ASSOCIATION OF VITAMIN D LEVEL AND SEVERITY OF COVID-19 DISEASE

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Abstract

Background: Studies indicate that vitamin D can lower the incidence of viral respiratory infections and is necessary for the human immune system to function properly. Vitamin D deficiency may be a risk factor for the severity of COVID-19, including mortality, hospitalization, and length of hospital stay.

Objectives: This study aimed to investigate the association between vitamin D levels and the severity of COVID-19 disease.

Methods: The participants were COVID-19 patients aged 18 years or older who tested positive for the virus on Real-Time PCR tests, treated as inpatients at Banphaeo General Hospital between September 1 and November 30, 2021. For each patient, baseline characteristics, including sex, weight, height, and underlying diseases, were collected. Three categories were used to categorize COVID-19 disease: mild, moderate, and severe. At the beginning of the study, blood tests were performed on each patient to determine their 25-hydroxyvitamin D levels.

Results: Of 97 patients, 64 were male (66%), with a mean age of 50.8±17.7 years. The mean vitamin D level was 27.8±9.6 ng/mL, with 45 (46.4%) showing vitamin D deficiency and 39 (40.2%) indicating vitamin D insufficiency. Among COVID-19 patients with vitamin D deficiency, 28 (63.6%) were classified as severe, compared to only 16 severe cases (36.4%) among those without vitamin D deficiency, demonstrating statistically significant differences (p=0.006). Patients with vitamin D deficiency had a 3.97 times higher risk of experiencing severity (95% CI: 1.67, 9.41, p=0.002) than those without a vitamin D deficit. After adjusting for variable factors, results indicated that patients with vitamin D deficiency had a 3.78-fold increased risk of getting severe illness than those without deficiency (95% CI: 1.28, 11.19, p=0.016).

Conclusion: These findings suggested that vitamin D deficiency was associated with the severity of COVID-19.

Keywords: COVID-19, vitamin D deficiency, vitamin D insufficiency, COVID-19 severity

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Introduction

The world has experienced a global outbreak of COVID-19, with acute respiratory distress syndrome (ARDS) emerging as the leading cause of mortality.[1] The intensity of COVID-19 disease is correlated with several factors, including advanced age, obesity, diabetes, hypertension, chronic kidney disease, and cardiovascular disorders.[2] Moreover, studies have demonstrated that vitamin D levels can affect the risk of COVID-19 infection hospitalization, mortality, and duration of hospital stay.[4]

Several investigations have demonstrated that vitamin D is essential for the human immune system to function properly and can lower the incidence of viral respiratory infections.[5] Antimicrobial peptides, which are essential to the body's antiviral defense systems, play a critical role in the body's antiviral defense mechanisms. [6] Vitamin D regulates the adaptive community and innate immunity by modulating cytokine production.[7] A meta-analysis indicates that vitamin D administration may aid in preventing respiratory infections. The Scientific Advisory Committee on Nutrition (SACN) recommends a low daily vitamin D intake to prevent the risk of respiratory infections.[8, 9] Moreover, studies have found that vitamin D can prevent the accumulation of Angiotensin II and reduce Angiotensin II-mediated inflammation in virus-infected patients. It can thereby lower the risk of developing ARDS and muscular inflammation.[10]

Previous studies have suggested that vitamin D deficiency may be significant in COVID-19 disease. A systematic review and meta-analysis found that individuals with vitamin D deficiency have a statistically significantly higher risk of contracting COVID-19.[11] A meta-analysis study suggests that vitamin D supplementation to patients with COVID-19 can reduce the length of ICU stays and the need for ventilators.[12] Ye et al. found that patients with more severe COVID-19 disease exhibited lower vitamin D levels than those with less severe infections.[13] Thailand is a country in Southeast Asia where tropical regions with year-round sunshine surround Thai people. However, they are susceptible to vitamin D deficiency because of dietary, cultural, lifestyle, and environmental variables.[14] Thus, this study aimed to investigate the potential correlation between vitamin D levels and the severity of COVID-19 disease among Thai patients.

Methods

The participants were patients with COVID-19 disease receiving inpatient care at Banphaeo General Hospital from September 1, 2021, to November 30, 2021. Patients with COVID-19 symptoms aged 18 or older had positive results from quick tests and had Real-Time PCR results confirmed were eligible for inclusion. Exclusion criteria were pregnant women, anyone taking vitamin D or unknown supplements, and those suffering from diseases that might affect vitamin D levels, such as lymphoma and tuberculosis. The Human Rights and Ethics Committee of Banphaeo General Hospital, Samut Sakhon Province, Thailand (REC 010/64), granted ethical approval. For every subject, written informed permission was obtained.

All patients had their medical history taken, preliminary physical examination, a review of their history of underlying diseases, and a history of regular medications. Baseline data, including sex, weight, and height, were collected for each patient. Three categories, mild, moderate, and severe illnesses, are used to clarify the severity of COVID-19 diseases as follows: [15]

Mild illness: Individuals who experienced any of the following signs and symptoms of COVID-19: fever (temperature 37.5 °C or higher), runny nose, coughing, sore throat, body aches, headache, loss of taste or smell, red eyes, rashes, nausea, vomiting, or diarrhea; without fast breathing, exhaustion, or abnormalities on radiographs.

Moderate illness: Individuals with any of various signs and symptoms: radiographic pneumonia, chest tightness, difficulty breathing during physical activity, rapid or labored breathing, difficulty breathing when coughing, or significant comorbidities where the blood oxygen level ≥ 94% at room air.

Severe illness: Individuals exhibited any of the following symptoms: breathing difficulties, chest tightness, chest pain when breathing, drowsiness, unconsciousness, or slow response;

pneumonia with lesions (lung infiltration) covering more than 50% of lung area; blood oxygen levels < 94% in room air or decreased by > 3% of the measured value while exerting; use of a respirator; and respiratory rate > 30 breaths/minute.

At the beginning of the study, all patients underwent blood tests to measure 25-hydroxyvitamin D (25[OH]D) levels using the electrochemiluminescence immunoassay. Following the Endocrine Society's Practice Guidelines on vitamin D, the collected data was used to determine the correlation between the severity of the symptoms and vitamin D levels. [16, 17]

A blood level of less than 20 ng/mL is considered vitamin D deficiency, 20–29 ng/mL is considered vitamin D insufficiency, and 30-100 ng/mL is considered vitamin D sufficiency.

Population size calculations and statistical analysis

According to a study by Palacios et al.[19], 45.2% of the sample population in Thailand had a vitamin D insufficiency at a 25(OD)D level < 30 ng/mL. Therefore, the study's sample size of 87 participants was established based on the prevalence of vitamin D deficiency and a 20% drop-out rate. The group data were presented using frequency (N) and percentage (%), while the quantitative variables were expressed as means and standard deviation (Mean ± SD). The quantitative data from the two groups were compared using the t-test or the Mann-Whitney U test. The comparative analysis of the group data was analyzed using the Chi-square test or Fisher's exact test, and the logistic regression analysis was used to rule out any potential complications in the outcome analysis.

Results

Of 97 patients, 64 were male (66%) with a mean age of 50.8±17.7 years. For most patients, 68 cases were ≤ 60 years old (70.1%), with 29 cases aged > 60. The average BMI was 27.4±6.9 kg/m^2, with 41 cases (42.3%) of a BMI ≤25 kg/m^2 and 56 cases (57.7%) of a BMI >25 kg/m^2. Fifty-one patients (52.6%) had underlying diseases. Among those patients, 39 (40.2%) had hypertension, 30 (30.9%) had diabetes, 28 (28.9%) had hyperlipidemia, 7 (7.2%) had asthma, 4 (4.1%) had chronic renal failure, 2 (2.1%) had systemic lupus erythematosus (SLE), and 1 (1%) had cancer **(Table 1)**.

Table 1. Demographic data of the enrolled participants (n=97)

Characteristics	n (%)
Sex, n (%)	
Female	33 (34%)
Male	64 (66%)
Age (y), mean ± SD., n (%)	50.8 ± 17.7
≤ 60	68 (70.1%)
> 60	29 (29.9%)
BMI (Kg/m^2), mean ± SD. n (%)	27.4 ± 6.9
≤ 25	41 (42.3%)
> 25	56 (57.7%)
Underlying disease, n (%)	51 (52.6%)
hypertension	39 (40.2%)
diabetes	30 (30.9%)
hyperlipidemia	28 (28.9%)
asthma	7 (7.2%)
chronic renal failure	4 (4.1%)
systemic lupus erythematosus	2 (2.1%)
cancer	1 (1%)

Table 1. Demographic data of the enrolled participants (n=97) (Cont.)

Characteristics	n (%)
Vitamin D level (ng/mL), mean ± SD., n (%)	21.8 ± 9.6
< 20 (Vitamin D deficiency)	45 (46.4%)
20-29 (Vitamin D insufficiency)	39 (40.2%)
≥ 30 (Vitamin D sufficiency)	13 (13.4%)

The vitamin D measurement showed an average level of 27.8± 9.6 ng/mL. Forty-five (46.4%) patients had vitamin D deficiency, 39 (40.2%) had vitamin D insufficiency, and 13 (13.4%) had normal levels (**Table 1**).

In terms of COVID-19 severity, 49 (50.5%) of the patients had mild symptoms, 44 (45.3%) had severe symptoms, and 4 (4.2%) had moderate symptoms. In patients with vitamin D deficiency, 28 (63.6%) experienced severe symptoms, compared with 16 (36.4%) without vitamin D deficiency. **Table 2** shows that the difference was statistically significant (p=0.006). Furthermore, patients with vitamin D deficiency had a 3.97-fold higher risk of severe COVID-19 (95% CI;1.67, 9.41, p=0.002) than those without vitamin D deficiency. After adjusting for sex, age, BMI, and underlying diseases, patients with vitamin D deficiency had a 3.78-fold higher risk of acquiring severe symptoms (95% CI;1.28,11.19, p=0.016) than those without vitamin D deficiency (**Table 3**). However, this study did not find a correlation between sex, age, BMI, underlying diseases, and vitamin D levels (**Table 4**).

Discussion

The predominated circulated COVID-19 variant in the study period was Delta (B.1.617.2). At that time, all patients with COVID-19, including mildly symptomatic patients, were admitted

Table 2. Association of COVID-19 severity to each level of vitamin D

	Levels of COVID-19 Severity			*p*-value
	Mild (n=49)	Moderate (n=4)	Severe (n=44)	
Vitamin D level				
<20 ng/mL	15 (30.6%)	2 (50%)	28 (63.6%)	0.006*
≥20 ng/mL	34 (69.4%)	2 (50%)	16 (36.4%)	

Table 3. Association between vitamin D deficiency and the severity of COVID-19 disease at moderate and severe levels

	Moderate		Severe	
Univariate analysis	**Crude OR (95%CI)**	***p*-value**	**Crude OR (95%CI)**	***p*-value**
Vitamin D level				
<20 ng/mL	2.27 (0.29, 17.64)	0.434	3.97 (1.67, 9.41)	0.002*
≥20 ng/mL	Reference	1	Reference	1
Multivariate analysis	**Adjusted OR (95%CI)**	***p*-value**	**Adjusted OR (95%CI)**	***p*-value**
Vitamin D level				
<20 ng/mL	3.15 (0.3, 33.24)	0.34	3.78 (1.28, 11.19)	0.016*
≥20 ng/mL	Reference	1	Reference	1

Table 4. Correlation between levels of vitamin D deficiency and sex, age, BMI, and underlying diseases

	Vitamin D level			Vitamin D level		
	< 20 ng/mL (n=45)	**≥ 20 ng/mL (n=52)**	***p*-value**	**< 30 ng/mL (n=84)**	**≥ 30 ng/mL (n=13)**	***p*-value**
Sex						
Female	19 (42.2%)	14 (26.9%)	0.113	30 (35.7%)	3 (23.1%)	0.371
Male	26 (57.8%)	38 (73.1%)		54 (64.3%)	10 (76.9%)	
Age (year)						
≤ 60	30 (66.7%)	38 (73.1%)	0.492	59 (70.2%)	9 (69.2%)	0.941
> 60	15 (33.3%)	14 (26.9%)		25 (29.8%)	4 (30.8%)	
BMI (kg/m^2)						
≤ 25	18 (40%)	23 (44.2%)	0.674	35 (41.7%)	6 (46.2%)	0.761
> 25	27 (60%)	29 (55.8%)		49 (58.3%)	7 (53.8%)	
Underlying diseases						
Yes	28 (62.2%)	23 (44.2%)	0.08	45 (53.6%)	6 (46.2%)	0.618
No	17 (37.8%)	29 (55.8%)		39 (46.3%)	7 (53.9%)	

to the inpatient department, following hospital policy. This study found that 46.4% of patients with COVID-19 had vitamin D deficiency, and 40.2% had vitamin D insufficiency. These rates were higher than the general population, with 5.7% of randomly selected patients from every region having vitamin D deficiency. However, there were fewer cases of vitamin D insufficiency in patients with COVID-19 compared to the 45.2%[20] found in randomly selected patients from every region. Similar levels of vitamin D deficiency, around 43%, were found in patients with COVID-19 compared to vitamin deficiencies in other diseases such as rheumatoid arthritis. [21] Compared to the rates of vitamin D deficiency and insufficiency in patients with COVID-19 in Turkey, a Turkish study found a higher rate of 69.1% vitamin D deficiency, more significant than the rate in this study. Additionally, the mean vitamin D levels in the Turkish study were lower than in this study; this could be due to individuals from different equatorial countries or of different races having varying levels of vitamin D.[22] However, the Turkish study found that lower levels of vitamins were associated with greater disease severity, similar to results found in this study and other studies conducted in China and Italy. [13, 18]

Annweiler et al. suggested that administering a single dose of 80,000 iu of vitamin D3 to patients with COVID-19 might reduce severity and increase survival rates compared to those not receiving vitamin D supplementation.[23] This study did not find any association between sex, age, and BMI levels with vitamin D levels. However, most studies have shown low vitamin D levels among obese and older women. [22, 24] The small sample size used in the study might have contributed to the lack of significant associations.

The mechanism by which vitamin D can reduce the severity of COVID-19 disease has been found to stimulate the innate immune system, as well as macrophages and respiratory epithelial cells, to produce the antimicrobial peptide cathelicidin LL-37. This peptide can help destroy the viral envelope, which may explain how vitamin D can effectively reduce COVID-19 severity.[25] Cathelicidins have been shown to prevent lung damage associated with oxygen toxicity potentially. [26] Moreover, vitamin D has also been shown to stimulate the adaptive immune system by decreasing the activity of T helper 1

and T helper [17], while increasing the activity of regulatory T cells,[27] ultimately mitigating the cytokine storm syndrome and preventing multi-organ dysfunction. In addition, vitamin D plays a crucial role in regulating the function of the renin angiotensin-aldosterone (RAAS) system. Specifically, vitamin D inhibits ACE2 expression, preventing the virus from entering the cells. Furthermore, it can prevent the increase in Angiotensin II, which is believed to cause ARDS, myocarditis, and other severe complications of COVID-19 disease.[28] Such evidence could explain the findings of this research that vitamin D is likely to protect against the severe of COVID-19 disease. However, the findings of a randomized controlled trial indicated that the administration of 200,000 IUs of vitamin D to patients with moderate symptoms did not demonstrate any significant difference compared to the administration of placebo in terms of the length of hospital stays, mortality rates, ICU admission, or use of respirators. [29]

Thus, the efficacy of vitamin D administration in patients with COVID-19 remains inconclusive. It might take more information from more research to prove its efficacy. Nevertheless, oral vitamin D supplementation appears to be a safe and cost-effective option for reducing the severity of COVID-19 disease. Further research is needed to determine whether vitamin D supplementation can effectively reduce the severity of COVID-19 in patients with varying levels of disease severity. The study can provide valuable information to improve the treatment of patients with COVID-19 and potentially lower the incidence of severe illness and mortality rates associated with this disease. This research encountered a limitation because it was a single-center study with a small sample size and lacked a control group for comparison.

Conclusion

Vitamin D deficiency revealed a correlation with severe cases of COVID-19 disease.

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Conflict of interest

The authors declare they have no conflict of interest.

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