

# The Association of 25 (OH) Vitamin D Levels and Severity and Outcome of COVID-19: A Cross-sectional Study

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## Research Article

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# Abstract

## Background

Coronavirus disease 2019 (COVID-19) is a pandemic disease. Experiments with influenza and severe acute respiratory syndrome (SARS) have shown supplemental vitamin D can reduce the risk of infection and death.

## Aim

This study was performed to evaluate the relationship between vitamin D levels and the severity and outcome of admitted patients with COVID-19.

## Material and Methods

This cross-sectional study was performed on COVID-19 cases diagnosed by examining RT-PCR assay for SARS-CoV-2 or a set of symptoms and typical findings in lung CT scan. Based on clinical and radiologic characteristics, the patients were categorized as mild, moderate, severe, and critical. Calcium, phosphorus, albumin, creatinine, and serum 25 hydroxy vitamin D were measured and their correlation with the severity and outcome were analyzed.

## Results

From May 1 to June 31, 2020, 508 patients ((442 patients in general wards and 66 patients in intensive care unit (ICU)) were included in this study. The participants were  $56 \pm 17$  years old (mean  $\pm$ SD) (range from 14 to 95 years) and 52% were male. According to the past medical history, 190 (37.4%) of them had comorbidity. Concerning severity, 13.2%, 42.3%, 35.4%, and 9.1% had the mild, moderate, severe, and critical disease, respectively. The in-hospital mortality rate was 10.8%. In the multivariate regression analysis, age had a positive correlation and use of vitamin D supplement, serum level of 25 OH vitamin D, calcium, and albumin had a negative correlation with disease severity and admission to ICU. Poor outcome was inversely related to serum levels of vitamin D, calcium, albumin, and renal function. Vitamin D deficiency increased the rate of ICU admission by 2.7 times (95%CI=1.288-5.91, P=0.009).

## Conclusion

In patients who are hospitalized due to COVID-19, low 25-hydroxyvitamin D, hypocalcemia, and hypoalbuminemia are associated with severe disease, ICU admission, and an increase in mortality.

## Introduction

In late 2019, a new coronavirus was identified as a cause of a cluster of pneumonia cases in China which is named COVID-19 disease.<sup>1</sup> Currently, COVID-19 is pandemic.<sup>2</sup> In Iran, 612,772 people as the definitive cases of COVID-19 have been reported by November 10, 2020, and 34,864 people have died.<sup>3</sup>

Manifestations of the COVID-19 range from asymptomatic carriers to acute respiratory failure and death.<sup>4</sup> Complications include acute respiratory failure, cytokine release syndrome, increased coagulation factors, and multi-organ damage which are associated with poor prognosis.<sup>5,6</sup> The overall mortality rate until November 18, 2020, is about 2.41% (1,333,742 deaths between 55,326,907 patients).<sup>7</sup> Old age, cardiovascular disease, diabetes, high blood pressure, chronic lung disease, cancer, chronic kidney disease, people with defective or suppressed immune systems, obesity, and chronic liver disease have been identified as risk factors for severe disease or mortality.<sup>4,6,8,9</sup> There is currently no specific treatment or effective vaccine against COVID-19.<sup>10</sup> Currently, the most important way to deal with this disease is prevention and control of the conditions that are considered as a risk factor for the more severe course, and complications.

There is evidence from influenza A and severe acute respiratory syndrome (SARS) epidemics suggesting a role for vitamin D in these diseases.<sup>11</sup> Previous studies have suggested an association between vitamin D deficiency and an increased chance of developing bacterial and/or viral pneumonia due to viruses such as SARS, MERS, and Influenza A. COVID-19 disease is more prevalent and severe in winter and is more common in people who are more likely to be deficient in vitamin D, such as black or obese people, diabetics, and people living in higher latitudes.<sup>12,13</sup>

About one-half of Iranian people have vitamin D deficiency and the burden of COVID-19 is catastrophically rising in Iran with a mortality rate of about 6.2%.<sup>14</sup> So, this study investigates the relationship between vitamin D levels and the severity and outcome of COVID-19 to plan for improving patients care and reducing morbidity and mortality by appropriate treatment protocols or even planning for primary prevention in the next studies.

## Materials And Methods

This cross-sectional study was at Masih Daneshvari Hospital (tertiary center for lung disease and tuberculosis and nowadays, COVID-19), Tehran, Iran. Sampling was done by a simple sampling technique of available cases. Therefore, all patients who were hospitalized from April 1 to June 31, 2020 due to COVID-19 and their serum vitamin D levels were checked were included in the study according to the inclusion and exclusion criteria. Patients with COVID-19 who were hospitalized for at least 24 hours were recruited and Cases with an uncertain diagnosis of COVID-19, pregnant women, and who without measurement of serum vitamin D levels were excluded. Informed consent is obtained for participation from participant and their medical history and clinical examination were obtained and recorded in the questionnaire. Patient height and weight were measured with a Seca stadiometer and digital scale. Diagnosis of COVID-19 was made based on reverse transcriptase-polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 from nasopharyngeal or oropharyngeal sampling or a set of symptoms and chest CT scan findings consistent with viral infections by an infectious disease specialist. The patients were categorized on the base of disease severity as mild, moderate, severe, and critical based on clinical symptoms, O<sub>2</sub> saturation, and chest imaging (described below). one ml of blood was taken from any

patient for biochemical tests and serum level of 25 OH vitamin D. Measurement of calcium, phosphorus, albumin, creatinine was performed by auto analyzer due photometric method (diagnostic kit of Pars Azmoon Company, Iran), and serum level of 25 OH vitamin D was measured by chemiluminescent immunoassay (CLIA) (Siemens Company kit, Germany). The outcome of the disease was classified as partial recovery, complete recovery, and death during hospitalization.

## Definitions

Vitamin D status: <sup>15, 16, 17</sup>

Severe vitamin D deficiency: 25 (OH) vitamin D <10 ng / ml

Moderate vitamin D deficiency: 25 (OH) vitamin D = 10-20 ng / ml

Mild vitamin D deficiency: 25 (OH) vitamin D = 21-30 ng / ml

Vitamin D adequacy: 25 (OH) vitamin D = 30-100 ng / ml

High Vitamin D: 25 (OH) vitamin D = 100-149 ng / ml

Vitamin D poisoning: 25 (OH) vitamin D > = 150 ng / ml

## Definitive COVID-19 infection:

A patient who has at least one PCR test of his or her respiratory sampling positive for the SARS-CoV-2 virus.<sup>18</sup>

## The severity of COVID-19 disease:

According to the guidelines of the World Health Organization based on the patient's respiratory status at the time of blood sampling, oxygen in the blood at rest and room air, as well as the respiratory rate were divided into four groups: mild, moderate, severe, and Critical:<sup>18</sup>

Mild pulmonary involvement:

O<sub>2</sub> sat at rest > 93% in room air and respiratory rate < 30 and normal lung CT

Moderate pulmonary involvement:

O<sub>2</sub> sat at rest > 93% in room air and respiratory rate < 30 and involvement in lung CT

Severe pulmonary involvement:

O<sub>2</sub> sat at rest < 93% in room air and/or respiratory rate > 30 and involvement in lung CT

## Critical pulmonary involvement:

- I. Need nasal high flow oxygen therapy
- II. Requires intubation and mechanical ventilation
- III. Acute Respiratory Distress Syndrome (ARDS)

## Outcome COVID-19 disease:

Partial Recovery: Need to O<sub>2</sub> therapy after discharge from the hospital or unable to live at home alone and needs to help for self-care.

Body Mass Index (BMI): BMI is obtained by dividing weight in kilograms by height squared in meters. <sup>19</sup>

## Statistical analysis:

All data were entered into SPSS statistical software version 22. Descriptive statistics including frequency tables and graphs and central and dispersion indices were used to describe and display the distribution of patients in the two groups based on demographic variables. Quantitative variables such as age, BMI, 25 OH vitamin D, creatinine, calcium, phosphor, and albumin did not have a normal distribution in the Kolmogorov-Smirnov Test. For these variables, we used a non-parametric test (Kruskal-Wallis Test). Statistical tests such as t-test, X<sup>2</sup>, and Fisher were used to examine the relationship between discipline variables. Logistic regression analysis was used to estimate the mortality rate.

## Results

During the study period, 556 patients were admitted, 482 cases in general wards, and 72 individuals in Intensive Care Units (ICU). Due to the death during the first 24 hours of admission, failure to send the patient's blood sample for the requested tests, or failure to perform a vitamin D test and exclusion criteria, only available data related to 442 patients admitted to the general wards and 66 patients admitted to the ICU were analyzed. The mean age of participants was 56±17 years (range from 14 to 95 years) and 52% were male. According to the past medical history taking from the patients, 190 (37.4%) of patients had comorbidities (diabetes mellitus, ischemic heart diseases, hypertension, etc.). Concerning disease severity, 13.2%, 42.3%, 35.4%, and 9.1% had a mild, moderate, severe, and critical disease, respectively. Eventually, 10.8% of patients died, and 89.2% were discharged from the hospital. People with critical illness had higher age, lower serum levels of vitamin D, calcium, albumin, and fewer vitamin D

supplements usage, and worse outcome than those with mild disease. The basic characteristics of the participants according to the severity of the disease are listed in Table 1.

Table 1  
Basic characteristics in participants categorized by disease severity

Variables	Total (n=508)	Disease Severity				P-value
		Mild (n=68)	Moderate (n=217)	Severe (n=157)	Critical (n=66)	
Age <sup>a</sup> (year)	56±17	48±17	56±17	56±16	63±15	<b>0.001</b>
Gender <sup>b</sup> ; Male	264 (52)	42 (62)	103 (47)	81 (52)	38 (58)	0.157
BMI <sup>a</sup> (kg/m <sup>2</sup> )	27±5	27±4	27±5	27±5	27±5	0.953
<b>Medical History<sup>b</sup></b>						
DM	116 (23)	13(19)	43 (20)	41 (26)	19 (29)	0.258
HTN	35 (7)	1 (1)	16 (7)	13 (8)	5 (8)	0.291
IHD	72 (14)	7 (10)	30 (14)	23 (15)	12 (18)	0.621
Immune System Suppression	31 (6)	2 (3)	11 (5)	15 (8)	3 (6)	0.380
Glucocorticoid Use	27 (5.3)	2 (3)	15 (7)	8 (5)	2 (3)	0.483
Vitamin D Supplement Use	88 (17)	14 (21)	42 (19)	31 (20)	1 (1)	<b>0.004</b>
<b>Disease Outcome<sup>b</sup></b>						<b>0.001</b>
Death	55 (10.8)	0 (0)	3 (1)	31 (17)	21 (46)	
Partial Recovery	253 (50)	12 (18)	111 (52)	111 (62)	19 (41)	
Complete Recovery	200 (39)	55 (82)	101 (47)	38 (21)	6 (13)	
<b>25 OH vitamin D<sup>a</sup></b> (ng/ml)	28.6±21.6	31.8±25.7	30.4±22.4	28.2±20.8	20.4±16.3	<b>0.001</b>
<b>Creatinine<sup>a</sup></b> (mg/dl)	1.4±1.2	1.5±1.9	1.3±1.0	1.4±1.1	1.6±1.0	0.284
<b>Calcium<sup>a</sup></b> (mg/dl)	8.8±0.7	9.0±0.8	8.8±0.6	8.7±0.6	8.5±0.8	<b>0.001</b>
<b>Phosphor<sup>a</sup></b> (mg/dl)	3.3±1.06	3.6±0.8	3.2±0.9	3.1±0.8	3.4±1.8	<b>0.020</b>
<b>Albumin<sup>a</sup></b> (mg/dl)	3.4±0.6	3.9±0.5	3.5±0.5	3.5±0.8	3.0±0.4	<b>0.001</b>
<sup>a</sup> (Mean±SD); <sup>b</sup> n (%); DM, Diabetes mellitus; HTN, Hypertension; IHD, ischemic heart disease; BMI, Body mass index						

The mean of 25 OH vitamin D was 28 ng/ml (1 to 160 ng/ml). Only 35.6% had sufficient vitamin D and 23.4%, 28%, 11.8% had mild, moderate, and severe deficiency, respectively. Others had a serum vitamin D level of more than 100 ng/ml. Serum vitamin D levels were directly related to disease severity ( $P=0.037$ ) (Figure 1). Vitamin D deficiency (25 OH Vitamin D < 30 ng/ml) was more common in women than men (69% vs. 56%,  $P=0.003$ ) and patients under ICU care than patients admitted in other wards (80% vs. 61%,  $P=0.011$ ). The prevalence of vitamin D deficiency and critical illness was lower in people taking vitamin D supplements ( $P=0.001$  for both). Vitamin D deficiency was more common in hypertensive than normotensive patients (77% vs. 61%) but this difference was not significant ( $P=0.052$ ). The prevalence of vitamin D deficiency was not different between patients with a history of comorbidities and those without it.

Table 2 summarized the patient's characteristics based on the outcome. The poor outcome is directly related to the patient's age and severity of the disease. The mortality rate of people older than 60 years was five times higher than that of people 30 or younger. Poor outcome is inversely related to serum levels of vitamin D, calcium, albumin, and renal function. Also, figure 2 shows an inverse correlation between vitamin serum D level and in-hospital mortality.



Table 2  
Characteristic of 508 COVID-19 cases categorized by disease outcome

Variables	Disease Outcome			P-Value
	Death (n=55)	Partial Recovery (n=253)	Complete Recovery (n=200)	
<b>Age<sup>a</sup></b>	65±15	58±17	51±16	<b>0.001</b>
<b>Sex<sup>b</sup>, Male</b>	25 (45.5)	118 (46.6)	101 (50.5)	0.660
<b>BMI<sup>a</sup> (kg/m<sup>2</sup>)</b>	26±5	27±5	27±5	0.615
<b>PMH<sup>b</sup>, yes</b>				
DM	13 (23.6)	64 (25.3)	39 (19.5)	0.341
HTN	4 (7.3)	22 (8.7)	9 (4.5)	0.214
IHD	8 (14)	44 (17)	20 (10)	0.081
Immune System Suppression	6 (10.9)	16 (6.3)	9 (4.5)	0.209
Glucocorticoid Use	4 (7.3)	12 (4.7)	11 (5.5)	0.742
Vitamin D Supplement Use	7 (12.7)	47 (18.6)	34 (17)	0.576
<b>Disease Severity<sup>b</sup></b>				<b>0.001</b>
Mild	0 (0)	12 (4.7)	55 (27.5)	
Moderate	3 (5.5)	111 (43.9)	0	
Severe	31 (56.4)	111 (43.9)	38 (19)	
Critical	21 (38.2)	19 (7.5)	6 (3)	
<b>25OH Vitamin D<sup>a</sup> (ng/ml)</b>	23.6±18.9	29.6±22.2	30.3±22.0	<b>0.037</b>
<b>Creatinine<sup>a</sup> (mg/dl)</b>	1.5±0.9	1.4±1.3	1.3±1.26	<b>0.007</b>
<b>Calcium<sup>a</sup> (mg/dl)</b>	8.5±0.6	8.8±0.7	8.9±0.6	<b>0.001</b>
<b>Phosphor<sup>a</sup> (mg/dl)</b>	3.4±1.8	3.2±0.9	3.3±0.9	0.248
<b>Albumin<sup>a</sup> (mg/dl)</b>	3.0±0.5	3.5±0.6	3.7±0.5	<b>0.001</b>
<sup>a</sup> (Mean±SD); <sup>b</sup> n (%); DM, Diabetes mellitus; HTN, Hypertension; IHD, Ischemic heart disease; BMI, Body mass index				

In the multivariate regression analysis, age had a positive correlation (OR=1.029; 95%CI=1.010-1.049, P=0.003) and vitamin D deficiency (OR=2.760; 95%CI=1.288-5.912, P=0.009), and serum level of

calcium(OR=0.594; 95%CI=0.398-0.886,P=0.011) had a negative correlation to ICU admission after adjustment for sex, BMI, past history of diabetes mellitus, hypertension and ischemic heart disease, and serum level of creatinine, and phosphor. Also, age had a positive correlation and serum level of 25 OH vitamin D, calcium and albumin had a negative correlation with in-hospital mortality. Details were showed in Table 3.

Table 3

Multivariate analysis of characteristics associated with in-hospital mortality of patients with COVID-19 <sup>a</sup>

Independent Variable	Multivariate analysis			
	Odds Ratio	95% CI for EXP(B)		P Value
		Lower	Upper	
Age	1.039	1.020	1.058	<0.001
Sex (male)	0.891	0.508	1.562	0.686
BMI	0.972	0.917	1.031	0.349
25 OH Vitamin D	1.020	1.001	1.040	0.036
Diabetes Mellitus	1.046	0.541	2.023	0.894
Hypertension	0.789	0.256	2.420	0.679
Ischemic Heart Disease	0.678	0.284	1.620	0.382
Creatinine	1.084	0.901	1.304	0.393
Calcium	0.533	0.357	0.796	0.002
Phosphor	1.134	0.898	1.432	0.291
Albumin	0.206	0.111	0.382	<0.001

<sup>a</sup> after adjustment for sex, BMI, past history of diabetes mellitus, hypertension, ischemic heart disease, creatinine, phosphor, albumin.

Abbreviations: COVID-19, coronavirus 2019 disease; CI, confidence interval; BMI, body mass index.

## Discussion

In this cross-sectional study, 556 patients were studied, 13% of them were admitted to the ICU ward. About half of them were men. Most of them were overweight or obese and one-third had minimally one comorbidity. In 44% of cases, the disease was severe or critical and the hospital mortality rate was 10.8%. Two-third of patients had vitamin D deficiency. There was a negative correlation between disease

severity and history of vitamin D supplementation, serum levels of 25 OH Vitamin D, calcium, phosphorus, and albumin. Also, there was a negative correlation between in-hospital mortality and serum levels of 25 OH vitamin D and calcium.

Age was both a risk factor for COVID-19 disease and its severity in this study. Patients with severe illness or those who died were 15 years older than those with mild illness or who have complete recovery (median age 49 vs. 65 years). The mortality rate in patients over 60 years of age is more than five times that of people  $\leq 30$  years. This finding is consistent with the findings of previous studies.<sup>20</sup> In these studies, the median age of patients with severe disease was 9-17 years higher than median age in people with the mild disease.<sup>21-23</sup> They have also reported that the age of 65 or older increases the risk of death by 3.7 to 6 times.<sup>24,25</sup> For every 5 years of increase in patient age in the USA, the chances of hospitalization and mortality in the hospital increase by 34% and 10-18%, respectively.<sup>26,27</sup> Numerous factors are involved in increasing the severity of the disease and mortality with age. The imbalance of the immune system and comorbidities intensifies the severity of the disease and consequently increases the mortality rate due to pathogens such as COVID-19 in elderly.<sup>28</sup>

In this study, there was no significant difference between gender and disease severity and outcome. In a review article, the male-to-female ratio in patients admitted for COVID-19 was similar in three studies in France, Spain, and Switzerland.<sup>29</sup> But, mortality among men was 1.7-1.8 times higher than women, and this ratio was higher in those under 60 years of age. Male sex hormones, concurrent diseases, behavioral differences, and more exposure of men to pathogens may play a role in this differences. Although, women have less access to medical services in some countries and the proportion of women with COVID-19 disease and their mortality may be underestimated.

There was no relationship between comorbidities such as diabetes mellitus and hypertension and ischemic heart disease with the severity of COVID-19 disease and its outcome in this study. In different studies, the prevalence of hypertension, diabetes, cardiovascular disease and obesity varied from 9-56%, 7-34%, 2-33%<sup>30,31</sup> and 13-69%<sup>32,33</sup>, respectively. Contrary to our study, in some studies, these factors have been associated with increased severity of COVID-19 disease and associated mortality. This discrepancy may be due to different method of study and participant characteristics. In this study, the diagnosis of comorbidities was based on medical history and drug taking history. We didn't online access to the patient's previous medical record. Differences in demographic characteristics such as age are also an important factor that explains the discrepancy in the studies results. In those studies, the average age of participants was at least a decade higher and the male prevalence was 10 percent higher than in our study. However, after adjusting for confounding factors such as age, sex, and co-morbidities, only the age relationship remained significant in some of these studies.<sup>34-37</sup>

In the present study forty percent of patients had 25 OH Vitamin D less than 20 ng/ml. Vitamin D deficiency was more common in women than men. Contrary to expectations, although Iran is a sunny

country, vitamin D deficiency is common in all age groups. The reason is the lack of intake through food, reduced synthesis of this vitamin in the skin, and the type of clothing.<sup>38-39</sup>

There was a negative correlation between disease severity and serum levels of 25 OH vitamin D in this study. The mean level of 25 OH Vitamin D in patients admitted to the intensive care unit was 11 ng / ml less than other groups, and also vitamin D deficiency was more common among them. This finding has been shown in other studies. In a cohort study by Baktash et al<sup>40</sup> on people with COVID-19 older than 65 years, the median level of 25 OH vitamin D was lower than that of healthy controls. The difference in 25 OH vitamin D between the two groups in their study was much greater than our study (62 vs. 11 ng / ml). Of course, they have compared patients with healthy people, but we have compared patients with different degrees of illness. The age of the study participants was at least 65 years, which is much higher than the average age of the participants in our study (81 vs. 53 years). But Hastie<sup>41</sup> and Panagiotou do not confirm these findings. In the Hastie study, vitamin D deficiency was associated with more severe disease, but after adjusting for confounding factors, this effect disappeared. In a study of vitamin D levels in COVID-19 patients, Panagiotou et al found that mean vitamin D levels were not associated with disease severity, but that vitamin D deficiency was more common in patients admitted to the intensive care unit. They treated patients with vitamin D supplements immediately after the diagnosis of vitamin D deficiency, which may have affected the course of the disease.<sup>42</sup>

Vitamin D supplementation (those who received at least 50,000 units of vitamin D in the past month) was associated with reduced disease severity and mortality in this study. There are articles point to the role of vitamin D in reducing the risk of COVID-19 disease and morbidity and mortality of this disease<sup>43</sup>.

There are evidences to suggest a link between vitamin D levels and COVID-19 disease, some of which we have already mentioned and will address in more detail here. In severe COVID-19 disease, the balance of the immune system is upset. The immune system does not have the proper response to prevent the multiplying and progressing virus infection. Instead, cytokine storms occur due to the release of excessive inflammatory factors. In several other observational and ecological studies, such as ours, vitamin D deficiency has been more common in patients with COVID-19. The multiple effects of vitamin D in reducing the incidence, severity and mortality of Covid-19 disease can be explained by several different mechanisms. First, vitamin D has antibacterial and antiviral property by regulating innate and adaptive cellular immunity, and physical barriers. Vitamin D produces antimicrobial peptides (AMPs) such as cathelicidins and defensins by activating immune cells. Cathelicidins inactivate viruses such as influenza A virus by destroying envelope proteins. A primary form of cathelicidins is known as LL-37, which prevents the virus from entering the cell. Second, one of the characteristic of severe COVID-19 disease is the presence of a "cytokine storm." In this condition, inflammatory cytokines such as IL-6, IL-8, CRP and ferritin are released without the control of the immune system. Inflammatory cytokines damage the integrity of the lungs by causing inflammation, leading to pneumonia, which in turn causes a vicious cycle. IL-6 increases the severity of COVID-19 by rearranging the angiotensin-converting enzyme (ACE2) receptors and inducing macrophage cathepsin L. Cathepsin L of macrophage cleaves the S1 subunit of

the corona virus spike glycoprotein. This is essential for the coronavirus to enter human host cells, fusion of endosome membrane of virus–host cell, and release of viral RNA. Vitamin D can modulate the immune system and reduce the production of pro-inflammatory markers. Vitamin D supplementation has reduced interleukin-6 levels in several clinical trials. Third, Vitamin D may reduce the risk of ARDS and mortality from COVID-19 by raising ACE2 levels. COVID-19 infection the SARS-COV-2 virus binds to the ACE2 receptor expressed on the surface of lung epithelial cells and causes over-accumulation of angiotensin II by ACE2 downregulation. In the in-vivo studies, vitamin D-binding protein has played a role in this interaction. Calcitriol, the active metabolite of vitamin D, increases ACE2 expression in the lungs in animal studies. Vitamin D replacement may reduce lung damage by increasing ACE2 expression and synthesis of  $\alpha$ -1-antitrypsin by CD4 + T cells.  $\alpha$ -1-Antitrypsin is critical for lung integrity and repair, and is required for further production of anti-inflammatory interleukins such as IL-10. Fourth, vitamin D improves endothelial dysfunction by reducing the oxidative stress of free oxygen radicals, TNF-alpha and interleukin-6 and suppressing the NF- $\kappa$ B pathway. Endothelial dysfunction causes vascular inflammation and increased blood coagulation, which is seen in severe COVID-19. Fifth, Vitamin D reduces the lung damage caused by COVID-19 by stimulating the proliferation and migration of alveolar epithelial cells type II and reducing their apoptosis. It also inhibits mesenchymal transition of epithelial cell which induced by TGF- $\beta$ . In COVID-19, the function of type II pneumocytes is impaired, and the surfactant concentration decreases at the alveolar surface, and the alveoli are collapsed. In some studies, 1 $\alpha$ , 25 (OH) 2D have caused an increase in surfactant and may be prevent from lung alveoli collapse. Sixth, Age, virus mutations, and race of patients may have influenced studies and altered results. Studies have shown that acute inflammatory disease can decrease serum levels of 25 hydroxyvitamin D. These changes were temporary and short-lived and resolved within 24-48 hours. Therefore, the timing of blood sampling from patients from the onset of symptoms and disease can change the results. And these complicate the interpretation of the results.<sup>44-52</sup>

In the present study, the prevalence of hypocalcemia, hypophosphatemia, and hypoalbuminemia was high, and patients with more severe disease had lower blood levels of calcium, phosphorus, and albumin. Also, hypocalcemia and hypoalbuminemia were directly related to poor outcome and mortality. Similar results have been found in other published articles. In one study, among patients with COVID-19, serum calcium levels were 0.8 mg/dl lower than in other patients and mean serum calcium levels can predict the prognosis with 73% accuracy.<sup>53, 54</sup> Patients who died of COVID-19 had a serum albumin level of 4.6 g / L lower than those who survived<sup>55</sup> and hypoalbuminemia was an independent predictor of mortality and increased the risk 6.3-fold (OR=6.39; 95% CI=1.31-31.09).<sup>56</sup> This relationship can be explained in several aspects. First, each of these substances (vitamin D, calcium, and albumin) have a special role in the function of the immune system and various parts of the body and through it exerts its effect. Second, The deficiency of these substances is an indirect index of the patient's nutritional status or concomitant conditions such as obesity, kidney failure, liver failure, and diabetes which are associated with vitamin D deficiency.

In this study, 44% of patients needed advanced respiratory care and 13% needed to be admitted to the ICU. The in-hospital mortality rate was 10.8%. In this study, the number of patients who admitted to ICU is 3.8 times and in-hospital mortality rate is twice the globally national death rate in Iran. According to the World Health Organization and the Ministry of Health of Iran, as of November 24, 2020, about 841,308 people have been infected with COVID-19, and 603,445 have recovered. 44,327 (5.2%) people have died and 5,796 (2.81%) are in critical condition and admitted to ICU.<sup>57,58</sup> This study was performed at the time of the first peak of the disease in Iran. At that time, the number of PCR tests performed to diagnose COVID-19 was low, and only symptomatic individuals referred to hospitals were tested. Our hospital is a tertiary and referral center for respiratory diseases and COVID-19. Therefore, more serious patients refer to this center and one-fifth of our patients had over 70 years old. Of course, in-hospital mortality in this study is lower than in other centers. About 32-40% of hospitalized patients need to be admitted to the ICU and their mortality rate is about 15-39% in other studies.<sup>59,60</sup> Experienced and well-trained personnel to care for patients with respiratory disorders and infectious disease and access to adequate facilities for non-invasive and invasive ventilation can justify these results.

## Conclusions

This study evaluated the association between vitamin D levels and the severity and outcome of patients with COVID-19 who admitted to hospital. The disease was severe or critical in 44% of admitted cases and 13% of them admitted to ICU. The mortality rate was 10.8%. Old age, vitamin D deficiency, hypocalcemia, hypophosphatemia, hypoalbuminemia, and renal failure are associated with disease severity and admission in ICU. Old age, disease severity, low 25 OH vitamin D, hypocalcemia, hypoalbuminemia, and renal failure increased mortality.

## Declarations

## Ethics approval and consent to participate

In this research, the ethical principles of research have been observed according to the Helsinki Convention. Written informed consent has been obtained for participation from participant. All data is confidential. The data will be printed in groups without mentioning the names and personal details of the participants. The proposal of this plan was approved by the Ethics Committee in Biomedical Research of National Research Institute of Tuberculosis and Lung Diseases - Shahid Beheshti University of Medical Sciences with the approval ID: IR.SBMU.NRITLD.REC.1399.132 on May 26 2020.

## Consent for publication

The authors wish to submit an original research article entitled "The association of 25 (OH) Vitamin D levels and severity and outcome of Coronavirus 2019 disease (Covid-19) - A cross sectional study" for consideration by Scientific Reports.

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

## Availability of data and material

All authors have had online access to patients records and data during the study.

## Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Authors' contributions

Maryam Vasheghani: Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Project administration; Nasrin Jannati: Investigation and data collection; Parvaneh Baghaei: Formal analysis; Mitra Rezaei: Investigation, Writing - Review & Editing; Majid Marjani: Methodology, Validation, Investigation, Resources, Supervision, Writing - Review & Editing

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## Figures

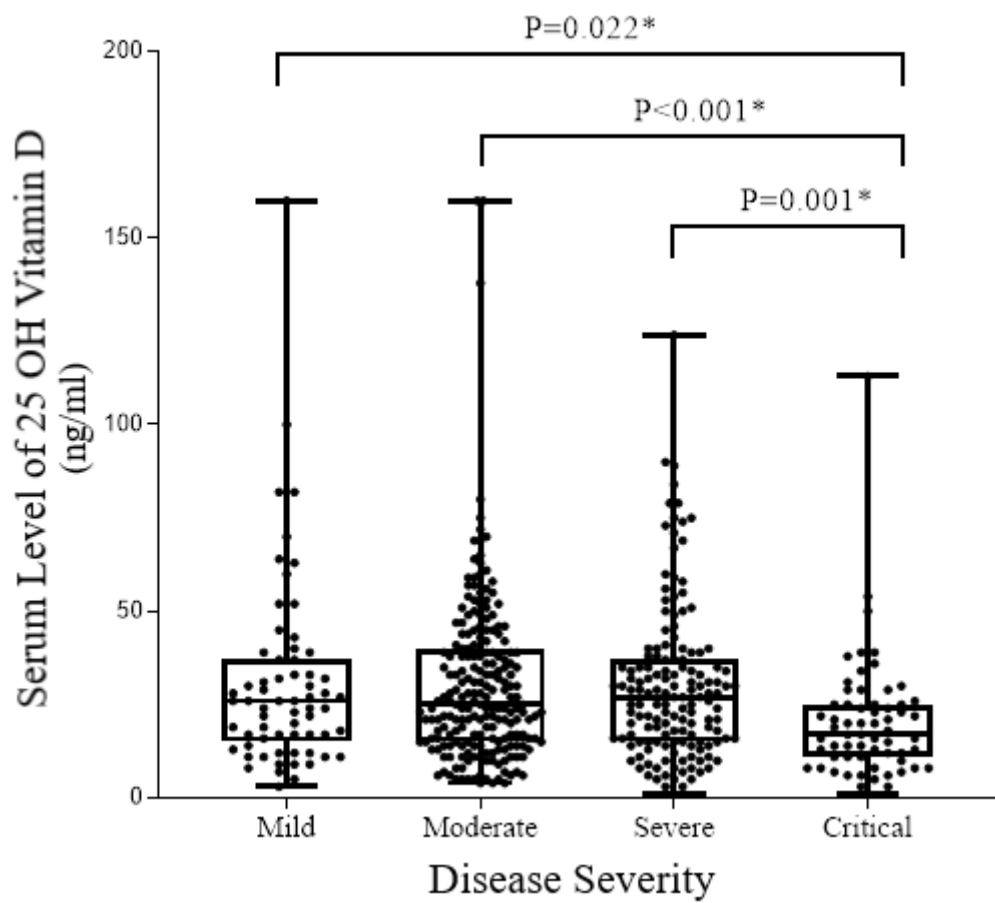
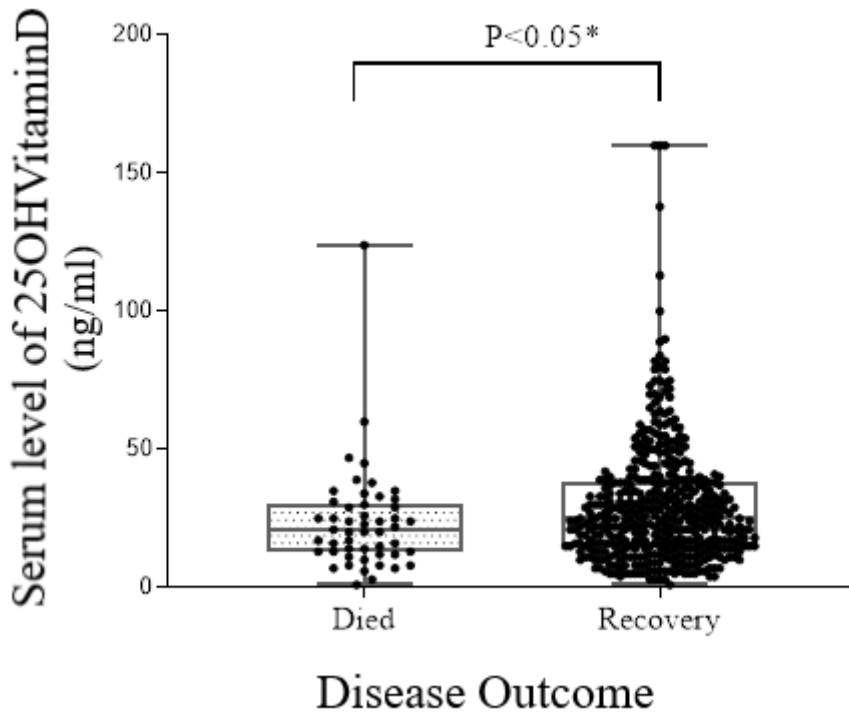


Figure 1

Box plot serum level of 25 OH vitamin D by disease severity



**Figure 2**

Characteristic of 508 COVID-19 cases categorized by disease outcome