

Meta-Analysis

OPTIMAL DOSE OF VITAMIN D FOR COVID-19 TREATMENT

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ABSTRACT

This meta-analysis aimed to determine whether there is any optimal dose of vitamin D for morbidity, length of hospitalization, and mortality in patients with COVID-19. We conducted a comprehensive search in three online databases for eligible studies until February 28, 2022. Odds ratio (OR) and standardized mean difference (SMD) were applied as summary statistics of primary outcomes. The study quality of the literatures collected was assessed using the Cochrane risk of bias tool version 2 (RoB 2). Eight randomized clinical trials (RCT) were included in the study. In our analysis, we found that there was no significant difference in morbidity when vitamin D was administered to COVID-19 patients [OR=0.50 (95% CI=0.13-1.96); SMD=-0.14 (95% CI=-0.55-0.28)]. Duration of hospitalization [SMD=-0.12 (95% CI=-0.39-0.15)] and mortality [OR 0.47 (95% CI=0.19-1.17)] of COVID-19 patients in five studies also showed no significant difference compared to patients who did not take vitamin D. However, when we analyzed two other studies, we found that in patients who did not take vitamin D, mortality was lower [SMD=0.43 (95% CI=0.29, 0.58)]. In conclusion, compared to a single high dose of vitamin D, the multi-day vitamin D administration of 1000-6000 IU in patients with COVID-19 resulted in improved patient morbidity, length of hospitalization, and patient mortality.

Keywords: Vitamin D therapy; COVID-19; morbidity; mortality; hospitalization; infectious disease

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Hi j i j t u

1. Vitamin D supplementations in different doses yield different outcomes.
2. Multi-day vitamin D administration of 1000-6000 IU in patients with COVID-19 has more positive impacts than a single high dose of vitamin D.
3. Patient morbidity, length of hospitalization, and patient mortality improved with multi-day vitamin D administration.

INTRODUCTION

The coronavirus (COVID-19) pandemic remains a public health concern. COVID-19 is caused by the SARS-CoV-2 virus, which belongs to the coronavirus family. This virus is highly contagious and is spreading rapidly worldwide (Rawaf et al. 2020, Centers for Disease Control and Prevention (CDC) 2022). COVID-19 has undergone many mutations and has given rise to several variants. The most recent study revealed the discovery of the most recent variant of COVID-19, the omicron variant (B.1.1.529), which was first identified in early November of 2021 in Botswana (Gao et al. 2022).

As research on COVID-19 progresses, many treatments are now available to treat COVID-19 that

have been approved by the Food and Drug Administration (FDA), ranging from antiviral drugs, monoclonal antibodies against SARS-CoV-2, anti-inflammatory drugs, and immune-modulating drugs (Cascella et al. 2022). As with other viral diseases, COVID-19 treatment remains primarily supportive care to correct the patient's condition, as there is no definitive treatment for COVID-19 that is highly effective (Stasi et al. 2020). Based on Sutadji JC et al. (2021), 10 of the 12 available studies found lower mortality when using anti-IL-6 therapy compared with standard care, although lower mortality in patients. Larger randomized controlled trials were needed to clarify the efficacy of anti-IL-6 therapy in severe COVID-19. Research continues to develop optimal treatments that can increase the COVID-19 recovery rate, including the use of vitamin D in the treatment process (Sánchez-Zuno et al. 2021, Sabico et al. 2021).

Vitamin D is known to play a key role in controlling the immune system, including protection against viral infections. Vitamin D deficiency can increase the severity of influenza and respiratory infections (Grant et al. 2020). Activation of vitamin D receptors on immune cells has shown direct effect by reducing the secretion of inflammatory cytokines, such as IL-6, and indirect effect through C-reactive protein (Ohaegbulam et al. 2020). Vitamin D supplementation has been suggested as a possible way to prevent infection, severity of illness, and death from the disease (Brenner 2021). Several studies with varying outcomes have demonstrated the differences in vitamin D levels between healthy individuals and COVID-19 patients, and the impact of vitamin D deficiency on the risk of developing COVID-19 and its complications. High doses of vitamin D (200,000 IU) once were not found to significantly shorten treatment duration. Meanwhile, administration of 60,000 IU vitamin D for 8 to 10 days significantly reduced inflammatory markers associated with COVID-19 without adverse effects. Two weeks of 5,000 IU vitamin D administration has been shown to shorten recovery time from ageusia and cough in patients with mild to moderate symptoms of COVID-19. Another study found that a dose of 10,000 IU vitamin D for two weeks improved the patient's clinical condition (Murai et al. 2021a, Sánchez-Zuno et al. 2021, Sabico et al. 2021, Lakkireddy et al. 2021).

The existence of different outcomes from treatment with vitamin D leaves the debate unresolved regarding the optimal dose of vitamin D in COVID-19 patients. This study aimed to determine if there is an optimal dose of vitamin D for morbidity, duration of hospitalization, and mortality associated with COVID-19.

MATERIALS AND METHODS

This systematic review and meta-analysis were carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines in a study by (Page et al. 2021). We conducted a digital data search for relevant studies published up until February 28, 2022 in PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). These search terms were entered: ("COVID-19" OR "COVID19" OR "SARS-CoV-2" OR "SARSCoV2" OR "SARS-Cov-19" OR "SARSCoV19" OR "2019-nCoV" OR "2019nCoV" OR "nCoV-2019" OR "nCoV2019" OR "coronavirus disease 2019" OR "novel coronavirus" OR "new coronavirus") AND ("vitamin D" OR "vitamin D3" OR "vitamin D dosage" OR "vitamin D therapeutic use" OR "vitamin D therapy") AND ("morbidity*" OR "mortality*" OR "death*" OR "hospitalization*" OR "hospitalisation*" OR "severity"). No publication date restrictions were set in all searches.

After removing the duplicates, the remaining articles were filtered by reviewing their titles. Abstracts of some articles that have relevant possibilities are further filtered. Lastly, the selected articles with available full-texts were retrieved and assessed according to the eligibility requirements. Two investigators (DMU and MARA) independently accomplished the overall study selection process. Disagreements were discussed with the other investigators until consensus was reached.

We included all studies investigating the association of vitamin D administration (by any definition) with COVID-19 morbidity, length of hospitalization, and mortality in populations aged 18 years or older. Exclusion criteria were: 1) irrelevant titles or abstracts; 2) irretrievable full-texts; 3) review articles, case reports, observational studies, case series, conference abstracts, or letters to editors; 4) non-English studies; or 5) insufficient data to calculate the effect sizes for all outcomes (COVID-19 morbidity, length of hospitalization, and mortality).

Out of three authors, two (DRR, MIM) separately extracted all the data, and then the third author (HTAF) double-checked its accuracy. Discussions were used to settle disagreements. The following relevant informations were gathered for each study that included the first author, publication year, study location, study design, COVID-19 diagnosis definition, the dosage of vitamin D administration, population age, female percentage, the sample size in each group (vitamin D group vs control), and vitamin D effects on patients with COVID-19 (morbidity, length of hospitalization, and mortality).

With the Cochrane RoB tool version 2 (RoB 2), two authors (MZT and JNS) independently evaluated the methodology quality from each study. The following five domains of observational studies were evaluated: 1) the randomization method; 2) deviations from the intended interventions; 3) missing result or outcome data; 4) outcome measurement; and 5) reported result choice. The signaling questions have five possible answers: No, Probably No, Probably Yes, Yes, and No Information. A recommended risk-of-bias judgment for every domain was mapped onto responses to signaling questions using algorithms included in the program. For each domain, there were three alternative risk-of-bias assessments: 1) low risk of bias; 2) some concerns; and 3) high risk of bias. When research is deemed to have a low risk of bias across all domains, the overall risk of bias assessment is low. Some concerns are assessed if the study is determined to raise some concerns in at least one domain but not to be highly biased in any domain. High risk of bias means that there is one domain or more where the study is considered to have a high risk of bias for this research result or there are numerous domains which have some concerns that significantly reduce confidence in the result.

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All analyses were conducted using the Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Primary analyses were conducted to evaluate the association between vitamin D administration with three different outcomes related to COVID-19: morbidity, length of hospitalization, and mortality. The OR and standard mean difference were applied as the summary statistics of primary outcomes. Meta-analysis for each outcome was conducted only if there were 2 or more studies reporting the same type of data. All analyses were performed both with and without outliers. A study was considered an outlier when its 95% confidence interval (CI) was outside the 95% CI of the pooled effect size. Outliers were identified by visually inspecting the forest plots.

The assessment of statistical heterogeneity between studies used I^2 , with significance at $p < 0.05$. A random-effect or fixed effect model will be selected based on the value of I^2 to assess pooled standardized mean differences (SMD) and pooled odds ratio (OR). When the value of $I^2 > 50\%$, a random-effect model should be used. Meanwhile, the fixed-effect model will be used if the value of $I^2 < 50\%$. A qualitative assessment of publication bias was carried out using a funnel plot.

RESULTS

Preliminary search of three databases (PubMed, Scopus, and Cochrane) using pre-compiled keywords yielded 1751 studies. The researcher also conducted a manual search and found a study that was not filtered in a keyword search. Of all these studies, there were 538 duplications, leaving 1214 studies to be screened for titles and abstracts. At the first screening, title discrepancies were found in 1117 studies and abstract discrepancies in 37 studies. The subsequent screening revealed the absence of full-text in 26 studies and one non-English study. In the eligibility assessment, there was 1 study with a population discrepancy based on the inclusion criteria, 1 study with an outcome that was not of interest to the study, and 22 studies with an inappropriate study design. In the end, 9 studies that were found met the eligibility criteria for a systematic review and 8 studies that could be analyzed were also processed quantitatively (Quesada-Gomez et al. 2020, Murai et al. 2021a, 2021b, Sánchez-Zuno et al. 2021, Beigmohammadi et al. 2021, Maghbooli et al. 2021, Soliman et al. 2022, Cannata-Andía et al. 2022). Overall this process is shown in the PRISMA flow chart (Figure 1).

The characteristics of nine randomized clinical trials (RCT) studies are summarized in Table 1. More than a thousand of participants (mean age: 48 to 58.5 years)

were successfully collected from the included studies (Quesada-Gomez et al. 2020, Murai et al. 2021a, 2021b, Sánchez-Zuno et al. 2021, Sabico et al. 2021, Beigmohammadi et al. 2021, Maghbooli et al. 2021, Soliman et al. 2022, Cannata-Andía et al. 2022). Female participants accounted for approximately half of the overall study population. The diagnostic definition of COVID-19 in all studies was by reverse transcriptase polymerase chain reaction (RT-PCR) tests. Vitamin D administration varied among studies. All studies were carried out on four major continents: America, Europe, Africa, and Asia. One of the studies was conducted in four countries and two continents (Cannata-Andía et al. 2022). Four studies involved similar participants in different numbers (Murai et al. 2021a, 2021b, Beigmohammadi et al. 2021, Maghbooli et al. 2021). The quality of each study assessed using RoB 2 is shown in Figure 2 and Figure 3. Two studies were determined to be at risk of bias (Sánchez-Zuno et al. 2021, Sabico et al. 2021), one study had some concerns (Beigmohammadi et al. 2021), and five other studies were at low risk of bias (Quesada-Gomez et al. 2020, Murai et al. 2021a, 2021b, Maghbooli et al. 2021, Soliman et al. 2022, Cannata-Andía et al. 2022).

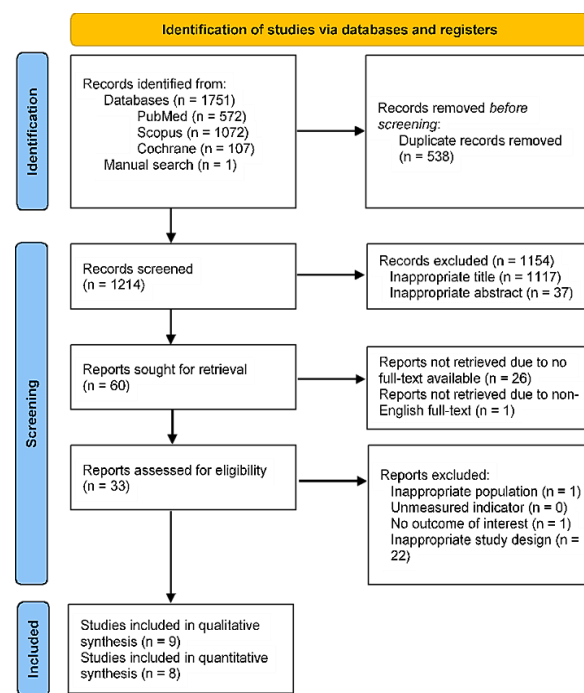


Figure 1. PRISMA flow chart of the study selection process (Page et al. 2021)

Analysis of five studies involving more than 300 subjects showed that administration of vitamin D offered no significant difference in COVID-19 morbidity compared to the groups who did not receive vitamin D as adjunctive therapy (Quesada-Gomez et al. 2020, Murai et al. 2021b, Sánchez-Zuno et al. 2021, Maghbooli et al. 2021, Soliman et al. 2022). However, the administration of vitamin D tended to have a protective effect in the COVID-19 morbidity [OR=0.50 (95% CI=0.13-1.96)] (Figure 4).



Table 1. Characteristics of the included studies

Author & Year	Study Location	Study Design	COVID-19 Diagnostic Definition	Vitamin D Administration	Age of Patients	Total Patients (% female)
Murai et al. (2021a)	Brazil, America	RCT	Nasopharyngeal swab PCR or CT scan	A single dose of 200,000 IU vitamin D3 dissolved in a 10-mL peanut oil solution by oral.	56.2±14.4*	273 (43.9)
Cannata-Andía et al. (2022)	Spain, Europe; Argentina, America; Guatemala, America; Chile, America	RCT	Nasopharyngeal swab with RT-PCR or antigen tests	A single oral bolus of 100,000 IU cholecalciferol	58.0**	543 (42.9)
Maghbooli et al. (2021)	Iran, Asia	RCT	RT-PCR and CT scan data from medical records	25,000 IU vitamin A given daily, 600,000 IU vitamin D given once during the study, 300 IU vitamin E given twice a day, 500 mg vitamin C given four times a day, and one daily ampule of B vitamins taken as Soluvit for 7 days	49.1±14.1*	106 (39.6)
Murai et al. (2021b)	Brazil, America	RCT	PCR or ELISA	Single dose of 200,000 IU vitamin D3	58.5±15.6*	32 (53.1)
Quesada-Gomez et al. (2020)	Spain, Europe	RCT	PCR	Oral calcifediol (0.532 mg) given on hospital admission. The treatment group continued with oral calcifediol (0.266 mg) on days 3 and 7, and then weekly until discharge or ICU admission	53±10*	76 (41)
Soliman et al. (2022)	Egypt, Africa	RCT	RT-PCR	A single dose of 200,000 units vitamin D given intramuscularly	NA	56 (NA)
Sánchez-Zuno et al. (2021)	Mexico, America	RCT	PCR	Daily supplementation of 10,000 IU vitamin D3 in soft capsule form for 14 days	43.0 (20-74)**	42 (52.3)
Beigmohammadi et al. (2021)	Iran, Asia	RCT	RT-PCR and CT scan data from medic records	25,000 IU vitamin A daily, 600,000 IU vitamin D once during the study, 300 IU vitamin E twice a day, 500 mg vitamin C four times a day, and a daily ampule of B vitamins taken as Soluvit for 7 days	52.00 (9.00)**	60 (48.4)
Sabico et al. (2021) ^x	Kingdom of Saudi Arabia, Asia	RCT	RT-PCR	Standard vitamin D therapy 1000 IU (control) or 5000 IU vitamin D3 for 14 days	49.8±14.3*	69 (52.2)

COVID-19, Coronavirus Disease 2019; IU, International Unit; RCT, Randomized Clinical Trial; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SD, standard deviation.

* Age of patients are provided in mean±SD

** Age of patients are provided in median (IQR) ^x study that is not included in the quantitative analysis

Study ID	D1	D2	D3	D4	D5	Overall	
Entrenas et al. (2020)	+	+	+	+	+	+	Low risk
Murai et al. (2021a)	+	+	+	+	+	+	Some concerns
Sabico et al. (2021)	-	+	+	+	+	-	High risk
Cannata-Andia et al. 2022	+	+	+	+	+	+	
Maghbooli et al. (2021)	+	+	+	+	+	+	D1 Randomisation process
Beigmohammadi et al. (2021)	+	!	+	+	+	!	D2 Deviations from the intended interventions
Murai et al. (2021b)	+	+	+	+	+	+	D3 Missing outcome data
Soliman et al. (2021)	+	+	+	+	+	+	D4 Measurement of the outcome
Sanchez-Zuno et al. (2021)	-	+	+	-	+	-	D5 Selection of the reported result

Figure 2. The assessments of study quality using Risk of Bias tool version 2

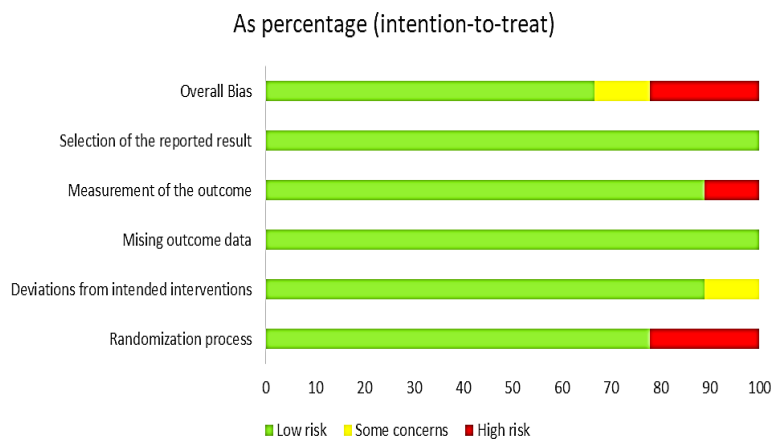


Figure 3. The overall bias of the study quality assessment as a percentage

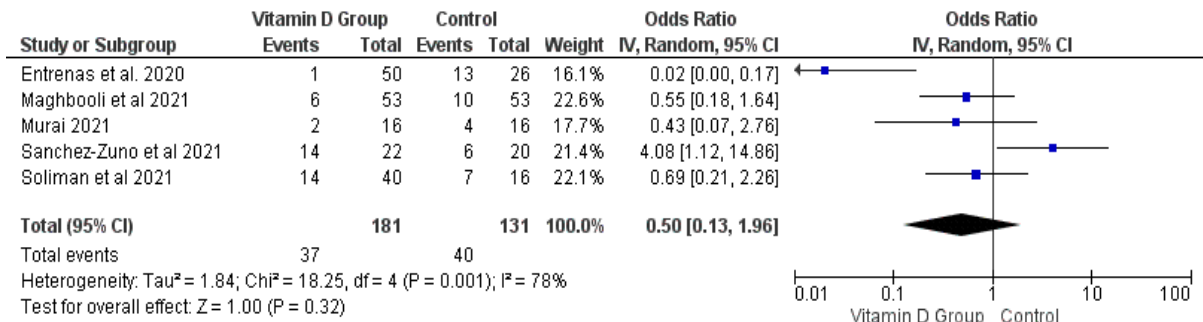


Figure 4. Odds ratio of vitamin D administration on the morbidity in patients with COVID-19

Meanwhile, the pooled analysis of the other two studies involving more than 700 subjects showed that vitamin D administration did not significantly reduce the morbidity in patients with COVID-19 [SMD=-0.14 (95% CI=-0.55-0.28)] (Murai et al. 2021a, Cannata-Andía et al. 2022) (Figure 5). The heterogeneities of all latter analyses were considered high (I²>50%). This was a possible bias from publications with asymmetric funnel plot results. (Figure 6), either for the first five

studies or the other two studies, on the morbidity in COVID-19 patients.

Four studies involving a total of approximately 200 subjects were further analyzed to determine the combined yield of vitamin D administration in the hospitalization day of patients with COVID-19 (Murai et al. 2021a, 2021b, Maghbooli et al. 2021, Cannata-Andía et al. 2022) (Figure 7).

Administering vitamin D in patients with COVID-19 did not significantly reduce the hospitalization day compared to patients not administered with vitamin D [SMD=-0.12 (95% CI=0.39-0.15)]. The heterogeneities

between studies in the analysis were low ($I^2=0\%$). The results of the funnel plot on the day of hospitalization in patients with COVID-19 revealed a tendency of no potential publication bias.

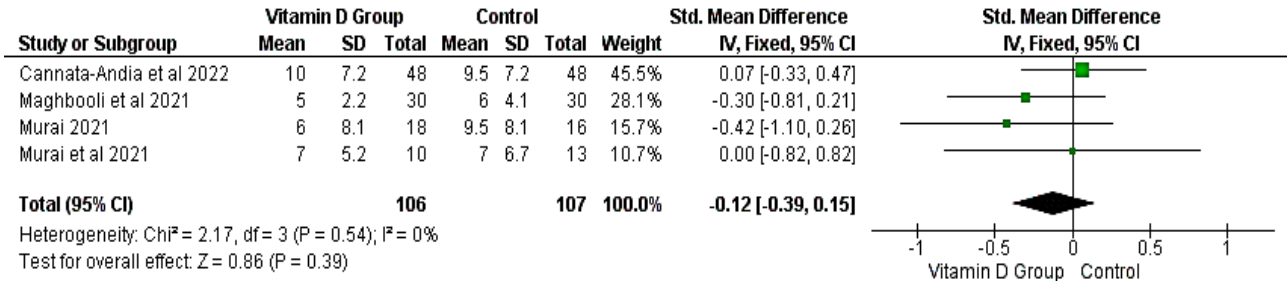


Figure 5. The standard mean difference of vitamin D administration on the morbidity in patients with COVID-19

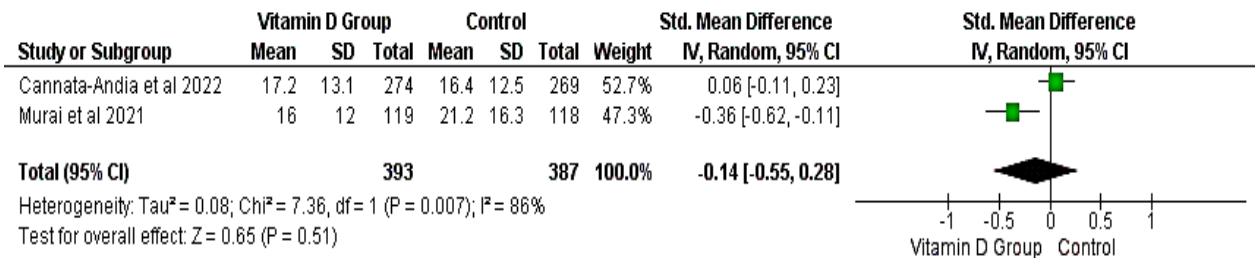


Figure 6. Funnel plots of the selected studies

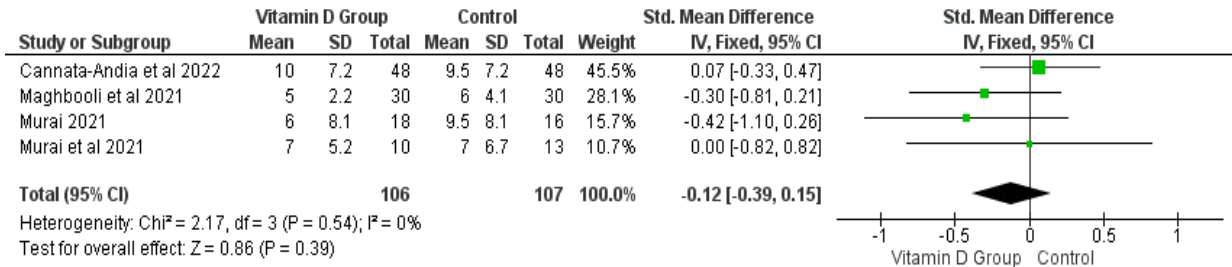


Figure 7. The standard mean difference of the effect of vitamin D administration on the hospitalization day in patients with COVID-19

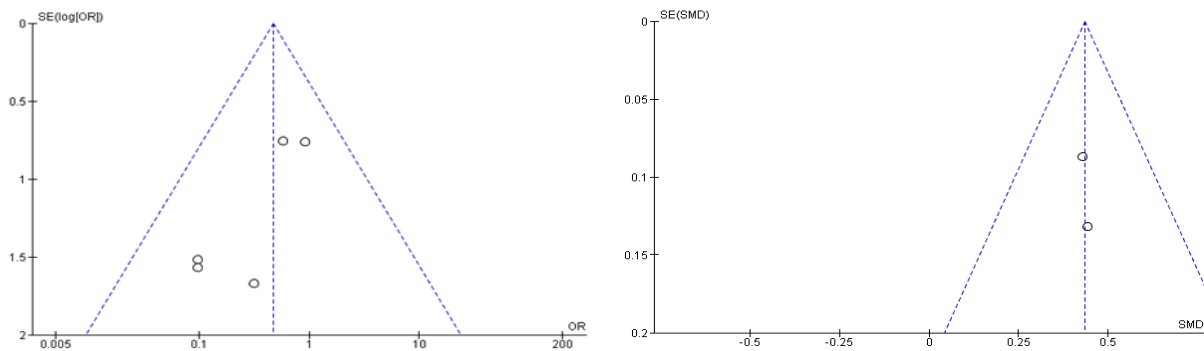


Figure 8. Funnel plot of the effect of vitamin D administration on the hospitalization day in patients with COVID-19

Results from five studies involving approximately 300 COVID-19 patients can be seen in Figure 9 (Quesada-Gomez et al. 2020, Murai et al. 2021b, Beigmohammadi et al. 2021, Maghbooli et al. 2021, Soliman et al. 2022). The OR was 0.47 (95% CI=0.19-1.17) that indicated vitamin D administration tended to have effectiveness in preventing from COVID-19 death. The heterogeneity of the latter analysis was considered low ($I^2=0\%$). However, in the analysis of

the other 2 studies, there was a significant difference, in which control patients without vitamin D administration had a low mortality rate [SMD=0.43 (95% CI=0.29-0.58)] with negligible heterogeneity ($I^2=0\%$) (Figure 10). The funnel plot in the COVID-19 mortality indicated the analysis results had a potential bias, while the second analysis indicated a tendency of no publication bias (Figure 11).

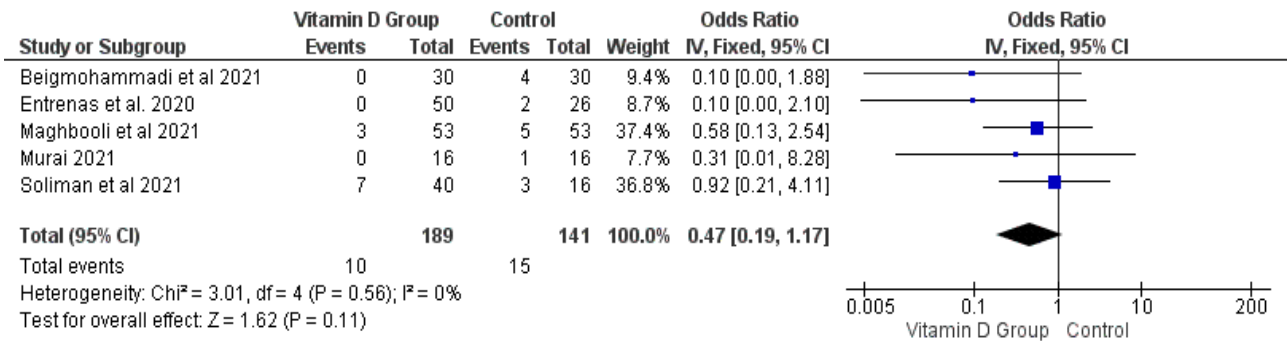


Figure 9. Odds ratio of the effect of vitamin D administration in patients with COVID-19

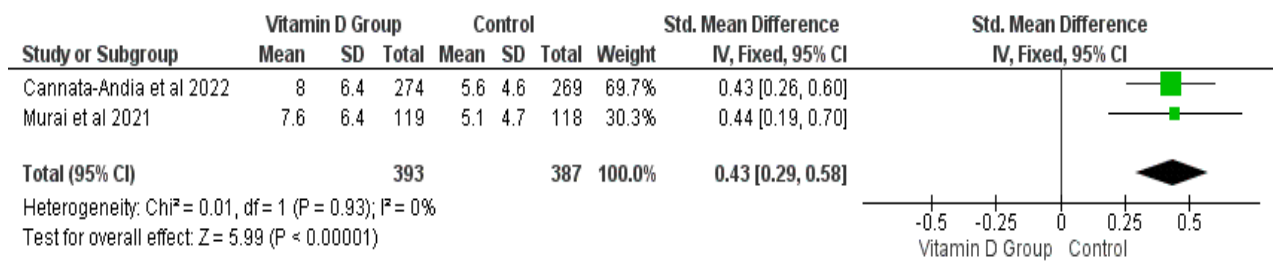


Figure 10. Standard mean difference of the effect of vitamin D administration in COVID-19 mortality

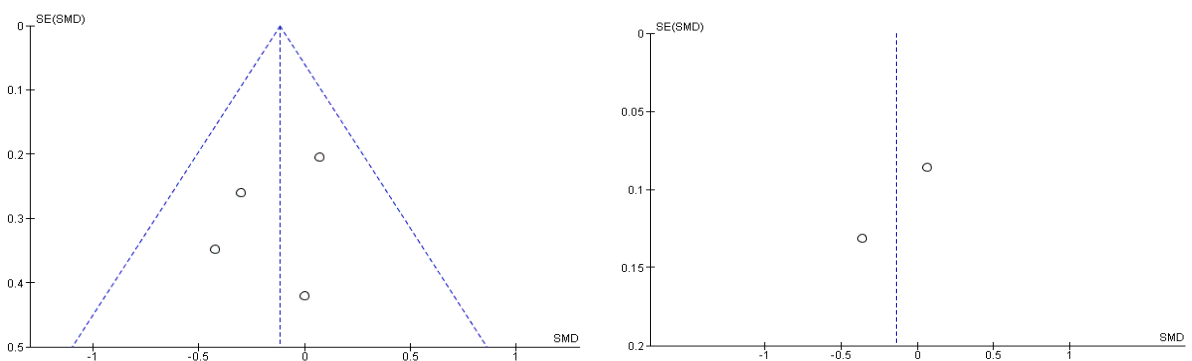


Figure 11. Funnel plots of the selected studies

DISCUSSION

Several studies suggest the prevention or treatment of COVID-19 using vitamin D because it can improve its insufficiency or deficiency, so that it can increase the percentage of blood lymphocytes and improve immune function (Mitchell 2020, Martineau & Forouhi 2020, Malaguarnera 2020, Maghbooli et al. 2021). This systematic review and meta-analysis aimed to determine the optimal dose of vitamin D administration that affect the morbidity, length of hospitalization, and mortality in COVID-19 patients. From this study, the administration of vitamin D did not provide a significant difference in the morbidity of COVID-19 patients compared to the ones who were not given vitamin D as an adjunct therapy. However, it tended to have a protective effect in the COVID-19 morbidity [OR=0.50 (95% CI=0.13-1.96)]. Meanwhile, the pooled analysis of the other two studies involving more than 700 subjects showed that vitamin D administration did not significantly diminish the morbidity in COVID-19 patients [SMD=-0.14 (95% CI=-0.55-0.28)] (Murai et al. 2021a, Cannata-Andía et al. 2022). According to Maghbooli et al., this may happen due to organ damage related to the cytokine storm.

When organ damage occurs, it is difficult to change, so that a more rapid increase in serum concentrations of 25(OH)D₃ could be advantageous in diminishing morbidity associated with infectious diseases such as COVID-19 (Maghbooli et al. 2021). The study by Sánchez-Zuno et al. (2021) proved that outpatients with vitamin D deficiency had more COVID-19 symptoms than patients with vitamin D deficiency. This is contrast to the study by Cannata-Andía et al. where there was not a significant difference in COVID-19 outcomes between patients who were given a single oral bolus of cholecalciferol at admission and those who were not given one (Cannata-Andía et al. 2022). According to Soliman et al. and Maghbooli et al., taking vitamin D supplements did not have a significant difference in diminishing the risk or severity of SARS-CoV-19 and the placebo group (Maghbooli et al. 2021, Soliman et al. 2022). The research in Brazil also supports the claim that in moderate to severe COVID-19 hospitalization, cholecalciferol administration did not diminish the use of mechanical ventilation and ICU admission because 25-hydroxyvitamin levels increase rapidly (Murai et al. 2021a).

The length of hospitalization stay is one indicator of clinical developments assessment in COVID-19 patients. Giving vitamin D supplementation to COVID-19 patients is considered to be able to reduce the length of hospitalization stay (Carpagnano et al. 2021). In our findings, administering vitamin D was

not significantly reduce the hospitalization day in COVID-19 patients [SMD=-0.12 (95% CI=-0.39-.15)] compared to the patients who did not receive vitamin D. A study by Cannata-Andía et al. (2022) showed that a single oral bolus of 100,000 IU cholecalciferol given at admission did not improve disease outcomes, including the length of hospitalization, compared to patients who did not receive it. Similar results were obtained in the other two studies conducted by Murai et al., where the administration of a single high doses (200,000 IU) vitamin D did not significantly reduce the length of stay in hospital both in the population of COVID-19 patients with non-severe and severe 25(OH)D deficiency (Murai et al. 2021a, 2021b). Contradictory results were demonstrated in a study by Maghbooli et al. (2021) which showed that oral consumption of calcifediol for 60 days at a dose equivalent to 3000-6000 IU vitamin D₃ per day proved to be safe and effective in maintaining optimal serum 25(OH)D₃ concentrations. Optimal 25(OH)D₃ serum in the body has potential benefits to improve immune function by increasing the percentage of lymphocytes and can reduce the length of hospitalization stay in COVID-19 patients (Maghbooli et al. 2021).

Our findings indicated that vitamin D administration tended to have a protective effect from COVID-19 mortality [OR=0.47 (95% CI=0.19-1.17)] although it was not significantly different compared to patients who did not receive vitamin D. However, in an analysis of two other studies found a significant difference where control patients who did not receive vitamin D had a lower mortality rate (Murai et al. 2021a, Cannata-Andía et al. 2022). This occurred due to several factors that can be biased, such as heterogeneous recruited population, more prevalence of hypertension, diabetes, and obesity in the group receiving vitamin D, and other influencing factors such as age and current illness (Murai et al. 2021a, Cannata-Andía et al. 2022). From another study, it was also stated that giving high doses of vitamin D for two weeks also did not affect the COVID-19 mortality (Sabico et al. 2021). The mode of administration and dosage of vitamin D in COVID-19 is currently still under controversy (Camargo et al. 2020, Mazess et al. 2021, Pal et al. 2022).

Many studies have proven that vitamin D is useful in treating COVID-19 patients. Nevertheless, the problem is that there is still no agreed optimal dose to guide the administration of vitamin D therapy in COVID-19 patients (Vimaleswaran et al. 2021). Various clinical trials have been conducted as an effort to determine the effect of giving vitamin D therapy at various doses on the outcome of COVID-19 patients. The different findings in these studies were explained by discussing the differences in vitamin D administration in each study. The basic differences in these studies were the

doses and durations of vitamin D administration. Studies with continuous vitamin D administration over a period of time have shown more promising results in clinical outcomes of COVID-19 patients. This is due to vitamin D levels that can be maintained stably and longer in the body compared to single-dose vitamin D administration (Apaydin et al. 2018). This was also found in the study by Sabico et al. where they compared the administration of 1000 IU and 5000 IU vitamin D in COVID-19 patients and for 14 days each. The study demonstrated clinically significant improvement in patients receiving 5000 IU vitamin D compared to patients receiving 1000 IU (Sabico et al. 2021).

Strength and limitation

The study has several limitations. The definition of morbidity used as the desired outcome of the study. Morbidity as a study outcome varies from the duration of hospitalization, the severity of conditions associated with medical intervention, and worsening of disease symptoms. Another limitation is the presence of variables other than vitamin D administered to patients that allow for biased results. In addition, some studies also contain data collected from many centers.

The main limitation of this study lies in the misalignment of the definition of morbidity used as the desired outcome of the study. Morbidity as a study outcome varies from the duration of hospitalization, the severity of conditions associated with medical intervention, and worsening of disease symptoms. Another limitation is the presence of variables other than vitamin D administered to patients that allow for biased results. In addition, some studies also contain data collected from many centers.

CONCLUSION

In conclusion, COVID-19 patients who are given vitamin D as adjunctive therapy tends to have lower but not significantly lower COVID-19 morbidity and mortality when compared to those who did not receive vitamin D. Continuous administration of vitamin D with a dose of 1000-6000 IU for several days in COVID-19 patients has shown better benefits on the morbidity, length of hospitalization stay, and mortality than a single high dose vitamin D. However, further study is still needed to find out which vitamin D dose given to COVID-19 patients is better than the other by comparing them one by one.

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Conflict of interest

There was no conflict of interest in this research.

Funding disclosure

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Author contribution

All authors were responsible for the manuscript preparation. DMU was responsible for conceptualization, data collection, and providing analysis. MARA was responsible for investigation of the data, data collection, manuscript revision, and grammatical checks. DRR was responsible for investigation of the data, data collection, and providing data analysis. MIM was responsible for investigation of the data, data collection and providing data analysis. MZT was responsible for data collection and data analysis. JNS was responsible for data collection and investigation of the data. HTAF was responsible for data collection and providing data analysis. BU was responsible as the supervisor, corresponding author, and also involved in manuscript preparation and validation. SF was responsible for supervision and manuscript preparation. All authors read and approved the final manuscript. Data sharing was not applicable.

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