DOI: 10.4274/csmedj.galenos.2025.2025-3-2

ORIGINAL ARTICLE

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Cam and Sakura Med J 2025;5(1):17-24

CSMJ

The Effect of Vitamin D Level on the Clinical Course of the Disease in Patients with Lower Respiratory Tract Infection

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What is known on this subject?

Vitamin D contributes to immune function and has been implicated in respiratory infection outcomes. Deficiency may elevate the risk of severe disease manifestations, including increased hospitalization, intensive care needs, and prolonged recovery in children.

What this study adds?

This study identifies a statistically significant link between low vitamin D levels and severe lower respiratory tract infection in infants. It demonstrates that deficient vitamin D status correlates with greater clinical support requirements and suggests that maintaining adequate levels may mitigate disease burden.

ABSTRACT

Objective: Vitamin D deficiency is a significant public healthcare issue worldwide. New research suggests that there is a link between vitamin D deficiency and the progression of various infectious diseases, particularly viral infections. The aim of this study is to evaluate the impact of vitamin D deficiency on the clinical course of lower respiratory tract infections (LRTIs) in hospitalised infants.

Material and Methods: This retrospective study included 178 pediatric patients (113 males, 65 females) aged 1-24 months, hospitalized with LRTI between October 15, 2017, and May 15, 2019. Patients were categorized into vitamin D deficient (<12 ng/mL, n=22), insufficient (12-20 ng/mL, n=31), and sufficient (>20 ng/mL, n=125) groups. Demographic, socio-economic, nutritional, and clinical characteristics were compared. The severity of LRTI was assessed using the Modified Wang Respiratory Scoring System. The association between indicators of disease severity [Wang score, intensive care unit (ICU) admission, oxygen therapy, length of hospitalization, and respiratory support] and vitamin D levels was analyzed.

Results: The mean 25(OH)D level was 26.53±12.14 ng/mL. A total of 29.78% (n=53) of patients had vitamin D levels below 20 ng/mL. Vitamin D levels were significantly higher in infants who received regular vitamin D supplementation during the first six months and in those who were fed with formula (p<0.001). Patients with severe LRTI had noticeably lower vitamin D levels than those with mild-to-moderate cases (median: 21.20 ng/mL vs. 27.20 ng/mL, p=0.021). Vitamin D deficiency was found to be an independent risk factor for severe LRTI [odds ratio (OR): 4.32, 95% confidence interval (CI): 1.63-11.47], ICU admission (OR: 4.74, 95% CI: 1.73-12.94), and the need for oxygen support (OR: 2.74, 95% CI: 1.30-5.96).

Conclusion: Vitamin D deficiency appears associated with more severe clinical courses in infants with LRTI. Optimizing vitamin D status could reduce morbidity. Larger prospective studies are warranted.

Keywords: Vitamin D deficiency, pediatric respiratory infection, disease severity, respiratory support, Wang score

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Received: 13.03.2025 **Accepted:** 30.04.2025 **Publication Date:** 22.07.2025

Cite this article as: Kangel D, Kıral A. The effect of vitamin D level on the clinical course of the disease in patients with lower respiratory tract infection. Cam and Sakura Med J. 2025;5(1):17-24

This article is based on the thesis titled "Investigation of the effect of vitamin D level on the clinical course of the disease in patients diagnosed with lower respiratory tract infections between 1 month and 24 months," written by Demet Kangel and submitted on 2019 (thesis no: 623556).

CAM & SAKURA MEDICAL JOURNAL

Introduction

Lower respiratory tract infections (LRTIs) represent a major cause of child morbidity and mortality, particularly in low-resource settings. The World Health Organization reports that LRTIs contribute to approximately 19% of deaths among children under five (1). Viral pathogens, particularly respiratory syncytial virus, are the leading cause of infection (2).

Recent studies have shown that vitamin D plays an essential role in the innate immune system by helping to fend off infection regardless of whether the body has encountered the pathogen before (3). Innate immunity involves the synthesis of peptides with antimicrobial properties, such as β-defensins and cathelicidins (e.g., hCAP-18/LL-37), that target viruses, bacteria and fungi. hCAP-18, the sole human cathelicidin, increases the killing of microorganisms in phagocytic vacuoles, attracts neutrophils and monocytes, and is regulated by a vitamin D-dependent pathway (4). Pathogenic antigens stimulate Toll-like receptors on macrophages, leading to increased expression of the vitamin D receptor and the 1α-hydroxylase enzyme, which converts 25(OH)D into its active form, 1,25-(OH)2D (5). This active metabolite then binds to the promoter of the cathelicidin gene, enhancing hCAP-18 production–a process observed in myeloid cells, bronchial epithelial cells, and keratinocytes (4,5,6). Additionally, Weber et al. (4) demonstrated that 25(OH)D can stimulate the production of intracellular hCAP-18 through autocrine activation of 1α-hydroxylase.

Evidence has shown that vitamin D can enhance the lung barrier function of epithelial cells, stimulate the synthesis of antimicrobial proteins and surfactants, promote the autophagy of cells infected with pathogens, and reduce the production of pro-inflammatory cytokines (7,8,9). Numerous observational studies and these laboratory studies have reported an independent association between low circulating 25(OH)D concentrations and an elevated risk for LRTIs caused by different microorganisms (10,11). This study aimed to investigate the association between vitamin D levels and the severity and prognosis of LRTIs in paediatric patients who were hospitalised.

Material and Methods

Study Design and Patient Selection

This retrospective study was conducted at İstanbul Medeniyet University, Göztepe Training and Research Hospital. The medical records of 178 infants aged 1-24 months, hospitalized with LRTI between October 2017 and May 2019, were collected. The study included patients between 1 month and 24 months of age who were hospitalized with a diagnosis of LRTI. Patients had no known chronic disease or malnutrition, and vitamin D levels were tested within 15 days before the diagnosis or within one month afterward. Patients with a history of birth below 32 weeks, immunosuppression, malnutrition, a diagnosis of bronchopulmonary dysplasia, chronic congenital respiratory disease, known or newly diagnosed hemodynamically significant structural cardiac disease, neuromuscular disease, multiple recurrent wheezing episodes, and vitamin D-25(OH) levels above the intoxication limit (>100 ng/mL) were excluded. The study design is summarized in Figure 1.

Definition

A diagnosis of pneumonia was made based on a temperature of over 38 °C, the detection of infiltrates on chest radiography, and the presence of tachypnoea and respiratory distress (12). The diagnosis of bronchiolitis was made with wheezing and/or rales on auscultation, signs of increased respiratory effort such as tachypnea, retraction, and absence of infiltration on chest radiography (13). Patients with more than one recurrent wheezing episode were excluded from the study.

Levels of serum 25(OH) vitamin D below 12 ng/mL were classified as “vitamin D deficiency,” between 12 and 19.9 ng/mL as “vitamin D insufficiency,” and levels of serum 25(OH) vitamin D 20 ng/mL and above as “vitamin D sufficiency” (14).

Data Collection

Vitamin 25 (OH) D levels, Ca, P, ALP values, treatments received during hospitalization, length of hospitalization, need for pediatric intensive care unit (PICU), and length of ICU admission were recorded. If available, the polymerase chain reaction test results for nasopharyngeal swab samples were recorded. The Modified Wang Scoring System was used to determine the severity of the disease (15).

Demographic characteristics of all patients were recorded. Patient age, gender, weight, height, season of birth, birth week, birth weight, type of birth, family history of atopy and asthma, smoking exposure at home, current vitamin D use (use of vitamin D-containing preparations in the last 1 month), use of vitamin D prophylaxis (regular use of ≥400 U vitamin D for ≥6 months), diet for the first 6 months, age at transition to supplementary food, maternal educational status, home heating type, number of siblings, number of people living at home and number of bedrooms in the house were recorded. The ratio of the number of people living in the house to the number of rooms was used to define household crowding (16,17).

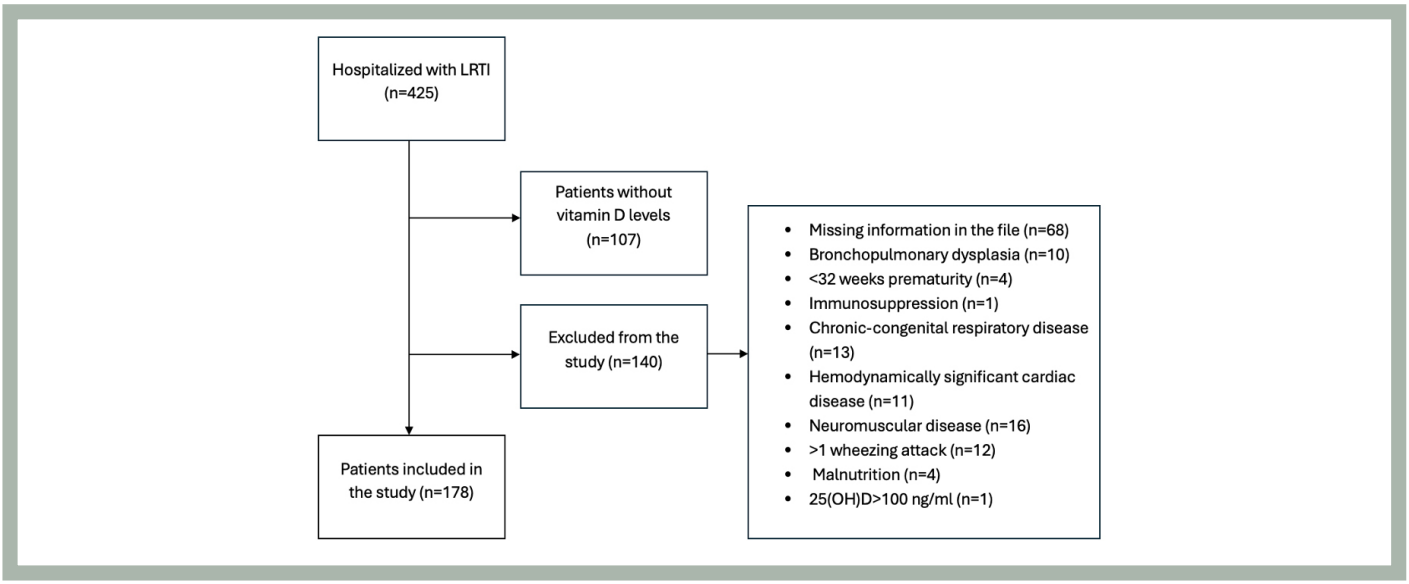

Figure 1. Design of the study
LRTI: Lower respiratory tract infection

Prior to study commencement, permission was received from the Ethics Committee of University of Health Sciences Turkey, İstanbul University Göztepe Training and Research Hospital (decision no: 2019/0255, date: 22.05.2019).

Serum 25 (OH) Vitamin D Level Measurement Technique

A 2 cc blood sample taken in a serum separator tube was measured with the Abbott Architect i2000 device using the Architect 25 (OH) vitamin D5P02 kit and chemiluminescence microparticle immunoassay method.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 17.0. The conformity of the variables to normal distribution was examined by histograms and the Kolmogorov-Smirnov test. Mean, standard deviation, median, and minimum-maximum values were used to present descriptive analyses. Nominal variables were compared with Pearson chi-square and Fisher's exact tests in univariate analyses. Logistic regression analysis was used for multivariate analysis. Mann-Whitney U test, was used for non-normally distributed (non-parametric) variables between two groups, and Kruskal-Wallis test, was used for comparing variables across more than two groups. Spearman's correlation test was used to analyze the relationships between the measured data variables. P values below 0.05 were considered statistically significant.

Outcome

The main aim of the study was to assess the relationship between serum vitamin D levels and the severity and prognosis of the disease.

Results

A total of 178 patients were included in our study: 113 boys (63.48%) and 65 girls (36.52%), aged between 1 and 24 months. The mean age of the patients was 7.53±6.36 months. Of these patients, 94 (53%) were hospitalised with pneumonia and 84 (47%) with bronchiolitis. During follow-up, 117 patients (66%) were managed with medical treatment, 49 patients (27%) required non-invasive mechanical ventilation (IMV), and 12 patients (7%) required IMV. Twenty-four patients (13%) required follow-up in the paediatric ICU. The mean length of stay in hospital was 6.86±4.2 days. For the 24 patients requiring PICU, it was 7.5±5.9 days. The mean 25(OH)D level was 26.53±12.14 ng/mL. None of the patients with vitamin D deficiency exhibited signs or symptoms of rickets and/or tetany.

In our study, when socio-demographic characteristics were examined according to vitamin D sufficiency status, no relationship was found between vitamin D deficiency and age, gender, mode of delivery, gestational week, birth weight, season of delivery, season of hospitalization, exposure to smoking, maternal educational status, heating type, and household crowding. 25 (OH) vitamin D levels were significantly higher ($p<0.001$) in those who were exclusively breastfed during the first 6 months compared to those who were not exclusively breastfed and both breastfed and formula-fed (Table 1).

When the relationship between vitamin D levels and patient characteristics was analyzed, the rate of vitamin D deficiency was higher in patients requiring PICU (25.00%) compared to those not requiring PICU (10.39%) ($p=0.047$).

Accordingly, the mean vitamin D level in patients requiring PICU (20.44±9.60 ng/mL) was lower than in patients not requiring PICU, (27.48±12.24 ng/mL) (p=0.01). When all patients were compared by treatment received, the rate of vitamin D deficiency was higher in patients receiving IMV (41.67%) compared to those receiving non-IMV (10.20%)

Table 1. Identify demographic characteristics, nutritional status, and vitamin D use factors that may impact vitamin D deficiency

		Deficiency (<12 ng/mL)		Insufficiency (12-20 ng/mL)		Sufficency (≥20 ng/mL)		p
		n	%	n	%	n	%	
Age (months)	<4	8	(11.11)	14	(19.44)	50	(69.44)	0.799
	≥4	14	(13.21)	17	(16.04)	75	(70.75)	
Gender	Male	13	(11.50)	14	(12.39)	86	(76.11)	0.056
	Female	9	(13.85)	17	(26.15)	39	(60.00)	
Type of birth	NSVD	9	(11.84)	10	(13.16)	57	(75.00)	0.378
	C/S	13	(12.87)	21	(20.79)	67	(66.34)	
Gestational age (week)	32-37	4	(12.90)	4	(12.90)	23	(74.19)	0.766
	>37	18	(12.24)	27	(18.37)	102	(69.39)	
Birth weight (gram)	<2500	2	(16.67)	2	(16.67)	8	(66.67)	0.105
	2500-3999	15	(9.93)	26	(17.22)	110	(72.85)	
	≥4000	5	(33.33)	3	(20.00)	7	(46.67)	
Season of birth	Winter	3	(6.25)	11	(22.92)	34	(70.83)	0.614
	Spring	3	(9.09)	5	(15.15)	25	(75.76)	
	Summer	7	(15.91)	7	(15.91)	30	(68.18)	
	Autumn	9	(16.98)	8	(15.09)	36	(67.92)	
Season of hospitalization	Winter	14	(11.76)	21	(17.65)	84	(70.59)	0.846
	Spring	3	(13.64)	3	(13.64)	16	(72.73)	
	Summer	1	(20.00)	2	(40.00)	2	(40.00)	
	Autumn	4	(12.50)	5	(15.63)	23	(71.88)	
Smoking exposure	No	18	(13.64)	21	(15.91)	93	(70.45)	0.511
	Yes	4	(8.70)	10	(21.74)	32	(69.57)	
Mother's educational status	Did not attend school	0	(0.00)	1	(14.29)	6	(85.71)	0.653
	Primary school	8	(14.29)	8	(14.29)	40	(71.43)	
	Secondary school	10	(16.95)	13	(22.03)	36	(61.02)	
	High school	2	(5.88)	6	(17.65)	26	(76.47)	
	College	2	(9.09)	3	(13.64)	17	(77.27)	
Way of heating	Natural gas	21	(13.91)	22	(14.57)	108	(71.52)	0.244
	Charcoal	1	(3.70)	9	(33.33)	17	(62.96)	
Person to bedroom ratio	≤1	9	(17.65)	7	(13.73)	35	(68.63)	0.235
	1-2	12	(13.19)	15	(16.48)	64	(70.33)	
	≥2	1	(2.78)	9	(25.00)	26	(72.22)	
Current use of vitamin D	No	20	(34.48)	19	(32.76)	19	(32.76)	**<0.001**
	Yes	2	(1.67)	12	(10.00)	106	(88.33)	
Vitamin D use in the first 6 months	No	14	(41.18)	13	(38.24)	7	(20.59)	**<0.001**
	Yes	8	(5.56)	18	(12.50)	118	(81.94)	
Nutrition for the first 6 months	Breast milk	18	(16.82)	27	(25.23)	62	(57.94)	**<0.001**
	Breast milk and formula	3	(4.92)	4	(6.56)	54	(88.52)	
	Baby formula	1	(10.00)	0	(0.00)	9	(90.00)	

NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section

and medical treatment (10.26%) (p=0.024). Patients were classified into two groups, mild-moderate and severe, based on the Wang score. When the mean vitamin D levels were analyzed, the mean 25 (OH) vitamin D level of the severe group (21.54±10.15 ng/mL) was found to be lower than that of the mild-moderate group (27.42±12.27 ng/mL) (p=0.021) (Table 2).

When the factors affecting intensive care needs, the Wang score and the need for oxygen support, were analysed using multivariable analysis, vitamin D deficiency was found to increase the need for intensive care by 4.74 times, [95% confidence interval (CI): 1.73-12.94], a severe Wang score by 4.32 times, (95% CI: 1.63-11.47) and the need for oxygen support by 2.48 times, (95% CI: 1.09-5.61) (Tables 3, 4 and 5).

Discussion

This study investigated how vitamin D deficiency influences the clinical progression of LRTIs in infants aged 1-24 months. The findings indicate that reduced serum 25(OH)D levels are significantly linked to a more severe disease trajectory, reflected in parameters such as the need for pediatric intensive care, oxygen supplementation, and longer hospitalization durations.

The inverse correlation observed between vitamin D levels and clinical severity, as measured by the Modified Wang Score, underscores this relationship. Children with severe LRTIs exhibited considerably lower serum vitamin D levels than those with mild to moderate disease (p=0.021). Notably, infants with vitamin D deficiency, showed a markedly higher

Table 2. **The disease characteristics and vitamin D levels**

		Deficiency (<12 ng/mL)		Insufficiency (12-20 ng/mL)		Sufficency (≥20 ng/mL)		p	Vitamin D (ng/mL)		p
		n	%	n	%	n	%		Mean	± SD	
Diagnosis	Pneumonia	13	(13.83)	19	(20.21)	62	(65.96)	0.415	25.45	11.78	0.380
	Bronchiolitis	9	(10.71)	12	(14.29)	63	(75.00)		27.74	12.48	
	Medical therapy	12	(10.26)	19	(16.24)	86	(73.50)		27.11	12.16	
Treatment	NIMV	5	(10.20)	11	(22.45)	33	(67.35)	**0.024**	26.54	11.92	0.345
	IMV	5	(41.67)	1	(8.33)	6	(50.00)		20.78	12.24	
Need for PICU	Yes	16	(10.39)	25	(16.23)	113	(73.38)	**0.047**	27.48	12.24	**0.010**
	No	6	(25.00)	6	(25.00)	12	(50.00)		20.44	9.60	
O_2 support needs	Yes	11	(10.19)	16	(14.81)	81	(75.00)	0.222	27.61	12.29	0.115
	No	11	(15.71)	15	(21.43)	44	(62.86)		24.86	11.79	
Wang score	Mild + moderate	16	(10.60)	24	(15.89)	111	(73.51)	0.069	27.42	12.27	**0.021**
	Severe	6	(22.22)	7	(25.93)	14	(51.85)		21.54	10.15	
Length of stay (day)	6	10	(9.17)	16	(14.68)	83	(76.15)	0.085	27.82	12.03	0.062
	>6	12	(17.39)	15	(21.74)	42	(60.87)		24.48	12.10	

IMV: Invasive mechanical ventilation, NIMV: Non-invasive machanical ventilation, PICU: Pediatric intensive care unit, SD: Standard deviation

Table 3. **Results of multivariate analysis of factors identified in univariate analysis as predictors of need for intensive care**

	β	SE	Wald	p	OR	95% confidence interval	
						Min	Max
Age (month)	-0.080	0.047	2.817	0.093	0.923	0.841	1.013
Male	1.361	0.605	5.054	**0.025**	3.900	1.191	12.775
Birth weight (>4000 gr)			9.651	**0.008**			
<2500 gr	3.298	1.276	6.679	**0.010**	27.046	2.218	329.745
2500-3999 gr	1.378	1.115	1.528	0.216	3.968	0.446	35.311
Vitamin D insuffiency (<20 ng/mL)	1.556	0.512	9.224	**0.002**	**4.742**	1.737	12.947

β: Beta coefficient, SE: Standard error, OR: Odd ratio, Min: Minimum, Max: Maximum

Table 4. **Results of multivariate analysis of factors identified in univariate analysis as predictors of Wang score**

	β	SE	Wald	p	OR	95% confidence interval	
						Min	Max
Age (month)	-0.049	0.041	1.401	0.237	0.952	0.878	1.033
Male	1.504	0.605	6.176	0.013	4.500	1.374	14.738
Family history	0.518	0.481	1.160	0.281	1.679	0.654	4.310
Birth weight (>4000 gr)			8.786	0.012			
<2500 gr	3.381	1.289	6.885	0.009	29.411	2.353	367.672
2500-3999 gr	1.649	1.121	2.167	0.141	5.204	0.579	46.787
Vitamin D insuffiency (<20 ng/mL)	1.465	0.497	8.668	0.003	4.326	1.632	11.470

β: Beta coefficient, SE: Standard error, OR: Odd ratio, Min: Minimum, Max: Maximum

Table 5. **Results of multivariate analysis of factors identified in univariate analysis as predictors of oxygen requirement**

	β	SE	Wald	p	OR	95% confidence interval	
						Min	Max
Age (month)	-0.069	0.030	5.194	**0.023**	0.934	0.880	0.990
Male	1.046	0.393	7.064	**0.008**	2.845	1.316	6.151
Family history	1.158	0.384	9.076	**0.003**	3.183	1.499	6.761
Birth weight (>4000 gr)			3.667	0.160			
<2500 gr	1.662	0.951	3.051	0.081	5.270	0.816	34.016
2500-3999 gr	1.235	0.698	3.132	0.077	3.437	0.876	13.492
Nutrition in the first 6 months - breastfed			3.500	0.174			
Breastfed & formula	-0.808	0.730	1.226	0.268	0.446	0.107	1.864
Formula	-1.301	0.754	2.976	0.085	0.272	0.062	1.194
Vitamin D insuffiency (<20 ng/mL)	0.909	0.417	4.756	**0.029**	**2.482**	1.096	5.619

β: Beta coefficient, SE: Standard error, OR: Odd ratio, Min: Minimum, Max: Maximum

probability of requiring intensive care (OR: 4.74, 95% CI: 1.73-12.94) and respiratory support (OR: 2.74, 95% CI: 1.30-5.96). These observations reinforce the role of vitamin D as an immunomodulatory agent in pediatric respiratory pathology and align with prior literature findings (17,18,19).

Vitamin D is known to activate innate immune responses by upregulating antimicrobial peptides such as cathelicidins and β-defensins (3,4). It further supports immune function by preserving epithelial barrier integrity and modulating inflammation. In our cohort, these immunological mechanisms may underlie the increased disease severity observed in vitamin D-deficient patients. Previous research has similarly demonstrated associations between lower vitamin D concentrations and increased incidence and severity of pneumonia, bronchiolitis, and other LRTIs (6,7,8), which our study corroborates.

Several published studies report heightened susceptibility to viral and bacterial respiratory pathogens among individuals with deficient vitamin D status. For instance, Ginde et al. (6) established a connection between reduced vitamin D levels and increased respiratory infection vulnerability. McNally et al. (17) identified higher deficiency rates in infants with severe bronchiolitis. Likewise, Ganmaa et al. (10) observed that vitamin D supplementation may alleviate infection severity. Our findings support the concept that that deficiency is not only linked to clinical severity but also that sufficient levels may have a protective, preventive role.

Given these outcomes, maintaining adequate vitamin D levels during infancy and early childhood emerges as a crucial strategy to mitigate LRTI-related morbidity. This is particularly pertinent for high-risk groups, including premature infants and those with recurrent infections or chronic conditions.

Regular monitoring and timely supplementation in these populations should be encouraged (11,17). On a broader scale, implementing universal vitamin D prophylaxis in early life may carry public health benefits (10).

Study Limitations

This study is not without limitations. Its retrospective nature limits the capacity to establish causality definitively. Furthermore, potentially confounding variables such as nutritional patterns, sunlight exposure, and genetic predispositions could not be comprehensively assessed. Additionally, as data were derived from a single center, results may not be generalizable to other regions. Larger, multicentric prospective studies are necessary to elucidate these associations more clearly and strengthen the evidence base regarding vitamin D's role in LRTI outcomes.

Conclusion

This study demonstrates a meaningful association between vitamin D deficiency and increased severity of LRTIs among hospitalized infants. Our results indicate that insufficient vitamin D levels correlate with greater need for intensive care, elevated respiratory support demands, and a more severe disease presentation. These outcomes underscore the immunoregulatory function of vitamin D and support the view that its deficiency represents a potentially modifiable contributor to the progression of LRTIs.

Maintaining sufficient vitamin D levels, especially within vulnerable pediatric populations, may serve as an effective preventive measure to reduce the morbidity burden related to LRTIs. Nevertheless, due to the retrospective nature of this research and its inherent limitations, future large-scale and prospective studies are essential to confirm these associations and further evaluate the therapeutic utility of vitamin D supplementation in clinical settings.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul University Göztepe Training and Research Hospital (decision no: 2019/0255, date: 22.05.2019).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.K., Concept: D.K., Design: D.K., Data Collection or Processing: D.K., Analysis or Interpretation: D.K., A.K., Literature Search: D.K., A.K., Writing: D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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