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Evaluation of the Effect of Underlying Diseases on Mortality of COVID-19 Patients: A Study of 19,985 Cases

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Abstract

Background: The outbreak of a new coronavirus in China in 2019 (COVID-19) caused a global health crisis.
Objectives: This study was performed to investigate the effect of different underlying diseases on mortality in patients with COVID-19.
Methods: This retrospective cohort study was performed on COVID-19 patients admitted to the Shahid Rahimi and Sohada-ye Ashayer teaching hospitals in Khorramabad, Iran, from 2019 to 2021. Data on disease severity, clinical manifestations, mortality, and underlying disorders were collected and analyzed using the SPSS software version 22 at a 95% confidence interval and 0.05 significance level.
Results: The study included 9653 men (48%) and 10332 women (52%). Patients with chronic kidney diseases, cancer, chronic obstructive pulmonary disease, hypertension, cardiovascular disease, and diabetes were at higher mortality risk than those without these underlying diseases, respectively. However, there was no significant relationship between asthma and mortality. Also, age $>$ 50 years, male gender, oxygen saturation $<$ 93 on admission, and symptoms lasting $\leq$ 5 days were associated with increased mortality.
Conclusions: Since patients with underlying diseases are at higher mortality risk, they should precisely follow the advice provided by health authorities and receive a complete COVID-19 vaccination series.

Keywords: Coronavirus, Mortality, SARS-CoV-2, Comorbidity

1. Background

Coronaviruses are a family of single-stranded ribonucleic acid viruses (1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to the coronavirus (COVID-19) pandemic. The first cases were observed in Wuhan, China, in late 2019, and the disease spread to other regions rapidly (2). As of 20 May 2022, 521,920,560 confirmed cases of COVID-19 were reported worldwide, leading to 6,274,323 deaths (3). In the Middle East, SARS-CoV-2 was first reported in Iran (4). COVID-19 patients may present with different symptoms; however, the respiratory system is mainly involved. Respiratory presentations of COVID-19 may vary from mild symptoms to acute respiratory distress syndrome (5). Reverse transcription polymerase chain reaction (RT–PCR) on samples collected via nasopharyngeal and oropharyngeal swabs is the ideal diagnostic test. Laboratory and radiographic studies have also been widely used (6). In a fraction of patients, COVID-19 leads to systemic disease identified by multisystem organ damage. Various factors such as advanced age, male gender, lymphopenia, and increased cytokine levels have been attributed to a worse prognosis in patients (7, 8). Furthermore, several underlying diseases are associated with a poorer prognosis, including hypertension, diabetes, malignancy, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and chronic liver disease (9, 10).

2. Objectives

Given the high burden of COVID-19 in Iran and the importance of recognizing prognostic factors in patients, this study was conducted to evaluate the effect of underlying diseases on mortality in COVID-19 patients admitted to the

Shahid Rahimi and Sohada-ye Ashayer teaching hospitals in Khorramabad, Iran, from 2019 to 2021.

3. Methods

3.1. Study Design and Participants

This was a retrospective cohort conducted in the Shahid Rahimi and Sohada-ye Ashayer teaching hospitals in Khorramabad, Iran. Inclusion criteria were all patients admitted to inpatient wards of the mentioned hospitals from the beginning of the pandemic in Iran to 21 May 2021 with a diagnosis of COVID-19 that was confirmed either with a positive RT–PCR or clinical symptoms and paraclinical evidence in favor of COVID-19 diagnosis, i.e., pulmonary ground glass opacities on chest computed tomography scan and reduced oxygen saturation. The patients were selected using the census sampling method. Patients with incomplete medical records were excluded.

3.2. Data Collection

In this study, a researcher-made checklist was used to collect the data. After obtaining written consent, demographic characteristics including age and gender, as well as data related to oxygen saturation on admission, duration of symptoms, time from admission to death, and previous history of hypertension, diabetes, brain diseases, malignancies, asthma, COPD, chronic kidney diseases, and CVD, were registered in the checklist.

3.3. Data Analysis

The collected data were analyzed using the SPSS software version 22. Qualitative indexes were used to describe the data, including frequency, percentage, mean, and standard deviation (SD). Also, chi-square and Fisher's exact tests were used to investigate the relationship between the variables and mortality in patients. The odds ratio (OR) and 95% confidence interval (95% CI) were estimated using logistics regression. The significance level was set at 0.05 for all tests.

4. Results

This study included 19985 COVID-19 patients, of whom1852 (9.3%) died from COVID-19, and 18133 (90.7%) survived. The relationship between demographic characteristics and mortality is shown in Table 1. There was a significant relationship between age and death from COVID-19 in patients $\geq$ 50 years ($P < 0.001$). Regarding gender, men were at higher mortality risk than women (OR = 1.379; CI = 1.252 - 1.518).

As shown in Table 2, oxygen saturation < 93 on admission and being symptomatic for $\leq$ 5 days were associated with higher mortality risk, with an OR (05% CI) of 3.475 (3.067 - 3.937) and 0.794 (0.703 - 0.896), respectively. The relationship between underlying diseases and mortality is shown in Table 3. Patients with chronic kidney diseases had the highest mortality risk due to COVID-19, with an OR (95% CI) of 3.064 (2.285 - 4.108). Also, patients with cancer, COPD, hypertension, CVD, and diabetes were at higher mortality risk than those without these underlying diseases, respectively. However, there was no significant relationship between asthma and mortality ($P = 0.241$).

The relationship between medications taken for underlying diseases and mortality in COVID-19 patients was investigated. Table 4 shows a significant relationship between drug history and death due to COVID-19 in patients with CVD, COPD, and chronic kidney diseases ($P < 0.05$). Anti-coagulants + antianginals had the highest frequency among CVD patients who died from COVID-19, and inhaled beta 2 agonists + corticosteroids had the highest frequency among those with COPD. Also, among 117 patients on dialysis, 44 (37.6%) died from COVID-19.

As shown in Table 5, a significant association was found between the age group and death due to COVID-19 in COPD patients. The majority of COPD patients (72.2%) who died from COVID-19 were older than 60 years. As shown in Table 6, no significant relationship was observed between the type of cancer and death due to COVID-19 ($P = 0.086$).

5. Discussion

This study aimed to investigate the effect of underlying diseases on mortality in COVID-19 patients admitted to the Shahid Rahimi and Sohada-ye Ashayer teaching hospitals in Khorramabad, Iran, from 2019 to 2021. Overall, 1852 of 19985 patients included (9.3%) died from COVID-19. Mortality rates due to COVID-19 vary significantly in different regions and countries (11). Economic and social factors affect public health considerably. People in crowded areas can hardly maintain principles of social distancing (12). An overall case fatality rate of 10.05% has been reported in Iran, which is consistent with our findings (13).

Advanced age is assumed to be associated with a higher mortality rate in COVID-19 patients (14, 15). Patients aged $\geq$ 50 years have been estimated to have a 15.4-folds mortality risk compared with those aged < 50 years (16). The highest mortality rate has been reported in individuals aged

Table 1. The Relationship Between Demographic Characteristics and Mortality in Patients with COVID-19 in Khorramabad

Characteristics	Death		OR (95% CI)	P-Value
	No, Frequency (%)	Yes, Frequency (%)		
Age group				
< 30	1738 (97.3)	49 (2.7)	-	-
30 - 39	2871 (98.3)	50 (1.7)	0.618 (0.415 - 0.920)	0.018
40 - 49	3243 (97.1)	96 (2.9)	1.050 (0.741 - 1.489)	0.784
50 - 59	3238 (94.2)	201 (5.8)	2.202 (1.360 - 3.025)	< 0.001
60 - 69	3463 (89.7)	398 (10.3)	4.076 (3.013 - 5.515)	< 0.001
70 - 79	2090 (82.7)	437 (17.3)	7.416 (5.483 - 10.032)	< 0.001
80 ≤	1490 (70.6)	621 (29.4)	14.783 (10.963 - 19.934)	< 0.001
Gender				
Female	9509 (92)	823 (8)	-	-
Male	8624 (89.3)	1029 (10.7)	1.379 (1.252 - 1.518)	< 0.001

Table 2. The Relationship Between Clinical Variables and Mortality in Patients with COVID-19 in Khorramabad

Variables	Death		OR (95% CI)	P-Value
	No, Frequency (%)	Yes, Frequency (%)		
Oxygen saturation on admission				
93 ≤	7525 (96)	314 (4)	-	-
< 93	10608 (87.3)	1538 (12.7)	3.475 (3.067 - 3.937)	< 0.001
Duration of symptoms				
≤ 5	8164 (90.4)	866 (9.6)	-	-
5 <	5046 (92.2)	425 (7.8)	0.794 (0.703 - 0.896)	< 0.001

≥ 80 years (17). Similarly, this study showed a significant relationship between age and death from COVID-19 in patients ≥ 50 years. This can be justified by the physiological aging process and accompanying comorbidities in the elderly, which reduce the capacity against infections (17, 18). In the studied population, men were at higher mortality risk than women. The higher mortality rate of COVID-19 observed in men agreed with previous studies (19-21). The effect of gender on immune response against viral infections has been widely studied. Women are less vulnerable to infections because of more intense and prolonged immune responses (22). More angiotensin-converting enzyme 2 (ACE2) receptors, higher smoking rates, and higher prevalence of underlying conditions among men are other possible reasons (23).

In this study, patients with oxygen saturation < 93 on admission or symptomatic for ≤ 5 were at higher mortality risk. In previous studies, oxygen saturation of less than 90% and less than 80% on admission have been suggested as predictors of mortality (24). Clinical mechanisms that lead to acute hypoxemia can also enhance hyperinflammation. Furthermore, hypoxemia is associated with higher mortality due to acute respiratory distress syndrome, a significant complication of COVID-19 (25). The shorter duration of symptoms in patients who died from COVID-19 has been reported in the literature.

Individuals who fail to fight against viral replication in the early stages are more susceptible to developing intense inflammatory responses, which may lead to hospitalization and death (26). This study investigated the relationship between underlying diseases and mortality among patients with COVID-19. We observed that patients with chronic kidney diseases had the highest mortality risk due to COVID-19. Furthermore, those with a history of cancer, COPD, hypertension, CVD, and diabetes were at higher mortality risk than those without these underlying diseases. However, there was no significant relationship between asthma and mortality. These findings are consistent with data from previous studies (10, 27, 28).

Akin to many other patients with chronic conditions,

Table 3. The Relationship Between Underlying Diseases and Mortality in Patients with COVID-19 in Khorramabad

Underlying Disease	Death		OR (95% CI)	P-Value
	No, Frequency (%)	Yes, Frequency (%)		
Chronic kidney diseases				
No	17937 (90.9)	1792 (9.1)	-	-
Yes	196 (76.6)	60 (23.4)	3.064 (2.285 - 4.108)	< 0.001
Cancer				
No	17981 (90.9)	1807 (9.1)	-	-
Yes	152 (77.2)	45 (22.8)	2.946 (2.105 - 4.123)	< 0.001
COPD				
No	17879 (90.9)	1780 (9.1)	-	-
Yes	254 (77.9)	72 (22.1)	2.847 (2.182 - 3.716)	< 0.001
Hypertension				
No	15310 (92.1)	1322 (7.9)	-	-
Yes	2823 (84.2)	530 (15.8)	2.714 (1.951 - 2.423)	< 0.001
CVD				
No	16754 (91.6)	1537 (8.4)	-	-
Yes	1379 (81.4)	315 (18.6)	2.490 (2.180 - 2.844)	< 0.001
Diabetes				
No	16290 (91.5)	1519 (8.5)	-	-
Yes	1843 (84.7)	333 (15.3)	1.938 (1.705 - 2.202)	< 0.001
Asthma				
No	17942 (90.8)	1827 (9.2)	-	-
Yes	191 (88.4)	25 (11.6)	1.285 (0.845 - 1.956)	0.241

individuals with chronic kidney diseases have an impaired immune system and are more susceptible to upper respiratory tract infections and pneumonia (29). A pooled OR of 5.58 is reported in patients with chronic kidney diseases (30), which almost doubles the OR estimated in the present study. We also found a significant relationship between treatment taken and death due to COVID-19 in these patients. Overall, 37.6% of the patients on dialysis died from COVID-19 infection. This agrees with a study by Valeri et al. (31) who reported a 31% mortality rate due to COVID-19 patients on dialysis.

The suggested mechanism of high mortality in patients with underlying diseases such as hypertension and CVD is the function of ACE2, which plays a significant role in the immune and cardiovascular systems (10). ACE2 is known as the primary host cellular receptor of SARS-CoV-2. Patients with heart diseases may have increased ACE2 expression, which acts as a target of the virus (32). Moreover, infections lead to increased myocardial demand that may cause myocardial injury or infarction (33). Diabetes, another comorbidity associated with increased mortality in COVID-19 patients, may boost infection by increased viral entry into cells and inadequate immune responses (34). Similarly, in cancer patients, the immune system is compromised in various ways, which makes them more vulnerable to viral infections (35). In a study, COVID-19 complications were seen in 55.8% of cancer patients, and 21.2% of them died (36). Although cancer was associated with increased mortality risk due to COVID-19, no significant relationship was observed between the type of cancer and death. However, in a previous study, patients with lung cancer were reported to be at a higher risk of progressing more rapidly with COVID-19 (37).

Due to increased ACE2 in the lungs and impaired immune system, COPD is a significant risk factor for hospitalization, intensive care unit stay, and death in patients with COVID-19 (38). In a systematic review, the pooled OR of COPD for mortality was 1.93 (39). This ratio was 2.847 in the current study. Our findings showed that most COPD patients who died from COVID-19 were older than 60 years.

Table 4. Analysis of the Relationship Between Drug History and Death in COVID-19 Patients

Variables	Death		Total	P-Value [a]
	No, Frequency (%)	Yes, Frequency (%)		
Antihypertensive medication				0.213
ACEI/ARB	1164 (41.2)	222 (41.9)	1386 (41.3)	
Diuretics	57 (2)	12 (2.3)	69 (2.1)	
Ca channel blockers	369 (13.1)	81 (15.3)	450 (13.4)	
Beta blockers	506 (17.9)	108 (20.4)	614 (18.3)	
ACEI/ARB + Diuretic	512 (18.1)	77 (14.5)	589 (17.6)	
ACE/ARB+ Ca channel blockers	37 (1.3)	6 (1.1)	43 (1.3)	
Others	46 (1.6)	8 (1.5)	54 (1.6)	
No medication	132 (4.7)	16 (3)	148 (4.4)	
Diabetes medication				0.163
Metformin	220 (11.9)	47 (14.1)	267 (12.3)	
Metformin + glibenclamide/gliclazide	591 (32.1)	103 (30.9)	694 (31.9)	
SGLT2 inhibitors	178 (9.7)	24 (7.2)	202 (9.3)	
Metformin + SGLT2 inhibitors	206 (11.2)	37 (11.1)	243 (11.2)	
DPP-4 inhibitors	135 (7.3)	17 (5.1)	152 (7)	
Metformin + DPP-4 inhibitors	117 (6.3)	14 (4.2)	131 (6)	
Insulin	205 (11.1)	45 (13.5)	250 (11.5)	
Others	87 (4.7)	20 (6.0)	107 (4.9)	
No medication	104 (5.6)	26 (7.8)	130 (6)	
CVD medication				0.048
Anti-coagulants	114 (8.3)	25 (7.9)	139 (8.2)	
Anti-arrhythmics	87 (6.3)	17 (5.4)	104 (6.1)	
Antianginals	273 (19.8)	53 (16.8)	326 (19.2)	
Digitalis	96 (7)	25 (7.9)	121 (7.1)	
Anti-coagulants + antianginals	524 (38)	145 (46)	669 (39.5)	
Others	143 (10.4)	33 (10.5)	176 (10.4)	
No medication	142 (10.3)	17 (5.4)	159 (9.4)	
Asthma medication				0.236
Inhaled beta 2 agonists	32 (16.8)	7 (28)	39 (18.1)	
Inhaled beta 2 agonists + corticosteroids	127 (66.5)	13 (52)	140 (64.8)	
Leukotriene antagonists + inhaled beta 2 agonists + corticosteroids	20 (10.5)	3 (12)	23 (10.6)	
Others	5 (2.6)	2 (8)	7 (3.2)	
No medication	7 (3.7)	0 (0)	7 (3.2)	
COPD medication				0.037
Inhaled beta 2 agonists + corticosteroid	193 (76)	49 (68.1)	242 (74.2)	
Long-acting muscarinic antagonists	18 (7.1)	9 (12.5)	27 (8.3)	
Others	30 (11.8)	14 (19.4)	44 (13.5)	
No medication	13 (5.1)	0 (0)	13 (4)	
Chronic kidney diseases treatment				< 0.001
Dialysis	73 (37.2)	44 (73.3)	117 (45.7)	
Oral medication	119 (60.7)	16 (26.7)	135 (52.7)	
No medication	4 (2)	0 (0)	4 (1.6)	

Abbreviation: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SGLT2, sodium-glucose Cotransporter-2; DPP-4, dipeptidyl peptidase-4.

[a] Chi-square test

Similarly, Puebla Neira et al. (40) found the highest mortality risk in COPD patients aged 65 to 79. This study showed asthma as the only underlying condition not associated with an increased mortality risk. In this regard, controversial findings have been reported. However, the results of a systematic review on the role of asthma in the COVID-19

Table 5. Analysis of the Relationship Between Age Group and Death Due to COVID-19 in COPD Patients

Variables	Death		Total	P-Value
	No, Frequency (%)	Yes, Frequency (%)		
COPD patients' age group				0.004
< 40	5 (2)	2 (2.8)	7 (2.1)	
40 - 60	119 (46.9)	18 (25)	137 (42)	
60 <	130 (51.2)	52 (72.2)	182 (55.8)	

Table 6. Analysis of the Relationship Between the Type of Cancer and Death Due to COVID-19 in COPD Patients

Variables	Death		Total	P-Value
	No, Frequency (%)	Yes, Frequency (%)		
Type of cancer				0.086
Breast	29 (19.1)	5 (11.1)	34 (17.3)	
Prostate	15 (9.9)	5 (11.1)	20 (10.2)	
Lung	8 (5.3)	9 (20)	17 (8.6)	
Colorectal	60 (39.5)	16 (35.6)	76 (38.6)	
Gastric	21 (13.8)	4 (8.9)	25 (12.7)	
Hematological	5 (3.3)	2 (4.4)	7 (3.6)	
Others	14 (9.2)	4 (8.9)	18 (9.1)	

course indicate that owing to the presence of asthma as a premorbid condition in only 1.6% of COVID-19 patients, either it does not contribute to the development and progression of COVID-19 or clinicians have been underreporting the premorbidities in patients (41).

A limitation we encountered during this study was the incompleteness of the medical records of some patients, which led to their exclusion from the study. Also, as this was a retrospective study, the patients' medical history was obtained from their medical files. Hence, there is a possibility that the condition had not been recorded in some patients with mild forms of underlying diseases.

5.1. Conclusions

The presence of underlying diseases such as hypertension, diabetes, cancer, COPD, chronic kidney disease, and CVD, as well as age over 50 years, male gender, oxygen saturation < 93 on admission, and duration of symptoms > 5 days, can increase the mortality risk in COVID-19 patients. Therefore, individuals with underlying diseases should follow health protocols and complete the vaccination series. Furthermore, in hospitalized patients with mentioned risk factors, the healthcare team should be more careful to prevent adverse outcomes.

Footnotes

Authors' Contribution: T.Z. conceptualized and designed the study, A.N. coordinated data collection, A.K.R. reviewed and revised the manuscript, and G.M. contributed to data collection and drafting. All authors read and approved the final manuscript.

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Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to ethical considerations.

Ethical Approval: This study was conducted with the permission of the Research Ethics Committee of Lorestan University of Medical Sciences with the ethical code IR.LUMS.REC.1400.254 (webpage: ethics.research.ac.ir/ProposalCertificateEn.php?id=243748).

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