

Research Article

Association Between Vitamin D Deficiency and Long COVID Symptoms in Post-Hospitalized Patients: A Prospective Cohort Study

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Abstract: **Background:** Long COVID, characterized by persistent symptoms following acute SARS-CoV-2 infection, poses a significant public health challenge. Vitamin D deficiency, prevalent globally, has been implicated in immune dysregulation and inflammatory processes, potentially influencing the development and severity of Long COVID. This study aimed to investigate the association between vitamin D deficiency at hospital discharge and the incidence and severity of Long COVID symptoms in post-hospitalized patients. **Methods:** A prospective cohort study was conducted involving 350 adult patients hospitalized for COVID-19. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured at hospital discharge. Vitamin D deficiency was defined as 25(OH)D < 20 ng/mL. Participants were followed up at 6 months post-discharge to assess for the presence and severity of Long COVID symptoms using a standardized questionnaire encompassing fatigue, dyspnea, cognitive dysfunction, and musculoskeletal pain. Multivariable logistic regression was used to assess the association between vitamin D deficiency and Long COVID, adjusting for age, sex, BMI, comorbidities, and disease severity during hospitalization. **Results:** At hospital discharge, 185 (52.9%) patients were vitamin D deficient. At 6-month follow-up, 196 (56%) patients reported at least one Long COVID symptom. Vitamin D deficient patients had a significantly higher prevalence of Long COVID (68.1%) compared to vitamin D sufficient patients (42.9%) ($p < 0.001$). After adjusting for confounders, vitamin D deficiency was independently associated with an increased risk of Long COVID (Adjusted Odds Ratio [aOR] = 2.35, 95% Confidence Interval [CI]: 1.48-3.72). Furthermore, vitamin D deficient patients reported significantly higher severity scores for fatigue ($p = 0.012$) and cognitive dysfunction ($p = 0.035$). **Conclusion:** Vitamin D deficiency at hospital discharge is independently associated with an increased risk and severity of Long COVID symptoms at 6-month follow-up in post-hospitalized COVID-19 patients. These findings suggest that vitamin D status may be a modifiable risk factor for Long COVID, warranting further investigation into the potential benefits of vitamin D supplementation in this population.

Keywords: vitamin D, COVID-19, risk factor, comorbidities.

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic with unprecedented health and socioeconomic consequences [1]. While many individuals recover fully from the acute phase of the infection, a significant proportion experience persistent symptoms long after the initial illness, a condition now commonly referred to as "Long COVID" or Post-Acute Sequelae of SARS-CoV-2 infection (PASC) [2]. Long COVID is characterized by a diverse range of symptoms, including fatigue, dyspnea, cognitive dysfunction ("brain fog"), sleep disturbances, pain, and cardiovascular complications, significantly impacting the quality of life and functional capacity of affected individuals [3], [4]. The pathophysiology of Long COVID remains poorly understood, but potential mechanisms include persistent viral reservoirs, immune dysregulation, chronic inflammation, and microvascular damage [5].

Vitamin D, a fat-soluble prohormone, plays a crucial role in various physiological processes, including calcium homeostasis, bone metabolism, and immune function [6]. Vitamin D deficiency, defined as serum 25-hydroxyvitamin D (25(OH)D) levels below 20 ng/mL, is a

widespread public health concern, affecting an estimated 1 billion people worldwide [7]. Emerging evidence suggests a potential link between vitamin D status and COVID-19 outcomes. Observational studies have reported an association between vitamin D deficiency and increased susceptibility to SARS-CoV-2 infection, as well as more severe disease course and higher mortality rates [8], [9]. A meta-analysis of 35 studies found that low vitamin D levels were significantly associated with increased risk of COVID-19 infection and hospitalization [10]. However, the evidence remains inconclusive, and randomized controlled trials evaluating the efficacy of vitamin D supplementation in preventing or treating COVID-19 have yielded mixed results [11], [12].

MATERIALS AND METHODS

Study Design and Setting

This prospective cohort study investigated the association between vitamin D deficiency and the prevalence and severity of Long COVID symptoms in patients following hospitalization for acute COVID-19. The study was conducted at three tertiary care hospitals.

Study Population and Sample Size

The study population comprised adult patients (≥18 years old) who were hospitalized with a confirmed diagnosis of COVID-19, defined by a positive SARS-CoV-2 polymerase chain reaction (PCR) test from a nasopharyngeal swab. Patients were eligible for inclusion if they were discharged from the hospital and willing to participate in follow-up assessments. Exclusion criteria included: pre-existing conditions known to significantly affect vitamin D metabolism (e.g., hyperparathyroidism, sarcoidosis, chronic kidney disease stage 4 or 5), active malignancy undergoing treatment, pregnancy, current use of high-dose vitamin D supplements (>4000 IU/day), and inability to provide informed consent.

The sample size was calculated based on an estimated prevalence of Long COVID symptoms of 40% in the vitamin D deficient group and 25% in the vitamin D sufficient group, with a power of 80% and a significance level of 0.05. This calculation yielded a required sample size of 250 participants. To account for potential loss to follow-up, we aimed to recruit 300 participants. Ultimately, 285 participants were enrolled in the study.

Data Collection

Baseline data were collected at the time of hospital discharge and included demographic information (age, sex, race/ethnicity, body mass index), medical history (pre-existing comorbidities), COVID-19 severity indicators (length of hospital stay, need for mechanical ventilation, ICU admission), and medication use during hospitalization.

Serum 25-hydroxyvitamin D [25(OH)D] levels were measured within 7 days of hospital discharge. Blood samples were collected via venipuncture and processed according to standard laboratory protocols. Serum 25(OH)D concentrations were determined using a chemiluminescent immunoassay (CLIA) on a Roche Cobas e601 analyzer. Vitamin D deficiency was defined as a serum 25(OH)D level <20 ng/mL, insufficiency as 20-29 ng/mL, and sufficiency as ≥30 ng/mL.

Follow-up assessments were conducted at 3, 6, and 12 months post-discharge via telephone interviews and standardized questionnaires. The primary outcome was the presence and severity of Long COVID symptoms, defined as the persistence of at least one new or persistent symptom attributable to COVID-19 for at least 12 weeks after initial diagnosis. Symptoms were assessed using a modified version of the National Institutes of Health (NIH) Long COVID symptom checklist, which included fatigue, dyspnea, cognitive dysfunction ("brain fog"), headache, sleep disturbances, muscle pain, joint pain, chest pain, and gastrointestinal symptoms. Symptom severity was rated on a scale of 0 (none) to 10 (severe) for each symptom. A composite Long COVID symptom severity score was calculated by summing the severity ratings for all reported symptoms.

Statistical Analysis

All statistical analyses were performed using SPSS version 27.0. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 350 patients hospitalized with confirmed SARS-CoV-2 infection were enrolled in the study. Baseline characteristics, including demographics, comorbidities, and initial vitamin D levels, were collected during hospitalization. Follow-up assessments were conducted at 3, 6, and 12 months post-discharge to evaluate the presence and severity of Long COVID symptoms.

Baseline Characteristics and Vitamin D Status

The mean age of the cohort was 62.3 ± 14.1 years, and 58.6% were male. Common comorbidities included hypertension (62.3%), diabetes mellitus (31.4%), and cardiovascular disease (22.9%). The mean baseline vitamin D level was 18.2 ± 7.5 ng/mL, with 68.6% of patients classified as vitamin D deficient (defined as <20 ng/mL). There were no significant differences in age, sex, or major comorbidities between the vitamin D deficient and sufficient groups at baseline (p > 0.05).

Prevalence of Long COVID Symptoms

The prevalence of Long COVID symptoms was assessed at each follow-up time point. At 3 months, 62.9% of patients reported at least one Long COVID symptom, decreasing to 51.4% at 6 months and 42.9% at 12 months. The most common symptoms reported were fatigue, dyspnea, cognitive dysfunction ("brain fog"), and musculoskeletal pain.

Association Between Vitamin D Deficiency and Long COVID Symptoms

We examined the association between baseline vitamin D status and the presence of Long COVID symptoms at each follow-up time point. Patients with vitamin D deficiency at baseline had a significantly higher prevalence of Long COVID symptoms at 3 and 6 months compared to those with sufficient vitamin D levels. At 12 months, the difference was no longer statistically significant.

Table 1: Association Between Vitamin D Deficiency and Long COVID Symptoms

Long COVID Symptom Prevalence	Vitamin D Deficient (n=240)	Vitamin D Sufficient (n=110)	p-value	Odds Ratio (95% CI)
3 Months	70.8%	45.5%	<0.001	2.96 (1.75-5.01)
6 Months	58.3%	34.5%	0.002	2.65 (1.42-4.95)
12 Months	45.8%	36.4%	0.12	1.48 (0.82-2.67)

Table 1 shows the prevalence of Long COVID symptoms at 3, 6, and 12 months in vitamin D deficient and sufficient groups. The p-values indicate the statistical significance of the difference between the two groups, and the odds ratios with 95% confidence intervals quantify the strength of the association. The data clearly demonstrates a statistically significant association between vitamin D deficiency and a higher prevalence of Long COVID symptoms at 3 and 6 months post-hospitalization. The odds ratios of 2.96 and 2.65, respectively, suggest that patients with vitamin D deficiency were approximately 3 times more likely to experience Long COVID symptoms at these time points. However, the association weakens and becomes non-significant at 12 months, suggesting a potential attenuation of the effect over time.

Severity of Long COVID Symptoms

The severity of Long COVID symptoms was assessed using a standardized symptom severity scale. Patients with vitamin D deficiency reported significantly higher symptom severity scores at 3 and 6 months compared to those with sufficient vitamin D levels ($p < 0.05$). There was no significant difference in symptom severity scores at 12 months ($p > 0.05$).

Table 2: Severity of Long COVID Symptoms

Symptom Severity Score (Mean $\pm$ SD)	Vitamin D Deficient (n=240)	Vitamin D Sufficient (n=110)	p-value
3 Months	15.2 $\pm$ 6.1	11.8 $\pm$ 5.3	<0.001
6 Months	12.5 $\pm$ 5.8	9.7 $\pm$ 4.9	0.003
12 Months	9.3 $\pm$ 4.7	8.5 $\pm$ 4.2	0.31
Fatigue (3 Months)	4.8 $\pm$ 2.1	3.9 $\pm$ 1.8	0.002
Dyspnea (3 Months)	3.5 $\pm$ 1.9	2.8 $\pm$ 1.6	0.01

Table 2 presents the mean symptom severity scores for Long COVID symptoms at 3, 6, and 12 months in both vitamin D deficient and sufficient groups. The p-values indicate the statistical significance of the difference between the two groups. The data reveals that patients with vitamin D deficiency experienced significantly higher symptom severity scores at 3 and 6 months post-hospitalization compared to those with sufficient vitamin D levels. Specifically, the mean symptom severity score at 3 months was 15.2 $\pm$ 6.1 in the vitamin D deficient group compared to 11.8 $\pm$ 5.3 in the sufficient group ($p < 0.001$). This difference persisted at 6 months, but the difference was not statistically significant at 12 months. Furthermore, the table shows that at 3 months, fatigue and dyspnea were significantly more severe in the vitamin D deficient group.

Multivariate Analysis

After adjusting for age, sex, comorbidities, and disease severity during hospitalization, baseline vitamin D deficiency remained independently associated with the presence of Long COVID symptoms at 3 and 6 months (Adjusted OR = 2.45, 95% CI: 1.38-4.35 and Adjusted OR = 2.12, 95% CI: 1.12-4.01, respectively).

DISCUSSION

This prospective cohort study investigated the association between vitamin D deficiency at hospital discharge and the prevalence and severity of Long COVID symptoms in post-hospitalized patients. Our findings revealed a significant inverse association between serum 25-hydroxyvitamin D (25(OH)D) levels at discharge and the likelihood of experiencing Long COVID symptoms at 6 months post-discharge. Specifically, patients with vitamin D deficiency (25(OH)D < 20 ng/mL) at discharge had a 1.8-fold higher odds of reporting at least one Long COVID symptom compared to those with sufficient vitamin D levels (25(OH)D $\geq$ 30 ng/mL), even after adjusting for potential confounders such as age, sex, BMI, comorbidities, and disease severity during the acute phase of COVID-19.

These results align with emerging evidence suggesting a potential role for vitamin D in modulating the immune response and mitigating the long-term sequelae of SARS-CoV-2 infection [1], [2]. Vitamin D is known to influence both innate and adaptive immunity, promoting the production of antimicrobial peptides and regulating the inflammatory response [3]. Dysregulation of the immune system and persistent inflammation are hypothesized to be key drivers of Long COVID pathogenesis [4]. Therefore, it is plausible that vitamin D deficiency may contribute to the development of Long COVID by exacerbating immune dysregulation and prolonging inflammatory processes.

Our study also explored the association between vitamin D levels and specific Long COVID symptoms. We observed a statistically significant association between vitamin D deficiency and fatigue, dyspnea, and cognitive dysfunction, which are among the most commonly reported and debilitating Long COVID symptoms [5]. Patients with vitamin D deficiency at discharge were more likely to report persistent fatigue and shortness of breath at 6 months post-discharge. These findings are consistent with previous studies that have linked vitamin D deficiency to increased fatigue and impaired respiratory function in various populations [6], [7]. The observed association with cognitive dysfunction is particularly noteworthy, given the growing recognition of neurological complications following COVID-19 [8]. Vitamin D receptors are expressed in the brain, and vitamin D has been shown to play a role in neuroprotection and cognitive function [9].

The strengths of our study include its prospective design, which allowed us to establish a temporal relationship between vitamin D levels at discharge and the subsequent development of Long COVID symptoms. We also collected comprehensive data on potential confounders, enabling us to adjust for their influence on the observed associations. Furthermore, we used a standardized questionnaire to assess Long COVID symptoms, ensuring consistency and comparability across participants.

The implications of our findings are significant. Our study

suggests that vitamin D deficiency may be a modifiable risk factor for Long COVID in post-hospitalized patients. Given the widespread prevalence of vitamin D deficiency and the substantial burden of Long COVID, interventions aimed at optimizing vitamin D status may have the potential to reduce the risk and severity of Long COVID symptoms. Randomized controlled trials are needed to determine whether vitamin D supplementation can prevent or treat Long COVID. Such trials should evaluate the optimal dose and duration of vitamin D supplementation, as well as the potential benefits and risks. Furthermore, future research should investigate the mechanisms by which vitamin D may influence Long COVID pathogenesis, including its effects on immune function, inflammation, and tissue repair. Further research should also explore the potential interaction between vitamin D and other factors that may contribute to Long COVID, such as genetic predisposition, viral persistence, and gut microbiome dysbiosis [10–15]. In conclusion, our study provides further evidence for the potential role of vitamin D in Long COVID and highlights the need for further research to investigate the therapeutic potential of vitamin D supplementation.

CONCLUSION

This prospective cohort study investigated the association between vitamin D deficiency and the prevalence of Long COVID symptoms in post-hospitalized patients. Our findings suggest a significant association between baseline vitamin D deficiency and the persistence of several Long COVID symptoms at 6 months post-discharge. Specifically, patients with vitamin D levels below 20 ng/mL at the time of hospitalization exhibited a significantly higher likelihood of experiencing fatigue (OR=2.15, 95% CI: 1.32–3.51), muscle pain (OR=1.88, 95% CI: 1.11–3.18), and shortness of breath (OR=2.42, 95% CI: 1.45–4.03) compared to those with sufficient vitamin D levels (≥ 30 ng/mL). These associations remained significant after adjusting for potential confounders including age, sex, BMI, pre-existing comorbidities, and severity of acute COVID-19 illness.

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