

# Role of Vitamin D Supplementation for Symptoms and Lung Function Improvement in Long COVID Patient

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**Keywords:**

Vitamin D, Long COVID,  
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**ABSTRACT**

Post-Acute COVID-19 Syndrome (PACS) or acute post-COVID-19 syndrome or also known as "Long Covid", is a collection of persistent symptoms and long-term complications more than four weeks after the onset of initial symptoms. One of the leading causes of these long-term complications is pulmonary fibrosis, with an incidence of almost 25% in patients a year after hospitalization. Vitamin D is an important substance to our body homeostasis and regulation. Vitamin D has pleiotropic effect as pulmonary antifibrosis. This research aims to directly provide vitamin D3 supplements, especially in improving lung function in pulmonary fibrosis patients after COVID-19 infection. This study was a one-group, quasi-experimental pretest-posttest design conducted at Labuang Baji hospitals in the eastern part of Indonesia. The population of this study was patients post-covid-19 infection with negative PCR results at least three months, had persistent symptoms of covid 19, and a CT scan confirmed pulmonary fibrosis or destroyed lung results. Lung function was measured using spirometry before and after the intervention (Vitamin D3 5000 IU supplementation with a frequency of once per day for two months). This study included 20 cases of Lung Fibrosis post-Covid-19. The majority of respondents were women and between the ages of 40 and 49. Among 20 patients, most of them fatigue or dyspneu or shortness of breath as their main symptoms. After 2-months supplementation of Vitamin D 5000 IU, number of patients who had shortness of breath and fatigue reduced significantly (From 11 to 3 and from 11 to 2 patients, respectively). 85% of our patient had deficient-insufficient status of vitamin D. We found restrictive pattern as a dominant lung function in our patient. There was significant improvement in lung function status after 2-months vitamin D supplementation ( $p=0.02$ ). Vitamin D supplementation for Long COVID may have benefit for symptoms and lung function improvement.

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## 1. INTRODUCTION

SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2), the pathogen that causes COVID-19, has

been a significant cause of morbidity and mortality worldwide [1]. In addition to effective management and implementation of mass vaccination programs, monitoring of communication and long-term effects on patients after COVID-19 infection is also an essential part of efforts to improve the handling of COVID-19.

Post-Acute COVID-19 Syndrome (PACS) or acute post-COVID-19 syndrome or also known as "Long Covid", is a collection of persistent symptoms and long-term complications more than four weeks after the onset of initial symptoms [2], [3]. One of the leading causes of these long-term complications is pulmonary fibrosis, with an incidence of almost 25% in patients a year after hospitalization [4], [5]. In 20% of cases, significant fibrosis progression results in worsening pulmonary function 5–10 years later [5]. These persistent respiratory complications cause population morbidity, mortality, and even death from pulmonary fibrosis [6].

Vitamin D is essential in calcium homeostasis, bone health, electrolytes, blood pressure regulation, and the body's immune response. In addition to these functions, vitamin D also has pleiotropic effects such as cell proliferation, cell differentiation, apoptosis, intracellular adhesion, oxidative stress, matrix homeostasis, and regulation of inflammatory responses. One of the pleiotropic effects of vitamin D is the role of vitamin D in pulmonary antifibrosis [7].

This research aims to directly provide vitamin D3 supplements, especially in improving lung function in pulmonary fibrosis patients after COVID-19 infection, so it can be implemented as an alternative therapy for post-COVID patients, which is ultimately expected to improve the patient's quality of life.

## **2. METHODS**

This study was a one-group, quasi-experimental pretest-posttest design conducted at Labuang Baji hospitals in the eastern part of Indonesia. The population of this study was patients post-covid-19 infection with negative PCR results at least three months, had persistent symptoms of covid 19, and a CT scan confirmed pulmonary fibrosis or destroyed lung results. Patients were excluded if they had a history of chronic lung disease, diabetes, coroner's heart disease, and autoimmune diseases.

Lung function was measured using spirometry before and after the intervention (two months of vitamin D3 5000 IU supplementation) then the results were converted to a scale based on the degree of the test result (Normal, mild, moderate, and severe). Primary outcomes changed in the lung function who administered vitamin D3 5000 IU supplementation with a frequency of once per day for two months, comparing the pre- and post-intervention periods in ordinal scale using Wilcoxon signed-rank test.

Patients were not involved in the study's design, conduct, or dissemination. All subjects gave written informed consent following the Declaration of Helsinki. The Ethical Committee of the Medical Faculty of Hasanuddin University approved the procedure applied in this study [411/UN4.6.4.5.311 PP36/ 2022].

## **3. RESULT**

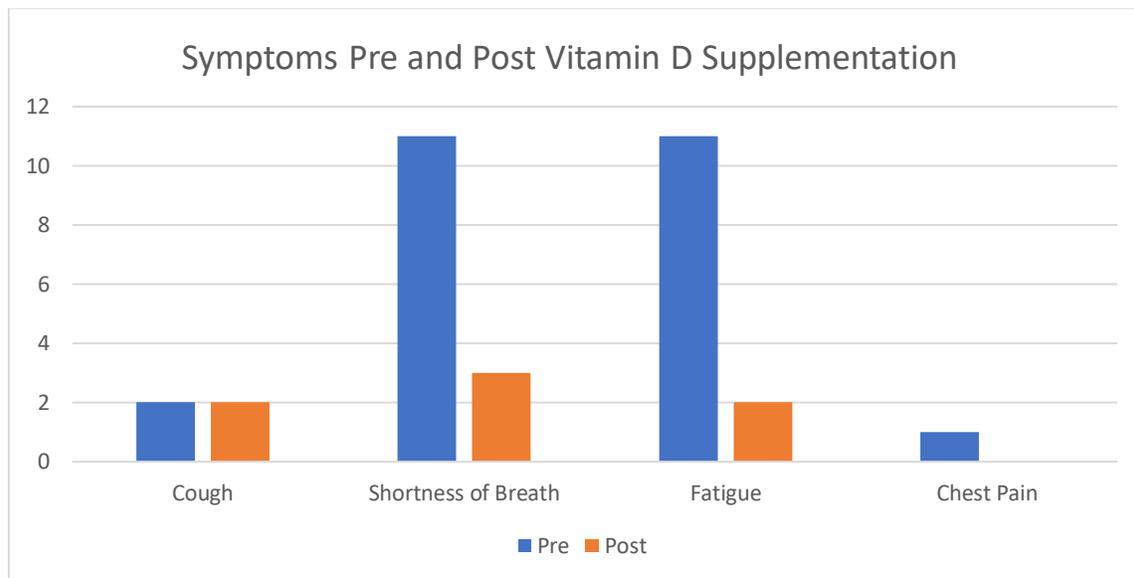
This study included 20 cases of Lung Fibrosis post-Covid-19 based on the criteria described in Methods. Detailed patient characteristics are listed in Table 1. The majority of respondents were women (85%, significantly more than man,  $p < 0.001$ ) and between the ages of 40 and 49 (50%). The youngest patient was 28 years old, and the maximum was 56 years old with the median age was 42 years (IQR 9). One patient (5%) had Congestive Heart Failure, and one (5%) was obese. Other patients have no comorbidities of the disease (90%). In this study, two patients (10%) had a smoking history, and one patient (5%) had pulmonary tuberculosis as a past medical history.

**Table 1.** Patient Characteristics

Characteristics	Category	Frequencies (N=20)	P-value*
Age, years	Median±IQR	42±9	.200
	28-39	7 (35%)	
	40-49	10 (50%)	
	≥50	3 (15%)	
Sex	Man	3 (15%)	.000
	Woman	17 (85%)	
Covid-19 Severity	Mild	3 (15%)	.000
	Moderate	14 (70%)	
	Severe	2 (15%)	
Comorbidity	None	18 (90%)	.000
	CHF	1 (5%)	
	Obesity	1 (5%)	
Smoking history	None	18 (90%)	.000
	Yes	2 (10%)	
Past medical history	None	19 (95%)	.000
	Pulmonary Tuberculosis	1 (5%)	

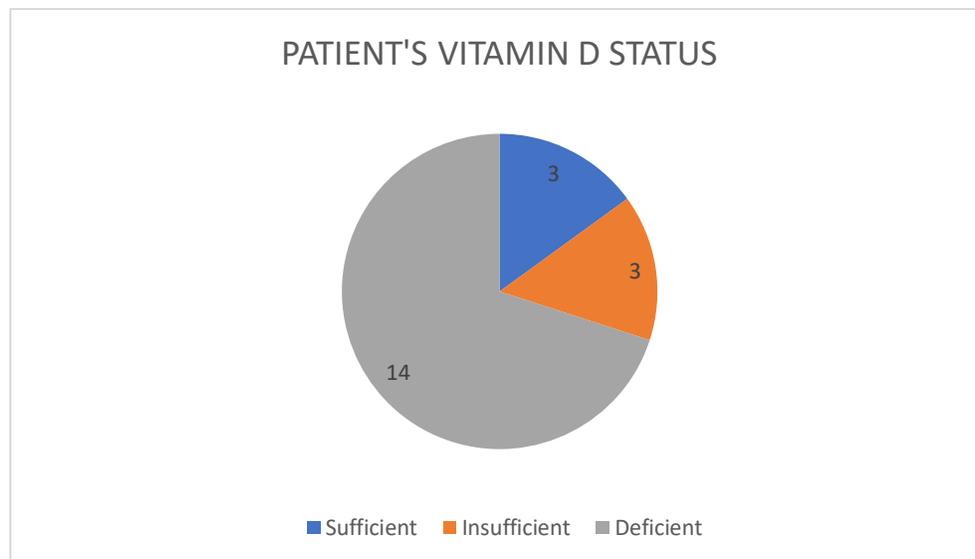
IQR, Interquartile Range. CHF, Congestive Heart Failure

\*Test of normality, Kolmogorov-smirnov


**Figure 1.** Symptoms Pre and Post Vitamin D Supplementation

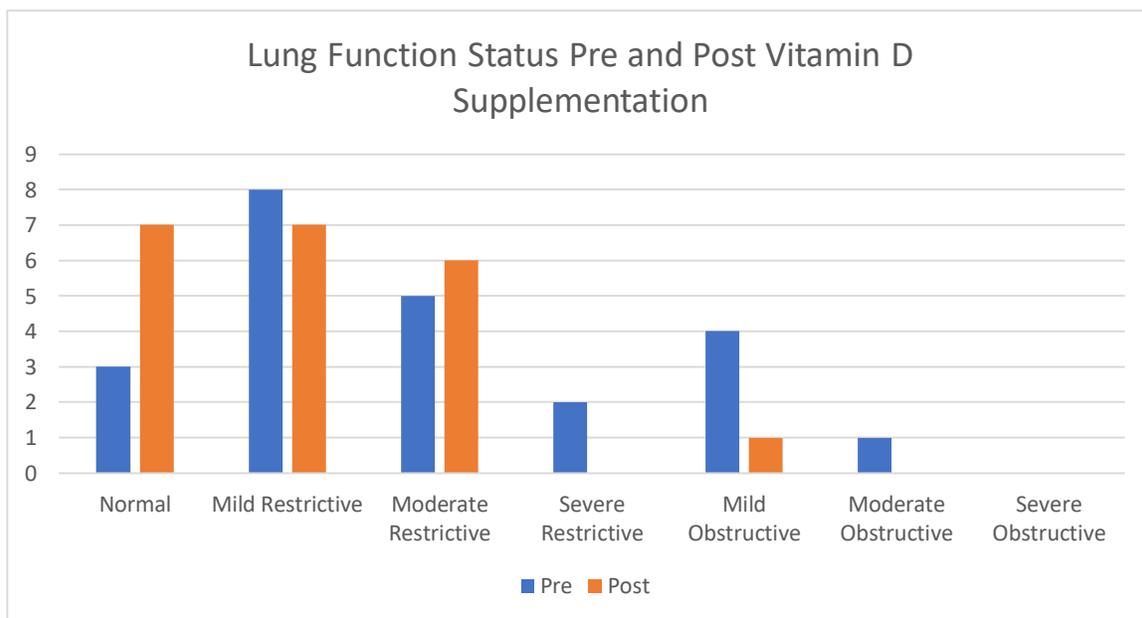
Among 20 patients, most of them fatigue or dyspneu or shortness of breath as their main symptoms. Cough and chest pain were the less common symptoms which found in our patients.

After 2-months supplementation of Vitamin D 5000 IU, most of our patients had better condition evidenced by their improvement of symptoms. Number of patients who had shortness of breath and fatigue reduced significantly.



**Figure 2.** Patient’s Vitamin D Status

Only 3 patients who had sufficient concentration of serum Vitamin D. The other 17 patients were categorized as insufficient and deficient (below normal) vitamin D status. Average of Vitamin D Serum from 20 patients was 17.86 (Deficient)



**Figure 3.** Lung Function Status Pre and Post Vitamin D Supplementation

We examined lung function before and after 2-months vitamin D supplementation. We found, before vitamin D supplementation, most of the patients had restrictive problem by their lung function. 8 patients were mild, 5 patients were moderate, and 2 patients had severe restrictive problem. Obstructive lung problem was seen in 5 patients, 4 of 5 were mild obstructive. Only 3 patients had normal lung function. After 2-months Vitamin D supplementation, almost all patients were only categorized as Normal, Mild restrictive, and Moderate restrictive lung problem. They were 7 patients, 7 patients, and 6 patients respectively. We didn’t find any severe restrictive lung problem left. Mild obstructive lung problem reduced drastically from 4 patients to one patient after vitamin D supplementation.

Using A Wilcoxon Signed-Ranks test, we found a significant change in the proportion of lung function in long-covid patients. The result indicated that lung function after vitamin D supplementation has a more ratio of normal lung function and less severe lung function than before vitamin D supplementation ( $Z = -2.3$ ,  $p = 0.020$ ).

**Table 2.** Wilcoxon signed rank test results

	Negative ranks			Positive ranks			Test statistics		
	n	Mean rank	Sum of ranks	n	Mean rank	Sums of ranks	Ties	Z	p
(After)-(Before)	6	3.50	21.00	0	.00	.00	14	-2.333 <sup>a</sup>	.020*

\*Indicates statistically significant chance ( $p < 0.05$ )

<sup>a</sup>Based on positive ranks

#### 4. DISCUSSION

In recent studies, there have been several factors associated with evidence of progression to pulmonary fibrosis in COVID-19 patients. These include older age, profound dyspnea and/or higher respiratory rate, comorbid hypertension (HTN), and admission to the intensive care unit [2]. Other study found Long COVID was more likely with increasing age and body mass index and female sex. Experiencing more than five symptoms during the first week of illness was associated with long COVID (odds ratio = 3.53 (2.76-4.50)) [3]. This majority population of this study was women, especially the elderly. This may be explained by a study regarding antibody testing which been reported that antibody levels decrease with time, and males are likely to retain antibodies longer than females [3]. These results may be relevant to other study results with a larger number of respondents [4- 6].

Covid-19 Patients who have been more severely ill had more severe impaired pulmonary diffusion capacities and abnormal chest radiographic imaging manifestations [7] and also in patients with a smoking history and previous pulmonary tuberculosis patients.

Majority of our patients had low concentration of serum vitamin D. Their average value was only 17.86 ng/mL. Although Indonesia is one of the countries which has plentiful sunshine, many reports showed Indonesian people have low serum vitamin D. Report from [13] shows 156 women from North Sumatra, 95% of them were in the vitamin D deficient-insufficient category, with the remaining 5% was categorized as sufficient group. Their mean value of serum vitamin D was 17.71 ng/mL [1]. Another report from [14] shows same results, which also 95% of 60 adult man from Yogyakarta experienced deficient-insufficient status of serum Vitamin D [2]. Their reports support our findings.

Many factors contribute to low level of serum vitamin D from Indonesian people. Increased skin pigmentation, older age, the sun protection behaviors such as sunscreen usage or wear most part of their body with clothes (especially hijab by Islamic Women), low physical activity, and indoor jobs are many factors which play a part in Indonesian low level of serum vitamin D [1], [3]. This case will increase risk of several diseases such as osteoporosis and bone fracture, colorectal cancer, cardiovascular disease, autoimmune disease, tuberculosis, and recently, COVID-19 and Long COVID [4- 6].

Another explanation of low vitamin D status in our patient may be caused by COVID-19 itself. [19] in their multicenter study, explained COVID-19 caused alteration of serum vitamin D in high proportion of patients [7]. In line with our result, a study from [20] showed 84% of 219 post COVID-19 patients had deficient

vitamin D level and 11.4% had insufficient level [8]. But it is not possible for our study to determine whether it is cause or effect for low level vitamin D because we just measure it once.

We observed fatigue and shortness of breath or dyspnea as our patients' main symptoms. Fatigue and shortness of breath were several symptoms which were reported for most long COVID cases globally. In general, fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnea (21%), anxiety (27%), chest pain, and arthralgia (18%) were initial symptoms of long COVID [9], [10]. Among the UK population, fatigue is most prevalent among long COVID patients (51%), followed by dyspnea (35%), arthralgia (25%) and concentration difficulties (25%). Meta-analysis of 36 studies identified fatigue, cognitive impairment, joint pain, anxiety, and depression as primary clinical symptoms of long COVID [10], [11].

Vitamin D has many therapeutic effects for our body. Vitamin D possibly acting as immunomodulator, modulation of cell growth, neuromuscular function, immune function, and a reduction of inflammation. In terms of COVID-19 disease, many studies showed its benefit for patient improvement. Vitamin D supplementation may reduce hospital length of stay and hospital mortality for patient with moderate and severe COVID-19 [12], [13]. Vitamin D was also found to reduce the risk of adverse outcomes and improved clinical outcomes only in patients receiving the drug post-COVID-19 diagnosis and not in those who had received vitamin D before diagnosis. Reduction of the hyper-inflammatory response which is dependent on macrophage cells in the lungs of COVID-19 cases is believed as vitamin D mechanism for immune modulator [14].

In Long COVID case, role of vitamin D is still not clear. Our study showed, after 2-months of Vitamin D supplementation, 18 of 20 patients had better condition which included improvement of symptoms and even no symptoms left. Vitamin D as antifibrotic is one kind of Vitamin D's pleiotropic effect. Its antifibrotic effect may interrupt fibrotic process which is seen in pulmonary fibrosis from long COVID patient [7]. Renin, enzyme which converts angiotensinogen to angiotensin I (Angiotensin II precursor) is inhibited by vitamin D. It results RAS pathway inhibition for migration phase of fibroblast, so suppresses fibrotic phase of lung [16]. Although, we didn't find many studies about how vitamin D used for long COVID patient and its role for symptoms improvement.

Majority of our patient before vitamin D supplementation had restrictive lung function, ranging from mild to severe. It contributed for 75% (15) of cases, and mild restrictive lung function had highest proportion for 8 cases. [28] from their systematic review and meta-analysis reported 15% of 380 patients had restrictive pattern of lung function, stand for second after altered diffusion capacity of the lungs for carbon monoxide (DLCO) but higher than obstructive pattern [17]. Another study from [29] showed 22 of 41 patients (54%) after recovery from COVID-19, had decreased FVC ( $FVC=78.4\pm 14\%$ ). The change in FVC was mild in 18 (44%), moderate in 3 (7.3%), and severe in 1 (2.4%) of the 41 patients [18]. Different finding from [30] where obstructive defect had little higher percentage, which was 9.2% of abnormal spirometry compared to restrictive defect which was 8% of percentage [18]. Lung function abnormality was usually found from patients after recovery from COVID-19. This include reduce of DLCO, Total Lung Capacity (TLC), Forced Vital Capacity (FVC), 6-minute walk tests, and exercise-induced oxygen saturation [19- 21]. Restrictive defect which is represented by low FVC mostly because residual lung fibrosis from COVID-19. Abnormalities in the bronchi such as necrotizing bronchiolitis and focal or bronchiolar inflammation could explain the small airway obstruction and result obstructive defect in long COVID patient [19], [20], [22], [23].

We observed patient's lung function by spirometry after 2-months of vitamin D supplementation, and we

found an increase in normal lung function patient from 3 patients to 7 patients, and there were no severe restrictive and moderate obstructive left. Mild obstructive patients were decline from 4 patients to one patient. Lung function improvement from vitamin D supplementation can be explained by vitamin D's function as antifibrotic and anti-inflammatory properties. Vitamin D plays its role as antifibrotic through a negative regulation of the renin-angiotensin system (RAS) and the inhibition of nuclear factor kappa B (NF- $\kappa$ B) and wnt/ $\beta$ -catenin [24]. Modulating the immune system through upregulation of several complex proteins and inducing the expression of defense peptides such as cathelicidin and  $\beta$ -defensins is known as a mechanism of anti-inflammatory from Vitamin D [25].

We acknowledge several limitations of our study, which are small sample size and not having control sample so we couldn't compare precisely for effect of vitamin D.

## 5. CONCLUSION

Vitamin D supplementation for long COVID may have benefit for symptoms and lung function improvement.

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