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Original Article

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The Association of Vitamin D Deficiency with COVID- 19 Severity and Mortality

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Abstract

***Background & Aims*:** There are few studies showing the association between vitamin D deficiency and COVID-19 severity and mortality. This study designed to investigate the relationship between vitamin D deficiency and the severity and mortality of COVID-19.

***Materials & Methods*:** The present cross-sectional study was conducted on 48 COVID-19 patients with positive PCR test results. Patients were divided into three groups according to their serum 25-OH vitamin D3 levels: group 1 <20 ng/mL, group 2. 20-50 ng/mL, and group 3, ≥50 ng/ml. The relationship of the levels of vitamin D3, as well as the history of diabetes, hypertension, Ischemic Heart Disease (IHD), Glomerular Filtration Rate (GFR) ≤60 mL/min, LDH ≥500 U/L, and Lymphocyte count ≤1500 with the severity of the disease and its mortality were investigated.

***Results*:** A significant relationship was observed between vitamin D ≤20 ng/mL and the severity (P<0.001) and mortality (P=0.001, adjusted OR=2.4) of the disease in COVID-19 patients. It was also shown that GFR ≤60 mL/min (P=0.02, adjusted OR=3.6), IHD (P=0.04, adjusted OR=2.8), LDH ≥500 U/L (P=0.027, adjusted OR=1.8), and lymphocyte count ≤1500 (P=0.002, adjusted OR=2.2) significantly affected the mortality.

***Conclusion*:** The present study showed a significant relationship between vitamin D deficiency and the severity of the disease and mortality in COVID-19 patients. These results suggest the need for appropriate health policies during the COVID-19 pandemic.

***Keywords*:** Vitamin D deficiency, COVID 19, mortality

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Introduction

COVID-19 is a type of pneumonia caused by the SARS-COV-2 viral agent, which has rapidly spread throughout the world and led to a pandemic (1,2). Variation in COVID-19 mortality rates among countries with different geographical latitudes has drawn the attention of the scientific community to vitamin D as a factor affected by sunlight exposure (3,4). The difference between mortality rates in countries with less and high exposure to sunlight is among the factors that have fostered the hypothesis of a possible role for vitamin D in COVID-19 Pathogenesis (3). However, different rates of success in controlling the spread of the disease, as well as various confounding factors, may have influenced mortality rates in these countries (4). The patients' age and underlying diseases are among these factors (5).

The SARS-COV-2 virus can increase the activity of the Renin-Angiotensin-Aldosterone System (RAAS) by reducing the expression of ACE2 after infecting the cells, and thus damage the lungs and other organs.. (6). Vitamin D may reduce pulmonary damages through its antiviral activity and by inhibiting RAAS function (7, 8). Various studies also point to the protective effects of vitamin D on tight junctions, which prevents the infiltration of immune cells in the lungs, and its role in the potentiation of antiviral mechanisms and reduction of pro-inflammatory cytokines (9–11). In animal tissues, vitamin D3 has protective effects against lung damage by reducing the level of pro-inflammatory and pro-fibrotic cytokines (12). Moreover, it has been shown that vitamin D deficiency and COVID-19 produce similar symptoms of anosmia or ageusia, a point that strengthens the hypothesis that vitamin D can have an effect on this disease (13).

Reduced vitamin D levels during the COVID-19 pandemic and lockdown could have major effects on the society and the health system, given the significant incidence of vitamin D insufficiency and inadequacy in the general population. (14, 15). So far, many studies have examined the effect of vitamin D on COVID-19. However, the contradictory results of these studies reveal the need for more evidence to make a decision. (3, 16-24).

There are few studies showing the association between vitamin D deficiency and COVID-19 severity and mortality. This study designed to investigate the relationship between vitamin D deficiency and severity and mortality of COVID-19.

Materials & Methods

The present cross-sectional study was conducted on 48 COVID-19 patients with positive PCR test results admitted to the COVID-19 ward of Shahid Mohammadi Hospital of Hormozgan University of Medical Sciences. Patients with acute renal failure, hypercalcemia, and those who had received contrast in the last three months were excluded. Using Abbott i1000 Instrument, Architect kit and Chemiluminence method, serum 25-OH vitamin D3 levels were checked in all patients. The patients were divided into three groups according to their vitamin D levels: Group 1:<20 ng/ml, group 2: 20 -50 ng/ml, and group 3: ≥50 ng/ml. Patients were also divided into three groups according to the severity of the disease:

1. Mild-comprising patients that required less than 48 hours of hospitalization, and had no hypoxia (SPO2 ≥90%).
2. Moderate-comprising patients, who were hospitalized ≥48 hours but did not require admission to ICU and did not die.
3. Severe-comprising patients, who required ICU admission and/or those who died.

Indications for ICU admission included SPO2 ≤90% on room air and severe respiratory distress (respiratory rate <30 breaths/min) (22).

The relationship of different levels of vitamin D, as well as the history of diabetes, hypertension, cardiovascular disease, GFR ≤60 mL/min, LDH ≥500 U/L, and lymphocyte count ≤1500, with the severity of the disease and mortality rate, were investigated.

Data collected were analyzed in SPSS version 22, using ANOVA test to examine mean values of quantitative variables and Binary Logistic Regression

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to find adjusted Odds Ratio (OR) for factors affecting the severity of the disease.

Results

The present study was conducted on 48 COVID-19 patients with a mean age of 53±17 years. Of the patients, 54% were men and 46% were women, and among them, 33%, had a history of diabetes, 18% of hypertension, 16% of ischemic heart disease (IHD), and 37% of smoking. In 19 patients (39%), vitamin D levels were <20 ng/mL, in 26 patients (54%), were between 20 and 50 ng/mL, and in 3 patients (7%), were >50 ng/ml. Among these 48 participating patients, 5 (10%) died. Patients were divided into three groups according to the severity of the disease: Mild group: Patients that required less than 48 hours of hospitalization. This group included 3 patients (6%). Moderate group: Who were hospitalized ≥48 hours but did not require admission to ICU. This group consisted of 38 patients (79%). Severe group: Patients who required ICU admission and/or those who died. This group included 7 patients (16%).

The mean age was 50±15 years in the group with severe disease, 54±17 years in the group of moderate disease, and 44±30 years in the group of mild disease, with a significant difference among them (P-value≤0.001) (Table 1). Men comprised 43% of the patients in the severe group, 57% in the moderate group, and 33% in the mild group (P-value=0.01) (Table 1).

There was a significant relationship between the severity of the disease and diabetes (P value=0.01), hypertension (P-value=0.02), and IHD (P-value<0.001) (Table 1). In the severe group, LDH ≥500 U/L was detected in 72% of the patients, 31% in the moderate group, and 0% in the mild group. LDH ≥500 U/L had a significant relationship with the severity of the disease (P-value=0.04) (Table 1). A lymphocyte count of less than 1500 was present in 100% of the patients with severe disease, 65% with moderate disease, and 33% with mild disease, constituting a significant relationship (P=0.03) (Table 1).

Table 1. The relationship between the severity of the disease and the variables of age, gender, smoking, blood pressure, diabetes, and Vitamin D

Variables	Mild Group		Moderate Group		Sever Group		P-value	Pearson's R
Age Mean±SD	44±30		54±17		50±15		<0.001	..
Gender								0.027
Male	1	33%	22	57%	3	43%	0.01	
Female	2	67%	16	43%	4	57%		
Smoking								0.019
Yes	1	33%	14	36%	3	43%	0.02	
No	2	67%	24	64%	4	75%		
DM								0.012
yes	1	33%	6	15%	2	28%	0.01	
no	2	67%	32	85%	5	72%		
Hypertension								0/024
YES	1	33%	15	40%	1	15%	0.02	
NO	2	67%	23	60%	6	85%		
IHD								0.031
Yes	1	34%	6	16%	1	15%	<0.0	
No	2	66%	32	84%	6	85%	01	
Vit. D (ng/ml)								0.026
≤20	0	0%	13	34%	6	85%		
20-50	3	100%	22	57%	1	15%	<0.0	
≥50	0	0%	3	9%	0	0%	01	
LDH (U/L)								0.034
500≥	0	0%	12	31%	5	72%	0.04	
<500	3	100%	26	69%	2	28%		
GFR (mL/min)								..
≤60	0	0%	4	10%	6	85%	0.00	

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>60	3	100%	34	90%	1	15%	1	
Lymph. Count								0.028
1500≤	1	33%	25	65%	7	100%	0.03	
>1500	2	67%	13	35%	0	0%	7	

In the present study, 85% of the patients from the severe group, 34% from the moderate group, and 0% from the mild group had vitamin D levels <20 ng/mL, with a significant relationship between vitamin D level and the severity of the disease (P value <0.001) (Table 1). Furthermore, in 85% of the patients in the severe group, 10% in the moderate group, and 0% in the mild group, GFR mL/min was ≤60, and the relationship between GFR and the severity of the disease was significant (P-value=0.001) (Table 1).

In the present study, Vitamin D <20 ng/mL (P-value=0.001, adjusted OR=2.4); GFR ≤60 mL/min (P-value=0.02, adjusted OR=3.6); IHD (P-value=0.04, adjusted OR=2.8); LDH ≥500 U/L (P-value=0.027, adjusted OR=1.8) and lymphocyte count <1500 (P-value=0.002, adjusted OR=2.2) were shown to affect patient mortality (Table 2).

Table 2. The factors affecting the patient's mortality

Variables	P-value	Adjusted OR
Vitamin D<20 ng/mL	0.001	2.4
GFR≤60 mL/min	0.02	3.6
Ischemic Heart Disease	0.04	2.8
LDH≥500 U/L	0.027	1.8
Lymph≤1500	0.002	2.2
DM	0.2	----
Hypertension	0.7	----

Discussion

The results of the present study revealed a significant relationship between vitamin D levels <20 ng/mL and the severity of COVID-19 and patient mortality (P-value<0.001, adjusted OR=2.4), respectively. Moreover, diabetes (P-value=0.01), hypertension (P-value=0.02), and IHD (P<0.001) showed a significant relationship with the severity of the disease. Factors affecting patient mortality were GFR ≤60 mL/min (P-value=0.02, adjusted OR=3.6), IHD (P-value=0.04, adjusted OR=2.8); LDH ≥500 U/L (P-value=0.027, adjusted OR=1.8) and lymphocyte count <1500 (P-value=0.002, adjusted OR=2.2).

The results from animal studies suggest that vitamin D deficiency has a role in increasing the Renin-Angiotensin-Aldosterone System (RAAS) activity and pro-fibrotic factors.(8). Other studies have shown that the level of angiotensin 2 significantly increases in COVID-19 patients in association with the viral load (25). SARS-COV-2 may also increase RAAS activity by binding to the ACE2 receptor, thereby causing cell damage in the lungs and other organs (6). The effect of vitamin D on other respiratory infections has been previously studied (26, 27). Despite finding a 6% reduction in the risk of respiratory tract infection in patients taking vitamin D supplements, a meta-analysis conducted by Vuichard Gysin et al. failed to reach a significant level due to heterogeneity and poor data quality (27). A study conducted by Martineau et al. showed a significant reduction in the risk of respiratory tract infection in patients taking vitamin D supplements (26). In some of the mentioned studies, the baseline vitamin D levels were measured, but the severity of the disease related to vitamin D levels was not investigated.

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So far, different studies have been published on the effect of vitamin D on COVID-19. (18, 20–24) In line with the results of the present study, D'Avolio et al. showed lower levels of vitamin D in SARS-Cov-2 patients with positive PCR results.(18). The present study showed the effect of vitamin D on COVID-19 severity and morality (P-value<0.001, adjusted OR= 2.4).

The results of the present study also showed a significant relationship between IHD and mortality in COVID-19 patients (P-value=0.04, adjusted OR=2.8). These results confirm the findings of other investigators regarding the effect of the underlying cardiovascular diseases on COVID-19. (28, 29). Inciardi et al. showed significantly poorer prognosis in COVID-19 patients with a history of heart diseases compared to those without such a history (28). These results emphasize the need for greater vigilance in the care of COVID-19 patients with a history of heart diseases. The relationship between other underlying diseases such as diabetes and hypertension, and the morality of COVID-19 patients were not measureable due to the small sample size.

In the present study, LDH ≥500 U/L had a significant relationship with the COVID-19 patient mortality rate (P-value=0.027, adjusted OR=1.8). Aggravation of COVID-19 with the increase in LDH levels has been reported in other studies.(30–32). A study conducted by Zhao et al. reported a significant increase in LDH levels in COVID-19 pneumonia compared to the non-COVID-19 group and suggested the use of LDH as a marker for evaluating COVID-19 patients (32).

Results of the present study further showed a significant relationship between a reduced lymphocyte count and the mortality rate in COVID-19 for lymphocyte counts ≤1500 (P-value=0.02, adjusted OR=2.2). This finding concurs with the result of other investigations. Other studies have further reported reduced lymphocyte count with increased total leukocytes in severe COVID-19. (33,34). The present study also showed a significant relationship between GFR ≤60 mL/min and an increased rate of mortality in COVID-19 patients. Similarly, other studies have found a significant relationship between the reduction in GFR and an increase in mortality rate in COVID-19 patients, which confirms the results of the present study.(35, 36).

The present study had several limitations including the small sample size, which reduced the statistical power in the analysis for some comorbidities in COVID-19 patients. Moreover, the patients' specific habits, lifestyle, diet, and exposure to sunlight were not investigated. In the present study, the pathological mechanisms underlying the effect of vitamin D on the severity of COVID-19 were not addressed, and thus, further studies on immune factors and other elements involved in vitamin D metabolism in these patients are recommended. Moreover, results of the present study do not elucidate the molecular mechanisms of action of vitamin D in preventing cell damage. However, earlier studies point to the possible role of vitamin D in the suppression of RAAS in these patients (6). Like Caccialanza et al., we recommend the correction and normalization of vitamin D levels in patients infected with SARS-COV-2 (37). Furthermore, the correction of vitamin D levels in uninfected people is also recommended as a possible preventive measure for reducing the risk during the COVID-19 pandemic.

Conclusion

The present study showed a significant relationship between vitamin D deficiency and COVID-19 severity and mortality. Further studies are recommended to investigate the protective mechanism of vitamin D against COVID-19 and the effect of geographic variations. Nonetheless, the results of the present study can be used in health policy-making and prevention during the COVID-19 pandemic.

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Conflict of interest

The authors have no conflict of interest in this study.

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