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# Vitamin D deficiency is Associated with Increased Risk of Delirium and Mortality among Critically Ill, Elderly Covid-19 Patients

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## ABSTRACT

**Background and aim:** Data on the associations of vitamin D levels with severe outcomes of coronavirus disease 2019 (COVID-19) among critically ill elderly patients are not conclusive and also no information is available about some outcomes such as delirium. Therefore, the current study was done to assess these associations in critically ill elderly COVID-19 patients.

**Methods:** In total, 310 critically ill COVID-19 patients, aged  $\geq 65$  years, were included in the current single center prospective study. All patients were hospitalized in the intensive care unit (ICU). We collected data on demographic characteristics, laboratory parameters, blood pressure, comorbidities, medications, and types of mechanical ventilation at baseline (the first day of ICU admission). Patients were categorized based on serum 25 (OH)D3 levels at the baseline [normal levels ( $>30$  ng/mL), insufficiency (20–30 ng/mL), deficiency ( $<20$  ng/mL)]. Data on delirium incidence, mortality, invasive mechanical ventilation (IMV) requirement during treatment, length of ICU and hospital admission, and re-hospitalization were recorded until 45 days after the baseline.

**Results:** Vitamin D deficiency and insufficiency were prevalent among 12 % and 37 % of study participants, respectively. In terms of baseline differences, patients with vitamin D deficiency were more likely to be older, have organ failure, take propofol, need IMV, and were less likely to need face mask compared to patients with normal levels of vitamin D. A significant positive association was found between vitamin D deficiency and risk of delirium. After controlling for potential confounders, patients with vitamin D deficiency had a 54 % higher risk of delirium compared to those with vitamin D sufficiency (HR: 1.54, 95 % CI: 1.02–2.33). Such a positive association was also seen for 45-day COVID-19 mortality (HR: 3.95, 95 % CI: 1.80–8.67). Also, each 10 ng/mL increase in vitamin D levels was associated with a 45 % and 26 % lower risk of 45-day mortality (HR: 0.55, 95 % CI: 0.40–0.74) and ICU mortality due to COVID-19 (HR: 0.74, 95 % CI: 0.60–0.92), respectively. In terms of other COVID-19 outcomes including IMV requirement during treatment, prolonged hospitalization, and re-hospitalization, we found no significant association in relation to serum 25(OH)D3 levels either in crude or fully adjusted models.

**Conclusion:** Vitamin D deficiency was associated with an increased risk of delirium and mortality among critically ill elderly COVID-19 patients.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic has become a major threat to global public health and has imposed a high cost to the health care system<sup>1</sup>. This disease has significantly increased the number of

hospitalizations during the last two years<sup>2</sup>. Hospitalized COVID-19 patients usually suffer from aggravated symptoms (i.e., cough, fever, acute respiratory failure, fatigue, and inflammation) and may have severe outcomes such as delirium, prolonged hospital and intensive care unit (ICU) admission, invasive mechanical ventilation (IMV) requirement,

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and death<sup>3,4</sup>. Overall, it is necessary to find contributing factors to the incidence of severe outcomes in hospitalized COVID-19 patients.

Previous studies have shown that advanced age, malnutrition, comorbidities, and pre-existing respiratory diseases are associated with severe outcomes in hospitalized COVID-19 patients<sup>5-9</sup>. Recently, it has been shown that the majority of COVID-19 patients have vitamin D deficiency<sup>10,11</sup>. Furthermore, the positive association between vitamin D deficiency and risk of hospitalization and mortality among COVID-19 patients has been reported<sup>12</sup>. In a large population-based study, Oristrell et al. reported that COVID-19 patients supplemented with vitamin D had normal levels of 25-hydroxy vitamin D3 [25(OH)D3] ( $\geq 30$  ng/mL) and better clinical outcomes compared with those who did not use this supplement<sup>13</sup>. Also, there is evidence indicating the preventive role of vitamin D consumption for COVID-19 disease<sup>14</sup>. Vitamin D has an important role in immune response and inflammation regulation<sup>15</sup>. In a review article, Mercola et al. found strong enough evidence that people and physicians can use or recommend vitamin D supplements to prevent or treat COVID-19 in light of their safety and wide therapeutic window<sup>16</sup>. However, findings on the associations of serum concentrations of vitamin D with severe outcomes of COVID-19 are conflicting. Some studies<sup>17,18,19</sup> demonstrated a positive association between vitamin D deficiency and COVID-19 severity and mortality. Also, Hariyanto et al.<sup>20</sup> suggested the beneficial effect of vitamin D supplementation on COVID-19 outcomes. However, some studies have shown that vitamin D levels are not associated with disease severity<sup>21,22</sup> and prolonged hospitalization in patients with COVID-19<sup>23</sup>. In addition, Chen et al. reported that vitamin D deficiency was not associated with death due to COVID-19<sup>24</sup>. Therefore, given the inconsistent results, further studies are required in this regard.

In addition to COVID-19 mortality, few studies have assessed IMV requirement and duration of hospital or ICU stay in relation to vitamin D levels in critically ill COVID-19 patients and data in this regard are not conclusive<sup>25-27</sup>. Nevertheless, as far as we know, the relationship between vitamin D deficiency and delirium incidence among ICU patients with COVID-19 has not been studied. Delirium is the most common form of acute brain dysfunction affecting approximately 80 % of ICU patients<sup>28</sup>. In total, this study was done to investigate the associations of vitamin D levels with severe outcomes of COVID-19 including mortality, prolonged hospitalization, delirium incidence, and IMV requirement among critically ill elderly COVID-19 patients.

## 2. Materials and methods

### 2.1. Study design and participants

This was a single center prospective study that was conducted in Khatam hospital, which was a government-designated hospital for patients with COVID-19. This study was conducted from 30 August 2021–5 January 2022. We recruited critically ill elderly cases of COVID-19 patients who were hospitalized in ICU. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was diagnosed by reverse transcriptase polymerase chain reaction (RT-PCR) test and also chest CT scan lesions. Based on the classification of the Guidance for Coronavirus Disease 2019 (6th edition), published by the National Health Commission of China<sup>29</sup>, we defined critically ill COVID-19 patients according to the following criteria: (1) respiratory failure requiring a form of mechanical ventilation; (2) septic shock;<sup>3</sup> having at least one organ failure necessitating monitoring and treatment in the intensive care unit (ICU). Other inclusion criteria were willingness to participate in the study and having an age range of  $\geq 65$  years. We did not include COVID-19 patients if (1) they were admitted to ICU for the second time; (2) they had severe comorbidities including any brain damage, severe liver or kidney disease, and cancer; (3) they had a history of pre-existing neurodegenerative disorders, mental illness, dementia, and cognitive disorders. In addition, COVID-19 patients who died or were discharged within the first 48 h of hospitalization were excluded because of the avoidance of

bias in collecting information on complications and reviewing the effectiveness of treatments prescribed in ICU. In total, 392 elderly patients with COVID-19 were included. We collected data on demographic characteristics, laboratory parameters, nutritional status, blood pressure, comorbidities, types of mechanical ventilation at baseline (the first day of ICU admission), and medications that were used for controlling the infection, and. Patients were followed up during the ICU admission and also until 45 days after the baseline. During the follow-up period, we recorded data on delirium incidence, mortality, IMV requirement, duration of ICU or hospital admission, and re-hospitalization for each patient.

#### 2.1.1. Ethics

We took written informed consent from each participant. If a patient was not conscious, the consent was taken from his/her first-degree relatives. Patients were reassured that data collected from medical records would be used for the current study in accordance with privacy laws. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. We conducted this study based on the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

#### 2.1.2. Sample size calculation

We calculated the required sample size using Power Analysis Software (PAS). By considering the type 1 error of 5 %, study power of 80 %, estimated hazard ratio (HR) of 1.2 for mortality, and mortality rate of 60 % among critically ill patients with COVID-19, we needed a sample size of 272 elderly COVID-19 patients. However, we recruited 392 patients in the current study to increase study power and consider the probable drop-out.

### 2.2. Baseline assessment

During the first 24 h of ICU admission, data on demographic characteristics, laboratory parameters, blood pressure, comorbidities, medications used for controlling the infection, and types of mechanical ventilation were collected.

#### 2.2.1. Demographic and clinical characteristics

We collected data on age, sex, weight, height, marital status, education, smoking, systolic and diastolic blood pressure, and history of alcohol consumption by evaluating the hospital's electronic medical records or questionnaires and also by a direct interview with patients if needed. Body mass index (BMI) was determined as weight in kilograms divided by height in meters squared. In addition, by reviewing the medical records, we obtained data on comorbidities including pulmonary diseases (i.e. asthma, chronic obstructive pulmonary disease, etc.), hyperlipidemia, diabetes, hypertension, cardiovascular disease (CVD), hypothyroidism, acute and chronic renal failure, liver disease, rheumatoid arthritis, incidence of organ failure from the time of entering in ICU, and ear and eye problems. The treatment protocols including medications and types of mechanical ventilation [IMV, non-invasive mechanical ventilation (NIMV), high-flow nasal cannula, face mask] used for controlling COVID-19 and its symptoms were also recorded. By using data on demographic (age), clinical (body temperature, mean arterial pressure, blood PH, heart rate, respiratory rate, oxygen partial pressure, Glasgow coma scale), and laboratory variables (sodium, potassium, creatinine, hematocrit, and white blood cells), we calculated acute physiology and chronic health examination II (APACHE II) score for each patient. APACHE II scores range between zero and 71, with higher scores indicating a more severe condition.

#### 2.2.2. Laboratory parameters

On the first day of ICU admission, patients' medical records were assessed to obtain data on fasting blood sugar (FBS), serum levels of inflammatory biomarkers [C-reactive protein (CRP) and interleukin-6

(IL-6)], albumin, creatinine, urea, bilirubin, and 25(OH)D3. Serum levels of 25(OH)D3 were measured using enzyme-linked immunosorbent assay (ELISA) (Immunoassays S.A., Belgium). The intra- and inter-assay precision by the coefficient of variation (CV) for the ELISA approach were less than 10% and 12%, respectively.

Serum levels of electrolytes including magnesium, phosphorous, calcium, sodium, and potassium were also assessed. We also collected data on hematological factors including white blood cells (neutrophil, lymphocyte), hematocrit, and platelet. Lactate dehydrogenase (LDH) levels were determined at baseline because previous studies have shown that higher LDH levels are associated with 6-fold increased odds of severe COVID-19 disease<sup>30</sup>.

### 2.2.3. Follow-up

The incidence of delirium and the need for a form of mechanical ventilation, particularly invasive ventilation, were recorded during the ICU admission. Delirium was diagnosed based on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)<sup>31</sup>. Accordingly, delirium has four features: (1) acute onset of changes or fluctuations in the course of mental status,<sup>2</sup> inattention,<sup>3</sup> disorganized thinking, and<sup>4</sup> an altered level of consciousness (other than alert). Patients were delirious if they had features 1 and 2 plus either feature 3 or 4. In the present study, delirium was evaluated every day using the CAM-ICU by an experienced ICU physician. To facilitate the assessment of acute onset or fluctuation of mental status changes, patients were followed up daily with the Glasgow coma scale. In addition to delirium, we recorded the occurrence of mortality and re-hospitalization during the ICU admission and also until 45 days after the baseline day. Duration of hospitalization in ICU or other wards of the hospital was another outcome of interest in the current study. ICU admission  $\geq 7$  days was considered as prolonged stay in ICU and hospitalization  $\geq 14$  days as prolonged stay in hospital.

### 2.2.4. Statistical analysis

All elderly COVID-19 patients were categorized based on serum 25(OH)D3 levels at the baseline [normal levels ( $>30$  ng/mL), insufficiency (20–30 ng/mL), deficiency ( $<20$  ng/mL)]. We used one-way ANOVA to compare continuous variables across different levels of 25(OH)D3 if the distribution of those variables was normal. For the non-normally distributed continuous variables, we used the Kruskal-Wallis test for the comparison. To determine the distribution of categorical variables across different levels of 25(OH)D3, we used the Chi-square test. In order to analyze the associations of serum 25(OH)D3 levels with mortality, delirium, and IMV therapy during treatment, we used univariable and multivariable Cox proportional hazards models. In the time-to-event analysis, follow-up time was considered as the day that outcome occurred or the day that patient was followed up. To assess the associations of serum 25(OH)D3 levels with prolonged stay in ICU ( $\geq 7$  days) or hospital ( $\geq 14$  days) and odds of re-hospitalization after discharge, we used univariable and multivariable binary logistic regression. We included potential confounders including age, gender, smoking, pre-existing pulmonary diseases, alcohol consumption, BMI, and blood levels of white blood cell (WBC), albumin, and CRP in the adjusted models. In all analyses, COVID-19 patients with the normal levels of 25(OH)D3 were considered as a reference group. All statistical analyses were done using the SPSS software version 18 (SPSS, Inc. Chicago, IL, USA).  $P < 0.05$  was considered significant.

## 3. Results

Of the 392 critically ill elderly COVID-19 patients at the baseline, 19 patients were excluded because they died during the first 48 h of hospitalization. Moreover, 63 patients with incomplete data on exposure and outcome variables were excluded. Finally, we performed the statistical analysis on 310 patients with complete data (Fig. 1). All the patients had received antiviral and antibiotic drugs. At the baseline, 12 % and 37 % of study participants have vitamin D deficiency and

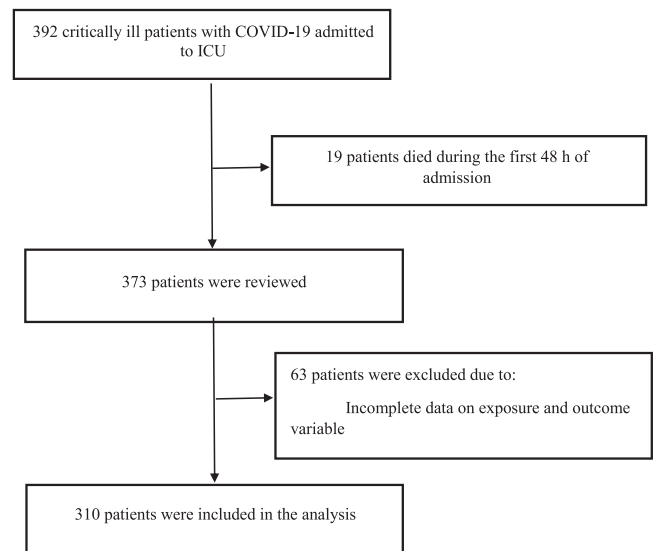


Fig. 1. Study flow diagram.

insufficiency, respectively. In addition, 1.6 % of participants had severe vitamin D deficiency ( $<12$  ng/mL). We recorded 132 (43 %) deaths during ICU admission and 190 (61 %) deaths during 45 days after the baseline. In addition, during the ICU admission, 217 (70 %) cases of delirium were observed and 35 (11 %) patients needed IMV therapy during treatment. Also, during the follow-up period, 65 (21 %) patients were hospitalized for the second time.

Baseline characteristics of patients across different levels of serum 25(OH)D3 are shown in Table 1. Patients with vitamin D deficiency had higher APACHE II scores, higher levels of WBC, platelet, lactate dehydrogenase, and lower values of albumin and hematocrit compared to patients with vitamin D sufficiency. Also, the mean age of participants was significantly different across different levels of 25(OH)D3. Patients with vitamin D deficiency were more likely to have the incidence of organ failure, take propofol, need IMV and NIMV therapies, and were less likely to need face mask than those with normal levels of vitamin D. We found no significant difference in terms of length of hospital and ICU stay, and other laboratory parameters, comorbidities, and medications. Also, vaccination status of patients (receiving at least one dose of the vaccine) was not significantly different across different levels of 25(OH)D3.

Multivariable-adjusted HRs and 95% confidence intervals (CIs) of delirium, COVID-19 mortality, and IMV therapy across different levels of serum 25(OH)D3 among critically ill elderly COVID-19 patients are indicated in Table 2. A significant positive association was found between vitamin D deficiency and the risk of delirium during ICU admission (HR: 1.48, 95 % CI: 1.00–2.19). This association remained significant even after controlling for potential confounders including demographic variables, smoking, history of pulmonary diseases, and blood/serum levels of WBC, albumin, and CRP; such that, patients with vitamin D deficiency had a 54 % higher risk of delirium compared to those with vitamin D sufficiency (HR: 1.54, 95 % CI: 1.02–2.33). Also, a non-significant inverse linear association was seen between vitamin D levels and delirium incidence based on a 10 ng/mL increase in serum 25(OH)D3 (HR: 0.86, 95 % CI: 0.73–1.01). In terms of COVID-19 mortality, we found a significant positive association with vitamin D deficiency. After taking potential confounders into account, vitamin D deficiency was associated with 3.95 times increased risk of 45-day COVID-19 mortality in critically ill elderly COVID-19 patients (HR: 3.95, 95 % CI: 1.80–8.67). Such a positive association was seen for COVID-19 mortality during ICU admission (HR: 1.66, 95 % CI: 1.00–2.78). However, this association was marginally significant ( $P = 0.05$ ). In addition, we found significant inverse associations between a 10 ng/mL increase

**Table 1**  
 Characteristics of critically ill elderly COVID-19 patients across categories of vitamin D levels.

	25 (OH)D3 levels				P-value*
	Total	Normal levels (>30 ng/mL)	Insufficiency (20–30 ng/mL)	Deficiency (<20 ng/mL)	
n	310	157	115	38	
<b>Demographic characteristics</b>					
Age, y	73 ± 7	72 ± 6	74 ± 8	74 ± 6	0.04
Weight, kg	73 ± 10	73 ± 8	71 ± 13	75 ± 11	0.06
BMI, kg/m <sup>2</sup>	27 ± 3	27 ± 3	26 ± 4	28 ± 4	0.12
Female, %	41	41	46	29	0.17
Smokers, %	26	29	22	29	0.35
Married, %	79	82	76	71	0.24
University educated, %	12	11	13	7.9	0.67
Alcohol intake, %	7.7	11	5.2	2.6	0.10
<b>Hematology</b>					
WBC, 10 <sup>3</sup> /μL	9 ± 5	9 ± 4	9 ± 5	11 ± 3	0.03
Neutrophil, 10 <sup>3</sup> /μL	83 ± 9	84 ± 8	82 ± 10	84 ± 7	0.18
Lymphocyte, 10 <sup>3</sup> /μL	12 ± 12	12 ± 14	13 ± 11	10 ± 5	0.42
Platelet, 10 <sup>3</sup> /μL	220 ± 71	220 ± 65	200 ± 71	250 ± 85	0.002
Albumin, g/dL	3.1 ± 0.7	3.2 ± 0.7	3 ± 0.6	2.7 ± 0.5	0.001
Hematocrit, %	36 ± 6	37 ± 6	35 ± 7	33 ± 6	0.001
<b>Biochemical assessment</b>					
CRP, mg/L	88 ± 47	89 ± 48	87 ± 48	84 ± 43	0.83
IL6, pg/mL	160 ± 220	140 ± 180	180 ± 260	200 ± 210	0.14
Creatinine, mg/dL	1.4 ± 0.6	1.3 ± 0.7	1.4 ± 0.5	1.6 ± 0.6	0.10
FBS, mg/dL	170 ± 54	170 ± 53	170 ± 57	173 ± 49	0.84
Lactate dehydrogenase, U/L	520 ± 260	490 ± 210	530 ± 280	630 ± 360	0.01
Vitamin D, ng/mL	30 ± 9	37 ± 4	25 ± 3	16 ± 3	< 0.001
Bilirubin, mg/dL	0.83 ± 1.1	0.80 ± 1.1	0.84 ± 1	0.95 ± 1.7	0.76
Urea, mg/dL	28 ± 16	29 ± 18	26 ± 14	28 ± 10	0.46
Magnesium, mEq/L	2 ± 0.4	2 ± 0.4	2 ± 0.4	1.9 ± 0.4	0.48
Phosphorous, mg/dL	3 ± 0.5	3 ± 0.5	3.1 ± 0.6	3 ± 0.4	0.81
Calcium, mg/dL	8.1 ± 0.57	8.1 ± 0.6	8.2 ± 0.5	8.3 ± 0.5	0.14
Sodium, mEq/L	140 ± 10	140 ± 4	130 ± 13	140 ± 5	0.71
Potassium, mmol/L	4 ± 0.7	4.1 ± 0.6	3.9 ± 0.7	4.1 ± 0.7	0.17
<b>Blood pressure</b>					
SBP, mmHg	139 ± 22	137 ± 21	140 ± 23	142 ± 24	0.43
DBP, mmHg	81 ± 15	80 ± 13	83 ± 16	82 ± 19	0.39
Mean arterial pressure, mmHg	100 ± 17	99 ± 15	102 ± 18	102 ± 20	0.39
<b>Comorbidities</b>					
Pulmonary disease, %	25	24	25	26	0.95
Hyperlipidemia, %	40	43	35	45	0.34
Diabetes, %	46	46	43	50	0.68
Hypertension, %	55	55	60	40	0.09
CVD, %	45	45	42	55	0.34
Hypothyroidism, %	21	22	18	24	0.37
Acute renal failure, %	27	26	24	37	0.29
Chronic renal disease, %	36	29	42	45	0.054
Liver disease, %	9.0	6.4	12	10	0.24
Stroke, %	5.5	3.9	7.8	5.3	0.37
Rheumatoid arthritis, %	1.3	1.3	0.9	2.6	0.70
Organ failure, % <sup>a</sup>	48	46	44	68	0.03
Ear problems, %	8.7	8.3	9.6	7.9	0.91
Eye problems, %	5.5	5.1	7.0	2.6	0.57
<b>Medication</b>					
Propofol, %	6.5	5.7	4.3	16	0.04
Opioid drugs, %	59	54	63	66	0.23
Glucocorticoids, %	66	64	66	71	0.68
Benzodiazepine, %	71	69	73	71	0.74
Vasopressor, %	47	49	45	42	0.68
<b>Oxygen therapy at baseline</b>					
Invasive MV, %	6.5	5.7	4.3	16	0.04
NIV, %	60	52	68	66	0.02
High flow nasal cannula, %	2.3	3.2	0.9	2.6	0.44
Face mask, %	59	67	57	29	< 0.001
<b>Hospitalization</b>					
Length of hospital stay (day)	14 (10–19)	14 (11–19)	14 (10–20)	12 (8–19)	0.24
Length of ICU stay (day)	8 (6–10)	8 (6–10)	7 (6–10)	8 (6–11)	0.51
APACHE II score	17 (11–21)	15 (10–20)	17 (12–20)	20 (17–22)	< 0.001
<b>Vaccination, %</b>					
	50	50	50	47	0.94

Data are presented as mean ± SD for normal-distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and percent for categorical variables: all numbers were rounded based on the Cole study<sup>57</sup>.

Abbreviations: BMI: body mass index, WBC: white blood cell, IL-6: interleukin – 6, CRP: C-reactive protein, FBS: fasting blood sugar, SBP: systolic blood pressure, DBP: diastolic blood pressure, CVD: cardiovascular disease, MV: mechanical ventilation, NIV: non-invasive ventilation, SD: standard deviation, APACHE II: acute physiology and chronic health examination II

<sup>a</sup> Considered as the incidence of failure of ≥ 2 organs



Obtained from one-way ANOVA (normal-distributed continuous variables), Kruskal–Wallis test (non-normally distributed continuous variables), or chi-square test (categorical variables)

**Table 2**

HRs (95% CIs) for the associations of serum 25(OH)D3 levels with some severe outcomes of critically ill elderly COVID-19 patients.

	n	25 (OH)D3 levels			Linear dose-response (per 10 ng/mL increase)
		Normal levels (>30 ng/mL)	Insufficiency (20–30 ng/mL)	Deficiency (<20 ng/mL)	
<b>Delirium</b>					
Cases	104	80	33	217	
Unadjusted	1	1.04 (0.77–1.39)	1.48 (1.00–2.19)	0.84 (0.73–0.98)	
Model 1	1	1.03 (0.76–1.39)	1.55 (1.04–2.31)	0.84 (0.72–0.98)	
Model 2	1	1.02 (0.76–1.38)	1.54 (1.02–2.33)	0.86 (0.73–1.01)	
<b>IMV requirement during treatment<sup>a</sup></b>					
Cases	20	11	4	35	
Unadjusted	1	1.50 (0.71–3.20)	0.83 (0.45–1.54)	0.83 (0.61–1.12)	
Model 1	1	1.64 (0.75–3.57)	0.70 (0.36–1.36)	0.84 (0.60–1.19)	
Model 2	1	1.57 (0.70–3.50)	0.69 (0.36–1.32)	0.88 (0.62–1.26)	
<b>45-day mortality</b>					
Cases	79	78	33	180	
Unadjusted	1	1.79 (1.01–3.16)	3.60 (1.70–7.62)	0.56 (0.41–0.75)	
Model 1	1	1.70 (0.94–3.08)	4.18 (1.96–8.92)	0.53 (0.40–0.72)	
Model 2	1	1.71 (0.94–3.10)	3.95 (1.80–8.67)	0.55 (0.40–0.74)	
<b>Death during ICU admission</b>					
Cases	56	53	23	132	
Unadjusted	1	1.33 (0.91–1.94)	1.68 (1.03–2.74)	0.73 (0.60–0.89)	
Model 1	1	1.49 (0.99–2.23)	1.86 (1.12–3.10)	0.70 (0.57–0.87)	
Model 2	1	1.37 (0.91–2.06)	1.66 (1.00–2.78)	0.74 (0.60–0.92)	

Data are presented as HR (95 % CI).

Abbreviations: BMI: body mass index, IMV: invasive mechanical ventilation, WBC: white blood cell, CRP: C-reactive protein, HR: hazard ratio

<sup>a</sup> With considering IMV therapy at baseline

Model 1: Adjusted for age, gender, smoking, history of pulmonary diseases, alcohol consumption, and BMI

Model 2: Further adjustments for WBC, albumin, and CRP levels

HRs were obtained from the Cox regression analysis

in 25(OH)D3 and COVID-19 mortality in ICU (HR: 0.74, 95 % CI: 0.60–0.92) and during 45 days (HR: 0.55, 95 % CI: 0.40–0.74). Regarding IMV requirement during treatment, we found no significant association with serum 25(OH)D3 levels either in crude or fully adjusted models. Such the non-significant association was also seen in the dose-response analysis.

Table 3 shows multivariable-adjusted odds ratios (ORs) and 95% CIs for the associations of serum 25(OH)D3 levels with re-hospitalization and prolonged stay in ICU and hospital among critically ill elderly COVID-19 patients. We found no evidence of a significant positive association between serum 25(OH)D3 levels and prolonged stay in ICU (OR: 1.37, 95 % CI: 0.61–3.07) and hospital (OR: 0.94, 95 % CI: 0.43–2.06). This association was non-significant even after taking potential confounders into account. In addition, serum 25(OH)D3 levels

were not significantly associated with re-hospitalization after discharge in both unadjusted and multivariable adjusted models (OR: 1.80, 95 % CI: 0.77–4.20). In the linear dose-response analysis, we found no significant association as well.

#### 4. Discussion

In the current study, we found that vitamin D deficiency was associated with an increased risk of delirium and COVID-19 mortality among critically ill elderly COVID-19 patients. These associations were obtained after controlling for potential confounding variables. For other outcomes of COVID-19 including IMV requirement and prolonged admission in ICU and hospital, we observed no significant association with serum 25(OH)D3 levels. To the best of our knowledge, the present prospective study is one of the few studies in the Middle East, if not the first, to determine the association of serum 25(OH)D3 levels with severe outcomes in elderly COVID-19 patients. As we know, most studies in this regard that were done in the Middle East were retrospective or cross-sectional<sup>32–35</sup>.

COVID-19 among elderly individuals, particularly those with comorbidities, is associated with severe prognosis and high mortality<sup>36</sup>. Some modifiable risk factors such as malnutrition or micronutrient deficiencies may aggravate the infection and increase the incidence of severe outcomes<sup>37,38</sup>. In the current study, vitamin D deficiency (<20 ng/mL) was associated with a higher risk of mortality among critically ill elderly COVID-19 patients. In line with our findings, a prospective study on 551 COVID-19 patients showed that vitamin D deficiency ( $\leq 12$  ng/mL or <30 nmol/L) was significantly associated with COVID-19 mortality after controlling for visceral fat (epicardial fat thickness)<sup>39</sup>. In a retrospective study on 257 COVID-19 patients, Jenei et al. reported that vitamin D deficiency is a potential risk factor for mortality among elderly COVID-19 patients with comorbidities (cancer, diabetes and/or pulmonary disease)<sup>40</sup>. In contrast, a single-center retrospective study on 39 patients with COVID-19 and acute respiratory distress syndrome (ARDS) indicated that vitamin D levels were not associated with COVID-19 survival<sup>41</sup>. Different findings in the last study might be due to the low sample size and its low power to detect a true association between vitamin D levels and COVID-19 mortality. However, further studies are needed to confirm the positive association between vitamin D deficiency and COVID-19 mortality.

Vitamin D deficiency is associated with higher concentrations of CRP and IL-6<sup>42,43</sup>. Therefore, COVID-19 patients with vitamin D deficiency may provide a greater inflammatory response that is positively associated with mortality risk<sup>44</sup>. Vitamin D has a modulatory role in the inflammatory response caused by COVID-19 through inhibiting adaptive immunity by decreasing B cell proliferation and production of antibodies<sup>45</sup>. This plays an important role in the regulation of T cell phenotype<sup>45</sup>. Therefore, a significant change occurs in the adaptive immune response from Th1 to a more regulatory Th2 response that increases the production of Th2 associated cytokines<sup>45</sup>. Moreover, vitamin D can increase the expression of angiotensin-converting enzyme-2 (ACE-2) and suppress the angiotensin-renin system and angiotensin II production, which is a pro-inflammatory biomarker<sup>42,46</sup>. As result, these processes may attenuate the cytokine storm perpetuating a pro-inflammatory state and worsening severe outcomes of COVID-19.

In the current study, we found a significant positive association between vitamin D deficiency and delirium risk among critically ill elderly COVID-19 patients hospitalized in ICU. In a review article, Menéndez et al. concluded that vitamin D is a neuroprotective agent in COVID-19 patients that may prevent delirium in these patients<sup>47</sup>. However, other reasons such as APOE e4 Genotypes have been shown to be associated with an increased risk of delirium during COVID-19-related hospitalizations. A cohort study also showed that delirium linked to APOE e4

**Table 3**

ORs (95 % CI) for the associations of serum 25(OH)D3 levels with re-hospitalization and prolonged stay in ICU and hospital among critically ill elderly COVID-19 patients.

	n	25 (OH)D3 levels			Linear dose-response (per 10 ng/mL increase)
		Normal levels (>30 ng/mL)	Insufficiency (20–30 ng/mL)	Deficiency (<20 ng/mL)	
Hospital stay $\geq$ 14 days		157	115	38	310
Cases		83	61	17	161
Unadjusted		1	1.00 (0.62–1.63)	0.72 (0.35–1.47)	1.13 (0.88–1.46)
Model 1		1	1.03 (0.61–1.72)	0.75 (0.35–1.57)	1.08 (0.82–1.40)
Model 2		1	1.14 (0.67–1.93)	0.94 (0.43–2.06)	0.96 (0.73–1.28)
ICU stay $\geq$ 7 days					
Cases		96	71	26	193
Unadjusted		1	1.02 (0.62–1.68)	1.37 (0.64–2.93)	0.90 (0.68–1.20)
Model 1		1	0.97 (0.58–1.64)	1.52 (0.69–3.33)	0.86 (0.65–1.13)
Model 2		1	0.96 (0.56–1.64)	1.37 (0.61–3.07)	0.89 (0.69–1.16)
Re-hospitalization					
Cases		33	20	12	65
Unadjusted		1	0.79 (0.42–1.46)	1.73 (0.79–3.80)	0.90 (0.66–1.23)
Model 1		1	0.79 (0.41–1.49)	1.94 (0.85–4.41)	0.89 (0.64–1.24)
Model 2		1	0.74 (0.38–1.41)	1.80 (0.77–4.20)	0.95 (0.67–1.33)

Data are presented as OR (95 % CI).

Abbreviations: BMI: body mass index, ICU: intensive care unit, WBC: white blood cell, CRP: C-reactive protein, OR: odds ratio

Model 1: Adjusted for age, gender, smoking, history of pulmonary diseases, alcohol consumption, and BMI

Model 2: Further adjustments for WBC, albumin, and CRP levels

ORs were obtained from the binary logistic regression

Genotypes in Covid-19 patients<sup>48</sup>. Also, the positive link between vitamin D deficiency and other neurological disorders such as dementia and Alzheimer's disease was reported in previous studies<sup>49</sup>. In addition, the association between vitamin D deficiency and delirium was assessed in other health conditions. In a retrospective study, a significant inverse association was reported between serum 25(OH)D3 concentrations and delirium risk among patients in a surgical ICU<sup>50</sup>. In a community-based cohort study of adults from 22 cities across the United Kingdom (the UK Biobank), Pilling et al. reported that progressively lower vitamin D levels predicted increased risk of incident hospital-diagnosed delirium<sup>51</sup>. In addition, Velayati et al. concluded that preoperative severe vitamin D deficiency was associated with the occurrence of delirium after coronary artery bypass grafting surgery<sup>52</sup>. It has been proposed that vitamin D has a neuroprotective role through preventing oxidative damage to nervous tissue and influencing on neurotransmitter synthesis<sup>53</sup>. Also, vitamin D receptor (VDR) has been found in some brain areas such as the hippocampus that are involved in Alzheimer's disease and other neurodegenerative conditions<sup>54</sup>. Another proposed mechanism is the influence of vitamin D on attenuating inflammation, which contributes to delirium pathogenesis<sup>55</sup>.

We found that serum levels of 25(OH)D3 were not significantly associated with IMV requirement, prolonged hospitalization, and re-hospitalization. In a retrospective study, vitamin D levels were not associated with the length of hospitalization; however, vitamin D deficiency was associated with prolonged IMV therapy<sup>41</sup>. In addition, Bulca-Acar et al. reported no significant association between serum 25 (OH)D3 levels and the length of hospital stay due to the COVID-19 in adult patients<sup>23</sup>. In contrast, Reiz et al. reported that COVID-19 patients with severe vitamin D deficiency (<10 ng/mL) exhibited a trend for longer hospital stay compared with those with normal concentrations of vitamin D<sup>56</sup>. Different findings on the link between vitamin D levels and prolonged hospitalization might be due to different treatment protocols, different hospital admission capacities, and controlling for different confounders among previous studies. Because of a high incidence of COVID-19 and limited hospital beds, patients may be discharged as soon as possible. Therefore, the lack of significant association between serum 25(OH)D3 levels and prolonged hospitalization should be considered with caution. Further studies are needed to confirm these findings.

Some limitations should be considered when interpreting our results. We included a low number of COVID-19 patients in the current study

and therefore, we could not perform subgroup analyses based on gender and other important variables. Also, the number of COVID-19 patients with vitamin D deficiency was too small which may reduce the robustness of the analysis result. Due to limited number of patients with severe vitamin D deficiency (<12 ng/mL), we could not assess the link between severe vitamin D deficiency and clinical outcomes of COVID-19 patients. Although we obtained data on serum 25(OH)D3 concentrations from medical records, the accuracy of these values was not clear. Despite controlling for several potential confounders, our results might be still affected by residual confounders such as lifestyle information and therapeutic protocols used for controlling COVID-19. Vaccination may distort our findings on the link between vitamin D deficiency and clinical outcomes of COVID-19 patients. However, the rate of vaccination was not different across the different levels of 25(OH)D3. In addition, we included vaccination status in the adjusted model and found no change in our results. Since this was a single-center study and the sample size was low, the generalizability of our findings to all COVID-19 patients should be done with caution.

In conclusion, vitamin D deficiency was associated with an increased risk of delirium and COVID-19 mortality among critically ill elderly COVID-19 patients. However, serum levels of vitamin D were not associated with other outcomes of COVID-19 such as IMV requirement, prolonged hospitalization, and re-hospitalization. Further prospective studies with a high sample size are needed to substantiate our findings. Also, future studies should examine the effect of vitamin D supplementation on severe outcomes of COVID-19 in critically ill patients.

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## Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Furthermore, we took written informed consent from each participant. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

## CRediT authorship contribution statement

ZGh, DY, HEZ, and ZVS designed the research project. ZGh and ZVS conducted the research; ZGh analyzed data; ZGh and ZVS wrote the paper; ZGh and ZVS had primary responsibility for final content. All authors read and approved the final manuscript.

## Declaration of Competing Interest

The authors report no declarations of interest.

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## Conflicts of interest

Authors declared no personal or financial conflicts of interest.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ctim.2022.102855](https://doi.org/10.1016/j.ctim.2022.102855).

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