Journal of Innovative and Creativity
Journal Homepage: https://joecy.org/index.php/joecy
e-mail: journaljoecy@gmail.com

Faculty of Education
University of Pahlawan Tuanku Tambusai
ISSN 2775-771X (Online)
ISSN 2962-570X (Printed)
6 (1) 2026, Page: 16986-16997

Effect of Adjunctive Vitamin D Therapy on COVID-19 Mortality : An Evidence-Based Case Report

Raihan Abdullah [1*], Azira Isnaini Salsabilla [2], Yolanda Safitri [3], Vivi Saharani Saputri [4], Nabilla Syaharani [5], Nur Khalisha Yahya [6]

Affiliation (Department, Faculty/Unit, University/Institution, Country)
[1]Bachelor Student of Faculty of Military Medicine, The Republic of Indonesia Defense University, Bogor, Indonesia.
[4]Bachelor Student of Faculty of Military Medicine, The Republic of Indonesia Defense University, Bogor, Indonesia.
[5]Bachelor Student of Faculty of Military Medicine, The Republic of Indonesia Defense University, Bogor, Indonesia.
[6]Bachelor Student of Faculty of Military Medicine, The Republic of Indonesia Defense University, Bogor, Indonesia.

Corresponding Author : namikazeraihan157@gmail.com

Published: March, 2026

ABSTRAK

Introduction: Vitamin D plays an essential role in immune modulation by enhancing antimicrobial peptide production (cathelicidin, defensin), suppressing proinflammatory cytokines (IL-6, TNF-α), and increasing anti-inflammatory cytokines (IL-10). These mechanisms may help reduce cytokine storm risk, a major cause of COVID-19 mortality. Observational studies have shown that low 25(OH)D levels are associated with increased disease severity and mortality, yet evidence from randomized controlled trials (RCTs) and meta-analyses remains inconsistent.
Methods: A systematic literature review was performed using PubMed, Scopus, and EBSCO databases. Eligible studies included RCTs, systematic reviews, and meta-analyses comparing standard COVID-19 therapy with or without vitamin D supplementation and reporting mortality outcomes. All selected studies were critically appraised for validity, importance, and applicability using the Centre for Evidence-Based Medicine (CEBM) tools.
Results: From 245 identified articles, six met inclusion criteria (one RCT and five systematic reviews/meta-analyses). Most reported a trend of lower mortality in the vitamin D group, though not statistically significant. One meta-analysis showed a 55% mortality risk reduction (OR = 0.45; 95% CI 0.24–0.86; p = 0.02) but with high heterogeneity (I^2 = 66.96%). Differences in dosage, formulation, baseline vitamin D levels, and disease severity likely contributed to inconsistent outcomes.
Conclusion: Vitamin D supplementation as adjunctive therapy shows no potential in reducing mortality among COVID-19 patients. Routine administration is not recommended; further large-scale studies with standardized doses and focus on vitamin D deficient subgroups are necessary to clarify its clinical benefits.

Keywords: COVID-19, vitamin D, mortality, adjunctive therapy

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has triggered a global health crisis since it was first reported in late 2019 in Wuhan, China.[1] The pandemic has resulted in millions of confirmed cases and deaths worldwide, exerting a profound impact on healthcare systems, economies, and social structures across nations.[2] In Indonesia, morbidity and mortality rates due to COVID-19 remain high, particularly among patients with risk factors such as advanced age, obesity, hypertension, diabetes mellitus, and

cardiovascular diseases.[3] These conditions highlight the urgent need for therapeutic strategies that not only focus on managing infection but also aim to reduce complications and mortality. In this context, adjuvant therapies including vitamin supplementation, immunomodulatory agents, and anti-inflammatory treatments represent additional approaches that may improve clinical outcomes and decrease mortality among patients with COVID-19.[4]

Vitamin D plays a critical role in regulating both innate and adaptive immune responses. It promotes the production of antimicrobial peptides such as cathelicidin and defensins, which enhance antiviral defenses in respiratory epithelial cells.[5] Moreover, vitamin D modulates the immune system by suppressing pro-inflammatory cytokines (e.g., IL-6, TNF-α) and promoting anti-inflammatory cytokines (e.g., IL-10), thus reducing the risk of cytokine storm a major cause of morbidity and mortality in severe COVID-19 cases.[6] Early observational studies have demonstrated a significant association between low serum 25-hydroxyvitamin D levels and increased susceptibility to SARS-CoV-2 infection as well as greater disease severity.[7,8]

A large cohort study in the United States found that patients with vitamin D deficiency had a higher likelihood of testing positive for SARS-CoV-2,[9] while another study reported that sufficient vitamin D levels were linked to reduced hospitalization and mortality among COVID-19 patients.[10] These findings suggest that vitamin D may play a protective role through its immunomodulatory and anti-inflammatory properties, supporting its potential as an adjunctive therapy in COVID-19 management.

Despite growing evidence linking vitamin D deficiency with increased susceptibility and severity of COVID-19, the current clinical evidence from randomized controlled trials (RCTs) remains limited and inconclusive.[11] Several observational and retrospective studies have suggested that low serum 25-hydroxyvitamin D levels are associated with worse outcomes, including higher rates of hospitalization, intensive care admission, and mortality.[12]

However, large-scale RCTs evaluating the direct impact of vitamin D supplementation on COVID-19 mortality have shown mixed results.[13] Some trials report that high-dose vitamin D supplementation does not significantly reduce hospital length of stay or mortality, while others indicate improvements in clinical recovery and reduced hospitalization, though mortality benefits are not consistently observed.[14]

These inconsistencies highlight the need for more detailed clinical documentation and evidence-based case reports to explore the potential role of adjunctive vitamin D therapy in improving patient outcomes. Evidence-based case reports can provide valuable real-world insights by integrating clinical experience with the best available research evidence, helping to bridge the current gap between theory and practice in the use of vitamin D as an adjunctive therapy for COVID-19.

In this case, a 58-year-old man presented to the emergency department with complaints of shortness of breath and productive cough that had persisted for five days prior to admission. The dyspnea had progressively worsened, particularly during walking or talking, and slightly improved with rest. The patient also reported high-grade fever, chills, and myalgia for approximately one week.

Physical examination revealed a dyspneic patient with a respiratory rate of 30 breaths per minute, oxygen saturation of 87% on room air, and a body temperature of 38.5°C. Laboratory findings showed elevated levels of D-dimer, ferritin, and C-reactive protein (CRP), with a positive RT-PCR test confirming COVID-19 infection. Serum 25-hydroxyvitamin D level was 22 ng/mL, indicating hypovitaminosis D.

Based on the clinical condition, the physician considered administering vitamin D supplementation as an adjunctive therapy in addition to the standard COVID-19 treatment regimen. However, there was uncertainty regarding the effectiveness of vitamin D supplementation in reducing mortality among COVID-19 patients.

METHODS

Search Strategy

A comprehensive literature search was independently conducted by six researchers to identify studies investigating vitamin D supplementation and its effect on mortality among patients with COVID-19. The PICO formulation for this review is as follows, Population (P) Patients diagnosed with COVID-19 (with or without vitamin D deficiency); Intervention (I) Vitamin D supplementation as an adjunctive therapy along with standard treatment; Comparison (C) Standard therapy without vitamin D supplementation or placebo; Outcome (O) Reduction in mortality among COVID-19 patients. The

literature search was performed across three electronic databases PubMed, Scopus, and EBSCO using keywords that corresponded to the clinical research question, as outlined in Table 1. The search strategy was implemented systematically and transparently in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as illustrated in Figure 1.

From the results obtained across the three electronic databases, all duplicate articles were removed prior to screening. The remaining records were then screened by evaluating their titles and abstracts based on the eligibility criteria established by the Evidence-Based Case Report (EBCR) framework. The final inclusion of studies was determined through a comprehensive full-text review of each article, followed by evaluation according to the predefined inclusion criteria.

Eligibility Criteria

The inclusion criteria for this review focused on adult patients aged over 18 years with confirmed COVID-19 infection, encompassing all levels of disease severity mild, moderate, and severe regardless of whether they had vitamin D deficiency. Eligible studies included Randomized Controlled Trials (RCTs), systematic reviews, and meta-analyses that investigated the relationship between vitamin D supplementation and mortality outcomes among COVID-19 patients.

Conversely, studies were excluded if they involved pediatric or pregnant populations, utilized vitamin D interventions without a comparison group receiving standard therapy or placebo, or did not include vitamin D supplementation as part of the study design. In addition, animal studies, in vitro research, and studies for which the full-text articles were unavailable were also excluded from the review.

Critical Appraisal

The assessment tool from the Centre for Evidence-Based Medicine (CEBM) was employed to systematically evaluate the quality of evidence included in this EBCR. The CEBM critical appraisal checklists for Randomized Controlled Trials (RCTs) and systematic reviews were applied according to the respective study designs. For the RCT appraisal checklist, the quality of each study was assessed based on internal validity, focusing primarily on aspects such as randomization, blinding, and the comparability of study groups, as well as clinical significance of the findings. In contrast, for systematic reviews, the assessment was conducted based on the completeness and appropriateness of the search strategy, the validity of the included studies, and the degree of heterogeneity among the studies evaluated.

RESULTS

Search Findings

As shown in Figure 1, the literature search was conducted through three electronic databases PubMed, Scopus, and EBSCO yielding a total of 245 articles related to vitamin D supplementation and mortality among COVID-19 patients. After removing 18 duplicate articles, a total of 227 records were screened based on their titles and abstracts. From this process, 109 articles were excluded for not addressing vitamin D supplementation, and 80 articles were excluded for not reporting mortality data. Subsequently, 38 articles underwent a full-text review, and after further selection based on inclusion and exclusion criteria, a total of six studies were included. These consisted of five systematic reviews or meta-analyses and one randomized controlled trial (RCT), which were selected and considered eligible for inclusion in this Evidence-Based Case Report (EBCR).

Critical Appraisal

Based on the CEBM appraisal tool by the University of Oxford, six studies were critically evaluated five systematic reviews/meta-analyses and one randomized controlled trial (RCT). Overall, most studies showed good methodological quality with clear PICO, appropriate inclusion criteria, and valid search strategies.

From Table 2, the majority of systematic reviews demonstrated consistent methodology but varied in outcome similarity and heterogeneity. Tentolouris et al. (2022) showed a non-significant reduction in mortality (OR = 0.597; 95% CI 0.318–1.121; p = 0.109) with moderate heterogeneity (I^2 = 62.4%). Mirghani & Begum (2024) and Kümmel et al. (2022) reported no significant association (OR = 1.16 and OR = 0.74, respectively) and low heterogeneity (I^2 = 18–19%), indicating more consistent

findings. Sartini et al. (2024) and Rawat et al. (2021) found non-significant results (OR = 0.80; RR = 0.55) despite trends favoring vitamin D, though Rawat et al. had moderate heterogeneity (I^2 = 58%).

From Table 3, the only RCT (De Niet et al., 2022) was categorized as Level 2 evidence with adequate randomization and blinding. Mortality was lower in the vitamin D group (4.8%) compared to placebo (12%), but the result was not statistically significant (p = 0.129). The calculated Number Needed to Treat (NNT) was 11.27, suggesting a potential clinical benefit though not statistically confirmed.

Vitamin D Mode of Administration and Dose

Across all included studies as shown in Table 4, several forms and regimens of vitamin D were reported. The predominant forms were cholecalciferol (vitamin D_3), calcifediol (25-hydroxyvitamin D_3), and calcitriol (1,25-dihydroxyvitamin D_3). Dosage and administration varied widely, ranging from low to moderate daily or weekly doses (1,000–25,000 IU) to high single or short-term bolus doses (200,000–500,000 IU). Some regimens employed stepwise loading followed by maintenance therapy, particularly with calcifediol formulations. Despite this variation, most studies reported no clear dose response relationship with mortality outcomes. The heterogeneity in formulations and dosing schedules may partly explain the inconsistency in observed results.

Abbreviations
RCT : Randomized Controlled Trial
OR : Odds Ratio
RR : Risk Ratio
NNT : Number Needed to Treat

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Figure 1. PRISMA diagram
Units of Measurement
Table 1. Search strategy

Database	Search Strategy	Hits	Selected Articles
Pubmed	(((((((COVID-19) OR (coronavirus disease 2019)) OR (SARS-CoV-2)) AND (Vitamin D)) OR (cholecalciferol)) OR (calcitriol)) OR (vitamin d3)) AND (Mortality) Filters: in the last 5 years, Free full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, English, Humans	105	3
SCOPUS	TITLE-ABS-KEY (COVID-19 OR SARS-CoV-2 AND Vitamin D OR Cholecalciferol OR Vitamin D3 AND Mortality OR Death)	64	1
EBSCO	#1 covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19 #2 supplementation or supplements or supplement	76	2

	#3 vitamin d or calcitriol or cholecalciferol or vitamin d3 #4 mortality or mortality rate or death or death rate #5 #1 AND #2 AND #3 AND #4

Figure 1. PRISMA diagram

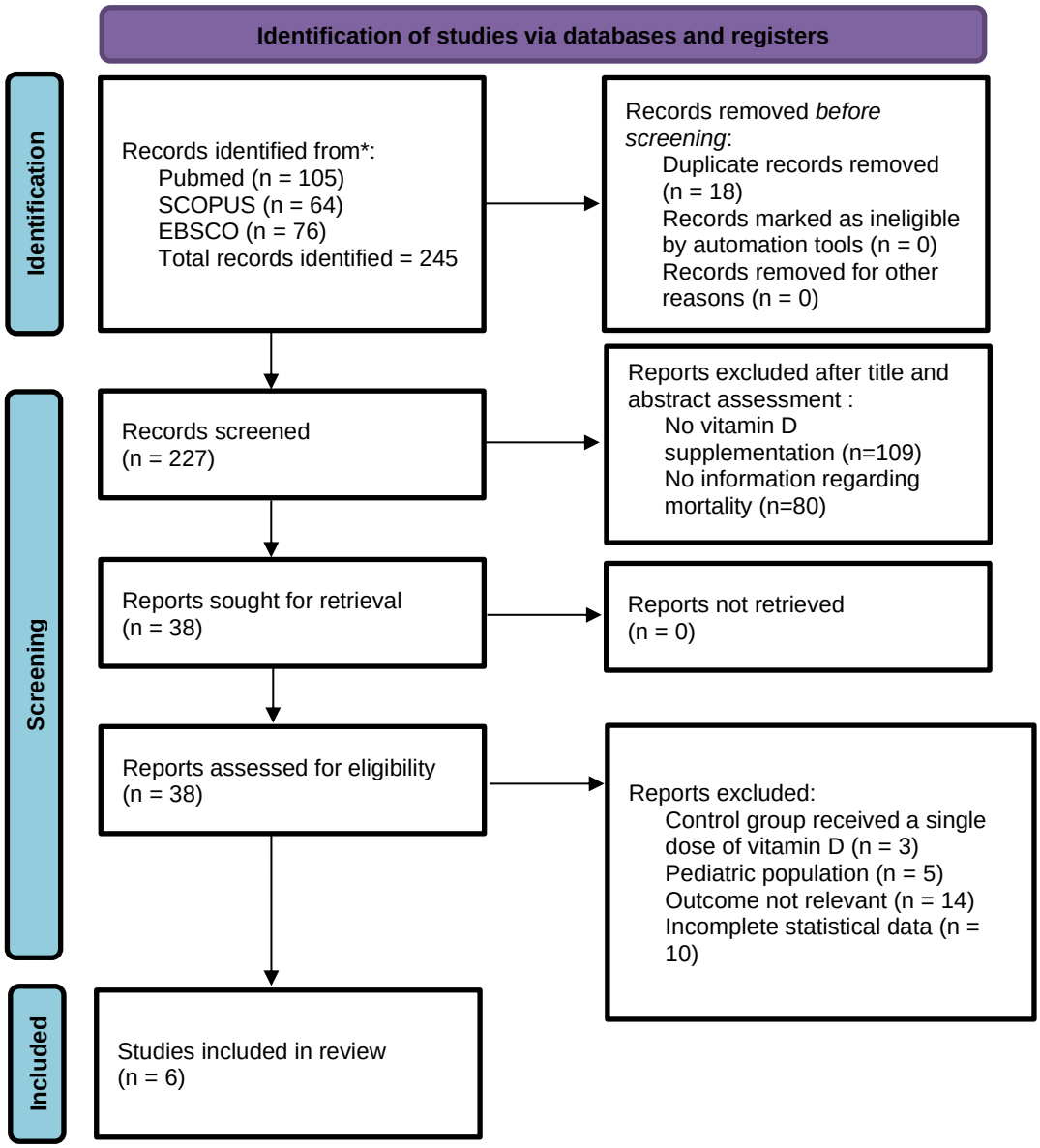


Table 2. Critical appraisal of the systemic reviews using the CEBM tool by the University of Oxford

	FAAT					Result		
Author	Clear PICO	Appropriate searching	Appropriate inclusion criteria	Study validity	Result similarity	Total 95% CI	Heterogeneity	Overall effect
Tentolouris et al., (2022)	+	+	+	+	-	OR 0.597 [0.318,1.121]	Q value = 21.27 Df = 8 P = 0.006 I^2 = 62.4%	Z= -1,604 (p=0,109)
Mirghani & Begum (2024)	+	+	+	+	+	OR 1.16 [0.84, 1.59]	Chi^2 = 11.10 Df = 9 P = 0.27 I^2 = 19%	Z = 0.91 (P = 0.36)
Kümmel et al., (2022)	+	+	+	+	+	OR 0.74 [0.32, 1.71]	P = 0.30 I^2 = 18%	Z = -0.70 (P = 0.48)
Sartini et al., (2024)	+	+	+	+	-	OR 0.80 [0.61, 1.04]	Not reported	Not reported
Dimple Rawat et al. (2021)	+	+	+	+	-	RR 0.55 [0.22, 1.39]	Tau^2 = 0.48 Chi^2 = 7.10 Df = 3 P = 0.07 I^2 = 58%	Z = 1.26 (P = 0.21)

Table 3. Critical appraisal of RCTs using the CEBM tool by the University of Oxford

Author	No. of Participants	LoE	Randomisation	Baseline Similarity	Equally Treated	Intention to Treat	Blinding	RR	ARR	RRR	NNT/ NNH	95% CI, P *value*
De Niet et al., (2022)	43	2	+	+	+	-	+	0.349	0.0887	0.651	NNT 11.27	-, 0.129

Table 4. Characteristics of studies that meet the selection criteria

Author	Study type	Intervention	Result
Tentolouris et al., (2022)	Systematic review and meta-analysis - 2 RCTs - 1 Quasi-experimental - 7 Observational study	Forms of Vitamin D Used: - Cholecalciferol (Vitamin D3) - Calcifediol (25-hydroxyvitamin D3) Types of dosage: - High-dose (bolus): 200,000–400,000 IU administered once or over a few days - Low to moderate dose (daily/weekly): 1,000–25,000 IU per day or per week	The pooled analysis demonstrated a lower mortality rate in the vitamin D group (10.46%) than in controls (25.81%), but the difference was not statistically significant (OR = 0.597; 95% CI 0.318–1.121; p = 0.109).
Mirghani & Begum (2024)	Meta-analysis of RCTs	Forms of Vitamin D Used: - Cholecalciferol (D3) - Calcifediol (25-hydroxy-D3), Calcitriol (1,25-dihydroxy-D3) - Alfacalcidol (1-hydroxy-D3) Types of dosage: - ranged from 1,000 IU/day to 500,000 IU single oral bolus	The meta-analysis showed no significant association between vitamin D supplementation and mortality (OR = 1.16; 95% CI 0.84–1.59; p = 0.36). Mortality rates were similar between intervention and control groups.
Kümmel et al., (2022)	Meta-analysis of RCTs	Forms of Vitamin D Used: - Cholecalciferol (Vitamin D3) - Calcifediol (25-hydroxyvitamin D3 - Calcitriol (1,25-dihydroxyvitamin D3) Types of dosage: - High single (bolus) dose:	The meta-analysis found a non-significant reduction in mortality (OR = 0.74; 95% CI 0.32–1.71; p = 0.48), indicating no statistically meaningful benefit in reducing death.

		5,000 μg (200,000 IU) - High daily doses: 1,500 μg per day (~60,000 IU) - Moderate daily doses: 125–250 μg per day (5,000–10,000 IU)	
Sartini et al., (2024)	Systematic review and meta-analysis - 19 RCT	Forms of Vitamin D Used: - Cholecalciferol (Vitamin D3) - Calcifediol (25-hydroxyvitamin D3) - Calcitriol (1,25-dihydroxyvitamin D3) Types of dosage: - High single-dose (bolus): 200,000 IU - High daily-dose (short-term): 60,000 IU/day for 7–14 days - Moderate daily-dose: 5,000–10,000 IU/day for 14 days	The pooled OR was 0.80 (95% CI: 0.61–1.04), indicating that vitamin D supplementation was associated with a reduction in mortality risk among COVID-19 patients, although this result was not statistically significant. The lack of significance may be explained by differences in vitamin D dosage, formulation, and timing of administration, as well as variability in disease severity across the included trials.
Dimple Rawat et al. (2021)	Systematic review and meta-analysis - 3 RCTs - 2 quasi-experimental studies)	Forms of Vitamin D Used: - Cholecalciferol (Vitamin D3) - Calcifediol (25-hydroxyvitamin D3) Types of dosage: - High single-dose (bolus): 80,000 IU – 200,000 IU - High short-term daily dose: 60,000 IU/day for 7–14 days - Stepwise loading + maintenance regimen: *Calcifediol* 0.532	The pooled effect showed no significant difference in mortality (RR = 0.55; 95% CI 0.22–1.39; p = 0.21). Mortality outcomes favored vitamin D but lacked statistical significance.

		mg initially, then 0.266 mg weekly	
De Niet et al., (2022)	Randomized Controlled Trial (RCT)	Oral vitamin D_3 supplementation (25,000 IU/day for 4 consecutive days, then 25,000 IU/week up to 6 weeks) in addition to standard COVID-19 therapy. The control group received placebo plus standard therapy	The mortality rate specifically related to COVID-19 was lower in the vitamin D group (4.8%) compared to the placebo group (12%). However, this difference was not statistically significant ($p = 0.129$), indicating that vitamin D supplementation did not significantly reduce COVID-19 related mortality in this study.

DISCUSSION

Six studies were appraised in this evidence-based case report, consisting of one randomized controlled trial (RCT) and five systematic reviews and meta-analyses evaluating the effect of adjunctive vitamin D supplementation on COVID-19 mortality. Overall, the included studies demonstrated a consistent direction of effect, showing a tendency toward lower mortality among patients receiving vitamin D supplementation, although most results did not reach statistical significance.

Tentolouris et al. (2022) included RCTs, quasi-experimental, and observational studies, using various forms and doses of vitamin D. The pooled analysis revealed a lower mortality rate in the vitamin D group (10.46%) compared to the control group (25.81%), with an odds ratio (OR) of 0.597 (95% CI: 0.318–1.121; $p = 0.109$). Although this reduction was not statistically significant, it indicated a potential protective trend. The study showed considerable heterogeneity ($I^2 = 62.4\%$), due to variations in study design, dosage, and patient populations.[15]

Similarly, Mirghani & Begum (2024) evaluated multiple vitamin D analogs (cholecalciferol, calcifediol, calcitriol, and alfacalcidol) across a wide dosing range (1,000 IU/day to 500,000 IU single bolus). Their meta-analysis found no significant association between vitamin D supplementation and mortality (OR = 1.16; 95% CI: 0.84–1.59; $p = 0.36$), with low heterogeneity ($I^2 = 19\%$), indicating consistency among included trials despite the lack of significant benefit.[16]

Kümmel et al. (2022) also reported a non-significant reduction in mortality (OR = 0.74; 95% CI: 0.32–1.71; $p = 0.48$). Similar to the previous review, heterogeneity was low ($I^2 = 18\%$), suggesting that, although the trend favored vitamin D, the pooled data did not confirm a clear mortality benefit.[13]

Sartini et al. (2024) demonstrated a pooled OR of 0.80 (95% CI 0.61–1.04), indicating a potential reduction in mortality risk. Although not statistically significant, the results aligned with other studies showing a protective tendency. Variations in dosage, duration of administration, and differences in disease severity may have contributed to this variability.[17]

Meanwhile, Rawat et al. (2021) analyzed three RCTs and two quasi-experimental studies, reporting no significant difference in mortality between the vitamin D and control groups (RR = 0.55; 95% CI: 0.22–1.39; $p = 0.21$). Nevertheless, the direction of the pooled estimate favored vitamin D, supporting the overall trend observed in other analyses.[18]

The only RCT appraised, De Niet et al. (2022), investigated oral vitamin D_3 supplementation (25,000 IU/day for four days followed by 25,000 IU/week for six weeks) as an adjunct to standard therapy. The COVID-19–related mortality rate was lower in the vitamin D group (4.8%) compared with the placebo group (12%), though the difference did not reach statistical significance ($p = 0.129$). The

relative risk reduction (RRR) was 65.1%, with an absolute risk reduction (ARR) of 8.87% and a number needed to treat (NNT) of 11. These values suggest a potential clinical benefit, even if statistical significance was not achieved.[10]

The inconsistency across studies may be explained by several factors. First, baseline vitamin D status appears to play a key role; patients with deficiency are more likely to benefit from supplementation than those with sufficient levels. Second, differences in dosage and formulation may influence outcomes. The reviewed studies used varying regimens, from low daily doses (1,000 IU) to high single boluses of up to 500,000 IU. Third, disease severity and timing of supplementation are also important determinants. Early administration during mild or moderate illness may enhance immune regulation, whereas delayed supplementation in severe disease might yield limited benefit.

Biologically, the role of vitamin D in immune regulation provides a plausible mechanism for its potential benefits in COVID-19. Vitamin D enhances innate immune responses by inducing antimicrobial peptides such as cathelicidin and defensins and modulates adaptive immunity by suppressing pro-inflammatory cytokines (e.g., IL-6, TNF-α) while increasing anti-inflammatory cytokines (e.g., IL-10). These immunomodulatory effects could mitigate the cytokine storm that contributes to severe COVID-19 outcomes. However, despite this mechanistic plausibility, clinical evidence remains inconclusive.

In summary, the current body of evidence indicates that adjunctive vitamin D supplementation may offer immunological and potential survival benefits for COVID-19 patients, particularly those with vitamin D deficiency, but the results are inconsistent and not statistically robust. Vitamin D supplementation remains safe, affordable, and biologically reasonable as an adjunctive therapy, yet current data are insufficient to recommend its routine use solely for reducing COVID-19 mortality.

Future studies should focus on large-scale, well-designed RCTs that control for baseline vitamin D levels, disease severity, and standardized dosing regimens. Such research would clarify whether specific subgroups especially vitamin D deficient or high-risk patients derive measurable survival advantages from adjunctive vitamin D therapy.

CONCLUSION

Vitamin D supplementation as an adjunctive therapy shows no potential in reducing mortality related to COVID-19. Therefore, it is not recommended to routinely add oral vitamin D to the current standard treatment regimen for patients with this disease. Further studies involving larger populations and standardized dosing regimens are needed to determine vitamin D supplementation's true effect on the general population of patients with this disease, particularly in regard to its safety, efficacy, and potential benefit for individuals with vitamin D deficiency.

IMPLICATION

STRENGTHS AND LIMITATION

This evidence-based case report has the advantage of using a comprehensive and systematic approach, integrating clinical observation with the best available evidence from randomized controlled trials, systematic reviews, and meta-analyses. The use of the CEBM (Centre for Evidence-Based Medicine) critical appraisal tool strengthens the methodological rigor and enhances the reliability of findings. Furthermore, this study highlights the clinical relevance of adjunctive vitamin D therapy in the context of COVID-19, providing practical insights for real-world clinical decision-making.

However, this study also has several limitations. The number of included studies is limited, and most evidence is derived from secondary data rather than primary clinical trials. Variability in vitamin D dosage, formulations, and patient characteristics across studies contributes to heterogeneity, which may affect the precision of conclusions. Additionally, as this is a single case-based report, generalization to broader populations should be made cautiously. These factors may influence the interpretation and applicability of the results.

CONFLICT OF INTEREST

All authors declare that there are no conflicts of interest regarding this publication

ACKNOWLEDGMENTS

None

DECLARATION OF USING AI

None

FUNDING SOURCES

This study did not require any funding

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