# Does vitamin D serum level affect prognosis of COVID-19 patients?

Maryam Nasiri[a,*], Javad Khodadadi[a], Sedigheh Molaei[b]

[a] Department of Infectious Diseases, Faculty of Medicine, Qom University of Medical Sciences, Qom, Iran
[b] Student Research Committee, School of Medicine, Qom University of Medical Sciences, Qom, Iran

A B S T R A C T

Background: Since the beginning of the Coronavirus disease 2019 (COVID-19) pandemic there have been contradictions and speculations about the relationship between vitamin D and COVID-19. Given that there is an association between vitamin D deficiency and some diseases – including cancer, autoimmune disease and some infectious diseases – a higher incidence and mortality rate in the vitamin-D-deficient COVID-19 population was not a surprise; conversely, some research would argue this relationship. Considering these contradictions, this study aimed to determine the relationship between prognosis and vitamin D level in cases with COVID-19.
Methods: In this cross-sectional study, 329 confirmed cases of COVID-19 – who were admitted to Kamkar-ArabNia Hospital in Qom city, Iran from March–July 2020 – were categorized into three groups according to vitamin D serum levels (ng/ml): sufficient (>30), insufficient (20–30) and deficient (<20). Prognosis was determined across the groups.
Results: There was a significant difference in hospital stay between patients with sufficient and insufficient vitamin D levels (P = 0.007). Adjusting vitamin D levels for confounding variables, linear regression underscored significant differences in the association between length of hospitalization and lower vitamin D levels, with a longer stay noted in insufficient groups (P = 0.002). However, there was no significant difference in the time interval to return to normal oxygen level (from SpO2 < 93%) or death rate between groups (P > 0.05).
Conclusion: There was a significant association between hospital stay and lower serum vitamin D levels. However, the relationship between vitamin D status and death rate or the time interval to return to normal oxygen levels was not significant.

## Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO) on 11 March 2020. It is caused by a member of the Coronaviridae family named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The symptom range is so wide from cough and dyspnea for respiratory disease to diarrhea, similar to influenza and other non-specific symptoms (Gostic et al., 2020). From the beginning of this pandemic, two interesting issues have been the relationship between the prognosis of COVID-19 and different blood groups, and COVID-19 and vitamin D. There have been contradictions and speculations around the vitamin D and COVID-19 relationship, not only in literature but also in the media (Nasiri et al., 2021; Lanham-New et al., 2020). Given that vitamin D has a supporting role in the production of antimicrobial peptides in the respiratory epithelium, there are studies suggesting vitamin D as a preventive supplement in respiratory tract infections; once-daily dosing was suggested rather than bolus dosage (Bergman et al., 2013).

As knowledge of vitamin D physiology increases, studies have found about 200 genes that are regulated by this vitamin, including cellular proliferation, differentiation and apoptosis genes and also about 15 genes in innate and adaptive immunity (McMahon et al., 2011). Certain cancers and some autoimmune and infectious diseases have also shown increased prevalence in vitamin-D-deficient populations (Harrison et al., 2020; Brown, 2019). Similarly, the COVID-19 infection rate and mortality have been found to be higher in countries with higher vitamin-D-deficient populations (e.g., Italy versus Nordic countries with lower vitamin D deficiency rates) (Panarese and Shahini, 2020). However, using some countries to debate this association (Moris and Schizas, 2020; Grigoriou et al., 2018) and considering other influences, this has not been elucidated. Meanwhile, some research has shown no

* Corresponding author at: Department of Infectious Diseases, Faculty of Medicine, Qom University of Medical Sciences, Qom, Iran.
E-mail address: parvaze100@yahoo.com (M. Nasiri).

association between vitamin D deficiency and COVID-19 infection rate, hospitalization or mortality, the latter of which, while not statistically significant, has been found to be higher in vitamin-D-deficient populations (Daneshkhah et al., 2020). As a result, the healthcare community still awaits a clear answer and vitamin D is not routinely prescribed for COVID-19 patients. There is also a gap in research to be adjusted for confounding factors (e.g. chronic kidney disease or nursing homes, and to be more precise, even considering all cases in one medical center) to ward off another bias. Therefore, this study examined the relationship between prognosis and vitamin D levels in COVID-19 patients.

## Methods

This cross-sectional study collected data from 329 COVID-19 inpatients in Kamkar-ArabNia Hospital in Qom city, Iran, from March–July 2020. The inclusion criterion was a positive nasopharyngeal RT-PCR test for COVID-19. Cases with nursing home residents, bedridden patients, or intubation at the beginning of hospitalization were excluded. Background data – including age, sex, social history, underlying disease or medical condition, including renal transplantation/dialysis, chemotherapy, etc. – were recorded in addition to COVID-19 symptoms.

The serum 25(OH)D level (ng/ml) was measured by routine blood samples on the first day of hospitalization. Patients were categorized into three groups: sufficient (>30), insufficient (20–30) and deficient (<20) serum 25(OH)D levels. Vitamin D deficiency is considered by most studies to be <30 ng/mL. This study considered serum 25(OH)D levels <20 ng/ml as deficient, <30 ng/ml insufficient, 30–100 ng/ml sufficient, and >100 ng/ml potential toxicity (Holick et al., 2011; Hossein-nezhad and Holick, 2012). After physical examination and checking vital signs, T (body temperature) and SpO2 (peripheral capillary oxygen saturation levels) were obtained. Considering SpO2 $\geq$ 93% and T $\leq$ 37.4 °C as normal, patients with abnormal findings in each one were followed until return to normal levels. This duration showed a patient's general condition and prognosis. Intubation during hospitalization was also considered as another important index along with hospital stay and mortality.

Statistical analysis was performed by SPSS (version 20.0) statistical software. P-values $\leq$0.01 were considered significant (if not, the other P-value levels were mentioned).

## Results

All 329 patients had positive nasopharyngeal RT-PCR tests for COVID-19. There were 167 males and 162 females. The mean age ($\pm$ standard deviation) was 64.7 $\pm$ 18.5 years, ranging 15–99 years. Age was <20 years in 13.1%, 20–30 years in 14.6% and >30 years in 72.3%. Mean hospital stay ($\pm$ standard deviation) was 8.27 $\pm$ 6.04 days, ranging 1–38 days. A total of 297 patients (90.3%) were discharged and 32 patients (9.7%) were deceased.

Three of the most common COVID-19 symptoms were 58.7% dyspnea, 46.5% cough (7.3% productive) and 38.3% fever; other symptoms are shown in Table 1.

Three of the most common background diseases were 39.8% hypertension, 25.8% diabetes mellitus and 22.6% heart diseases; other background diseases are shown in Table 2. In previous social history, 2.1% and 3.3% were smokers and addicts, respectively.

The mean body T ($\pm$ standard deviation) was 37.16 $\pm$ 0.87 ºC, ranging from 35–41 °C. The mean first SpO2 level ($\pm$ standard deviation) was 90.47 $\pm$ 7.08%, ranging from 40%–99%. To evaluate each patient's condition, there was a daily check of SpO2 and T to determine the time to return to normal. Fifty-eight (17.6%) patients had a history of taking vitamin D supplement in the past month. Mean serum 25(OH)D concentration was 53.70 $\pm$ 36.13, ranging

**Table 1**
COVID-19 symptoms in order of prevalence.

| Variable | % |
| --- | --- |
| Dyspnea | 58.7 |
| Cough | 46.5 |
| Fever | 38.3 |
| Chills | 27.7 |
| Weakness | 24.3 |
| Myalgia | 20.1 |
| Nausea and vomiting | 17.6 |
| Diarrhea | 8.2 |
| Headache | 6.1 |
| Anorexia | 5.2 |
| Loss of consciousness | 5.2 |
| Chest pain | 4 |
| Vertigo | 3.3 |
| Abdominal pain | 2.4 |
| Urinary symptoms | 1.5 |
| Sore throat | 0.9 |
| Palpitations | 0.3 |
| Seizure | 0.3 |
| Hematemesis | 0.3 |

**Table 2**
COVID-19 background diseases in order of prevalence.

| Background diseases | % |
| --- | --- |
| Hypertension | 39.8 |
| Diabetes mellitus | 25.8 |
| Heart diseases | 22.6 |
| Chronic obstructive pulmonary disease | 5.5 |
| Stroke | 5.2 |
| Benign prostate hyperplasia | 5.2 |
| Asthma | 4.6 |
| End-stage renal disease | 4.3 |
| Chronic kidney disease | 3.3 |
| Alzheimer's disease | 3.3 |
| Rheumatoid arthritis | 2.1 |
| Hypothyroidism | 1.8 |
| Gastric problems | 1.8 |
| Deep vein thrombosis | 1.8 |
| Liver disease | 1.5 |
| Epilepsy | 1.2 |
| Cancer | 1.2 |
| Kidney transplant | 0.9 |
| Lung tuberculosis | 0.9 |
| Anemia | 0.6 |
| Chemotherapy in the last 30 days | 0.3 |
| Migraine | 0.3 |

from 4 to 193.4 ng/ml, and patients were categorized into three groups: sufficient (>30), insufficient (20–30) and deficient (<20) vitamin D levels, which were seen in 72.3%, 14.6% and 13.1% of patients, respectively. Overall, 7.6% of cases were intubated with an endotracheal tube; of these, 4.25% had sufficient (>30), 1.51% insufficient (20–30) and 1.82% deficient (<20) serum 25(OH)D levels.

Figure 1 shows the hospitalization duration according to serum vitamin D level. Pearson correlation indicated a significant relationship between vitamin D level and hospital stay (P = 0.007; r = 0.553). Using ANOVA, the relation between groups was also significant (P = 0.006); this was followed by post hoc tests, which indicated a significant difference between sufficient and insufficient vitamin D groups (P = 0.007) at P-value 0.05. Finally, following Chi-square tests, the relationship between vitamin D and death was not significant (P = 0.928).

Tables 3–5 show the regression results. Adjusting vitamin D levels for confounding variables (e.g., age, sex and underlying diseases), linear regression showed significant difference between hospitalization duration and vitamin D levels, which was higher in
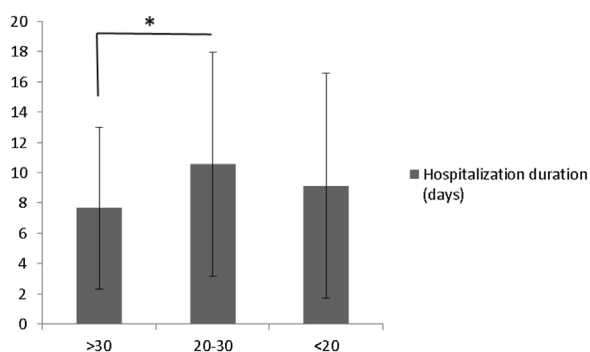
**Figure 1.** Hospitalization duration for different vitamin D serum levels. Horizontal axis shows vitamin D serum levels (ng/ml).
*P value ≤0.05.

**Table 3**

Linear regression analysis of vitamin D serum levels and the time interval to return to normal oxygen levels for patients with low SpO2 levels.

|  |  | Beta | 95% CI | P-value |
|---|---|---|---|---|
| Unadjusted | <20 | −1.384 | −5.706 to 2.939 | 0.700 |
| 25(OH)D | 20–30 | −0.506 | −4.670 to 3.657 | 0.314 |
|  | >30 | 1 | References |  |
| Adjusted | <20 | −2.380 | −6.707 to 1.947 | 0.446 |
| 25(OH)D | 20–30 | −1.832 | −6.087 to 2.424 | 0.226 |
|  | >30 | 1 | References |  |

Adjusted for age, sex, diabetes mellitus, hypertension, smoking, end-stage renal disease, heart failure.

**Table 4**

Linear association between vitamin D serum levels and hospital stay.

|  |  | Beta | 95% CI | P-value |
|---|---|---|---|---|
| Unadjusted | <20 | 1.480 | −0.449 to 3.409 | 0.133 |
| 25(OH)D | 20–30 | 2.882 | 1.040 to 4.724 | 0.002 |
|  | >30 | 1 | References |  |
| Adjusted | <20 | 1.297 | −0.693 to 3.287 | 0.202 |
| 25(OH)D | 20–30 | 3.003 | 1.131 to 4.875 | 0.002 |
|  | >30 | 1 | References |  |

Adjusted for age, sex, diabetes mellitus, hypertension, smoking, end-stage renal disease, heart failure.

**Table 5**

Multiple logistic regression analysis of vitamin D serum levels and death rate.

|  |  | OR | 95% CI | P-value |
|---|---|---|---|---|
| Unadjusted | <20 | 0.915 | 0.301–2.781 | 0.875 |
| 25(OH)D | 20–30 | 0.811 | 0.268–2.453 | 0.710 |
|  | >30 | 1 | References |  |
| Adjusted | <20 | 0.918 | 0.261–3.227 | 0.894 |
| 25(OH)D | 20–30 | 1.145 | 0.336–3.905 | 0.828 |
|  | >30 | 1 | References |  |

Adjusted for age, sex, diabetes mellitus, hypertension, smoking, end-stage renal disease, heart failure.

the insufficient group (P = 0.002). However, there was no significant difference in the time interval to return to normal oxygen levels between serum vitamin D-based groups. Also, logistic regression showed an insignificant relationship between vitamin D levels and death rate.

## Discussion

This study examined 329 COVID-19 patients admitted to Kamkar-ArabNia hospital in Qom city, Iran, from March–July 2020, in terms of their prognosis upon vitamin D status categorization. There was a significant difference between hospital stay according to serum vitamin D levels. However, the relationship between vitamin D status and death rate or the time interval to return to normal oxygen levels was not significant.

Consistent with the current data, hypovitaminosis D due to climate conditions and the calculated COVID-19 mortality rate from 12 European countries has revealed an inverse correlation (Biesalski, 2020). Additionally, higher latitudes in African American or black ethnicity have shown increased mortality rates. However, exceptions have been noted such as Brazil, where government quarantine management may have impacted mortality rates (Sajadi et al., 2020).

Knowing the role of vitamin D on the immune system, from its receptors on the majority of immune cells to raising anti-inflammatory cytokine production versus pro-inflammatory or even production of an antimicrobial peptide against enveloped viruses (such as corona viruses), the efficacy of adding vitamin D as a protective supplement against acute viral respiratory infections is not surprising (Fabbri et al., 2020), especially with 86% vitamin D deficiency in the Iranian population (Lips et al., 2019). While SARS-CoV-2 down-regulates the angiotensin-converting enzyme 2 (ACE2), which is exploited as an entry receptor, leading to renin-angiotensin-aldosterone system (RAS) overactivation and proinflammatory cytokine release, and as a result more comorbidity, vitamin D up-regulates ACE 2 expression, which in the lungs has shown a protective effect against acute lung injury (Zhang et al., 2020). Older age also affects this system and vitamin D production. In consideration of these findings, there was a need to research the impact on COVID-19 prognoses in different populations. The current study, through adjustment of vitamin D levels for confounding variables and underlying disease, revealed significant differences in length of hospital stay and vitamin D deficiency. However, some research has reported that patients who were severely vitamin D deficient experienced the most benefit from receiving a diet-based supplement (Ilie et al., 2020); in the current study, the deficient vitamin D group showed no significant difference in outcomes.

A limitation of this study may have been the study design, with a small sample size. A larger sample size would increase the power and robustness of the comparisons. Randomized controlled trials are warranted to show the role of vitamin D supplement on COVID-19 prognosis.

## Conclusion

There was a significant difference in hospitalization duration in patients according to their vitamin D serum levels. However, the relationship between vitamin D status and death rate or the time interval to return to normal oxygen levels was not significant. Overall, considering the vitamin D physiological cycle, reduced sunlight exposure and indoor living during the COVID-19 era may have worsened the low vitamin D status; therefore, it should be considered more during routine check-ups.

## Authors' contributions

All of the authors contributed to all parts of this study.

## Conflict of interest

There are no conflicts of interest to declare.

## Funding

**Ethical approval and consent to participate**

This study was approved by the Ethics Committee of the Qom University of Medical Sciences (IR.MUQ.REC.1399.058).

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