Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Public Health 200 (2021) 33–38

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

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

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ARTICLE INFO

Article history:
Received 19 February 2021
Received in revised form
17 August 2021
Accepted 3 September 2021
Available online 14 September 2021

Keywords:
Coronavirus disease 2019 (COVID-19)
Death
Iran
Cohort study
Prognostic factors
In-hospital mortality

ABSTRACT

Objectives: COVID-19 continues to cause devastation throughout the world. Various factors influence the perioperative course and prognosis of COVID-19. This study aims to collate the independent prognostic factors among hospitalised COVID-19 patients in east Iran.
Study design: In this cohort study, all patients with a confirmed diagnosis of COVID-19 between 19 February 2020 and 1 August 2020 who were admitted to nine public hospitals of South Khorasan province, Iran, were enrolled.
Methods: Univariate analysis (chi-square [χ^2], and Mann–Whitney U test) and multiple logistic regression were performed.
Results: This study included 1290 participants; 676 patients (52.4%) were male. A total of 1189 (92.2%) recovered, and 101 (7.8%) died. The results show that in-hospital mortality increases with advanced age (the optimal cut-off point = 62 years). The following three variables were shown to have the most significant role in in-hospital mortality: age >60 years (odds ratio [OR] = 8.01, 95% confidence interval [CI] 4.8–13.35), shortness of breath (OR = 2.65, 95% CI: 1.4–69.17) and atypical radiological manifestations in a chest X-ray on admission (OR = 2.16, 95% CI: 1.3–28.64). In the univariate analysis, associated comorbidities, such as cardiovascular diseases, influenced the in-hospital mortality rate, while the same could not be replicated in the multiple variable analysis.
Conclusions: This study revealed the potential predictors of COVID-19 and highlighted the need to be cautious with advanced age and heightened clinical symptoms at the time of admission.

Introduction

Coronaviruses are positive-strand RNA viruses that are widely distributed among humans, other mammals and birds. In December 2019, the outbreak of a novel strain of coronavirus commenced; cases of pneumonia with an unknown cause started occurring in Wuhan, Hubei province, China.[1] Finally, in February 2020, it was named COVID-19 by the World Health Organization (WHO).[2] In March 2020, the COVID-19 epidemic evolved into a pandemic.[3] The global malaise associated with COVID-19 varies from asymptomatic, mild upper respiratory tract manifestations, severe viral pneumonia infections to respiratory failures and even death.[4–6] In addition to the respiratory system, gastrointestinal (diarrhoea, nausea and vomiting), musculoskeletal (myalgia) and neurological (headache or decrease in the level of consciousness) manifestations may be observed.[7] The disease typically initiates

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https://doi.org/10.1016/j.puhe.2021.09.007
0033-3506/

with non-specific symptoms, including fever, dry cough and tiredness. Fever has been reported to be the most common symptom among COVID-19 patients.[4,5,8] Moreover, considering the psychological effects, a recent study in South Khorasan province, Iran, showed that the COVID-19 epidemic has led to extra anxiety and stress in the general population, and the community has been confronted with this new situation in which various dimensions of health have deteriorated.[9]

Up to 1 August 2020, based on WHO data, a total of 17,396,943 confirmed cases and 675,060 deaths had been reported worldwide. Moreover, 304,204 confirmed cases and 16,766 deaths have been reported in Iran. The global mortality rate was estimated at 3.9%, while the mortality rate in Iran was 5.5% (as of 1 August 2020).[10] Moreover, according to different studies conducted on COVID-19 inpatients in Tehran (north Iran), Shiraz (southwest Iran), Hormozgan (southeast Iran), Ardabil (northwest Iran) and Mashhad (northeast Iran), the mortality rate was reported to be 10.8%, 8.0%, 12.5%, 8.5% and 15.4%, respectively.[11–15]

Numerous studies have been published in the literature investigating the associations between various risk factors and COVID-19–related mortality. Diabetes, cardiovascular disease and hypertension are the most common chronic comorbidities in people with severe COVID-19,[8,16,17] while respiratory failures and/or circulatory failures were the most common causes of death in hospitalised patients.[18] For example, according to the study of 12,870 COVID-19 patients in a major referral centre in Tehran, Iran, 10.89% of patients had a least one comorbidity. This study notes that chronic respiratory diseases, hypertension, diabetes, cardiovascular diseases, chronic kidney diseases and cancer were the most common comorbidities among these patients. The researchers also mentioned that older age, male gender and having underlying diseases were significantly correlated with mortality.[19] However, there is still controversy over incidence, the association of modifiable risk factors and mortality of COVID-19.

In the current study, we collated information from all patients with confirmed COVID-19 diagnoses admitted to nine public hospitals of South Khorasan province, Iran, between 19 February 2020 and 1 August 2020. This study was designed to explore the independent prognostic factors of COVID-19 among hospitalised patients. Moreover, this study aimed to explore the age cut-off point in modelling predictors of in-hospital mortality.

Methods

Study design and participants

All consecutive patients with a confirmed diagnosis of COVID-19 between 19 February 2020 and 1 August 2020 who were admitted to the nine public hospitals of South Khorasan province, Iran, after considering inclusion and exclusion criteria, were enrolled in this cohort study. A confirmed COVID-19 case was defined as a positive result of the real-time polymerase chain reaction (RT-PCR) test for the presence of severe acute respiratory syndrome (SARS)-CoV-2 in both pharyngeal and nasal swab specimens.[20] The inclusion criterion was the confirmed diagnosis of COVID-19, which was performed by a virologist. Patients with suspicious results of the RT-PCR test were sampled again. Patients with unreliable positive or negative test results and missing data were excluded. Between 19 February 2020 and 1 August 2020, according to the electronic medical records, a total of 6739 RT-PCR tests were performed for hospital-admitted patients in South Khorasan province, Iran, of which 1329 tests were positive. After considering the inclusion and exclusion criteria, a total of 1290 confirmed cases were included in our study. Informed consent was obtained from all participants. This study was approved by the Birjand University of Medical Science's Research Ethics Committee (Approval ID: IR.BUMS.REC.1399.080).

Data collection

Demographic information (gender and age), underlying comorbidities (immune-deficiency diseases, cardiovascular diseases, diabetes, renal diseases, hepatic diseases, chronic pulmonary diseases, chronic neurological diseases and malignancies), non-specific symptoms of COVID-19 (fever, shortness of breath, cough, weakness, pain and contusion, confusion and irritability, sore throat, rhinorrhoea, diarrhoea, nausea and vomiting, headache, chest pain, stomachache, arthralgia, pharynx exodus, redness of the conjunctive, abnormal breath sounds [wheezes, crackles, etc.], atypical radiological manifestations in a chest X-ray on admission, convulsions and coma), chest computed tomographic (CT) scans and outcomes (recovered/dead) were derived from the electronic medical records. The date of onset of the illness was described as the day symptoms were identified. The data were collected and reviewed by two infectious disease specialists. In case of any conflicts, both infectious disease specialists consulted with each other to reach a single point of view.

Outcome and follow-up

The main outcome of the study was the in-hospital mortality rate of COVID-19–confirmed patients. The total in-hospital mortality rate was described as the percentage of patients who died following the diagnosis of COVID-19. The follow-up process was continued until the patients recovered or died. Patients who were on the road to recovery displayed improvement in temperature, respiratory symptoms and pulmonary inflammation; improvement in the chest radiograph; improvement in blood oxygen saturation levels; or being in good general condition and confirmation by a negative RT-PCR test.

Statistical analysis

The statistical analysis was carried out using SPSS version 22 (IBM, Chicago, USA). Qualitative variables were reported as percentages and compared using the Chi-square (χ^2) test or Fisher exact test. Quantitative variables were presented as median (interquartile range) and examined using the Mann–Whitney U test. The P-value <0.05 was considered statistically significant. The univariate regression model integrated all variables correlated with the main outcomes. Variables with the level of $P < 0.25$ in the previous analysis were included into multiple logistic regression models, and the simultaneous effect of the variables on the main outcomes was determined using the odds ratio (OR) with 95% confidence intervals (95% CIs).[21] The multiple logistic regression model was validated by the Hosmer–Lemeshow test and receiver operating characteristic (ROC) curve analysis. In addition, ROC curve analysis was used for determining the optimal cut-off point for the age variable.

Results

This study included 1290 patients with a confirmed diagnosis of COVID-19 in the nine public hospitals in South Khorasan province, Iran. In total, 676 patients (52.4%) were male. The most common age group was 30–39 years, with 231 patients (17.9%). Based on the prognosis and outcome of the disease, patients were divided into two groups: recovered or dead. Based on this classification, a total of 1189 (92.2%) recovered (with a mean age of 50.1 ± 19.3 years) and 101 (7.8%) died (with a mean age of 71.8 ± 16.0 years) (Table 1).

Table 1
Comparison of in-hospital mortality due to COVID-19 by age and sex in South Khorasan province, Iran.

Variables	Recovered [n (%)]	Dead [n (%)]	Total [n (%)]	*P*-value
Sex				0.29
Male	618 (91.4)	58 (8.6)	676 (100)	
Female	571 (93.0)	43 (7.0)	614 (100)	
Age group (years)				<0.001
0–9	14 (100)	0 (0.0)	14 (100)	
10–19	29 (100)	0 (0.0)	29 (100)	
20–29	133 (100)	0 (0.0)	133 (100)	
30–39	224 (97.0)	7 (3.0)	231 (100)	
40–49	196 (97.5)	5 (2.5)	201 (100)	
50–59	207 (96.3)	8 (3.7)	215 (100)	
60–69	169 (91.4)	16 (8.6)	185 (100)	
70–79	121 (80.7)	29 (19.3)	150 (100)	
≥80	96 (72.7)	36 (27.3)	132 (100)	
Total	1189 (92.2)	101 (7.8)	1290 (100)	

Results showed that a higher percentage of men died than women but this difference was not statistically significant (8.6% vs 7.0%, *P*-value = 0.29). According to the results, no fatalities were reported in the <30 years age groups. The results also showed that in-hospital mortality increases with advanced age ($P\text{-value}_{trend} = 0.001$). The highest in-hospital mortality was observed in the ≥80 years age group with 36 patients (27.3%) (Table 1).

Chronic pulmonary diseases, cardiovascular diseases, acquired or congenital immunodeficiency diseases and diabetes were significantly associated with in-hospital mortality (*P*-value <0.05). According to our results, the highest in-hospital mortality was observed in patients with immunodeficiency (60.0%) and chronic pulmonary diseases (26.8%) (Table 2).

A study of patients' non-specific symptoms of COVID-19 showed that having the triad of fever, cough and shortness of breath, simultaneously, shortness of breath (as a single symptom), abnormal breath sounds (wheezes, crackles, etc.) and atypical radiological manifestations in a chest X-ray on admission were significantly associated with in-hospital mortality (*P*-value <0.05). Results showed that in-hospital mortality was higher in patients with symptoms of abnormal breath sounds and atypical radiological manifestations in a chest X-ray on admission (30.6% and 17.2% of cases, respectively) than in patients without these symptoms (Table 3).

Although in the univariate analysis immune-deficiency diseases, cardiovascular diseases, diabetes and chronic pulmonary diseases were correlated with the in-hospital mortality rate, none of these diseases had a significant correlation with the in-hospital mortality rate in the multiple variable analysis. However, according to the results of logistic regression modelling, the following three variables had the most significant role in in-hospital mortality of patients with COVID-19: age >60 years (OR = 8.01, 95% CI: 4.8–13.35), shortness of breath (OR = 2.65, 95% CI: 1.4–69.17) and atypical radiological manifestations in a chest X-ray on admission (OR = 2.16, 95% CI: 1.3–28.64). Accordingly, after adjusting for underlying diseases and clinical manifestations of COVID-19, the chance of in-hospital mortality for patients aged <60 years was 8.01 times higher than the reference category, which was age <60 years (Table 4).

In addition, based on the ROC curve analysis, the optimal cut-off point for the age variable was determined to be 62 years (Sensitivity and specificity of the cut-off points were 78.2% and 72.3%, respectively). Moreover, the area under the curve (AUC) was determined to be 0.803 (Fig. 1).

Discussion

Baseline descriptions

This study was designed to determine the potential predictive factors that can impact the in-hospital mortality rate of patients with COVID-19. Demographic information (gender and age), non-specific symptoms of COVID-19 (fever, shortness of breath, cough, etc.), underlying diseases (cardiovascular disease, malignancies, etc.) and the prognosis of confirmed patients with COVID-19 was extracted from the electronic medical records.

According to our results, the in-hospital mortality rate of COVID-19 was not significantly different between males and females. Gender and its risk of in-hospital mortality has conflicting results in the literature. A few studies suggest that sex differences may exist in COVID-19 patients with severe conditions, where men are more likely to have worse in-hospital outcomes and a difficult recovery or mortality compared with women.[20,22–24]

The current study confirms age as a prognostic factor for COVID-19–induced in-hospital mortality.[22,25–29] In the same vein, previous studies on middle-east respiratory syndrome and SARS have highlighted age as a prognostic factor.[30,31] The innate immune system in the elderly rebuts a sturdier response to the cytokine storm than the young because of increased expression of inflammation-related genes, while the adaptive immune system becomes weakened and fails to with age. The senescent immune system amplifies the pathogenicity of the virus and increases the risk of morbidity and mortality.[25]

According to the results of the current study, and similar to other studies, in-hospital mortality due to COVID-19 in patients with underlying diseases was significantly higher than individuals without the comorbidity.[22,25–29] The highest in-hospital mortality was seen in patients with chronic pulmonary diseases and cardiovascular diseases, which is consistent with similar studies.[22,23,29] Chronic pulmonary diseases cause damage to the respiratory system and reduce respiratory function, in addition to viral resistance seen in these patients.[29] Cardiovascular diseases are also significant risk factors of mortality because of the weak heart and vascular damage resulting from chronic stress and

Table 2
Comparison of in-hospital mortality due to COVID-19 by underlying diseases in South Khorasan province, Iran.

Variables	Recovered [n (%)]	Dead [n (%)]	Total [n (%)]	*P*-value
Immune-deficiency diseases	2 (40.0)	3 (60.0)	5 (100)	<0.001[a]
Cardiovascular diseases	202 (84.9)	36 (15.1)	238 (100)	<0.001
Diabetes	131 (86.8)	20 (13.2)	151 (100)	0.008
Renal diseases	26 (92.9)	2 (7.1)	28 (100)	0.891
Hepatic diseases	12 (92.3)	1 (7.7)	13 (100)	0.985[a]
Chronic pulmonary diseases	30 (73.2)	11 (26.8)	41 (100)	<0.001
Chronic neurological diseases	11 (84.6)	2 (15.4)	13 (100)	0.308[a]
Malignancies	8 (88.9)	1 (11.1)	9 (100)	0.713[a]
Another underlying disease	319 (85.1)	56 (14.9)	375 (100)	<0.001

[a] Fisher exact test.

Table 3
Comparison of in-hospital mortality due to COVID-19 by clinical manifestations in South Khorasan province, Iran.

Variables	Recovered [n (%)]	Dead [n (%)]	Total [n (%)]	*P*-value
Fever, cough and shortness of breath	123 (87.9)	17 (12.1)	140 (100)	0.044
Fever	482 (92.2)	41 (7.8)	523 (100)	0.991
Cough	531 (92.3)	44 (7.7)	575 (100)	0.832
Shortness of breath	423 (86.5)	66 (13.5)	489 (100)	<0.001
Weakness	320 (91.4)	30 (8.6)	350 (100)	0.545
Pain and contusion	327 (94.0)	21 (6.0)	348 (100)	0.145
Confusion and irritability	59 (86.8)	9 (13.2)	68 (100)	0.088
Sore throat	107 (96.4)	4 (3.6)	111 (100)	0.083
Rhinorrhoea	48 (94.1)	3 (5.9)	51 (100)	0.597
Diarrhoea	72 (93.5)	5 (6.5)	77 (100)	0.653
Nausea and vomiting	140 (94.6)	8 (5.4)	148 (100)	0.243
Headache	236 (95.1)	12 (4.8)	248 (100)	0.051
Chest pain	64 (88.9)	8 (11.1)	71 (100)	0.286
Stomachache	45 (90.0)	5 (10.0)	90 (100)	0.560
Arthralgia	98 (95.1)	5 (4.9)	103 (100)	0.241
Pharynx exodus	6 (100)	0 (0.0)	6 (100)	0.474[a]
Redness of the conjunctiva	11 (91.7)	1 (8.3)	12 (100)	0.948[a]
Abnormal breath sounds (wheezes, crackles, etc.)	25 (69.4)	11 (30.6)	36 (100)	<0.001
ARM-CX	130 (82.8)	27 (17.2)	157 (100)	<0.001
Convulsions	0 (0.0)	1 (100)	1 (100)	0.001[a]
Coma	1 (50.0)	1 (50.0)	2 (100)	0.026[a]

ARM-CX: Atypical radiological manifestations in a Chest X-ray on admission.
[a] Fisher Exact Test.

Table 4
Predictors of in-hospital mortality due to COVID-19 using logistic regression.

Variables	Coefficient	Standard error	Adjusted[a] odds ratio (95% confidence interval)	*P*-value
Age >60 years	2.08	0.26	8.01 (4.8–13.35)	<0.001
Shortness of breath	0.98	0.23	2.65 (1.4–69.17)	<0.001
ARM-CX	0.77	0.27	2.16 (1.3–28.64)	0.002

ARM-CX: Atypical radiological manifestations in a chest X-ray on admission.
[a] The variables listed in Table 2 (i.e. underlying diseases) and Table 3 (i.e. clinical manifestations of COVID-19) have been adjusted in logistic regression modelling.

inflammation.[29] Similar to other studies, mortality in patients with diabetes was significantly higher than that in patients without diabetes.[22,29] Another study conducted in Shahid Modarres Hospital, Tehran, Iran, also showed that diabetes plays an important role in the mortality rate of hospitalised COVID-19 patients.[32] It is important to note that the incidence of diabetes mellitus in Iran is high;[33,34] therefore, the Iranian population might be at a considerably higher risk for COVID-19 complications. Patients with diabetes are more prone to vascular damages, and the immune system, especially innate immunity, is weaker in diabetic patients.[29,35–37] Studies show that, on its own, diabetes is not enough to predict the condition of a patient with COVID-19, and age and blood pressure are two determining factors in combination with diabetes to predict the outcome of disease.[35] In addition, pro-inflammatory responses to cytokines are impaired in patients with diabetes and can be a reason for increased COVID-19 severity and mortality.[37–39]

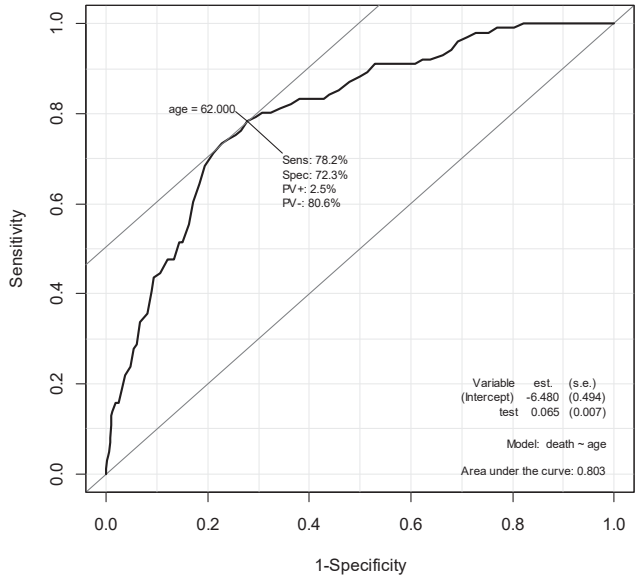

Fig. 1. Determining the optimal cut-off point for age based on the data obtained up to 1 August 2020. Based on the receiver operating characteristic (ROC) curve analysis, the optimal cut-off point for the age variable was determined to be 62 years (Sensitivity and specificity of the cut-off point were 78.2% and 72.3%, respectively). Moreover, the area under the curve (AUC) was determined to be 0.803.

According to the results, the in-hospital mortality rate of patients with COVID-19 who had shortness of breath was higher than in patients without shortness of breath; these results are similar to other studies.[29] Shortness of breath can indicate poor lung function and lack of proper oxygen supply; therefore, shortness of breath increases the mortality rate of patients with COVID-19.[29] In the present study, having a fever did not differ significantly between the recovered and dead groups, and this finding is in contrast to similar studies.[29] Fever indicates the competence of the immune system against the pathogen. According to previous studies, the mortality rate was higher in patients with COVID-19 who had shortness of breath and no fever.[29] In-hospital mortality was lower in patients with gastrointestinal symptoms than in patients without gastrointestinal symptoms, which is consistent with a similar study, and COVID-19 patients with gastrointestinal symptoms usually experienced mild to moderate severity of COVID-19.[27]

Based on the results of logistic regression analysis, the following three clinical variables had a statistically significant impact on morbidity and mortality of COVID-19: age >60 years, shortness of breath and atypical radiological manifestations in a chest X-ray on admission. According to the logistic regression analysis performed in this study, the prognostic role of underlying diseases for the prognosis of COVID-19 was less important than age >60 years, shortness of breath and atypical chest X-ray; thus, none of the underlying diseases showed a significant effect in the presence of other variables.

The age cut-off point in modelling predictors of in-hospital mortality due to COVID-19 was 3 years lower than that in a similar regression model analysis performed in China (62 years vs 65 years).[40] Determination of the cut-off point of 62 years indicates that, in patients with COVID-19, the in-hospital mortality rate increases significantly above the cut-off point, and these patients should be monitored carefully. However, studies in Italy and Korea have shown that approximately 90% and 80% of deaths have occurred in individuals aged ≥60 years and >70 years, respectively.[41,42] Moreover, a recent investigation of 16,000 COVID-19 patients in Tehran, Iran, showed that, although approximately 70% of confirmed and suspected COVID-19 patients were aged 25–64 years, approximately 60% of the deaths were in patients aged >65 years.[43] In addition, a study in Mashhad, northeast Iran, showed that the likelihood of death in COVID-19 patients aged >50 years was significantly higher than those aged ≤50 years.[44] However, another study in west Tehran, Iran, showed that mortality due to COVID-19 increased significantly in patients aged >60 years.[45] According to a study conducted on 4000 COVID-19 patients in Khorasan, east Iran, patients aged ≥60 years were associated with an almost five-fold case fatality rate.[46] Based on the results, it is very important to evaluate and take a complete clinical history of patients at the beginning of referral to medical centres to predict the course and prognosis of the disease. In addition, these factors help the physicians in effective medical management of patients.

Strengths and limitations

The strength of the study lies on using advanced statistical analysis and a large sample size. Similar medical management of patients recommended by the Iran Ministry of Health and Medical Education ensured uniformity across the study population. In addition, the follow-up process was continued until patients either recovered or died.

However, the study does have some limitations. The limited period of follow-up may alter the 'recovered' group as increasing numbers of patients are experiencing post-COVID-19 symptoms and may require continuous monitoring, especially as the pandemic is ongoing. Epidemiological data in the electronic medical records were potentially not complete, and laboratory findings might influence the disease severity, which was not considered in our study. In addition, the time of admission to the hospital can be a determining factor of COVID-19 outcome and may skew our findings.

Conclusion

In conclusion, using detailed primary-care records, we have determined early predictors associated with COVID-19–related in-hospital mortality that had reached 7.8% in east Iran. The associated comorbidities (cardiovascular diseases, diabetes and chronic pulmonary diseases) and senescent immune system increases the risk of morbidity and mortality associated with COVID-19.

The statistical power and precision achieved using the multiple regression model focuses on three significant parameters: higher age groups (>60 years), shortness of breath and atypical radiological manifestations in a chest X-ray on admission as prognostic factors for in-hospital mortality, negating the other comorbidities. We recommend the need to be diligent when caring for individuals in higher age groups and with heightened clinical symptoms at the time of admission.

In addition, it is not plausible to ascertain whether the link between risk factors and COVID-19–related in-hospital mortality is due to increased susceptibility to infection, severe illness following infection or a mixture of both. The outcome of all COVID-19 deaths provides information on the disease severity, independent of clinical decisions, hospital management and availability of resources, which are all likely to influence the inpatient admissions, intensive-care unit admissions or solely in-hospital deaths.

However, additional validations across heterogeneous populations and using larger datasets can provide reliable information for the implementation of new protocols in healthcare systems, which ultimately leads to the best performance of the system.

Author statements

Acknowledgements

The authors wish to thank the Deputy of Research and Technology of Birjand University of Medical Sciences for support (grant number: 456203).

Ethical approval

This study was approved by Birjand University of Medical Science's Research Ethics Committee (Approval ID: IR.BUMS.REC.1399.080). Moreover, the informed consent was obtained from all participants.

Funding

This study was performed with the financial support of Birjand University of Medical Sciences (grant number: 456203). The authors also indicate that they did not have a financial relationship with the organisation that sponsored the research and had full control of all primary data.

Competing interests

The authors have no conflicts of interest.

Authors' contributions

Conceptualisation: Seyed Mohammad Riahi, Farshid Abedi; Methodology: Seyed Mohammad Riahi, Fatemeh Salmani; Formal analysis and investigation: Seyed Mohammad Riahi, Fatemeh Salmani, Mehrnaz Navayi; Writing - original draft preparation: Ali Fanoodi, Mehrnaz Navayi; Writing - review and editing: Seyed Mohammad Riahi, Ali Fanoodi, Mehrnaz Navayi, Fatemeh Salmani, Farshid Abedi, Sameep Shetty; Supervision: Seyed Mohammad Riahi.

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