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Intensive care unit admission and associated factors in patients hospitalised for COVID-19: A national retrospective cohort study in Iran

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ABSTRACT

Objectives This study aimed to determine factors associated with intensive care unit (ICU) admission in patients hospitalised due to COVID-19.

Design Retrospective cohort.

Setting Confirmed hospitalised patients from all over Iran were considered for the study.

Participants All patients with COVID-19 admitted to the hospital from March 2020 to May 2021 were included by census. ICU admission was defined by the following criteria: (1) admission to the ICU ward; (2) level of consciousness (loss of consciousness); and (3) use of invasive ventilation.

Methods This is a secondary data analysis from the Medical Care Monitoring Center. The association between different variables and ICU admission was assessed by forward Logistic regression and restricted cubic spline method.

Results The mean age of the 1 469 620 patients with COVID-19 was 54.49±20.58 years old, and 51.32% of the patients were male. The prevalence of ICU admission was 19.19%. The mean age of patients admitted to the ICU was higher than that of other hospitalised patients (62.49±19.73 vs 52.59±20.31 years). The prevalence of ICU admission was 17.17% in the first, 21.52% in the second, 19.72% in the third, 21.43 in the fourth and 17.4% in the fifth wave. In the multivariable model, age groups, sex, waves of the epidemic, comorbidities and saturation of peripheral oxygen (SpO_2) <93% and acute respiratory distress syndrome (ARDS) were associated with an increased odds of ICU admission. The OR for ICU admission indicates a significant protective effect at a young age and then a significant risk factor for admission to the ICU ward at an old age.

Conclusions Men, older adults, people who suffer from ARDS, patients with SpO_2 levels of less than 93% and cases with comorbidities had the highest odds of ICU admission. Therefore, these groups should take all necessary precautions to avoid contracting COVID-19.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ More than 1.4 million patients with COVID-19 have been investigated.
⇒ A restricted cubic spline method was used to assess the non-linear relationship between age and COVID-19 admission instead of the usual logistic regression.
⇒ Variables like pregnancy and blood disorders have been addressed despite previous studies.
⇒ The criteria for intensive care unit admission may have varied over time and between different waves of COVID-19 epidemy.

INTRODUCTION

In December 2019, a new contagious disease called novel COVID-19 emerged in Wuhan City, Hubei Province, China.[1] The pandemic is a rapidly evolving global emergency and poses an important and urgent threat to global health, and many people are suffering from respiratory illnesses due to this disease.[2] By April 2022, the disease had infected more than 497 million people and killed nearly 6 199 793 people. Several factors influence the occurrence, severity and prognosis of COVID-19. Most people infected with the new COVID-19 suffer from mild to moderate respiratory disease and recover without requiring special treatment.[3]

In addition, it has been reported that the rate of intensive care unit (ICU) admissions is as high as 30% in hospitalised infected patients and that those admitted to the ICU are more susceptible.[4] Based on previous research, ICU admission is an indicator of severe illness (COVID-19).[5–7] This is because people admitted to this ward experience conditions such as acute hypoxemic respiratory failure, hypercapnia, acute respiratory distress syndrome (ARDS), shock, myocardial dysfunction and arrhythmia.[8]

Hospital and ICU admission depends on age, sex and the presence of underlying diseases. Up to 50% of patients reported having at least one comorbidity with COVID-19 on hospital admission, and comorbidities were observed in approximately 70% of patients requiring ICU care.[9] Age is the main risk factor in patients with COVID-19, making the pandemic COVID-19 a high risk for older adults. Older adults appear to be more susceptible to the virus. Seventy-five per cent of known infections affect persons aged 50 years and older.[10] In addition, older adults are particularly at risk for severe infection and have a higher risk of dying as a result of the disease.

The study by Mudatsir *et al*[11] showed that among comorbid factors, chronic respiratory disease, cardiovascular disease (CVD), diabetes mellitus (DM) and hypertension were associated with a higher risk of severe COVID-19 and among clinical manifestations, dyspnoea, anorexia, fatigue and dizziness were associated with severe COVID-19.[11] In older adults and people with chronic diseases such as HIV, tuberculosis and anaemia, severe forms of COVID-19 occur, leading to hospitalisation and admission to the ICU.[12]

As recently commented by the Centers for Disease Control and Prevention, psychological, social and behavioural differences between men and women may play an important role in exposure to COVID-19, the presence of comorbidities, treatment initiation, compliance and ultimately COVID-19 mortality.[13]

According to WHO reports, COVID-19 in Iran has currently passed through its eighth peak, and a total of 7 611 138 Iranian people were confirmed to be infected with COVID-19 from 3 January 2020 to 24 May 2023, of which 146 230 died.[14] Cases may occur with different symptoms and comorbidities.[15] So studies are needed to investigate factors affecting the prognosis of COVID-19 in Iran. Moreover, no national and comprehensive studies have been conducted in Iran on the epidemiological and demographic characteristics of COVID-19 and to investigate the aetiological factors, especially the risk factors for ICU admission. Such studies across the country can play a crucial role in providing scientific and evidence-based advice to policymakers. Therefore, this study was conducted to determine factors associated with ICU admission in patients hospitalised due to COVID-19 in Iran.

METHODS

Data source

This retrospective cohort study used Medical Care Monitoring Center (MCMC) data. The MCMC system was created to organise the monitoring and control of medical services through effective and efficient communication, expedite the delivery of services, improve the quality of services, optimise processes and enable integrated management. This system collects information from hospital patients (more than 1 500 000 confirmed patients have been admitted to hospitals across Iran).

The information includes demographic characteristics (including age, sex, province and place of residence), clinical symptoms (including fever, cough, runny nose, muscle pain, shortness of breath, decreased consciousness), gastrointestinal problems (including abdominal pain, nausea, vomiting, diarrhoea and loss of appetite), headache, dizziness, limb paralysis and palsy, chest pain, inflammation or skin lesions), physical examination (including respiratory rate, blood oxygen saturation (SpO_2) and body temperature), underlying comorbidities (including cancer, chronic liver and kidney disease, diabetes, blood disorders, AIDS/HIV, congenital or acquired immunodeficiency, pregnancy, heart disease, asthma, chronic neurologic disorders, history of hypertension) and other (route to medical centre, type of ward, close contact with a patient with COVID-19, intubation, oxygen saturation, length of hospital stay, ICU hospitalisation, ventilator status, discharge date and date of death).

The study was conducted nationally from March 2020 to May 2021. First, data from MCMC for a period of 14 months were pooled, and then variables were checked for duplicates and missing data and cleaned. A telephone call was also used to complete and correct the information.

Definition of ICU admission

Because of the limited number of intensive care beds in hospitals during the COVID-19 pandemic, some patients required to be admitted to the ICU were admitted to other wards. Hence in this study, we defined ICU admission using the following three criteria:

(1) admission to the ICU ward (200 297 patients); (2) level of consciousness (loss of consciousness) (73 893 patients); and (3) use of invasive ventilation (includes an endotracheal tube and a mechanical ventilator) (106 288 patients).

Identification of COVID-19 waves

Wave analysis was also performed based on the shape of the epidemic curve according to the number of hospitalised patients in all provinces of Iran. A wave was considered approximately from the time of the first ascend in the epidemic curve to the time of the next ascend as follows:

First wave: 29 February 2020–28 April 2020; Second wave: 29 April 2020–26 May 2020; Third wave: 27 May 2020–1 September 2020; Fourth wave: 2 September 2020–5 January 2021; Fifth wave: 30 March 2021–25 June 2021.

Missing data imputation

In this research, we used the last observation carried forward (LOCF) method to replace the missing data. In LOCF imputation, first, the data on each variable in each province are sorted in terms of days, and the last observation is replaced through the forward method; then, the data on the same variable are sorted in a reverse order of days. Then, the previous observation is replaced with the missing values through the backward method. Finally, the

missing value is replaced with the average values obtained in the two steps of the forward and backward methods.

Statistical analysis

After data collection and cleaning, there were 35 946 impossible ages (35 787 patients aged zero years and 159 patients aged >110 years) that were removed from the analysis. In addition, cases whose second admission occurred less than 7 days after the admission date (from the first admission date) were considered duplicates and excluded from the analysis (24 169 cases). The mean (SD) and count (percentage) were used to describe the quantitative and qualitative variables. The distribution and frequency of the different variables by hospitalisation in the ICU were compared. Logistic regression was used to determine the association of the different variables with ICU admission (univariable and multivariable). In multivariate analysis, the forward variable selection approach was used to obtain the final logistic model. The restricted cubic spline method was used to evaluate the non-linear relationship between age and ICU admission. The median of the low-risk group for age (age=31.5 years) was the reference group for OR. Data were analysed using Stata (V.14) and R software (V.3.6.3), and a p value of <0.05 was considered significant.

RESULTS

The mean age of the 1 445 451 patients with COVID-19 was 54.44±20.59 years old, and 51.30% of the patients were male. The prevalence of ICU admission was 19.26%. The mean age of patients admitted to the ICU was higher than that of other hospitalised patients (62.51±19.73 vs 52.59±20.33 years) (p<0.001). About 54.47% of patients admitted to the ICU were discharged. The highest frequency of hospitalisations occurred in the fifth (32.75%), fourth (31.24%) and third (19.29%) waves, respectively. About 65% of ICU admissions occurred in the fourth and fifth waves (table 1). In addition, the prevalence of ICU admission in patients with COVID-19 was 17.19% in the first, 21.55% in the second, 19.72% in the third, 21.51% in the fourth and 17.48% in the fifth wave (ICU to hospitalisation ratio per wave). During their hospitalisation, 7.35% of patients were intubated, and 5.11% of hospitalised patients had lost consciousness. About 11.36% of patients died, which was more than 10 times higher in patients admitted to the ICU than other hospitalised patients (table 1).

The most common comorbidities were diabetes (13.12%), CVD (11.35%) and chronic disease (7.53%) in all patients; CVD (19.40%), diabetes (18.38%) and chronic disease (9.65%) in patients admitted to the ICU; and diabetes (11.87%), CVD (9.42%) and chronic disease (7.02%) in other hospitalised patients. The prevalence of SpO_2 <93% and ARDS was higher in patients admitted to the ICU than in other hospitalised patients (67.83% vs 46.65% and 59.20% vs 46.50%, respectively) (p<0.001). Less common symptoms were muscle pain (29.78%) and fever (36.25%) (table 2).

In a univariable model, a significant association was found between ICU admission and age groups, sex, waves of the epidemy, comorbidities and signs and symptoms (p<0.05). In the multivariable model, age groups, sex, waves of the epidemy, comorbidities and SpO_2 <93% and ARDS were associated with increased odds of ICU admission. More details on the associated factors are presented in table 3.

Using restricted cubic spline function, there was a significant non-linear association between the ICU admission and increase in age after adjustment for comorbidities and signs and symptoms by sex. In both sexes, the OR for ICU admission indicates a significant risk factor for admission in the ICU ward at a young and an old age and a protective effect at a middle age (figure 1).

DISCUSSION

By assessing the epidemiological data related to more than 1 500 000 patients with COVID-19 infection, we were able to describe the demographic and clinical aspects of ICU admission in these cases at the national level. According to our findings, the odds of ICU admission is higher in men, older adults, people who suffer from ARDS and those whose SpO_2 levels are below 93%. Also, people with comorbidities such as CVD, chronic liver disease, a blood disorder, chronic kidney disease, cancer, DM, mental disorder, HIV/AIDS, immunosuppression and other chronic diseases had the highest odds of hospitalisation in the ICU. Another interesting finding from this research was that until April 2022, COVID-19 had five waves in Iran, in which highest odds of ICU admission belonged to the second wave.

Our results indicated that the male sex was independently associated with ICU admission. Based on previous research, testosterone hormone in the male gender is associated with suppressive effects on immune function, which may explain the greater susceptibility to infectious diseases observed in men. Moreover, men, in general, had a higher prevalence of high-risk behaviours, including smoking and alcohol consumption, and were more likely to work in high-risk jobs, including driving, which increases their risk of exposure to the infection or presents later when symptoms are worse, potentially explaining, at least in part, the higher severity of infections in men and consequent outcomes. On the other hand, this limited sensitivity of women to viral contaminations can be assigned to the protection from sex hormones and the X chromosome, which play a crucial function in intrinsic and adaptive stability.[16–18] Our analysis also indicated that a low level of SpO_2 is associated with ICU admission. Previous research in the field of factors related to ICU admission in patients with COVID-19 has also shown that patients with SpO_2 of 93% or less in a resting state had the worst CT scan score than ordinary patients with COVID-19 .[19 20]

Table 1 Characteristics of patients admitted to the ICU in Iran due to COVID-19, 2020–2021

Variables	All patients N=1 445 451	ICU admission		P value*
		Yes=278 439 (19.26)	No=1 167 012 (80.74)	
Age (years) (mean±SD)	54.44±20.59	62.51±19.73	52.59±20.33	<0.001†
Age groups	N (%)	N (%)	N (%)	<0.001
1–5	30 388 (2.10)	3290 (1.17)	27 135 (2.33)	
5–18	39 482 (2.73)	5908 (2.09)	33 679 (2.89)	
19–44	390 837 (27.04)	41 796 (14.82)	349 665 (29.96)	
45–64	478 061 (33.07)	81 399 (28.86)	397 693 (34.08)	
65–79	340 201 (23.54)	90 919 (32.23)	250 414 (21.46)	
≥80	166 482 (11.52)	58 747 (20.83)	108 426 (9.29)	
Sex				<0.001
Male	741 509 (51.30)	152 881 (54.91)	588 628 (50.44)	
Female	703 942 (48.70)	125 558 (45.09)	578 384 (49.56)	
Patient's status				<0.001
Inpatient	29 640 (2.05)	7212 (2.59)	22 428 (1.92)	
Temporary hospitalisation	29 758 (2.06)	351 (0.13)	29 407 (2.52)	
Dispatch	6974 (0.48)	2098 (0.75)	4876 (0.42)	
Death	164 260 (11.36)	117 110 (42.06)	47 150 (4.04)	
Discharge	1 214 819 (84.04)	151 668 (54.47)	1 063 151 (91.10)	
Wave				<0.001
First	196 418 (13.59)	33 778 (12.13)	162 640 (13.94)	
Second	45 182 (3.13)	9739 (3.50)	35 443 (3.04)	
Third	278 865 (19.29)	55 004 (19.75)	223 861 (19.18)	
Fourth	451 560 (31.24)	97 154 (34.89)	354 406 (30.37)	
Fifth	473 426 (32.75)	82 764 (29.72)	390 662 (33.48)	
Death				<0.001
Yes	164 260 (11.36)	117 110 (42.06)	47 150 (4.04)	
No	1 281 191 (88.64)	161 329 (57.94)	1 119 862 (95.96)	

*Based on χ^2 test.
†Based on t-test.
ICU, intensive care unit.

The current study verified that ageing was associated with ICU admission in patients with COVID-19. The older adults suffer from more severe forms of the disease due to inadequate nutrition and the relative weakness of the body's defence system, which increases their chances of hospitalisation in the ICU. Also, patients with COVID-19 from the older group had higher rates of common comorbidities, where hypertension, diabetes, chronic heart disease and COPD reached statistical significance. On admission, the severe/critical type rate was significantly higher in the older group than in the younger group, increasing their chances of ICU hospitalisation.[21–23]

Our national study demonstrated that patients with diabetes with COVID-19 infection have a higher risk of being admitted to ICU during the illness. Based on the initial evidence about the COVID-19 pandemic, patients with DM have been more likely to develop more severe clinical forms of the infection.[24] A recent meta-analysis of 1382 patients with diabetes showed that patients with COVID-19 with diabetes had a higher risk of ICU admission.[24] Some studies have shown that glycaemic control in people with diabetes appears to be an important prognostic factor for infection, and hyperglycaemia is a risk factor for the poor prognosis of COVID-19 with DM and is even associated with a higher risk of hospitalisation in ICU and mortality.[25–27] On the other hand, compared with non-DM patients, patients with DM had a higher level of aspartate aminotransferase (AST). AST higher than 40 U/L was associated with increasing odds of ICU admission of patients with COVID-19 with DM.[28]

The current study revealed that patients with cancer infected with COVID-19 had a higher risk of ICU admission than patients without cancer. A higher risk could be due to immunosuppression, increased coexisting medical conditions, and, in cases of lung malignancy, underlying pulmonary compromise.[29 30] Patients with cancer or those

Table 2 Comorbidities and signs and symptoms in patients admitted to ICU in Iran due to COVID-19, 2020–2021

Variables	All patients N=1 445 451	ICU admission		P value*
		Yes=278 439 (19.26)	No=1 167 012 (80.74)	
Comorbidities (yes)				
Asthma	29 036 (2.01)	6074 (2.18)	22 962 (1.97)	<0.001
Cardiovascular disease	163 989 (11.35)	54 030 (19.40)	109 959 (9.42)	<0.001
Chronic liver disease	6830 (0.47)	2208 (0.79)	4622 (0.40)	<0.001
Blood disorder	8236 (0.57)	2116 (0.76)	6120 (0.52)	<0.001
Chronic kidney disease	31 029 (2.15)	10 549 (3.79)	20 480 (1.75)	<0.001
Cancer	27 943 (1.93)	9760 (3.51)	18 183 (1.56)	<0.001
Diabetes	189 661 (13.12)	51 191 (18.38)	138 470 (11.87)	<0.001
Mental disorder	20 387 (1.41)	7601 (2.73)	12 786 (1.10)	<0.001
HIV/AIDS	845 (0.06)	262 (0.09)	583 (0.05)	<0.001
Immunosuppression	3376 (0.23)	856 (0.31)	2520 (0.22)	<0.001
Chronic diseases	108 803 (7.53)	26 878 (9.65)	81 925 (7.02)	<0.001
Pregnancy	12 899 (0.89)	1238 (0.44)	11 661 (1.00)	<0.001
Signs and symptoms (yes)				
Cough	642 138 (44.42)	95 098 (34.15)	547 040 (46.88)	<0.001
Fever	523 943 (36.25)	86 491 (31.06)	437 452 (37.48)	<0.001
SpO_2 <93%	733 272 (50.73)	188 859 (67.83)	544 413 (46.65)	<0.001
Acute respiratory distress syndrome	707 519 (48.95)	164 831 (59.20)	542 688 (46.50)	<0.001
Muscle pain	430 438 (29.78)	60 326 (21.67)	370 112 (31.71)	<0.001

*Based on χ^2 test.
ICU, intensive care unit.

receiving active chemotherapy treatment might be most vulnerable to complications due to increased immunosuppression. Compared with the general population, patients affected by cancer harbour a higher risk of contracting an infection.[31] This increased susceptibility is partially due to cancer, exerting a chronic immunosuppressive state, and can be exacerbated by cytotoxic therapies. Therefore, it is expected that patients with cancer be at higher risk, both of infection and complications (such as ICU admission) during the COVID-19 pandemic.[29]

Regarding mental disorders, our study showed that people with at least one mental disorder are more prone to ICU admission. This can be justified as follows; social and lifestyle factors such as diet, physical inactivity, social isolation, high alcohol and tobacco use, sleep disturbances and also a higher prevalence of somatic comorbidities, for example, diabetes, CVD and respiratory disease might also increase the risk of ICU admission in this group of patients.[22 23] On the other hand, due to exposure to antipsychotic and anxiolytic drug treatments initiated before contracting COVID-19, patients with mental disorder have a higher chance of adverse effects of COVID-19 and hospitalisation in the ICU.[24] According to previous research, this group of drugs might precipitate cardiovascular and thromboembolic risk, interfere with an adequate immune response and cause pharmacokinetics and pharmacodynamics interactions with drugs used to treat COVID-19.[25 26]

Our study found a positive association between having CVD in COVID-19 infected people and ICU admission. A recent study of 187 cases also suggested that patients with COVID-19 with CVD are more likely to experience acute cardiac injury associated with ICU admission and fatal outcomes.[22] The mechanism of this association is still unclear but is increasingly being recognised with dysfunctional immune systems.[23] There is also evidence that shows SARS-CoV-2 binds to human ACE2 to infect the cells, which are highly expressed in the lungs and heart. The binding of SARS-CoV-2 to ACE2 in the heart can result from acute myocardial injury.[24] COVID-19 has been associated with thrombotic events and coagulation disorders, which might lead to hypercoagulability and coronary thrombosis, resulting in acute myocardial infarction. These can increase the risk of ICU admission in patients with SARS-CoV-2 who suffer from CVD.[25]

Other comorbidities and chronic conditions (eg, chronic liver and kidney disease and immunosuppression) can also increase the chances of ICU admission for reasons, such as a weakened immune system, drug interactions between previous treatments that was consumed for control of chronic situations and drugs used for COVID-19 infection.[32–36]

Table 3 Factors associated with intensive care unit admission in patients hospitalised due to COVID-19 in Iran, using logistic regression

	Univariable		Multivariable	
Variables	OR	95% CI	OR	95% CI
Age groups				
1–5	1.01	0.98 to 1.05	1.12	1.07 to 1.16
5–18	1.46	1.42 to 1.51	1.52	1.44 to 1.57
19–44	Ref	–	Ref	–
45–64	1.71	1.69 to 1.73	1.36	1.34 to 1.37
65–79	3.04	3.00 to 3.08	2.06	2.04 to 2.09
≥80	4.55	4.48 to 4.61	2.90	2.86 to 2.94
Sex				
Male	1.19	1.18 to 1.20	1.20	1.19 to 1.21
Female	Ref	–	Ref	–
Wave				
First	Ref	–	Ref	–
Second	1.32	1.28 to 1.35	1.20	1.16 to 1.23
Third	1.18	1.16 to 1.20	1.04	1.02 to 1.06
Fourth	1.31	1.30 to 1.33	1.08	1.06 to 1.00
Fifth	1.02	1.005 to 1.03	0.90	0.88 to 0.91
Comorbidities (yes)				
Asthma	1.11	1.07 to 1.14	0.93	0.91 to 0.96
Cardiovascular disease	2.31	2.28 to 2.34	1.58	1.56 to 1.60
Chronic liver disease	2.01	1.91 to 2.11	1.75	1.66 to 1.85
Blood disorder	1.45	1.38 to 1.52	1.27	1.21 to 1.35
Chronic kidney disease	2.20	2.15 to 2.25	1.59	1.55 to 1.63
Cancer	2.29	2.23 to 2.35	2.11	2.05 to 2.16
Diabetes	1.67	1.65 to 1.69	1.22	1.21 to 1.24
Mental disorder	2.53	2.46 to 2.61	2.05	1.98 to 2.11
HIV/AIDS	1.88	1.62 to 2.18	1.51	1.30 to 1.77
Immunosuppression	1.42	1.31 to 1.54	1.53	1.41 to 1.66
Chronic diseases	1.41	1.39 to 1.43	1.17	1.15 to 1.19
Pregnancy	0.94	0.92 to 0.97	1.09	1.03 to 1.17
Signs and symptoms (yes)				
Cough	0.58	0.58 to 0.59	0.66	0.65 to 0.67
Fever	0.75	0.74 to 0.76	0.84	0.84 to 0.85
SpO_2 <93%	2.41	2.39 to 2.43	1.95	1.93 to 1.97
Acute respiratory distress syndrome	1.66	1.65 to 1.68	1.22	1.21 to 1.23
Muscle pain	0.59	0.58 to 0.60	0.68	0.67 to 0.69

At the time of this study (14 May 2022), we were in the fifth wave of COVID-19; accordingly, the results of the multivariate regression model indicated that the chance of ICU admission decreases with the increasing number of COVID-19 waves. One can legitimately assume that the experience gained during the first wave may have contributed to better management and outcome among critically ill patients with COVID-19 admitted during the other waves. It can also be attributed to the better understanding of COVID-19 with significant treatment modification, including systematic and early administration of glucocorticoids as well as intermediate/full-dose thromboprophylaxis.[37 38]

The main strength of this study is that it is conducted at the national level and investigated the epidemiological and clinical aspects of ICU admission in many patients with COVID-19 in Iran. Our study had some limitations. First, data were collected by the hospital information

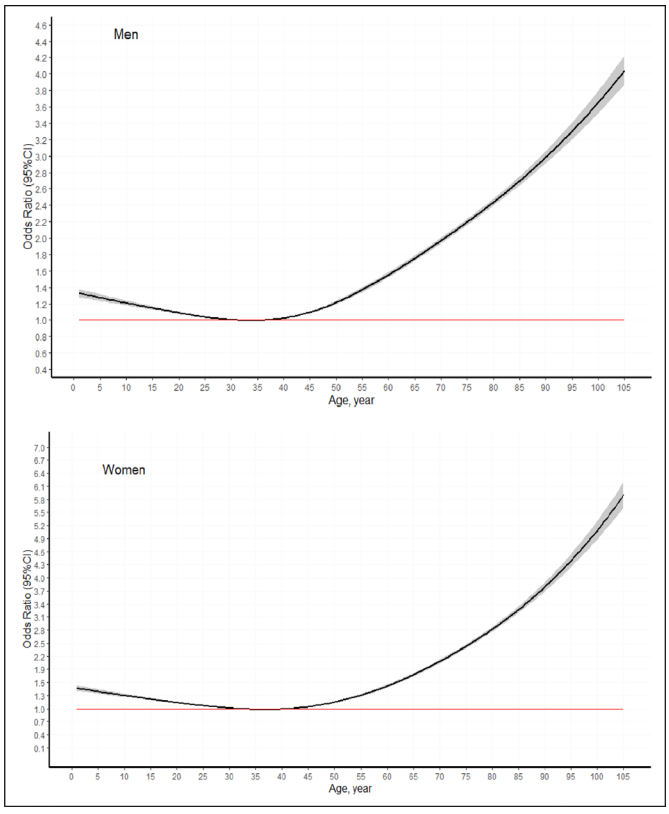

Figure 1 The dose–response association of age and intensive care unit inhalation by gender and age based on the restricted cubic spline model (five knots were located at the 19, 41, 56, 69 and 85 years old); solid line represents the fitted trend and coloured area represents 95% CI.

registration system, and it was not possible to directly verify the data accuracy by interviewing patients directly. Second, some data were missing that we imputed them. Third, criteria for ICU admission may have varied over time and between different waves with improved knowledge of the disease by physicians.

CONCLUSION

In this study, we found that patients admitted to the ICU are mainly older adults, men suffering from chronic conditions and comorbidities and people with ARDS with oxygen saturation under 93%. Therefore, these groups, especially patients with comorbidities, should take all necessary precautions to avoid getting infected with COVID-19, as they usually have the worst prognosis. Also, these people may be predictive markers of severe clinical pictures.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval All procedures performed in the study were approved by the ethical committee of the National Institute for Medical Research Development (approval ID = IR.NIMAD.REC.1400.114). All methods were carried out following relevant guidelines and regulations.

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Data availability statement Data are available upon reasonable request. The datasets used or analysed during the current study are available from the corresponding author upon reasonable request.

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