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EFFECT OF VITAMIN D SUPPLEMENTATION ON CLINICAL OUTCOMES IN CRITICALLY ILL ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS WITH SUBGROUP ANALYSIS BY BASELINE VITAMIN D STATUS

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ABSTRACT

Introduction: Vitamin D deficiency is highly prevalent among critically ill patients and has been associated with increased morbidity and mortality. Despite strong biological plausibility and supportive observational data, randomized controlled trials (RCTs) evaluating vitamin D supplementation in this population have yielded inconsistent results. This study aimed to systematically evaluate the effect of vitamin D supplementation on clinical outcomes, particularly mortality, in critically ill adult patients. **Methods**: A systematic review and meta-analysis of RCTs was conducted in accordance with PRISMA guidelines. Electronic databases (PubMed, Scopus, ScienceDirect, and Cochrane) were searched for studies published between January 2015 and December 2025. Eligible studies included RCTs involving adult

critically ill ICU patients receiving vitamin D supplementation compared with placebo. The primary outcome was all-cause mortality. Secondary outcomes included ICU length of stay, hospital length of stay, and duration of mechanical ventilation. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Risk of bias was assessed using the Cochrane RoB 2 tool. **Results**: Five RCTs comprising 1,736 critically ill patients (871 in the intervention group and 865 in the control group) were included. Vitamin D supplementation was associated with a no statistically significant difference in mortality between groups (RR 0.74; 95% CI 0.53–1.05; p = 0.09). Substantial heterogeneity was observed (I^2 = 71.1%, p = 0.008), with a wide prediction interval (0.28–1.96). Larger trials demonstrated neutral effects, whereas smaller studies reported more pronounced benefits, suggesting a potential small-study effect. Secondary outcomes were inconsistently reported and showed variable findings, precluding quantitative synthesis. **Discussion**: The findings suggest that vitamin D supplementation does not provide a consistent mortality benefit in unselected critically ill populations. The observed heterogeneity, variation in study design, and potential influence of small-study effects contribute to the uncertainty of the overall estimate. While biological plausibility and subgroup signals indicate possible benefit in selected patients, current evidence remains insufficient to support routine use for mortality reduction. **Conclusion**: Vitamin D supplementation in critically ill adult patients was associated with a non-significant trend toward reduced mortality, with substantial heterogeneity across studies. Routine use of high-dose vitamin D for mortality reduction cannot be recommended

based on current evidence. Further large-scale, well-designed trials focusing on clearly defined subgroups are needed.

Keywords: Vitamin D; critical illness; intensive care unit; mortality; randomized controlled trial; meta-analysis

INTRODUCTION

Vitamin D deficiency is highly prevalent among critically ill patients and has been consistently associated with increased morbidity and mortality. Observational studies have reported that low serum 25-hydroxyvitamin D [25(OH)D] levels are linked to adverse clinical outcomes, including prolonged intensive care unit (ICU) stay, increased risk of infection, and higher mortality rates.[1,2] The biological plausibility of these findings is supported by the role of vitamin D in modulating both innate and adaptive immune responses, regulating inflammatory pathways, and maintaining endothelial and epithelial integrity.[3,4]

Vitamin D deficiency may contribute to worse outcomes in critically ill patients through several interconnected pathophysiological mechanisms. At the immune level, vitamin D plays a crucial role in enhancing innate immunity by inducing antimicrobial peptides such as cathelicidin (LL-37) and defensins, which are essential for pathogen clearance.[4] In parallel, vitamin D modulates the adaptive immune response by suppressing excessive proinflammatory cytokine production, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), thereby potentially reducing the risk of cytokine-mediated tissue damage.[5] Additionally, vitamin D is involved in maintaining endothelial integrity and regulating the renin–angiotensin–aldosterone system (RAAS), both of which are critical in the pathogenesis of sepsis, acute respiratory distress syndrome (ARDS), and multiorgan dysfunction.[6,7] Deficiency in vitamin D may therefore exacerbate systemic inflammation, increase vascular permeability, and impair host defence mechanisms, ultimately contributing to disease severity and poorer clinical outcomes in critically ill patients.

In critically ill patients, several factors contribute to vitamin D deficiency, including reduced sunlight exposure, impaired hepatic and renal hydroxylation, fluid resuscitation–related hemodilution, and increased metabolic consumption during systemic inflammation. These mechanisms have led to the hypothesis that vitamin D

supplementation may improve clinical outcomes in this population, particularly in patients with severe deficiency.[8]

Despite strong observational evidence, randomized controlled trials (RCTs) evaluating vitamin D supplementation in critically ill patients have yielded inconsistent results. Early trials suggested potential benefits in selected subgroups, particularly among patients with severe vitamin D deficiency.[9] However, larger and more recent trials, such as the VIOLET study, failed to demonstrate a significant reduction in mortality or other clinically relevant outcomes with high-dose vitamin D supplementation.[10] These conflicting findings raise important questions regarding the true clinical effectiveness of vitamin D supplementation and the potential role of baseline vitamin D status as an effect modifier.

Furthermore, smaller RCTs have frequently reported more favourable outcomes compared to larger trials, suggesting the possibility of small-study effects or methodological heterogeneity influencing the observed results. Variations in study design, dosing regimens, timing of administration, and patient populations further complicate the interpretation of existing evidence.[11]

Given these inconsistencies, a comprehensive synthesis of current RCT evidence is necessary to clarify the role of vitamin D supplementation in critically ill patients. Therefore, this study aims to systematically review and synthesize randomized controlled trials evaluating the effect of vitamin D supplementation on clinical outcomes, particularly all-cause mortality, in critically ill adult patients.

METHODS

Study Design

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of vitamin D supplementation on clinical outcomes in critically ill adult patients. The study design and reporting were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] A comprehensive

and structured approach was applied to identify, select, and synthesize relevant studies. The review process included predefined eligibility criteria, systematic literature search, independent screening, and standardized data extraction.

Only randomized controlled trials were included to ensure a high level of evidence and minimize bias associated with observational studies. The primary outcome of interest was all-cause mortality, including 28-day, 90-day, or in-hospital mortality, depending on the definitions used in the included studies. Secondary outcomes included ICU length of stay, hospital length of stay, and duration of mechanical ventilation. Studies without sufficient data for quantitative synthesis were included in qualitative analysis where appropriate.

Search Strategy

A comprehensive literature search was conducted to identify relevant randomized controlled trials evaluating the effect of vitamin D supplementation on clinical outcomes in critically ill adult patients. The search was performed in multiple electronic databases, including Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, ScienceDirect, and Scopus covering studies published from January 2015 to December 2025.

The search strategy combined controlled vocabulary (e.g., MeSH terms) and free-text keywords related to vitamin D and critical illness. The following key terms were used: “vitamin D”, “cholecalciferol”, “ergocalciferol”, “critical illness”, “intensive care unit”, “ICU”, “sepsis”, and “randomized controlled trial”. Boolean operators (“AND”, “OR”) were applied to refine the search, and filters were used to limit results to human studies and randomized controlled trials.

In addition to database searching, the reference lists of relevant articles and previous systematic reviews were manually screened to identify additional eligible studies. Grey literature and ongoing trials were also reviewed through clinical trial registries; however, studies without available outcome data were not included in the quantitative synthesis. The search process and study selection were conducted in accordance with PRISMA guidelines to ensure transparency and reproducibility.[12]

Inclusion and Exclusion Criteria

Studies were considered eligible for inclusion if they met the following criteria: (1) randomized controlled trials (RCTs); (2) involved adult patients (≥18 years) who were critically ill and admitted to an intensive care unit (ICU); (3) evaluated vitamin D supplementation as the primary intervention, including cholecalciferol or ergocalciferol administered via any route and dosage; and (4) reported clinically relevant outcomes, particularly all-cause mortality, including 28-day, 90-day, or in-hospital mortality. Studies that reported additional outcomes such as ICU length of stay, hospital length of stay, and duration of mechanical ventilation were also considered, provided that mortality data were available.

Studies were excluded if they met any of the following criteria: (1) non-randomized studies, including observational studies, cohort studies, case–control studies, reviews, or trial emulation analyses; (2) studies involving pediatric populations or non-critically ill patients; (3) studies conducted in non-ICU settings or focusing on prevention rather than treatment of critical illness (e.g., studies assessing ICU admission as an outcome in non-ICU patients); (4) trials in which vitamin D was administered in combination with other interventions (e.g., vitamin C or other supplements), making it impossible to isolate the independent effect of vitamin D; and (5) studies that did not report extractable clinical outcome data relevant for quantitative synthesis, such as trials reporting only biochemical or immunological markers without clinical endpoints.

In addition, studies with insufficient numerical data for effect size calculation, as well as ongoing trials or studies with unpublished results, were excluded from the meta-analysis but could be described narratively in the systematic review.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data collection form. Extracted information included study characteristics (first author, year of publication, study design, and sample size),

intervention details (form of vitamin D, dosage, route, timing, and duration), and comparator characteristics (placebo or standard care).

Outcome data were extracted for all-cause mortality as the primary outcome. Secondary outcomes included ICU length of stay, hospital length of stay, and duration of mechanical ventilation. Dichotomous outcomes were extracted as event counts, while continuous outcomes were recorded as means with standard deviations when available. Studies reporting medians and interquartile ranges were documented but were not pooled when transformation was not feasible.

When available, additional variables such as baseline serum 25-hydroxyvitamin D [25(OH)D] levels and illness severity scores (e.g., SOFA) were also extracted. However, due to inconsistent reporting across studies, these variables were not included in quantitative synthesis and were considered qualitatively in the interpretation of findings. Discrepancies between reviewers were resolved through discussion and consensus.

Risk of Bias Assessment

The risk of bias of the included studies was assessed independently by two reviewers using the Cochrane Risk of Bias tool for randomized controlled trials (RoB 2).[13] This tool evaluates potential sources of bias across several domains, including bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results.

Each domain was judged as “low risk,” “some concerns,” or “high risk” of bias according to the RoB 2 guidelines.[13] An overall risk of bias judgment was then assigned to each study based on the highest level of risk identified across the domains. Particular attention was given to allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, and consistency between reported outcomes and study protocols.

Given that several included trials were small and single-center studies, additional consideration was given to potential sources of bias such as baseline

imbalances, selective outcome reporting, and deviations from the intended intervention. Studies with unclear or insufficient reporting were classified conservatively as having "some concerns" to avoid overestimation of study quality.

Any disagreements between reviewers were resolved through discussion until consensus was reached. When necessary, the full text of the original article was re-examined to clarify unclear methodological details before assigning the final judgment. The results of the risk-of-bias assessment were presented narratively and summarized in tabular and graphical form to support interpretation of the overall findings.[13]

Statistical Analysis

Quantitative synthesis was performed for outcomes reported by at least two studies with sufficient numerical data. The primary outcome, all-cause mortality, was analyzed using pooled risk ratios (RRs) with 95% confidence intervals (CIs). A random-effects model (DerSimonian and Laird method) was applied due to expected clinical and methodological heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic and chi-square test.

Planned subgroup analyses included evaluation based on baseline vitamin D status; however, these analyses could not be performed due to inconsistent reporting across studies. Instead, exploratory subgroup analysis based on study size (larger vs smaller trials) was conducted to assess potential sources of heterogeneity. Sensitivity analysis was performed by excluding smaller studies with potential methodological limitations to evaluate the robustness of the pooled estimates.

Quantitative synthesis of continuous outcomes was not performed due to heterogeneity in reporting formats and insufficient comparable data across studies. Assessment of publication bias using funnel plots or Egger's regression test was not performed due to the limited number of included studies (<10). All statistical analyses were conducted using appropriate meta-analysis software, and a two-sided p-value <0.05 was considered statistically significant.

RESULTS

Study Selection

A comprehensive literature search identified a total of 66 records from electronic databases, including PubMed, Scopus, ScienceDirect, and Cochrane CENTRAL. After removal of duplicates, 39 studies remained for title and abstract screening. Of these, 24 articles were excluded based on predefined eligibility criteria. The full texts of 15 potentially relevant studies were then assessed, resulting in a final inclusion of five randomized controlled trials (RCTs) for qualitative and quantitative synthesis. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

The included studies comprised a total of 1736 critically ill adult patients admitted to the intensive care unit (ICU). The characteristics of the included trials are summarized in Table 1. Two large multicenter RCTs, VIOLET (2019) and VITdAL-ICU (2014), accounted for the majority of participants, while the remaining studies were smaller single-center trials with sample sizes ranging from approximately 30 to 120 patients.

All included studies evaluated vitamin D supplementation compared with placebo. The intervention regimens varied across studies, with most trials administering high-dose vitamin D_3 as a single bolus (e.g., 300,000 - 540,000 IU), while one study employed a loading dose followed by maintenance therapy. The route of administration included enteral and intramuscular delivery.

The study populations were heterogeneous, including patients with sepsis, ventilator-associated pneumonia (VAP), and general critically ill ICU populations. Baseline vitamin D deficiency was reported in most studies, although the definition and severity thresholds varied. Mortality outcomes were reported in all included trials, although the timing differed, including 28-day, 90-day, or in-hospital mortality. Secondary outcomes such as ICU length of stay and duration of mechanical ventilation were also variably reported.

Overall, while the included studies were similar in design as randomized controlled trials, there was notable variability in patient populations, vitamin D dosing strategies, and outcome definitions, indicating potential clinical heterogeneity across studies.

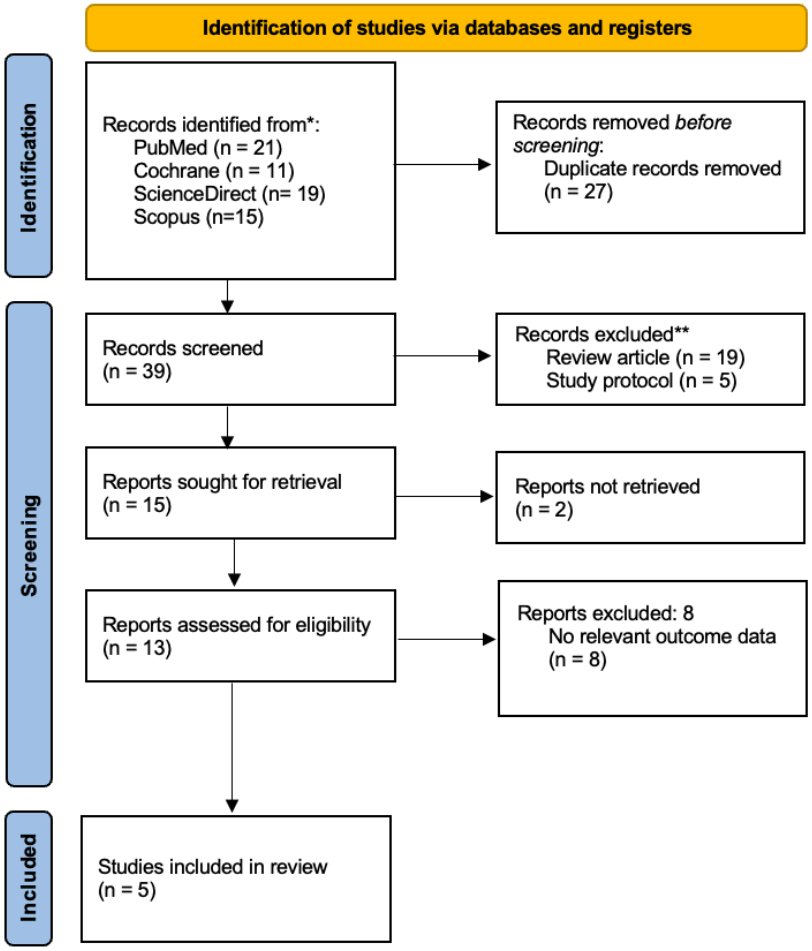

Figure 1. PRISMA 2020 flow diagram; study selection process[12]

Study Characteristics

A total of five RCTs were included in this study, comprising critically ill adult patients admitted to the ICU. The detailed characteristics of the included studies are

presented in Table 1. The included trials varied considerably in terms of sample size, study design, and patient populations. Two large multicenter RCTs, VIOLET (2019)[10] and VITdAL-ICU (2014)[9], accounted for the majority of participants, while the remaining three studies (Bhattacharyya et al., 2021[14]; Miroliaee et al., 2017[15]; and Sistanizad et al., 2021[16]) were smaller single-center trials with relatively limited sample sizes.

Table 1. Summary characteristics of included randomized controlled trials

Characteristic	Value
Number of studies (participants)	5 (n = 1,736)
Study design	Randomized controlled trials
Population	Critically ill adult patients (ICU), including sepsis, VAP, and general ICU populations
Geographical distribution	Europe (2), Asia (3)
Sample size (range)	30 – 1,078 participants
Mean/median age (reported range)	~55 – 74 years
Sex distribution	Predominantly male in most studies
Baseline vitamin D status	Deficiency or insufficiency in all included studies
Intervention type	High-dose vitamin D_3 (cholecalciferol or calcifediol)
Dosing regimens	Single high-dose bolus (300,000–540,000 IU) or loading dose with maintenance
Route of administration	Oral/enteral (majority), intramuscular (2 studies)
Comparator	Placebo

Characteristic	Value
Primary outcome assessed	Mortality (28-day, 90-day, hospital, or 6-month)
Secondary outcomes	Length of stay, duration of mechanical ventilation, inflammatory and biochemical markers
Follow-up duration	28 days to 6 months

All studies evaluated vitamin D supplementation compared with placebo in critically ill patients. The intervention regimens differed across trials, with most studies administering high-dose vitamin D_3 as a single bolus (ranging from 300,000 IU to 540,000 IU), while one study used a loading dose followed by maintenance supplementation. The route of administration also varied, including enteral and intramuscular delivery. The study populations were heterogeneous. Some trials focused on general critically ill patients with vitamin D deficiency, whereas others included specific subgroups such as patients with sepsis or ventilator-associated pneumonia (VAP). Baseline vitamin D deficiency was reported in most studies, although the definition and severity thresholds were not uniform.

All included studies reported mortality outcomes, although the timing differed, including 28-day, 90-day, or in-hospital mortality. Secondary outcomes such as ICU length of stay, hospital length of stay, and duration of mechanical ventilation were also variably reported across studies. Baseline vitamin D status and illness severity variables were inconsistently reported across the included trials. Although most studies enrolled patients with vitamin D deficiency, the definition and reporting of baseline 25-hydroxyvitamin D [25(OH)D] levels varied, and only a limited number of trials provided detailed quantitative data suitable for synthesis. Similarly, illness severity scores, such as the Sequential Organ Failure Assessment (SOFA), were not uniformly reported across studies. Due to this heterogeneity and incomplete reporting, these variables could not be quantitatively pooled and were therefore not

included in formal subgroup or meta-regression analyses. Nevertheless, available data were considered qualitatively in the interpretation of findings, particularly regarding the potential influence of baseline vitamin D deficiency on treatment effects. Overall, despite similarities in study design, there was notable clinical heterogeneity among the included trials in terms of patient characteristics, intervention strategies, and outcome definitions.

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Table 2. Study Characteristic

No	Author (Year)	Title	Population	Sample Size (n)	Intervention	Comparison	Primary Outcome	Secondary Outcomes
1	National Heart, Lung, and Blood Institute PETAL Clinical Trials Network (2019)[10]	Early High-Dose Vitamin D_3 for Critically Ill, Vitamin D–Deficient Patients (VIOLET)	Critically ill adult patients with vitamin D deficiency (<20 ng/mL)	1059 (531 intervention, 528 control)	Single enteral high-dose vitamin D_3 (540,000 IU)	Placebo	90-day all-cause mortality	Not reported
2	Amrein et al. (2015)[9]	Effect of High-Dose Vitamin D_3 on Hospital Length of Stay in Critically Ill Patients With Vitamin D Deficiency (VITdAL-ICU Trial)	Critically ill adult patients with vitamin D deficiency	475 (237 intervention, 238 control)	High-dose vitamin D_3: loading dose 540,000 IU followed by monthly 90,000 IU for 5 months	Placebo	Hospital mortality	ICU mortality, 28-day mortality, 6-month mortality
3	Bhattacharyya et al. (2021)[14]	Effect of Early Administration of Vitamin D on Clinical Outcome in Critically Ill Sepsis Patients	Adult critically ill patients with sepsis	126 (63 intervention, 63 control)	Single high-dose vitamin D_3 (540,000 IU bolus)	Placebo	90-day all-cause mortality	Subgroup: patients with vitamin D deficiency (<12 ng/mL)

No	Author (Year)	Title	Population	Sample Size (n)	Intervention	Comparison	Primary Outcome	Secondary Outcomes
4	Miroliaee et al. (2017)[15]	Effect of Vitamin D Administration on CRP and Interleukin-6 as Prognostic Biomarkers in Ventilator-Associated Pneumonia	Adult ICU patients with ventilator-associated pneumonia (VAP)	46 (24 intervention, 22 control)	Single intramuscular high-dose vitamin D (300,000 IU)	Placebo	28-day mortality	IL-6, CRP
5	Sistanizad et al. (2021)[16]	High-Dose Vitamin D Improves Total Serum Antioxidant Capacity and ICU Outcome in Critically Ill Patients	Critically ill adult ICU patients on mechanical ventilation	30 (16 intervention, 14 control)	Single intramuscular high-dose vitamin D (300,000 IU)	Placebo	ICU length of stay, duration of mechanical ventilation, 28-day mortality	Total antioxidant capacity (TAC)

Risk of Bias

The risk of bias assessment of the included studies is summarized in Figure 2. Overall, one study (VIOLET, 2019)[10] was judged to have a low risk of bias across all domains, while the remaining studies demonstrated some concerns in at least one domain. Regarding the randomization process (Domain 1), most studies adequately described random sequence generation; however, some concerns were identified in smaller trials due to limited reporting of allocation concealment and baseline comparability. Bias related to the timing of identification and recruitment of participants (Domain 1b) was generally low across all studies.

For deviations from intended interventions (Domain 2), the majority of studies were assessed as low risk, reflecting appropriate adherence to randomized allocation and, in most cases, adequate blinding procedures. Similarly, bias due to missing outcome data (Domain 3) was generally low, although one study showed some concerns due to incomplete follow-up data. Outcome measurement (Domain 4) was considered low risk across all studies, as the primary outcome of interest, mortality, is an objective endpoint that is unlikely to be influenced by measurement bias.

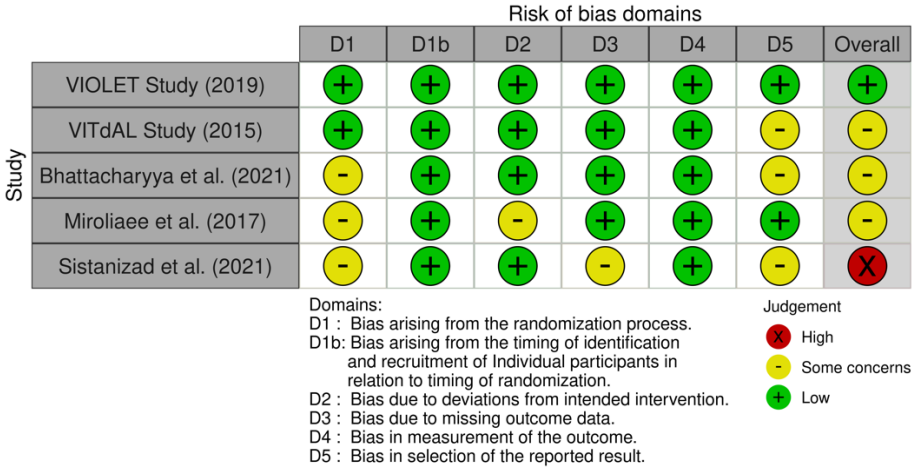

Figure 2. Risk of bias assessment using the RoB 2 tool[13]

In contrast, bias in the selection of the reported results (Domain 5) raised some concerns in several studies, particularly those in which mortality was not the primary outcome and reporting may have been influenced by selective emphasis on secondary or exploratory endpoints. Overall, while the largest multicenter trial demonstrated a low risk of bias, smaller single-center studies were more likely to exhibit methodological limitations, contributing to an overall assessment of some concerns or high risk of bias in the evidence base. These findings suggest that the pooled results should be interpreted with caution, particularly given the potential influence of smaller studies with less robust methodological rigor.

Primary Otucome: Mortality

A total of five randomized controlled trials comprising 1,736 critically ill patients (871 in the vitamin D group and 865 in the control group) were included in the mortality analysis. Across individual studies, the effect estimates varied across studies, with some trials suggesting lower mortality in the vitamin D group, while others demonstrated neutral or non-significant effects, except for the VIOLET trial, which showed a non-significant increase in mortality risk.

Using a random-effects model, vitamin D supplementation was associated with a non-significant reduction in mortality compared with placebo (risk ratio [RR] 0.74; 95% confidence interval [CI] 0.53–1.05; p = 0.09). Despite the overall direction of effect favoring the intervention, the confidence interval crossed unity, indicating the absence of a statistically significant benefit.

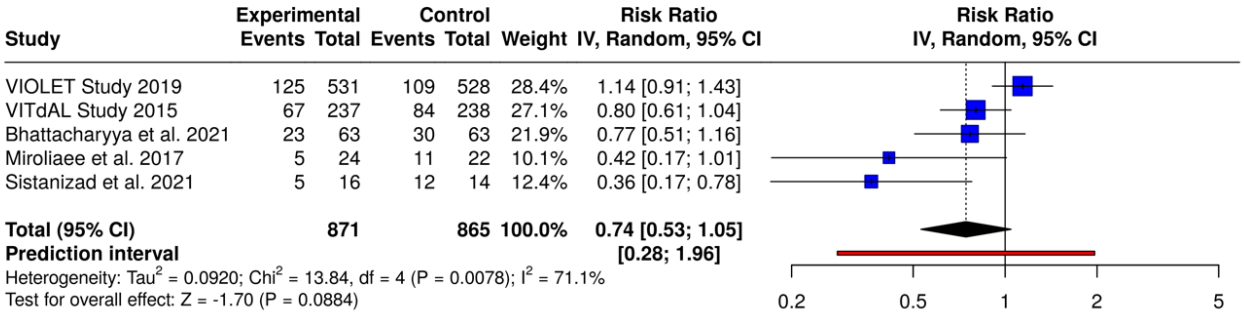

Figure 3. Forest plot of randomized controlled trials evaluating the effect of vitamin D supplementation on mortality in critically ill patients

Substantial heterogeneity was observed among the included studies ($I^2 = 71.1\%$, $p = 0.008$), indicating considerable variability in effect estimates beyond chance. The prediction interval was wide (0.28–1.96), suggesting that the true effect in different clinical settings could range from a clinically meaningful reduction to a potential increase in mortality risk. This level of heterogeneity suggests that the included studies may not be estimating a single common treatment effect, limiting the interpretability of the pooled estimate.

Notably, larger trials with lower risk of bias, particularly the VIOLET and VITdAL studies, contributed the greatest statistical weight and demonstrated neutral or non-significant effects. In contrast, smaller trials with fewer participants tended to report larger effect sizes favoring vitamin D supplementation. This pattern suggests a potential small-study effect and highlights the influence of study size and methodological quality on pooled estimates. Overall, while vitamin D supplementation showed directionally lower point estimates in several studies; however, the overall evidence remains inconclusive due to lack of statistical significance and substantial heterogeneity.

Secondary Outcomes

Secondary outcomes across the included studies were reported heterogeneously and included length of stay in the intensive care unit (ICU), duration of mechanical ventilation, and changes in inflammatory and biochemical markers. Regarding clinical outcomes, two studies evaluated ICU or hospital length of stay. The VITdAL trial reported no significant difference in hospital length of stay between the vitamin D and placebo groups.[9] Similarly, Bhattacharyya et al. found no significant reduction in ICU or hospital length of stay following early high-dose vitamin D administration.[14] In contrast, Miroliaee et al. and Sistanizad et al. reported shorter ICU length of stay in the vitamin D group; however, these findings were derived from smaller studies with limited sample sizes.[15,16]

The duration of mechanical ventilation was assessed in a limited number of studies. Sistanizad et al. observed a reduction in ventilation duration in patients receiving vitamin D supplementation compared to controls.[16] However, this outcome was not consistently reported across the larger trials, limiting comparability. Biomarker outcomes were variably reported. Miroliaee et al. demonstrated significant reductions in inflammatory markers, including interleukin-

6 (IL-6) and C-reactive protein (CRP), in the vitamin D group.[15] Additionally, Sistanizad et al. found a significant increase in total antioxidant capacity (TAC) in the intervention group.[16] Secondary outcomes were inconsistently reported and demonstrated variable findings across studies, precluding quantitative synthesis.

Subgroup Analysis

Subgroup analysis was performed based on study size to explore potential sources of heterogeneity. Trials were categorized into larger randomized controlled trials (VIOLET and VITdAL) and smaller trials (Bhattacharyya et al., Miroliaee et al. and Sistanizad et al.). In the subgroup of larger trials, vitamin D supplementation did not demonstrate a reduction in mortality, with effect estimates close to the null. In contrast, smaller trials consistently showed a greater reduction in mortality, with more pronounced effect sizes favoring vitamin D. These findings suggest that study size may influence the observed treatment effect, with smaller studies tending to report larger benefits. However, due to the limited number of studies within each subgroup, formal statistical comparison between subgroups was not performed. Subgroup analysis based on baseline vitamin D status could not be performed due to inconsistent reporting across studies. Meta-regression was not performed due to the limited number of included studies.

Sensitivity Analysis

A sensitivity analysis was performed by excluding smaller trials with limited sample sizes to evaluate the robustness of the pooled estimate. Following exclusion, the overall effect estimate shifted toward the null, with attenuation of the treatment effect compared with the primary analysis. The direction of the effect remained consistent; however, the confidence interval continued to cross unity, indicating the absence of a statistically significant benefit.

These findings suggest that the observed reduction in mortality in the primary analysis may be partially influenced by smaller studies reporting larger effect sizes, rather than reflecting a consistent treatment effect across all studies. Assessment of publication bias using funnel plot or Egger's test was not performed due to the limited number of included studies (<10), in accordance with recommended methodological guidance.

DISCUSSION

Interpretation of Results

The present meta-analysis suggests that vitamin D supplementation was associated with no statistically significant association with reduced mortality, although point estimates in several studies favored the intervention. Although the pooled effect estimate favored the intervention, the overall association did not reach statistical significance, indicating that the currently available randomized evidence does not support a clear mortality benefit. This finding is broadly consistent with the results of the largest included trials. In the VIOLET trial, early high-dose vitamin D_3 did not reduce 90-day mortality compared with placebo (23.5% vs 20.6%).[10] Similarly, the VITdAL-ICU trial found no significant reduction in hospital mortality or 6-month mortality in the overall study population, despite a numerical trend favoring vitamin D.[9]

At the same time, the pooled direction of effect should not be dismissed as entirely neutral, because several smaller trials consistently showed point estimates favoring vitamin D supplementation. Bhattacharyya et al. reported lower 90-day mortality in the intervention arm than in the placebo arm, although the difference was not statistically significant.[14] Miroliaee et al. observed a significantly lower 28-day mortality in the vitamin D group than in the placebo group, based on a very small sample.[15] Likewise, Sistanizad et al. reported markedly lower mortality in the intervention group, but this finding was derived from a very small single-center trial with substantial event imbalance between groups.[16] Taken together, these findings suggest that the overall result is better interpreted as inconclusive rather than definitively negative: the current evidence does not demonstrate a statistically proven survival advantage, but neither does it fully exclude the possibility of benefit in selected patients.

Another important aspect of the findings is the presence of substantial between-study heterogeneity, which implies that the included trials may not be estimating a single common treatment effect. This heterogeneity is clinically plausible, given the marked differences in patient populations, baseline vitamin D status, route and timing of administration, and outcome definitions across studies. In this context, the absence of statistical significance in the pooled analysis should

not be interpreted as proof of no biological effect, but rather as evidence that any effect is likely to be context-dependent and not consistently reproducible across all critically ill populations. Overall, the most balanced interpretation is that vitamin D supplementation does not currently have sufficient evidence to justify routine use for mortality reduction in unselected critically ill adults, while the observed signal toward benefit warrants further investigation in more clearly defined subgroups.[9,10,14–16]

Why the Effect Was Not Statistically Significant

Several factors may explain why vitamin D supplementation did not produce a statistically significant mortality benefit in the present meta-analysis. First, the largest and methodologically strongest trials showed neutral results.[9,10] When the most influential studies are neutral, smaller positive studies are usually insufficient to shift the pooled estimate to statistical significance.

Second, the included trials were clinically heterogeneous. The study populations ranged from general critically ill ICU patients to more specific groups such as patients with sepsis or ventilator-associated pneumonia. The timing of vitamin D administration also differed substantially, from very early administration after admission to later supplementation during ongoing critical illness. In addition, treatment regimens varied across studies, including enteral versus intramuscular administration and single bolus dosing versus loading plus maintenance strategies. Such variability reduces comparability across studies and increases between-study heterogeneity, making it less likely that a consistent pooled treatment effect will emerge.[9,10,14–16]

Third, a true effect of vitamin D may depend on baseline deficiency severity, and this may have been diluted in the pooled analysis. In the VITdAL-ICU trial, a reduction in hospital mortality was observed only in the predefined subgroup with severe vitamin D deficiency, whereas no significant benefit was found in the overall population.[9] Similarly, Bhattacharyya et al. reported a trend toward lower 90-day mortality in patients with severe deficiency, although the subgroup result did not reach statistical significance.[14] This raises the possibility that supplementation may benefit only selected patients with profound deficiency, while showing little or no effect in broader ICU populations.

Fourth, vitamin D may influence intermediate biological processes without translating into measurable survival benefit. Some smaller studies found favorable changes in inflammatory or oxidative stress markers after supplementation. Miroliaee et al. reported reduced IL-6 levels and lower short-term mortality in patients with ventilator-associated pneumonia, while Sistanizad et al. observed improved total antioxidant capacity together with better ICU outcomes.[15,16] However, improvement in surrogate markers does not necessarily produce a detectable effect on mortality, particularly in critically ill patients whose outcomes are determined by multiple interacting factors such as severity of illness, infection burden, organ dysfunction, and comorbidities.

Finally, several smaller trials may have been underpowered for mortality endpoints. Bhattacharyya et al. explicitly designed their study around ICU length of stay rather than mortality, and the sample size was limited.[14] The same limitation applies to other small single-center trials included in this review. As a result, although some of these studies showed point estimates favoring vitamin D, their precision was limited and their results were not stable enough to overcome the neutral findings of larger trials.

Taken together, the lack of statistical significance in this meta-analysis likely reflects not a single explanation but a combination of factors: neutral results in the largest trials, important heterogeneity in populations and interventions, possible effect restriction to severely deficient subgroups, and inadequate power of smaller studies to detect mortality differences.[9,10,14–16]

Small-Study Effect

An important pattern observed in this meta-analysis is the discrepancy between effect estimates reported by smaller trials and those from larger, more methodologically robust studies. Smaller studies consistently demonstrated larger effect sizes favoring vitamin D supplementation, whereas larger trials such as VIOLET and VITdAL showed neutral results.[9,10]

This pattern is characteristic of a small-study effect, a phenomenon in which smaller studies tend to report more extreme treatment effects compared to larger trials. Several factors may contribute to this observation. First, small studies are more susceptible to random error, leading to wider variability and occasionally exaggerated effect estimates. Second, methodological limitations, such as incomplete allocation concealment, deviations from intention-to-treat analysis, or selective

outcome reporting, are more common in small single-center trials and may bias results toward apparent benefit.

In the present analysis, the influence of small-study effects is supported by sensitivity analysis, where exclusion of smaller trials attenuated the pooled effect size toward the null. Furthermore, some of the smaller studies included had design features that may have amplified treatment effects. For example, in the study by Sistanizad et al., patients who died early after enrollment were excluded from analysis, which may have introduced post-randomization bias.[16] Similarly, Miroliaee et al. reported a large mortality reduction in a very small cohort, increasing the likelihood of overestimation.[15]

Taken together, these findings suggest that the apparent signal toward mortality reduction may be partly driven by small, less precise studies rather than a consistent treatment effect across all levels of evidence. This highlights the importance of weighting conclusions toward larger, well-conducted trials when interpreting meta-analytic results.

Comparison with Previous Studies

Some earlier studies suggested that vitamin D supplementation may reduce mortality in critically ill patients, particularly in those with severe deficiency. However, these findings were often driven by smaller trials or subgroup analyses and were not consistently confirmed in larger, high-quality RCTs. This discrepancy mirrors the pattern observed in the present study, where the overall effect estimate is influenced by smaller studies reporting larger benefits. Subgroup analyses from the VITdAL-ICU trial suggested a mortality benefit in patients with severe deficiency, although this was not observed in the overall population. Similar trends have been reported in other trials, but the evidence remains inconsistent and underpowered for definitive conclusions.[9]

Compared with previous reviews, the present analysis reinforces the growing consensus that vitamin D supplementation does not provide a consistent mortality benefit in unselected critically ill populations. At the same time, any potential benefit may be limited to specific subgroups, such as patients with severe vitamin D deficiency; however, this remains a hypothesis-generating observation, as subgroup analyses based on baseline vitamin D status could not be performed due to inconsistent reporting across studies. Overall, the findings of this study align with the broader

literature in demonstrating a lack of robust mortality benefit, while also emphasizing the heterogeneity and uncertainty that continue to characterize this field.[17]

Clinical Implications

The findings of this meta-analysis have important implications for clinical practice. Based on the current evidence, routine high-dose vitamin D supplementation cannot be recommended for the purpose of reducing mortality in critically ill patients. The absence of consistent benefit in large, well-conducted randomized trials, combined with the influence of smaller studies on pooled estimates, suggests that the overall effect is uncertain and not sufficiently robust to support widespread implementation.[10,18]

However, these results should not be interpreted as evidence that vitamin D has no role in critical care. Given its established safety profile and biological plausibility, vitamin D supplementation may be considered on an individual basis, particularly in patients with documented deficiency, although evidence for outcome benefit remains uncertain. Current evidence suggests that any potential clinical benefit is likely to be context-dependent, rather than universally applicable across all critically ill populations.[10,17]

Importantly, clinicians should avoid extrapolating improvements in surrogate outcomes, such as inflammatory markers or antioxidant capacity, to meaningful clinical endpoints such as survival. While several studies demonstrated favorable effects on biological markers, these changes have not translated into consistent reductions in mortality, highlighting the need for cautious interpretation of such findings. In practice, vitamin D supplementation in critically ill patients should therefore be individualized, taking into account baseline vitamin D status, overall nutritional needs, and clinical context, rather than applied as a routine therapeutic strategy for outcome improvement.[17,19]

Limitations

Several limitations of this study should be acknowledged. First, the number of included randomized controlled trials was relatively small, limiting the statistical power of the meta-analysis and reducing the ability to perform more robust subgroup analyses. In particular, the small number of studies precluded formal assessment of publication bias, which may have influenced the

observed effect estimates. Second, there was substantial clinical and methodological heterogeneity among the included trials. Differences in patient populations (e.g., general ICU patients, sepsis, and ventilator-associated pneumonia), baseline vitamin D status, dosing regimens, route of administration, and timing of intervention may have contributed to variability in treatment effects. This heterogeneity limits the comparability of studies and complicates the interpretation of pooled results.

Third, several included trials had relatively small sample sizes and were conducted in single-center settings. These studies are more prone to bias and random error, and their inclusion may have introduced a small-study effect, potentially inflating the observed treatment benefit. Although sensitivity analysis was performed to address this issue, the overall findings remained sensitive to the inclusion of these smaller trials. Fourth, outcome definitions were not fully standardized across studies. Mortality was reported at different time points (e.g., 28-day, 90-day, or hospital mortality), and secondary outcomes such as length of stay and duration of mechanical ventilation were inconsistently reported. This variability may have further contributed to heterogeneity and limited the ability to perform pooled analyses for secondary outcomes.

Finally, although most studies included patients with vitamin D deficiency, the severity of deficiency and threshold definitions varied, and individual patient-level data were not available. As a result, this analysis could not adequately explore whether specific subgroups, such as patients with severe deficiency, derive greater benefit from supplementation.

CONCLUSION

In this meta-analysis of randomized controlled trials, vitamin D supplementation in critically ill adult patients was not associated with a statistically significant reduction in mortality. Although point estimates in several studies favored the intervention, the overall effect was inconsistent and accompanied by substantial heterogeneity, limiting the reliability of the pooled estimate.

These findings do not support the routine use of high-dose vitamin D supplementation for mortality reduction in unselected critically ill populations. The observed variability in treatment

effects and the influence of smaller trials suggest that any potential benefit may be context-dependent rather than universal.

Future research should focus on well-designed, adequately powered randomized trials targeting clearly defined patient subgroups, particularly those with severe vitamin D deficiency, and should aim to standardize intervention strategies and outcome measures to reduce heterogeneity and improve interpretability.

REFERENCES

1. Mayr Ulrich, Fahrenkrog-Petersen Leonie, Batres-Baires Gonzalo, et al. Vitamin D Deficiency Is Highly Prevalent in Critically Ill Patients and a Risk Factor for Mortality: A Prospective Observational Study Comparing Noncirrhotic Patients and Patients With Cirrhosis. *J Intensive Care Med*. 2020;35(10):992-1001. doi:10.1177/0885066618803844

2. Cutuli SL, Ferrando ES, Cammarota F, et al. Update on vitamin D role in severe infections and sepsis. *Journal of Anesthesia, Analgesia and Critical Care*. 2024;4(1):4. doi:10.1186/s44158-024-00139-5

3. Chen KW, Chen CW, Yuan KC, et al. Prevalence of Vitamin D Deficiency and Associated Factors in Critically Ill Patients: A Multicenter Observational Study. *Front Nutr*. 2021;Volume 8-2021. https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2021.768804

4. Ao T, Kikuta J, Ishii M. The effects of vitamin D on immune system and inflammatory diseases. *Biomolecules*. *MDPI*. 2021;11(11). doi:10.3390/biom11111624

5. Wimalawansa SJ. Infections and Autoimmunity—The Immune System and Vitamin D: A Systematic Review. *Nutrients*. *Multidisciplinary Digital Publishing Institute (MDPI)*. 2023;15(17). doi:10.3390/nu15173842

6. Shang S, Chen D, Wei Y, et al. The Role of Vitamin D and Vitamin D Receptor in Sepsis. *Curr Issues Mol Biol*. *Multidisciplinary Digital Publishing Institute (MDPI)*. 2025;47(7). doi:10.3390/cimb47070500

7. Carpagnano GE, Di Lecce V, Quaranta VN, et al. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. *J Endocrinol Invest*. 2021;44(4):765-771. doi:10.1007/s40618-020-01370-x

8. Cuñat T, Ojeda A, Calvo A. Vitamin D deficiency in critically ill patients diagnosed with COVID - 19. Are we doing enough? A retrospective analysis of 226 patients. Preprint posted online May 22, 2020. doi:10.21203/rs.3.rs-30390/v1

9. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3on hospital length of stay in critically ill patients with vitamin D deficiency: The VITdAL-ICU randomized clinical trial. *JAMA - Journal of the American Medical Association*. 2014;312(15):1520-1530. doi:10.1001/jama.2014.13204

10. The National Heart L and BIPCTN. Early High-Dose Vitamin D3 for Critically Ill, Vitamin D–Deficient Patients. *New England Journal of Medicine*. 2019;381(26):2529-2540. doi:10.1056/NEJMoa1911124

11. Gibbons JB, Norton EC, McCullough JS, et al. Association between vitamin D supplementation and COVID-19 infection and mortality. *Sci Rep*. 2022;12(1). doi:10.1038/s41598-022-24053-4

12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj*. 2021;372.

13. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*. 2019;366.

14. Bhattacharyya A, Subramaniam R, Baidya DK, Aggarwal P, Wig N. Effect of early administration of vitamin d on clinical outcome in critically ill sepsis patients: Randomized placebo-controlled trial. *Indian Journal of Critical Care Medicine*. 2021;25(10):1145-1152. doi:10.5005/jp-journals-10071-23993

15. Miroliaee AE, Salamzadeh J, Shokouhi S, Sahraei Z. The study of vitamin D administration effect on CRP and Interleukin-6 as prognostic biomarkers of ventilator associated pneumonia. *J Crit Care*. 2018;44:300-305. doi:10.1016/j.jcrc.2017.08.040

16. Sistanizad M, Kouchek M, Miri MM, et al. High dose vitamin D improves total serum antioxidant capacity and ICU outcome in critically ill patients - A randomized, double-blind clinical trial. *Eur J Integr Med*. 2021;42. doi:10.1016/j.eujim.2020.101271

17. Liu D, Meng X, Tian Q, et al. Vitamin D and Multiple Health Outcomes: An Umbrella Review of Observational Studies, Randomized Controlled Trials, and Mendelian Randomization Studies. *Advances in Nutrition*. *Oxford University Press*. 2022;13(4):1044-1062. doi:10.1093/advances/nmab142

18. Wang Y, Sha S, Gwenzi T, Schöttker B, Brenner H. Impact of vitamin D supplementation on all-cause mortality: Randomized trials revisited. *Clinical Nutrition*. 2026;58:106597. doi:https://doi.org/10.1016/j.clnu.2026.106597

19. velayati A, vafa M, Yadollahzadeh M, Shariat panahi ZV, sarbakhsh parvin, salemi H. Clinical randomized trial of vitamin D and C supplementation in critically ill patients with respiratory failure. *Nutr J*. 2025;24(1):145. doi:10.1186/s12937-025-01214-5