Vitamin D Insufficiency in Disease Severity and Prognosis of the Patients With SARS Corona Virus-2 Infection

Ali Asgari[1], Ebrahim Hazrati[2], Saeed Soleiman-Meigooni[1], Mohsen Rajaeinejad[3], Sam Alahyari[4], Malihe Nasiri[5]

[1] Infectious Diseases Research Center, AJA University of Medical Sciences, Tehran, Iran

[2] Department of Anesthesiology and Critical Care, AJA University of Medical Sciences, Tehran, Iran

[3] AJA Cancer Epidemiology Research and Treatment Center (AJA- CERTC), AJA University of Medical Sciences, Tehran, Iran

[4] Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[5] Department of Biostatics, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract- The global crisis caused by the SARS Corona virus-2 infection is continuing through 2021, with more than 3.5 million deaths. Several risk factors for this virus's severity and death were documented, including diabetes, hypertension, and ischemic heart disease. To evaluate the relation between serum vitamin D3 level, the disease severity, and prognosis of the patients with SARS Corona virus-2 infection. Patients with COVID-19 were evaluated for serum vitamin D levels and laboratory data. Correlation between vitamin D levels and laboratory data with disease severity and prognosis was assessed. Cox and logistic regression tests, as well as ROC curves, were used for data analysis. Ninety-eight patients with Corona virus-2 disease (COVID-19), which consisted of sixty patients with moderate COVID-19 in the general wards, and thirty-eight patients with severe COVID-19 in the intensive care unit (ICU), were evaluated. The mean age in the general wards was lower than in ICU (60.96±14.86 compared to 67.94±16.46, *P*=0.001), and the mean serum vitamin D level in the patients admitted in the general wards was higher than in the ICU (31 ng/mL compared to 20.57 ng/mL, *P*=0.003). Furthermore, vitamin D deficiency (25 (OH) D <25 ng/ml) significantly increased the risk of severe disease. (odds ratio=2.91, *P*=0.019) and mortality (odds ratio=3.64, *P*=0.026). Vitamin D deficiency is a risk factor for disease severity and poor prognosis in COVID-19. Vitamin D levels of 25 ng/mL can be used as a cut-off value for predicting severity and prognosis.

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Introduction

The SARS Coronavirus-2 (SARS-CoV-2) infection's global pandemic started in December 2019 and affected more than 179 million people worldwide and 3.8 million death by June 2021 (1). Symptoms of pneumonia caused by SARS-CoV-2 include fever or respiratory illness, lymphopenia, and radiologic abnormality (2-4). This virus uses angiotensin-converting enzyme-2 as a receptor for entry into alveolar and gastrointestinal epithelial cells (5). Numerous drugs for the treatment of the disease have been evaluated in clinical trials. The safety and efficiency of these antiviral drugs are not yet proven to be efficacious and are under investigation (6-7). There is currently little information on the protective agents against this virus. There is some evidence of the protective effect of vitamin D (1,25-dihydroxyvitamin D;1,25$(OH)_2$ D) against this infection. Vitamin D deficiency is a global health problem for all ages (8). It was found in several studies that vitamin D has a significant role in local "respiratory homeostasis" by stimulating the exposure of antimicrobial peptides or directly interfering with replicating respiratory viruses (9). A study found a direct association between vitamin D

Corresponding Author: S. Alahyari
Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 9124335985, Fax: +98 2122719014, E-mail address: allahyarisam@yahoo.com

deficiency and chronic lung disease (10). Studies have also shown that increasing serum levels of vitamin D effectively reduces respiratory infections (11). Various studies have shown that vitamin D is an immunomodulator by inhibiting antigen-presenting cells, inhibiting inflammatory cytokines, and IL-12 (12-13). Therefore, vitamin D deficiency affects the function of the immune system (14). This study aimed to evaluate the relationship between serum vitamin D levels and the disease severity, laboratory changes, and survival of the patients admitted for moderate to severe COVID-19. A cut-off is also determined to predict the severity and prognosis of the disease.

Materials and Methods

In this study, we evaluated the patients admitted for moderate to severe COVID-19 pneumonia from 21 May 2020 to 4 September 2020 in a University Hospital in Tehran. Consecutive sampling method was used. All patients with a positive polymerase chain reaction (PCR) for SARS Coronavirus-2 infection and the presence of clinical symptoms of COVID-19 enrolled in the study. Inclusion criteria were the presence of clinical symptoms of COVID-19 (dyspnea, fever, cough, myalgia, etc.) and a positive PCR test. If the PCR test was negative despite clinical symptoms, the patient would be retested for PCR. Exclusion criteria included two negative PCR tests, presence of underlying hematological diseases (e g, acute and chronic leukemia), immunodeficiency, active lymphoma, and undergoing chemotherapy. The research process was explained to all patients and informed consent was obtained. Patients were divided into moderate and severe groups according to the severity of the disease. Severe disease included fever and symptoms of respiratory infection with one of the followings: 1- Respiratory rate more than 30 per minute 2- Severe respiratory distress 3- Oxygen saturation less than 93% in room air 4- lung infiltrates >50% of the lung field within 24-48 hours. We used a questionnaire to collect the demographic and clinical data (Age, sex, past medical history, vital signs on admission). Patients were also evaluated for laboratory variables including C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), hepatic aminotransferases, alkaline phosphatase, creatinine, Lactate dehydrogenase (LDH), Blood urea nitrogen (BUN), total serum 25(OH)D levels and whole blood tests. Patients were followed up until death or discharge from the hospital. Vitamin D was classified as adequate (more than 30 ng/mL), mild deficiency (between 20-30 ng/mL), moderate deficiency (between 10-20 ng / mL), and severe deficiency (less than 10 ng / mL) (15-16). Laboratory variables were compared between patients admitted to the ICU and patients admitted to other wards.

Statistical analysis

We analyzed the data by the SPSS software version 25 (IBM Corporation) using descriptive statistics for the quantitative variables and independent t, chi-square, exact fisher, and Pearson correlation test to compare the means. Kolmogorov-Smirnov test was used to test the normality in continuous variables. The binary logistic regression model was performed to investigate the correlation between 25 (OH) D deficiency and mortality as well as disease severity; To evaluate the intensity and direction of the relationship, odds ratio (OR) and 95% confidence interval were calculated. Also, Cox regression analysis was also used to assess the risk of mortality in patients with COVID-19. ROC curves were also used to determine the cut-off level of 25(OH)D for predicting prognosis and severity. $P<0.05$ was considered statistically significant.

Ethics statement

The study was performed in accordance with the Declaration of Helsinki and was approved by the AJA University of Medical Sciences ethical committee (ethical code: IR.AJAUMS.REC.1399.060). The research process was explained to all patients, and written informed consent was obtained.

Results

Patients' clinical and laboratory characteristics

We studied 98 patients consisting of 60 severe cases and 38 moderate cases. There were 55 male patients and 43 female patients. The mean age of moderate cases was 60.96±14.86 and for those admitted in the ICU was 67.94±16.46 years. Twenty patients died during admission, consisting of three moderate cases and 17 severe cases. The most common primary symptoms were shortness of breath (62.24%), weakness (60.2%), and fever (56.12%). In severe patients, the levels of CRP, creatinine, BUN, and CPK were significantly higher than in moderate patients. We found that 25(OH)D was significantly lower in severe patients ($P=0.001$) (Table 1).

Table 1. Demographic, clinical, and laboratory characteristics of the patients

Baseline and laboratory characteristics	ICU Patients N=38	Non-ICU patients N=60	*P*
Age	67.94±16.46	60.96±14.86	*0.034
Sex (male)	23 (61%)	32 (53%)	**0.18
Duration of hospitalization (days)	16.21	10.93	*0.002
Dead patients	17 (45%)	3 (5%)	**0.001
Discharged patients	21 (55%)	57 (95%)	**0.001
Systolic blood pressure on admission	126±21.89	126±15.10	*0.99
Diastolic blood pressure on admission	76±13.48	75±9.11	*0.65
Pulse rate on admission	91±20.19	85±11.58	*0.08
Respiratory rate on admission	24±7.94	20±4.22	*0.001
Temperature on admission	37.5±0.74	37±0.73	*0.001
Oxygen saturation on admission (%)	88±5.91	91±3.38	*0.003
Diabetes Mellitus (number)	8 (21%)	11 (18%)	**0.74
Hypertension (number)	14 (37%)	16 (27%)	**0.29
Ischemic Heart disease (number)	12 (32%)	9 (15%)	**0.051
Rheumatoid Arthritis (number)	3 (8%)	2 (3%)	***0.37
Asthma (number)	0 (0%)	2 (3%)	***0.52
COPD (number)	2 (5%)	3 (5%)	***0.99
CRP (mg/l)	63.32±35.20	40±32.72	*0.001
ESR (mm/hr)	44.44±29.18	49±29.98	*0.50
AST (U/L)	40.78±30.92	31±14.21	*0.084
ALT (U/L)	31.05±29.45	31±15.65	*0.95
ALP (U/L)	203.94±130.14	196±53.49	*0.74
25(OH)D (ng / mL)	20.57±14.21	31±16.84	*0.001
Cr (mg/dl)	1.45±0.56	1±0.34	*0.032
BUN (mg/dl)	27.34±16.27	21±12.82	*0.028
LDH (U/L)	693.42±397.91	603±844.13	*0.54
WBC (*1000C/ml)	7.53±4.28	7±2.89	*0.27
Hemoglobin (gr/dl)	12.93±2.36	13±2.22	*0.74
Platelet (*1000 C/ml)	182.23±73.38	190±92.24	*0.67
CPK (U/lit)	468.17±679.30	128±108.80	*0.008

*t-test
**chi-square test
***Fisher exact test

However, there was no significant relationship between 25(OH)D level and duration of hospitalization in severe and moderate cases (*P*=0.645 and *P*=0.251, respectively). In this study, the relationship between 25(OH)D levels, inflammatory factors (CRP, ESR, LDH), and oxygen saturation at the time of admission with prognosis was investigated (Table 2).

Table 2. Correlation of vitamin D, inflammatory factors and oxygen saturation with prognosis

Factors	Dead Patients (Mean±Std)	Discharged Patients (Mean±Std)	*P*
25(OH)D	18.41±14.61	29.08±16.75	0.011
Oxygen saturation	86.40±6.28	91.08±3.93	0.004
CRP	66.77±37.06	44.82±34.34	0.014
ESR	38.75±29.19	49.12±30.09	0.17
LDH	804.15±491.71	595.15±759.23	0.25

Among these factors, 25(OH)D, oxygen saturation, and CRP were found to have a significant relationship with patients' prognoses. However, no significant relationship was observed between ESR and LDH levels with patients' prognosis (*P*=0.17 and *P*=0.25, respectively).

The optimal cut-off value for predicting prognosis

As shown in Figure 1, with a cut-off of 25 ng/mL for prognosis, the sensitivity was 60%, and the specificity was 70%. The area under the curve was 0.72 (*P*=0.001).

In addition, considering cut-off 12.75 ng / mL, the sensitivity and specificity were 88% and 60%,

respectively. The area under the curve was 0.72 (*P*=0.003).

Vitamin D and risk of mortality and severe disease

Vitamin D deficiency (less than 25 ng/mL) has a significant effect on the prognosis of patients with COVID-19. Cox regression analysis showed that patients with vitamin D deficiency had a higher risk of mortality than patients with adequate vitamin D levels (HR=1.82, *P*=0.019). In addition, logistic regression analysis showed that the odds of death were significantly higher in patients with vitamin D deficiency in both unadjusted and adjusted models (Table 3 and Figure 2).

Vitamin D deficiency also plays a role in the severity of COVID-19 disease. As displayed in Table 4, Logistic analysis revealed that the chances of developing severe COVID-19 disease and ICU hospitalization were significantly higher in patients with vitamin D deficiency (OR=2.91, *P*=0.019).

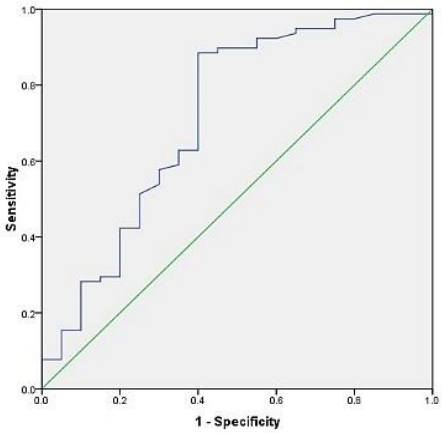

Figure 1. ROC curve analysis results to achieve predictive values of 25(OH)D in prognosis. Area under curve was 0.72(95% CI 0.58-0.86) for 25(OH)D of 25ng / mL (P=0.001)

Table 3. Correlation between vitamin D and prognosis and mortality risk in patients with COVID-19

Models	Variables	Logistic model		Cox model	
		OR (95%CI)	*P*	HR (95% CI)	*P*
Model 1	25(OH) D deficiency	2.86 (1.00-8.24)	0.05	1.69 (1.60-2.69)	0.027
Model 2	Age	0.99 (0.95-1.03)	0.81	1.00 (0.98-1.01)	0.96
	Sex	0.69 (0.23-2.12)	0.52	0.83 (0.52-1.34)	0.46
	Comorbidity	6.32 (1.59-25.13)	0.009	1.67 (0.97-2.87)	0.065
	25(OH) D deficiency	3.64 (1.16-11.38)	0.026	1.82 (1.10-3.01)	0.019

Model 1: unadjusted effect, Model 2: adjusted effect
OR: Odds Ratio, HR: Hazard Ratio, CI: Confidence interval

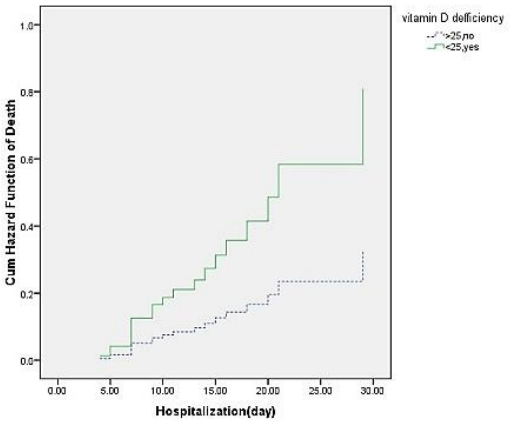

Figure 2. Cox regression analysis and cumulative hazard ratio of mortality with and without deficiency. The hazard ratio was 1.82 (95% CI: 1.10-3.01)

Table 4. Odds ratio of severity of disease in vitamin D deficient patients with COVID-19

Models	Variables	OR (95% CI)	*P*
Model 1	25(OH) D deficiency	2.88 (1.19-7.09)	0.014
Model 2	Age	0.98 (0.95-1.01)	0.20
	Sex	0.66 (0.26-1.63)	0.37
	Comorbidity	1.84 (0.69-4.86)	0.21
	25(OH) D deficiency	2.91 (1.19-7.09)	0.019

Model 1: crude effect, Model 2: adjusted effect
OR: Odds Ratio, HR: Hazard Ratio, CI: Confidence interval

Discussion

The world is currently experiencing the third epidemic curve of *SARS Coronavirus-2* infection in many countries (17). During the past months, it seems that the virus has become more contagious. Considering the variety of clinical symptoms caused by the virus, it can be concluded that COVID-19 is a multi-organ disease, and efforts should be focused on inflammation control to increase the survival rate (18). Most studies are now focused on finding ways to eradicate the virus. While finding modulatory factors for hyper-inflammation is of paramount importance. One of these factors is vitamin D. Some studies have shown that vitamin D has a protective role against respiratory infections and diseases (19-22). Vitamin D can also increase macrophages' and monocytes' antimicrobial activity by factors such as defensin β2 and cathelicidin antimicrobial peptide (23-24). It can also increase chemotaxis, autophagy, and phagolysosomes fusion in the innate immune system cells (25). Some studies have reported that vitamin D suppresses the acquired immune system by down-regulating the T-helper one-mediated immune response and inhibiting the production of inflammatory cytokines (26).

In this study, the effect of 25(OH)D levels on disease severity and prognosis in patients with pneumonia caused by COVID-19 was investigated. In ninety-eight patients included in the study, we found that the mean 25(OH)D in patients admitted to ICU is significantly lower than patients admitted in general wards and may be associated with disease severity and death. However, we did not find any relationship between 25(OH)D and duration of hospitalization.

A study on 186 patients with COVID-19 found that the vitamin D levels in patients with COVID-19 was significantly lower than the control group (P=0.0016). It also found that serum levels of vitamin D in men with COVID-19 were significantly lower than in controls (P<0.001) (27).

Another study found that vitamin D deficiency in COVID-19 patients was significantly associated with disease severity and prognosis. This effect is probably due to the modulation of the immune system's response to *SARS Coronavirus-2* (28).

Tan *et al*., Examined the effect of vitamin D, magnesium and vitamin B12 administration in patients with COVID-19 over the age of 50 years. Criteria for increasing the severity of the disease were the need for oxygen therapy or hospitalization in the ICU. Finally, it was found that patients receiving vitamin D, magnesium and vitamin B12 needed less oxygen therapy or ICU admission than the control group. (P=0.006) (29).

Our study also found that the CRP level, 25(OH)D, and oxygen saturation were significantly associated with the prognosis of patients with SARS-CoV-2. Some studies showed that CRP levels play a prognostic factor in COVID-19, averaging 40 mg/L in discharged patients and 125 mg/L in patients who have died (30). Also, a significant difference was reported between serum levels of CRP, D-dimer, and procalcitonin in severe patients compared to non-severe patients (P<0.001) (31).

The current study found that patients with vitamin D levels below 25 ng/mL experienced a significant increase in the chances of severe disease and a poor prognosis. Therefore, vitamin D supplements in patients with COVID-19 may improve the prognosis. In one study, it was suggested that vitamin D supplementation (At a dose of 50,000 IU twice a week) should be considered in patients with low circulating levels of vitamin D (below 50 nmol/L). This intervention can be continued at a dose of 50,000 IU once a week in the second and third weeks of treatment (32). It was also observed that vitamin D supplementation significantly reduces the odds of developing at least one acute respiratory infection. In patients with a serum25 (OH) D level less than 10 ng, this protective effect was more significant (11).

This study was performed cross-sectionally, so it is not possible to describe the reasons for the reduction of disease severity and improvement of prognosis in patients with insufficient vitamin D levels. Explaining the cause of these obsevations and evaluating the effect of vitamin

D in the treatment of COVID-19 patients requires large clinical trials.

We found that low serum vitamin D3 is associated with disease severity and death. CRP level and oxygen saturation are also a prognostic factor in COVID-19 patients. Level 25 ng/mL of vitamin D can also be used as a cut-off to predict the prognosis and severity of the disease in patients with COVID-19. By conducting prospective studies and comparing the prognosis in patients with COVID-19 with vitamin D treatment deficiency compared to patients with vitamin D deficiency, a more accurate assessment of the effect of vitamin D on the pneumonia process caused by COVID-19 will be possible.

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