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Study on correlation between Vitamin D status and proinflammatory cytokines in children with RSV bronchiolitis

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Abstract

The objective of our study was to evaluate vitamin D status and serum levels of C-reactive protein (CRP) alongside the proinflammatory cytokines IL-1β, IL-6, and TNF-α, in order to investigate their correlation with the incidence and severity of acute RSV bronchiolitis in children. The study included 39 children, aged 1 month to 2 years, divided into two subgroups: children with acute RSV bronchiolitis (n=20) and a control group of healthy children (n=19). No significant difference in vitamin D status was found between the patient and control groups. The patient group exhibited elevated levels of IL-1β and TNF-α compared to healthy children, while IL-6 levels did not differ significantly between the two groups. Correlation analysis demonstrated a positive, statistically significant association between IL-6 and TNF-α. However, no statistically significant correlations were observed between the severity of broncho obstructive syndrome and other indicators, including 25(OH)D, parathyroid hormone (PTH), IL-1β, IL-6, TNF-α, and CRP. Furthermore, no correlation was found between vitamin D levels and any of the cytokines. These findings suggest that while inflammatory markers may play a role in RSV bronchiolitis, vitamin D status does not appear to be a contributing factor to the incidence or severity of the disease in the pediatric population studied.

Keywords: RSV; Bronchiolitis; Vitamin D; Proinflammatory cytokines

1. Introduction

Lower respiratory tract infections continue to be a major cause of illness and death among children under 5 years of age globally [1,2]. In this demographic, human respiratory syncytial virus (RSV) is the most frequently identified pathogen, known for causing bronchiolitis, which is the primary reason for hospitalization in infants under one year old in developed countries [3-6]. The clinical presentation of acute bronchiolitis can vary significantly in severity, characterized by broncho-obstructive symptoms such as wheezing, cough, tachypnea, chest retractions, prolonged expiration, and bronchiolar inflammation. This spectrum can range from mild respiratory distress to severe respiratory failure [7,8]. In this context, the immune system plays a crucial role in regulating the body's response to viral pathogens, which influences the severity of the disease. Therefore, modulating the antiviral immune response in the respiratory tract is essential for improving clinical outcomes. Recent studies have emphasized that vitamin D may play a pivotal role in enhancing this immune response, highlighting its significance in respiratory viral infections. [9].

Vitamin D is a fat-soluble steroid primarily recognized for its vital role in preventing rickets in children by regulating calcium and phosphorus levels in the body. Current understanding has revealed that its active metabolite, 1,25(OH)D (calcitriol), can also be synthesized in peripheral (non-renal) tissues. Immune cells, in particular, express vitamin D

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receptors, which allow vitamin D to bind and influence the regulation of both adaptive and innate immune responses, thereby reducing inflammatory processes. [10]. A notable example of this regulatory function is the ability of vitamin D to inhibit T cell activation in both in vitro and in vivo settings, along with its effect on reducing the monocyte production of pro-inflammatory cytokines, including IL-1, IL-6 and TNF-α [11-13]. Several studies have investigated the presence of the aforementioned pro-inflammatory cytokines in the airways of children with RSV bronchiolitis, confirming their significant role and the correlation between elevated serum concentrations and disease severity. Furthermore, some research highlights interactions among these cytokines, particularly noting that IL-1 and TNF-α can stimulate the production of IL-6, while IL-6 exerts an inhibitory effect on both TNF-α and IL-1. [14,15]

These findings highlight the critical role of vitamin D status in the pathogenesis and progression of acute bronchiolitis. However, the literature presents conflicting reports; while some studies indicate that children with RSV bronchiolitis have low vitamin D levels, others suggest the opposite. [16]

In light of this, our study seeks to address these inconsistencies and contribute to the development of future therapeutic strategies for managing this condition

2. Material and methods

A prospective clinical study was carried out at the University Hospital 'Dr. G. Stranski' in Pleven, within the Department of Pediatrics. The study involved 39 children, divided into two subgroups: those with acute RSV bronchiolitis (n=20) and a control group of healthy children (n=19). Inclusion criteria encompassed children aged 1 month to 2 years who were hospitalized with acute bronchiolitis and tested positive for RSV. Exclusion criteria included children within the same age range who had other acute or chronic respiratory infections, as well as those with acute bronchiolitis who tested negative for RSV.

RSV detection in nasal swabs was conducted using Real-Time RT-PCR (Reverse Transcription Polymerase Chain Reaction). Serum levels of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, were measured via Enzyme-Linked Immunosorbent Assay (ELISA) on a Stat Fax 2100 Microplate Reader. Serum 25(OH) Vitamin D3 levels were analyzed with an electrochemiluminescent immunoassay on the Roche Cobas e411 immunological analyzer, and C-reactive protein (CRP) levels were quantified via immunoturbidimetry. The clinical severity of bronchiolitis was assessed using the Respiratory Syncytial Virus Network (ReSVinet) Scale, ranging from 0 to 20 points [17]. Serum vitamin D reference values followed the criteria of the Bulgarian Society of Endocrinology, with deficiency defined as <25 nmol/L, insufficiency as 25-50 nmol/L, and sufficiency as 50-120 nmol/L. All measurements were taken on the day of hospital admission.

The study received approval from the Ethics Commission at the Medical University – Pleven (Approval Code: 694, Approval Date: May 31, 2022; Approval Code: 695, Approval Date: June 3, 2022), and informed consent for clinical trials was obtained from the parents or guardians of all included patients.

In the statistical analysis, IBM SPSS Statistics v.26.0 for Windows and Microsoft Office Excel 2019 were used. Descriptive statistics summarized the sociodemographic and clinical characteristics of the patients. For qualitative variables, we conducted frequency analysis, presenting data as absolute and relative frequencies (number and %). Quantitative variables with a normal distribution were reported as mean ± standard deviation (Mean ± SD), while skewed data were summarized as median (Me) and interquartile range (IQR). The Kolmogorov-Smirnov test assessed normality of quantitative variables. Differences between groups were evaluated using the non-parametric $\chi 2$ test and the Mann-Whitney U test, with statistical significance set at a p-value < 0.05. Correlations were analyzed using Spearman's rank correlation coefficient (Spearman's rho, rs), the non-parametric equivalent of Pearson's coefficient, with significance considered at the 0.05 level (2-tailed).

3. Results

A total of 39 children were enrolled in the study, including 12 girls (30.8%) and 27 boys (69.2%). The mean age of the study population was 6.5 ± 5.072 months. Our analysis identified statistically significant differences between the patient and control groups in the following variables: weight (U=113.500, N=39, z=-2.155, p=0.030); PTH (U=303.000, N=39, z=3.176, p=0.001); IL-1β (t=2.155, df=37, p=0.038); and TNF-α (U=323.500, N=39, p=0.000). No statistically significant differences were observed between the groups for age (U=147.000, N=39, z=-1.216, p=0.235); height (U=124.000, N=39, z=-1.858, p=0.065); IL-6 (U=238.500, N=39, z=1.363, p=0.175); or 25OHD (t=0.713, df=36.693, p=0.480).

The descriptive statistics for patient demographic and clinical characteristics are presented in Table 1.

Table 1 Descriptive statistics of patient demographic and clinical characteristics

Indicators	**Sick (n=20)**	**Healthy (n=19)**	**Total(n=39)**
DEMOGRAPHIC CHARACTERISTICS			
Gender (%, number)			
Female	4 (20.0%)	8 (42.1%)	12 (30.8%)
Male	16 (80.0%)	11 (57.9%)	27 (69.2%)
Age – months (Mean±SD; Me, IQR)	7.15±4.891 6, 7	5.79±5.298 4, 5	6.5±5.072 5, 5
Height – sm (Mean±SD; Me, IQR)	63.6±7.755 63, 9	59.5±8.585 56, 7	61.6±8.321 60, 11
Weight – kg (Mean±SD; Me, IQR)	7.6±2.428 7, 4.1	6.132±1.572 6, 2.2	6.885±2.161 6.5, 2.5
CLINICAL CHARACTERISTICS			
Diagnosis (%, number) RSV Bronchiolitis	20 (100.0%)	-	20 (51.3%)
25OHD (Mean±SD; Me, IQR)	125.6±58.847	111.9±61.183	118.9±59.606
	129.85, 52.23	96.8, 84.75	117.10, 80.71
PTH (Mean±SD; Me, IQR)	8.6±8.053	23.0±18.632	15.6±15.816
	4.23, 15.68	18.01, 12.13	15.53, 17.57
IL-1-b (Mean±SD; Me, IQR)	11.0±1.712	8.9±3.832	10.0±3.079
	10.70, 1.70	8.40, 4.46	10.3, 2.8
IL-6 (Mean±SD; Me, IQR)	7.9±7.859	21.5±36.760	14.5±26.817
	4.30, 1.83	12.60, 19.07	5.65, 16.31
TNF-α (Mean±SD; Me, IQR)	1.5±0.285	2.8±2.158	2.1±1.642
	1.54, 0.43	1.88, 0.60	1.65, 0.52

The following findings emerged from comparing serum 25(OH)D levels between children with RSV bronchiolitis and healthy controls: 15% of children with RSV had vitamin D insufficiency, compared to 10.5% in the healthy group. The difference in deficiency levels was minimal, with 5% in the RSV group and 5.3% in the healthy group. Vitamin D sufficiency was more common among healthy children, observed in 47.4% compared to 25% in the RSV group. Interestingly, hypervitaminosis was higher in the RSV group, with 55% affected, compared to 36.8% in the healthy group. These results are presented in Figure 1.

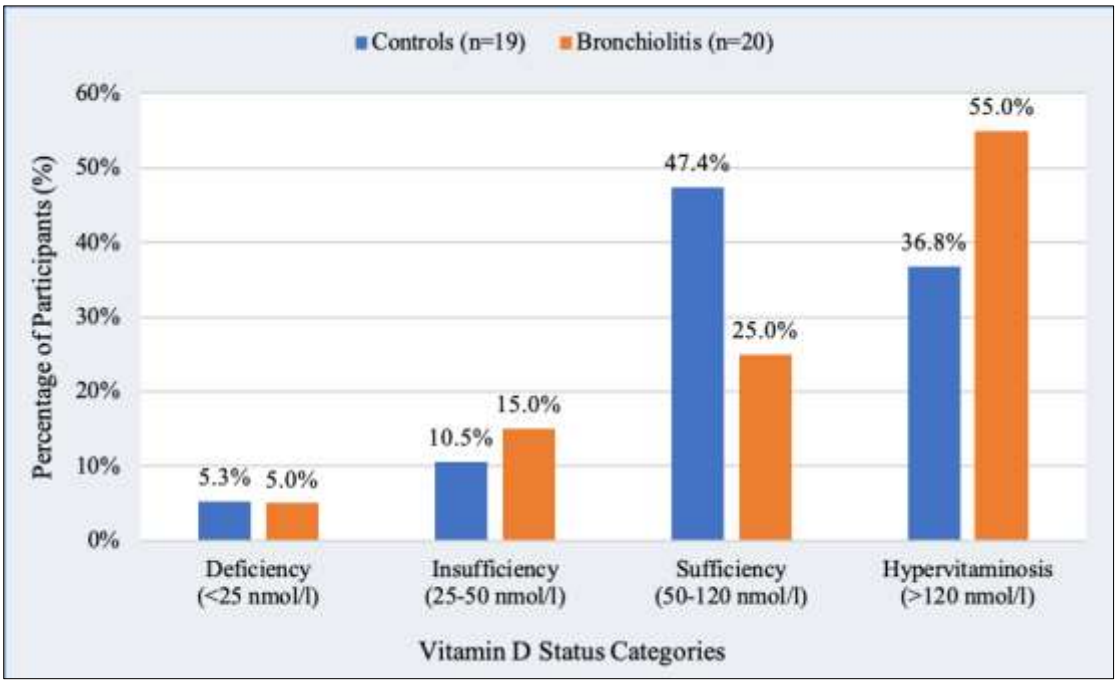

Figure 1 Vitamin D status in children with respiratory syncytial virus (RSV) compared to healthy controls

Regarding the clinical severity of acute RSV bronchiolitis, as assessed by the ReSVinet score, our study found that among the 20 children with bronchiolitis, 2 (10%) had severe RSV bronchiolitis, 6 (30%) had mild RSV bronchiolitis, and 12 (60%) had moderate RSV bronchiolitis. The results are presented in Figure 2.

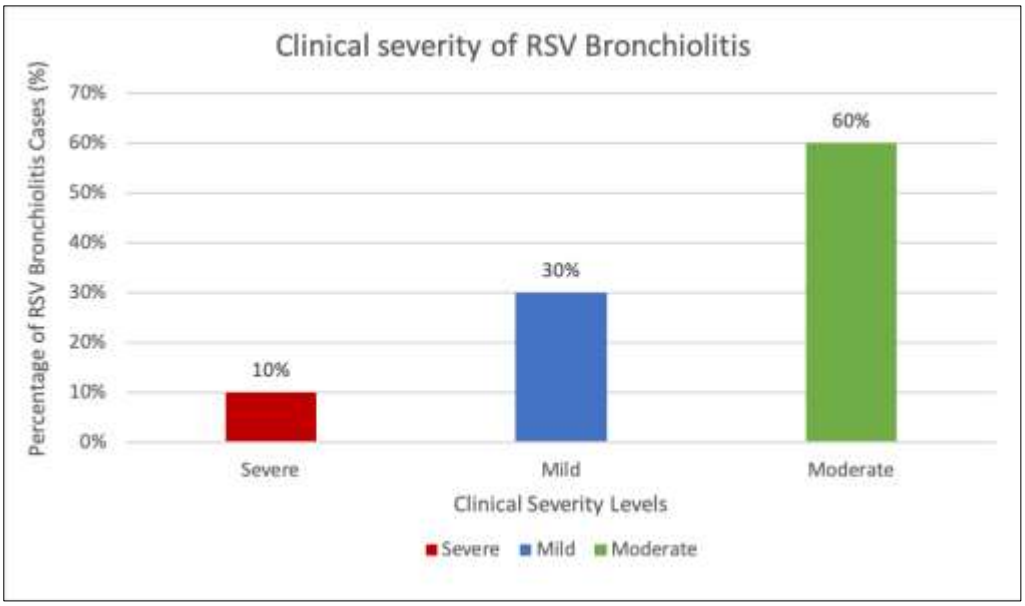

Figure 2 Distribution of clinical severity of RSV bronchiolitis among children

Correlation analysis revealed no statistically significant relationship between 25(OH)D and IL-1β, IL-6, or TNF-α levels in children with RSV. However, a statistically significant positive correlation was observed between IL-6 and TNF-α levels (r_s=0.554, N=20, p=0.013), indicating that as IL-6 levels increase, TNF-α levels also rise. These results are presented in Table 2 and Figure 3.

Table 2 Correlations between 25OHD, IL-1-b, IL-6 and TNF-α in RSV children

		25OHD	**IL-1-b**	**IL-6**	**TNF-α**
25OHD	Spearman's rho	1.000	0.148	-0.84	-0.235
	Sig. (2-tailed)	0.000	0.533	0.094	0.318
	N	20	20	20	20
IL-1-b	Spearman's rho	0.148	1.000	0.180	0.403
	Sig. (2-tailed)	0.533	0.000	0.447	0.078
	N	20	20	20	20
IL-6	Spearman's rho	-0.384	0.180	1.000	0.544*
	Sig. (2-tailed)	0.094	0.447	0.000	0.013
	N	20	20	20	20
TNF-α	Spearman's rho	-0.235	0.403	0.544*	1.000
	Sig. (2-tailed)	0.318	0.078	0.013	0.000
	N	20	20	20	20
*. Correlation is significant at the 0.05 level (2-tailed).					

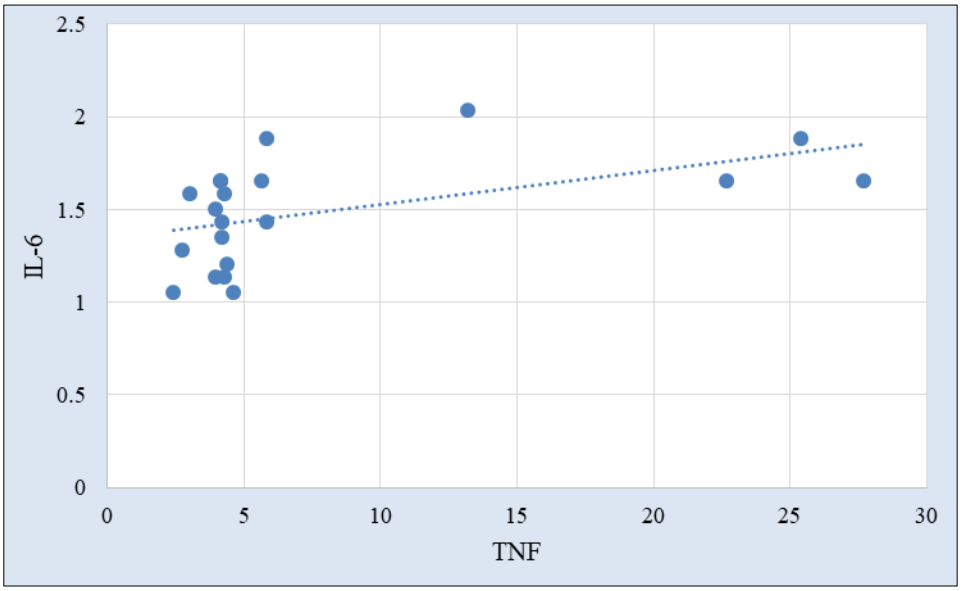

Figure 3 Scatter plot showing the correlation between IL-6 and TNF-α levels in patients with RSV.

No correlation was found between CRP and the following indicators (Table 3): 25(OH)D (rs= -0.170, N=38, p=0.308); IL-1β (rs= 0.159, N=38, p=0.319); IL-6 (rs= -0.081, N=38, p=0.629); TNF-α (rs= -0.051, N=38, p=0.760).

Table 3 Correlations between CRP and 25(OH)D, Il-1β, Il-6, and TNF-α in the full study cohort (RSV and control group)

Correlations							
			CRP	**25OHD**	**IL-1-b**	**IL-6**	**TNF-α**
Spearman's rho	CRP	Correlation Coeff.	1,000	-0.170	0.159	-0.081	-0.051
		Sig. (2-tailed)	0.000	0.308	0.341	0.629	0.760
		N	38	38	38	38	38
	25OHD	Correlation Coeff.	-0.170	1,000	0.341*	0.109	0.304
		Sig. (2-tailed)	0.308	0.000	0.034	0.510	0.060
		N	38	39	39	39	39
	IL-1-b	Correlation Coeff.	0.159	0.341*	1,000	-0.092	-0.083
		Sig. (2-tailed)	0.341	0.034	0.000	0.577	0.615
		N	38	39	39	39	39
	IL-6	Correlation Coeff.	-0.081	-0.109	-0.092	1,000	0.511**
		Sig. (2-tailed)	0.629	0.510	0.577	0.000	0.001
		N	38	39	39	39	39
	TNF-a	Correlation Coeff.	-0.051	-0.304	-0.083	0.511**	1.000
		Sig. (2-tailed)	0.760	0.060	0.615	001	0.000
		N	38	39	39	39	39

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

No statistically significant correlation was observed between the severity of RSV bronchiolitis and the following indicators: 25(OH)D, PTH, IL-1β, IL-6, TNF-α, and CRP (Table 4).

Table 4 Correlations between the severity of RSV bronchiolitis and 25(OH)D, PTH, IL-1β, IL-6, TNF-α, and CRP

Correlations									
			Severity of RSV	**25OHD**	**ПТХ**	**IL-1-b**	**IL-6**	**TNF-a**	**CRP**
Spearman's rho	Severity of BOS	Correlation Coeff.	1.000	0.136	0.005	0.264	0.146	0.149	0.002
		Sig. (2-tailed)	0.000	0.566	0.983	0.261	0.538	0.530	0.993
		N	20	20	20	20	20	20	19
	25OHD	Correlation Coeff.	0.136	1.000	-0.321*	0.341*	-0.109	-0.304	-0.170
		Sig. (2-tailed)	0.566	0.000	0.047	0.034	0.510	0.060	0.308
		N	20	39	39	39	39	39	38
	ПТХ	Correlation Coeff.	0.005	-0.321*	1.000	-0.241	0.109	0.463**	-0.118
		Sig. (2-tailed)	0.983	0.047	0.000	0.139	0.507	0.003	0.480
		N	20	39	39	39	39	39	38
	IL-1-b	Correlation Coeff.	0.264	0.341*	-0.241	1.000	-0.092	-0.083	0.159

		Sig. (2-tailed)	0.261	0.034	0.139	0.000	0.577	0.615	0.341
		N	20	39	39	39	39	39	38
	IL-6	Correlation Coeff.	0.146	-0.109	0.109	-0.092	1.000	0.511**	-0.081
		Sig. (2-tailed)	0.538	0.510	0.507	0.577	0.000	0.001	0.629
		N	20	39	39	39	39	39	38
	TNF-a	Correlation Coeff.	0.149	-0.304	0.463**	-0.083	0.511**	1.000	-0.051
		Sig. (2-tailed)	0.530	0.060	0.003	0.615	0.001	0.000	0.760
		N	20	39	39	39	39	39	38
	CRP	Correlation Coeff.	0.002	-0.170	-0.	0.159	-0.081	-0.051	1.000
		Sig. (2-tailed)	0.993	0.308	0.005	0.341	0.629	0.760	0.000
		N	19	38	0.983	38	38	38	38

*. Correlation is significant at the 0.05 level (2-tailed).; **. Correlation is significant at the 0.01 level (2-tailed).

4. Discussion

The implications of vitamin D deficiency have been a longstanding area of scientific inquiry. In recent years, researchers have gained a deeper understanding of the immunomodulatory effects of active vitamin D, particularly its local synthesis in the lungs, immune system cells, and various extrarenal tissues. [18]. A wealth of studies has investigated the relationship between vitamin D status and respiratory infections. Notably, children hospitalized with bronchiolitis have been found to have significantly lower vitamin D levels. However, some researchers have reported no such differences in their findings [19-21].

In our study, 55% of children with acute bronchiolitis exhibited hypervitaminosis D, defined by the Bulgarian Endocrinology Society as vitamin D levels exceeding 120 nmol/L. In contrast, only 15% of these children were found to have insufficient levels (less than 50 nmol/L), while 5% were classified as deficient (less than 25 nmol/L). Notably, the percentages observed in the control group were similar, with 36.8% exhibiting hypervitaminosis D, 10.5% classified as insufficient, and 5.3% as deficient. Consequently, no statistically significant differences in vitamin D levels were found between the case and control groups, nor between vitamin D levels and the severity of acute bronchiolitis.

These findings are partially consistent with research conducted in Tashkent in 2022, which reported that 51.28% of acute bronchiolitis patients had sufficient vitamin D levels (defined as >75 nmol/L), while 20.51% were insufficient (vitamin D levels between 52.5 and 72.5 nmol/L) and 28.2% were deficient (vitamin D <50 nmol/L). This Tashkent study also found no correlation between vitamin D levels and the severity of acute bronchiolitis; however, it did not examine the viral pathogens present in the study group.[22]. In another study conducted in Turkey, 52.2% of children with acute bronchiolitis were found to have normal vitamin D levels (greater than 50 nmol/L), and a higher percentage than that observed in our study for vitamin D insufficiency (29.7% with levels between 30 and 50 nmol/L) and deficiency (18% with levels less than 30 nmol/L). However, in contrast to our findings and those from the Tashkent study, the Turkish research reported a statistically significant association between vitamin D insufficiency or deficiency and severe bronchiolitis [23]. In contrast to our findings, a study conducted in China in 2023 reported a statistically significant difference in vitamin D levels between children with RSV acute respiratory infections and healthy controls. [24]. Additionaly, recent research from 2024 suggests that infants with insufficient vitamin D levels (less than 50 nmol/L) exhibited more severe cases of RSV bronchiolitis.

Our study assessed the levels of proinflammatory cytokines IL-1β, IL-6, and TNF-α. We found a statistically significant difference in the serum levels of IL-1β and TNF-α between the case and control groups, whereas no significant difference was detected in IL-6 levels. Furthermore, a positive correlation was observed between IL-6 and TNF-α levels, suggesting that an increase in IL-6 is associated with a rise in TNF-α levels. Similar studies investigating cytokine levels in RSV patients conducted between 1986 and 2001 reported elevated serum levels of IL-6, IL-1, and TNF-α in affected children, correlating with the severity of RSV infection. Notably, the most recent study from 2001 implicated only IL-1 in relation to the chemokine RANTES as a factor associated with the severity of the disease [25]. Unfortunately, we were unable to

find any recent studies addressing this topic, including research on the correlation between vitamin D levels and proinflammatory cytokines in the context of RSV bronchiolitis in children.

Lastly, our study has several limitations. We were unable to obtain accurate information regarding the current vitamin D supplementation among the included patients, as many of them came from low socioeconomic backgrounds. Additionally, in Bulgaria, there is an ongoing vitamin D prophylaxis program during the first year of life. Another limitation is the small sample size of children in both the control and case groups, which was constrained by the fact that this research was part of a scientific project with limited financial support.

5. Conclusion

In conclusion, our study highlights the complex relationship between vitamin D levels and proinflammatory cytokines in children with acute bronchiolitis. We found a significant prevalence of hypervitaminosis D among the patient population, alongside notable differences in cytokine levels, specifically IL-1β and TNF-α, when compared to healthy controls. While previous research has shown associations between elevated cytokine levels and the severity of RSV bronchiolitis, our findings did not reveal a significant correlation between vitamin D levels and the severity of the disease. Additionally, we noted a lack of recent studies addressing the interplay between vitamin D and proinflammatory cytokines in this context. Future research is needed to further elucidate these relationships and their implications for the management of RSV bronchiolitis in children.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest or competing interests regarding the publication of this manuscript. This statement includes any affiliations, financial arrangements, or products mentioned in the manuscript that may influence the outcomes of the study presented.

Statement of informed consent

Informed consent was obtained from the parents or guardians of all included patients

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