



# Vitamin D Deficiency in Pediatric with Thermal Injury: A Prospective Cohort Study

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## Abstract

**Background:** Vitamin D deficiency is frequently observed in children with burn injuries and can influence clinical outcomes. This study aimed to explore the relationship between vitamin D status and clinical results in children with severe thermal injuries.

**Methods:** This study was a prospective cohort involving 220 children (aged 0–18 yr) who experienced severe thermal burns [ $\geq 20\%$  Total Body Surface Area (TBSA)] and were hospitalized between July 2021 and October 2022. The participants were categorized into two groups based on their admission 25-hydroxyvitamin D [25(OH)D] levels: a sufficient vitamin D group (n=110) and an insufficient vitamin D group (n=110). The primary outcome was the incidence of infections. Secondary outcomes included hospital Length of Stay (LOS), the number of surgical procedures, wound pain scores, itching, Body Mass Index (BMI), blood glucose levels, and albumin levels.

**Results:** Children with low vitamin D levels experienced a longer length of stay (11.43 vs. 10.7 days,  $p=0.045$ ) and a considerably higher incidence of infections (90.9 vs. 62.7%,  $p<0.001$ ) compared to children with sufficient vitamin D levels. However, the groups showed no statistically significant difference regarding the number of surgical procedures. Similarly, no significant differences were found in wound pain, pruritus, BMI, albumin, or blood sugar levels.

**Conclusion:** This research indicated that vitamin D deficiency in children with thermal injury may be linked to a higher risk of infections and extended hospital stays. Understanding the underlying mechanisms and evaluating the possible benefits of vitamin D supplementation in this population requires more research.

**Keywords:** Burns, Child, Pain, Vitamin D

## Introduction

Severe burn injuries in children pose a significant public health challenge, often resulting in prolonged hospital stays, serious complications, and long-lasting consequences (1). Recent evidence emphasizes the immediate focus on wound care and the long-term impact of micronutrient deficiencies such as vitamin D. Vitamin D deficiency, a common occurrence among children and adults with burn injuries, has been linked to various adverse outcomes (2). Studies indicate a potential connection between low vitamin D levels and a higher risk of infections, such as sepsis, a significant complication in burn patients (3). This may be due to vitamin D's immunomodulatory properties, influencing innate and adaptive immune responses (3). Furthermore, the complex inflammatory response triggered by burn trauma can further deplete vitamin D stores (4). The complex relationship between vitamin D status and burn injuries highlights the need for a deeper understanding of their interaction and its potential effect on clinical outcomes in children. Much research has examined the statistical relationship between vitamin D levels and burn-related parameters. For example, prior research has demonstrated an association between low vitamin D levels, increased burn surface area, and greater burn depth (5).

Additionally, research suggests a potential correlation between vitamin D deficiency and impaired protein synthesis during the acute phase of burn injury, potentially hindering wound healing (6). However, the existing knowledge on the influence of vitamin D on pediatric burn outcomes remains fragmented. Inconsistencies in study design, patient demographics, and outcome measures make it challenging to draw definitive conclusions (7). Therefore, further research is crucial to elucidate the precise mechanisms by which vitamin D levels impact clinical outcomes in children with burn injuries. This knowledge can pave the way for targeted interventions to optimize vitamin D status and potentially improve recovery trajectories in this vulnerable population.

## Materials and Methods

### Study design

This prospective cohort study investigated the relationship between baseline vitamin D status and

clinical outcomes in children with burn injuries.

### Setting and participants

Eligible participants were children aged 0-18 years admitted to Velayat Hospital with thermal burns  $\geq 20\%$  Total Body Surface Area (TBSA) between July 2021 and October 2022. The exclusion criteria included age over 18, pregnancy, cancer, electrical or chemical burns, and early discharge or transfer. Vitamin D sufficiency was defined as a 25(OH)D level  $\geq 30\text{ ng/ml}$ , aligning with Endocrine Society guidelines (8). The patients were categorized as sufficient or insufficient based on their admission of 25(OH)D levels. A sample size calculation ensured adequate power for the key outcome analyses. The study was reported in line with STROCSS criteria.

### Data collection

Standardized data included demographics, burn characteristics (TBSA, depth, inhalation injury), laboratory parameters (blood sugar, albumin, 25(OH)D), Body Mass Index (BMI), infection status, pain scores, and Length of Stay (LOS) in ICU and hospital. 25(OH)D levels were measured on Day 1 using ELISA. Blood sugar was monitored on Days 1, 7, 14, 21, and discharge. Albumin was measured on Days 1, 14, and discharge. Infection evaluation relied on clinical signs and relevant tests. Pain scores were recorded on Days 1, 14, and discharge. All the participants were followed up until discharge.

### Statistical analysis

Descriptive statistics were presented as mean $\pm$ SD for normally distributed continuous variables and as frequencies and percentages for the categorical variables. The normality of the data was assessed utilizing the Shapiro-Wilk and Kolmogorov-Smirnov tests. Independent-sample t-tests were used to compare continuous variables between groups with normal distributions. To analyze the continuous variables measured at multiple time points within groups, Generalized Estimating Equations (GEE) were applied. The chi-square test was used to analyze the categorical variables. All the statistical analyses were conducted with a two-tailed significance level of  $\alpha=0.05$ . Data analysis was performed using SPSS version 28.

### Ethics statement

This study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Guilani University of Medical Sciences (IR.GUMS.REC.1400.222). Written informed consent was obtained from all the participants or their legal guardians. All the patients' data were anonymized to ensure the confidentiality and privacy. Additionally, all the data management procedures were conducted using stringent protocols to protect the participants' personal information and comply with relevant data protection regulations.

### Results

A total of 220 children with thermal injury participated in the study, equally divided into sufficient (n=110) and insufficient (n=110) vitamin D groups based on the admission levels. The mean 25(OH)D level in the insufficient vitamin D group was 14.9 ng/ml, compared to 38.2 ng/ml in the sufficient group.

In comparing the baseline characteristics of the patients with sufficient and insufficient vitamin D levels (Table 1), the mean age in the sufficient and insufficient vitamin D groups was  $44.8 \pm 59.28$  and  $48.9 \pm 33.11$  years, respectively, with no significant difference ( $p=0.258$ ).

Similarly, the percentage of the male patients was 62.7% in the sufficient vitamin D group and 77.3% in the insufficient vitamin D group, with no statistically significant difference ( $p=0.663$ ). Furthermore, there were no significant differences in mean BMI (sufficient:  $17.4 \pm 3.87$ , insufficient:  $17.1 \pm 2.12$ ,  $p=0.844$ ), TBSA (sufficient:  $25.2 \pm 4.11$ , insufficient:  $26.6 \pm 8.31$ ,  $p=0.814$ ), and the incidence of inhalation injury (sufficient: 9.09%, insufficient: 10.90%,  $p=0.566$ ) between the two groups. The groups showed no statistically significant difference regarding pain ( $p=0.316$ ), itching ( $p=0.293$ ), BMI ( $p=0.844$ ), albumin levels ( $p=0.472$ ), and blood sugar levels ( $p=0.440$ ) (Table 2).

**Table 1.** Comparison of baseline characteristics between patients with sufficient and insufficient vitamin D levels

Variables	Sufficient vitamin D (n=110)	Insufficient vitamin D (n=110)	p-value
Age, median years	44.8±59.28	48.9±33.11	0.258 *
Gender, n (%)			
Male	69 (62.7)	85 (77.3)	0.663 **
Female	41 (37.3)	25 (22.7)	
BMI, mean kg/m <sup>2</sup>	17.4±3.87	17.1±2.12	0.844 *
%TBSA	25.2±4.11	26.6±8.31	0.814 *
Inhalation Injury	10(9.09)	12(10.90)	0.566 **

\* Independent Samples t-test. \*\* Chi-Square Test. Body Mass Index: BMI, Total Body Surface Area: TBSA

**Table 2.** Comparison of baseline characteristics between patients with sufficient and insufficient vitamin D levels in the investigated times using GEE

Parameter	Vitamin D levels	B	Std. error	Wald Chi-Square	Sig.
Blood sugar level	Insufficient	11.48	14.86	0.59	0.440
	sufficient	0	-	-	-
Albumin level	Insufficient	-0.21	0.29	0.51	0.472
	sufficient	0	-	-	-
Itch	Insufficient	1.90	0.57	6.31	0.293
	sufficient	0	0	-	-
Pain	Insufficient	3.35	0.31	35.65	0.316
	sufficient	0	-	-	-
Bodyd Mass Index (BMI)	Insufficient	-0.026	1.36	0.04	0.844

\* GEE: Generalized Estimating Equations

**Table 3.** Comparison of outcomes between patients with sufficient and insufficient vitamin D levels

Variables	Sufficient vitamin D (n=110)	Insufficient vitamin D (n =110)	p-value
Hospital LOS, Mean±SD (days)	10.74±2.65	11.43±2.41	0.045**
ICU-LOS Mean±SD (days)	0.51±2.32	1.10±2.02	0.042**
Operations, Mean±SD	2.71±1.11	2.51±2.34	0.419**
Infection, n (%)			
Yes	69(62.7)	100(90.9)	<0.001*
No	41(37.3)	10(9.1)	

\* Pearson Chi-Square. \*\* Independent Samples Test. Length of Stay: LOS

Children with insufficient vitamin D levels experienced a significantly higher infection rate than those with sufficient levels (90.9 vs. 62.7%,  $p<0.001$ ). Moreover, children with insufficient vitamin D levels exhibited a prolonged hospital stay (11.43 vs. 10.7 days,  $p=0.045$ ). However, the two groups showed no statistically significant difference in the number of surgical procedures ( $p=0.419$ ) (Table 3).

## Discussion

Several studies have demonstrated an association between vitamin D deficiency and adverse clinical outcomes in burn patients (9–13). This association is likely due to the disruption of cutaneous vitamin D synthesis following a major burn, significantly reducing the effective body surface area available for vitamin D production. Vitamin D plays a critical role in calcium homeostasis and metabolism, which are essential for healthy skin regeneration. Consequently, its deficiency can create a detrimental feedback loop, hindering calcium absorption and impairing the skin's healing process (9). In addition to these effects, vitamin D influences clinical outcomes in burn patients through several specific mechanisms. First, its immunomodulatory effects are crucial in regulating both innate and adaptive immune responses (14). Vitamin D enhances the production of antimicrobial peptides, such as cathelicidins and defensins, which disrupt bacterial membranes and reduce the risk of infections (15). It also modulates inflammatory responses by suppressing pro-inflammatory cytokines (e.g., IL-6 and TNF- $\alpha$ ) and promoting anti-inflammatory cytokines (e.g., IL-10), thus mitigating excessive inflammation in burn patients (16,17). This

highlights the potential importance of investigating the role of vitamin D supplementation in burn patients to optimize their recovery.

In our study, the analysis showed no significant differences in age ( $p=0.258$ ) and gender ( $p=0.663$ ) between the groups with sufficient and insufficient vitamin D levels. This aligns with studies conducted by Cho *et al* (5,18) and Alizadeh *et al* (19), which reported no significant differences in age or gender between groups stratified by vitamin D levels. The absence of such differences indicates the homogeneity of our study groups, eliminating potential confounding effects from these demographic variables. Contrary to the findings, Garner *et al* (20) reported significant differences in age and gender distributions across vitamin D levels. Such discrepancies could stem from differences in population characteristics or the study design. Consistent with previous findings reported by Cho *et al* (5) and Alizadeh *et al* (19), the current study identified no significant difference in BMI between the two groups. However, Garner *et al* (20) reported a significant association between lower BMI and sufficient vitamin D levels, suggesting that nutritional status and baseline health variations may influence this relationship. In the current study, the mean hospital stay was significantly longer in patients with insufficient vitamin D levels. These findings are consistent with prior studies, including those by Rech *et al* (2), Blay *et al* (21), and Cho *et al* (18), which demonstrated prolonged LOS in patients with lower vitamin D levels. Prolonged hospitalization in these patients may be attributed to the role of vitamin D in wound healing and immune modulation. Zavala *et al* (22) also reported an extended LOS among burn

patients with vitamin D deficiency, emphasizing the impact of vitamin D on recovery time. Among the patients, 16.7% required ICU admission, with those in the vitamin D-deficient group experiencing significantly longer ICU stays ( $p=0.045$ ). These findings agree with studies by Alizadeh *et al* (19), Rech *et al* (2), and Zavala *et al* (22) which also reported a significant association between vitamin D deficiency and prolonged ICU stays. The increased length of stay in vitamin D-deficient patients in the ICU can be attributed to higher rates of infectious complications and delayed recovery. Blay *et al* (21) and Cho *et al* (18) found similar results, showing that patients with sufficient vitamin D levels had shorter ICU stays. In contrast, De Haan *et al* (23) observed no significant relationship between vitamin D levels and ICU duration in burn patients, highlighting the variability in findings across different populations and study designs. Nevertheless, most evidence supports the notion that vitamin D sufficiency may mitigate the severity of complications requiring prolonged ICU care.

The study found a significant link between vitamin D deficiency and a higher risk of infections, affecting 23.3% of the participants. Patients with insufficient vitamin D levels were more likely to develop infections than those with adequate levels. This finding is supported by a meta-analysis by De Haan *et al* (23), which demonstrated a strong association between vitamin D deficiency and an increased risk of infections, sepsis, and mortality in burn patients. Similar results were reported by Zavala *et al* (22) where vitamin D-deficient patients had higher rates of infectious complications. Vitamin D's role in immune modulation may explain these findings. It enhances the production of antimicrobial peptides such as cathelicidins, which play a critical role in preventing infections. The current study's observed increase in infection rates underscores the potential benefits of addressing vitamin D deficiency in burn patients to reduce infectious morbidity and associated complications.

The study found no significant differences between the groups in blood glucose or albumin levels. These findings are consistent with Blay *et al* (21) and Gottschlich *et al* (24), who reported no significant association between vitamin D levels

and these parameters. However, Gottschlich *et al* (24) highlighted the potential benefits of vitamin D supplementation in improving glucose control, suggesting that the findings might reflect baseline conditions without supplementation. Interestingly, the study revealed no statistically significant difference in the frequency of surgical interventions between the two groups. This suggests that while vitamin D status may influence recovery and immune response, its direct impact on surgical intervention needs further exploration. However, further studies with larger sample sizes are warranted to validate these findings and explore potential confounding factors that may influence surgical management decisions. The study found no significant differences in pain or itching at wound sites between the groups ( $p=0.316$ ). Mauck *et al* (11) reported that vitamin D deficiency exacerbates pain-related symptoms in burn patients, contrasting with the present study's findings. This discrepancy may be due to differences in pain assessment methods or the patient characteristics.

Supplementation with vitamin D3 was suggested to correlate with reduced mortality in the general population. Furthermore, vitamin D levels appear to influence health outcomes in critically ill patients, although limited clinical studies have specifically explored the effects of vitamin D supplementation in this group. For example, the VITdAL-ICU trial, conducted by Amrein *et al* in 2014 (25), investigated high-dose vitamin D3 supplementation in critically ill adults. This study found that high-dose vitamin D3 supplementation did not significantly impact hospital LOS or overall mortality rates at hospital discharge and six-month follow-up. However, a subgroup analysis revealed a significant reduction in mortality among patients with severe vitamin D deficiency at the start of the study. These findings align with a systematic review and meta-analysis of seven randomized controlled trials (RCTs) encompassing 716 critically ill patients (26). This analysis demonstrated that vitamin D supplementation was associated with lower mortality rates, with no severe adverse events reported. In contrast, another analysis of six RCTs comprising 695 patients found no significant improvement in clinical outcomes for critically ill individuals receiving vitamin D supplementation (27). These conflicting results were

attributed to differences in trial inclusion criteria, using different vitamin D forms (cholecalciferol *vs.* calcitriol), dosing regimens, and administration routes (enteral *vs.* intravenous). These findings underscore the complexity of evaluating vitamin D supplementation in critically ill patients and highlight the need for further research to determine the optimal dosage, route of administration, and the subset of patients who would benefit most from vitamin D supplementation. This study adds to the growing evidence of the critical role of vitamin D in managing burn injuries and underscores the need for routine screening and potential supplementation of vitamin D in burn patients to optimize recovery outcomes. Further research exploring the optimal timing, dosage, and long-term effects of vitamin D supplementation in this population is warranted to provide clearer clinical guidance.

### **Limitations of the study**

This study had several limitations that should be acknowledged. Firstly, the single-center design may limit the generalizability of the findings to broader populations. Different healthcare settings might have varying management protocols, which could influence the observed outcomes. Secondly, the potential for selection bias exists, as the participants were recruited from a single hospital and included only those with burns covering  $\geq 20\%$  TBSA. This could restrict the applicability of the results to patients with less extensive burns. Another limitation is the reliance on a single measurement of vitamin D levels at admission. Vitamin D levels can fluctuate due to various factors, including dietary intake, seasonal variation, and sun exposure, which were not controlled for in this study. This might introduce measurement errors and affect the accuracy of the association between vitamin D deficiency and clinical outcomes. Finally, the relatively small sample size and lack of long-term follow-up data might limit the study's power to detect certain effects and assess the sustainability of the observed outcomes. Future multicenter studies with larger sample sizes and longitudinal follow-ups are recommended to address these limitations and provide more comprehensive insights.

### **Implications of the findings**

The findings of this study highlight the critical role of maintaining sufficient vitamin D levels in pediatric burn patients to improve clinical outcomes. The observed associations between vitamin D insufficiency, increased infection rates, and prolonged hospitalization suggest that early assessment and correction of vitamin D levels should be integral to burn care protocols. Implementing targeted supplementation strategies may enhance immune response and recovery rates and reduce the burden on healthcare systems by minimizing hospital stays and associated complications. Future research focusing on optimizing vitamin D supplementation could pave the way for more comprehensive treatment approaches, ultimately improving pediatric burn patients' prognosis and quality of life.

### **Conclusion**

The current study provided valuable insights into the nexus between vitamin D status and clinical outcomes in pediatric burn patients. The observed associations between vitamin D insufficiency, infection incidence, and hospital LOS underscore the potential benefits of optimizing vitamin D levels for holistic management strategies for pediatric burn injuries. Further research is warranted to elucidate the underlying mechanisms and explore the therapeutic implications of vitamin D supplementation in this vulnerable population. By unraveling the intricate interplay between micronutrients and clinical outcomes, we could strive to improve the quality of care and long-term prognosis for pediatric burn patients.

### **Ethics approval**

The study was performed in accordance with the declaration of Helsinki and approved by the Ethics Committee of Guilani University of Medical Sciences (IR.GUMS.REC.1400.222).

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## Conflict of Interest

The authors declare that they have no conflict of interest concerning this study.

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