Research Paper

The Association Between Vitamin D Serum Level and Severity of COVID-19: A Cross-sectional Study

Shahrzad Izadi[1], Masoume Bitaraf[2], Fatemeh Rahaei[3], Seyedeh Pardis Naghibi Rokni[1], Kamyar Mansori[3], Mohammad Memarian[2*]

1. Department of Surgery, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran.
2. Department of Internal Medicine, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran.
3. Clinical Research Development Unit, Valiasr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran.

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ABSTRACT

Background and Purpose: This study aimed to determine the association between vitamin D serum levels and the severity of COVID-19 in Iran.

Materials and Methods: This cross-sectional study was done on 121 COVID-19 patients referred to Kowsar Hospital of Semnan City, Iran, in 2022. The patients were assigned to the mild/moderate (n=80) and severe (n=41) COVID-19 groups. The data collection tool was a checklist that included demographics, clinical variables, and laboratory parameters extracted from the medical file and interviews with the patient. Also, patients' serum vitamin D level was measured using the liquid chromatography-tandem mass spectrometry method. Data were entered in Stata software, version 14 and analyzed by multivariate logistic regression. P<0.05 were considered significant.

Results: The mean age of severe and mild/moderate groups were 67.66±16.15 and 48.5±18.7 years, respectively. About 61% and 55% of mild/moderate and severe groups were male. The multivariate logistic regression model showed vitamin D (odds ratio [OR]=0.55; 95% CI, 0.42%, 0.83%) is the most important factor predicting the severity of COVID-19 so that, for one ng/mL increase in vitamin D level, the odds of contracting the severe form of COVID-19 decreases by about 45%.

Conclusion: The present study shows that low vitamin D levels may increase the risk of severe COVID-19. However, further studies with larger sample sizes are recommended.

Keywords: Vitamin D, COVID-19, Cross-sectional study, Iran

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*** Corresponding Author:**
Mohammad Memarian, Assistant Professor.
Address: *Department of Internal Medicine, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.*
Tel: *+98 (912) 1318691*
E-mail: *dr.memarian20@gmail.com*

Introduction

Coronavirus disease 2019 (COVID-19) is a pneumonic pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was first detected in December 2019 in Wuhan (China) [1, 2]. Approximately 15% of cases progress to severe (pneumonic) disease [3]. COVID-19 affects different systems and organs of the body, including the pulmonary, cardiovascular, nervous, and renal systems. Therefore, it is necessary to find ways to reduce the risk of severe infection and its morbidity and mortality [4].

The immune system is influenced by several factors that may contribute to the risk of mortality related to COVID-19. Meanwhile, vitamins may play an important role in the proper response of the body's immune system against infection and diseases [5, 6]. Vitamin D plays an essential role in modulating innate and acquired immune responses. Vitamin D can be synthesized in the human body with the help of sunlight or obtained from food sources. Serum 25-hydroxyvitamin D (25 [OH] D) level is a reliable index to evaluate serum vitamin D in the body [7, 8].

Studies have shown that adequate vitamin D levels may reduce the duration of hospitalization and the severity of respiratory diseases [9, 10]. Recent studies have highlighted the important role of vitamin D in supporting immune system function, especially in balancing the inflammatory response to viral infection [11, 12]. For example, a cohort study demonstrates that serum vitamin D levels are lower in SARS-CoV-2 positive cases than negative ones [13]. Similarly, in another study, the reduction of serum vitamin D levels shows a significant relationship with the severity of complications in COVID-19 patients [14]. From both epidemiological data and biochemical and immunological evidence, vitamin D may be an important modulating factor in the severity of COVID-19 and other respiratory infectious diseases [15, 16]. However, based on our knowledge, studies on the role of vitamin D supplementation in reducing the risk of contracting COVID-19 are limited. Therefore, considering the limitations of the studies and the controversial effect of vitamin D serum level on the risk of infection, we conducted this study to determine the association between vitamin D serum level and severity of COVID-19 in Iran.

Materials and Methods

Study design and subjects

This cross-sectional study was performed to determine the association between vitamin D serum level and the severity of COVID-19 in patients referred to Kowsar Hospital of Semnan City, Iran, in 2022. The samples were recruited by convenience sampling. A total of 121 COVID-19 patients based on lung CT or polymerase chain reaction (PCR) tests were assigned to mild/moderate (n=80) and severe (n=41) COVID-19 groups. The inclusion criteria comprised age ≥18 years, diagnosis of COVID-19 based on lung computed tomography (CT) scan or positive PCR test of nasopharyngeal swab sample, and willingness to participate in the research. The exclusion criteria consisted of lack of consent to participate in the study, parathyroid disorders, kidney failure, chronic liver disease, and liver cirrhosis.

Data collection

In the current study, the diagnosis of COVID-19 was based on lung CT or PCR test. Then, based on Centers for Disease Control and Prevention (CDC) criteria, the patients with a fever 5-6 days after infection and mild respiratory symptoms were categorized as mild/moderate COVID-19, and patients with symptoms of shortness of breath, respiratory rate more than 30 per minute, hypoxia, SpO_2 <93% and or lung penetration >50% of the lung field during 24 to 48 hours were classified as severe COVID-19. Also, patients with symptoms of respiratory failure, multiple organ dysfunction/failure, and septic shock were considered as severe COVID-19.

The data collection tool was a checklist including the variables of age, sex, body mass index (BMI), erythrocyte sedimentation rate (ESR), length of hospitalization, SpO_2, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), vitamin D level, smoking history, underlying disease, outcome, duration of hospitalization in intensive care unit (ICU), intubation and hospitalization complications were extracted through interview and the patient's medical file. However, to measure the serum level of vitamin D, 10 mL of blood was taken from all patients with COVID-19, and then the level of this vitamin was measured by liquid chromatography-tandem mass spectrometry method.

Statistical analysis

Data were analyzed using Stata software, version 14. The Mean±SD, and percentages were reported for de-

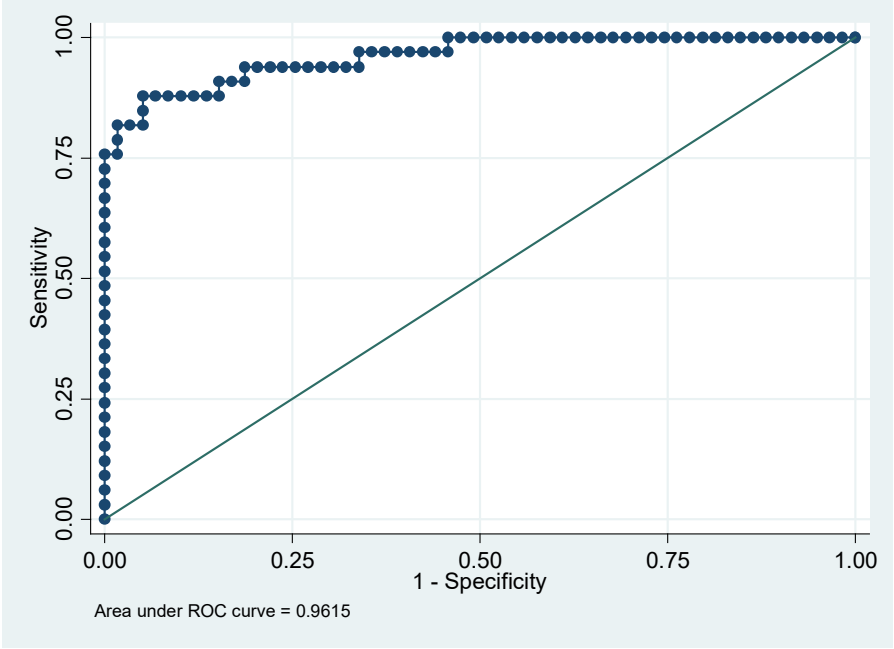

Figure 1. The area under the curve for variables entered in multivariate logistic regression model

scriptive analyses. Then, the univariate and multivariate logistic regression model was used to determine the relationship between vitamin D serum level and other variables under study with the severity of COVID-19.

Results

A total of 121 COVID-19 patients were examined in the mild/moderate (n=80) and severe (n=41) groups. Tables 1 and 2 present patients' demographic and clinical characteristics in mild/moderate and severe groups. The mean age of severe and mild/moderate groups were 67.66±16.15 and 48.5±18.7 years, respectively. The numbers (%) of males were 25(61%) and 44(55%) severe and mild/moderate groups, respectively. The Mean±SD values of SpO_2, ESR, CRP, LDH, and ferritin in the mild/moderate vs severe COVID-19 groups were 83.36±8.17 vs 92.31±4.67, 45.02±27.29 vs 28.71±21.94, 96.31±42.27 vs 49.88±41.41, 602.26±293.83 vs 392.08±146.5 and 324±356.38 vs 191.87±222.47, respectively. Also, the mean vitamin D levels of severe and mild/moderate groups were 16.78±6.74 and 20.88±7.14 ng/mL, respectively. The percentages of smokers in the two groups was 17(41.5%) and 20(25%), respectively.

Table 3 presents the predictive factors of the severity of COVID-19 by univariate logistic regression model. Age, vitamin D, LDH, ferritin, smoking, and underlying disease were the important factors predicting the severity of COVID-19 (P≤0.20).

Table 4 shows the odds ratio and 95% CI derived from a multivariate logistic regression model for the predictive factors of the severity of COVID-19. After adjusting for the confounding variables, vitamin D (odds ratio [OR]=0.55; 95% CI, 0.42%, 0.83%) was the most important factor predicting the severity of COVID-19 so that, for one ng/mL increase in vitamin D level, the odds of contracting the severe form of COVID-19 decreases by about 45%.

The area under the ROC curve was 0.9515 for significant variables included in the multivariate logistic regression model, demonstrating this model's high discriminative power (Figure 1).

Discussion

This present study was conducted to determine the association between vitamin D serum levels and the severity of COVID-19 in Iran. Our results show that the mean age of severe and mild/moderate groups were 67.66±16.15 and 48.5±18.7 years, respectively.

The percentages of males were 25(61%) and 44(55%) in the severe and mild/moderate groups, respectively. The multivariate logistic regression model shows that vitamin D (OR=0.55; 95% CI, 0.42%, 0.83%) was the most important factor predicting the severity of COVID-19 so that, for one ng/mL increase in vitamin D level, the odds of contracting the severe form of COVID-19 decreases by about 45%.

Table 1. Demographic and clinical characteristics of patients in two groups

Quantitative Variables	Group	No.	Mean±SD
Age (y)	Severe	41	67.66±16.15
	Mild/Moderate	80	48.5±18.7
BMI (kg/m^2)	Severe	41	27.43±6.02
	Mild/Moderate	80	26.7±5.07
Hospitalization (d)	Severe	41	10.05±8.4
	Mild/Moderate	80	4.56±2.17
Blood oxygen saturation (SpO_2)	Severe	41	83.36±8.17
	Mild/Moderate	80	92.31±4.67
ESR	Severe	41	45.02±27.29
	Mild/Moderate	80	28.71±21.94
CRP	Severe	41	96.31±42.27
	Mild/Moderate	80	49.88±41.41
LDH	Severe	41	602.26±293.83
	Mild/Moderate	80	392.08±146.5
Ferritin	Severe	41	324±356.38
	Mild/Moderate	80	191.87±222.47
Vitamin D (ng/mL)	Severe	41	16.78±6.74
	Mild/Moderate	80	20.88±7.14

Abbreviations: CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase.

Vitamin D is a steroid hormone produced endogenously by the action of ultraviolet rays on the skin. It is also available from exogenous food sources or dietary supplements [17]. Recently, various studies have shown a potential association between vitamin D deficiency and respiratory infections [17, 18]. Vitamin D deficiency affects the functions of the immune system and increases innate immunity by secreting antiviral peptides and improving mucosal defenses [19, 20]. Studies have demonstrated that low serum vitamin D levels may contribute to respiratory infections [21, 22]. In a meta-analysis study, vitamin D serum levels less than <20 ng/mL increased the risk of pneumonia by 64% [23].

In line with our study, some studies have suggested that vitamin D deficiency may compromise the function of the respiratory immune system and the risk of severe COVID-19 and related mortality [24]. Also, some observational studies have shown the correlation between vitamin D with severity and mortality in COVID-19 patients [25-27]. In a meta-analysis study of 1403715 COVID-19 patients, low vitamin D levels are associated with increased ICU hospitalization, disease severity, and mortality from COVID-19 [28]. D'Avolio et al. and Radujkovic et al. suggested that the vitamin D level was lower in people with a positive PCR test than in a negative PCR [13, 29]. Other studies have also shown an inverse relationship between vitamin D serum levels and levels of interleukin-6 and CRP in pneumonia and acute respiratory distress syndrome (ARDS) [23, 30, 31].

Vitamin D has an important role in immune system function, especially in balancing the inflammatory response to viral infection. It has been suggested that vitamin D can reduce the risk of infection through several mechanisms [11, 12]. These mechanisms include the induction of cathelicidins and defensins, which can reduce the speed of virus replication and the concentration of pro-inflamma-

Table 2. Demographic and clinical characteristics of patients in two groups

Qualitative Variables		No. (%)	
		Mild/Moderate	Severe
Sex	Male	44(55)	25(61)
	Female	36(45)	16(39)
Smoking	No	60(75)	24(58.5)
	Yes	20(25)	17(41.5)
Vaccination history (doses)	<2	15(18.8)	6(14.6)
	2	32(40)	13(31.7)
	3	28(35)	22(53.7)
	4	5(6.3)	0(0)
Underlying disease	No	32(40)	9(22)
	Yes	48(60)	32(78)
Outcome	Live	80(100)	29(70.7)
	Death	0(0)	12(29.3)
Hospitalization in the intensive care unit	No	77(96.3)	0(0)
	Yes	3(3.7)	41(100)
Intubation	No	80(100)	26(63.4)
	Yes	0(0)	15(36.6)
Complications of hospitalization	No	77(96.3)	0(0)
	Yes	3(3.7)	41(100)

tory cytokines [32]. Vitamin D mechanisms in reducing the risk of viral infections and mortality are different, as mentioned. For example, to reduce the risk of colds, vitamin D uses three pathways of physical barrier, natural cellular immunity, and adaptive immunity to increase immunity. The study of Grant et al. showed that vitamin D supplementation can reduce the risk of influenza and COVID-19 infection and mortality [32]. This vitamin plays a role in reducing viral infections by increasing cellular immunity and reducing cytokine storm by affecting interferon γ and tumor necrosis factor α and regulating adaptive immunity by inhibiting T helper cell type 1 responses and stimulating the induction of T cells [33]. Talmor's study also shows that calcitriol 1 25 OH 2D inhibits the production of pro-inflammatory cytokines such as interleukin-2, interferon-gamma, and tumor necrosis factor-alpha [34]. Evidence suggests that calcitriol 1,25 OH 2D leads to upregulating nuclear factor kappa B inhibitors in respiratory syncytial virus-infected A549 alveolar cells and primary human tracheobronchial epithelial cells. In addition, vitamin D increases the expression of angiotensin-converting enzyme 2, the main host cell receptor of COVID-19, and also downregulates renin at the transcriptional level [35]. The combination of vitamin D effects on the inflammatory pathway and angiotensin-converting enzyme 2 expression may be uniquely relevant to the pathogenesis and severity of COVID-19 [36].

Conclusion

Our study showed that the serum level of vitamin D is an important predictor of the severity of COVID-19, so a decrease in this vitamin can increase the risk of severe COVID-19. However, in order to confirm this finding, it is recommended that detailed studies with a larger sample size be conducted in this field.

Table 3. Predictive factors of the severity of COVID-19 by univariate logistic regression model

Variables		Crude Odds Ratio (95% CI)	P
Age (y)		1.06 (1.03-1.08)	<0.001
BMI (kg/m^2)		1.01 (0.95-1.08)	0.676
Lactate dehydrogenase		1.05 (1.01-1.08)	<0.001
Ferritin		1.03 (1.01-1.06)	0.032
Vitamin D		0.91 (0.86-0.97)	0.004
Sex	Female	Reference	0.530
	Male	1.27 (0.59-2.75)	
Smoking	No	Reference	0.110
	Yes	1.46 (0.92-2.31)	
Vaccination history (doses)	<2	Reference	-
	2	1.01 (0.32-3.19)	0.979
	≥3	1.96 (0.65-5.89)	0.229
Underlying disease	No	Reference	0.050
	Yes	2.37 (0.99-5.62)	

Study limitations

The most important limitation was the low sample size and the unequal number of patients in the two groups of mild/moderate and severe COVID-19, which can reduce the statistical efficiency. The second limitation is the study's cross-sectional nature and the one-time vitamin D serum level measurement, which necessitates conducting cohort studies with a large sample size.

Ethical Considerations

Compliance with ethical guidelines

This study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of the Research and Ethics Committee of Semnan University of Medical Sciences, Semnan, Iran (Code: IR.SEMUMS.REC.1400.283).

Table 4. Predictive factors of the severity of COVID-19 by multivariate logistic regression model

Variables		Adjusted Odds Ratio (95% CI)	P
Age		1.09 (0.99-1.21)	0.115
Lactate dehydrogenase		0.97 (0.98-1.07)	0.079
Ferritin		0.96 (0.95-1.02)	0.073
Vitamin D		0.55 (0.42-0.83)	0.005
Smoking	No	Reference	0.612
	Yes	1.59 (0.35-7.83)	
Underlying disease	No	Reference	0.615
	Yes	1.82 (0.26-13.87)	

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Authors contributions

Data collection, statistical analysis: Shahrzad Izadi and Mohammad Memarian; Study design, and data analysis: Masoume Bitaraf, Fatemeh Rahaei, and Seyedeh Pardis Naghibi Rokni; Conceptualization, review and editing: Kamyar Mansori, Shahrzad Izadi and Mohammad Memarian; Writing the original draft and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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