




Review

Evaluation of Vitamin D Supplementation in Critically Ill Patients—A Narrative Review of Randomized Controlled Trials Published in the Last 5 Years

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Abstract: The prevalence of vitamin D deficiency among intensive care unit (ICU) patients is potentially associated with an increased risk of mechanical ventilation, sepsis, prolonged hospital stays, and mortality. Although ICU patient care has significantly improved in recent years, the role of vitamin D supplementation remains under investigation. A literature review was conducted using PubMed, Web of Science, Embase, and Cochrane databases, focusing on randomized controlled trials published in the past five years on vitamin D supplementation in adult ICU patients. Patients' baseline vitamin D levels, administration routes, doses, biomarker changes, mechanical ventilation duration, length of hospital stay, and mortality were analyzed. Although vitamin D supplementation appears safe and may reduce ICU stay duration and mechanical ventilation time and improve SOFA scores, its impact on overall mortality remains uncertain. Routine supplementation for all ICU patients is not currently recommended; clinical decisions should consider individual baseline vitamin D levels, patient characteristics, severity of illness, doses, and administration methods.

Keywords: clinical outcomes; vitamin D deficiency; vitamin D replacement; critically ill patients; vitamin D doses



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1. Introduction

It is reported that 40–70% of intensive care unit (ICU) patients present with vitamin D deficiency [1]. Vitamin D (calciferol) is a fat-soluble vitamin synthesized in the skin through UV exposure and obtained from food or dietary supplements. It undergoes hydroxylation in the liver to form 25-hydroxyvitamin D (calcidiol or calcifediol, supplement analog D3/cholecalciferol) and is further hydroxylated in the kidney into active metabolite 1,25-dihydroxyvitamin D (calcitriol, supplement analog D2/ergocalciferol) [2]. Cholecalciferol, ergocalciferol, and calcitriol are commonly used for supplementation in clinical settings [3].

Previous studies have shown that vitamin D is essential for immune function, a necessity for critical illness recovery. Vitamin D is also known to regulate gene expression,

cell proliferation, and apoptosis [4]. Additionally, it controls the proliferation of T and B cells, modulates immunoglobulin production, and decreases proinflammatory cytokine levels [1,4,5]. Vitamin D has also been shown to upregulate cathelicidin and other antimicrobial peptides, which are essential for immune defense in critically ill patients [6].

Vitamin D deficiency (25-hydroxyvitamin D < 20 ng/mL) leads to higher levels of inflammation in certain tissues, including nervous and lung tissues [7,8]. Studies found that vitamin D deficiency may also increase the risk of respiratory failure [9,10]. Vitamin D deficiency is found to be associated with sepsis, infection, and increased morbidity and mortality [10]. Studies evaluating the efficacy of vitamin D replacement in critically ill patients have demonstrated conflicting results. This review aims to investigate the latest literature on the effects of vitamin D replacement in critically ill adult patients with regard to clinical outcomes while also evaluating respective vitamin D dosages.

2. Materials and Methods

Two reviewers independently screened four databases (PubMed, Embase, Cochrane, and Web of Science) using predefined search terms—(vitamin D OR Cholecalciferol OR ergocalciferol OR calcitriol) AND (ICU OR intensive care OR critically-ill)—to identify human studies meeting all four of the following criteria: (1) the study design had to be a randomized controlled clinical trial (RCT); (2) the study had to be performed in an adult population (age ≥ 18 years); (3) the studies must have been published between 2019 and November 2024; (4) the full-length publications must have been available in the English language; and (5) vitamin D was the only variable studied in the clinical outcomes. Retrospective studies, observational studies, and meta-analyses were excluded (see Figure 1).

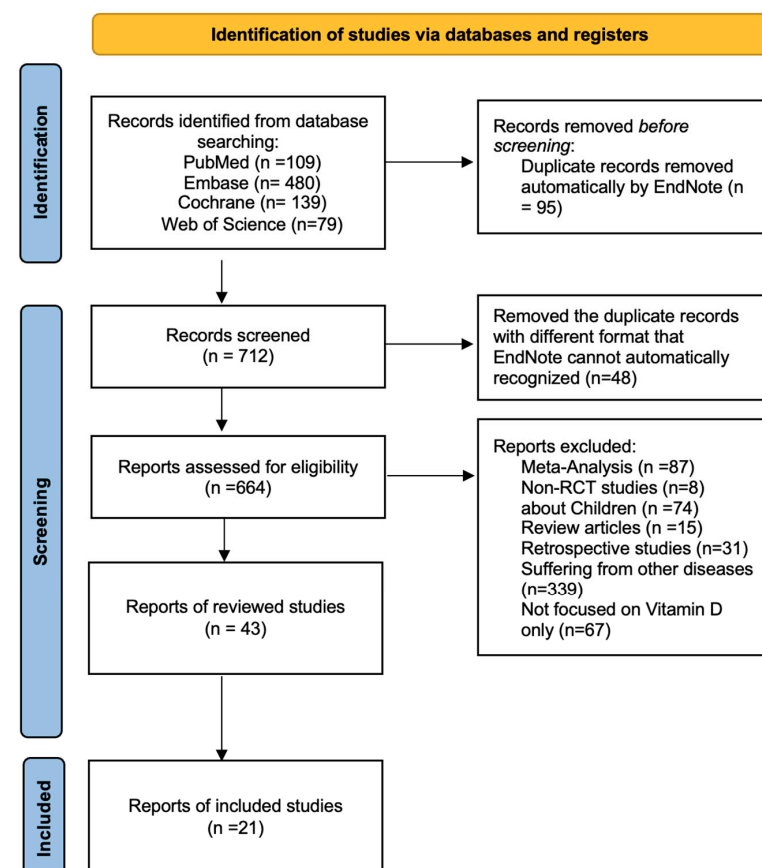


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection based on inclusion and exclusion criteria [11].

Detailed data were extracted from each trial, including baseline vitamin D levels, patient population characteristics, sample size analyzed, vitamin D replacement routes/doses, duration of replacement, dose duration, and study outcomes.

In this review, the term vitamin D level refers to serum 25-hydroxyvitamin D [25(OH)D] level.

Retrospective, observational, and meta-analysis papers were excluded. Table 1 presents baseline vitamin D status, patient populations, dosing regimens, and reported outcomes. Given the heterogeneity in study designs, each eligible study was assessed qualitatively.

Table 1. Summary of randomized controlled trials (RCTs) from 2019 to 2024.

| Study | Year | Baseline Vit D Level (ng/mL) | Sample Size | Patient Population | Vit D Replacement Dose | Duration | Notes |
|--|------|------------------------------|-------------|---------------------------------------|---|---|--|
| Ashoor et al. [10] | 2024 | <20 | 80 | Sepsis on mechanical ventilation | HD: enteral 50,000 IU/d vs. LD: enteral 5000 IU/d | 5 days | Significant difference in procalcitonin, LL-37 reduction, improved SOFA, and hospital LOS |
| Singh et al. [12] | 2024 | 12 vs. 13 | 90 | COVID-19 | Enteral 600,000 IU | Once | Significantly improved SOFA score at Day 7 and 28-day mortality |
| Masbough et al. [13] | 2024 | 15.95 vs. 17.84 | 35 | Traumatic brain injury | IM 300,000 IU | Once | Statistically significant increase in GCS scores, reduction in inflammatory markers, improvement in the GOS-E score; no difference in 28-day mortality, ICU LOS, MV needs |
| Thampi et al. [6] | 2024 | Not reported | 152 | Sepsis | Calcitriol IM 300,000 IU | Once | No significant difference in APACHE II scores, 28-day mortality, MV days, ICU LOS, and hospital-acquired infections |
| Sistanizad et al. [3] | 2024 | 11.37 vs. 13.96 | 28 | Sepsis | Calcitriol IV 1 mcg/day | 3 days | No significant difference in procalcitonin level, ICU LOS, and 28-day mortality |
| Zamanian et al. [14] | 2024 | 23.06 vs. 25.68 | 61 | COVID-19 | IM 300,000 IU | Once | No significant difference in mortality or hospital LOS |
| Wang et al. [15] | 2024 | <20 | 61 | Vitamin D deficient | Enteral 569,600 IU | Once divided by 8 bottles | Only 41.5% of the patients achieved serum 25(OH)D levels higher than 30 ng/mL in the supplementation group. They had significantly lower 30-day mortality. |
| Domazet Bugarin et al. [16] | 2023 | 25.3 vs. 27.3 | 155 | COVID-19 | Enteral 10,000 IU vs. placebo | Once | No statistical significance in MV days, secondary outcomes |
| Bychinin et al. [5] | 2022 | 9.6 vs. 11 | 110 | COVID-19 | PO 60,000 IU weekly, then 5000 IU/daily | During hospital stay | Significantly increased NK and NK T cell counts. No difference in mortality, need for MV, or incidence of nosocomial infection; ICU and hospital LOS were longer in the vitamin D3 replacement group |
| Sistanizad et al. [1] | 2021 | <20 | 36 | ICU ventilated | IM 300,000 IU vs. placebo | Once | No statistically significant results were identified due to the small sample size |
| Bhattacharyya et al. [4] | 2021 | 12.05 vs. 15.47 | 126 | Sepsis | Enteral 540,000 IU vs. placebo | Once | No statistical difference in ICU LOS, hospital LOS, MV duration/requirements, or 90-day mortality |
| Han et al. [17] | 2021 | 15.2 vs. 13.1 | 95 | Vitamin D deficient | Enteral 540,000 IU | Once | No significant difference in long-term global cognition or executive function |
| Naguib et al. [18] | 2021 | 21 vs. 19.1 | 86 | Elective mechanical valve replacement | Alfacalcidol 2 µg/day PO | Starting 2 days before surgery until the end of hospital stay | Statistically significant reduction in ICU LOS and postoperative infection rate. No significant difference in hospital mortality |
| Hajimohammadebrahim-Ketabforoush et al. [19] | 2021 | <20 | 60 | Craniotomy for brain tumor resection | IM 300,000 IU | Once | Significant reduction in ICU LOS and hospital LOS |

Table 1. *Cont.*

| Study | Year | Baseline Vit D Level (ng/mL) | Sample Size | Patient Population | Vit D Replacement Dose | Duration | Notes |
|-----------------------|------|------------------------------|-------------|---|---|---------------------------|---|
| Ingels et al. [20] | 2020 | 6.8 vs. 9.2 | 24 | Prolonged ICU stay (>10 days) | 200 µg loading dose once, then 15 µg/day | Loading dose then 10 days | No difference in SOFA score or MV duration |
| Sharma et al. [7] | 2020 | 18.30 vs. 15.15 | 35 | Traumatic brain injury | Enteral 120,000 IU vs. placebo | Once | Significant improvement in GCS score, MV duration, IL-6, and TNF-α |
| Padhy et al. [21] | 2020 | ≤20 | 60 | Vitamin D-deficient, sepsis | G1: enteral 60,000 IU once/wk; G2: 60,000 IU twice/wk | During hospital stay | No difference was found in ICU LOS, duration of MV, and 28-day ICU mortality. Patients in group 2 required less inotropic support ($p = 0.037$) |
| Hasanloei et al. [22] | 2020 | 10–30 | 72 | Ventilated, traumatic injury | G1: PO 50,000 IU/day; G2: IM 300,000 IU vs. placebo | G1: 6 days; G2: once | Significant improvement in IL6, ESR, CRP, SOFA score, duration of MV, ICU LOS |
| Karsy et al. [23] | 2020 | 14.6 vs. 13.9 | 267 | Neurocritical care, vitamin D-deficient | PO 540,000 IU vs. placebo | Once | No statistical difference in hospital LOS or ICU LOS |
| Miri et al. [24] | 2019 | 8.43 vs. 11.35 | 40 | ICU ventilated | IM 300,000 IU vs. placebo | Once | Significant reduction in 28-day mortality |
| PETAL group [8] | 2019 | 11.2 vs. 11.0 | 1078 | Vitamin D-deficient | Enteral 540,000 IU vs. placebo | Once | No statistical difference in 90-day mortality and other clinical outcomes |

3. Results

Out of 807 studies identified, 21 studies met the criteria and were included in this narrative review (Figure 1). For each included study, study details were extracted into Table 1. Two authors independently verified the extracted data for all studies. Eight of the 21 studies included did not show clinical benefits of vitamin D replacement in critically ill patients. The remaining 13 studies demonstrated that vitamin D replacement in ICU patients had a positive impact on certain clinical outcomes. Six of these 13 trials reported that vitamin D supplementation led to a decreased ICU or hospital length of stay (LOS), three trials showed an improvement in Sequential Organ Failure Assessment (SOFA) scores, three trials found a decrease in mechanical ventilation (MV) duration, three trials revealed a decrease in 30-day mortality, two trials demonstrated positive outcomes in the Glasgow Coma Scale (GCS), and six trials reported positive biomarker results. Table 1 summarizes the key findings of the trials included in this narrative review. Table 2 highlights the positive versus negative clinical outcomes following vitamin D replacement.

Table 2. Summary of positive vs. negative clinical outcomes.

| Year | Author | Clinical Results | | | | | | | | | | Biomarkers |
|------|-----------------------------|------------------|--------------|------------|--------------|-----------|------------------|------------------|------------------|-----|------------------------|------------|
| | | ICU LOS | Hospital LOS | SOFA Score | MV Du-ration | MV Needs | 90-Day Mortality | 28-Day Mortality | 30-Day Mortality | GCS | Less Inotropic Support | |
| 2024 | Ashoor et al. [10] | | HD | HD | | | | | | | HD: pct, IL-37 | |
| 2024 | Singh et al. [12] | | | | | | | | | | | |
| 2024 | Masbough et al. [13] | | | | | | | | | | IL-1b, IL-6 | |
| 2024 | Thampi et al. [6] | | | | | | | | | | | |
| 2024 | Sistanizad et al. [3] | | | | | | | | | | | |
| 2024 | Zamanian et al. [14] | | | | | | | | | | | |
| 2024 | Wang et al. [15] | | | | | | | | | | | |
| 2023 | Domazet Bugarin et al. [16] | | | | | | | | | | | |
| 2022 | Bychinin et al. [5] | | | | | All-cause | | | | | NK, NKT, CRP, pct | |
| 2021 | Sistanizad et al. [1] | | | | | | | | | | | |
| 2021 | Bhattacharyya et al. [4] | | | | | | | | | | | |

Table 2. Cont.

| Year | Author | Clinical Results | | | | | | | | | Biomarkers | |
|------|---|------------------|--------------|------------|-------------|----------|------------------|------------------|------------------|-------------|------------------------|-------------------------|
| | | ICU LOS | Hospital LOS | SOFA Score | MV Duration | MV Needs | 90-Day Mortality | 28-Day Mortality | 30-Day Mortality | GCS | Less Inotropic Support | |
| 2021 | Han et al. [17] | | | | | | | | | RBANS score | | |
| 2021 | Naguib et al. [18] | | | | | | | | | | | |
| 2021 | Hajimohammadebra Ketabforoush et al. [19] | | | | | | | | | | | |
| 2020 | Sharma et al. [7] | | | | | | | | | | | IL-6, TNF- α |
| 2020 | Ingels et al. [20] | | | | | | | | | | | CRP, WBC, IL-37, sCD163 |
| 2020 | Padhy et al. [21] | | | | | | | | | | | |
| 2020 | Hasanloei et al. [22] | | | | | | | | | | | IL-6, ESR, CRP |
| 2020 | Karsy et al. [23] | | | | | | | | | | | |
| 2019 | Miri et al. [24] | | | | | | | | | | | |
| 2019 | PETAL group [8] | | | | | | | | | | | |

Tables 1 and 2: ■: Vitamin D positively affected clinical outcomes; ■: Vitamin D negatively affected clinical outcomes; ■: Vitamin D had no effect on clinical outcomes; ■: Not reported; HD: high dose of vitamin D (enteral 50,000 IU daily for 5 days) versus. low dose of vitamin D (enteral 5000 IU daily for 5 days); LOS: length of stay; APACHE II: acute physiologic assessment and chronic health evaluation II; SOFA: Sequential Organ Failure Assessment; MV: mechanical ventilator; All-cause: all-cause mortality; RBANS score: Repeatable Battery for the Assessment of Neuropsychological Status; GCS: Glasgow Coma Scale; IM: intramuscular injection; PO: by mouth; pct: procalcitonin; CRP: C-reactive protein; NK: natural killer cell; NKT: natural killer T cell; ESR: erythrocyte sedimentation rate; WBC: white blood cell; IL: interleukin; TNF- α : tumor necrosis factor-alpha; GOS-E: Glasgow outcome scale-extended.

Various dosing replacement strategies were adopted in these 21 studies. Trials that showed a benefit of vitamin D replacement reported the following doses: oral 50,000 International Units (IU) daily for 5 days; oral 120,000 IU single dose, oral 600,000 IU single dose, and IM dose 300,000 IU single dose.

4. Discussion

Several meta-analyses and systematic reviews have examined the role of vitamin D supplementation in critically ill patients over the past five years. However, most meta-analyses were completed in or before 2022 [25–31]. Since then, multiple randomized controlled trials (RCTs) have been conducted, which we have included in our review.

Furthermore, our study categorizes clinical outcomes into three groups: positive impact, negative impact, and no impact of vitamin D supplementation in this patient population. Additionally, we compared different dosing strategies used in these RCTs to determine which dosages were most commonly administered and which were associated with the most positive clinical outcomes.

Overall, these studies on vitamin D replacement in ICU patients demonstrated conflicting results over the past 5 years. The VIOLET trial conducted by The National Heart, Lung, and Blood Institute's PETAL clinical trial group (2019) showed that early enteral administration of a single 540,000 IU vitamin D3 high dose in critically ill patients with vitamin D deficiency (25-hydroxyvitamin D level < 20 ng/mL) increased vitamin D serum levels but did not demonstrate any clinical benefit over the placebo in terms of 90-day mortality or other nonfatal outcomes [8]. The authors conducted an ancillary study, VIOLET Long-term Brain Outcomes in Vitamin D Deficient Patients (VIOLET-BUD) [17]. The subsequent study evaluated the same single enteral high dose vitamin D3 versus placebo in patients with vitamin D deficiency, focusing on their long-term cognitive outcomes at a median follow-up of 443 days (interquartile range: 390–482 days). Long-term cognitive outcomes were evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [32], while executive function was assessed using a composite score derived from

three subscales of the Delis–Kaplan Executive Function System (D-KEFS) [33]. It concluded that a single high dose of enteral vitamin D did not improve long-term global cognition or executive function in critically ill, vitamin D-deficient patients. Akbas et al. showed that vitamin D replacement had a positive impact on biomarkers such as procalcitonin, cathelicidin, LL-37, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) levels [34]. Miri et al. demonstrated that vitamin D improved the SOFA score, GCS score, post-op infection rate, duration of mechanical ventilation, and ICU and hospital LOS [24]. Ingels et al. found that vitamin D replacement in ICU patients did not increase serum 25-(OH)-D levels as much as expected [20]. This is partly because serum calcitriol concentrations are more tightly regulated than 25-(OH)-D concentrations. Additionally, although 25-(OH)-D undergoes a second hydroxylation in the kidneys to produce circulating calcitriol for bone and muscle, it is also known to be activated in vitamin D-dependent tissues, including pancreatic islets and immune system cells. It is speculated that CYP27B1 (also known as 1-alpha hydroxylase) is downregulated during critical illness, which compromises the conversion of 25-(OH)-D to 1,25(OH)₂D, and possibly shifts the metabolization of 25-(OH)-D to other compounds. A small increase in 24, 25 (OH)₂D was also noticed, which might serve as a feedback mechanism for avoiding vitamin D toxicity [35]. Critical illness lowers serum 25-(OH)-D concentrations, though the underlying mechanisms remain unclear. Therefore, analyses using baseline 25-(OH)-D values—those measured from admission samples—are preferable. However, none are entirely free from this confounder, as patients requiring critical care are typically severely ill or have undergone major surgery. The vitamin D supplementation dose in the study by Ingels et al. was very low (loading dose of 8000 IU and daily maintenance of 600 IU × 10 days) compared to vitamin D doses in other studies. This could also explain why Ingels et al. did not find any significant benefit of vitamin D replacement in ICU patients.

The dosing and delivery strategies for vitamin D varied across studies and may be specific to institutional protocols. In studies that showed vitamin D replacement with positive clinical outcomes, the dose ranged from 5000 IU to 540,000 IU as a single dose or multiple-day replacement, given either via the enteral or the intramuscular route. Kearns et al. found significant changes in biochemical markers when evaluating a single dose of 600,000 IU of vitamin D₃, highlighting the need for greater caution when administering single doses exceeding 500,000 IU [35]. Fortunately, no toxicity from vitamin D supplementation was reported in patients in all the studies reviewed.

The role of vitamin D in patients with severe vitamin D deficiency has been identified and confirmed in several studies [5,7,10,12–21]. In VITdAL-ICU, the use of vitamin D supplementation did not show beneficial effects on hospital or ICU LOS, hospital mortality, or 90-day mortality. A post-hoc subgroup analysis of patients with severe vitamin D deficiency (defined as vitamin D level ≤ 12 ng/mL) in the VITDAL-ICU study identified a significant reduction in 28-day mortality (HR 0.52, [0.30–0.89]) [36]. Similarly, Bhattacharyya et al. showed that vitamin D replacement significantly decreased the need for mechanical ventilation and trended toward reducing 90-day mortality (HR 0.449, [0.198–1.017]) [4]. VITDALIZE is designed to enroll 2400 patients, with a primary endpoint of 28-day mortality [36]. The outcome of this trial is expected to be reported in 2026 and may provide us with more robust evidence of the efficacy of vitamin D supplementation in patients with severe vitamin D deficiency.

Thampi et al., Sistanzid et al., and Naguib et al. used synthetic vitamin D analogs as a vitamin D replacement form [3,6,18]. They used calcitriol in septic patients and found no benefit of vitamin D replacement. Naguib et al. administered alfacalcidol orally to patients scheduled for elective mechanical valve replacement surgery [18]. Although Naguib et al. showed no significant difference in hospital mortality, there was a significant reduction in

ICU length of stay and postoperative infection rate. Generally, vitamin D analogs were not suitable for vitamin D replacement due to their narrow therapeutic range and lack of feedback control, resulting in an increased risk of hypercalcemia. Analogs are indicated for hypocalcemia, osteoporosis, and the prevention of corticosteroid-induced osteoporosis [36]. Given the high incidence of acute kidney injury in acute illness and the high level of monitoring in ICUs, it is arguable that active or partially active vitamin D analogs are more suitable for the critically ill population. Further studies should be designed to evaluate their efficacy and safety in this context.

The role of vitamin D in critically ill COVID-19 patients was explored in several studies. A search using the keywords “calcifediol”, “COVID”, and “critically ill” identified only one randomized controlled trial (RCT): Entrenas Castillo et al. (2020) [37]. However, this study was conducted at a time when COVID-19 treatment options were poorly understood and included hydroxychloroquine, which was later found to have no therapeutic effect against COVID-19. Due to the inclusion of hydroxychloroquine in the treatment protocol, we deemed this study invalid and excluded it from our review.

Other research studies on vitamin D in COVID-19 patients had significant limitations. Bishop et al. (2022) [38] did not investigate its effects on critically ill COVID-19 patients, while De Niet et al. (2022) [39] did not focus on ICU patients in their analysis. Maghbooli et al. (2022) [40] reported that calcifediol supplementation was associated with an increased percentage of lymphocytes and a decreased neutrophil-to-lymphocyte ratio. A lower neutrophil-to-lymphocyte ratio was significantly linked to reduced ICU admission duration and mortality. However, since the study’s primary outcome was not a direct clinical endpoint, it was not included in our literature review.

Masbough et al. and Sharma et al. both investigated vitamin D replacement in traumatic brain injury patients [7,13]. Surprisingly, both studies found a statistically significant increase in GCS scores. Sharma et al. reported improvement in biomarkers and shorter mechanical ventilation days. Similarly, Hansaloei et al. reported a significant reduction in biomarkers, SOFA scores, duration of mechanical ventilation days, and length of ICU stay in critically ill patients with traumatic injuries [22]. The impact of preoperative vitamin D supplementation was examined by Hajimohammadebrahim-Ketabforoush et al. in patients undergoing craniotomy for brain tumor resection and by Naguib et al. in those undergoing elective mechanical valve replacement surgery. Both studies reported a statistically significant reduction in ICU length of stay [18,19]. Low vitamin D level was associated with adverse outcomes with various surgical procedures. With a relatively low patient population enrolled in these trials, the positive findings regarding GCS scores and reduced ICU length of stay suggest that this area could benefit from further exploration with larger patient enrollment.

The root cause of vitamin D deficiency in ICU patients can be attributed to both a pre-existing deficiency and a decline in levels during acute illnesses [41,42]. Mechanisms contributing to reduced vitamin D levels during acute illness may include hemodilution, interstitial extravasation, decreased synthesis of binding proteins, and renal loss [43]. In addition, acute fluid resuscitation in the ICU can significantly lower vitamin D levels, which may take up to 24 h to resolve [44]. Thus, interpretations of vitamin D levels in patients with acute illnesses should be performed with caution.

Absorption of vitamin D supplementation can vary in different patient populations. For example, higher BMI is linked to a smaller increase in serum 25(OH)D concentrations. Obesity reduces 25(OH)D responses to vitamin D treatment not only due to increased dilution of available 25(OH)D but also because it specifically decreases the activity of 25-hydroxylase in the liver and other tissues responsible for 25(OH)D production. Obesity is associated with the repression of the enzyme CYP2R1, which is primarily responsible for

25-hydroxylation of vitamin D in the liver, leading to decreased serum levels of 25(OH)D (the active form of vitamin D) due to reduced production of this metabolite; essentially, obesity inhibits the key step in the activation of vitamin D, resulting in lower circulating levels of the active form [45,46].

Calcium intake and the type of vitamin D (D2-ergocalciferol or D3-cholecalciferol) can affect the dose–response of 25(OH)D to vitamin D. Compared to ergocalciferol, cholecalciferol has better biological efficacy in improving vitamin D status [47]. Following oral intake, vitamin D is rapidly absorbed, reaching the maximum level after around 24 h. The levels of 25(OH)D increase gradually, peaking at 7–14 days, depending on the dose. It is not known how the 25(OH)D concentrations were affected in studies that used only single-dose vitamin D supplementation. Patients with malabsorption issues, such as gastrectomy or bariatric patients, might need higher doses of vitamin D [44]. Lastly, baseline vitamin D levels reflect coexisting conditions, especially in critically ill patients, which could cause residual confounding effects when analyzing results [8].

Given the wide therapeutic index of vitamin D, clinicians may feel comfortable with high-dose vitamin D replacement even in the absence of a baseline vitamin D level. However, vitamin D toxicity may occur when serum levels of 25(OH)D are greater than 150 ng/mL, accompanied by normal or elevated values of 1,25(OH)₂D concentration. The most common cause of vitamin D toxicity is excessive vitamin D supplementation without frequent monitoring of vitamin D levels. While most cases of vitamin D toxicity do not lead to serious complications or sequelae, it may cause hypercalcemia and acute renal failure, which are important considerations in critical care settings. If a high-dose vitamin D replacement is given, it is reasonable to consider monitoring vitamin D levels together with electrolyte levels and kidney function. Studies have shown why large bolus doses of vitamin D can be ineffective, both for preventing rickets and reducing the risks of respiratory infections. This is because it induces increased 24-hydroxylation of circulating 25(OH)D, an effect that is normally protective against vitamin D toxicity. Furthermore, this adverse effect can last for a full month after a single large bolus dose of vitamin D [48]. In COVID-19 patients, larger bolus doses of vitamin D proved ineffective despite the known protective effects of hormonal vitamin D against infection—such as boosting innate immunity, downregulating excessive adaptive immune responses that trigger cytokine storms, and reducing the risk of acute respiratory distress syndrome (ARDS). One possible reason is that vitamin D₃ takes approximately two weeks to raise low serum 25(OH)D levels to normal, whereas COVID-19 severity progresses more rapidly. Another potential explanation is that extremely high doses of vitamin D induce protective mechanisms against D₃ toxicity, including increased activity of the 25-hydroxylase enzyme in the liver and other tissues; this, in turn, reduces the availability of 25(OH)D, the precursor required for the production of hormonal vitamin D (calcitriol) in tissues. Smaller bolus doses (<100,000 IU), however, may be more effective in COVID-19 patients [49–53]. Further studies are needed to determine the optimal dosing strategies for vitamin D supplementation in critically ill patients.

5. Limitations

This review has several limitations. First, no quantitative statistical analysis was conducted, which reduces certainty and introduces the potential for bias in the findings. Second, we did not perform a meta-analysis in our review. Previous meta-analyses have suggested that vitamin D supplementation may be associated with a reduced mortality rate and lower ICU admission rates [54].

Additionally, due to the heterogeneity of study designs and variability in vitamin D dosing, this review is limited by its approach of evaluating studies on an individual basis.

6. Conclusions

Vitamin D supplementation in critically ill patients may shorten ICU or hospital length of stay, improve SOFA scores, or reduce the duration of mechanical ventilation. Its ability to lower 28-day mortality remains uncertain, and large randomized controlled trials are needed to confirm its efficacy in this setting. Additionally, identifying the highest bolus dose of vitamin D that can be administered without triggering mechanisms that reduce its activation remains a critical research priority.

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References

1. Sistanizad, M.; Kouчек, M.; Miri, M.; Salarian, S.; Shojaei, S.; Moeini Vasegh, F.; Seifi Kafshgari, H.; Qobadighadikolaei, R. 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*, 101271. [\[CrossRef\]](#)
2. Bikle, D.D. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem. Biol.* **2014**, *21*, 319–329. [\[CrossRef\]](#) [\[PubMed\]](#) [\[PubMed Central\]](#)
3. Sistanizad, M.; Salarian, S.; Kouчек, M.; Shojaei, S.; Miri, M.; Masbough, F. Effect of Calcitriol Supplementation on Infectious Biomarkers in Patients with Positive Systemic Inflammatory Response: A Randomized Controlled Trial. *Ann. Med. Surg.* **2024**, *86*, 875–880. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Bhattacharyya, A.; Subramaniam, R.; Baidya, D.K.; Aggarwal, P.; Wig, N. Effect of Early Administration of Vitamin D on Clinical Outcome in Critically Ill Sepsis Patients: A Randomized Placebo-Controlled Trial. *Indian J. Crit. Care Med.* **2021**, *25*, 1147–1154. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Bychinin, M.V.; Klypa, T.V.; Mandel, I.A.; Yusubalieva, G.M.; Baklaushev, V.P.; Kolyshkina, N.A.; Troitsky, A.V. Effect of Vitamin D3 Supplementation on Cellular Immunity and Inflammatory Markers in COVID-19 Patients Admitted to the ICU. *Sci. Rep.* **2022**, *12*, 18604. [\[CrossRef\]](#)
6. Thampi, S.J.; Basheer, A.; Thomas, K. Calcitriol in Sepsis—A Single-Centre Randomised Control Trial. *J. Clin. Med.* **2024**, *13*, 3823. [\[CrossRef\]](#)
7. Sharma, S.; Kumar, A.; Choudhary, A.; Sharma, S.; Khurana, L.; Sharma, N.; Kumar, V.; Bisht, A. Neuroprotective Role of Oral Vitamin D Supplementation on Consciousness and Inflammatory Biomarkers in Determining Severity Outcome in Acute Traumatic Brain Injury Patients: A Double-Blind Randomized Clinical Trial. *Clin. Drug Investig.* **2020**, *40*, 327–334. [\[CrossRef\]](#)
8. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network; Ginde, A.A.; Brower, R.G.; Caterino, J.M.; Finck, L.; Banner-Goodspeed, V.M.; Grissom, C.K.; Hayden, D.; Hough, C.L.; Hyzy, R.C.; et al. Early High-Dose Vitamin D3 for Critically Ill, Vitamin D-Deficient Patients. *N. Engl. J. Med.* **2019**, *381*, 2529–2540. [\[CrossRef\]](#)
9. Moromizato, T.; Litonjua, A.A.; Braun, A.B.; Gibbons, F.K.; Giovannucci, E.; Christopher, K.B. Association of Low Serum 25-Hydroxyvitamin D Levels and Sepsis in the Critically Ill. *Crit. Care Med.* **2014**, *42*, 97–107. [\[CrossRef\]](#)
10. Ashoor, T.M.; Abd Elazim, A.E.H.; Mustafa, Z.A.E.; Anwar, M.A.; Gad, I.A.; Mamdouh Esmat, I. Outcomes of High-Dose versus Low-Dose Vitamin D on Prognosis of Sepsis Requiring Mechanical Ventilation: A Randomized Controlled Trial. *J. Intensive Care Med.* **2024**, *39*, 1012–1022. [\[CrossRef\]](#)
11. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Singh, A.; Rastogi, A.; Puri, G.D.; Ganesh, V.; Naik, N.B.; Kajal, K.; Kahlon, S.; Soni, S.L.; Kalaria, N.; Saini, K.; et al. Therapeutic High-Dose Vitamin D for Vitamin D-Deficient Severe COVID-19 Disease: Randomized, Double-Blind, Placebo-Controlled Study (SHADE-S). *J. Public Health* **2024**, *46*, 256–266. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Masbough, F.; Kouчек, M.; Koosha, M.; Salarian, S.; Miri, M.; Raoufi, M.; Taherpour, N.; Amniati, S.; Sistanizad, M. Investigating the Effect of High-Dose Vitamin D3 Administration on Inflammatory Biomarkers in Patients with Moderate to Severe Traumatic Brain Injury: A Randomized Clinical Trial. *Iran. J. Med. Sci.* **2024**, *49*, 643–651. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Zamanian, M.; Javadfar, Z.; Salimi, Y.; Rahimi, M.A.; Rabieenia, E.; Rahimi, A. Effect of High-Dose Vitamin D on Mortality and Hospital Length of Stay in ICU Patients with COVID-19: A Randomized Clinical Trial. *J. Kermanshah Univ. Med. Sci.* **2024**, *28*, e140510. [\[CrossRef\]](#)

15. Wang, A.-Y.; Yeh, Y.-C.; Cheng, K.-H.; Han, Y.-Y.; Chiu, C.-T.; Chang, C.-C.; Wang, I.-T.; Chao, A. Efficacy and Safety of Enteral Supplementation with High-Dose Vitamin D in Critically Ill Patients with Vitamin D Deficiency. *J. Formos. Med. Assoc.* **2024**. [\[CrossRef\]](#)
16. Domazet Bugarin, J.; Dosenovic, S.; Ilic, D.; Delic, N.; Saric, I.; Ugrina, I.; Stojanovic Stipic, S.; Duplancic, B.; Saric, L. Vitamin D Supplementation and Clinical Outcomes in Severe COVID-19 Patients-Randomized Controlled Trial. *Nutrients* **2023**, *15*, 1234. [\[CrossRef\]](#)
17. Han, J.H.; Ginde, A.A.; Brown, S.M.; Baughman, A.; Collar, E.M.; Ely, E.W.; Gong, M.N.; Hope, A.A.; Hou, P.C.; Hough, C.L.; et al. Effect of Early High-Dose Vitamin D3 Repletion on Cognitive Outcomes in Critically Ill Adults. *Chest* **2021**, *160*, 909–918. [\[CrossRef\]](#)
18. Naguib, S.N.; Sabry, N.A.; Farid, S.F.; Alansary, A.M. Short-Term Effects of Alfacalcidol on Hospital Length of Stay in Patients Undergoing Valve Replacement Surgery: A Randomized Clinical Trial. *Clin. Ther.* **2021**, *43*, e1–e18. [\[CrossRef\]](#)
19. Hajimohammadebrahim-Ketabfroush, M.; Shahmohammadi, M.; Keikhaee, M.; Eslamian, G.; Vahdat Shariatpanahi, Z. Single High-Dose Vitamin D3 Injection and Clinical Outcomes in Brain Tumor Resection: A Randomized, Controlled Clinical Trial. *Clin. Nutr. ESPEN* **2021**, *41*, 153–159. [\[CrossRef\]](#)
20. Ingels, C.; Vanhorebeek, I.; Van Cromphaut, S.; Wouters, P.J.; Derese, I.; Dehouwer, A.; Møller, H.J.; Hansen, T.K.; Billen, J.; Mathieu, C.; et al. Effect of Intravenous 25OHD Supplementation on Bone Turnover and Inflammation in Prolonged Critically Ill Patients. *Horm. Metab. Res.* **2020**, *52*, 168–178. [\[CrossRef\]](#)
21. Padhy, S.S.; Malviya, D.; Harjai, M.; Tripathi, M.; Das, P.K.; Rastogi, S. A Study of Vitamin D Level in Critically Ill Patients and Effect of Supplementation on Clinical Outcome. *Anesth. Essays Res.* **2020**, *14*, 474–477. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Hasanloei, M.A.V.; Rahimlou, M.; Eivazloo, A.; Sane, S.; Ayremlou, P.; Hashemi, R. Effect of Oral versus Intramuscular Vitamin D Replacement on Oxidative Stress and Outcomes in Traumatic Mechanical Ventilated Patients Admitted to Intensive Care Unit. *Nutr. Clin. Pract.* **2020**, *35*, 548–558. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Karsy, M.; Guan, J.; Eli, I.; Brock, A.A.; Menacho, S.T.; Park, M.S. The Effect of Supplementation of Vitamin D in Neurocritical Care Patients: Randomized Clinical Trial of hypovitaminosis D (RECTIFY). *J. Neurosurg.* **2020**, *133*, 1103–1112. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Miri, M.; Kouchek, M.; Rahat Dahmardeh, A.; Sistanizad, M. Effect of High-Dose Vitamin D on Duration of Mechanical Ventilation in ICU Patients. *Iran. J. Pharm. Res.* **2019**, *18*, 1067–1072. [\[CrossRef\]](#)
25. Meng, J.; Li, X.; Liu, W.; Xiao, Y.; Tang, H.; Wu, Y.; Xiong, Y.; Gao, S. The role of vitamin D in the prevention and treatment of SARS-CoV-2 infection: A meta-analysis of randomized controlled trials. *Clin. Nutr.* **2023**, *42*, 2198–2206. [\[CrossRef\]](#)
26. Chiodini, I.; Gatti, D.; Soranna, D.; Merlotti, D.; Mingiano, C.; Fassio, A.; Adami, G.; Falchetti, A.; Eller-Vainicher, C.; Rossini, M.; et al. Vitamin D Status and SARS-CoV-2 Infection and COVID-19 Clinical Outcomes. *Front. Public Health* **2021**, *9*, 736665. [\[CrossRef\]](#)
27. Rawat, D.; Roy, A.; Maitra, S.; Shankar, V.; Khanna, P.; Baidya, D.K. Vitamin D supplementation and COVID-19 treatment: A systematic review and meta-analysis. *Diabetes Metab. Syndr.* **2021**, *15*, 102189. [\[CrossRef\]](#)
28. D'Ecclesiis, O.; Gavioli, C.; Martinoli, C.; Raimondi, S.; Chiocca, S.; Miccolo, C.; Bossi, P.; Cortinovis, D.; Chiaradonna, F.; Palorini, R.; et al. Vitamin D and SARS-CoV2 infection, severity and mortality: A systematic review and meta-analysis. *PLoS ONE* **2022**, *17*, e0268396. [\[CrossRef\]](#)
29. Sirbu, A.C.; Sabin, O.; Bocşan, I.C.; Vesa, Ş.C.; Buzoianu, A.D. The Effect of Vitamin D Supplementation on the Length of Hospitalisation, Intensive Care Unit Admission, and Mortality in COVID-19-A Systematic Review and Meta-Analysis. *Nutrients* **2023**, *15*, 3470. [\[CrossRef\]](#)
30. Varikasuvu, S.R.; Thangappazham, B.; Vykunta, A.; Duggina, P.; Manne, M.; Raj, H.; Aloori, S. COVID-19 and vitamin D (Co-VIVID study): A systematic review and meta-analysis of randomized controlled trials. *Expert Rev. Anti-Infect. Ther.* **2022**, *20*, 907–913. [\[CrossRef\]](#)
31. Gao, Z.; Xie, J.; Li, C.; Liu, L.; Yang, Y. High Dose Vitamin D3 Supplementation Is Not Associated With Lower Mortality in Critically Ill Patients: A Meta-Analysis of Randomized Control Trials. *Front. Nutr.* **2022**, *9*, 762316. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Randolph, C.; Tierney, M.C.; Mohr, E.; Chase, T.N. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary Clinical Validity. *J. Clin. Exp. Neuropsychol.* **1998**, *20*, 310–319. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Shunk, A.W.; Davis, A.S.; Dean, R.S. TEST REVIEW: Dean C. Delis, Edith Kaplan & Joel H. Kramer, Delis Kaplan Executive Function System (D-KEFS), the Psychological Corporation, San Antonio, TX, 2001. \$415.00 (complete Kit). *Appl. Neuropsychol.* **2006**, *13*, 275–279. [\[CrossRef\]](#)
34. Akbas, E.M.; Gungor, A.; Ozcicek, A.; Akbas, N.; Askin, S.; Polat, M. Vitamin D and Inflammation: Evaluation with Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio. *Arch. Med. Sci.* **2016**, *12*, 721–727. [\[CrossRef\]](#)
35. Kearns, M.D.; Alvarez, J.A.; Tangpricha, V. Large, single-dose, oral vitamin D supplementation in adult populations: A systematic review. *Endocr. Pract.* **2014**, *20*, 341–351. [\[CrossRef\]](#)
36. Amrein, K. The VITDALIZE Study: Effect of High-Dose Vitamin D3 on 28-Day Mortality in Adult Critically Ill Patients (VITDALIZE). Available online: <https://clinicaltrials.gov/study/NCT03188796> (accessed on 19 January 2025).

37. Entrenas Castillo, M.; Entrenas Costa, L.M.; Vaquero Barrios, J.M.; Alcalá Díaz, J.F.; López Miranda, J.; Bouillon, R.; Quesada Gomez, J.M. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. *J. Steroid Biochem. Mol. Biol.* **2020**, *203*, 105751. [\[CrossRef\]](#)
38. Bishop, C.W.; Ashfaq, A.; Melnick, J.Z.; Vazquez-Escarpanter, E.; Fialkow, J.A.; Strugnelli, S.A.; Choe, J.; Kalantar-Zadeh, K.; Federman, N.C.; Ng, D.; et al. REsCue trial: Randomized controlled clinical trial with extended-release calcifediol in symptomatic COVID-19 outpatients. *Nutrition* **2023**, *107*, 111899. [\[CrossRef\]](#)
39. De Niet, S.; Trémège, M.; Coffiner, M.; Rousseau, A.-F.; Calmes, D.; Frix, A.-N.; Gester, F.; Delvaux, M.; Dive, A.-F.; Guglielmi, E.; et al. Positive Effects of Vitamin D Supplementation in Patients Hospitalized for COVID-19: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* **2022**, *14*, 3048. [\[CrossRef\]](#)
40. Maghbooli, Z.; Sahraian, M.A.; Jamalimoghadamsiahkali, S.; Asadi, A.; Zarei, A.; Zendehdel, A.; Varzandi, T.; Mohammadnabi, S.; Alijani, N.; Karimi, M.; et al. Treatment with 25-Hydroxyvitamin D3 (Calcifediol) Is Associated with a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients with COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-Blinded Clinical Trial. *Endocr. Pract.* **2021**, *27*, 1242–1251. [\[CrossRef\]](#)
41. Amrein, K.; Papinutti, A.; Mathew, E.; Vila, G.; Parekh, D. Vitamin D and Critical Illness: What Endocrinology Can Learn from Intensive Care and Vice Versa. *Endocr. Connect.* **2018**, *7*, R304–R315. [\[CrossRef\]](#)
42. Gomes, T.L.; Fernandes, R.C.; Vieira, L.L.; Schincaglia, R.M.; Mota, J.F.; Nóbrega, M.S.; Pichard, C.; Pimentel, G.D. Low Vitamin D at ICU Admission Is Associated with Cancer, Infections, Acute Respiratory Insufficiency, and Liver Failure. *Nutrition* **2019**, *60*, 235–240. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Krishnan, A.; Ochola, J.; Mundy, J.; Jones, M.; Kruger, P.; Duncan, E.; Venkatesh, B. Acute Fluid Shifts Influence the Assessment of Serum Vitamin D Status in Critically Ill Patients. *Crit. Care* **2010**, *14*, R216. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Ramasamy, I. Vitamin D Metabolism and Guidelines for Vitamin D Supplementation. *Clin. Biochem. Rev.* **2020**, *41*, 103–126. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Ekwaru, J.P.; Zwicker, J.D.; Holick, M.F.; Giovannucci, E.; Veugelers, P.J. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. *PLoS ONE* **2014**, *9*, e111265. [\[CrossRef\]](#)
46. Elkhwanky, M.S.; Kumm, O.; Piltonen, T.T.; Laru, J.; Morin-Papunen, L.; Mutikainen, M.; Tavi, P.; Hakkola, J. Obesity Represses CYP2R1, the Vitamin D 25-Hydroxylase, in the Liver and Extrahepatic Tissues. *JBM R Plus* **2020**, *4*, e10397. [\[CrossRef\]](#)
47. Balachandar, R.; Pullakhandam, R.; Kulkarni, B.; Sachdev, H.S. Relative Efficacy of Vitamin D₂ and Vitamin D₃ in Improving Vitamin D Status: Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, 3328. [\[CrossRef\]](#)
48. Ketha, H.; Thacher, T.D.; Oberhelman, S.S.; Fischer, P.R.; Singh, R.J.; Kumar, R. Comparison of the effect of daily versus bolus dose maternal vitamin D₃ supplementation on the 24,25-dihydroxyvitamin D₃ to 25-hydroxyvitamin D₃ ratio. *Bone* **2018**, *110*, 321–325. [\[CrossRef\]](#)
49. Cannata-Andía, J.B.; Díaz-Sottolano, A.; Fernández, P.; Palomo-Antequera, C.; Herrero-Puente, P.; Mouzo, R.; Carrillo-López, N.; Panizo, S.; Ibañez, G.H.; Cusumano, C.A.; et al. A single-oral bolus of 100,000 IU of cholecalciferol at hospital admission did not improve outcomes in the COVID-19 disease: The COVID-VIT-D-a randomised multicentre international clinical trial. *BMC Med.* **2022**, *20*, 83. [\[CrossRef\]](#)
50. Martucci, G.; McNally, D.; Parekh, D.; Zajic, P.; Tuzzolino, F.; Arcadipane, A.; Christopher, K.B.; Dobnig, H.; Amrein, K. Trying to Identify Who May Benefit Most from Future Vitamin D Intervention Trials: A Post Hoc Analysis from the VITDAL-ICU Study Excluding the Early Deaths. *Crit. Care* **2019**, *23*, 200. [\[CrossRef\]](#)
51. Joshi, D.; Center, J.R.; A Eisman, J.A. Vitamin D Deficiency in Adults. *Aust. Prescr.* **2010**, *33*, 103–106. [\[CrossRef\]](#)
52. Iglar, P.J.; Hogan, K.J. Vitamin D Status and Surgical Outcomes: A Systematic Review. *Patient Saf. Surg.* **2015**, *9*, 14. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Quraishi, S.A.; Camargo, C.A., Jr. Vitamin D in Acute Stress and Critical Illness. *Curr. Opin. Clin. Nutr. Metab. Care* **2012**, *15*, 625–634. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Argano, C.; Mallaci Bocchio, R.; Natoli, G.; Scibetta, S.; Lo Monaco, M.; Corrao, S. Protective Effect of Vitamin D Supplementation on COVID-19-Related Intensive Care Hospitalization and Mortality: Definitive Evidence from Meta-Analysis and Trial Sequential Analysis. *Pharmaceuticals* **2023**, *16*, 130. [\[CrossRef\]](#) [\[PubMed\]](#)

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