Review

Evaluation of Vitamin D Supplementation in Critically Ill Patients - A Systematic Review of the Last 5 Years

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Abstract: Vitamin D deficiency was found to be associated with increased risks of infection, morbidity, and mortality in critically ill patients. However, current critical care guidelines do not recommend routine vitamin D supplementation. We conducted a literature search using Medline, Embase, Web of Science and Cochrane databases for randomized controlled trials published in the past five years on vitamin D supplementation in ICU patients. We analyzed data from 21 studies, reviewing dosing strategies, administration routes, baseline vitamin D levels, and clinical outcomes such as biomarker changes, mechanical ventilation duration, hospital length of stay, and mortality. Our results suggest that vitamin D supplementation may be safe and potentially beneficial in reducing ICU length of stay and time on mechanical ventilation. However, the impact on overall mortality remains uncertain. Our findings emphasize the need for individualized clinical decision-making regarding vitamin D supplementation in critically ill patients, considering baseline vitamin D levels, patient characteristics, severity of illness, and administration methods.

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

1. Introduction

It is reported that 40-70% of ICU patients present with vitamin D deficiency [1]. Vitamin D (calciferol) is a fat-soluble vitamin that endogenously forms in the skin from UV exposure or food or dietary supplementation. It hydroxylated in the liver to become 25-hydroxyvitamin D (calcidiol, D3/cholecalciferol is the supplement analogue), and hydroxylated again in the kidney into active metabolite 1,25-dihydroxyvitamin D(calcitriol, D2/ergocalciferol is the supplement analogue) [2]. Cholecalciferol, ergocalciferol and calcitriol are used for supplementation in clinical settings [3].

Previous studies have found that vitamin D also plays an important role in immune function that is crucial to recovery in critical illness. It is known that vitamin D regulates gene expression, cell proliferation, and apoptosis [4]. It also regulates the proliferation of T and B cells, modulates immunoglobulin production, and decreases proinflammatory cytokine levels [1,4,5]. Furthermore, vitamin D has been shown to upregulate cathelicidin and other antimicrobial peptides, which are essential to immune defense in critically ill patients [6]. Vitamin D deficiency leads to higher levels

 doi:10.20944/preprints202501.1623.v1

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 (25-hydroxyvitamin D<20 ng/mL) is associated with sepsis, infection, increased morbidity and mortality [10]. However, the benefit of vitamin D supplements in patients with critical illness remained unanswered. In fact, studies evaluating efficacy of vitamin D replacement in critically ill patients have demonstrated conflicting results. This review aimed to investigate the updated literature on the effects of vitamin D supplementation on clinical outcomes in adult intensive care unit (ICU) patients, as well as assessing the vitamin D doses used in various studies.

2. Materials and Methods

Two reviewers independently screened four databases (PubMed, Embase, and Cochrane, 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 following 4 criteria: 1) the study design must be a randomized clinical trials (RCT); 2) the study had to be performed in adult population (age ≥ 18 years); 3) the studies must have been published between 2019 to November 2024; and 4) the publications must have been written in full length and in the English language. 5) vitamin D is the only study variable for the clinical outcomes. Retrospective, observational studies and meta-analysis were excluded. Detailed information from each trial was extracted including baseline vitamin D levels, patient population, sample size included in analysis, vitamin D replacement routes and doses, duration of replacement, dose duration and study outcomes. Due to heterogeneous design of clinical trials, no quantitative statistical analysis was performed. Each eligible study was individually evaluated by authors.

3. Results

Out of 807 studies identified, 21 studies met the criteria and were included in this review, see Figure 1. For each included study, one author independently extracted the study details in Table 1. Two authors independently verified the extracted data for all trials.

Eight of the 21 trials included did not show clinical benefit of vitamin D replacement in critically ill patients. The remaining 13 trials demonstrated that replacement of vitamin D in ICU patients with vitamin D deficiency had a positive impact in certain clinical outcomes. Six of these 13 trials found that vitamin D supplementation led to a decreased ICU or hospital length of stay (LOS), three trials found an improvement in Sequential Organ Failure Assessment (SOFA) score, three trials found a decrease in mechanical ventilation (MV) duration, three trials found a decrease of 30-day mortality, two trials found positive outcomes in the Glasgow Coma Scale (GCS), and six trials found positive results in biomarkers. Table 1 summarizes the findings of the studies included in this systematic review. Table 2 highlights whether the study showed a statistically improved outcome of vitamin D replacement.

Various dosing replacement strategies have been used. Of the ones that showed benefit of vitamin D replacement, oral 50,000 International Units (IU) daily for 5 days; oral 120,000 IU single dose, oral 600,000 IU single dose, as well as IM dose 300,000 IU single dose are mostly commonly seen.

 doi:10.20944/preprints202501.1623.v1

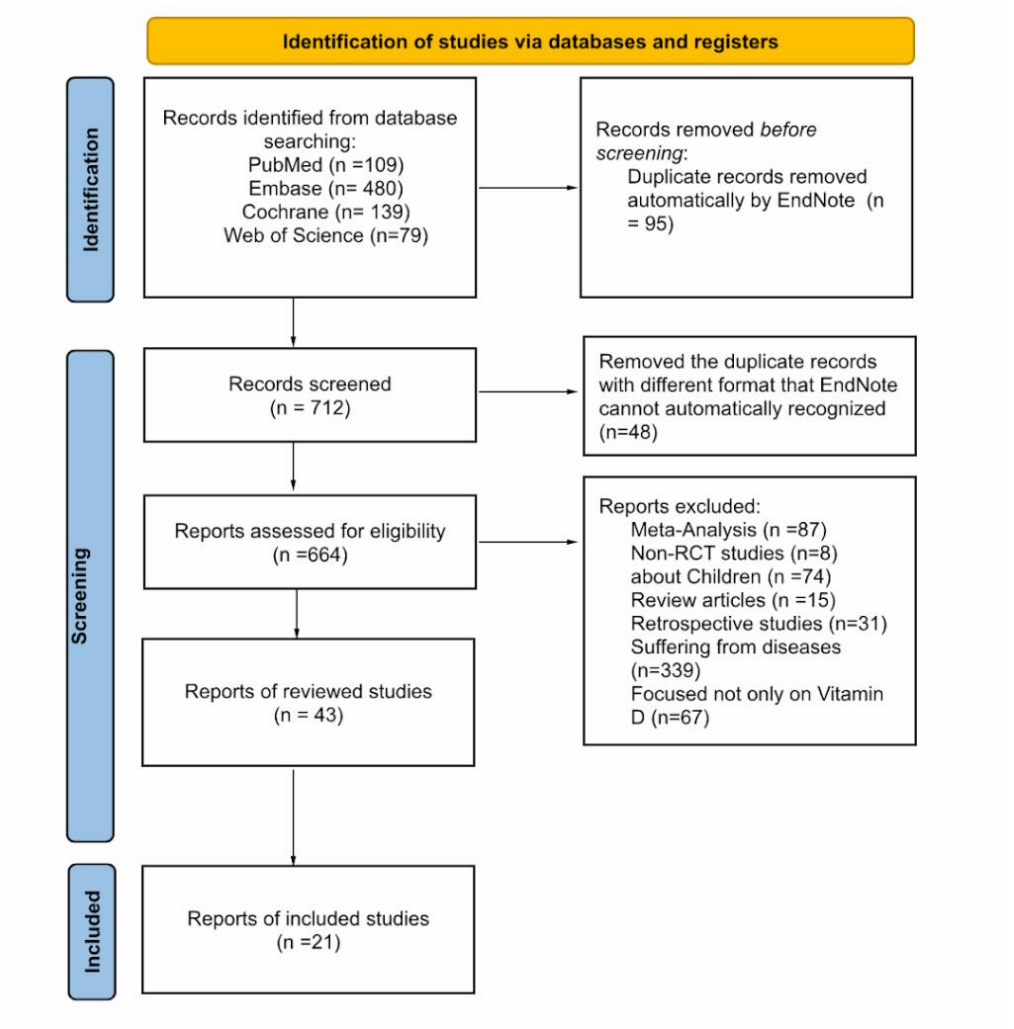

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection based on inclusion and exclusion criteria [11].

 doi:10.20944/preprints202501.1623.v1

Table 1. Summary of randomized clinical trials (RCT) 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 50,000IU/d vs LD: enteral 5,000IU/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 600,000IU	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 300,000IU	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 300,000IU	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 different in procalcitonin level, ICU LOS and 28-day mortality
Zamanian et al [14]	2024	23.06 vs 25.68	61	COVID-19	IM 300,000IU	Once	No significant difference in mortality or hospital LOS
Wang et al [15]	2024	<20	61	Vitamin D-deficient	Enteral 569,600IU	Once divided by 8 bottles	Less than half of the treatment group who achieved vit D level>30 ng/ml. They had significantly lower 30-day mortality than those who did not
Domazet Bugarin et al [16]	2023	25.3 vs 27.3	155	Covid-19	Enteral 10,000IU vs placebo	Once	No statistically significant in MV days, secondary outcomes
Bychinin et al [5]	2022	9.6 vs 11	110	COVID-19	PO 60,000IU weekly then 5,000IU/daily	During hospital stay	Significantly increased NK and NK T cell counts. No difference in mortality; need for MV or incidence of nosocomial infection
Sistanizad et al [1]	2021	<20	36	ICU ventilated	IM 300,000IU vs placebo	Once	No statistically significant results identified due to small sample size
Bhattacharyya et al [4]	2021	12.05 vs 15.47	126	Sepsis	Enteral 540,000IU vs placebo	Once	No statistically difference in ICU LOS, hospital LOS, MV duration/requirements, or 90-day mortality

 doi:10.20944/preprints202501.1623.v1

Han et al [17]	2021	15.2 vs 13.1	95	Vitamin D-deficient	Enteral 540,000IU	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, postoperative infection rate. No significantly difference in hospital mortality
Sharma et al [7]	2020	18.30 vs 15.15	35	Traumatic brain injury	Enteral 120,000IU vs placebo	Once	Significant improvement in GCS score, MV duration and IL-6, TNF-α
Hajimohammadebrahim-Ketabforoush et al [19]	2020	<20	60	Craniotomy for brain tumor resection	IM 300,000IU	Once	Significantly reduction in ICU LOS and hospital LOS
Ingels et al [20]	2020	6.8 vs. 9.2	24	Prolonged ICU stay(>10 days)	200μg loading dose once then 15μg/day	Loading dose then 10 days	No difference in SOFA score or MV duration
Padhy et al [21]	2020	≤20	60	Vitamin D-deficient, sepsis	G1: enteral 60,000IU once/wk; G2: 60,000IU 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 50,000IU /day; G2: IM 300,000IU 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 540,000IU vs placebo	Once	No statistically difference in hospital LOS or ICU LOS
Miri et al [24]	2019	8.43 vs. 11.35	40	ICU ventilated	IM 300,000IU vs placebo	Once	Significant reduction in 28-day mortality
PETAL group [8]	2019	11.2 vs 11.0	1078	Vitamin D-deficient	Enteral 540,000IU vs placebo	Once	No statistically difference in 90-day mortality and other clinical outcomes

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

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	
2024	Ashoor et al [10]		HD	HD								HD: pct, IL-37
2024	Singh et al [12]											

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2024	Masbough et al [13]																				IL-1b, IL-6
2024	Thampi et al [6]																				
2024	Sistanizad et al [3]																				pct
2024	Zamanian et al [14]																				
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]																				
2021	Han et al [17]																	BRANS score			
2021	Naguib et al [18]																				
2020	Sharma et al [7]																				IL-6, TNF-α
2020	Hajimohammadebrahim-Ketabforoush et al [19]																				
2020	Ingels et al [20]																				CRP, WBC, IL-37, sCD163
2020	Wang et al [15]																				
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]																				

[1] **Table 1 & 2: : Vitamin D showed statistically significant improvement; : Vitamin D showed no effects; : No trial has reported yet.** HD: high-dose of vitamin D; LD: low-dose of vitamin D; G1: group 1; G2: group 2; LOS: length of stay; APACHE II: acute physiologic assessment and chronic health evaluation II; SOFA: sequential organ failure assessment; mNUTRIC: the modified Nutrition Risk in Critically ill; MV: mechanical ventilator; All-cause: all-cause mortality; 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.

 doi:10.20944/preprints202501.1623.v1

4. Discussion

Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial conducted by The National Heart, Lung, and Blood Institute PETAL clinical trial group (2019) showed early administration of a single high-dose 540,000 IU of vitamin D3 enterally in critical-ill patients with vitamin D deficiency ((25-hydroxyvitamin D level, <20 ng/ml) increases vitamin D serum level but did not demonstrate any clinical benefit over placebo in 90-day mortality or other nonfatal outcomes [8]. This group conducted an ancillary study, VIOLET Long-term Brain Outcomes in Vitamin D Deficient Patients (VIOLET-BUD) [17] . This study evaluated the same single enteral high dose of vitamin D vs placebo in vitamin D deficiency patients on their long-term cognitive outcomes at a median of 443 days (interquartile range, 390-482 days). Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [25] was evaluated for long term cognitive outcomes and executive function (composite score derived from three Delis-Kaplan Executive Function System Subscales [26]). It concluded that a single high dose of enteral vitamin D did not improve long-term global cognition or executive function in critically ill patients with vitamin D deficiency.

Overall, conflicting results were demonstrated in the randomized controlled trials in the past 5 years regarding the clinical impact of vitamin D replacement on critically ill patients. Several studies showed vitamin D replacement has positive results in biomarkers such as procalcitonin, Cathelicidin LL-37, neutrophil-to-lymphocyte ratio(NLR) and platelet-to-lymphocyte ratio (PLR) levels [27]. Other studies demonstrated that vitamin D improved SOFA score, GCS score, post-op infection rate, duration of mechanical ventilation, and ICU and hospital length of stay [24]. On the contrary, studies also demonstrated no differences between the vitamin D replacement group and placebo group in regards to ICU and hospital LOS and duration of mechanical ventilation. In one of the biggest studies, with a cohort of 1078 patients, early administration of high-dose enteral vitamin D3 540,000 IU did not improve 90-day mortality and other clinical outcomes of vitamin D–deficient patients [8].

It was demonstrated that the vitamin D supplementation in ICU patients with low baseline vitamin D levels does not increase the serum 25-(OH)-D levels as much as expected [20]. This may be due to an increased distribution volume or an accelerated breakdown [20]. Additionally, vitamin D supplementation increased the serum level of 25-(OH)-D but there was no rise in 1, 25 (OH)2D, suggesting that 25-(OH)-D is not metabolized to the active hormone 1, 25 (OH)2D. It is speculated that CYP27B1 (also known as 1-alpha hydroxylase) is downregulated during critical illness, which compromises the conversion of 25OHD to 1, 25(OH)2D, and possibly shifts the metabolization of 25OHD to other compounds. Small rise in 24, 25 (OH)2D was also noticed, which might serve as a feedback mechanism of avoiding vitamin D toxicity. These findings could be part of an adaptive response to critical illness [20]. On the other hand, the vitamin D supplementation dose in the study of Ingels et al. is very low (loading dose of 8,000 IU and daily maintenance of 600 IU x10 days), compared to vitamin D doses in other studies. This could be the reason why Ingels et al did not find any significant benefit of vitamin D replacement in ICU patients.

The strategies to replace vitamin D also vary across studies. The dose and route of vitamin D replacement remains institutional and protocol-specific. In studies that show vitamin D replacement with positive clinical impacts, the vitamin D dose ranges from 5,000 IU to 540,000 IU as a single dose or multiple-day replacement. The vitamin D was given either via enteral or intramuscular route. In several studies, vitamin D was supplemented in patients who were found to have vitamin D deficiency; in other studies, the critically ill patients were supplemented with high dose vitamin D without knowing their baseline vitamin D level. The optimal timing of vitamin D replacement upon intubation is also unclear. Fortunately, no toxicity from vitamin D supplementation was reported in patients among all studies reviewed.

The promising role of vitamin D in patients with severe vitamin D deficiency has been identified and confirmed in several studies [5,7,10,12,13,18,19,22]. Even though in VITdAL-ICU, the use of vitamin D3 supplement did not show beneficial effects on duration of hospital stay or ICU stay as well as hospital mortality and 90-day mortality, one of the post-hoc study of VITDAL-ICU focused on the subgroup analysis on patients with severe vitamin D deficiency (defined as vitamin D level ≤

 doi:10.20944/preprints202501.1623.v1

12ng/ml) identified a significant reduction in 28-day mortality with the use of vitamin D3 supplements (HR 0.52, [0.30-0.89]) [28]. Bhattacharyya et al performed a subgroup analysis in regards to clinical effects of vitamin D3 supplements on patients with severe vitamin D deficiency (vitamin D levels <12 ng/mL) [4]. The results showed that vitamin D replacement significantly decreased the use of mechanical ventilation, as well as a trend in reducing 90-day mortality (HR 0.449, [0.198–1.017]). An ongoing trial VITDALIZE trial has specifically focused on the critically ill patients with severe vitamin D deficiency [29]. This study is designed to enroll 2400 patients with a primary endpoint of 28-day mortality. The outcome of this trial is expected to be reported in 2026, which may provide us with more robust evidence on vitamin D replacement in patients with severe vitamin D deficiency.

Of all trials included, Thampi et al, Sistanzid et al, and Naguib et al used synthetic vitamin D analogs as a vitamin D replacement form [3,6,18]. Thamp et al and Sistanzid et al used calcitriol in the sepsis population and no significant results were identified [3,6]. Naguib et al used alfacalcidol orally for patients scheduled for elective mechanical valve replacement surgery [18]. Although no significant difference in hospital mortality was identified, 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 its narrow therapeutic range, lack of feedback control resulting in increased risk for hypercalcemia [30]. It is indicated for hypocalcemia, osteoporosis, and the prevention of corticosteroid-induced osteoporosis [31]. Given the high incidence of acute kidney injury in acute illness and high level of monitoring in ICU, 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.

Masbough et al. and Sharma et al. both investigated vitamin D in traumatic brain injury patients [7,13]. Surprisingly, both studies found a statistically increase in GCS scores. Sharma et al. reported improvement in biomarkers and shorter mechanical ventilation days. Similarly, Hansaloei et al. reported significant reduction in biomarkers, SOFAscore, duration of mechanical ventilation days and length of ICU stay in traumatic injury patients admitted to ICU [20]. The effect of preoperative vitamin D replacement was investigated by Hajimohammadebrahim-Ketabforoush et al and Naguib et al. for craniotomy for brain tumor resection and elective mechanical valve replacement surgery, respectively, both reported statistically significant reduction in ICU length of stay [18,19]. Low vitamin D level was associated with adverse outcomes with various surgical procedures [32]. 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 to confirm these results and potentially identify a reduction in other outcomes in surgical patients.

Vitamin D deficiency in ICU patients is attributed to both pre-existing insufficiency and a decline in levels during acute illnesses [33,34]. Mechanisms contributing to reduced vitamin D levels during acute illness may include hemodilution, interstitial extravasation, decreased synthesis of binding proteins, and renal loss [35]. In addition, acute fluid resuscitation in ICU can significantly lower vitamin D level, which may take up to 24 hours to resolve [36]. Thus, interpretations of vitamin D level in acute illness 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. Calcium intake and type of vitamin D (D2- ergocalciferol or D3-cholecalciferol) can affect the dose response of 25 (OH)D to vitamin D. Following oral intake, vitamin D is rapidly absorbed to reach a maximum level at around 24 hours. Levels of 25 (OH)D increase gradually to peak at 7-14 days depending on the dose. For studies that used only single dose vitamin D supplementation, it is questionable how the 25(OH)D concentrations played out. Patients with malabsorption issues such as gastrectomy or bariatric patients might need higher doses of vitamin D compared to others [37]. Lastly, baseline vitamin D levels reflect coexisting conditions, especially in critically ill patients, which could cause residual confounding effects when analyzing results [8].

 doi:10.20944/preprints202501.1623.v1

The impact in clinical outcomes in vitamin D replacement in critically ill patients remains uncertain. High doses of vitamin D up to 540,000 IU have been used in studies to explore impact on duration of mechanical ventilation and length of stay. Given the wide therapeutic index of vitamin D, clinicians may feel comfortable with high dose vitamin D replacement even in absence of baseline vitamin D level. Vitamin D toxicity may occur when serum levels of 25(OH)D concentration 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 electrolytes and kidney functions. More studies need to be performed to determine the optimal dosing strategies to replace vitamin D in critically ill patients.

5. Limitations

This review has several limitations. First, no quantitative statistical analysis was conducted, resulting in reduced certainty and a potential for bias in the findings. Secondly, we did not perform meta-analysis on our review. It was previously discussed that vitamin D supplementation may be associated with a decrease in mortality rate and ICU admission [38]. Additionally, due to heterogeneity of the study design and the various vitamin D doses, the review is constrained by its approach of discussing each study individually.

6. Conclusions

Vitamin D supplementation is safe to be used in critically ill patients, even when their baseline vitamin D level is not known, because of rare incidence of vitamin D toxicity. The majority of clinical trials showed clinical benefits of vitamin D supplementation in ICU patients in shorter ICU or hospital length of stay, improvement of SOFA score, decrease in duration of mechanical ventilation or 28-day mortality. Therefore, Vitamin D supplementation deserves being considered in the ICU setting, especially with closely monitored vitamin D level.

Acknowledgments: We would like to express our sincere appreciation of Dr. Yongxia Zhang PhD for her assistance of literature search.

Conflicts of Interest: The authors declare no conflict of interest.

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