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Original Research Article

A Study on Vitamin D Deficiency and Its Prognostic Significance in Intensive Care Unit Patients

Sanjeev Kumar Chawriya[1], Reecha Panghal[2], Pankaj Kumar[3], Poonam Rani[4]

[1]Assistant Professor, Department of Anaesthesiology and Critical Care, Adesh Medical College & Hospital, Mohri Shahbad, Haryana, India

[2]Assistant Professor, Department of Anaesthesiology and Critical Care, Adesh Medical College & Hospital, Mohri Shahbad, Haryana, India

[3]Assistant Professor, Department of Anaesthesiology and Critical Care, Adesh Medical College & Hospital, Mohri Shahbad, Haryana, India

[4]Assistant Professor, Department of Anaesthesiology and Critical Care, Adesh Medical College & Hospital, Mohri Shahbad, Haryana, India

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Corresponding Author: Dr. Sanjeev Kumar Chawriya

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Abstract:

Background: "Vitamin D deficiency is common among critically ill patients and may influence immune function, inflammation, and clinical outcomes in the intensive care unit (ICU).

Aim: To assess the prevalence of vitamin D deficiency and its association with disease severity and 28-day mortality in ICU patients.

Methodology: This hospital-based cross-sectional observational study included 80 adult ICU patients over 12 months. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured within 24 hours of admission and classified as deficient (≤20 ng/ml), insufficient (21–29 ng/ml), or sufficient (≥30 ng/ml). Severity was assessed using APACHE II and SOFA scores. Associations with laboratory parameters and 28-day mortality were analyzed, and ROC curve analysis was performed to determine predictive value.

Results: Vitamin D deficiency was observed in 60% of patients, with a mean level of 19.4 ± 8.7 ng/ml. Deficient patients had significantly higher APACHE II and SOFA scores, elevated CRP and lactate levels, and lower serum calcium ($p < 0.05$). Mortality was significantly higher in deficient patients (83.3% of" non-survivors; $p = 0.003$). ROC analysis showed good predictive ability (AUC 0.79), with 83.3% sensitivity and 71.4% specificity at ≤18 ng/ml.

Conclusion: Vitamin D deficiency is highly prevalent in ICU patients and is significantly associated with increased severity and 28-day mortality.

Keywords: Vitamin D deficiency, ICU, APACHE II, SOFA score, Mortality, Critical illness.

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Introduction

The fat-soluble secosteroid, vitamin D, has been discovered to be a key modulator of non-skeletal physiological functions such as immune response, cellular growth, inflammation, and cardiovascular activity [1] despite its long-standing recognition as an important regulator of calcium homeostasis and bone metabolism. The biologically active vitamin D, 1,25-dihydroxyvitamin D (calcitriol) acts through the vitamin D receptor (VDR), which is found in many other tissues in addition to the traditional locations of bone and intestine, including immune cells, endothelial cells, and heart muscle. The wide tissue distribution highlights the pleiotropic effects of vitamin D and offers a mechanism of its role in the pathophysiological reaction to critical disease. During the last 20 years, the rates of vitamin D deficiency in hospitalized patients admitted to intensive care units (ICUs) have gained more investigations, and in such cases, systemic inflammation, oxidative stress, and metabolic dysregulation meet and predetermine morbidity and mortality [2].

Vitamin D deficiency, which is commonly defined as circulating level of 25-hydroxyvitamin D [25(OH)D] less than 20 ng/mL (50 nmol/L) is common worldwide and is disproportionately prevalent in people with limited access to sunlight, older age, chronic diseases, or malnutrition [3]. Some epidemiological surveys have reported very high levels of deficiency with prevalence rates of 40-90% based on geographical area, assay technique and cut off point. This prevalence is explained by the combination of

several overlapping factors, such as underlying deficiency in the general population, stress-induced changes in the metabolism of vitamin D, fluid and hemodilution. Additionally, acute inflammatory conditions that are typical of the critical conditions like sepsis, trauma, and acute respiratory distress syndrome (ARDS) can also worsen deficiency by reducing carrier protein synthesis, changing hepatic synthesis, and the activity of the vitamin D converting enzymes [4].

Pathophysiologically, vitamin D deficiency in patients in critical care is no longer a biomarker of ill health but may actually promote the dysregulated host response of severe illness. Vitamin D affects both innate and adaptive immunity, improving the work of macrophage and monocytes, triggering the production of antimicrobial peptides such as cathelicidin and defensins, and controlling the differentiation of T-cells [5]. This is especially applicable to sepsis and other infectious critical diseases since immune competence is the most important factor in these conditions. Vitamin D has anti-inflammatory and anti-atherogenic effects, endothelial-stabilizing effects, and possibly anti-pro-coagulant effects in the vascular system, which are essential in the systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction. Also, deficiency was found to cause an impaired function of the muscles, weakness, which is relevant to respiratory mechanics and long-term ventilator dependence in ICU patients [6].

Observational and interventional studies have concentrated on the clinical implications of vitamin D deficiency in the ICU environment [7]. The connections between low levels of 25(OH)D on ICU admission and adverse outcomes, such as predisposition to infections, longer mechanical ventilation, higher rates of acute kidney injury (AKI), longer ICU stay, and mortality, were determined in several cohort studies [8]. The example is that critically ill patients of severe deficiency seem to have stronger systemic inflammatory profile and more tendency to develop sepsis than those with sufficient levels. These relationships were also observed with adjustment of possible common confounders including age, comorbidities, severity of illness scores, and nutritional status, implying that the vitamin D status can be an independent outcome predictor of critical illness.

The interventional research on the role of vitamin D supplementation in intensive care unit patients has provided contradictory outcomes, which may be considered as the lack of simplicity in the dosing strategy, timing, baseline deficiency severity, and patient heterogeneity [9]. Randomized controlled trials investigating high-dose cholecalciferol or calcifediol have attempted to find out whether repletion provides any benefits in the form of immune functionality, length of stay, ventilator-free days and mortality. Although there is limited evidence that show improvements in the chosen surrogate endpoints, including increased antimicrobial peptide expression or a better decrease in inflammatory markers, there is little strong evidence of a demonstrable benefit of mortality or uniform clinical benefit. According to meta-analyses, specific supplementation of the deficient populations can be used to minimize the rate of infections and the duration of ICU stay, yet more substantial and well-planned studies will be required to provide conclusive clinical guidelines.

Besides such direct outcomes on immunity and organ functioning, the problem of vitamin D deficiency in critically ill patients overlaps with other areas of ICU services, such as nutritional support, metabolic stress, and rehabilitation prospects. Deficiency is further exacerbated by the prolonged hypercatabolic states, malabsorption of nutrients and lowered sunlight exposure on the critically ill patients. Thus, the evaluation of vitamin D condition at ICU admission and the reflection of the measures to restore it can be a component of a complex of severe care, especially in the high-risk groups of individuals with heavy deficiency and adverse results.

Overall, deficiency in vitamin D is extensively common in ICU patients who are admitted with severe illnesses and linked to immune dysregulation, increased inflammation, and negative patient outcomes. Despite the support of observational evidence of its relevance as a prognostic marker, the current intervention trials highlight the necessity of standard supplementation regimens and additional research on the causal effect of vitamin D replacement on critical illness progression. These dynamics can be explored further to inform clinical practice and enhance outcomes in this population of vulnerable patients.

Methodology

Study Design: The present study was a hospital-based cross-sectional observational study conducted to assess the prevalence and clinical significance of Vitamin D deficiency among critically ill patients admitted to the Intensive Care Unit (ICU). The study was carried out after obtaining approval from the Institutional Clinical Research Ethics Committee. Written informed consent was obtained from all patients or their legally authorized representatives prior to enrollment and

Study Area: The study was conducted in the Department of Anaesthesiology and Critical Care, Adesh Medical College & Hospital, Haryana, India.

Study Duration: The duration of the study was 12 months.

Study Participants: A total of 80 critically ill adult patients admitted to the ICU during the study period

were included in the study. Patients were recruited consecutively based on eligibility criteria.

Inclusion Criteria

- Patients aged ≥18 years admitted to the ICU.
- Patients admitted for medical, surgical, or traumatic conditions requiring intensive care.
- Patients with ICU stay of more than 24 hours.
- Patients (or their legally authorized representatives) who provided written informed consent.

Exclusion Criteria

- Pregnant women.
- Patients with prior ICU admission within the last one year.
- Patients hospitalized for ≥7 days before ICU admission.
- Patients with known malabsorption syndromes (including post-gastrectomy or bariatric surgery, inflammatory bowel disease).
- Patients diagnosed with hyperparathyroidism, hyperthyroidism, or chronic renal failure.
- Patients with granulomatous disorders.
- Patients receiving antiepileptic drugs, antiretroviral therapy, vitamin D supplementation, or medications affecting bone metabolism such as bisphosphonates.

Sample Size: The sample size for the study was 80 patients.

Procedure: The ICU admission process required the collection of complete demographic and clinical information which included age, gender, admission diagnosis, existing medical conditions, and specific treatment information. The medical assessment of the patient's condition used the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sequential Organ Failure Assessment (SOFA) score which were measured during the first day of hospital admission. The three patient groups medical, surgical, and trauma were formed according to the main reason that each patient entered the ICU.

Venous blood samples were gathered within 24 hours after patients entered the ICU under strict aseptic conditions to conduct laboratory tests. The hospital laboratory used chemiluminescence immunoassay techniques to determine serum 25-hydroxyvitamin D [25(OH)D] levels which were reported in ng/ml. The laboratory tests measured serum glucose and parathyroid hormone and total calcium and ionized calcium and albumin and prealbumin and creatinine and sodium and potassium and phosphorus and magnesium and C-reactive protein and procalcitonin and lactate levels and liver function tests and complete blood count and coagulation profile. The hospital laboratory conducted all laboratory tests according to established standardized procedures which are typical for their operations.

The study used Endocrine Society (2011) guidelines to classify Vitamin D status because they established deficiency conditions, which required serum 25(OH)D to be less than or equal to 20 ng/ml while they determined insufficiency to exist between 21 and 29 ng/ml and they set sufificiency at levels above 30 ng/ml. The study defined acute kidney injury according to Acute Kidney Injury Network criteria which required clinical and laboratory assessments during the first 24 hours of patient observation in the intensive care unit. The medical team monitored patients throughout their intensive care unit period until they died which happened within 28 days after they entered the unit.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 27.0. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean ± standard deviation or median with interquartile range, depending on data distribution. The normality of data was assessed using the Kolmogorov–Smirnov test.

For comparison between groups, the chi-square test or Fisher's exact test was used for categorical variables. Independent sample t-test or Mann–Whitney U test was applied for quantitative variables as appropriate. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal cut-off value of serum 25(OH)D for predicting mortality. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Binary logistic regression analysis was performed to identify independent predictors of mortality, including variables with $p < 0.1$ in univariate analysis. A p-value < 0.05 was considered statistically significant.

Result

Table 1 presents the demographic and clinical characteristics of the 80 study participants, demonstrating that the majority of patients were in the 41–60 years age group (40.0%), followed closely by those aged above 60 years (37.5%), while 22.5% were between 18–40 years, with an overall mean age of 54.8 ± 15.6 years, indicating a predominantly middle-aged to elderly population. In terms of gender distribution, males constituted a higher proportion (57.5%) compared to females (42.5%). Regarding the type of admission, nearly half of the patients were admitted for medical reasons (47.5%), followed by surgical cases (32.5%) and trauma cases (20.0%). The mean APACHE II score of 19.6 ± 6.2 and mean SOFA score of 7.8 ± 3.1 reflect a moderately severe level of illness and organ dysfunction among the study participants, suggesting that a substantial proportion of patients required intensive monitoring and management.

Table 1: Demographic and Clinical Characteristics of Study Participants (n = 80)

Variable	Frequency (n)	Percentage (%)
Age (years)		
18–40	18	22.5
41–60	32	40.0
>60	30	37.5
Mean Age (years)	54.8 ± 15.6	—
Gender		
Male	46	57.5
Female	34	42.5
Type of Admission		
Medical	38	47.5
Surgical	26	32.5
Trauma	16	20.0
Mean APACHE II Score	19.6 ± 6.2	—
Mean SOFA Score	7.8 ± 3.1	—

Table 2 shows the distribution of serum Vitamin D [25(OH)D] levels among the 80 study participants. A majority of the subjects, 48 (60.0%), were classified as Vitamin D deficient (≤20 ng/ml), indicating a high prevalence of deficiency in the study population. Additionally, 20 participants (25.0%) had insufficient Vitamin D levels (21–29 ng/ml), while only 12 individuals (15.0%) had sufficient levels (≥30 ng/ml). The mean serum 25(OH)D concentration was 19.4 ± 8.7 ng/ml, which falls within the deficient range, further emphasizing the overall low Vitamin D status of the participants. These findings suggest that a substantial proportion of the study population had suboptimal Vitamin D levels, with deficiency being the most common category.

Table 2: Distribution of Serum Vitamin D Levels (25(OH)D) (n = 80)

Vitamin D Status	Serum 25(OH)D (ng/ml)	Frequency (n)	Percentage (%)
Deficient	≤20	48	60.0
Insufficient	21–29	20	25.0
Sufficient	≥30	12	15.0
Mean 25(OH)D level (ng/ml)	19.4 ± 8.7	—	—

Table 3 demonstrates a significant association between vitamin D status and 28-day ICU mortality. Among the total 80 patients, 48 (60%) were vitamin D deficient, 20 (25%) were insufficient, and 12 (15%) were sufficient. A markedly higher proportion of non-survivors were vitamin D deficient (20 out of 24; 83.3%) compared to survivors (28 out of 56; 50%), indicating that deficiency was more common among patients who died. In contrast, vitamin D insufficiency and sufficiency were more frequently observed among survivors, with only 2 deaths each reported in these categories. The p-value of 0.003 suggests that the association between vitamin D deficiency and increased ICU mortality is statistically significant. Overall, the findings indicate that lower vitamin D levels, particularly deficiency, are strongly associated with higher 28-day mortality in ICU patients.

Table 3: Association Between Vitamin D Status and ICU Mortality (28-day)

Vitamin D Status	Survivors (n=56)	Non-Survivors (n=24)	Total	p-value
Deficient	28	20	48	0.003
Insufficient	18	2	20	
Sufficient	10	2	12	
Total	56	24	80	

Table 4 demonstrates a significant association between vitamin D status and clinical severity as well as laboratory parameters. Patients in the vitamin D deficient group (n=48) had markedly higher mean APACHE II Score (22.4 ± 5.8) compared to the non-deficient group (16.2 ± 4.9), with a highly significant p-value (<0.001), indicating greater disease severity among deficient patients. Similarly, the mean SOFA Score was significantly elevated in the deficient group (9.2 ± 2.8) versus the non-deficient group (5.6 ± 2.4) ($p < 0.001$), reflecting increased organ dysfunction. Serum calcium levels were significantly lower in vitamin D deficient patients (8.1 ± 0.6 mg/dl) compared to non-deficient patients (8.8 ± 0.5 mg/dl) ($p = 0.002$). Inflammatory and metabolic markers were also significantly higher in the

deficient group, with elevated C-reactive protein (68.5 ± 24.2 mg/L vs. 42.3 ± 18.6 mg/L; p = 0.001) and lactate levels (3.8 ± 1.4 mmol/L vs. 2.4 ± 1.1 mmol/L; p = 0.004). Overall, vitamin D deficiency was associated with higher severity scores, greater inflammatory response, metabolic derangement, and hypocalcemia, suggesting a strong correlation between deficiency status and poorer clinical condition.

Table 4: Comparison of Laboratory and Severity Parameters According to Vitamin D Status

Parameter	Deficient (n=48)	Non-Deficient (n=32)	p-value
APACHE II Score	22.4 ± 5.8	16.2 ± 4.9	<0.001
SOFA Score	9.2 ± 2.8	5.6 ± 2.4	<0.001
Serum Calcium (mg/dl)	8.1 ± 0.6	8.8 ± 0.5	0.002
C-Reactive Protein (mg/L)	68.5 ± 24.2	42.3 ± 18.6	0.001
Lactate (mmol/L)	3.8 ± 1.4	2.4 ± 1.1	0.004

Table 5 presents the ROC curve analysis evaluating serum Vitamin D levels as a predictor of 28-day mortality. The Area Under the Curve (AUC) was 0.79 (95% CI: 0.68–0.89), indicating good discriminatory ability of Vitamin D levels in distinguishing between survivors and non-survivors. An optimal cut-off value of ≤18 ng/ml was identified, at which the sensitivity was 83.3% and specificity was 71.4%, demonstrating that the test correctly identified a high proportion of patients who died within 28 days while maintaining acceptable accuracy in identifying survivors. The positive predictive value (PPV) of 55.5% suggests that just over half of the patients with Vitamin D levels ≤18 ng/ml experienced mortality, whereas the high negative predictive value (NPV) of 90.0% indicates that patients with levels above this threshold were highly likely to survive. The statistically significant p-value (0.001) confirms that Vitamin D level is a significant predictor of 28-day mortality in the studied population.

Table 5: ROC Curve Analysis of Vitamin D Level for Prediction of 28-Day Mortality

Parameter	Value
Area Under Curve (AUC)	0.79 (95% CI: 0.68–0.89)
Optimal Cut-off Value	≤18 ng/ml
Sensitivity	83.3%
Specificity	71.4%
Positive Predictive Value (PPV)	55.5%
Negative Predictive Value (NPV)	90.0%
p-value	0.001

Discussion

The present study demonstrated a high prevalence of vitamin D deficiency (60%) and insufficiency (25%) among critically ill patients, findings that are consistent with earlier international data. In a landmark study published in the New England Journal of Medicine, Lee P et al. (2009) [10] reported that approximately 57% of ICU patients had vitamin D levels below 20 ng/ml, closely paralleling our observed mean serum 25(OH)D level of 19.4 ± 8.7 ng/ml. Similarly, Lucidarme O et al. (2010) [11] found deficiency in nearly 69% of critically ill patients at ICU admission, supporting the concept that hypovitaminosis D is highly prevalent irrespective of geographic region. These similarities suggest that acute critical illness itself, rather than environmental exposure alone, substantially contributes to reduced circulating vitamin D levels.

Our finding of a significant association between vitamin D deficiency and 28-day mortality (83.3% vs. 50%, p = 0.003) aligns with several observational studies. Venkatram S et al. (2011) [12] reported that ICU patients with vitamin D levels <20 ng/ml had a mortality rate of 24% compared to 9% in non-deficient patients. Likewise, Braun A et al. (2012) [13] demonstrated that patients in the lowest vitamin D quartile had a significantly higher adjusted risk of mortality (odds ratio approximately 1.8). These findings are comparable to our results, where deficiency was markedly more frequent among non-survivors, reinforcing the hypothesis that vitamin D status may influence short-term outcomes in critical illness.

However, contrasting evidence exists. The FINNAKI study by Ala-Kokko TI et al. (2016) [14], involving over 600 patients with severe sepsis, found no independent association between vitamin D deficiency and 90-day mortality. In that cohort, mortality rates were comparable between deficient and non-deficient groups after adjustment for confounders. This discrepancy may be attributed to differences in patient populations, as the FINNAKI cohort was limited to septic patients, whereas our study included a broader spectrum of critically ill individuals. Furthermore, variations in deficiency cut-off

values and timing of measurement could partly explain the heterogeneity of findings across studies.

Our study also demonstrated that vitamin D deficient patients had significantly higher APACHE II (22.4 ± 5.8 vs. 16.2 ± 4.9) and SOFA scores (9.2 ± 2.8 vs. 5.6 ± 2.4), indicating more severe physiological derangement. Comparable observations were reported by Moraes RB et al. (2015) [15], who found that vitamin D deficient ICU patients had significantly higher severity scores and an independent association with mortality (hazard ratio 2.2). Additionally, Amrein K et al. (2014) [16] reported that severe deficiency (<12 ng/ml) was associated with increased hospital mortality, particularly in septic patients. These findings support our conclusion that vitamin D deficiency correlates closely with disease severity at admission.

Inflammatory and metabolic markers in our study further strengthen this association. Higher CRP and lactate levels among deficient patients reflect augmented systemic inflammation and tissue hypoperfusion. Moromizato T et al. (2014) [17] similarly observed that low vitamin D levels were associated with increased risk of sepsis and inflammatory complications in surgical ICU patients. The biological plausibility of this association is supported by vitamin D's immunomodulatory role, including regulation of cytokine production and maintenance of endothelial function.

Our ROC analysis revealed an AUC of 0.79 for predicting 28-day mortality, with a cut-off ≤18 ng/ml yielding sensitivity of 83.3% and specificity of 71.4%. This discriminatory performance is comparable to prior studies. Venkatram S et al. (2011) reported that vitamin D levels <15 ng/ml significantly predicted ICU mortality, while Amrein K et al. (2014) identified severe deficiency (<10–12 ng/ml) as the strongest mortality predictor. Although our cut-off was slightly higher, it falls within the range reported in earlier literature, suggesting that moderate to severe deficiency carries prognostic implications.

Interventional trials, however, have produced mixed results. The VITdAL-ICU trial by Amrein K et al. (2014) demonstrated that high-dose vitamin D3 supplementation significantly increased serum 25(OH)D levels and reduced hospital length of stay in severely deficient patients, but did not significantly reduce overall mortality. Similarly, randomized trials by Nair P et al. (2015) [18] and Han JE et al. (2016) [19] showed biochemical correction without consistent mortality benefit. These findings suggest that while deficiency is strongly associated with poor outcomes, supplementation during acute illness may not uniformly translate into survival advantage, possibly due to timing, dosing strategies, or the complex pathophysiology of critical illness.

Overall, our findings are largely concordant with major observational studies conducted between 2009 and 2015, which consistently report a 50–70% prevalence of deficiency and a significant association with severity and mortality. At the same time, conflicting prospective and interventional data indicate that vitamin D deficiency may function both as a marker of illness severity and as a potential modifiable risk factor. The present study adds to the growing body of evidence suggesting that serum 25(OH)D measurement at ICU admission may serve as a valuable prognostic biomarker. Nevertheless, large multicenter randomized trials are required to clarify causality and determine whether targeted correction of deficiency can meaningfully improve clinical outcomes in critically ill patients.

Conclusion

The research showed that 60% of critically ill patients who entered the ICU had vitamin D deficiency while their average serum 25(OH)D level fell below the deficient threshold. Vitamin D deficiency caused patients to exhibit more severe disease symptoms which doctors measured through increased APACHE II and SOFA scores and higher inflammatory markers and hypocalcemia and elevated lactate levels. The study found a strong statistical link between vitamin D deficiency and which patients died in the ICU after 28 days because most non-survivors had vitamin D deficiency. The ROC analysis confirmed that serum vitamin D level accurately predicts mortality because it had good sensitivity and specificity when testing patients with levels below 18 ng/ml. The findings show that vitamin D deficiency occurs widely in critically ill patients while it also serves as a valuable clinical indicator which can predict their health outcomes.

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