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Early Vitamin D Repletion in Critically Ill Adults: A Prospective Dose-Stratified Quasi-Experimental Study

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ABSTRACT: Vitamin D deficiency is frequent in critical illness, but whether rapid biochemical correction translates into clinical benefit remains uncertain. This prospective, non-randomized, dose-stratified quasi-experimental study evaluated 43 critically ill adults with serum 25-hydroxyvitamin D [25(OH)D] <30 ng/mL in an Indonesian intensive care unit. Participants were stratified as vitamin D deficient (<20 ng/mL) or insufficient (20–29 ng/mL) and received cholecalciferol 10,000 or 50,000 IU/day for three consecutive days. The primary outcome was the change in serum 25(OH)D concentration from baseline to day 4. Secondary outcomes were change in Sequential Organ Failure Assessment (SOFA) score from baseline to day 4, ventilator-free days at day 28 (VFD28), and 28-day all-cause mortality. Serum 25(OH)D increased significantly in all four groups (all $p \leq 0.011$), with a significant between-group difference in change ($p = 0.002$). A day-4 25(OH)D concentration ≥ 30 ng/mL was achieved in 53.5% of participants overall and more frequently in the 50,000-IU groups. SOFA scores decreased significantly within all groups, but the between-group difference in Δ SOFA did not reach statistical significance ($p = 0.051$). No significant between-group differences were observed in VFD28 ($p = 0.686$), or 28-day mortality ($p = 0.884$). Short-term 50,000 IU/day cholecalciferol produced faster biochemical repletion than 10,000 IU/day, but corresponding superiority in short-term clinical outcomes was not demonstrated.

1. INTRODUCTION

Vitamin D deficiency is common in critical illness and may reflect pre-existing low stores and acute changes in intake, absorption, fluid balance, binding proteins, and metabolism. In a multicenter ICU cohort, 59% of patients had serum 25-hydroxyvitamin D [25(OH)D] <20 ng/mL; deficiency was associated with higher SOFA scores, longer mechanical ventilation [1]. Mortality evidence is less consistent: Xie et al. (2022) found no independent association between deficient 25(OH)D and hospital mortality [2], whereas Sistanian et al. (2024) reported an independent association with 28-day mortality [3].

Biological plausibility is supported by vitamin D receptor expression and effects on innate and adaptive immunity, antimicrobial peptide production, and inflammatory signaling [4,5]. However, clinical evidence remains heterogeneous. Meta-analyses have reported shorter mechanical ventilation in some datasets, while others found no significant benefit in mortality, ventilation

duration, or length of stay [6–8]. A newer meta-analysis reported reductions in short-term mortality, and mechanical ventilation duration, although trial-sequential analysis indicated that additional evidence is required [9].

Treatment strategy may contribute to these differences. A single 540,000-IU dose did not improve major clinical outcomes in septic ICU patients [10], whereas 50,000 IU/day for five days improved SOFA score and hospital stay compared with 5,000 IU/day in mechanically ventilated patients with sepsis [11]. Even with high-dose enteral supplementation, biochemical correction is variable [12], and no consensus regimen has emerged for critically ill patients [13]. The absence of an established dosing regimen creates uncertainty regarding the dose required to achieve rapid vitamin D repletion during the relatively short therapeutic window of critical illness. To our knowledge, no previous prospective study in Indonesia has directly compared repeated daily cholecalciferol doses in critically ill adults with low vitamin D status. We therefore compared 10,000 versus 50,000 IU/day cholecalciferol for three consecutive days to evaluate their relative effectiveness for early biochemical repletion, with change in serum 25(OH)D as the primary outcome and change in SOFA score, VFD28, and 28-day mortality as secondary outcomes.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This prospective, non-randomized, dose-stratified quasi-experimental study was conducted in the adult intensive care unit (ICU) of Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia, from April to July 2026. Participants were classified according to baseline serum 25-hydroxyvitamin D [25(OH)D] concentrations as vitamin D deficient (<20 ng/mL) or insufficient (20–29 ng/mL). Within each stratum, Vitamin D supplementation doses of 10,000 IU/day and 50,000 IU/day were assigned alternately, resulting in four study groups: deficiency + 10,000 IU, deficiency + 50,000 IU, insufficiency + 10,000 IU, and insufficiency + 50,000 IU. The study did not include an untreated or placebo group.

2.2 Participants

Adult patients aged ≥ 18 years were eligible if they had been admitted to the ICU within 24 hours before screening, had a baseline serum 25(OH)D concentration <30 ng/mL, had achieved hemodynamic stability, were undergoing their first ICU admission, and had available baseline SOFA and APACHE II assessments.

Patients were excluded if they had received vitamin D supplementation within the preceding 30 days; had hypercalcemia; had renal dysfunction with an estimated glomerular filtration rate <60 mL/min/1.73 m² or required dialysis; had Child–Pugh C cirrhosis; were pregnant or breastfeeding; had known hypersensitivity to vitamin D, parathyroid disorders, recent gastrointestinal surgery, hematologic disorders, or a contraindication to enteral supplementation; or were receiving long-term corticosteroid therapy or chemotherapy.

Sample-size estimation was based on the early biochemical response in serum 25-hydroxyvitamin D [25(OH)D]. In a randomized trial of critically ill patients with severe sepsis or septic shock, Quraishi et al. [14] estimated that six evaluable participants per group were required to detect a clinically relevant change in serum 25(OH)D, assuming a common standard deviation of 10 ng/mL, a two-sided α of 0.05, and 80% statistical power. Additional participants were recruited to account for potential withdrawal, intolerance, or death during follow-up. The present study included 43 evaluable participants distributed across four groups ($n=9$ –12 per group), exceeding the minimum evaluable requirement.

2.3 Vitamin D Stratification and Intervention

Baseline serum 25(OH)D was measured before supplementation and used to stratify participants into deficient and insufficient vitamin D groups. Within each stratum, participants were assigned alternately to one of two cholecalciferol regimens. Vitamin D3 was supplied as 5,000-IU tablets (Hi-D). The tablets were crushed and administered orally or enterally through a nasogastric tube. Participants received either 10,000 IU/day or 50,000 IU/day for three consecutive days. Baseline assessments were performed on day 0. Serum 25(OH)D, total calcium, and SOFA score were reassessed on day 4 after completion of the three-day supplementation regimen, while VFD28 and 28-day mortality were assessed through day 28.

2.4 Biochemical and Clinical Assessments

Serum total 25(OH)D was measured from 3–5 mL of venous blood using a chemiluminescent microparticle immunoassay (CMIA; Architect i2000SR, Abbott) on days 0 and 4. Vitamin D deficiency was defined as a serum 25(OH)D concentration

<20 ng/mL and insufficiency as 20–29 ng/mL. A day-4 concentration ≥ 30 ng/mL was considered achievement of the study-defined sufficiency threshold. Change in 25(OH)D ($\Delta 25[\text{OH}]\text{D}$) was calculated as the day-4 value minus the baseline value.

Organ dysfunction was assessed using the Sequential Organ Failure Assessment (SOFA) score at baseline and on day 4. The total SOFA score ranges from 0 to 24 and incorporates respiratory, coagulation, hepatic, cardiovascular, neurologic, and renal function. ΔSOFA was calculated as the day-4 score minus the baseline score; therefore, negative values indicated improvement in organ dysfunction. APACHE II was recorded during the first 24 hours of ICU care as an additional baseline severity measure.

The primary outcome was the change in serum 25(OH)D concentration from baseline to day 4 ($\Delta 25[\text{OH}]\text{D}$). Secondary outcomes were the change in SOFA score from baseline to day 4 (ΔSOFA), ventilator-free days at day 28 (VFD28), and 28-day all-cause mortality. Achievement of a day-4 serum 25(OH)D concentration ≥ 30 ng/mL was evaluated as an additional biochemical response measure.

VFD28 was defined as the number of days alive and free from invasive mechanical ventilation during the 28 days following the intervention. Participants who died within 28 days or remained mechanically ventilated on day 28 were assigned a VFD28 value of 0. Successful liberation from mechanical ventilation required remaining free from invasive ventilation for at least 48 hours. If reintubation occurred, all periods of invasive ventilation were summed. Twenty-eight-day mortality was defined as death from any cause within 28 days after the intervention, whether during ICU admission or after ICU discharge. Total serum calcium was measured on days 0 and 4 as a biochemical safety parameter during supplementation.

2.5 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro–Wilk test within each of the four study groups. Normally distributed variables were summarized as mean $\pm$ standard deviation (SD), whereas non-normally distributed variables were reported as median with the first and third quartiles [median (Q1–Q3)]. Categorical variables were presented as frequency and percentage.

Baseline continuous characteristics were compared across the four groups using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Categorical characteristics were compared using the Fisher–Freeman–Halton exact test when expected cell counts were small.

For longitudinal outcomes, a consistent nonparametric approach was used when evidence of non-normality was present in at least one study group. Baseline-to-day-4 changes in serum 25(OH)D and SOFA score within each group were assessed using the Wilcoxon signed-rank test. Differences in $\Delta 25(\text{OH})\text{D}$ and ΔSOFA across the four groups were evaluated using the Kruskal–Wallis test.

Because the overall comparison of $\Delta 25(\text{OH})\text{D}$ was statistically significant, post-hoc pairwise comparisons were performed using the Mann–Whitney U test. Six pairwise comparisons were possible; therefore, a Bonferroni-adjusted significance threshold of $p < 0.0083$ was applied. The proportion of participants attaining a day-4 25(OH)D concentration ≥ 30 ng/mL was compared using the Fisher–Freeman–Halton exact test.

VFD28 were compared across groups using the Kruskal–Wallis test. Twenty-eight-day mortality was compared using the Fisher–Freeman–Halton exact test. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant except for Bonferroni-adjusted post-hoc comparisons.

3. RESULTS AND DISCUSSION

3.1 Participant Characteristics

Of 51 participants enrolled, 8 did not complete follow-up, leaving 43 participants for the final analysis. Baseline demographic and clinical characteristics are presented in Table 1. No statistically significant between-group differences were observed in age, sex, mechanical ventilation use, admission type, comorbidity, APACHE II category, baseline SOFA score, or serum calcium (all $p > 0.05$). Baseline 25(OH)D concentrations differed significantly across groups ($p < 0.001$), as expected because participants were prospectively stratified according to baseline vitamin D status before allocation to the two supplementation doses.

Table 1. Baseline characteristics according to intervention group

Variable	Deficiency + 10,000 IU (n=11)	Deficiency + 50,000 IU (n=12)	Insufficiency + 10,000 IU (n=11)	Insufficiency + 50,000 IU (n=9)	p value
Age, years	50.55 ± 13.43	45.33 ± 20.16	55.91 ± 11.91	57.00 ± 13.86	0.277 ^a
Female sex, n (%)	9 (81.8)	8 (66.7)	6 (54.5)	6 (66.7)	0.608 ^c
Mechanical ventilation, n (%)	10 (90.9)	12 (100.0)	11 (100.0)	9 (100.0)	0.721 ^c
Medical admission, n (%)	6 (54.5)	6 (50.0)	8 (72.7)	8 (88.9)	0.253 ^c
Comorbidity, n (%)	3 (27.3)	2 (16.7)	4 (36.4)	3 (33.3)	0.744 ^c
APACHE II ≥15, n (%)	1 (9.1)	2 (16.7)	3 (27.3)	1 (11.1)	0.740 ^c
SOFA score	5.00 (1.00–7.00)	7.00 (6.00–8.75)	4.00 (2.00–7.00)	7.00 (3.00–10.00)	0.110 ^b
25(OH)D, ng/mL	17.10 (13.50–18.50)	17.10 (10.10–19.00)	23.00 (22.70–25.50)	23.70 (20.65–25.60)	<0.001 ^{b*}
Calcium, mg/dL	7.50 (7.00–8.40)	7.10 (7.00–7.45)	7.70 (7.40–8.00)	7.50 (7.30–8.30)	0.152 ^b

Notes: Values are presented as mean ± SD, median (Q1–Q3), or n (%), according to variable type and distribution. ^a One-way ANOVA. ^b Kruskal–Wallis test. ^c Fisher–Freeman–Halton exact test. *p<0.05. Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; 25(OH)D, 25-hydroxyvitamin D.

Serum 25(OH)D increased significantly from baseline to day 4 in all four intervention groups (all p≤0.011). The magnitude of increase differed significantly across groups (p=0.002). After Bonferroni correction for six pairwise comparisons, the increase was significantly greater in the deficiency + 50,000 IU group than in the deficiency + 10,000 IU group (p=0.002) and the insufficiency + 10,000 IU group (p=0.003); no other pairwise comparison met the adjusted significance threshold of p<0.0083. A day-4 25(OH)D concentration ≥30 ng/mL was achieved in 23 of 43 participants (53.5%), with achievement rates of 0.0%, 83.3%, 54.5%, and 77.8% across the four groups, respectively (p<0.001).

SOFA scores decreased significantly from baseline to day 4 within each intervention group (p=0.041, p=0.005, p=0.027, and p=0.015, respectively). However, the magnitude of SOFA change did not differ significantly across the four groups (p=0.051), although numerically larger reductions were observed in the higher-dose groups.

Table 2. Changes in serum 25(OH)D and SOFA score according to intervention group

Parameter	Group	Baseline	Day 4	Δ Day 4–baseline	Within-group p value	Between-group p value for Δ
25(OH)D, ng/mL	Deficiency + 10,000 IU (n=11)	17.10 (13.50–18.50)	21.00 (18.10–25.00)	5.20 (2.20–9.00)	0.011 ^{a*}	0.002^{b*}
	Deficiency + 50,000 IU (n=12)	17.10 (10.10–19.00)	47.65 (37.50–51.33)	31.50 (19.70–38.10)	0.003 ^{a*}	
	Insufficiency + 10,000 IU (n=11)	23.00 (22.70–25.50)	30.40 (26.00–33.00)	4.90 (0.50–9.00)	0.008 ^{a*}	

	Insufficiency + 50,000 IU (n=9)	23.70 (20.65–25.60)	46.00 (31.45–54.20)	25.70 (5.20–29.10)	0.008 ^{a*}	
SOFA score	Deficiency + 10,000 IU (n=11)	5.00 (1.00–7.00)	4.00 (1.00–6.00)	0.00 (–2.00–0.00)	0.041 ^{a*}	0.051^b
	Deficiency + 50,000 IU (n=12)	7.00 (6.00–8.75)	3.50 (2.00–6.00)	–3.00 (–4.75 to –1.00)	0.005 ^{a*}	
	Insufficiency + 10,000 IU (n=11)	4.00 (2.00–7.00)	2.00 (0.00–4.00)	–1.00 (–3.00–0.00)	0.027 ^{a*}	
	Insufficiency + 50,000 IU (n=9)	7.00 (3.00–10.00)	1.00 (0.00–4.00)	–4.00 (–9.00 to –2.00)	0.015 ^{a*}	

Notes: Values are presented as median (Q1–Q3). Δ was calculated as day 4 minus baseline; therefore, a negative Δ SOFA indicates improvement. ^a Wilcoxon signed-rank test. ^b Kruskal–Wallis test. Post-hoc pairwise comparisons for Δ 25(OH)D were performed using Mann–Whitney U tests with Bonferroni correction (significance threshold $p < 0.0083$); significant differences were observed for deficiency + 10,000 versus deficiency + 50,000 IU ($p = 0.002$) and deficiency + 50,000 versus insufficiency + 10,000 IU ($p = 0.003$). * $p < 0.05$. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; SOFA, Sequential Organ Failure Assessment.

Changes in SOFA score from baseline to day 4 are illustrated in Figure 1. Median Δ SOFA was 0.00 (–2.00 to 0.00), –3.00 (–4.75 to –1.00), –1.00 (–3.00 to 0.00), and –4.00 (–9.00 to –2.00) in the deficiency + 10,000 IU, deficiency + 50,000 IU, insufficiency + 10,000 IU, and insufficiency + 50,000 IU groups, respectively. Although larger numerical reductions were observed in the 50,000 IU groups, the overall between-group difference in Δ SOFA did not reach statistical significance (Kruskal–Wallis $p = 0.051$).

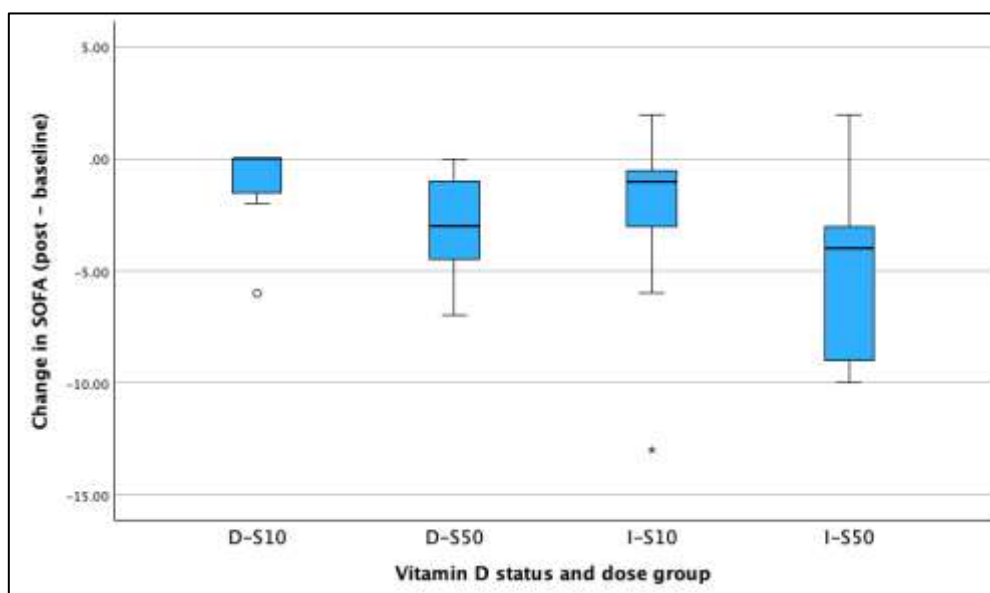


Figure 1. Change in SOFA score from baseline to day 4 according to intervention group. **Negative values indicate improvement in SOFA score.**

Clinical outcomes did not differ significantly across the four intervention groups (Table 3). VFD28 ($p = 0.686$) did not differ significantly across groups. Overall, 18 of 43 participants (41.9%) died within 28 days, with no significant between-group difference in 28-day mortality ($p = 0.884$).

Table 3. Clinical outcomes according to intervention group

Outcome	Deficiency + 10,000 IU (n=11)	Deficiency + 50,000 IU (n=12)	Insufficiency + 10,000 IU (n=11)	Insufficiency + 50,000 IU (n=9)	p value
Ventilator-free days at day 28	13.00 (0.00–26.00)	3.00 (0.00–25.25)	26.00 (0.00–26.00)	25.00 (0.00–26.00)	0.686 ^a
28-day mortality, n (%)	5 (45.5)	6 (50.0)	4 (36.4)	3 (33.3)	0.884 ^b

Notes: Values are presented as median (Q1–Q3) or n (%). ^a Kruskal–Wallis test. ^b Fisher–Freeman–Halton exact test.

3.2 Discussion

The present study demonstrated a clear dose-related biochemical response, with substantially larger increases in serum 25(OH)D among participants receiving 50,000 IU/day. By day 4, 83.3% of deficient and 77.8% of insufficient participants in the 50,000-IU groups achieved 25(OH)D concentrations ≥ 30 ng/mL. This rapid response is consistent with evidence that high-dose enteral vitamin D can substantially increase circulating 25(OH)D in critical illness, although target attainment remains variable. In a multicenter randomized trial, Wang et al. (2025) reported that only 41.5% of patients receiving 569,600 IU enterally achieved >30 ng/mL by day 7 despite a marked increase in serum 25(OH)D [12]. This variability suggests that administered dose alone does not determine biochemical response, particularly in critically ill patients.

The more important question is whether faster biochemical correction translates into improved organ function. SOFA scores decreased significantly from baseline to day 4 within all four groups, but the magnitude of change did not differ significantly across groups ($p=0.051$). The larger numerical reductions in the 50,000-IU groups therefore cannot be interpreted as evidence of between-dose superiority. Ashoor et al. (2024) reported greater SOFA improvement with 50,000 versus 5,000 IU/day for five days among mechanically ventilated patients with sepsis [11]. Their population was restricted to sepsis, treatment continued for five days, and the comparator dose was lower than in the present study. By contrast, Bhattacharyya et al. (2021) found no significant overall differences in mechanical ventilation duration or mortality after a 540,000-IU loading dose in patients with sepsis [10].

Biochemical and clinical responses need not evolve in parallel during critical illness. In a randomized study of prolonged critically ill patients, intravenous 25OHD increased serum 25OHD from a median of 9.2 to 16.1 ng/mL, but this was not accompanied by an increase in circulating 1,25(OH)₂D or measurable changes in innate immune function. The investigators attributed the attenuated biological response partly to illness-related alterations in vitamin D metabolism and/or distribution [15]. Thus, the rapid increase in 25(OH)D observed in our higher-dose groups does not necessarily imply an equally rapid improvement in downstream organ dysfunction.

No statistically significant between-group differences were observed in VFD28, or 28-day mortality. This is consistent with the broader literature, which remains heterogeneous. Lan et al. (2020) found no significant benefit for 28-day mortality, or ventilation duration across nine RCTs involving 1,867 patients [16]. Shen et al. (2021) reported shorter mechanical ventilation without a significant overall mortality effect [6], whereas Menger et al. (2022) reported reductions in mortality, and ventilation duration [7]. Kaur et al. (2022) found no statistically significant benefit across these major outcomes [8]. Similarly, Gao et al. (2022) found fewer ventilator days with high-dose vitamin D but no significant reduction in 28- or 90-day mortality [17]. More recently, Zheng et al. (2025) reported reductions in short-term mortality and ventilation duration [9], although trial-sequential analysis indicated that further evidence was needed to confirm the mortality finding.

Differences in patient selection and supplementation strategy probably contribute to these disparate results. In a small randomized trial, Sistanizad et al. (2021) reported shorter mechanical ventilation duration after a single 300,000-IU intramuscular dose, although only 30 participants completed the study [18]. Observationally, Yang et al. (2023) found vitamin D supplementation during ICU admission to be associated with lower in-hospital, 28-day, and 90-day mortality in patients with sepsis after several propensity-based adjustment; the nonrandomized design prevents exclusion of residual confounding [19]. A recent narrative review of 21 RCTs likewise found mixed clinical responses across markedly different populations, doses, formulations, and administration strategies [20]. Geiger et al. (2024) similarly emphasized the substantial heterogeneity of the randomized evidence base [21].

Recent evidence also raises the possibility that treatment effects depend on baseline status and regimen. Huang (2026) reported lower pooled mortality with vitamin D supplementation overall and identified subgroup signals according to baseline 25(OH)D, dose category, and administration route [22]. In particular, mortality reduction was reported with doses $\leq 300,000$ IU and parenteral administration, while the estimate among patients with baseline 25(OH)D < 20 ng/mL was borderline (RR 0.87, $p=0.05$). These subgroup findings do not directly establish an optimal regimen, but they reinforce the importance of distinguishing baseline vitamin D status and supplementation strategy when comparing studies.

The within-group reductions in SOFA in the present study should also be interpreted in the context of its design. Without an untreated control group, these changes demonstrate clinical improvement over time but cannot be attributed solely to vitamin D supplementation; concurrent critical care, treatment of the underlying illness, and natural recovery may also have contributed. Conversely, the absence of statistically significant between-group differences should not be interpreted as equivalence, particularly with 43 participants and individual group sizes of 9–12.

Strengths of this study include its prospective design, predefined stratification by baseline vitamin D status, direct comparison of two repeated daily cholecalciferol regimens, and simultaneous assessment of biochemical response and clinically relevant outcomes. To our knowledge, this is the first prospective dose-stratified study in Indonesia to directly compare 10,000 and 50,000 IU/day cholecalciferol in critically ill adults with low vitamin D status. This direct dose comparison addresses an important evidence gap because an optimal vitamin D dosing regimen for critically ill patients has not yet been established. Importantly, the study was designed to determine which regimen could achieve more rapid biochemical repletion in this population rather than to establish clinical superiority. Limitations include nonrandomized alternating allocation, the single-center setting, small group sizes, heterogeneous ICU diagnoses, absence of an untreated comparator, and the short interval between supplementation and day-4 SOFA assessment. In addition, although participants who had received vitamin D supplementation within 30 days before enrollment were excluded, the vitamin D content of concomitant nutritional support during ICU care was not standardized or quantified and therefore could not be controlled for in the analysis. The study therefore provides evidence that 50,000 IU/day achieves substantially faster biochemical repletion than 10,000 IU/day, while superiority in short-term organ dysfunction or patient-centered clinical outcomes was not demonstrated in this cohort.

4. CONCLUSION

Three days of vitamin D3 supplementation produced a significant increase in serum 25-hydroxyvitamin D [25(OH)D] across all study groups, with the largest increase observed in vitamin D-deficient patients receiving 50,000 IU/day. Although SOFA scores decreased significantly from baseline to day 4 within each group, the magnitude of SOFA change did not differ significantly across the four groups. Likewise, no statistically significant between-group differences were observed in ventilator-free days at day 28, or 28-day mortality. These findings indicate that 50,000 IU/day achieves more rapid biochemical vitamin D repletion than 10,000 IU/day, but this biochemical advantage was not accompanied by demonstrable superiority in short-term organ dysfunction or patient-centered clinical outcomes in this cohort. Given the non-randomized allocation, absence of an untreated control group, small sample size, and short follow-up for SOFA assessment, causal clinical effects cannot be established. Larger randomized studies with longer follow-up are warranted to determine whether rapid vitamin D repletion translates into clinically meaningful benefits in critically ill patients.

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AUTHOR CONTRIBUTIONS

Angelia Winly Keles: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing – Original Draft, and Project Administration.

Suryani As'ad: Conceptualization, Methodology, Supervision, Validation, Interpretation of Findings, and Writing – Review & Editing.

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Faisal Muchtar: Methodology, Validation, Interpretation of Clinical Outcomes, and Writing – Review & Editing.

All authors critically reviewed the manuscript, approved the final version, and agreed to be accountable for the accuracy and integrity of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University (Protocol No. UH26010196; Approval No. 316/UN4.6.4.5.31/PP36/2026; approved 4 March 2026). The study also received institutional research authorization from Dr. Wahidin Sudirohusodo General Hospital (No. DP.04.03/D.XVIII.2/5455/2026). Written informed consent was obtained from all participants or their legally authorized representatives before enrollment.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical and institutional restrictions.

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