Systematic Review/Meta-analysis

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Efficacy of vitamin D supplementation in the treatment of patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

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Context: COVID-19 has substantial effects on respiratory health and overall well-being. Recent studies suggest vitamin D as a potential treatment, but the results are inconclusive.

Objective: The authors conducted a systematic review of randomized controlled trials (RCTs) to examine the link between vitamin D and patients with COVID-19.

Data sources: The authors searched electronic databases PubMed, Cochrane, CINAHL, EMBASE and Google Scholar from their inception till August 2023.

Study selection: Inclusion criteria used in our systematic review include: (1) patients who tested positive for COVID-19, (2) intervention was vitamin D supplementation, (3) the comparator was either a placebo, standard care of treatment, or, no treatment, (4) at least one of the clinical outcomes of interest were investigated, (5) study design being RCTs.

Data extraction: Two independent reviewers manually extracted information from selected articles, including study characteristics, patient characteristics, and the primary outcomes: all-cause mortality, ICU and hospital stay length and secondary outcomes: mechanical ventilation, supplemental oxygen, ICU admission, and adverse events. Risk ratios or mean differences and 95% CIs were calculated using a random-effects model.

Data synthesis: The authors' analysis included 14 RCTs with 2165 patients. Vitamin D significantly reduced ICU admissions and lowered the need for mechanical ventilation compared to placebo. However, it did not significantly affect hospital stay length, ICU stay length, mechanical ventilation duration, mortality, or the need for supplemental oxygen.

Conclusion: Vitamin D does not significantly improve certain clinical outcomes, such as hospital and ICU stay length, for patients with COVID-19. However, it still may be significantly beneficial in decreasing the burden on intensive care services.

Keywords: calcitriol, coronavirus, COVID-19, randomized controlled trials, vitamin D

Introduction

COVID-19 is a highly contagious and potentially severe respiratory illness caused by the novel coronavirus, known as SARS-CoV-2. The first cases of this disease were reported in December 2019 in Wuhan, China. By March 2020, the disease had spread globally, leading the WHO to declare it a healthcare pandemic[1–3]. Despite advances in therapeutic strategies and worldwide vaccine deployment, COVID-19 remains a major global healthcare challenge. As of 3 September 2023, there have been ~694 million confirmed cases and 6.9 million deaths worldwide[4]. These statistics drive ongoing research efforts to identify new solutions for combating COVID-19, including the potential role of vitamin D supplementation.

Vitamin D serves as a signaling molecule that influences both the innate and adaptive components of the immune system. It accomplishes this function by inducing the production of anti-microbial peptides, promoting the maturation of monocytes, reducing the production of pro-inflammatory cytokines (such as IL-6, IL-8, etc.), and upregulating anti-inflammatory responses by inhibiting the NF-κB pathways[5–7]. Not only has vitamin D

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deficiency been linked to an increased risk of chronic cardiovascular and metabolic disorders[8], but it has also been associated with a poor prognosis in viral respiratory tract infections including SARS-CoV-2[9,10], leading to higher disease severity and mortality rates[11,12]. Recent evidence suggests the potential of vitamin D to affect SARS-CoV-2 gene expression and to regulate the renin-angiotensin system, including the expression of angiotensin-converting enzyme 2 (ACE2), which is an important mediator in COVID-19 pathogenesis[13,14]. Due to its physiological actions, good safety profile, easy availability, and low cost, researchers have become interested in exploring its potential role as a COVID-19 prevention and treatment option.

Numerous studies have investigated the impact of vitamin D supplementation on various COVID-19 outcomes. Some of these studies support the beneficial role of Vitamin D in COVID-19, such as improvement in the severity of infection and reduced mortality[15–18], while others suggest no significant improvement with the administration of Vitamin D[19,20]. Moreover, one study also reported evidence of vitamin D's potential to enhance the immune response when used as an adjunct to the COVID-19 vaccine[21]. However, it is worth noting that this benefit of vitamin D is not consistent across all studies. An observational study reported a two-fold increase in mortality among patients receiving vitamin D supplementation[22].

The association between vitamin D therapy and COVID-19 has undergone scrutiny through numerous systematic reviews and meta-analyses. Several of these analyses conclude that vitamin D supplementation can reduce hospitalization duration, lower ICU admissions, and decrease mortality rates in SARS-CoV-2-infected patients[23–25]. Nevertheless, one meta-analysis, while supporting some of these findings, suggests that vitamin D may not significantly improve COVID-19 susceptibility and might not be particularly effective as a prophylactic measure[26].

Prior meta-analyses evaluating the role of Vitamin D in patients with COVID-19 are limited by the quality of randomized controlled trials and/or the inclusion of observational studies, which confers the risk of confounding bias[27,28], Hence, due to inconsistent results among various trials and the availability of several recent randomized controlled trials that were not included in previous reviews, we conducted this meta-analysis to rigorously assess the efficacy of vitamin D supplementation in the treatment of patients with COVID-19.

HIGHLIGHTS

- A systematic review of 14 RCTs with 2165 patients to examine the link between vitamin D and COVID-19 patients.
- Vitamin D significantly reduced ICU admissions and the need for mechanical ventilation as compared to placebo.
- Vitamin D did not significantly affect hospital stay, ICU stay, mechanical ventilation length, mortality, or the supplemental oxygen need.
- While vitamin D might not significantly improve quality of life.
- However, it may be significantly beneficial in decreasing the burden on intensive care services.

Methodology

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A579) statement[29]. The study protocol has been registered in PROSPERO.

Search strategy

Two investigators (M.A. and I.A.) independently performed a comprehensive systematic search of existing literature using the databases: MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Embase, and Google Scholar from inception till August 2023, with no restrictions applied. The search strategy consisted of keywords and Medical Subject Headings (MeSH) related to "COVID-19", "SARS CoV-2", "Vitamin D", and "ergocalciferol". The detailed search strategy for each database is provided in (Supplementary Information Table S1, Supplemental Digital Content 2, http://links.lww.com/MS9/A580). Additionally, manual screening of reference lists of relevant studies was also conducted to identify any eligible studies.

Study criteria and selection

The following predetermined inclusion criteria were used in our systematic review: (1) patients who tested positive for COVID-19 according to WHO guidelines[30], (2) intervention was vitamin D supplementation irrespective of dose, duration or formulation, (3) comparator was either a placebo, standard care of treatment, or, no treatment, (4) at least one of the following relevant clinical outcomes were investigated: mortality, length of hospital stay, ICU admission, mechanical ventilation use, and supplemental oxygen use, (5) study design being randomized controlled trials (parallel or cross-over). All the study designs apart from RCTs such as observational studies, reviews, and case studies were excluded from our review. Additionally, studies employing other types of vitamin supplementations, not performing recommended COVID-19 testing, and not assessing any of our pre-defined outcomes were also excluded.

All search results were imported into Clarivate Endnote: Reference Management Tool (version 20)[31] and duplicates were removed. The remaining articles were screened by two independent reviewers (M.A. and I.A.) based on title and abstracts, followed by full-text screening against the aforementioned selection criteria. In case of any discrepancies, a third independent reviewer (S.V. or M.M.S.) was consulted.

Data extraction

The following information was extracted from the selected articles by two independent reviewers (M.A. and I.A.): (1) study characteristics including study design, author name, year of publication, and sample sizes, (2) participant characteristics including demographic variables such as age and sex, (3) dosages of intervention and control groups, (4) primary and secondary outcomes. Our primary outcomes included: All-cause mortality, length of ICU stay, and length of hospital stay. Our secondary outcomes were the need and length of mechanical ventilation, need for supplemental oxygen, admission to ICU, and incidence of adverse events. Length of hospital stay, ICU admission, and mechanical ventilation usage were expressed in terms of days. Where standard error of the mean (SEM) was reported, it was

converted to SD for inclusion in the meta-analysis. In case of any important missing data, authors were contacted via e-mail for assistance. The extracted data was reviewed for any errors and finally organized into a comprehensive table.

Risk of bias assessment

Two independent reviewers (S.V. and M.M.S.) performed a quality assessment of included RCTs using the Cochrane "Risk of Bias" tool for randomized controlled trials (RoB 2.0)[32]. This tool assesses articles based on five domains: (1) bias arising from the randomization process, (2) bias due to deviations from the intended interventions, (3) bias due to missing outcome data, (4) bias in the outcome measurement, (5) bias in selection of the reported results. Each domain is rated low to high risk and then combined to indicate the overall risk of bias in a study. In case of any disagreements, a third reviewer (M.A.) was consulted, and consensus was reached.

Statistical analysis

This meta-analysis was performed using Review Manager (RevMan v5.4.1). For continuous outcomes, mean difference (MD) along with SD were reported, whereas, for dichotomous outcomes, effect sizes were expressed as risk ratios (RR), along with 95% CI. Statistical heterogeneity among studies was assessed using the χ^2 test and I^2 statistic. Cochrane Handbook for Systemic Reviews of Interventions Section 10.10 was used in the interpretation of I2 values[33]. Significant heterogeneity was considered when the I^2 value was greater than or equal to 50%, with a P value less than 0.1, in which case, a random-effects model was used to perform the meta-analysis instead of the fixed-effects model. Two subsets of data were created, one comparing vitamin D with control, whereas the other comparing high dosages of vitamin D with low dosages to assess heterogeneity. The data from both subsets were pooled and the cumulative effect of intervention on outcomes of interest was derived using the inverse variance method and displayed in a forest plot. Publication bias was assessed using a funnel plot through visual inspection for the primary outcomes.

Results

Study selection

A thorough search of existing literature identified a total of 489 studies. Following the removal of 32 duplicate entries, the titles and/or abstracts of the remaining 457 citations were examined, resulting in the retrieval of 38 articles for full-text screening. Ultimately, 14 studies met the inclusion criteria for the review[15,17,19,34–44]. The selection process is illustrated in a PRISMA flowchart (Fig. 1).

Study characteristics

Fourteen studies ($n = 14$) were included in our review with a total of 2165 patients. All of the trials included individuals aged older than 18 years old with a mean age of 62 years old, with 42.1% being females. Among the included randomized trials, 6 were open-label[15,34–36,38,39] while 9 studies were blinded trials[17,19,37,40–44], not disclosing any information to the subjects; 7 studies were multicenter studies[17,19,34,35,40,41,44] while the rest were conducted in a single center[15,36–39,42,43]. Lastly, 9 of them compared vitamin D supplementation with a control placebo group[17,19,35,37,40–44], whereas, the rest did not use a comparator[15,34,36,38,39]. The majority of the trials administered oral cholecalciferol with a dosage ranging from 5000 UI (17) to 500,000 UI (41), mostly being administered daily and lasting from 1 day to 2 weeks. Additionally, most trials scheduled follow-up period was at day 7 and day 14, upon discharge, or at death. Mortality, hospitalization length, and ICU admission were the most commonly reported outcomes (refer to Study Characteristics Table 1 for the complete study demographics).

Risk of bias assessment and publication bias

Amongst the 14 studies assessed for risk of bias by the Cochrane RoB 2 Tool, 6 were evaluated at a low risk of bias, 7 at some concerns, and 1 at high risk due to reasons such as suspected biases in the randomization process, deviating from intended intervention or not establishing a clear statistical analysis plan before analyzing. (Supplementary Information Figure 1, Supplemental Digital Content 2, http://links.lww.com/MS9/A580).

In terms of publication bias, funnel plots were generated. Funnel plots regarding ICU admission and Length of Hospital stay showed no asymmetry; however, a certain degree of deviation from funnel shape was found in the funnel plot of mortality at the end of follow-up (Supplementary Information Figures 2–4, Supplemental Digital Content 2, http://links.lww.com/MS9/A580).

Length of hospital stay

Eight studies assessed the impact of vitamin D supplementation, when compared to a placebo, on the duration of hospital stay[19,34,36–38,40–42]. A pooled analysis of the aforementioned studies using the random-effects model revealed that vitamin D supplementation is associated with a slight reduction in the duration of hospital stay with considerable heterogeneity (MD = -0.72, 95% CI: – 2.18, 0.73, $I^2 = 82\%$, Fig. 2); however, the test for the overall effect was not statistically significant ($P = 0.33$).

Additionally, two studies compared high-dose vitamin D against low-dose vitamin D in reducing the duration of hospital stay[17,44]. Pooled analysis revealed no statistically significant difference between the two groups in reducing length of hospital stay (MD = -1.08, 95% CI: – 4.75, 2.59, $P = 0.57$). The heterogeneity was found to be considerable ($I^2 = 82\%$). (Fig. 2)

Need for ICU admission

Eight studies evaluated the effect of vitamin D, when compared to a placebo, on the need for ICU admission for SARS-CoV-2 infected patients[15,19,34,38–42]. Our results find vitamin D supplementation to be associated with less frequent admissions to ICU (RR = 0.63, 95% CI: 0.41, 0.99, $P = 0.04$, random-effects model; Fig. 3).

Furthermore, pooled analysis of three trials[17,44,45] concluded that a higher dose of vitamin D is significantly more effective than a lower dose in reducing the need for ICU admission in SARS-CoV-2 infected patients (RR = 0.62, 95% CI: 0.44, 0.87, $P = 0.006$, $I^2 = 0\%$, random-effects model; Fig. 3) with minimal heterogeneity ($I^2 = 0\%$).

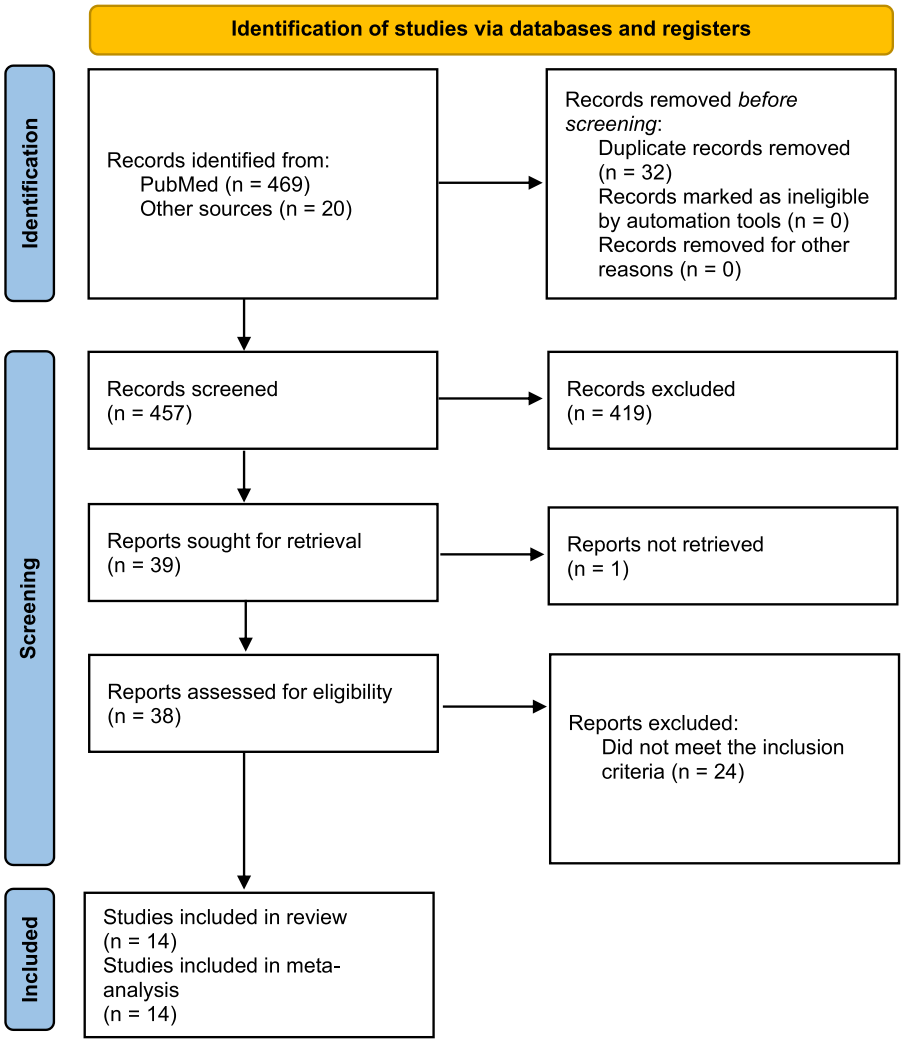

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram.

Length of ICU stay

A pooled analysis of four studies demonstrated that vitamin D has no statistically significant impact on the duration of ICU admission in COVID-19 hospitalized patients (MD = 0.29, 95% CI: – 3.82, 4.40, $P = 0.89$ random-effects model; Fig. 4). The estimated heterogeneity was considerable ($I^2 = 82\%$).

Mortality

A meta-analysis of nine studies[15,19,34,36–38,40–42] did not find a significant difference between the Vitamin D group and control regarding mortality (RR = 0.91, 95% CI: 0.67, 1.23, $P = 0.53$, $I^2 = 18\%$, random-effects model; Fig. 5)

An additional subset of four studies investigated the effects of different dosages of vitamin D in reducing mortality rates[17,35,44,45]. No significant difference regarding mortality was found between the two groups (RR = 0.89, 95% CI: 0.65, 1.22, $P = 0.46$, $I^2 = 0\%$, random-effects model).

Need for mechanical ventilation

Five studies compared vitamin D supplementation with a placebo to assess the need for mechanical ventilation in COVID-19 hospitalized patients[19,37,40–42]. Our results show that vitamin D supplementation is significantly associated with a reduced need for mechanical ventilation in COVID-19 patients (RR = 0.80, 95% CI: 0.65, 0.99, $P = 0.04$, random-effects model; Fig. 6). The estimated heterogeneity was minimal ($I^2 = 0\%$).

One study also compared a high dose of vitamin D against a low dose in reducing the need for a mechanical ventilation device in COVID-19 patients[44]. The trial reported that a low dose of vitamin D is significantly associated with a decreased need for mechanical ventilation in COVID-19 patients (RR = 2.05, 95% CI: 1.36, 3.09, $P = 0.0006$). Since there was only one study present in this subset, a meta-analysis could not be performed.

Length of mechanical ventilation

Our meta-analysis of two studies demonstrated that there is no significant difference between vitamin D and placebo on the duration of mechanical ventilation (MD = 1.80, 95% CI: – 3.91, 7.50, $P = 0.54$, random-effects model; Fig. 7). The estimated heterogeneity was considerable ($I^2 = 91\%$).

Table 1

Study characteristics of the included studies ($n = 14$ studies; year of extraction = 2023).

Author, year	No. participants (experimental group/ control group)	Mean age of participants (experimental group/ control group)	No. female participants (experimental group/ control group)	Treatment in experimental group	Treatment in control group	Follow-up time	Type of study
Andia *et al.*, 2022[34]	274/269	59/57	93/97	100 000 IU vitamin D	Nothing	Followed from hospital admission to discharge or death	Randomized, open-label, multicenter
Annweiler *et al.*, 2022[35]	127/127	87/89	66/82	400 000 IU vitamin D	50 000 IU vitamin D	Followed from hospital admission to days 7, 14, and 28	Randomized, open-label, multicenter
Bugarin *et al.*, 2023[36]	75/77	65/65.5	23/19	10 000 IU vitamin D	Nothing	Followed from hospital admission to days 7, and 14	Randomized, open-label, single center
Bychinin *et al.*, 2022[37]	52/54	64.5/63.5	30/23	60 000 IU vitamin D	Standard treatment (15 ml sunflower oil once a week and 10 mL sunflower oil daily)	Followed from hospital admission to discharge or death	Randomized, double-blind, single center
Castillo *et al.*, 2020[15]	50/26	53.14/52.77	23/8	On admission day, 0.532 mg vitamin D followed by 0.266 mg on day 3 and 7. 0.266 mg weekly until discharge or ICU admission.	Nothing	Followed from hospital admission to discharge or death	Randomized, double-blind, single center
Elamir *et al.*, 2022[38]	25/25	69/64	13/12	0.5 mcg vitamin D daily for 14 days	Nothing	Followed from hospital admission to day 14 or until discharge from the hospital	Randomized, open-label, multicenter
Karonava *et al.*, 2022[39]	56/54	57/64	31/32	100 000 IU vitamin D	Nothing	Followed from hospital admission to day 9	Randomized, open-label, single center
Maghbooli *et al.*, 2021[40]	53/53	50/49	22/20	25 micrograms vitamin D	Nothing	Followed from hospital admission to 1 month after admission, and 2 months after admission	Randomized, double-blind, multicenter
Mariani *et al.*, 2022[41]	115/103	59.8/58.3	51/52	500 000 IU vitamin D	Placebo	Followed from hospital admission to day 8, day 30, until discharge or death	Randomized, double-blind, multicenter
Murai *et al.*, 2021[19]	119/118	56.5/56	49/55	200 000 IU Vitamin D	Placebo	Followed from hospital admission to 2 months	Randomized, double-blind, multicenter
Niet *et al.*, 2022[42]	21/22	63.24/68.73	8/12	25 000 IU vitamin D daily for 4 days, followed by 25 000 IU per week up to 6 weeks	Placebo	Followed from hospital admission to 3-weeks	Randomized, double-blind, single center
Sabico *et al.*, 2021[17]	36/33	46.3/53.5	15/20	5000 IU vitamin D daily for 2 weeks	1000 IU vitamin D daily for 2 weeks	Followed from hospital admission to day 7 or on discharge day and 30 days after discharge	Randomized, open-label, multicenter
Sarhan *et al.*, 2022[43]	58/58	66.1/65.7	20/12	200 000 IU vitamin D	1 microgram vitamin D	Not available	Randomized, single center
Torres *et al.*, 2022[44]	41/44	67/65.3	11/14	10 000 IU vitamin D per day for 14 days	2000 IU vitamin D per day for 14 days	Followed from hospital admission to day 7 and day 14	Randomized, single-blind, multicenter

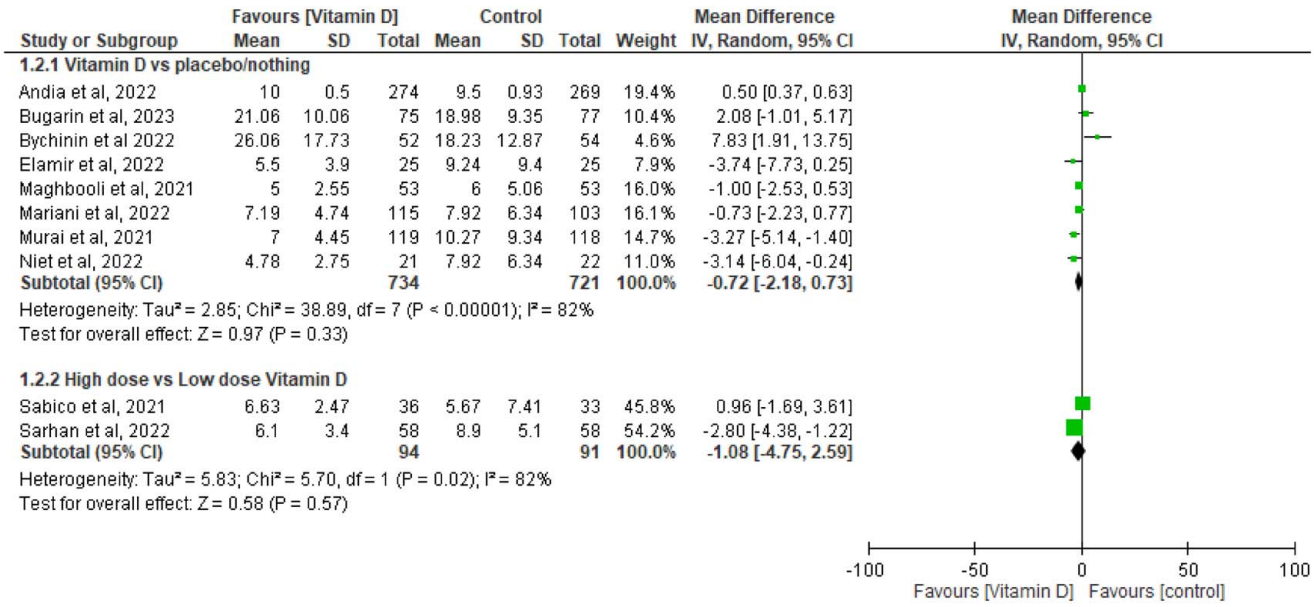

Figure 2. Length of hospital stay (days).

Need for supplemental oxygen

A meta-analysis of 3 studies revealed that there was no significant difference between vitamin D supplementation and placebo regarding the need for supplemental oxygen (RR = 0.97, 95% CI: 0.78, 1.20, $P = 0.78$, $I^2 = 0\%$, random-effects model; Fig. 8).

Only one study evaluated the impact of different dosages of Vitamin D on the need for supplemental oxygen and found no significant difference between the two groups (RR = 0.90, 95% CI: 0.62, 1.30, $P = 0.58$; Fig. 8). Due to the scarcity of data, a meta-analysis was not viable.

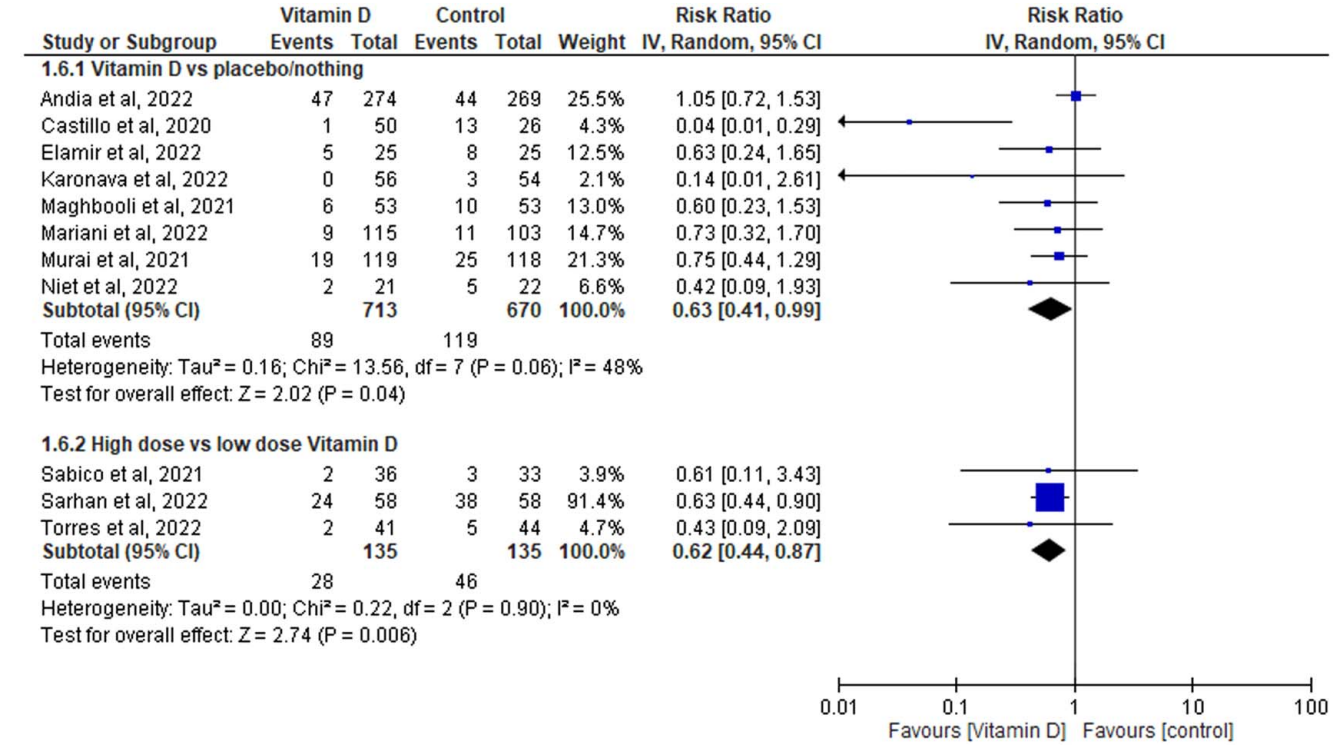

Figure 3. Need for ICU admission.

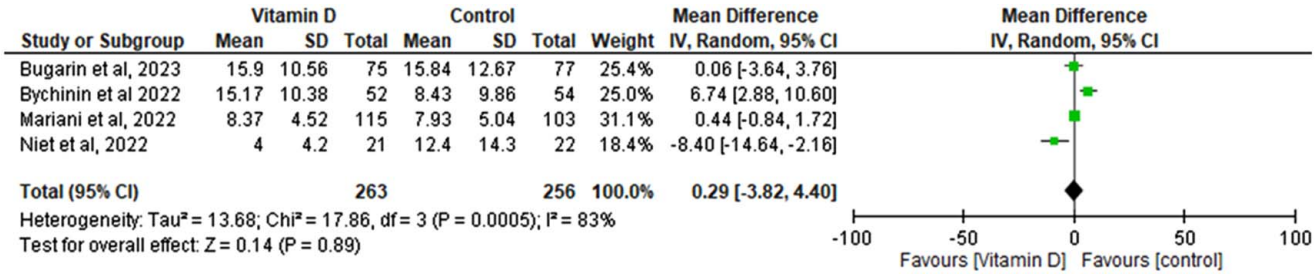

Figure 4. Length of ICU stay (days).

Adverse events

Four studies reported adverse events resulting either from vitamin D, or placebo administration in patients diagnosed with COVID-19[35,38,41,45]. Three of these studies[35,41,45] reported a higher incidence of adverse events in the vitamin D group (14.8%, 42.5%, 19.5%, respectively) as compared to the placebo group (11.7%, 34.6%, 15.9%, respectively), whereas one study[38] reported lesser adverse events in the vitamin D group (0%) than the placebo group (16%). Additionally, three of the aforementioned studies[35,38,41] also reported on the percentage of adverse events being kidney-related (Vitamin D: 0.8%, 0%, 1.7% vs. Placebo: 0.8%, 16%, 1.9%, respectively). Due to the limited amount of data available, a meta-analysis was not performed.

Discussion

This meta-analysis of 14 randomized controlled trials assessed the efficacy of vitamin D supplementation in the treatment of patients with COVID-19. Vitamin D supplementation did not significantly decrease the duration of hospital stay, mortality rates, and need for supplemental oxygen compared to placebo. Furthermore, vitamin D significantly lowered the frequency of ICU admissions and mechanical ventilation usage. Furthermore, certain studies documented instances of adverse events occurring throughout the treatment period, particularly related to kidney issues, and these events exhibited varying incidence rates.

Multiple theories have been proposed to explain vitamin D's curative effect on the pathophysiology of COVID-19. It is

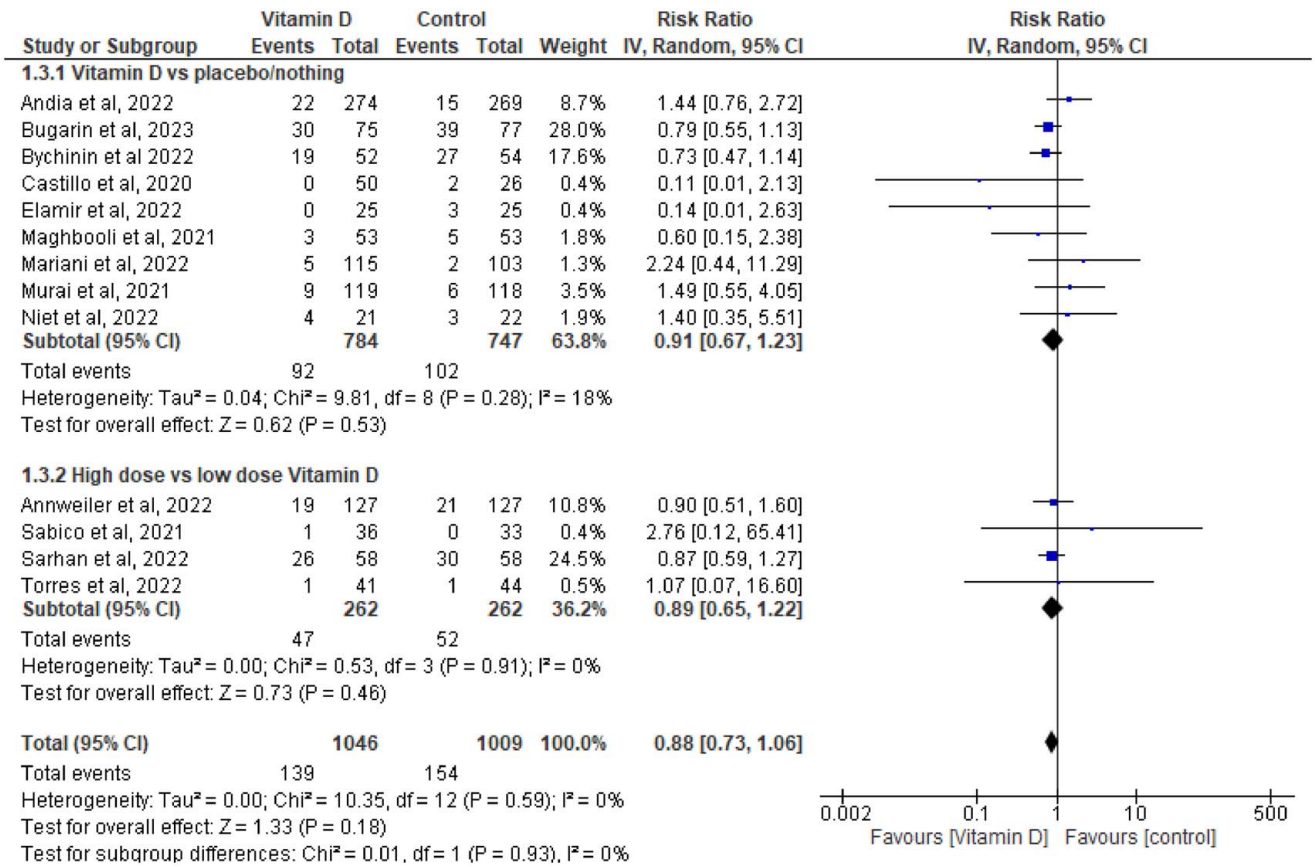

Figure 5. Mortality at the end of follow-up.

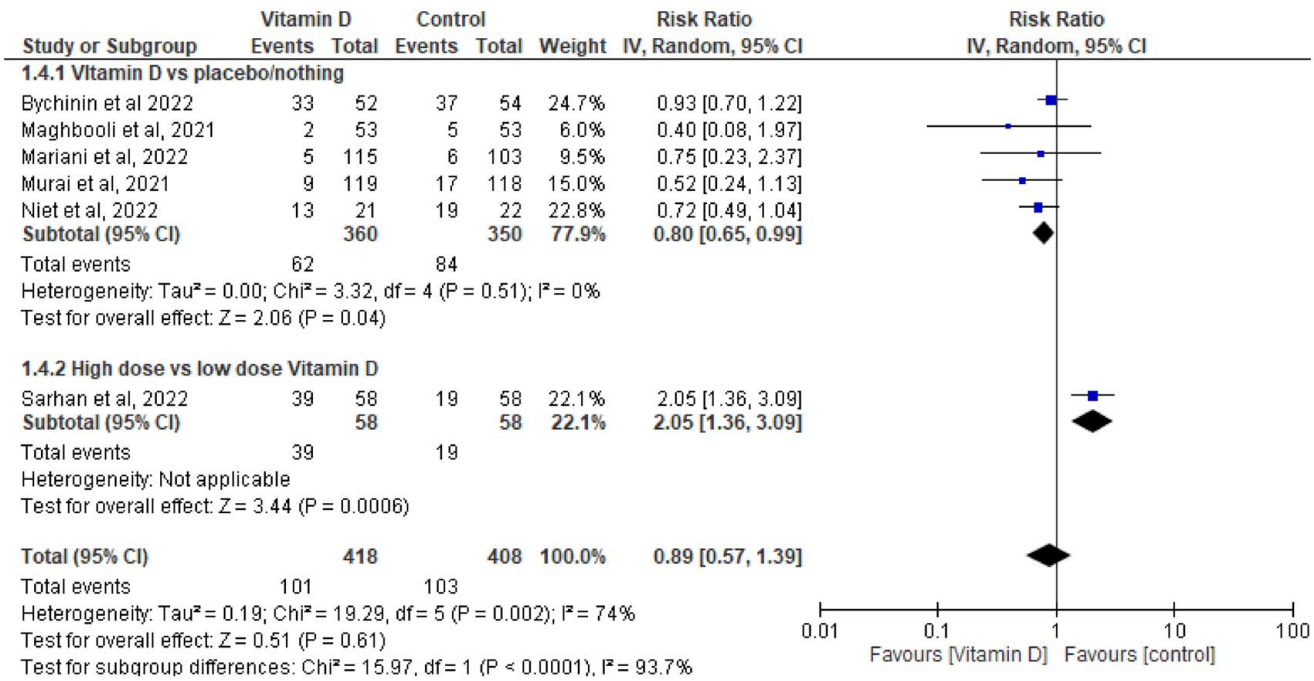

Figure 6. Need for mechanical ventilation.

important to note that vitamin D exerts most of its effects in its active form known as calcitriol[45]. One theory suggests that vitamin D aids the body's defense mechanism by stimulating macrophages and epithelial cells to produce cathelicidin (LL-37) and defensins against the virus. These substances interfere with the viral envelope and bind to the SARS-CoV-2 protein, which hinders the virus's ability to enter host cells. Intriguingly, higher LL-37 levels lower the levels of interleukin-17 (IL-17), which plays a vital role in the manifestation of COVID-19 complications, such as thrombosis and acute respiratory distress syndrome (ARDS)[46]. Meanwhile, another proposed hypothesis has been linked to cytokine production. Vitamin D is associated with a shift from an inflammatory state to an anti-inflammatory state by upregulating the production of anti-inflammatory cytokines such as IL-10 while decreasing the production of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor[47]. Lastly, vitamin D interacts with the renin-angiotensin-aldosterone system (RAAS) by inhibiting the production of renin, which can lead to decreased production of angiotensin II, thus reducing the risk of vasoconstriction and ARDS. Furthermore, it stimulates the production of ACE2, an enzyme that counteracts the effect of angiotensin II by converting it into angiotensin I, which is believed to cause vasodilation and has anti-inflammatory properties[45–50]. This property of vitamin D contributes to the regulation of the ACE: ACE2 balance, which, in its absence, gets disrupted by the binding of the SARS-CoV-2 protein to ACE2 in the respiratory mucosa[50].

The slight reduction in the length of hospitalization with vitamin D supplementation, as concluded from our meta-analysis, while not statistically significant, carries potential clinical relevance. Even a small reduction in hospital stay can have meaningful implications for both patient care and the efficient utilization of healthcare resources. Our findings align with studies conducted by Kummel *et al*., Sirbu *et al*., and Zaazouee *et al*.[24,25,51], where vitamin D supplementation and hospitalization duration showed a similar association. In a study conducted by Zaazouee *et al*.[51], a statistically insignificant relationship was initially reported. However, after sensitivity analysis, excluding one particular trial, significant results were observed in favor of the intervention group. These findings suggest that the effects of vitamin D may be influenced by many factors such as dosage or forms administered, or patient characteristics such as baseline

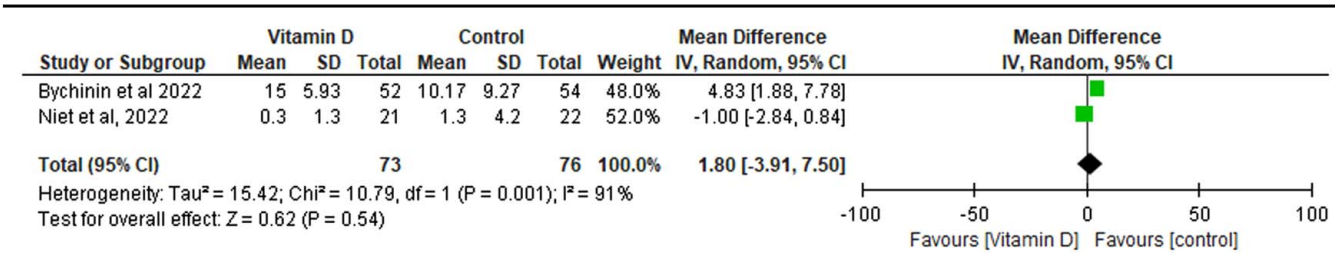

Figure 7. Length of mechanical ventilation (days).

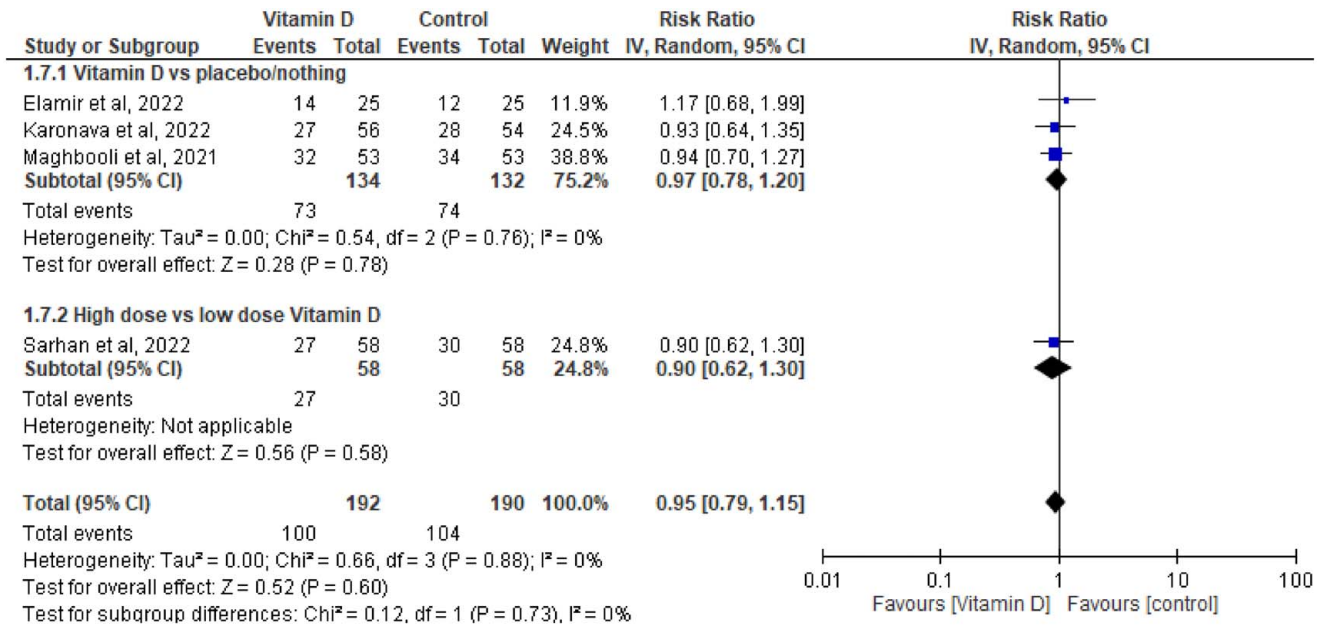

Figure 8. Need for supplemental oxygen.

vitamin D levels, gender, age, or existing comorbidities. Kummel and colleagues' study also corroborated with the aforementioned findings Kummel and colleagues pooled RCTs in which vitamin D was repeatedly administered, resulting in a continuous increase in serum concentrations. Although their analysis reported statistically insignificant results, much stronger effects of vitamin D on reduced hospital stay, as well as other COVID-19 outcomes, were observed[24]. This indicates that the dosing regimen may play a key role in vitamin D's benefits.

The most promising result of this meta-analysis is vitamin D supplementation significantly reducing the frequency of ICU admissions. However, findings reported in the previous systematic reviews regarding this outcome are mixed; Kummel *et al.*[24] reported a statistically insignificant association, while on the contrary, Hosseini *et al.*[26] concluded that vitamin D therapy decreases the rate of ICU admissions. Similarly, Zaazouee *et al.*[51] reported a significantly lower incidence of patients requiring ICU admission in the vitamin D group compared to the placebo group. The underlying differences among studies mentioned may be attributed to high heterogeneity in their included articles, which, in turn, might be due to varied intervention characteristics, different outcome measurement methods, or diverse patient population characteristics, including age, sex, BMI, or their pre-existing health conditions. Differences might also arise from the fact that each review has laid down its selection criteria, with some including observational studies due to the scarcity of data and others excluding them due to a high risk of bias.

This analysis indicated a non-significant pattern of reduced mortality with vitamin D supplementation. Comparing these results with existing literature revealed that while some analyses agreed with our results[24,26], findings from Argano *et al.* and Eccleisiis *et al.*'s research[52,53] contradicted them. These contradictions might be explained by the small number of pooled articles in Argano and colleagues' study and the high risk of bias resulting from the inclusion of observational studies in Eccleisiis and colleagues' research. Nonetheless, such differences warrant the need for more extensive research since it is crucial to understand the biological mechanisms through which vitamin D influences COVID-19 outcomes.

Tentolouros *et al.*[45]'s study emphasized a key area; it investigated whether "high" and "low" doses had a different effect on the outcomes. Interestingly, low doses significantly reduced mortality rates and ICU admissions, while high doses did not. Contrarily, this meta-analysis favoured the high-dose group in reducing ICU admissions, length of hospital stays, and mortality. One plausible explanation for Tentolouros and colleagues results may be that a high bolus dose of vitamin D upregulates the 24-hydroxylase CYP24A1 enzyme, which converts active calcitriol to inactive forms, and secondly, it upregulates FGF-23, which decreases mRNA 1-a-hydroxylase levels, the enzyme required for the hydroxylation of calcidiol to calcitriol[54].

Interestingly, vitamin D supplementation can induce vitamin K deficiency by negatively affecting vitamin K levels[55,56]. Past studies have reported that low vitamin K concentrations are associated with a higher risk of developing severe COVID-19 and increased IL-6 levels. Hence, vitamin D treatment for COVID-19 should be employed with caution, and further research should be conducted to evaluate serum vitamin K concentration in the context of vitamin D insufficiency, as well as the role of vitamin D supplementation in vitamin K levels and its related outcomes in the COVID-19 population[57–59].

The potential benefits of vitamin D supplementation, especially in reducing ICU admissions, could be monumental in the global fight against COVID-19. Hospitals and healthcare institutions might consider this low-cost intervention as an adjunct to current treatment protocols. Healthcare providers may consider integrating Vitamin D as part of a multifaceted approach to patient care, particularly with a focus on minimizing the burden on ICU resources. However, it's crucial to avoid overreliance on

Vitamin D as a standalone treatment as the optimal dosage, frequency, and patient populations suitable for this intervention require further clarification. It is important to note that our meta-analysis possesses crucial strengths that underscore its validity. Firstly, the inclusion of fourteen randomized controlled trials makes our findings more reliable and at a lower risk of bias compared to analyses with observational studies. Furthermore, we used multiple databases and gray literature sources using an exhaustive search strategy with no restrictions placed on language, region, age, or gender to retrieve all the relevant RCTs enhancing the reliability of our findings, ensuring that they are representative of a broader population. Moreover, we also evaluated the impact of high-dose vs. low-dose vitamin D supplementation on various outcomes in COVID-19 patients. These analyses provided insights into potential variations in treatment effects based on dosage and compared to baseline conditions.

Limitations

However, this present study is not without its limitations. A significant challenge was the high heterogeneity observed in certain pooled results. This variability might arise from different study methodologies or patient populations and could affect the overall consistency of our conclusions. Additionally, studies included had differences in the amounts and forms of vitamin D administered, and considering they were conducted in diverse geographical locations, this could potentially result in varying levels of sun exposure among patients. These differences in vitamin D levels due to sunlight exposure may introduce variability in the study results, potentially impacting the outcomes. Furthermore, some of the trials in this analysis were conducted in an open-label fashion, which has the potential to introduce bias into our study.

Conclusion

Vitamin D supplementation may be beneficial in decreasing the number of ICU admissions with no difference in other clinical outcomes such as length of hospital stay, length of ICU stay, length of mechanical ventilation, mortality, and need for mechanical ventilation or supplemental oxygen. Further large-scale RCTs are needed to evaluate the impact of different doses of vitamin D on COVID-19 and to provide definite conclusions.

Ethical approval

Ethics approval was not required for this systematic review.

Consent

Informed consent was not required for this systematic review.

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None.

Author contribution

M.A.: conceptualization, data curation, formal analysis, investigation, methodology, project. administration, methodology, software, visualization. M.M.S.: project administration, resources, validation, investigation, visualization, writing—original draft. S.V.: data curation, investigation, investigation, writing—original draft. M.E.: Validation, resources, writing—review and editing. I.A.: data curation, methodology, investigation, resources. E.A.: data curation, methodology, writing—review and editing. M.O.O.: writing—review and editing, visualization, and validation.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article

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