Cohort	*****
Javanmard SH	2020	508	67.7 ± 15.1	F/M	Cross-sectional	*****
Karami M	2021	749	53.97 ± 19.04	F/M	Cross-sectional	*****
Karami M	2022	9674	NA	F/M	Cross-sectional	*****
Khankeh H	2021	34 039	66.48 ± 15	F/M	Cross-sectional	*****
Kashefizadeh A	2020	53	58.48 ± 13.6	F/M	Cohort	*****
Kazemi MA	2020	91	58.04 ± 16.5	F/M	Cross-sectional	*****
Khoshnood RJ	2021	1083	50.73 ± 19.33	F/M	Cross-sectional	*****
Kolivand P	2022	6788	NA	F/M	Cohort	*****
Kouhsari E	2022	256	55.78 ± 18.61	F/M	Cohort	*****
Malekpour Alamdari N	2020	459	61.79 ± 11.89	F/M	Cross-sectional	*****
Marateb HR	2021	630	57.1 ± 15.4	F/M	Cohort	*****
Mirjalili M	2021	1465	56.92 ± 17.78	F/M	Case -cohort	*****
Moftakhar L	2021	40 957	38.75 ± 15.6	F/M	Retrospective	*****
Moradinia M	2021	367	57.01 ± 16.25	F/M	Descriptive study	*****
Moradzadeh R	2021	3050	70 ± 15	F/M	Retrospective	*****
Nabavi S	2021	200	69.75 ± 6.39	F/M	Cross-sectional	*****
Navayi M	2021	1290	60.95 ± 17.65	F/M	Cohort	*****
Pazoki M	2021	574	56.8 ± 16.3	F/M	Descriptive study	*****
Pishgahi M	2021	680	55.15 ± 10.92	F/M	Cross-sectional	*****
Pourfarzi F	2021	776	NA	F	Case-control	*****
Rashidi F	2021	1529	56 ± 17.2	F/M	Cohort	*****
Rastad H	2020	2957	54.8 ± 16.9	F/M	Retrospective	*****

(continued)

Table 1. (continued).

First Author	Year	Sample Size	Age	Gender	Study Type	Score of Quality Assessment
Rezaei N	2021	37 338	63.6 ± 13.6	F/M	Cohort	*****
Riahi T	2021	984	62.94 ± 18.6	F/M	Cross-sectional	*****
Sadeghi A	2020	214	58.14 ± 16.99	F/M	Retrospective	*****
Seif M	2022	2360	NA	F/M	Retrospective	*****
Shahidsales S	2021	185	62	F/M	Case-control	*****
Shayganfar A	2021	178	57.5 ± 16.1	F/M	Retrospective	*****
Toofan F	2021	2597	62.1 ± 16.8	F/M	Cross-sectional	*****
Zahirian Moghadam T	2021	3088	NA	F/M	Case-control	*****
Zamanian M	2020	245	54.68 ± 19.21	F/M	Retrospective	*****
Zandkarimi E	2020	1831	52.74 ± 22.16	F/M	Cross-sectional	*****
Zandkarimi E	2021	1856	58.48 ± 13.6	F/M	Retrospective	*****

Table 2. Association of Demographic, Clinical Characteristics and Laboratory Parameters with Death in Patients with COVID-19.

Variables	Measure of Association Tools	Number of Studies	Estimation	P Value	I ² (%)	P for Heterogeneity
Demographics characteristics						
Age(yr)	Odds Ratio(95% CI)	26	1.04 (1.03, 1.06)	<.001	96.8	<.001
	Hazard Ratio(95% CI)	9	1.03 (1.02, 1.04)	<.001	66.3	.003
Gender: Male versus Female	Odds Ratio(95% CI)	27	1.21 (1.05, 1.38)	.007	84.6	<.001
	Hazard Ratio(95% CI)	3	1.18 (0.85, 1.65)	.326	24.0	.268
Smoking	Odds Ratio(95% CI)	8	1.47 (0.87, 2.48)	.152	74.8	<.001
Comorbidities						
Diabetes	Odds Ratio(95% CI)	19	1.76 (1.48, 2.09)	<.001	62.3	<.001
	Hazard Ratio(95% CI)	4	1.77 (1.46, 2.14)	<.001	2.6	.380
Hypertension	Odds Ratio(95% CI)	16	1.64 (1.20, 2.25)	.002	91.5	<.001
	Hazard Ratio(95% CI)	2	1.42 (1.05, 1.93)	.022	0.0	.513
Cardiovascular diseases	Odds Ratio(95% CI)	18	1.74 (1.45, 2.08)	<.001	90.3	<.001
	Hazard Ratio(95% CI)	4	2.01 (1.63, 2.47)	<.001	20.1	.289
Cerebrovascular disease	Odds Ratio(95% CI)	3	3.29 (1.49, 7.27)	.003	47.3	.150
Pulmonary diseases	Odds Ratio(95% CI)	7	1.71 (1.20, 2.43)	.003	61.8	.015
	Hazard Ratio(95% CI)	3	1.40 (0.67, 2.93)	.367	72.3	.027
Chronic kidney disease	Odds Ratio(95% CI)	10	2.27 (1.47, 3.50)	<.001	70.3	<.001
	Hazard Ratio(95% CI)	4	2.24 (1.39, 3.61)	.001	45.8	.137
Chronic liver disease	Odds Ratio(95% CI)	5	1.60 (0.92, 2.77)	.095	35.8	.182
Cancer	Odds Ratio(95% CI)	11	2.40 (1.44, 3.98)	.001	81.1	<.001
	Hazard Ratio(95% CI)	3	2.78 (1.85, 4.18)	<.001	.0	.588
Symptoms and signs						
Fever	Odds Ratio(95% CI)	7	1.23 (0.91, 1.65)	.173	79.1	<.001
Cough	Odds Ratio(95% CI)	5	0.75 (0.48, 1.17)	.207	86.3	<.001
Headache	Odds Ratio(95% CI)	4	0.67 (0.46, 0.98)	.037	65.1	.035
Dyspnea	Odds Ratio(95% CI)	9	1.75 (1.31, 2.35)	<.001	74.0	<.001
Chest pain	Odds Ratio(95% CI)	4	1.07 (0.47, 2.42)	.874	88.7	<.001
Laboratory parameters						
Increased White Blood Cell	Odds Ratio(95% CI)	6	1.42 (1.05, 1.91)	.023	89.6	<.001
Decreased Lymphocyte	Odds Ratio(95% CI)	7	1.68 (1.32, 2.14)	<.001	97.2	<.001
Increased Neutrophil	Odds Ratio(95% CI)	5	1.00 (0.97, 1.02)	.788	39.3	.159
Decreased Platelet count	Odds Ratio(95% CI)	5	1.00 (0.99, 1.00)	.225	43.6	.150
Decreased Hemoglobin	Odds Ratio(95% CI)	4	0.97 (0.75, 1.25)	.802	80.6	.001
Increased BUN	Odds Ratio(95% CI)	8	1.05 (1.00, 1.10)	.046	83.9	<.001
Increased Creatinine	Odds Ratio(95% CI)	5	1.82 (1.29, 2.56)	.001	71.1	.008
Increased CRP	Odds Ratio(95% CI)	7	1.03 (0.99, 1.06)	.131	92.3	<.001
Increased LDH	Odds Ratio(95% CI)	7	1.00 (1.00, 1.01)	.045	92.7	<.001
Vitamin D deficiency	Odds Ratio(95% CI)	5	2.64 (1.86, 3.76)	<.001	0.0	.495
	Hazard Ratio(95% CI)	2	1.86 (1.38, 2.51)	<.001	9.0	.333

Abbreviations: BU.; Blood Urea Nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase.

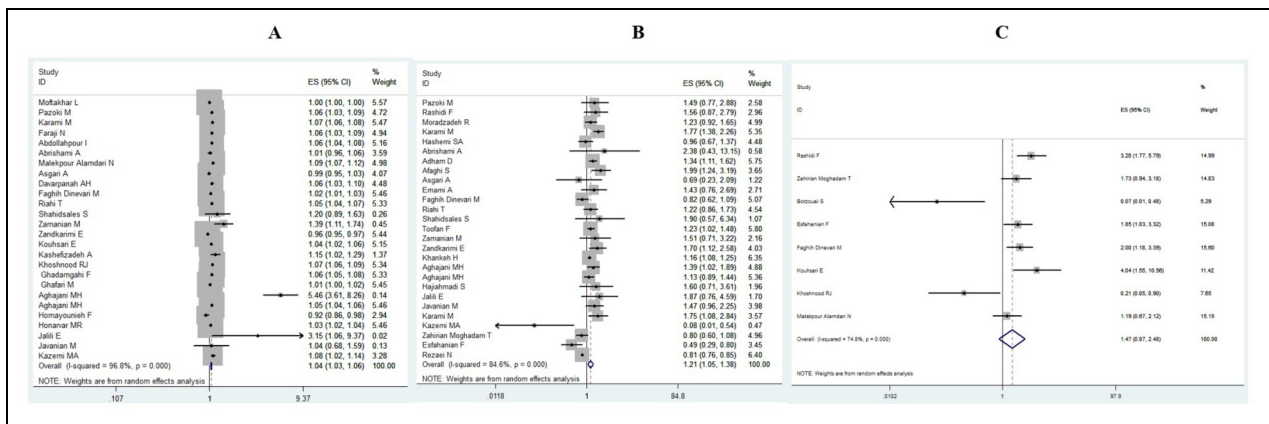


Figure 2. Meta-analysis to assess the risk of death for (A) age (B) sex, male. (C) Smoking.

COVID-19 disease have been mentioned in the studies conducted in Iran.

Our study showed a significant association between diabetes and hypertension with death from COVID-19. Some studies similar to our results showed that diabetes and hypertension are important factors in COVID-19 mortality. A systematic review showed that diabetic ketoacidosis (DKA) in COVID-19 patients portends a poor prognosis with a mortality rate approaching 50%. Differentiating isolated DKA from combined DKA/HHS (hyperglycemic hyperosmolar syndrome) is essential as the latter represents nearly one-fifth of the DKA cases and tends to have higher mortality than DKA alone.⁹⁷ Another study suggests that diabetes and hypertension were associated with higher COVID-19 mortality, contributing to nearly 30% of death from COVID-19 s.⁹⁸ A meta-analysis study showed that COVID-19 severity and death were associated with Diabetes Mellitus, ARDS, and disease progression in patients with COVID-19. The association was weaker in the older and hypertensive patients.⁹⁹ According to the latest national study, it has been shown that diabetes, cardiovascular disease, CKD, and hypertension, as diseases with significant prevalence, have a great impact on increasing the burden of diseases in Iran.¹⁰⁰ It seems that one of the reasons for the high mortality rate due to COVID-19 in Iran, in some periods, has been related to the high incidence of COVID-19 in populations with chronic disease and the elderly population. In line with the findings of our study, Mirjalili et al.¹⁰¹ showed that diabetes, hypertension, CKD, and cardiovascular disease in people with COVID-19 increased mortality and severity by about 55%. Other studies also showed that these diseases positively affect Death from COVID-19.^{102–104} Although the World Health Organization has emphasized that the elderly and people with chronic diseases are at risk of death from COVID-19,¹⁰⁵ the importance of this problem is not addressed in the management strategies of this epidemic. The present study showed a significant association between older age and Death from COVID-19, similar to some research done in Iran.^{106,107} In addition, the Iranian elderly mostly have chronic diseases such as diabetes, cardiovascular and hypertension, which were immunized in

the first step of nationwide vaccination; the clinical and treatment interventions performed were uniform for all populations, and more specialized services for the elderly and underlying patients could prevent death. Previous studies showed that elderly people usually experience a decrease in their immune system ability,^{108,109} and the coexistence of aging and chronic diseases can play a vital role in increasing the death from COVID-19.¹¹⁰ In the clinical management of elderly patients, medical staff should consider the higher mortality risk and make more critical decisions in this age group to prevent more deaths. Our results showed that men have higher mortality due to COVID-19 than women, and other similar studies have also demonstrated this relationship.^{111–113} It can be said that the X chromosome in women seems to reduce susceptibility to infection, and sex hormones play a role in innate and adaptive immunity.¹¹⁴ Besides, men maybe are at a greater risk of getting COVID-19 infection due to being more active in society, working in places with others, and not paying more attention to self-care than women, which ultimately leads to an increase in mortality.

Regarding symptoms, the present study showed that headache has an inverse relationship with death from COVID-19. Previous studies have also investigated this issue. In line with this study, other studies also showed a better prognosis for patients with headaches.^{115–117} Some studies have shown that having a headache is associated with decreased inflammatory biomarkers, such as C-reactive protein (CRP) and lower and more stable levels of interleukin-6 (IL-6) during hospitalization.^{118,119} A study investigating headache phenotypes related to covid-19 showed that tension headaches are related to decreased levels of CRP and procalcitonin.¹²⁰ However, there is still no clear epidemiological and clinical knowledge about the relationship between headache and higher death from COVID-19, and more studies can help find this relationship in patients with different clinical, laboratory, and diagnostic characteristics. Various studies have seen dyspnea as a symptom associated with higher death from COVID-19.^{121,122} These findings were also observed in our study. A systematic review study has shown that considering the dyspnea

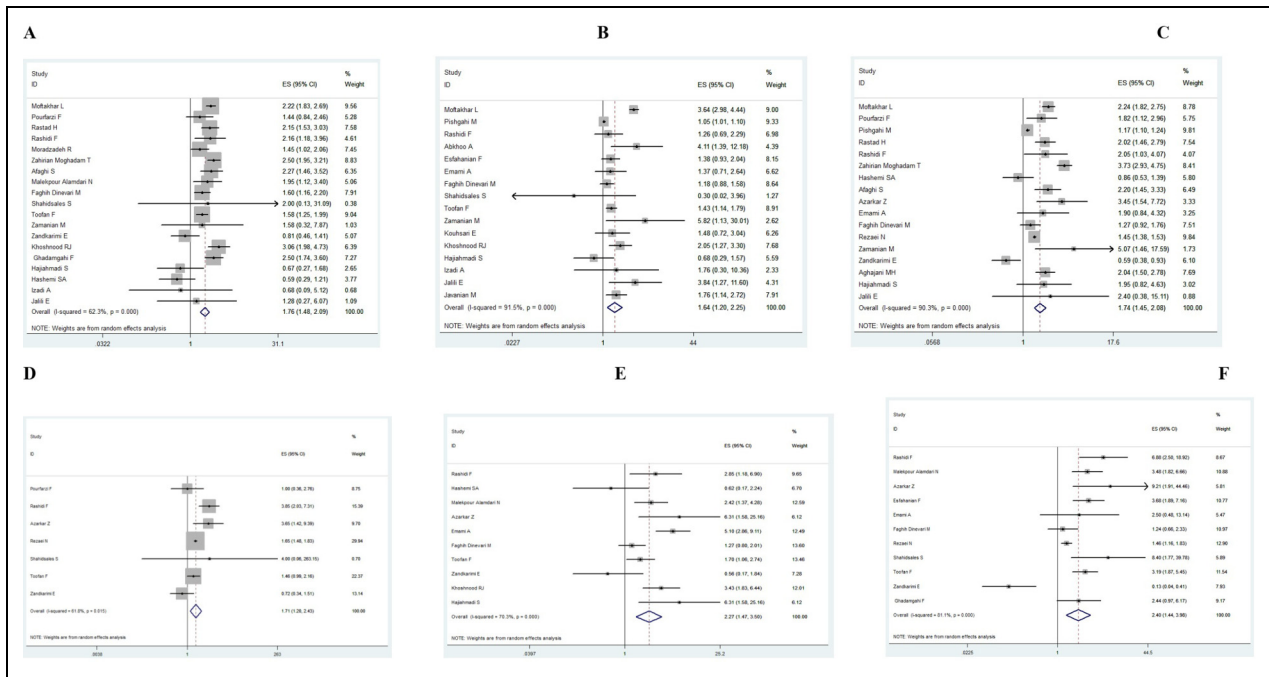


Figure 3. Meta-analysis to assess the risk of mortality for (A) diabetes (B) hypertension. (C) Cardiovascular disease. (E) Chronic kidney disease. (F) Cancer.

Table 3. Association of Demographic and Clinical Characteristics with Disease Severity in Patients with COVID-19.

Variables	Measure of Association Tools	Number of Studies	Estimation	P Value	I ² (%)	P for Heterogeneity
Demographics characteristics						
Age(yr)	Odds Ratio(95% CI)	5	1.03 (1.00, 1.06)	.087	91.7	<.001
Gender: Male versus Female	Odds Ratio(95% CI)	4	0.52 (0.19, 1.43)	.205	71.7	.014
Comorbidities						
Diabetes	Odds Ratio(95% CI)	3	1.10 (0.86, 1.41)	.438	99.3	<.001
Cardiovascular diseases	Odds Ratio(95% CI)	3	2.42 (2.27, 2.59)	<.001	2.8	.357
Chronic kidney disease	Odds Ratio(95% CI)	3	1.37 (0.89, 2.11)	.150	0.0	.618

Table 4. Meta-Regression Analysis for Characteristics of the Included Studies According to the Sample Size and Age of the Patients.

Predictor	Multivariate Analysis (P Value)	
	Age	Sample Size
Smoking	.549	.761
Diabetes	.170	.408
Hypertension	.100	.003
Cardiovascular diseases	.280	.918
Pulmonary diseases	.325	.908
Chronic kidney disease	.382	.155
Cancer	.578	.566
Fever	.515	.487
Cough	.198	.211
Headache	.926	.269
White Blood Cell	.310	.105
Lymphocyte	.045	.170
BUN	.220	.064
Creatinine	.577	.039
CRP	.359	.722
LDH	.778	.309

symptom is even more important than fever in terms of diagnosis and prognosis,¹²³ and identifying this symptom can be important before making clinical decisions.

Blood markers in COVID-19 patients can be important in clinical and treatment planning. Some studies consider the status of such markers for diagnostic evaluation, survival, and prognosis of patients.^{124,125} We observed a significant association between increased WBC, decreased lymphocyte, increased BUN, increased creatinine, vitamin D deficiency, and death from COVID-19. In line with our results, Henry et al.¹²⁶ showed in their meta-analysis study that WBC as an increasing marker in patients with the acute condition of COVID-19 could be considered a good marker for predicting their prognosis. Lan et al.¹²⁷ also showed that people with a shorter survival from COVID-19 infection had a decrease in lymphocytes, and the odds of mortality in patients with low blood lymphocytes were nine times higher than in those with high lymphocytes. Similar studies also showed a relationship between death from COVID-19 and vitamin D deficiency.^{128–130} In countries such as Iran, which are facing the limitation of testing for the

diagnosis of COVID-19 and the patients ignore their disease, blood markers can be an important indicator to consider the patients' clinical profile to educate and adhere to the treatment.

Regarding the limitations of this study, some factors could not be included in the final analysis due to the lack of sufficient studies to measure its effects, and increasing the number of similar studies in the future may change the results of related meta-analyses. The lack of sufficient access to national data in Iran to conduct more valid epidemiological studies is one of the limitations of all studies. However, for the first time, this study has simultaneously shown the effects of some factors related to the severity and death-related COVID-19 in Iran. There is a heterogeneity among studies included the meta-analysis in terms of the place (ICU, wards or emergency rooms) where the studies were conducted. It may influence the results of laboratory parameters, as the clinical condition of ICU patients is more severe than patients in wards.

Conclusion

Our study showed some factors related to severity and death associated with COVID-19 in Iran. Clinical decisions are usually chosen by knowing the factors affecting prognosis, severity, and death. Since this study showed the effect of some blood markers, co-morbidities, headache and dyspnea, aging, and male gender, the diagnostic value of these factors can be used for medical teams and therapeutic and clinical decisions.

Author Contributions

Conceptualization: KA, SSHN. Search strategy searching: AM, NT. Formal analysis: SSG, SSHN. Methodology: AM, KE, SSHN. Project administration: SSHN, AM. Visualization: NI, FS, YM. Writing—original draft: AS, SF, RF. Searching team: ER, SSG, KFB, ZB, AM.

Declaration of Conflicting Interests

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Ethics Statement

The Ethical Committee of Shahid Beheshti University of Medical Sciences approved this study with ID: IR.BMSU.REC.1399.095.

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References

- Cucinotta D, Vanelli M. WHO Declares COVID-19 a pandemic. *Acta Bio Medica: Atenei Parmensis*. 2020;91(1):157.
- Sohrabi C, Alsafi Z, O'Neill N, et al. World health organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76(1):71-76.
- Petersen E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis*. 2020;20(9):e238-e244.
- Poudel K, Subedi P. Impact of COVID-19 pandemic on socioeconomic and mental health aspects in Nepal. *International Journal of Social Psychiatry*. 2020;66(8):748-755.
- Singh J, Singh J. COVID-19 and its impact on society. *Electron Res J Soc Sci Humanities*. 2020;2(1).
- who. Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/>
- COVID I. Coronavirus Statistics: whorld health organization. <https://www.who.int/countries/irn>
- Wang H, Paulson KR, Pease SA, et al. Estimating excess mortality due to the COVID-19 pandemic: A systematic analysis of COVID-19-related mortality, 2020–21. *The Lancet*. 2022;399(10334):1513-1536.
- Machado BAS, Hodel KVS, Fonseca L, et al. The importance of vaccination in the context of the COVID-19 pandemic: A brief update regarding the use of vaccines. *Vaccines (Basel)*. 2022;10(4):591.
- Organization WH. *Strategic preparedness, readiness and response plan to end the global COVID-19 emergency in 2022*. 2022.
- Siripanthong B, Asatryan B, Hanff TC, et al. The pathogenesis and long-term consequences of COVID-19 cardiac injury. *Basic to Translational Science*. 2022;7(3_Part_1):294-308.
- Castelpietra G, Knudsen AKS, Agardh EE, et al. The burden of mental disorders, substance use disorders and self-harm among young people in Europe, 1990–2019: Findings from the global burden of disease study 2019. *The Lancet Regional Health-Europe*. 2022;16(1):100341.
- Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. 2022;28(3):583-590.
- Abd-Elseyed A, D'Souza RS. The burden of coronavirus disease 2019–related cases, hospitalizations, and mortality based on vaccination status and mandated mask use: Statewide data from wisconsin and narrative review of the literature. *Anesth Analg*. 2022;134(3):524-531.
- Shankar PR, Palaian S, Vannal V, Sreeramareddy CT. Non-pharmacological infection prevention and control interventions in COVID-19: What does the current evidence say? *Int J Prev Med*. 2022;12(12):12-174 (18 December 2021) DOI: 10.4103/ijpvm.IJPVM_604_20.
- Chen J-M, Chen Y-Q. China Can prepare to end its zero-COVID policy. *Nat Med*. 2022;28(6):1-2.
- Khiat A E, Hamdan YA, Tamegart L, et al. Therapeutic management of COVID-19 patients: pharmacological and non-pharmacological approaches. In: *Handbook of research on pathophysiology and strategies for the management of COVID-19*. IGI Global; 2022:210-220.
- Stefan MS, Eltanbedawi A, Devoe NC, et al. Death among patients hospitalized with symptomatic COVID-19: Implications for high-risk patients. *J Hosp Med*. 2022;17(4):252-258.
- Windsor L, Benoit E, Pinto R M, Sarol J. Optimization of a new adaptive intervention using the SMART design to increase COVID-19 testing among people at high risk in an urban community. *Trials*. 2022;23(1):1-16.

20. Page MJ, Moher D, McKenzie JE. Introduction to PRISMA 2020 and implications for research synthesis methodologists. *Res Synth Methods*. 2022;13(2):156-163.
21. Health NIo. *Coronavirus disease 2019 (COVID-19) treatment guidelines*. 2020.
22. Del Sole F, Farcomeni A, Loffredo L, et al. Features of severe COVID-19: A systematic review and meta-analysis. *Eur J Clin Investig*. 2020;50(10):e13378.
23. White H, Thygesen K, Alpert JS, Jaffe A. Universal MI definition update for cardiovascular disease. *Curr Cardiol Rep*. 2014;16(6):1-10.
24. Nixon AM, Gunel M, Sumpio BE. The critical role of hemodynamics in the development of cerebral vascular disease: A review. *J Neurosurg*. 2010;112(6):1240-1253.
25. Sharma A, Nagalli S. Chronic liver disease. In: *StatPearls [Internet]*. StatPearls Publishing; 2021:37
26. Bernard G, Artigas A, Brigham K, et al. Report of the American-European consensus conference on ARDS: Definitions, mechanisms, relevant outcomes and clinical trial coordination. *Intensive Care Med*. 1994;20(3):225-232.
27. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000.
28. Abdollahi A, Mahmoudi-Aliabadi M, Mehrtash V, Jafarzadeh B, Salehi M. The novel coronavirus SARS-CoV-2 vulnerability association with ABO/Rh blood types. *Iran J Pathol*. 2020;15(3):156.
29. Abdollahpour I, Aguilar-Palacio I, Gonzalez-Garcia J, et al. Model prediction for in-hospital mortality in patients with COVID-19: A case-control study in Isfahan, Iran. *Am J Trop Med Hyg*. 2021;104(4):1476.
30. Abkhoo A, Shaker E, Mehrabinejad M-M, Azadbakht J, Sadighi N, Salahshour F. Factors predicting outcome in intensive care unit-admitted COVID-19 patients: using clinical, laboratory, and radiologic characteristics. *Crit Care Res Pract*. 2021;1(1):9941570
31. Abrishami A, Dalili N, Mohammadi Torbati P, et al. Possible association of vitamin D status with lung involvement and outcome in patients with COVID-19: A retrospective study. *Eur J Nutr*. 2021;60(4):2249-2257.
32. Abrishami A, Eslami V, Arab-Ahmadi M, Alahyari S, Azhideh A, Sanei-Taheri M. Prognostic value of inflammatory biomarkers for predicting the extent of lung involvement and final clinical outcome in patients with COVID-19. *J Res Med Sci*. 2021;26(1).
33. Adham D, Habibzadeh S, Ghobadi H, Jain SA, Abbasi-Ghahramanloo A, Moradi-Asl E. Epidemiological characteristics and mortality risk factors among COVID-19 patients in Ardabil, Northwest of Iran. *BMC Emerg Med*. 2021;21(1):1-6.
34. Afaghi S, Tarki FE, Rahimi FS, et al. Prevalence and clinical outcomes of vitamin D deficiency in COVID-19 hospitalized patients: A retrospective single-center analysis. *Tohoku J Exp Med*. 2021;255(2):127-134.
35. Aghajani MH, Sadeghi R, Miri R, et al. Is cardiac Troponin I considered as A predictor of in-hospital mortality among COVID-19 patients? A retrospective cohort study. *Bulletin of Emergency & Trauma*. 2022;10(1):9.
36. Aghajani MH, Sistanizad M, Pourhoseingholi A, Asadpoordezaki Z, Taherpour N. Development of a scoring system for the prediction of in-hospital mortality among COVID-19 patients. *Clin Epidemiol Glob Health*. 2021;12(1):100871.
37. Aghajani MH, Toloui A, Aghamohammadi M, et al. Electrocardiographic findings and in-hospital mortality of COVID-19 patients; a retrospective cohort study. *Archives of Academic Emergency Medicine*. 2021;9(1):45.
38. Ahmadi A, Ardeshiri S, Nezhadi VR, et al. Risk Factors for Mortality in Hospitalized Patients with COVID-19: A Cross-Sectional Study in Southwestern Iran. *Iran Red Crescent Med J*. 2021;23(9):32-36.
39. Alamdari NM, Afaghi S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. *Tohoku J Exp Med*. 2020;252(1):73-84.
40. Aliasgarzade S, Matin S, Javaheri N, Aliasgarzade J, Aghamohammadi V. Coagulation disorders in hospitalized COVID-19 patients and relationship with disease outcome: A cross-sectional study. *Arch Clin Infect Dis*. 2021;16(5):e114213.
41. Asgari A, Hazrati E, Soleiman-Meigooni S, Rajaeinejad M, Nasiri M. Vitamin D insufficiency in disease severity and prognosis of the patients with SARS corona virus-2 infection. *Acta Med Iran*. 2021;59(11):662-668.
42. Azarkar Z, Salehiniya H, Kazemi T, Abbaszadeh H. Epidemiological, imaging, laboratory, and clinical characteristics and factors related to mortality in patients with COVID-19: A single-center study. *Osong Public Health Res Perspect*. 2021;12(3):169.
43. Borzouei S, Mohammadian-Khoshnoud M, Omidi T, et al. Predictors of COVID-19 related death in diabetes patients: A case-control study in Iran. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2021;15(4):102149.
44. Davarpanah AH, Asgari R, Moharamzad Y, et al. Risk factors for poor outcome in patients with severe viral pneumonia on chest CT during the COVID-19 outbreak: A perspective from Iran. *SN comprehensive Clinical Medicine*. 2020;2(9):1366-1376.
45. Derakhshanian H, Rastad H, Ghosh S, et al. The predictive power of serum vitamin D for poor outcomes in COVID-19 patients. *Food Sci Nutr*. 2021;9(11):6307-6313.
46. Emami A, Akbari A, Basirat A, et al. The role of comorbidities on mortality of COVID-19 in patients with diabetes. *Obesity Medicine*. 2021;25(1):100352.
47. Esfahanian F, SeyedAlinaghi S, Janfaza N, Tantuoyir MM. Predictors of hospital mortality among patients with COVID-19 in Tehran, Iran. *SAGE Open Med*. 2021;9(1):20503121211051573.
48. Faghieh Dinevari M, Somi MH, Sadeghi Majd E, Abbasalizad Farhangi M, Nikniaz Z. Anemia predicts poor outcomes of COVID-19 in hospitalized patients: A prospective study in Iran. *BMC Infect Dis*. 2021;21(1):1-7.
49. Faraji N, Alizadeh N, Akrami M, et al. Investigating the survival-related factors in the hospitalized elderly patients with COVID-19. *Iran J Epidemiology*. 2021;16(5):60-69.
50. Fatemi A, Ardehali SH, Eslamian G, Noormohammadi M, Malek S. Association of vitamin D deficiency with COVID-19 severity and mortality in Iranian people: A prospective observational study. *Acute and Critical Care*. 2021;36(4):300-307.
51. Fathi M, Taghizadeh F, Mojtahedi H, Jame SZB, Moghaddam NM. The effects of Alzheimer's and Parkinson's disease on 28-day mortality of COVID-19. *Rev Neurol (Paris)*. 2022;178(1-2):129-136.
52. Ghadamgahi F, Tapak L, Bashirian S, Amiri R, Roshanaei G. The effect of underlying diabetes disease on clinical outcome and survival in patients with COVID-19: A propensity score matching study. *Journal of Diabetes & Metabolic Disorders*. 2021;20(2):1675-1683.

53. Ghaffari M, Ansari H, Beladimoghdam N, et al. Neurological features and outcome in COVID-19: Dementia can predict severe disease. *J Neurovirol.* 2021;27(1):86-93.
54. Ghamari A, Rezaei N, Ranjbar M, Farzadfar F. The effect of hookah use on COVID-19 related adverse outcomes: Lessons learned from integrating STEPs 2016 and national COVID-19 registration databases. *Tob Induc Dis.* 2022;20(11):36.
55. Hajiahmadi S, Shayganfar A, Janghorbani M, et al. Chest computed tomography severity score to predict adverse outcomes of patients with COVID-19. *Infect Chemother.* 2021;53(2):308.
56. Hashemi S, Holakoui-Naeini K, Mansournia M, et al. Mortality risk factors in patients with COVID-19 infection: A case-control study in northeast of Iran. *Iranian Journal of Epidemiology.* 2021;17(3):224-235.
57. Homayounieh F, Zhang EW, Babaei R, et al. Clinical and imaging features predict mortality in COVID-19 infection in Iran. *Plos one.* 2020;15(9):e0239519.
58. Honarvar MR, Roshandel G, Shirzad-Aski H, et al. Epidemiological and clinical characteristics of the COVID-19 epidemic and associated factors for mortality in Golestan province, Iran: A retrospective cohort study. *J Prev Med Hyg.* 2021;62(2):E298.
59. Izadi A, Darban M, Geremi MK, et al. The Laboratory and Clinical Factors Associated with Mortality in COVID-19 Patients. *Middle East J Rehabil Health Stud.* 2021;8(3):e113451.
60. Soltanian AR. Demographic and clinical features association with mortality in patients with COVID-19: A cross-sectional study in the west of Iran. *Acta Med Iran.* 2021;59(10):587-594.
61. Javanian M, Bayani M, Shokri M, et al. Risk factors for mortality of 557 adult patients with COVID 19 in Babol, northern Iran: A retrospective cohort study. *Bratisl Lek Listy.* 2021;122(1):34-38.
62. Karami M, Khazaei S, Shahbazi F, et al. Epidemiological features of COVID-19 epidemic in Hamadan province, finding of a ten-month period. *Iranian Journal of Epidemiology.* 2021;17(3):244-253.
63. Karami M, Mirzaei M, Shahbazi F, et al. Predictors of death in patients with COVID-19: A cross-sectional study in west of Iran. *Med J Islam Repub Iran.* 2021;35(1):103.
64. Kashefzadeh A, Ohadi L, Golmohammadi M, et al. Clinical features and short-term outcomes COVID-19 in Tehran, Iran: An analysis of mortality and hospital stay. *Acta Bio Medica: Atenei Parmensis.* 2020;91(4):e2020147.
65. Kazemi MA, Ghanaati H, Moradi B, et al. Prognostic factors of initial chest ct findings for icu admission and mortality in patients with COVID-19 pneumonia. *Iran J Radiol.* 2020;17(4):e106879.
66. Khankeh H, Farrokhi M, Ghadicolaei HT, et al. Epidemiology and factors associated with COVID-19 outbreak-related deaths in patients admitted to medical centers of Mazandaran University of Medical Sciences. *J Educ Health Promot.* 2021;10(1):426.
67. Khoshnood RJ, Ommi D, Zali A, et al. Epidemiological characteristics, clinical features, and outcome of COVID-19 patients in northern Tehran, Iran; a cross-sectional study. *Adv J Emerg Med.* 2020;127(104378):10.1016.
68. Kolivand P, Fathi M, Kheyrati L, Lak M. Exposure to sulfur mustard increases the risk for mortality in patients with COVID-19 infection: A cohort study. *Am J Emerg Med.* 2022;51(1):144-149.
69. Kouhsari E, Sadeghifard N, Karimian M, et al. The effectiveness of laboratory parameters in predicting the in-hospital mortality of Iranian patients with coronavirus disease 2019 (COVID-19). *Annali di Igiene: Medicina Preventiva e di Comunita.* 2022;34(2):128-136.
70. Marateb HR, von Cube M, Sami R, et al. Absolute mortality risk assessment of COVID-19 patients: The Khorshid COVID cohort (KCC) study. *BMC Med Res Methodol.* 2021;21(1):1-9.
71. Mirjalili M, Dehghani M, Raadabadi M, Dehghani A. Death risk among COVID-19 patients in Yazd, Iran: A hospital-based case-cohort study. *Journal of Military Medicine.* 2021;23(3):274-282.
72. Moftakhar L, Piraei E, Mohammadi Abnavi M, Moftakhar P, Azarbaksh H, Valipour A. Epidemiological features and predictors of mortality in patients with COVID-19 with and without underlying hypertension. *Int J Hypertens.* 2021(1):33.
73. Moradzadeh R, Jamalians SM, Nazari J, et al. Age-standardized mortality rate and predictors of mortality among COVID-19 patients in Iran. *J Educ Health Promot.* 2021;10(1):169.
74. Nabavi S, Javidarabshahi Z, Allahyari A, et al. Clinical features and disease severity in an Iranian population of inpatients with COVID-19. *Sci Rep.* 2021;11(1):1-9.
75. Navayi M, Fanoodi A, Salmani F, Abedi F, Shetty S, Riahi SM. Over 60 years of age as an independent prognostic factor of in-hospital mortality among COVID-19 patients: A cohort study in an Iranian high-incidence area. *Public Health.* 2021;200(1):33-38.
76. Pazoki M, Keykhaei M, Kafan S, et al. Risk indicators associated with in-hospital mortality and severity in patients with diabetes mellitus and confirmed or clinically suspected COVID-19. *Journal of Diabetes & Metabolic Disorders.* 2021;20(1):59-69.
77. Pishgahi M, Toudeshki KK, Safari S, Youseffard M. Echocardiographic abnormalities as independent prognostic factors of in-hospital mortality among COVID-19 patients. *Arch Acad Emerg Med.* 2021;9(1):e21.
78. Pourfarzi F, Rahim Pouran S, Dargahi A, et al. The healthy behaviours and COVID-19 mortality among Iranian women: A case-control study. *BMC Womens Health.* 2021;21(1):1-8.
79. Rashidi F, Barco S, Kamangar F, et al. Incidence of symptomatic venous thromboembolism following hospitalization for coronavirus disease 2019: Prospective results from a multi-center study. *Thromb Res.* 2021;198(1):135-138.
80. Rastad H, Karim H, Ejtahed H-S, et al. Risk and predictors of in-hospital mortality from COVID-19 in patients with diabetes and cardiovascular disease. *Diabetol Metab Syndr.* 2020;12(1):1-11.
81. Rezaei N, Montazeri F, Malekpour M-R, et al. COVID-19 in patients with diabetes: Factors associated with worse outcomes. *Journal of Diabetes & Metabolic Disorders.* 2021;20(2):1605-1614.
82. Riahi T, Shokri S, Faiz SHR, et al. Clinical and laboratory predictors of mortality in hospitalized COVID-19 patients. *Iran Red Crescent Med J.* 2021;23(5):e531.
83. Seif M, Sharafi M, Ghaem H, Kasraei F. Factors associated with survival of Iranian patients with COVID-19: Comparison of Cox regression and mixture cure model. *Trop Dis Travel Med Vaccines.* 2022;8(1):1-7.
84. Shahidsales S, Aledavood SA, Joudi M, Molaie F, Esmaily H, Javadinia SA. COVID-19 in cancer patients may be presented by atypical symptoms and higher mortality rate, a case-controlled study from Iran. *Cancer Rep.* 2021;4(5):e1378.
85. Toofan F, Hosseini SM, Alimohammadzadeh K, Jafari M, Bahadori M. Impact of comorbidities on mortality in hospitalized patients with COVID-19: An experience from Iran. *J Educ Health Promot.* 2021;10(1):21.

86. Zahirian Moghadam T, Rahimpouran S, Dargahi A. The effect of working-based individual protective behaviors (WIPB) on COVID-19 mortality in north-west of Iran: A case-control study. *Journal of Occupational Health and Epidemiology*. 2021;10(3):158-168.
87. Zamanian M, Foroozanfar Z, Izadi Z, et al. Association of underlying diseases and clinical characteristics with mortality in patients with 2019 novel coronavirus in Iran. *Arch Clin Infect Dis*. 2020;15(5):e104621.
88. Zandkarimi E. Factors affecting the recovery of Kurdistan province COVID-19 patients: A cross-sectional study from March to June 2020. *Epidemiol Method*. 2021;10(1):26.
89. Zandkarimi E, Moradi G, Mohsenpour B. The prognostic factors affecting the survival of Kurdistan province COVID-19 patients: A cross-sectional study from February to May 2020. *Int J Health Policy Manag*. 2022;11(4):453-458.
90. Goshayeshi L, Akbari Rad M, Bergquist R, Allahyari A, Hashemzadeh K, Hoseini B. Demographic and clinical characteristics of severe COVID-19 infections: A cross-sectional study from Mashhad University of medical sciences, Iran. *BMC Infect Dis*. 2021;21(1):1-8.
91. Hashemi-Shahri SM, Tabatabaei SMN, Ansari-Moghaddam A, et al. Epidemiological and clinical risk factors related to severe COVID-19 in Iran: A multi-center study. *BMC Infect Dis*. 2022;22(1):1-11.
92. Hosseinzadeh R, Goharrizi MASB, Bahardoust M, et al. Should all patients with hypertension be worried about developing severe coronavirus disease 2019 (COVID-19)? *Clinical Hypertension*. 2021;27(1):1-7.
93. Javanmard SH, Vaseghi G, Manteghinejad A, Nasirian M. Neutrophil-to-Lymphocyte ratio as a potential biomarker for disease severity in COVID-19 patients. *J Glob Antimicrob Resist*. 2020;22(1):862.
94. Moradinia M, Sameie M, Mohamadebrahimi H, Shahraki S, Dorri S. Factors related to the hospital admissions of COVID-19 patients in the intensive care unit of selected Iranian navy hospitals. *Iranian Journal of War and Public Health*. 2021;13(2):109-113.
95. Sadeghi A, Eslami P, Moghadam AD, et al. COVID-19 and ICU admission associated predictive factors in Iranian patients. *Caspian J Intern Med*. 2020;11(Suppl 1):512.
96. Shayganfar A, Sami R, Sadeghi S, et al. Risk factors associated with intensive care unit (ICU) admission and in-hospital death among adults hospitalized with COVID-19: A two-center retrospective observational study in tertiary care hospitals. *Emerg Radiol*. 2021;28(4):691-697.
97. Pal R, Banerjee M, Yadav U, Bhattacharjee S. Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: A systematic review of literature. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(6):1563-1569.
98. Mahamat-Saleh Y, Fiolet T, Rebeaud ME, et al. Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: A systematic review and meta-analysis of observational studies. *BMJ open*. 2021;11(10):e052777.
99. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia—a systematic review, meta-analysis, and meta-regression. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(4):395-403.
100. Khorrami Z, Rezapour M, Etemad K, et al. The patterns of non-communicable disease multimorbidity in Iran: A multilevel analysis. *Sci Rep*. 2020;10(1):1-11.
101. Mirjalili H, Dastgheib SA, Shaker SH, et al. Proportion and mortality of Iranian diabetes mellitus, chronic kidney disease, hypertension and cardiovascular disease patients with COVID-19: A meta-analysis. *Journal of Diabetes & Metabolic Disorders*. 2021;20(1):905-917.
102. Bajgain KT, Badal S, Bajgain BB, Santana MJ. Prevalence of comorbidities among individuals with COVID-19: A rapid review of current literature. *Am J Infect Control*. 2021;49(2):238-246.
103. Sepandi M, Taghdir M, Alimohamadi Y, Afrashteh S, Hosamirudsari H. Factors associated with mortality in COVID-19 patients: A systematic review and meta-analysis. *Iran J Public Health*. 2020;49(7):1211.
104. 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. *Aging Male*. 2020;23(5):1416-1424.
105. Statement – Older people are at highest risk from COVID-19, but all must act to prevent community spread: World Health Organization. <https://www.who.int/europe/news/item/03-04-2020-statement-older-people-are-at-highest-risk-from-covid-19-but-all-must-act-to-prevent-community-spread>
106. Nikpouraghdam M, Farahani AJ, Alishiri G, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. *J Clin Virol*. 2020;127(1):104378.
107. Ghasemian R, Alizadeh-Navaei R, Boskabadi J, Rezaei Kalantari K. Clinical features and paraclinical findings of patients died of COVID-19 in a referral hospital in sari, Iran, February 2020-May 2020. *Journal of Mazandaran University of Medical Sciences*. 2021;31(198):119-132.
108. Bajaj V, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, immunity, and COVID-19: How age influences the host immune response to coronavirus infections? *Front Physiol*. 2021;11(1):571416.
109. Weiskopf D, Weinberger B, Grubeck-Loebenstien B. The aging of the immune system. *Transpl Int*. 2009;22(11):1041-1050.
110. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943.
111. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun*. 2020;11(1):1-10.
112. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of sex, age, and comorbidities with mortality in COVID-19 patients: A systematic review and meta-analysis. *Intervirology*. 2021;64(1):36-47.
113. Galbadage T, Peterson BM, Awada J, et al. Systematic review and meta-analysis of sex-specific COVID-19 clinical outcomes. *Front Med (Lausanne)*. 2020;7(1):348.
114. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. *Clin Rev Allergy Immunol*. 2019;56(3):308-321.
115. Caronna E, Ballvé A, Llauradó A, et al. Headache: A striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. *Cephalalgia*. 2020;40(13):1410-1421.
116. Trigo J, García-Azorín D, Planchuelo-Gómez Á, et al. Factors associated with the presence of headache in hospitalized

- COVID-19 patients and impact on prognosis: A retrospective cohort study. *J Headache Pain*. 2020;21(1):1-10.
117. Gil-Rodrigo A, Miró Ò, Pinera P, et al. Analysis of clinical characteristics and outcomes in patients with COVID-19 based on a series of 1000 patients treated in spanish emergency departments. *Emergencias: Revista de la Sociedad Espanola de Medicina de Emergencias*. 2020;32(4):233-241.
 118. Gonzalez-Martinez A, Fanjul V, Ramos C, et al. Headache during SARS-CoV-2 infection as an early symptom associated with a more benign course of disease: A case-control study. *Eur J Neurol*. 2021;28(10):3426-3436.
 119. Membrilla JA, De Lorenzo Í, Sastre M, Diaz de Teran J. Headache as a cardinal symptom of coronavirus disease 2019: A cross-sectional study. *Headache: The Journal of Head and Face Pain*. 2020;60(10):2176-2191.
 120. Planchuelo-Gómez Á, Trigo J, de Luis-García R, Guerrero ÁL, Porta-Etessam J, García-Azorín D. Deep phenotyping of headache in hospitalized COVID-19 patients via principal component analysis. *Front Neurol*. 2020;11(1):583870.
 121. Allali G, Marti C, Groscurin O, Morélot-Panzini C, Similowski T, Adler DE. Dyspnea: The vanished warning symptom of COVID-19 pneumonia. *J Med Virol*. 2020;92(11):2272-2273.
 122. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Clin Virol*. 2020;127(1):104371.
 123. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *Journal of Infection*. 2020;81(2):e16-e25.
 124. Li X, Liu C, Mao Z, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: A systematic review and meta-analysis. *Crit Care*. 2020;24(1):1-10.
 125. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. *Am J Emerg Med*. 2021;42(1):60-69.
 126. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2020;58(7):1021-1028.
 127. Yang L, Jin J, Luo W, Gan Y, Chen B, Li W. Risk factors for predicting mortality of COVID-19 patients: A systematic review and meta-analysis. *PLoS One*. 2020;15(11):e0243124.
 128. Akbar MR, Wibowo A, Pranata R, Setiabudiawan B. Low serum 25-hydroxyvitamin D (vitamin D) level is associated with susceptibility to COVID-19, severity, and mortality: a systematic review and meta-analysis. *Front Nutr*. 2021;8(660420):37.
 129. Ghasemian R, Shamshirian A, Heydari K, et al. The role of vitamin D in the age of COVID-19: A systematic review and meta-analysis. *Int J Clin Pract*. 2021;75(11):e14675.
 130. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: Systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2022;62(5):1308-1316.