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Review

# Effectiveness of vitamin D-based therapy in reducing clinical impact of Covid-19 patients: A systematic review

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## Abstract

Cases of the COVID-19 pandemic have spread throughout the world and caused a high mortality rate. This virus is self-limiting, so the healing process is related to the immune system. One of the medical therapies given to hospitalized COVID-19 patients is vitamin D-based therapy to boost the immune system against the COVID-19 virus. This paper aimed to determine the effectiveness of vitamin D-based therapy to reduce the clinical impact on COVID-19 patients. The clinical impacts observed in this systematic review were the length of hospital stay, length in the ICU stay, cure rate, severity, mortality rate, and signs of inflammation. A literature search was carried out on the Scopus, Sciencedirect, and PUBMED databases. Search articles using the keyword vitamin D therapy in COVID-19 patients. The final result of the search found 6 articles that met the specified inclusion and exclusion criteria. Vitamin D in its active form (1,25(OH)2D3) can enhance chemotaxis, phagocytic response, and production of antimicrobials such as cathelicidin from macrophages as a series of innate immune responses. Administration of vitamin D-based therapy can also reduce the severity, decrease pro-inflammatory cytokines, and mortality in COVID-19 patients. The paper shows that vitamin D-based therapy can reduce the clinical impact in COVID-19 patients.

**Keywords:** medical therapy, vitamin D, clinical impact, COVID-19.

## Background and aims

In mid-December 2019 in Wuhan-China, there were cases of pneumonia-like illness (with symptoms of fever, difficulty breathing, cough, and found invasive lesions on the lungs) caused by the coronavirus agent (2019-nCoV) [1]. From early January to mid-February 2020, the incidence of the coronavirus continued to increase to all regions in China and even to several countries around China [2, 3]. In Indonesia, the first case of COVID-19 was found on March 2, 2020, as many as two cases [4]. As of July 5, 2021, there were 2,284,084 positive cases in Indonesia, 1,928,274 recovered cases, and 60,582 deaths. Meanwhile, as of July 5, 2021, 201 countries were exposed to the COVID-19 virus with 171,296,445 confirmed cases, and 3,737,020 deaths*.

*Coronavirus* is an RNA virus with a positive single strain, has a capsule, and lacks segments [5]. This virus belongs to the order *Nidovirales*, the Coronaviridae family [5]. The structure of the coronavirus is cuboid with S protein on its surface [5]. This S protein plays a role in the attachment of the virus to the host cell [5]. This virus will enter the respiratory tract and the virus will multiply in the epithelial cells, then this double-involved virus will circulate to the lower respiratory tract. In cases of acute infection, the virus undergoes decay into the cells of the digestive tract [6].

The incubation period for the COVID-19 virus occurs for 3–7 days after exposure to the

virus until the appearance of the disease. Infection with the COVID-19 virus causes several symptoms, either mild, moderate, or severe. The most common clinical manifestations are fever (body temperature >38°C), cough, and difficulty breathing. While the accompanying symptoms are fatigue, muscle aches, tightness conditions that are getting worse, and symptoms in the digestive tract which as diarrhea. Some COVID-19 patients experience shortness of breath after a week. In severe cases accompanied by the presence of ARDS disease, sepsis, metabolic acidosis, bleeding symptoms of shortness of breath can occur several days after exposure to the virus. Some patients with COVID-19 do not feel fever and some mild symptoms [6].

Currently, the Indonesian government is starting to gradually vaccinate the community. The purpose of this vaccination is to increase the immune system. This is due to the coronavirus is self-limiting, so the healing process is related to the immune system [7]. Meanwhile, in some cases of COVID-19, one of the treatments is by providing vitamin D-based medical therapy. Vitamin D is a fat-soluble vitamin that has various functions, one of which plays a role in the body's immunity. Vitamin D can improve the cellular immune system by inducing antimicrobial peptides, which consist of cathelicidin, LL-37, 1,25-dihydroxy vitamin D, and defensins, as well as increasing the secretion of hydrogen peroxide in monocyte cells [8]. Vitamin D also contains steroid molecules that are used in various body metabolisms.

Meeting the needs of vitamin D apart from supplementation can also be done by consuming sources of vitamin D and exposure to sunlight. Foods that are good sources of vitamin D include fish oil, eggs, liver, butter, fish, and fortified products derived from milk and cereals [9].

## Material and method

### Sample and research design

COVID-19 patients receiving vitamin D therapy, either in the form of supplements or other vitamin D-based medical therapies, are the sample in this systematic review. The literature review is an observational research method and aims to see the effectiveness of vitamin D in reducing the clinical impact of COVID-19 patients.

### Literature search strategy

Search articles, journals and other libraries are carried out on Scopus, Sciencedirect, and PUBMED. The literature is selected based on inclusion and exclusion criteria. The inclusion criteria that have been determined are journals published in 2020-2021; subjects used by COVID-19 patients; speak English and/or Indonesian; is original research with an observational research design; research themes related to vitamin D therapy in COVID-19 patients. While the exclusion criteria are research results published only in abstracts and cannot be accessed in full text, and research on experimental animals (Table 1).

The literature selection process is plotted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. The literature used in the review was critically appraised independently by the two authors using the Oxford Center for Evidence-Based Medicine Critical Appraisal tool. Risk bias was assessed independently by the two authors using the Cochrane Risk of Bias Tool which was classified into low (low), high (high), and unclear (unclear) risk.

Based on the results of an article search using the keyword "vitamin D therapy in COVID-19 patients", 19, 1,083, and 8 articles were found on Scopus, Sciencedirect, and Pubmed. A total of 298 articles on Sciencedirect are research articles. Meanwhile, 8 articles in Pubmed are research articles with the type of clinical research articles. And found 12 articles on Scopus which are research articles. The final result of the search found 6 articles that met the specified inclusion and exclusion criteria (Figure 1).

## Result

Based on the article search study, 6 articles were found that matched the specified inclusion and exclusion criteria. The six articles are


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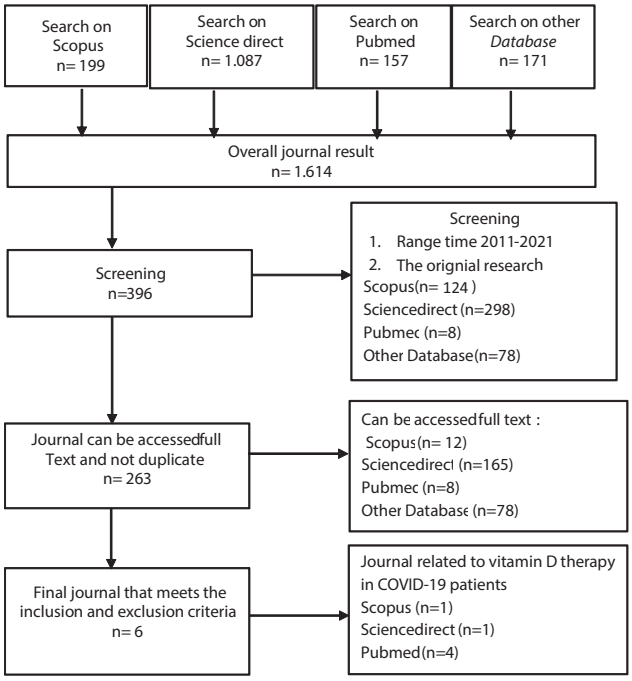


Figure 1. Journal search chart.

observational studies with research designs which include 3 articles with randomized control trial research designs, 2 quasi-experimental articles, and 1 cohort article. Research respondents from the six articles were patients who were hospitalized with a diagnosis of COVID-19, either showing mild symptoms, severe symptoms, or those being treated in the ICU. The outcomes of the six articles are various clinical impacts that occur in COVID-19 patients, which include the length of treatment, severity, mortality, recovery, and signs of inflammation. The six articles have different doses regarding the administration of vitamin D therapy in COVID-19 patients. Based on the six included research articles,

Based on Figures 2 and 3, it can be seen that in general, the 6 articles have a low to high risk of bias. In the fifth article the risk of bias is included the high category related to research outcomes, and blinding of participants.

## Discussion

Based on 6 research articles, 5 articles stated that there was a significant relationship between the administration of vitamin D-based therapy and depression the clinical impact of COVID-19 patients. The clinical impact observed in the six articles included were the length of hospital stay, ICU stay, cure rate, severity, mortality, and signs of inflammation.

Vitamin D is a fat-soluble vitamin, the need for vitamin D in the body can be met through three ways, namely supplementation, exposure to sunlight, and consumption of food sources of vitamin D (such as milk, egg yolks, mushrooms, and others). Vitamin D functions in bone health and strength, in addition, vitamin D also plays a role in the immune system. The regulation of vitamin D in the immune system involves dendritic cells. Dendritic cells are found in the bone marrow and are precursors of monocytes in the blood [16]. Vitamin D in its active form (1,25(OH)2D3) can enhance chemotaxis, phagocytic response, and production of antimicrobials such as cathelicidin from macrophages as a series of innate immune responses [16]. Vitamin D metabolism requires fat as a solvent [17]. In the liver, vitamin D that is bound in fat is converted to 25-OHD, and in the kidneys, it will be converted into the active form, namely 1,25 (OH)2D3 with the help of the 1 hydroxylase enzyme which is excreted by macrophages [17]. 1,25 (OH)2D3 then enters the cell nucleus with the help of a receptor called RVD (Vitamin D Receptor), in the nucleus 1,25 (OH)2D3 plays a role in the formation of mRNA which will later form protein [18]. These proteins are divided into two types, namely B-defensins and cathelicidins. Cathelicidins protein increases vascular permeability so that more macrophages are released to kill the virus. Macrophages will then release MHC II which then expresses the antigen, the antigen will then bind to naive T cells (Tho cells). The bond between MHC II, antigen, and naive T cells is called CD 4. Tho cells with IL-4 rocks will form Th2 cells, then with the help of vitamin D, IL-4, and IL-5 Th2 cells are converted into B cells which then change Once again become a plasma cell, this plasma cell plays a role in increasing the phagocytic function of macrophages [18]. On the other hand, Tho cells will form Th1 cells with the help of IL-12. Th1 cells will secrete IFN which stimulates the release of pro-inflammatory cytokines such as IL-1, IFN, IL-6, IL-8, and CXCL [18]. Th1 cell formation can be inhibited by

Table 1: Literature review matriculation.

| Title | Author, Year | Research design | Sample | Dose | Research result |
|---|---|---|---|---|---|
| Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: A randomized clinical trial [10] | Murai et al., 2021 | Randomized control trial | The number of samples was 240 COVID-19 patients with treatment group (n=120) and control group (n=120) | 200,000 IU during treatment | Giving vitamin D3 supplements to COVID-19 patients did not significantly reduce the length of stay in the hospital (p-value=0.59; HR=0.62) |
| Vitamin D supplementation associated to better survival in hospitalized Frail elderly COVID-19 Patients: The GERIA-COVID Quasi-experimental study [11] | G. Annweiler et al., 2020 | Quasi experimental | The total sample of 77 COVID-19 patients was divided into 3 groups: group 1 (supplementation in the previous year) (n=29), group 2 (supplementation after being diagnosed) (n=16), and group 3 (no supplementation) (n=32) | 80,000 IU | There is a relationship between vitamin D supplementation and the severity of COVID-19 (p value=0.047 for group 1 and group 3), the highest percentage of recovered patients was in group 1 (93.1%) |
| Vitamin D and survival in COVID-19 patients: A quasi-experimental study [12] | C. Annweiler et al., 2020 | Quasi experimental | The number of samples was 66 COVID-19 patients with the treatment group (n=57) and the control group (n=9) | 80,000 IU/2-3 months | There is a relationship between vitamin D supplementation and healing of COVID-19 (p-value=0.023; HR=0.11), the highest percentage of recovered patients in the treatment group (82.5%) |
| Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study [13] | Entrenas Castillo et al., 2020 | Parallel pilot randomized | Total sample of 76 COVID-19 patients with treatment group (n=50) and control group (n=26) | 0.532 mg on the first day, and 0.266 on days 3 and 7. | There is a relationship between giving treatment and care in the ICU (p value p≤0.001, and OR=0.02), the percentage of patients treated in the ICU is the smallest in the treatment group (2%) |
| Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease [14] | Lakkireddy et al., 2021 | *Randomized prospective* | The number of samples was 87 COVID-19 patients with the treatment group (n=44) and the control group (n=43) | 60,000 IU/day (duration of administration depends on BMI value, BMI = 18-25 given 8 days; BMI = >25 given 10 days) | There was no difference in length of treatment (p value=0.9), in the treatment group, the therapy gave an impact on reducing inflammation (p value≤0.0001 for CRP; <0.0001 for LDH; <0.0001 for IL -6; 0.0004 for ferritin; and 0.0003 for neutrophils/lymphocytes) |
| **Calcifediol treatment and hospital mortality due to COVID-19: A cohort study [15]** | Alcala-Diaz et al., 2021 | Cohort | The number of samples was 537 COVID-19 patients with the treatment group (n=79) and the control group (n=458) | 0.266 mg/capsule (2 capsules on day 1; and 1 capsule on days 3,7,14,21, and 28) | The mortality rate in the treatment group was lower (5%) with an odd ratio (OR) of 0.22 |

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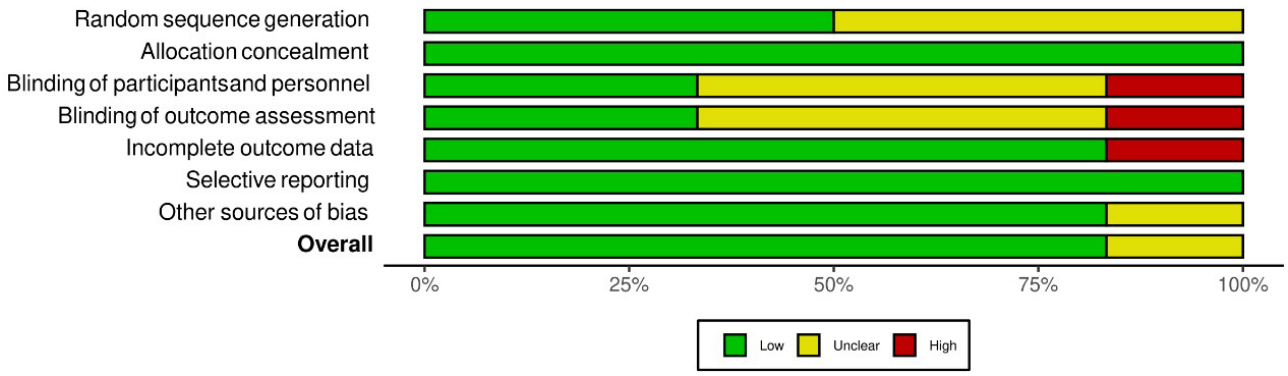


Figure 2: Risk of bias graph from the included literature study.

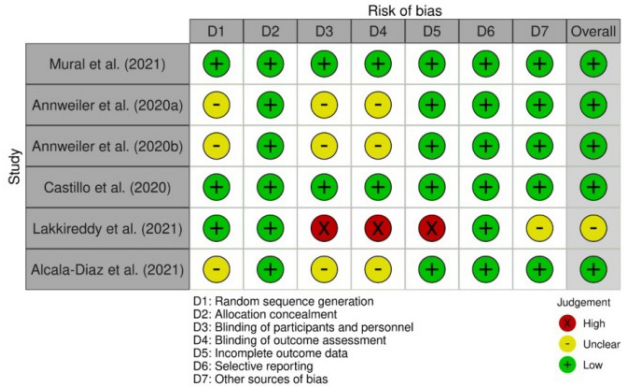


Figure 3: Table of risk of bias from the included literature study.

vitamin D and IL-10 released by Th2. Cells [18]. In a meta-analysis study, it was stated that IL-6 is an outcome of COVID-19, the value of IL-6 is three times higher in patients with severe symptoms and is associated with mortality [19].

Based on research, it was found that vitamin D deficiency was most commonly found in COVID-19 patients with severe symptoms or those being treated in the ICU [20–23]. Identification of vitamin D deficiency can be done by measuring serum levels of 25-(OH)D, this serum level is a reflection of the skin's production of vitamin D3 and vitamin D (D2 and D3) from food. Due to the longer half-life of 25-(OH)D than 1.25(OH)2D, 25-(OH)D is more recommended as an indicator of vitamin D deficiency. The half-life of 25-(OH)D is 3–4 weeks, whereas 1,25(OH)2D is only 4–6 hours. In addition, when vitamin D deficiency occurs, serum levels of 1,25(OH)2D increase due to an increase in compensatory parathyroid hormone, the thyroid hormone then stimulates the kidneys to secrete 1,25(OH)2D [24].

Decreased serum 25-(OH)D levels are associated with increased signs of inflammation, namely increased cytokine secretion as a manifestation of the presence of the COVID-19 virus. The cytokine that has an important role, in this case, is IL-6. IL-6 is produced by immune cells (such as B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, and mast cells) [14, 25]. Based on the study, it was found that COVID-19 patients with serum levels of 25-(OH)D>20 ng/ml had lower serum IL-6 levels than patients with serum levels of 25-(OH)D<20 ng/m [14, 23].

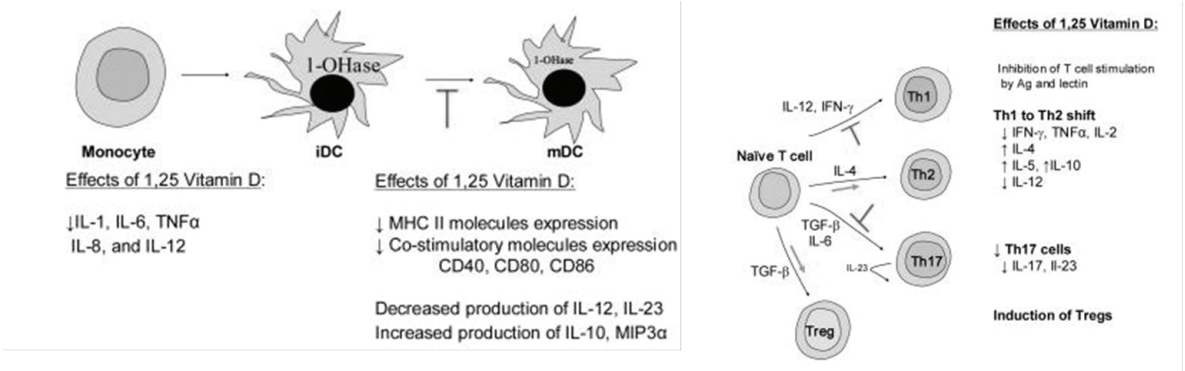


Figure 3: The figure of the role of 1.25 vitamin D A. The role of 1.25 vitamin D in monocytes and dendritic cells. B. The role of 1.25 vitamin D in the formation of helper T cells [18].

## Conclusion

Administration of vitamin D-based medical therapy which includes vitamin D supplementation and administration of calcifediol (25-hydroxyvitamin D) therapy can reduce the clinical impact in COVID-19 patients. This medical therapy aims to increase serum vitamin D levels, if the serum vitamin D value is in the normal category, it can reduce signs of inflammation, especially IL-6.

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