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Risk Factors Associated with Mortality in Hospitalized COVID-19 Patients: A Case Study from Southeast Iran

Ahmad Mohtashami[1,2], Milad Ahmadi Gohari[2], Abbas Bahrampour[1,2], Mohammad Hossein Mehrolhassani[3], Yunes Jahani[1,2*]

[1]Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
[2]Department of Biostatistics and Epidemiology, School of Public Health, Kerman University of Medical Sciences, Kerman, Iran
[3]Health Services Management Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

*__Corresponding Author:__ Yunes Jahani, Emails: u.jahani@kmu.ac.ir, yonesjahani@yahoo.com

Abstract
Background: This study aimed to identify mortality risk factors among hospitalized COVID-19 patients in southeast Iran.
Methods: This cross-sectional study used data from the COVID-19 patients admitted to Afzalipour teaching hospital in Kerman, Iran, from February 2020 to September 2021. The demographic and clinical data of 6,057 patients were analyzed using Bayesian network and logistic regression models.
Results: Out of 6,057 patients, 333 (5.5%) died. The most important risk factors for COVID-19 mortality were age, gender, fever, headache, decreased level of consciousness (LoC), chronic liver disease, blood oxygen level (BOL), admission season, and length of stay (LoS). Fever, headache, and longer LoS were protective and mortality-reducing variables.
Conclusion: Following model estimation results, it is recommended that older male patients with low oxygen levels and a lower LoC, as well as patients with chronic liver disease, receive additional medical care and not be discharged prematurely. Early medical interventions for high-risk patients may reduce COVID-19 mortality risk.
Keywords: Bayesian network, Logistic regression, Mortality, COVID-19

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Introduction

COVID-19 was a major healthcare challenge of this century. This new disease greatly impacted the lives of the world's population. It directly and indirectly caused many deaths in most countries. Until January 7, 2023, more than 667.86 million people had been infected with this disease, and 6.7 million people had died directly due to this disease worldwide (1). Like other involved countries, Iran adopted various policies to prevent the COVID-19 outbreak (2,3), but until January 7, 2023, about 7.56 million people had been infected, and 144.7 thousand people had died as a result (1). However, the real number of deaths in the country are believed to be higher than this (4).

Extensive studies have shown that the deaths caused by COVID-19 will have negative effects on the mental and psychological health of people in addition to the widespread economic and social consequences of the disease in the community (5,6). Fortunately, most patients with COVID-19 show mild to moderate symptoms, and only about 5% enter the critical phase of the disease (7). Different studies have shown that risk factors, including age, male gender, cardiovascular diseases, blood pressure, and diabetes, can expose the patient to critical conditions and death (8-11). The most common clinical symptoms of patients who died due to COVID-19 were shortness of breath, fever, dry cough, and impaired consciousness (8,10).

Although the prevalence of the disease has decreased drastically with widespread vaccination in different countries, countries will still not be safe from the risk of COVID-19 re-epidemic for years to come, as substrains of the Omicron variant have spread rapidly in China and Japan and have caused politicians to turn to the implementation of quarantine policy again. Thus, identifying important risk factors for patient death can effectively prioritize vaccination programs and improve healthcare services. Besides, the timely diagnosis of the referred patients can be helpful for special healthcare services in the early stages of the disease (12).

Various studies have shown that people's education and ethnicity determine the severity of COVID-19 and the number of deaths caused by it (9). Some studies have suggested that air pollution can increase the severity of COVID-19 directly by endangering the immunity of the lungs or indirectly due to the exacerbation of respiratory or cardiovascular diseases (13-15). Studies have also shown that temperature and humidity can affect the spread of COVID-19 (16). The health effects of COVID-19 vary in different regions because different social, economic, health, and environmental factors are at play (17). Studies have indicated that the areas with more economic and environmental problems often face more challenges against COVID-19 (18). Hence, depending on the demographic characteristics of different regions, the risk factors associated with mortality in COVID-19 patients vary (19). Therefore, an awareness of the most important factors affecting the death of hospitalized COVID-19 patients in southeastern Iran seemed necessary.

The present study sought to identify mortality risk factors among hospitalized COVID-19 patients in southeastern Iran. The insights from this study can help physicians in the rapid diagnosis of critically ill COVID-19 patients to prevent their death and to identify high-risk groups to allocate vaccines and other healthcare services in time.

Materials and Methods

Study design and sampling

This cross-sectional study utilized the data collected from 6057 COVID-19 patients hospitalized in the general ward of Afzalipour hospital in Kerman, Iran, between February 23, 2020, and September 7, 2021. Afzalipour hospital in Kerman, which provided care during the COVID-19 epidemic, is a referral hospital in southeast Iran.

Variables

The independent variables in this study were demographic characteristics (i.e., age, gender, residence, history of smoking and drug – opium – use, and season of admission), initial symptoms (e.g., fever, cough, muscle pain, headache, respiratory distress, compromised consciousness, anorexia, mitigated sense of smell and taste, chest pain, nausea, vomiting, dizziness, and diarrhea), history of diseases (such as hypertension, diabetes, cardiac disease, cancer, chronic lung diseases, chronic liver, blood, and kidney diseases, COVID-19, and chronic neurological disorders), and clinical variables (including blood oxygen level [BOL], oxygen therapy status, history of contact with COVID-19-infected people, duration of infection after the onset of symptoms, and length of stay (LoS). The status of the hospitalized patient at the time of discharge (recovered or deceased) served as the dichotomous response variable in this study.

Statistical analysis

The association between the independent variables and the outcome variable, i.e., the mortality of hospitalized patients with COVID-19, was determined using the Bayesian network and logistic regression models.

Bayesian networks have drawn increasing interest due to their efficacy in tackling complex problems and their assistance with decision-making under uncertain conditions (20). As integrated graphs, Bayesian networks can identify and visualize causal relationships between disease etiology and mortality (21). In addition, logistic regression is an effective and powerful method for analyzing the effect of a set of independent variables on a binary outcome.

GeNIe 3.0 academic software was used to fit the Bayesian network model. For the structural learning of the Bayesian network, the parent-offspring algorithm was employed, followed by the expectation-maximization algorithm for the network's parametric learning. A Bayesian network model portrays interrelationships as conditional distributions for a set of random variables. The output of the Bayesian network model was displayed as a directed acyclic graph, with nodes representing random variables and directed arcs representing the structure of conditional distributions. In addition, the conditional probabilities of mortality for various combinations of independent variables were calculated and tabulated.

In addition, R 4.1.2 was utilized to fit the logistic regression model. First, a univariate logistic regression model was run, and the variables with P-values less than 0.20 were selected as the inputs in the multiple logistic model. The backward method was used, and the variables with P-values less than 0.05 were considered significant in the final model.

The odds ratio (OR) of mortality, its confidence interval, and the P values were reported in tables. To confirm the validity of the models, indices such as accuracy, sensitivity, specificity, and areas under the ROC curve were calculated. Notably, the higher levels of these indices in each model indicate the model's good fit.

Results

Description of the data

Of the hospitalized patients, 5724 (94.5%) recovered and were discharged, while 333 (5.5%) died. In addition, 56.5% of the deceased patients were over 69 years old. Moreover, 2952 (51.9%) of the patients were male.

Most of the admitted patients were locals of Kerman. The median (min-max) of LoS in our study was 5 (1–30) days for recovered patients and 6 (1–30) days for deceased patients.

Approximately 67% of the patients admitted to the hospital had respiratory distress, which was the most common clinical symptom in the patients. About 96% of the patients were from Kerman. Only 0.40% of patients had a history of COVID-19. Figure 1 shows the demographic and clinical data of the patients.

The duration of infection after the onset of symptoms was more than six days in 53.7% of the patients. Besides, 92.4% of the patients stayed in the hospital for more than one day. The BOL of 57.5% of patients was less than 93%, and the most common underlying disease was hypertension (15.9%). Moreover, 5.5% of patients died due to COVID-19 (Figure 2).

The results of the logistic regression model

The multiple logistic regression model revealed a significant relationship between mortality and the variables of age, gender, fever, headache, altered level of consciousness (LoC), chronic liver disease, BOL, admission season, and LoS. Other variables were not significant. Table 1 displays the frequency (percent) of deceased patients, the odds ratio of death, and its 95% confidence interval for the significant variables.

The odds of death are greater in old age than in youth. Men's mortality odds were 1.29 times that of women. Patients with a decreased LoC were 4.97 times more likely to die than others.

The mortality odds of patients with chronic liver disease were 3.5 times that of other patients. In patients whose oxygen level was below 93, the odds of death were 1.43 times that of other patients. Additionally, summer and autumn had higher mortality odds than other seasons. The variables of fever, headache, and LoS had a protective effect against mortality, meaning that the presence of a fever, a headache, or longer LoS decreased the odds of mortality.

Bayesian network model results

According to the Bayesian network model, the variables of age, fever, decreased LoC, and LoS are the parent variables related to COVID-19 mortality. These variables have a direct and significant relationship with mortality and are more important (Figure 3).

Table 2 displays the conditional probability of death obtained from the Bayesian network. Only conditional probabilities greater than or equal to 0.5 are displayed in this table. As shown in this table, the subgroup of patients who were over 69 years old, did not have fever, had a lower LoC, and were hospitalized for less than one day had the highest probability of death (0.93).

Model evaluation

For the Bayesian network model, the sensitivity, specificity, and accuracy indices were 0.7928, 0.742, and 0.7448, and the corresponding values for the logistic regression model were 0.7568, 0.7926, and 0.7907, respectively. The area under the ROC curve (95% CI) was 0.829 (0.805–0.853) for the Bayesian network model and 0.846 (0.824–0.868) for the logistic regression model. Both models had a good and acceptable fit.

Discussion

This study investigated and identified the risk factors, including clinical and demographic variables, that

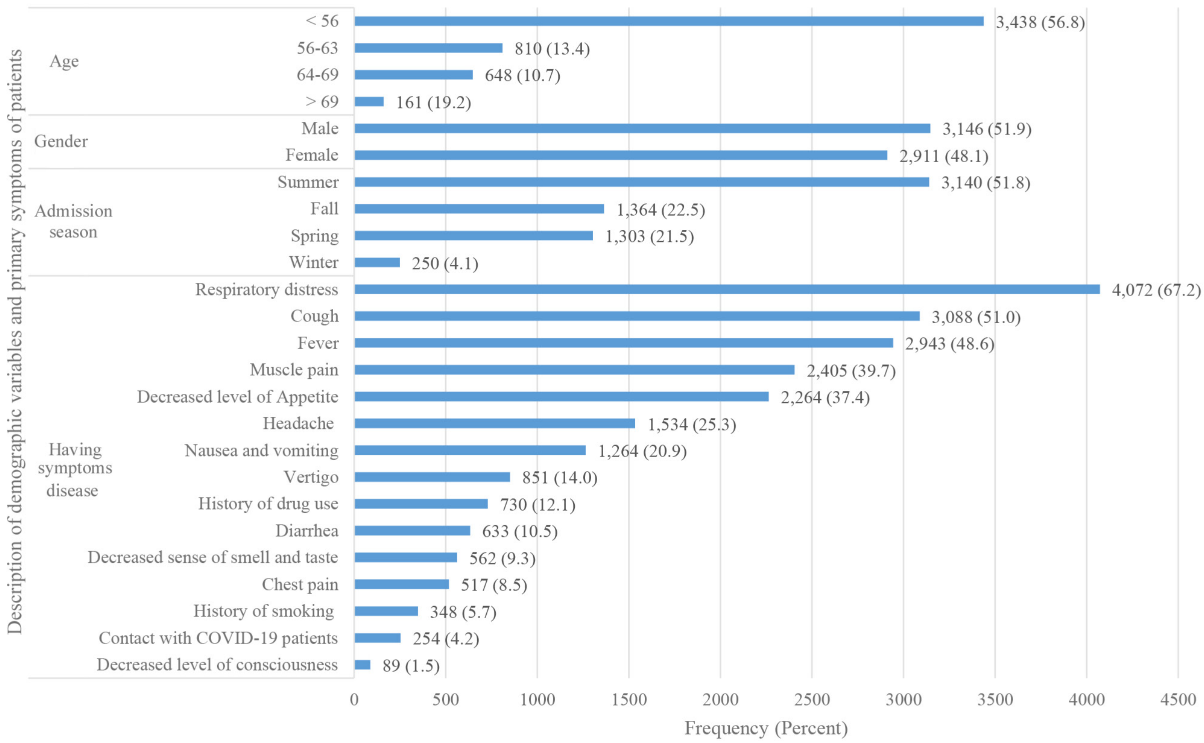

Figure 1. A description of the patient's demographic data and primary symptoms

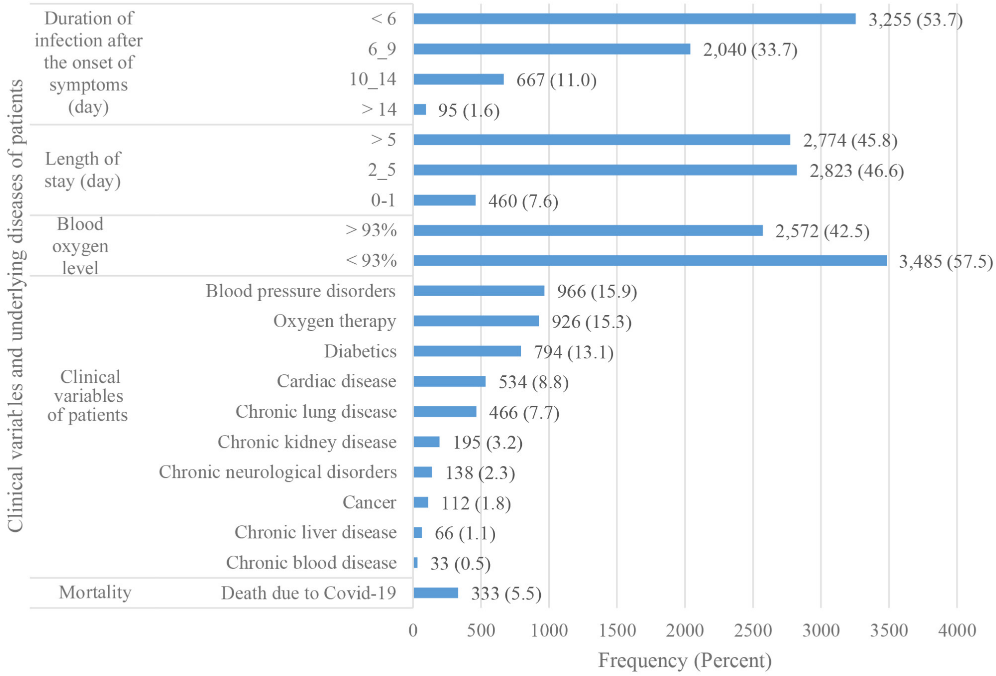

Figure 2. Descriptive statistics for the patient's clinical data and underlying diseases

Table 1. Multiple logistic regression results for hospitalized patients

Variables		Frequency (percent) of deceased patients	Odds ratio (95% confidence interval)	*P* value
Age	<56	64 (19.2)	Ref	Ref
	56–63	35 (10.5)	2.52 (1.62–3.91)	<0.001
	64–69	46 (13.8)	4.37 (2.89–6.59)	<0.001
	>69	188 (56.5)	9.78 (7.14–13.41)	<0.001
Gender	Female	139 (41.7)	Ref	Ref
	Male	194 (58.3)	1.29 (1.7–1)	0.046
Fever	No	226 (67.9)	Ref	Ref
	Yes	107 (32.1)	0.63 (0.49–0.82)	0.001
Headache	No	282 (84.7)	Ref	Ref
	Yes	51 (15.3)	0.70 (0.5–0.97)	0.033
Decreased LoC	No	303 (91.0)	Ref	Ref
	Yes	30 (9.0)	4.97 (2.78–8.9)	<0.001
Chronic liver diseases	No	324 (97.3)	Ref	Ref
	Yes	9 (2.7)	3.5 (1.57–7.80)	0.002
BOL	>93%	100 (30.0)	Ref	Ref
	<93%	233 (70.0)	1.43 (1.1–1.87)	0.009
Admission season	Spring	37 (11.1)	Ref	Ref
	Summer	186 (55.9)	2.27 (1.54–3.35)	<0.001
	Fall	100 (30.0)	2.15 (1.42–3.28)	<0.001
	Winter	10 (3.0)	0.979 (0.45–2.1)	0.96
LoS (days)	0–1	121 (36.3)	Ref	Ref
	2–5	121 (36.3)	0.14 (0.1–0.2)	<0.001
	>5	91 (27.3)	0.09 (0.06–0.1)	<0.001

Table 2. The conditional probability of death obtained from the Bayesian network

Age subgroups	Fever	Decreased LoC	LoS	Conditional probability of death
<59	No	No	0–1	0.8
<59	Yes	Yes	0–1	0.5
56–63	Yes	Yes	0–1	0.88
56–63	Yes	Yes	2–5	0.5
56–63	Yes	Yes	>5	0.5
64–69	No	Yes	0–1	0.5
64–69	No	Yes	>5	0.67
64–69	Yes	Yes	0–1	0.5
>69	No	No	0–1	0.61
>69	No	Yes	0–1	0.93
>69	Yes	Yes	0–1	0.88

affected the mortality of hospitalized COVID-19 patients in southeastern Iran. The results showed that the patient's age, gender, fever, headache, decreased LoC, chronic liver disease, BOL, admission season, and LOS exhibited a significant relationship with COVID-19 deaths.

A major variable that significantly affected the mortality of hospitalized COVID-19 patients was age. Our data showed that with an increase in the patient's age, the risk of death from the disease increased significantly. Many studies have identified increasing age as a serious risk factor for the death of COVID-19 patients (22-24).

A meta-analysis revealed that adults aged 65 and older are five times more likely to be in critical condition or die (25). Older patients probably show a weaker immune response to the disease. Thus, they are more susceptible

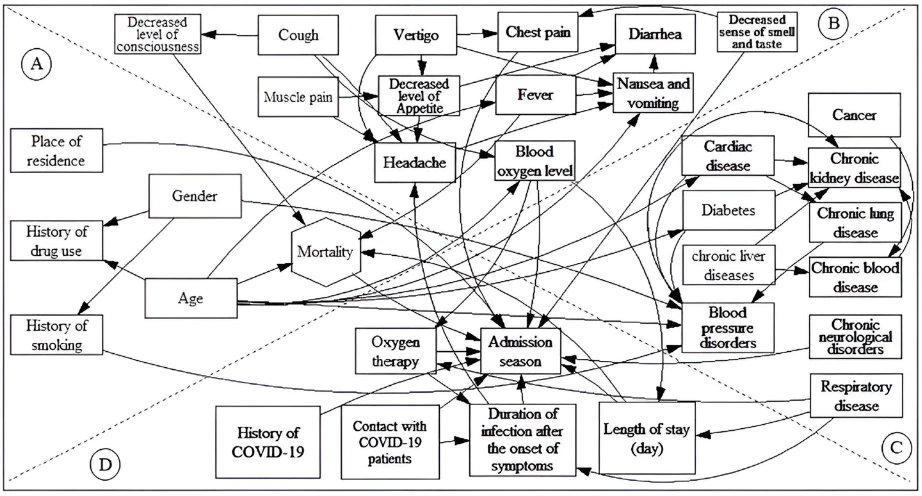

Figure 3. Bayesian network of risk factors affecting the mortality of patients with COVID-19. A: Personal variables; B: Clinical variables; C: Underlying disease variables; D: COVID-19 variables

to acute respiratory distress syndrome (ARDS) and mortality (26).

Another important risk factor identified was the male gender. More than half of the patients in the current study were male. Our study showed that the odds of COVID-19 death in men were 1.29 times that of women (OR = 1.29), as evident in other studies. A meta-analysis study of 3,111,714 reported global cases showed that men are more likely to die from COVID-19 than women (OR = 1.39), so the male gender is considered an important risk factor for the deaths caused by COVID-19 (27) possibly due to sex hormone differences and the number of X chromosomes in the two sexes. Studies have shown that a woman's body produces more type-1 interferons than men, which is vital to patients' initial response to COVID-19 (27, 28).

Fever, cough, muscle pain, headache, respiratory distress (shortness of breath), decreased LoC, anorexia, compromised sense of smell and taste, dizziness, chest pain, nausea, vomiting, and diarrhea were the principal initial symptoms among the hospitalized COVID-19 patients in this study.

Fever and headache had protective effects, and decreased LoC had an aggressive and significant effect on the mortality of patients in the present study. Various studies have shown that decreased LoC can be related to the increased risk of COVID-19 deaths (29,30). When the patient reaches the critical stages of the disease, they usually have a decreased LoC and may die.

The present study showed that, consistent with previous studies, BOL was a significant risk factor for COVID-19 deaths (25), i.e., patients whose BOL is less than 93 must receive oxygen therapy and undergo stronger medication.

Many studies have shown fever among the most common COVID-19 symptoms (31,32). In addition, studies have suggested that high fever is more likely to increase ARDS (33). However, some studies have found no significant relationship between fever and COVID-19 deaths (34). Some studies have indicated that fever in critical COVID-19 patients was significantly lower compared to the non-critical group, indicating that fever may protect COVID-19 patients from severe and critical disease outcomes (34,35). Besides, studies have shown that headaches cause a lower mortality risk and have a protective effect in hospitalized COVID-19 patients (36,37), as confirmed in the present study. A possible reason is that the patients who had symptoms of fever and headache went to the hospital earlier and received effective and timely treatment. Thus, further studies are needed to explore this issue.

LoS in this study was 5 (1–30) days for recovered patients and 6 (1–30) days for deceased patients. A systematic review showed that out of 52 studies that examined LoS, the average LoS varied from 4 to 53 days in China and from 4 to 21 days outside China, which is in line with the present study results (38).

In addition, other studies have also identified LoS as an effective factor for mortality (25,39). Factors like patient's age, delay in access to health care, and hospital discharge criteria can affect the LoS. Iran was among the countries with a high number of infected and deceased patients. Consequently, as a measure to enhance the capacity of hospitals in response to the epidemic, particularly during the peaks of the COVID-19 outbreak, some patients were discharged from hospitals with partial recovery and were cared for in their homes (25).

Multiple studies have demonstrated that underlying diseases are among the most significant mortality risk factors (39). More specifically, studies conducted in Iran have revealed that underlying diseases significantly impact COVID-19-related mortality (39,40). Our study revealed that chronic liver disease increases the risk of death among hospitalized COVID-19 patients. Noor et al. reported similar results for chronic liver patients (41). Furthermore, patients with a history of chronic liver disease have reported a significant increase in the levels of liver enzymes such as ALT and AST as a result of COVID-19 infection, which indicates liver cell damage (42).

Conclusion

This study revealed that the majority of patients who died from COVID-19 were over the age of 69. Male gender, a history of chronic liver disease, BOL less than 93, mitigated LoC, and a short LoS significantly increased the odds of mortality. In addition, fever and headaches had a protective effect and were associated with decreased mortality. Moreover, summer and fall were linked with a higher mortality rate than other seasons. Therefore, it is recommended that older male patients with low oxygen levels and low consciousness, as well as chronic liver patients, should receive further medical care and stay at the hospital longer. These high-risk patients may be less likely to die from this disease if they receive medical care early on.

Limitations of the study

Unfortunately, the COVID-19 virus undergoes constant mutations over time, altering transmission, severity, and case-fatality risk, thus possibly influencing the effect of mortality-related factors. Additionally, the treatment approach for hospitalized patients evolves, which can impact patient mortality. Therefore, the type of mutation and treatment are significant variables not addressed in this study. Moreover, the present study did not address the duration and severity of underlying diseases. Thus, these variables need to be explored in future research.

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Authors' Contribution

Conceptualization: Ahmad Mohtashami, Abbas Bahrampour, Yunes Jahani.
Data curation: Mohammad Hossein Mehrolhassani, Yunes Jahani.
Formal Analysis: Ahmad Mohtashami, Milad Ahmadi Gohari, Abbas Bahrampour, Yunes Jahani.
Funding acquisition: Yunes Jahani.
Investigation: Ahmad Mohtashami, Yunes Jahani.
Methodology: Ahmad Mohtashami, Abbas Bahrampour, Yunes Jahani.
Project administration: Yunes Jahani.
Resources: Ahmad Mohtashami, Mohammad Hossein Mehrolhassani, Yunes Jahani.
Software: Ahmad Mohtashami, Yunes Jahani.
Supervision: Yunes Jahani.
Validation: Ahmad Mohtashami, Abbas Bahrampour, Mohammad Hossein Mehrolhassani, Yunes Jahani.
Visualization: Ahmad Mohtashami, Milad Ahmadi Gohari, Yunes Jahani.
Writing–original draft: Ahmad Mohtashami, Yunes Jahani.
Writing–review & editing: Milad Ahmadi Gohari, Abbas Bahrampour, Mohammad Hossein Mehrolhassani.

Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

The study protocol was approved by the Ethics Committee of Kerman University of Medical Sciences (ethics code No. IR.KMU.REC.1400.561).

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