Prevalence of Psychiatric Symptoms Associated with Vitamin D Level in Long COVID: Preliminary Study

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Abstract:

Background: Long COVID is a condition where individuals continue to experience persistent symptoms after recovering from the initial COVID-19 infection. Vitamin D is one of the vital minerals for maintaining normal health conditions and may be associated with the psychiatric symptoms of long COVID.

Objective: To examine the prevalence of psychiatric symptoms in long COVID-19 patients in association with vitamin D levels.

Materials and Method: This study employed a cross-sectional descriptive design, focusing on 170 patients who had previously contracted the COVID-19 virus at Foresta Clinic. The data collected included demographic data, vitamin D levels, and psychiatric symptoms in long COVID (anxiety, depression, and sleep disorders).

Result: The study results indicated a female-to-male ratio of 1.1:1 among the patients, with a mean age of 45.87 ± 8.65 years. Additionally, 62.4% had received three doses of the COVID-19 vaccine. The median blood vitamin D level was 22.96 ng/mL (IQR 18.77, 31.7), with 41.2% of participants showing insufficiency, 30.6% showing deficiency, and 28.2% having sufficient levels. Overall, psychiatric symptoms were found in 30.0% of the patients, with anxiety occurring in 15.3%, depression in 7.1%, and sleep disorders in 21.2%. Participants with psychiatric symptoms had significantly lower blood vitamin D levels compared to those without symptoms ($p < 0.05$). The prevalence of psychiatric symptoms was highest among those with vitamin D deficiency (46.2%), followed by those with vitamin D insufficiency (25.7%), and it was lowest in the vitamin D sufficient group (18.8%).

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Conclusion: Maintaining and assessing vitamin D levels in long-term COVID patients may help prevent or reduce the severity of psychiatric symptoms. Further research is needed to evaluate the effectiveness of vitamin D supplementation in long COVID patients with low vitamin D levels, as well as to monitor and assess psychological tests continuously.

Keywords: Long COVID, COVID-19, Psychiatric Symptoms, Vitamin D

Introduction

Coronavirus Disease 2019, also known as COVID-19, is caused by a respiratory infection from a newly emerged strain of the coronavirus, SARS-CoV-2, which underwent a natural mutation to form a new variant. The subsequent global outbreaks have caused significant repercussions worldwide, influencing public health, economies, and societies.[1] COVID-19 can lead to both immediate and prolonged health issues. Even after recovery, some patients may not fully regain their pre-illness physical condition and may experience persistent or new symptoms. People commonly refer to this condition as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC). The World Health Organization (WHO) defines "long COVID" as a condition that occurs in individuals with a probable or confirmed history of SARS-CoV-2 infection. It typically occurs within 3 months of the initial infection and involves symptoms lasting for at least 2 months, which cannot be attributed to other diagnoses.[2] The National Institute for Health and Care Excellence (NICE) defined post-COVID-19 syndrome as "signs and symptoms that develop during or after acute COVID-19 for more than 4 weeks. This condition is divided into 2 phases: post-acute COVID-19, which refers to signs and symptoms that last or recur between 4 and 12 weeks after infection, and chronic COVID-19, which refers to signs and symptoms that persist for 12 weeks or longer." [3]

Long COVID can be found in 10-30% of COVID-19 patients[4], with over 200 symptoms impacting various organ systems.[5] These symptoms include general symptoms, respiratory system, cardiovascular system, nervous system, skin system, gastrointestinal system, musculoskeletal system, as well as psychological symptoms that may also occur in long COVID. A study of 120,970 COVID-19 patients found a prevalence of mental health disorders in 20.3% of patients with long COVID. The study classified these disorders into the following categories: 13.6% had post-traumatic stress disorder (PTSD), 18.9% had anxiety, 16.1% had depression, and 17.8% had sleep disorders.[6] Psychiatric disorders can arise from various factors, including encephalitis/cerebral hypoxia, medical interventions, physical isolation, psychosocial impact, and social stigma. Additionally, increased inflammation in the body caused by SARS-CoV-2 infection (high levels of CRP, IL-6, and ferritin) heightens the risk of psychiatric symptoms like depression.[7] Furthermore, deficiencies in essential vitamins and minerals can also negatively impact overall bodily function.[8] Vitamin D, especially, is stored in fatty tissues and is a fat-soluble vitamin with a chemical derived from cholesterol. It plays a significant role in supporting overall health by regulating the immune system's response—both innate and adaptive immunity.[9] Additionally, it supports the immune responses to antimicrobial and antiviral agents.[10]

There are currently no conclusive findings about the role of vitamin D in residual psychiatric symptoms after COVID-19

recovery. Therefore, we are interested in exploring the relationship between vitamin D levels and the prevalence of psychiatric symptoms associated with long COVID. The findings from this study will enhance our understanding of the role of vitamin D deficiency or insufficiency and its potential link to psychiatric symptoms in long COVID patients.

Materials and Method

This study was a descriptive cross-sectional study, approved by the Ethics Committee of Mae Fah Luang University (COA: 166/2024, EC 24104-20). The sample group consisted of 170 patients who were previously infected with COVID-19, confirmed by either the Covid-Ag or RT-PCR methods. The inclusion criteria included patients aged 18-59 years with mild symptoms who had their serum 25(OH)D levels assessed within two months before infection and who received treatment at the Foresta Clinic. The sample size was calculated using a formula for comparing two independent means, based on research by Filippo LD et al.,[10] with an α at 0.05 and a β at 0.20. An additional 10% was added to the calculated sample size, resulting in 85 patients per group, for a total of 170 patients in the study.

The psychiatric symptoms of long COVID encompassed anxiety, depression, and sleep disorders, which were assessed using a numerical rating scale ranging from 0 to 10 points (0 indicating signs absent or no change compared to prior infection and 10 indicating the most severe symptoms). We adapted this questionnaire from the Department of Medical Services' Long-Term Health Impact Questionnaire for COVID-19 Survivors, which had a Kuder-Richardson coefficient of reliability of 0.8638.

The instruments used in this study comprised a data collection form divided into three parts: demographic data, vitamin D levels, and psychiatric symptoms of long COVID. We collected the demographic data and psychiatric symptoms section using self-administered questionnaires. Demographic data included gender, age, and body mass index (BMI). The psychiatric symptoms of long COVID encompassed anxiety, depression, and sleep disorders, which were assessed using a numerical rating scale ranging from 0 to 10 points (0 indicating no symptoms and 10 indicating the most severe symptoms). This scale was adapted from the Long-Term Health Impact Questionnaire for COVID-19 patients developed by the Department of Medical Services. We obtained serum 25(OH) D from the clinic's medical database and measured it in ng/mL. These levels were categorized according to the guidelines of the Endocrine Society of the United States into three levels: vitamin D deficiency (<20 ng/mL), insufficient vitamin D levels (20–30 ng/mL), and sufficient vitamin D levels (> 30 ng/mL).

Statistical Analysis

We used descriptive statistics to present demographic data and psychiatric symptoms associated with long-term COVID. For continuous data, the mean, standard deviation (SD), median, and interquartile range (IQR) were calculated, while categorical data were summarized using frequencies and percentages. The demographic data of patients were compared across three groups based on their vitamin D levels using one-way ANOVA and the chi-square test. We used the Mann-Whitney U test to assess the relationship between vitamin D levels and the presence of psychological symptoms in long-term COVID. We conducted data analysis using STATA statistical software (StataCorp. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC; 2023). All tests were two-tailed. Statistical significance was set at the 0.05 level ($\alpha = 0.05$).

Results

Demographic data were analyzed from 170 COVID-19 patients, showing a female-to-male ratio of 1.1:1. The mean age was 45.87 ± 8.65 years. The mean height was 162 ± 6.07 cm, and the mean weight was 65.42 ± 11.48 kg. The mean body mass index (BMI) was 24.90 ± 4.72 kg/m^2, with the majority being classified as overweight (62.1%). Table 1 shows no statistically significant differences in the demographic factors across the three vitamin D level groups ($p > 0.05$).

Table 1 Demographic data of COVID-19 patients

	Total (n = 170)	Vitamin D status			*p*-value
		Deficiency (n = 52)	Insufficiency (n = 70)	Sufficiency (n = 48)	
Sex, n (%)					
Male	83 (48.8)	26 (50.0)	34 (48.6)	23 (47.9)	0.977
Female	87 (51.2)	26 (50.0)	36 (51.4)	25 (52.1)	
Age (years), mean ± SD	45.87 ± 8.65	45.85 ± 8.87	45.17 ± 8.85	46.92 ± 8.18	0.563
Height (cm), mean ± SD	162 ± 6.07	163.12 ± 6.58	162.06 ± 5.94	162.21 ± 5.73	0.612
Weight (kg), mean ± SD	65.42 ± 11.48	65.94 ± 11.37	64.03 ± 11.30	66.88 ± 11.85	0.387
BMI (kg/m^2), mean ± SD	24.90 ± 4.72	24.87 ± 4.55	24.48 ± 4.67	25.54 ± 5.01	0.489
< 18.5	17 (10.1)	4 (7.8)	8 (11.4)	5 (10.4)	
18.5 – 22.9	47 (27.8)	16 (31.4)	20 (28.6)	11 (22.9)	0.866
> 23.0	105 (62.1)	31 (60.8)	42 (60.0)	32 (66.7)	

Data were analyzed with chi-square test and one-way ANOVA; * statistically significant at the 0.05 level ($\alpha = 0.05$)

The prevalence of psychiatric symptoms was 30.0% (95% CI 23.2, 37.4). These symptoms included anxiety at a rate of 15.3%, with a mean severity level of 3.12 ± 1.07; depression at 7.1%, with a mean severity level of 2.67 ± 1.78; and sleep disorders at 21.2%, with a mean severity level of 4.44 ± 2.08 (Table 2).

Table 2 Prevalence and severity of psychiatric symptoms in Long COVID patients

Psychiatric symptoms	n (% [95%CI])	Severity score, mean ± SD
Overall psychiatric symptoms	**51 (30.0 [95%CI 23.2, 37.4])**	
Anxiety	26 (15.3)	3.12 ± 1.07
Depression	12 (7.1)	2.67 ± 1.78
Sleep disorder	36 (21.2)	4.44 ± 2.08

The study on how common psychiatric symptoms is in long COVID patients related to their vitamin D levels showed that patients lacking vitamin D had the most psychiatric symptoms (46.2%), followed by those with low vitamin D (25.7%) and those with enough vitamin D (18.8%). These differences were statistically significant at the 0.05 level ($p = 0.007$). In the same way, patients with vitamin D deficiency had a much higher rate of anxiety, depression, and sleep disorders than those with insufficient or sufficient vitamin D levels, and this was statistically significant at the 0.05 level (Table 3).

Table 3 Prevalence of psychiatric symptoms according to vitamin D status

Psychiatric symptoms	Vitamin D status			*p*-value
	Deficiency (n = 52)	Insufficiency (n = 70)	Sufficiency (n = 48)	
Overall psychiatric symptoms	**24 (46.2)**	**18 (25.7)**	**9 (18.8)**	**0.007***
Anxiety	14 (26.9)	8 (11.4)	4 (8.3)	0.018*
Depression	10 (19.2)	2 (2.9)	0 (0.0)	< 0.001*
Sleep disorder	21 (40.4)	10 (14.3)	5 (10.4)	< 0.001*

Data was analyzed with chi-square test; * statistically significant at the 0.05 level ($\alpha = 0.05$)

Discussion

This study found a prevalence of psychiatric symptoms in 30.0% of patients (95% CI 23.2, 37.4), divided into 15.3% with anxiety, 7.1% with depression, and 21.2% with sleep disorders. In several intriguing aspects, the findings of this study are both consistent with and different from other studies. This study can be compared to the systematic review and meta-analysis conducted by Kokolevich ZM, et al.[11] which revealed a similar prevalence of anxiety and sleep disorders, with 14.5% for anxiety and 20.0% for sleep disorders. This consistency may reflect general trends in psychiatric symptoms among patients. The systematic review and meta-analysis by Gennaro FD et al.[6], which included data from 120,970 patients, showed a slightly lower overall prevalence of psychiatric symptoms (20.3%) compared to this study. However, the rates of anxiety (18.9%) and sleep disorders (17.8%) were comparable, while depression had a higher prevalence (16.1%). This discrepancy may be attributed to the diversity of populations and variations in data collection methods. In contrast, a study in China found a significantly higher prevalence of anxiety (30.2%) and sleep disorders (29.2%).[12] Cultural, social, or environmental factors specific to China may account for this difference. A study conducted in Thailand with 364 patients found a prevalence of psychiatric symptoms of 21.3%, which was lower than this study.[13] This difference may be due to several factors, such as sample size, study period, or differing characteristics of the population. It is evident that psychiatric symptoms, particularly anxiety and sleep disorders, are common problems in patients, consistent with studies from various countries, despite some differences in details. The variation between studies may reflect differences in populations, data collection methods, and distinct cultural and social factors.

A study comparing vitamin D levels in patients with and without psychiatric symptoms from long COVID found that

those with symptoms like anxiety, depression, and sleep problems had much lower average blood vitamin D levels than those without these symptoms, and this difference is statistically significant at the 0.05 level. The results suggest that levels of vitamin D are associated with the psychiatric symptoms in long COVID, including anxiety, depression, and sleep disorders. Patients with vitamin D deficiency are 3.86 times more likely to develop psychiatric symptoms compared to those with sufficient levels of vitamin D. This information is consistent with the study by Algin S, et al,[14] which reported a mean vitamin D level of 19.9 ± 11.8 ng/mL in patients with mental disorders, with low vitamin D levels as high as 87.8%. Of these, 62.0% had levels below 20 ng/mL, and 25.8% had levels between 21 and 30 ng/mL. Similarly, the study by Hikmet RG, et al,[15] found that 89.0% of individuals with low vitamin D levels experienced sleep disorders.

Vitamin D not only plays a vital role in serotonin synthesis but also supports the function of nerve cells, protects neurons, and affects neurotransmitters essential for sensory perception, cognitive function, and emotional control. Neurological symptoms like headaches, dizziness, and sensory loss are common in long COVID patients and are thought to be caused by the virus's impact on the nervous system. A deficiency of vitamin D can hinder neuropsychiatric recovery in these patients. When vitamin D levels are low, it can increase inflammation in the nervous system, potentially damaging the cranial and olfactory nerves. This damage may worsen symptoms such as dizziness, headaches, and loss of smell or taste.

This finding matches a study by Algin et al. that showed patients with psychiatric disorders had an average vitamin D level of 19.9 ± 11.8 ng/mL, with 87.8% of them having low vitamin D levels, including 62.0% with levels below 20 ng/mL and 25.8% with levels between 21 and 30 ng/mL. Vitamin D plays a crucial role in mental health and the nervous system, particularly in the context of long COVID.

A deficiency in vitamin D can affect the synthesis of neurotransmitters, particularly serotonin, which plays a crucial role in regulating mood. Moreover, vitamin D has protective properties for the nervous system, helping to shield brain cells from damage and supporting brain development and function. Vitamin D deficiency may contribute to neurological disorders that affect cognition and mood. In long COVID, chronic inflammation is a key factor linking psychiatric symptoms. Vitamin D helps modulate the immune response by reducing the levels of pro-inflammatory cytokines. A deficiency in vitamin D can make inflammation worsen, negatively affecting brain function and leading to emotional disturbances. Vitamin D is also involved in regulating the hypothalamic-pituitary-adrenal (HPA) axis, which plays a critical role in the response of stress. Vitamin D sufficiency can promote the HPA axis and decrease the risk of mental health issues.

Vitamin D plays a crucial role in mental health and the nervous system, particularly in the context of long COVID. It may influence neurotransmitter synthesis, especially serotonin, which affects mood regulation and increases the risk of depression and anxiety. Additionally, vitamin D has neuroprotective properties, helping to shield brain cells from damage and supporting the brain's development and function. Therefore, a deficiency in vitamin D could lead to neurological disorders, affecting both cognitive function and mood.[16] In the case of long COVID, chronic inflammation is a significant factor linked to psychiatric symptoms. Vitamin D helps modulate immune responses by reducing the levels of cytokines that promote inflammation. A deficiency in vitamin D

could cause severe inflammation, affecting brain function and leading to mood disorders.[17] Furthermore, vitamin D is involved in regulating the hypothalamic-pituitary-adrenal (HPA) axis, which plays a critical role in stress response. A deficiency in vitamin D may impair the functioning of the HPA axis, increasing the risk of mental health issues.[18] Moreover, studies on the effectiveness of vitamin D supplementation in randomized controlled trials have reported that receiving 60,000 IU of vitamin D per week significantly reduces anxiety, though it does not appear to alleviate depression.[19] However, some studies have found no association between vitamin D levels and symptoms of anxiety, depression, or sleep disorders.[15]

The reason for studying how vitamin D affects long COVID is that vitamin D is important for controlling inflammation in the body by both promoting and reducing it. Vitamin D deficiency can lead to chronic inflammation, which is common in long-term COVID patients who continue to experience inflammation even after recovering from the infection, resulting in persistent fatigue —for example, chronic fatigue syndrome and brain fog. Additionally, vitamin D is important for energy production and mitochondrial function. When low vitamin D levels decrease mitochondrial efficiency, leading to reduced energy production in the body, which can manifest as fatigue. Another symptom commonly seen in long COVID is fever, which is a general response to infection and inflammation triggered by the release of cytokines. Low vitamin D levels may lead to the continuous release of cytokines, causing prolonged or recurrent fever. On the other hand, maintaining sufficient vitamin D levels can help reduce the production of pro-inflammatory cytokines and diminish free radicals. In summary, sufficient vitamin D levels are important for regulating inflammation, mitochondrial function, and cytokine production. These processes are not only associated with chronic fatigue but also with neuropsychiatric symptoms via the regulation of neurotransmitter synthesis. When it comes to the possible advantages of vitamin D for mental health, vitamin D is important for making neurotransmitters, helps nerve cells work properly, protects neurons, reduces harmful substances like tau and beta-amyloid proteins, and influences neurotransmitters that are crucial for how we perceive things, think, and manage our emotions.

Vitamin D also contributes to sleep disorders, as brain regions that regulate sleep contain vitamin receptors. It is believed that vitamin D influences the production of melatonin, a hormone that regulates the sleep-wake cycle. Vitamin D deficiency may disrupt melatonin production, leading to sleep disorders.[20] Even in patients with long COVID, vitamin D deficiency could worsen symptoms, increasing stress in managing the condition. Such conditions can lead to deteriorating mental health, difficulties in emotional regulation, heightened anxiety, and sleep disorders.[21]

This study suggests that vitamin D levels are associated with psychiatric symptoms in long COVID patients. Therefore, healthcare professionals should prioritize monitoring and assessing vitamin D levels in this group of patients, as it may have the potential to prevent and reduce the severity of psychiatric symptoms. Additionally, vitamin D supplementation should be considered for those with a deficiency. Further research is needed to evaluate the efficacy of vitamin D supplementation in preventing or decreasing psychiatric symptoms in long COVID patients, particularly regarding anxiety, depression, and sleep disorders. Moreover, cultural, social, and environmental factors that may influence patient responses should

be considered. Health care should adopt a holistic care approach, addressing physical, psychological, and nutritional factors to develop effective and appropriate treatment strategies for each individual. However, our findings showed that vitamin D status and psychiatric disorders are independent of BMI.

Conclusion

This study identified a significant association between vitamin D levels and psychiatric symptoms in patients with long COVID, particularly in relation to anxiety, depression, and sleep disorders. The findings indicate that patients exhibiting psychiatric symptoms often have lower vitamin D levels. This vitamin D deficiency may negatively impact nervous system function, immune response, inflammatory processes in the body, stress regulation, and the production of hormones associated with the sleep-wake cycle, all of which can affect the mental health of patients. Health care should also consider other factors, such as cultural, social, and environmental, which may affect the manifestation and response to psychiatric symptoms.

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Contribution

Conceptualization: Karn Matangkha and Jarasphol Rintra; Methodology: Karn Matangkha and Jarasphol Rintra; Formal analysis: Karn Matangkha and Jarasphol Rintra; Investigation: Vichit Punyahotara and Phakkharawat Sittiprapaporn; Writing-original draft preparation: Karn Matangkha and Phakkharawat Sittiprapaporn; Writing-review and editing, Phakkharawat Sittiprapaporn; Project administration: Jarasphol Rintra and Vichit Punyahotara. All authors have read and agreed to the published version of the manuscript.

Disclosure of interest

The authors report no conflict of interest.

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