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# VITAMIN D SUPPLEMENTATION AND COVID-19 OUTCOMES : A SYSTEMATIC REVIEW

**Stephanie Talilah***

**Faculty of Medicine, Indonesian Christian University, Email id: stephytalilah@yahoo.co.id*

***Corresponding Author:**
*stephytalilah@yahoo.co.id*

## Abstract

*The COVID-19 infection is a pandemic that is still continuing strong and is marked by significant morbidity and fatality rates. It is imperative that clinical and biological predictors of severity and mortality associated with COVID-19 infection be identified as quickly as possible in order to make efficient use of the resources that are available. The development of efficient vaccinations and therapeutic compounds is currently the primary focus of research efforts; however, many industry professionals stress the need of enhancing one's immune system through a variety of nutritional approaches. A study investigation into the numerous treatment options available for COVID-19 infection has led them to lay an increased emphasis on the function of micronutrients as supplementary and supportive components of therapy regimens. According to a number of studies, higher levels of vitamin D in the body or taking vitamin D supplements is connected with a lower risk of dying. Those who took vitamin D supplements had a longer life expectancy, despite the fact that the levels of vitamin D in their bodies were not evaluated after receiving the supplementation in several of the trials.*

**Keyword:** *COVID-19; Mortality; Vitamin D*

## INTRODUCTION

The World Health Organization (WHO) has declared the 2019–20 coronavirus outbreak a Public Health Emergency of International Concern (PHEIC). Evidence of local disease transmission was found in multiple countries across all six WHO regions as of 7 March 2020.[1] COVID-19 infection is an ongoing pandemic characterized by high morbidity and mortality. There is an urgent need to identify clinical and biological predictors of severity and mortality associated with COVID-19 infection for judicious use of limited resources.[2]

There have been more than 16 million cases of COVID-19 and more than 500,000 cases of death related to COVID-19 reported worldwide. The rate of new infections appears to be exceeding the scale of public health preparedness and response, especially in countries with limited economic capabilities. The strategy for handling COVID-19 implemented by South Korea, Taiwan and Singapore can be emulated even though it is a challenge for many countries.[3]

Current research is focused on developing effective vaccines and therapeutic agents, but many experts emphasize the importance of boosting the immune system through various nutritional interventions. Zhang and Liu researching various treatment options for COVID-19 infection has placed increasing focus on the role of micronutrients as supporting and complementary components of treatment regimens.[4]

Grant recommends intake of vitamin D3 at 10,000 IU/day for several weeks followed by 5,000 IU/day until serum 25(OH)D concentrations reach 100-150 nmol/L as a precaution against COVID-19 in people at risk. There is existing evidence for the potential role of enhanced nutrition for augmenting the immune system. Vitamins A, B complex, C, D and E and many trace elements, such as iron, zinc, selenium, magnesium and copper, deficiencies of these micronutrients can impair immune function in viral infections. Compliance with dietary micronutrients has been reported as a way to enhance or optimize immune function against viral infections.[5,6]

Vitamin D is known to play a key role in the maintenance of bone health and the calcium–phosphorus metabolism; however, many other functions of this vitamin have recently been postulated. One of these functions is the modulation of the immune response in infectious diseases as well as autoimmune diseases. There are fat-soluble secosteroids in vitamin D, and these secosteroids are responsible for a wide range of immunomodulatory, anti-inflammatory, anti-fibrotic, and anti-oxidant activities.[7,8]

Vitamin D3 (also known as cholecalciferol) and vitamin D2 (also known as ergocalciferol) are the most common forms of vitamin D found in humans. The vitamin D2 subtype is turned into 25-hydroxyergocalciferol when it is processed by the liver, while vitamin D3 is converted into calcifediol (25-hydroxycholecalciferol). 25-hydroxyvitamin D, often known as 25(OH)D, is the primary metabolite of these two forms of vitamin D. Its concentration in serum can be analyzed to determine an individual's vitamin D status.[9,10]
This article investigate the association between vitamin D supplementation and COVID-19 outcomes.

## METHODS

### Protocol

The standards outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist were adhered to throughout the course of this systematic review. These guidelines served as the basis for the regulations that governed the procedures to be followed in the course of this systematic evaluation.

### Eligibility Criteria

This systematic review was developed to analyze papers on "vitamin D supplementation" and "COVID-19 outcomes". These are the topics that were discussed at length in the research that was taken into consideration, and they are included below. In order for your work to be taken into consideration, the following criteria need to be satisfied: 1) All articles must be written in the English language. 2) The articles must have been published after the year 2020 but before to the creation of this systematic review.
Textual contributions of the following varieties will under no circumstances be considered for inclusion in the anthology: 1) Editorial letters, 2) contributions that do not have a Digital Object Identifier (DOI), and 3) article reviews and submissions that are comparable to those that have previously been published in the journal. Article reviews and submissions that are comparable to those that have previously been published in the journal.

### Search Strategy

The search for studies to be included in the systematic review was carried out from November 30th, 2022 using the PubMed and SagePub databases by inputting the words: "vitamin D supplementation" and "COVID-19 outcomes". Where *("vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR*

*"sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("outcome"[All Fields] OR "outcomes"[All Fields])* is used as search keywords.

**Data retrieval**

After completing a literature analysis and reviewing the titles and abstracts of previously published research, the author of the study altered the criteria for what should and should not be included in the study. After reviewing previously published studies, the author made these adjustments. During the compilation of the systematic review, only those research projects that met each and every criterion were taken into account. This was done to guarantee that the review is as comprehensive as possible. It is possible to collect information about each individual study, including its title, author, publication date, study location of origin, research design, and research variables. This information can be provided in a variety of distinct formats.

**Quality Assessment and Data Synthesis**

The writers did their own independent reviews of a selection of the research listed in the titles and abstracts of the papers in order to decide which studies could be appropriate for consideration. After this step, the full texts of the studies that meet the criteria for inclusion in the systematic review will be read in order to determine which studies can be utilized as final inclusions for the purpose of the review. This will be done so that the question, "Which studies can we use for the review?" can be answered.

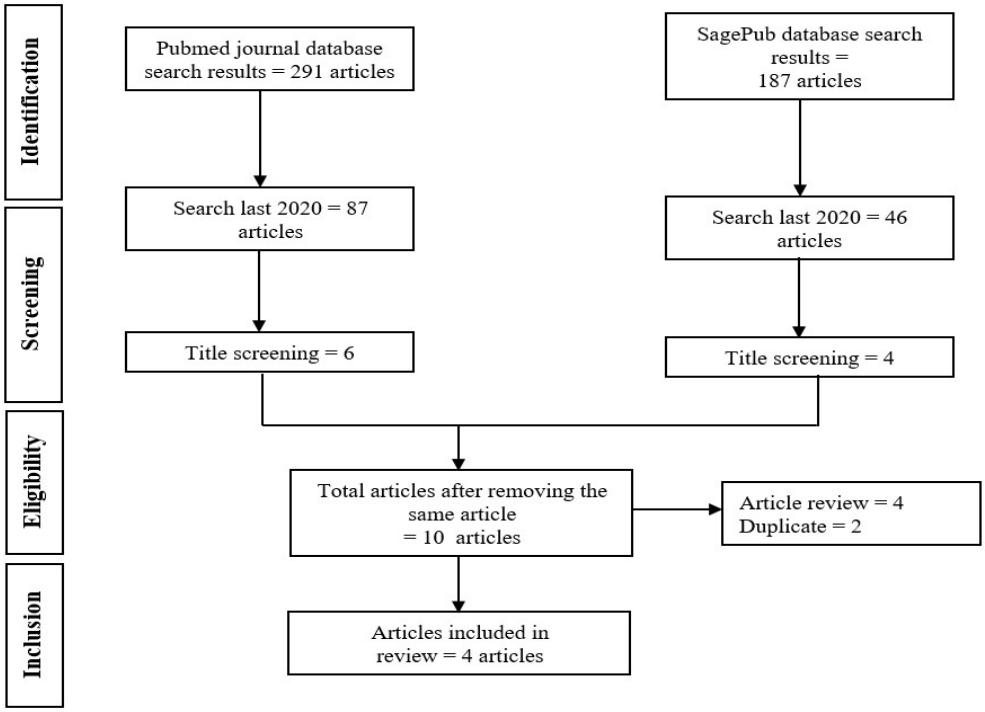


**Figure 1. Article search flowchart**

**RESULT**

Rastogi et al (2022) showed both the intervention group and the control group had serum 25(OH)D levels that ranged from 8.6 (7.1 to 13.1) and 9.54 (8.1 to 12.5) ng/ml (p = 0.730), respectively, at the beginning of the study. 10 out of 16 patients were able to attain 25(OH)D>50 ng/ml by day seven, and another two patients were able to do so by day fourteen [day-14]. 25(OH)D levels in the intervention group were 51.7 (48.9 to 59.5) ng/ml, while the control group's 25(OH)D levels were 15.2 (12.7 to 19.5) ng/ml (p <0.001). 10 participants (62.5%) in the intervention group and 5 participants (20.8%) in the control arm became SARS-CoV-2 RNA negative (p = 0.018). In contrast to other inflammatory indicators, fibrinogen levels significantly decreased after taking cholecalciferol (intergroup difference 0.70 ng/ml; P = 0.007).[11]

Castillo et al (2020) study showed one of the fifty patients who were treated with calcifediol needed to be admitted to ICU (2%), while thirteen of the twenty-six patients who were not treated needed to be admitted (50%) p value $X^2$ Fischer test p <0.001. When comparing patients who received Calcifediol medication to those who did not, the univariate risk estimate odds ratio for ICU admission was 0.02 (95% CI = 0.002-0.17). Patients who received calcifediol treatment had a multivariate risk estimate odds ratio for ICU admission of 0.03 (95% CI = 0.003-0.25), whereas patients who did not get calcifediol treatment had a 0.25 (95% CI) odds ratio for ICU admission. Two of the patients who were admitted to the intensive care unit passed away, while the other 11 were eventually released.[12]

The three groups (n = 77; mean ± SD = 88 ± 5 years; 49% women) were similar at baseline (except for woman proportion, p = 0.02), as were the treatments used for COVID-19. In Group 1 (n = 29) = 93.1% of COVID-19 participants survived at day 14, compared to 81.2% survivors in Group 2 (n = 16) (p = 0.33) and 68.7% survivors in Group 3 (n = 32) (p = 0.02). While considering Group 3 as reference (hazard ratio (HR) = 1), the fully-adjusted HR for 14-day mortality was HR = 0.07 (p = 0.017) for Group 1 and HR = 0.37 (p = 0.28) for Group 2. Group 1 had longer survival time than Group 3 (log-rank p = 0.015), although there was no difference between Groups 2 and 3 (log-rank p = 0.32). Group 1, but not Group 2 (p = 0.40), was associated with lower risk of OSCI score ≥5 compared to Group 3 (odds ratio = 0.08, p = 0.03).[13] Vitamin D can reduce the associated risk of COVID-19 infection, which is the focus of this study. In the population of US veterans, we show that Vitamin D2 and D3 fills were associated with reductions in COVID-19 infection of 28% and 20%, respectively [(D3 Hazard Ratio (HR) = 0.80, [95% CI 0.77, 0.83]), D2 HR = 0.72, [95% CI 0.65, 0.79]]. Mortality within 30-days of COVID-19 infection was similarly 33% lower with Vitamin D3 and 25% lower with D2 (D3 HR = 0.67, [95% CI 0.59, 0.75]; D2 HR = 0.75, [95% CI 0.55, 1.04]).[14]

**Table 1.** The litelature include in this study

| Author | Origin | Method | Sample Size / Characteristic | Dose of Vitamin D | Result |
|---|---|---|---|---|---|
| Rastogi, 2022[11] | India | Randomised, placebo-controlled | Forty SARS-CoV-2 RNA positive individuals were randomised to intervention (n=16) or control (n=24) group | Participants were randomised to receive daily 60 000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH)D>50 ng/ml (intervention group) or placebo (control group). | In the intervention and control groups, baseline serum 25(OH)D was 8.6 (7.1 to 13.1) and 9.54 (8.1 to 12.5) ng/ml (p=0.730). 10 of 16 patients reached 25(OH)D>50 ng/ml by day-7 and two by day-14 [day-14]. 25(OH)D levels were 51.7 (48.9 to 59.5) ng/ml in intervention and 15.2 (12.7 to 19.5) in control (p<0.001). 10 (62.5%) intervention participants and 5 (20.8%) control participants (p<0.018) became SARS-CoV-2 RNA negative. Unlike other inflammatory indicators, cholecalciferol supplementation lowered fibrinogen (intergroup difference 0.70 ng/ml; P=0.007). |
| Castillo, 2020[12] | Spain | Parallel pilot randomized open label, double-masked clinical trial | 76 consecutive patients hospitalized with COVID-19 infection | Eligible patients were allocated at a 2 calcifediol:1 no calcifediol ratio through electronic randomization on the day of admission to take oral calcifediol (0.532 mg), or not. Patients in the calcifediol treatment group continued with oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission. | Of 50 patients treated with calcifediol, one required admission to the ICU (2%), while of 26 untreated patients, 13 required admission (50%) p value $X^2$ Fischer test p <0.001. Univariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment versus without Calcifediol treatment: 0.02 (95% CI = 0.002−0.17). Multivariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment ICU (adjusting by Hypertension and T2DM): 0.03 (95% CI = 0.003-0.25). Of the patients treated with calcifediol, none died, and all were discharged, without complications. The 13 patients not treated with calcifediol, who were not admitted to the ICU, were discharged. Of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged. |
| Annweiler, 2020[13] | France | Quasi-experimental study | Seventeen participants experienced severe COVID-19 | "Group 1" : 50,000 IU Vit D3/month, 80,000 IU or 100,000 IU every 2–3 months. "Group 2" with Vit D 80,000 IU. "Group 3" was not received vitamin D | The three groups (n = 77; mean SD = 88 5 years; 49% women) and COVID-19 treatments were similar at baseline (except for women, p = 0.02). Group 1 (n = 29) COVID-19 participants survived at day 14, compared to 81.2% in Group 2 (n = 16) (p = 0.33) and 68.7% in Group 3 (n = 32) (p = 0.02). Using Group 3 as a reference (HR = 1), Group 1's fully-adjusted HR for 14-day mortality was 0.07 (p = 0.017) and Group 2's was 0.37 (p = 0.28). Group 1 survived longer than Group 3 (log-rank p = 0.015), whereas Groups 2 and 3 did not vary (log-rank p = 0.32). Group 1 had a decreased risk of OSCI 5 than Group 3 (OR = 0.08, p = 0.03), but not Group 2 (p = 0.40). |
| Gibbons, 2022[14] | United State | Retrospective cohort study | 34,710 supplemented with vitamin D2, and 407,860 untreated patients | Dosage options included 20 IU, 40 IU, 100 IU, 125 IU, 200 IU, 250 IU, 400 IU, 500 IU, 800 IU, 1000 IU, 2000 IU, 5000 IU, 8000 IU, and 50,000 IU. | Vitamin D2 and D3 fills were associated with reductions in COVID-19 infection of 28% and 20%, respectively [(D3 Hazard Ratio (HR) = 0.80, [95% CI 0.77, 0.83]), D2 HR = 0.72, [95% CI 0.65, 0.79]]. Mortality within 30-days of COVID-19 infection was similarly 33% lower with Vitamin D3 and 25% lower with D2 (D3 HR = 0.67, [95% CI 0.59, 0.75]; D2 HR = 0.75, [95% CI 0.55, 1.04]). |

## DISCUSSION

In this first cholecalciferol intervention study for SARS-CoV-2 positive individuals who were asymptomatic or mildly symptomatic, we found that a greater proportion of patients could attain SARS CoV-2 RNA negativity on high-dose vitamin D supplementation at 25(OH)D >50 ng/ml compared to vitamin D-deficient individuals. This was due to the fact that these patients had higher levels of vitamin D in their blood. Because achieving SARS-CoV-2 negativity in greater proportions is likely to be beneficial, the most recent recommendations made by the CDC and other regulatory bodies, including the ICMR, do not mandate repeat SARS CoV-2 RNA testing to document SARS CoV-2 negative before discharge of asymptomatic individuals.[11]

Vitamin D receptors affect monocytes, macrophages, T and B lymphocytes, and other immune cells. The 25(OH)D-1α-hydroxylase available on these cells converts 25-hydroxyvitamin D [25(OH)D] to its active form, 1,25-dihydroxyvitamin D. Vitamin D status is correlated with several autoimmune and inflammatory diseases. Vitamin D has the ability to promote monocyte differentiation into macrophages.[15] Respiratory tract infections can exacerbate chronic diseases leading to an increased risk of death. Vitamin D may act through several mechanisms to reduce the risk of respiratory infections, including pneumonia.[16]

This finding is supported by Zhou's findings showing that vitamin D deficiency is associated with an increased risk of pneumonia. A meta-analysis showed that vitamin D supplementation was safe and protected against acute respiratory infections and most beneficial in patients with vitamin D deficiency per week to non-critical COVID-19 patients with serum 25-hydroxycholecalciferol levels of 20-30 ng/respectively mL or ≤ 20 ng/mL.[15] Grant et al suggest administering 10,000 IU of vitamin D3 per day to prevent infection among individuals at risk of developing influenza or COVID-19. Pregnant women who are undergoing a quarantine system and experiencing decreased exposure to sunlight can be given vitamin D in low doses or amounts, so taking vitamin D supplements together with eating nutritious food is also necessary.[16]

There have been prior studies conducted on the immunomodulatory effect of vitamin D in bacterial as well as viral infections; however, these studies did not include SARS-CoV-2 infection. Vitamin D affects the expression of a number of genes that are involved in the immune system (innate immunity, adaptive immunity), as well as the downstream inflammatory cascade. As a result, vitamin D can have an effect on how susceptible a person is to bacterial and viral infections, as well as how severe those infections are.[17,18] Vitamin D can increase the production of the antimicrobial peptide cathelicidin (LL-37) in neutrophils, natural killer cells, and monocytes, which results in a lower level of the herpes simplex virus.[19,20]

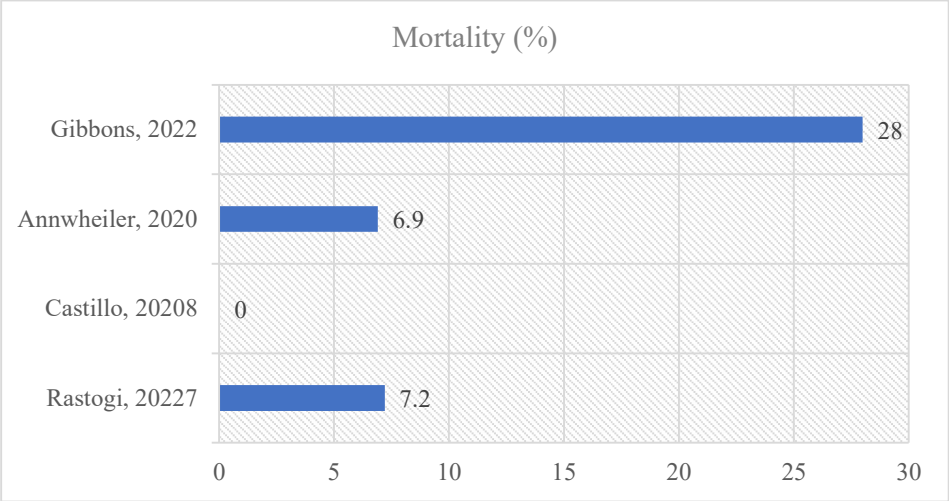


**Figure 2.** Mortality patient with supplementation Vit D

Vitamin D supplementation was found to reduce the incidence of acute respiratory tract infections in a recent meta-analysis of intervention trials [incidence rate ratio 0.96 (0.92–0.997), p=0.04]. In the same manner, vitamin D deficiency during a SARS-CoV-2 infection may lead to a pro-inflammatory cytokine milieu, which in turn may exacerbate the severity of the disease. There is evidence that the SARS CoV-2 strain can attach to the ubiquitously expressed ACE-2 (ACE-2) receptor on the cell surface and then proceed to ingress inside the cell. Vitamin D may inhibit the production of ACE-2, so preventing viruses from entering cells and causing infection.[10,21,22]

In addition, in order to treat vitamin D insufficiency in critically ill patients. It is possible that taking vitamin D supplements could either reduce the risk of getting SARS-CoV-2 or hasten the process by which the virus is eliminated from the body. It has been discovered that having vitamin D levels more than 30 ng/ml is connected with a sizeable reduction in the severity of SARS-CoV-2 infections as well as the risk of dying from them. A study showed impact that high dosages of vitamin D supplementation had on the chance of viral clearance in those who were positive for SARS and CoV-2.[5,6]

Greater doses of vitamin D are required than what is often recommended. It's possible that calcifediol has some benefits that native vitamin D does not. It has a more consistent intestinal absorption (near to 100%), and it can swiftly restore blood concentrations of 25OHD because it does not require hepatic 25-hydroxylation. Both of these benefits are due to the fact that it does not require hepatic 25-hydroxylation. This is especially significant in clinical settings where quick restoration of serum 25OHD levels is desired and CYP2R1 expression is compromised.[23–25]

This type of CYP2R1 activity impairment has been reported in individuals who suffer from COPD or asthma, in addition to having been well documented in various animal models. In addition, calcifediol is more powerful than vitamin D3 when taken orally. In subjects with a deficient state of vitamin D, when physiological doses of vitamin D are administered (up to 25 g or 1000 IU daily), approximately 1 in 3 molecules of vitamin D appear as 25OHD. When pharmacological doses of vitamin D/25OHD are used, the efficacy of conversion is lower (about 1 in 10 molecules).[23,24]

## CONCLUSION

According to a number of studies, higher levels of vitamin D in the body or taking vitamin D supplements is connected with a lower risk of dying. Those who took vitamin D supplements had a longer life expectancy, despite the fact that the levels of vitamin D in their bodies were not evaluated after receiving the supplementation in several of the trials.

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