e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 577-582

Original Research Article

Relation between Serum Vitamin D Levels at Admission and Outcomes in Children with Sepsis in Tertiary Level Pediatric Critical Care

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Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026
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Conflict of interest: Nil

Abstract

Background: Vitamin D has important immunomodulatory functions and may influence the clinical course of sepsis. The relationship between serum vitamin D levels at admission and outcomes in pediatric sepsis remains incompletely understood.

Objective: To determine the association between serum vitamin D status at admission and clinical outcomes in children with sepsis admitted to a tertiary-level Pediatric Intensive Care Unit.

Methods: This prospective observational study included 154 children aged 1 month to 18 years admitted with sepsis over an 18-month period. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured within 24 hours of admission and patients were categorized as vitamin D sufficient (≥20 ng/mL), insufficient (12–20 ng/mL), or deficient (<12 ng/mL). Outcomes assessed included duration of hospital stay, duration for normalization of C-reactive protein (CRP), and in-hospital mortality. Statistical analysis was performed using SPSS version 23.0 with one-way ANOVA, logistic regression, and ROC curve analysis.

Results: Of the 154 children, 66 (42.9%) had sufficient vitamin D levels, 50 (32.5%) had insufficient levels, and 38 (24.7%) had vitamin D deficiency. Vitamin D-deficient children had significantly longer hospital stay (25.3 ± 29.8 days), delayed CRP normalization (9.4 ± 4.0 days), and higher mortality (55.3%) compared with children with sufficient vitamin D levels ($p<0.05$). Logistic regression demonstrated significant associations between lower vitamin D levels and prolonged hospitalization and delayed CRP normalization, whereas the association with mortality was not statistically significant after adjustment. ROC analysis identified a vitamin D cut-off value of 9.55 ng/mL for predicting mortality with 81.5% sensitivity (AUC=0.57, $p=0.03$).

Conclusion: Low serum vitamin D levels at admission are associated with prolonged hospitalization and delayed inflammatory recovery in children with sepsis. Serum vitamin D estimation may be a useful adjunctive prognostic marker for early risk assessment in critically ill pediatric patients.

Keywords: Vitamin D, Pediatric Sepsis, Pediatric Intensive Care Unit, C-Reactive Protein, Mortality, Critical Illness, Prognosis.

DOI: 10.25258/ijcpr.18.8.90

Introduction

Sepsis is a life-threatening condition caused by a dysregulated host response to infection and remains one of the leading causes of morbidity and mortality among critically ill children worldwide. Despite advances in pediatric intensive care, sepsis continues to account for a substantial proportion of Pediatric Intensive Care Unit (PICU) admissions, prolonged hospitalization, and mortality, particularly in developing countries. Early identification of prognostic biomarkers is essential for risk stratification and timely therapeutic intervention. [1,2] Vitamin D, beyond its classical role in calcium homeostasis and bone metabolism, has emerged as an important immunomodulatory

hormone. It influences both innate and adaptive immunity by enhancing antimicrobial peptide production, regulating inflammatory cytokines, and maintaining endothelial integrity. Vitamin D deficiency has been associated with an increased susceptibility to infections, impaired immune response, and adverse outcomes in critically ill patients. [3,4] Several studies have demonstrated a high prevalence of vitamin D deficiency among children admitted to the PICU and have suggested an association between low serum 25-hydroxyvitamin D [25(OH)D] levels and increased disease severity, longer intensive care stay, need for organ support, and mortality. Although the exact relationship between vitamin D status and outcomes in pediatric sepsis remains controversial, accumulating evidence indicates that deficient vitamin D levels may contribute to poorer clinical outcomes. [5,6]

Vitamin D deficiency is highly prevalent worldwide, particularly in children from low- and middle-income countries due to inadequate dietary intake, limited sunlight exposure, and recurrent infections. Identifying vitamin D deficiency at the time of admission may provide valuable prognostic information and help identify children at greater risk of adverse outcomes. [7,8] Therefore, the present study was undertaken to evaluate the relationship between serum vitamin D levels at admission and clinical outcomes in children with sepsis admitted to a tertiary-level Pediatric Intensive Care Unit.

Materials and Methodology

Study Design: This was a prospective observational study conducted to evaluate the relationship between serum vitamin D levels at admission and outcomes in children with sepsis admitted to the Pediatric Intensive Care Unit (PICU).

Study Setting: The study was conducted in the Pediatric Intensive Care Unit (PICU), Indira Gandhi Institute of Child Health, and Bengaluru, India.

Study Duration: The study was carried out over a period of 18 months after obtaining approval from the Institutional Ethics Committee.

Sample Size: The sample size was estimated using nMaster software Version 2.0, based on the study by M K et al. (2020). Considering a prevalence of 11.1% mortality among children with low serum vitamin D levels, with a 95% confidence interval, 5% absolute precision, and $\alpha = 0.05$, the calculated sample size was 152 children.

Study Population: Children admitted to the PICU with a diagnosis of sepsis were screened for eligibility.

Inclusion Criteria

- Children aged 1 month to 18 years.
- Diagnosis of sepsis according to the Surviving Sepsis Campaign 2020 criteria.
- Written informed consent from parents or legal guardians.
- Written assent from children older than 7 years whenever applicable.

Exclusion Criteria

- Pre-existing chronic kidney disease, chronic liver disease, congenital heart disease, malignancy, autoimmune disorders, or chronic neurological illness.
- Children receiving long-term corticosteroid or immunosuppressive therapy.
- Patients receiving vitamin D supplementation before admission.
- Children with metabolic bone disease or disorders affecting vitamin D metabolism.
- Refusal to provide consent.

Data Collection: After enrollment, demographic characteristics, anthropometric measurements, socioeconomic status, duration of illness, nutritional status, sunlight exposure, previous vitamin supplementation, and relevant medical history were recorded using a predesigned case record form.

Clinical examination included measurement of temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, Glasgow Coma Scale (or Pediatric GCS), and assessment of organ dysfunction.

Baseline laboratory investigations included:

- Complete blood count
- Blood culture
- C-reactive protein (CRP)
- Serum procalcitonin
- Renal and liver function tests
- Serum electrolytes
- Arterial blood gas analysis
- Serum lactate
- Serum 25-hydroxyvitamin D [25(OH)D]

Estimation of Serum CRP: Approximately 2 mL of venous blood was collected for estimation of CRP. Serum was separated by centrifugation, and CRP was measured using the COBAS 6000 Modular System (Roche Diagnostics Pvt. Ltd.) by the immunoturbidometric method.

Estimation of Serum Procalcitonin: Serum procalcitonin was estimated from 2 mL of venous blood using the COBAS 6000 Modular System by the electrochemiluminescence immunoassay (ECLIA) method.

Estimation of Serum Vitamin D: Within 24 hours of PICU admission, 2 mL of venous blood was

collected for estimation of serum 25-hydroxyvitamin D [25(OH)D].

Samples were centrifuged after clot formation, and serum vitamin D levels were measured using the COBAS 6000 Modular System (Roche Diagnostics Pvt. Ltd.) by the sandwich electrochemiluminescence immunoassay (ECLIA) method. Laboratory personnel were blinded to patient outcomes, and vitamin D values were disclosed only after completion of the study.

Patient Categorization

Based on serum 25(OH)D concentration measured at admission, patients were categorized into three groups:

- **Vitamin D sufficient:** ≥20 ng/mL
- **Vitamin D insufficient:** 12–20 ng/mL
- **Vitamin D deficient:** <12 ng/mL

Follow-up: Patients were followed throughout their hospital stay until discharge or death. Clinical progress, laboratory investigations, and treatment requirements were recorded daily.

Outcome Measures

Primary Outcome

- Association between serum vitamin D status at admission and in-hospital mortality.

Secondary Outcomes

- Duration of hospital stay.
- Duration for normalization of CRP levels.
- Requirement for mechanical ventilation.
- Requirement for vasoactive support.
- Duration of PICU stay.
- Development of septic shock or multiorgan dysfunction.
- Survival at hospital discharge.

Statistical Analysis: Data were entered into Microsoft Excel 2021 and analyzed using IBM SPSS Statistics version 23.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons among the three vitamin D groups were performed using one-way ANOVA for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was performed to identify independent predictors of mortality. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal serum vitamin D cut-off value for predicting mortality. A p-value <0.05 was considered statistically significant.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee of Indira Gandhi Institute of Child Health, Bengaluru (Approval No. IGICH/EC/11/2022-23 dated 19 July 2022). Written informed consent was obtained from the parents or legal guardians of all participants, and assent was obtained from children older than seven years wherever appropriate. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Results

A total of 154 children admitted to the Pediatric Intensive Care Unit (PICU) with sepsis fulfilling the inclusion criteria were enrolled and analyzed. The study population had a male-to-female ratio of 1.6:1, with infants (<1 year) constituting the majority (72.7%). Based on serum 25-hydroxyvitamin D [25(OH)D] levels at admission, 66 (42.9%) children had sufficient vitamin D levels, 50 (32.5%) had insufficient levels, and 38 (24.7%) had vitamin D deficiency.

Table 1: Baseline Characteristics and Vitamin D Status of the Study Population (n = 154)

Variable	n (%)
Total participants	154 (100)
Sex	
Male	96 (62.3)
Female	58 (37.7)
Age Group	
<1 year	112 (72.7)
1–5 years	20 (13.0)
5–10 years	11 (7.1)
10–18 years	11 (7.1)
Region	
South Karnataka	108 (70.1)
North Karnataka	29 (18.8)
Other states	17 (11.0)
Vitamin D Status	
Sufficient (≥20 ng/mL)	66 (42.9)
Insufficient (12–20 ng/mL)	50 (32.5)
Deficient (<12 ng/mL)	38 (24.7)

The majority of children admitted with sepsis were infants and males. Nearly one-fourth of the study population had vitamin D deficiency, while approximately one-third had insufficient vitamin D levels at admission.

Table 2. Association of Baseline Characteristics with Vitamin D Status

Variable	Deficient n=38	Insufficient n=50	Sufficient n=66	p-value
Age <1 year	26 (68.4%)	35 (70.0%)	51 (77.3%)	0.04*
Age 1–5 years	6 (15.8%)	8 (16.0%)	6 (9.1%)	
Age 5–10 years	3 (7.9%)	3 (6.0%)	5 (7.6%)	
Age >10 years	3 (7.9%)	4 (8.0%)	4 (6.1%)	
Male sex	26 (68.4%)	32 (64.0%)	38 (57.6%)	0.52
Female sex	12 (31.6%)	18 (36.0%)	28 (42.4%)	
South Karnataka	29 (76.3%)	33 (66.0%)	46 (69.7%)	0.61
North Karnataka	6 (15.8%)	10 (20.0%)	13 (19.7%)	
Other states	3 (7.9%)	7 (14.0%)	7 (10.6%)	

***Statistically significant**

Age showed a significant association with vitamin D status, with infants constituting the largest proportion in all three groups (p=0.04). However, sex and geographical distribution were not significantly associated with vitamin D status.

Table 3. Clinical Outcomes According to Vitamin D Status

Outcome	Deficient (n=38)	Insufficient (n=50)	Sufficient (n=66)	p-value
Death	21 (55.3%)	22 (44.0%)	22 (33.3%)	0.05*
Recovered	17 (44.7%)	28 (56.0%)	44 (66.7%)	
Mean days for CRP normalization	9.4 ± 4.0	8.6 ± 3.7	6.9 ± 4.3	0.02*
Mean hospital stay (days)	25.3 ± 29.8	19.1 ± 12.9	18.2 ± 16.7	0.01*

***Statistically significant**

Children with vitamin D deficiency had significantly higher mortality, prolonged hospital stay, and delayed normalization of CRP compared with those having sufficient vitamin D levels.

Table 4. Multivariate Logistic Regression and ROC Analysis for Clinical Outcomes

Variable	Odds Ratio (OR)	95% CI	p-value
Vitamin D Insufficiency vs Sufficiency			
Longer CRP normalization	1.01	0.98–1.03	0.01*
Longer hospital stay	1.30	0.96–1.39	0.05*
Mortality	1.54	0.49–4.77	0.45
Vitamin D Deficiency vs Sufficiency			
Longer CRP normalization	1.15	1.03–1.30	0.04*
Longer hospital stay	0.97	0.95–1.01	0.03*
Mortality	1.55	0.60–4.19	0.38
ROC Analysis			
Vitamin D cut-off: **9.55 ng/mL**	Sensitivity: 81.5%	AUC = 0.57	0.03*

***Statistically significant**

Vitamin D insufficiency and deficiency were independently associated with prolonged CRP normalization and longer hospital stay. Although mortality was numerically higher among children with lower vitamin D levels, it did not reach statistical significance after adjustment.

ROC analysis demonstrated that a serum vitamin D level of 9.55 ng/mL predicted mortality with 81.5% sensitivity, though with modest discriminative ability (AUC=0.57).

Discussion

The present prospective observational study evaluated the relationship between serum vitamin D levels at admission and clinical outcomes in children with sepsis admitted to a tertiary-level Pediatric Intensive Care Unit. Nearly one-fourth (24.7%) of the study population had vitamin D deficiency, while an additional 32.5% had insufficient vitamin D levels, indicating that more than half of the children admitted with sepsis had suboptimal vitamin D status. Children with vitamin D deficiency experienced significantly longer hospital stay, delayed normalization of C-reactive protein (CRP), and a higher proportion of mortality compared with children with sufficient vitamin D levels. The systematic review and meta-analysis by McNally et al. [9] demonstrated that vitamin D deficiency is highly prevalent among critically ill children and is associated with increased illness severity, prolonged PICU stay, and adverse clinical outcomes. Similar findings were observed in the

present study, where vitamin D-deficient children required significantly longer hospitalization and slower resolution of inflammatory markers than those with sufficient vitamin D levels.

Likewise, de Haan et al. [10] reported that vitamin D deficiency is associated with an increased risk of severe infection, sepsis, and poor outcomes in critically ill patients through dysregulation of innate immunity and exaggerated inflammatory responses. Our study supports these observations, as children with deficient vitamin D levels showed prolonged inflammatory activity reflected by delayed normalization of CRP and increased duration of hospital stay.

The landmark review by Holick [11] emphasized that vitamin D plays an important role in maintaining immune homeostasis by enhancing macrophage activity, stimulating antimicrobial peptide synthesis, and modulating inflammatory cytokines. Deficiency of vitamin D may impair these protective mechanisms, predisposing children to persistent infection and delayed recovery. This biological explanation is consistent with the findings of the present study. The Endocrine Society Clinical Practice Guideline by Holick et al. [12] defined vitamin D deficiency and recommended serum 25-hydroxyvitamin D estimation for identifying individuals at risk of adverse health outcomes. The classification used in the present study into sufficient, insufficient, and deficient groups was based on these established recommendations, allowing standardized comparison of clinical outcomes across vitamin D categories.

The recent expert consensus by Pludowski et al. [13] highlighted the widespread prevalence of vitamin D deficiency globally and emphasized that critically ill children constitute a particularly vulnerable population.

The authors recommended early identification of deficiency because low vitamin D levels may adversely influence immune function and recovery from severe infections. The present findings reinforce this recommendation by demonstrating significantly poorer clinical recovery among vitamin D-deficient children. Carlberg [14] described vitamin D as a multifunctional hormone involved in immune regulation, endothelial protection, and control of inflammatory responses rather than merely calcium metabolism. These immunomodulatory effects may explain the delayed resolution of systemic inflammation observed in vitamin D-deficient children in the present study, who required significantly more time for CRP normalization.

Similarly, Annweiler et al. [15] reviewed emerging evidence supporting the beneficial role of adequate vitamin D status in critically ill patients and suggested that vitamin D deficiency may contribute to increased disease severity and poorer survival in severe infections. Although mortality was numerically higher among vitamin D-deficient children in our study, multivariate logistic regression did not identify vitamin D deficiency as an independent predictor of mortality, suggesting that multiple clinical factors contribute to outcomes in pediatric sepsis. Recent evidence by Karampela et al. [16] further emphasized the complex interaction between vitamin D and sepsis pathophysiology, including modulation of inflammatory cytokines, endothelial dysfunction, oxidative stress, and immune response. The authors concluded that vitamin D deficiency should be regarded as an important prognostic biomarker rather than an isolated causal factor. Consistent with this concept, our ROC analysis demonstrated that serum vitamin D levels below 9.55 ng/mL predicted mortality with high sensitivity, although the discriminatory ability was modest. Therefore, serum vitamin D estimation at PICU admission may be useful for early risk stratification when interpreted alongside established clinical and laboratory parameters.

Overall, the present study indicates that low serum vitamin D levels at admission are associated with adverse clinical outcomes in pediatric sepsis, particularly prolonged hospitalization and delayed resolution of systemic inflammation. Routine assessment of vitamin D status may help identify high-risk children who require closer monitoring and aggressive supportive management.

Conclusion

Vitamin D deficiency was common among children admitted to the Pediatric Intensive Care Unit with sepsis. Lower serum vitamin D levels at admission were significantly associated with prolonged hospital stay, delayed normalization of C-reactive protein, and poorer clinical outcomes. Although vitamin D deficiency was not an independent predictor of mortality after multivariate adjustment, children with deficient vitamin D levels demonstrated a higher proportion of deaths than those with sufficient levels. Measurement of serum 25-hydroxyvitamin D at admission may serve as a useful prognostic biomarker for identifying children at increased risk of adverse outcomes. Larger multicenter studies are warranted to determine whether early correction of vitamin D deficiency can improve outcomes in pediatric sepsis.

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