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Original article

Diagnostic value of cytokine profiles in children with atopic bronchial asthma and concurrent vitamin D deficiency

Naila Sultanova[1], Aytan Jafarova[1], Rana Karimova[2], Mushfig Orujov[3], Ismail Gafarov[4]

[1]II Department of Pediatric Diseases, Azerbaijan Medical University, Baku, Azerbaijan; [2]Scientific Research Center, Azerbaijan Medical University, Baku, Azerbaijan; [3]Department of Pathological Anatomy, Azerbaijan Medical University, Baku, Azerbaijan; [4]Department of Medical and Biological Physics, Azerbaijan Medical University, Baku, Azerbaijan

Abstract. *Background:* Atopic bronchial asthma in children is often associated with immune dysregulation and altered cytokine profiles. Identifying reliable biomarkers for early diagnosis and assessment of disease severity remains a clinical priority. *Objective:* To assess the sensitivity and specificity of cytokines against the background of vitamin D deficiency in children with atopic bronchial asthma. Methods: A total of 85 children (59 boys, 26 girls) aged 4-17 years with atopic bronchial asthma were monitored at two medical centers in Baku. Inclusion criteria required a minimum disease duration of two years and a history of recurrent asthma attacks. Data were collected retrospectively from medical records. The control group consisted of 20 healthy children (12 boys, 8 girls). Sample sizes for both groups were calculated using the formula: $n = (t^2\ \sigma^2) / \delta^2$ to ensure adequate statistical power. *Results:* The general diagnostic values (GDV) were: IL-2 – 93.8 ± 3.0%, IL-13 – 90.6±3.6%, and IL-17 – 95.3±2.6%. The diagnostic accuracy of both positive and negative test results was evaluated, with positive results rated as 'excellent' and negative results as 'good' for these cytokines. A significant positive correlation was found between vitamin D deficiency and IL-2, while IL-13 and IL-17 showed negative correlations with vitamin D in the patient group. Levels of pro-inflammatory cytokines IL-13 and IL-17 were significantly higher in children with bronchial asthma compared to controls ($p < 0.01$). Specifically, mean serum IL-13 concentration was 13.8 ± 0.8 pg/ml in patients versus 5.3 ± 0.7 pg/ml in controls. While the correlations between vitamin D levels and cytokines (IL-2, IL-13, IL-17) were statistically significant, their moderate strength suggests the possible influence of additional contributing factors. *Conclusion:* Significant correlations between vitamin D status and cytokine levels highlight the potential of IL-2, IL-13, and IL-17 as biomarkers of disease severity and therapeutic targeting. These results suggest that routine assessment and correction of vitamin D deficiency should be considered an integral part of childhood asthma management. (www.actabiomedica.it)

Key words: Atopic bronchial asthma, Children, Vitamin D Deficiency, Cytokines, Interleukin

Introduction

Bronchial asthma ranks among the most prevalent chronic allergic diseases worldwide, affecting people of all ages. Its incidence varies significantly by country, with an estimated 350 million individuals living with the condition globally (1-3). Reported prevalence rates range from 4–5% in the United States, 9% in Russia, 4-7% across European countries, to 13.4% in Japan (4).

Current understanding explains the morphological basis of bronchial asthma as the accumulation of eosinophils in the bronchial mucosa following mast cell degranulation. This process elevates the production of allergic inflammatory mediators such as histamine and serotonin, which trigger bronchial hyperreactivity and

obstruction (5, 6). The disease involves interactions between respiratory system cells and tissues, along with allergic inflammatory mediators driving the inflammatory process (7, 8).

This inflammation causes acute bronchospasm and structural changes in the respiratory tract, pushing the disease towards a chronic state. As a result, asthma contributes to disability in children, lowers their quality of life, and imposes economic burdens on families and society (2, 9, 10).

Moreover, cytokines produced by various cell types play a key role in the allergic inflammatory responses underlying bronchial asthma (11, 12). Cytokines are proteins that act effectively at picomolar concentrations. Unlike hormones, which maintain stable homeostasis, cytokines respond to foreign substances and can trigger immune system damage, inflammation, as well as repair and regeneration processes (13). Because cytokine cascades in blood serum vary with asthma severity, they remain a key focus in allergology and pediatrics. Many children with atopic bronchial asthma also carry additional risk factors that complicate disease control (14). Research concludes that the disease involves interactions among respiratory cells, allergic inflammatory mediators, and other markers (15-17).

Recent advances have explored the molecular effects of vitamin D—one such marker—on apoptosis, and on immune, cardiovascular, reproductive, and other systems (2, 12, 18). Researchers at the University of Pennsylvania, USA, report that vitamin D receptors (VDR) in lymphocytes promote Th2 cell proliferation and stimulate synthesis of interleukins such as IL-13, IL-17, IL-10, and IL-4. Vitamin D suppresses neutrophilic inflammation in the bronchial mucosa by blocking T-helper cell differentiation into the Th-17 subpopulation, reducing asthma severity (14, 19). Hence, vitamin D's role in immune regulation makes it a significant factor influencing asthma severity (20- 22).

Several studies document lower serum vitamin D levels in bronchial asthma patients compared to healthy controls, indicating a possible role in disease susceptibility and progression. However, results vary, especially between pediatric and adult populations. Vitamin D deficiency seems more common in children with asthma, although geographic, lifestyle, and seasonal factors cause variability (23, 24). These findings support the hypothesis that vitamin D status may represent an important modifiable factor in managing bronchial asthma, especially in children.

Despite increasing recognition of vitamin D's role in immune function, the specific relationship between vitamin D deficiency and cytokine imbalance in pediatric atopic bronchial asthma has not been sufficiently investigated.

This study aims to assess the association between serum vitamin D levels and cytokine profiles (IL-2, IL-13, and IL-17) in children with atopic asthma, to explore their potential as biomarkers for disease severity and to inform future immunomodulatory treatment strategies.

The aim of the study is to evaluate the sensitivity and specificity of cytokines against the background of vitamin D deficiency in children with atopic bronchial asthma.

Materials and Methods

A total of 85 children [59 boys (69.4%) and 26 girls (30.6%)] aged 4 to 17 years with atopic bronchial asthma were monitored at the Children's Clinical Hospital No. 6 in Baku and the Educational-Therapeutic Hospital of the Azerbaijan Medical University. All patients had a history of recurrent asthma attacks, and only those with a disease duration of at least two years were included, based on the study's inclusion criteria. Data were obtained through a retrospective review of medical records. Children with bronchial asthma included in the study were selected according to the following criteria. They had persistent mild to moderate atopic bronchial asthma. The diagnosis of bronchial asthma was confirmed based on functional pulmonary tests. Atopic bronchial asthma was further confirmed by elevated total serum IgE levels and positive allergen-specific IgE test results. A total of 20 healthy children, comprising 12 boys (60.0%) and 8 girls (40.0%), were incorporated into the control group.

Children with bronchial asthma were excluded from the study based on the following criteria. Patients with severe persistent atopic bronchial asthma were excluded. Those who had received vitamin D or

any multivitamin complexes within the last 6 months prior to examination were also excluded. Children with chronic somatic diseases were excluded. Patients with bone system pathologies were excluded as well. Additionally, any children who had experienced bone fractures within 12 months prior to the start of the study were excluded. Children included in the control group were selected based on the following criteria. Their age range was between 6 and 17 years. Bronchial asthma diagnosis was excluded. There was no history of allergic diseases in their medical records. No bone system pathology was present. Total IgE levels were below 100 IU/ml.

The total sample size for the control group and the group of patients with bronchial asthma was determined based on the calculation of the minimum required sample size using the following formula: $n = \frac{t^2 s^2}{d^2}$.

The concentration of 25(OH)D3 in the blood serum was determined by the enzyme immunoassay method on a Roche Diagnostics analyzer (manufactured in Germany). To study the role of vitamin D metabolism in the regulation of inflammatory processes in atopic bronchial asthma, serum levels of the most important cytokines involved in the pathogenesis of this disease were analyzed. In the study participants, the levels of interleukin 2 (IL-2), interleukin 13 (IL-13), and interleukin 17 (IL-17) were measured using solid-phase enzyme immunoassay with commercial IFA-Best test systems manufactured by Vector Best JSC (Russia).

The data were analyzed using variance analysis (Mann-Whitney U), Spearman correlation, ROC analysis, and Evidence-Based Medicine methods, with calculations done in EXCEL-2016 and SPSS-22. Results were considered statistically significant at $p < 0.05$.

Results

The assessment of vitamin D levels was conducted using specific criteria: a concentration of 25(OH) D3 between 30 and 100 ng/ml is classified as normal, 20 to 29 ng/ml indicates a mild deficiency, 10 to 19 ng/ml signifies a moderate deficiency, and levels below 10 ng/ml are indicative of a severe deficiency in vitamin D (25, 26). Vitamin D levels were at the lower threshold of the normal range in 7 out of 85 children. Severe vitamin D deficiency was observed in 21 patients (24.7%), moderate deficiency in 34 patients (40%), and mild deficiency in 23 patients (27.1%). Vitamin D deficiency was present in one individual in the control group.

The average concentration of vitamin D in children diagnosed with bronchial asthma was found to be 17.4±0.9 ng/ml, whereas the control group exhibited a mean level of 45.3±2.2 ng/ml. The mean vitamin D concentration in children with asthma was 17.4 ± 0.9 ng/ml, significantly lower than that of the control group (45.3 ± 2.2 ng/ml, $p < 0.001$; Figure 1).

The study further examined the cytokine profile characteristics in children suffering from atopic bronchial asthma alongside vitamin D deficiency. When analyzing the amount of cytokines in the blood serum of children with bronchial asthma, significant differences were found compared to the indicators of children in the control group. The analysis of anti-inflammatory cytokine IL-2 levels revealed that patients with bronchial asthma and vitamin D deficiency exhibited a significantly lower concentration, measuring 2.5±0.3 pg/ml ($p<0.001$), in comparison to the control group of children. The mean value of this parameter in the control group was 10.8±0.7 pg/ml. The evaluation of pro-inflammatory cytokines IL-13 and IL-17

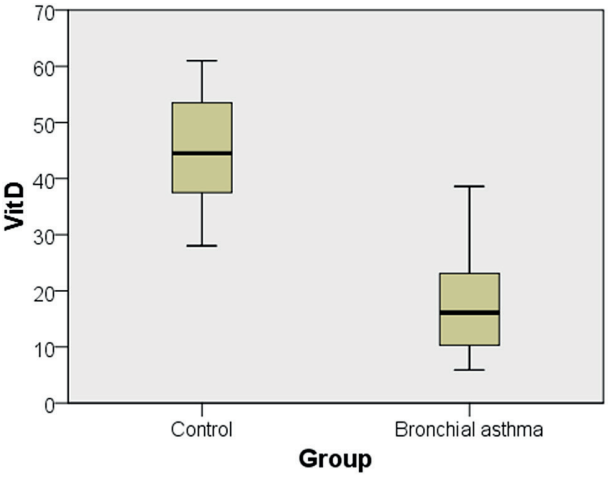


Figure 1. Vitamin D levels in study groups.

demonstrated that children with bronchial asthma had significantly higher serum levels compared to the control group ($p < 0.01$).

Thus, the average serum concentration of IL-13 in patients was 13.8 ± 0.8 pg/ml, compared to 5.3 ± 0.7 pg/ml in the control group. In the examination of IL-17 concentration, it was observed that individuals diagnosed with bronchial asthma presented significantly higher levels, with an average of 9.4 ± 0.8 pg/ml, compared to the control group, which had an average of 5.0 ± 0.4 pg/ml ($p < 0.05$) (Figure 2).

At the next stage of the study, ROC analysis of these indicators was performed to evaluate the informativeness of cytokines in children with atopic bronchial asthma. The specificity and sensitivity of each cytokine were assessed, and the ROC curve was constructed. The quantitative characteristic of the ROC curve was evaluated by the area under the curve (AUC). To assess the accuracy of the curve, the standard error of the area and the 95% confidence interval (95% CI) were calculated. If the area under the ROC curve lies on the same side as 0.5, the obtained results are considered statistically significant.

As a result of ROC analysis the informativeness of cytokine indicators in children with atopic bronchial asthma is presented in Figure 3. Thus, the area under

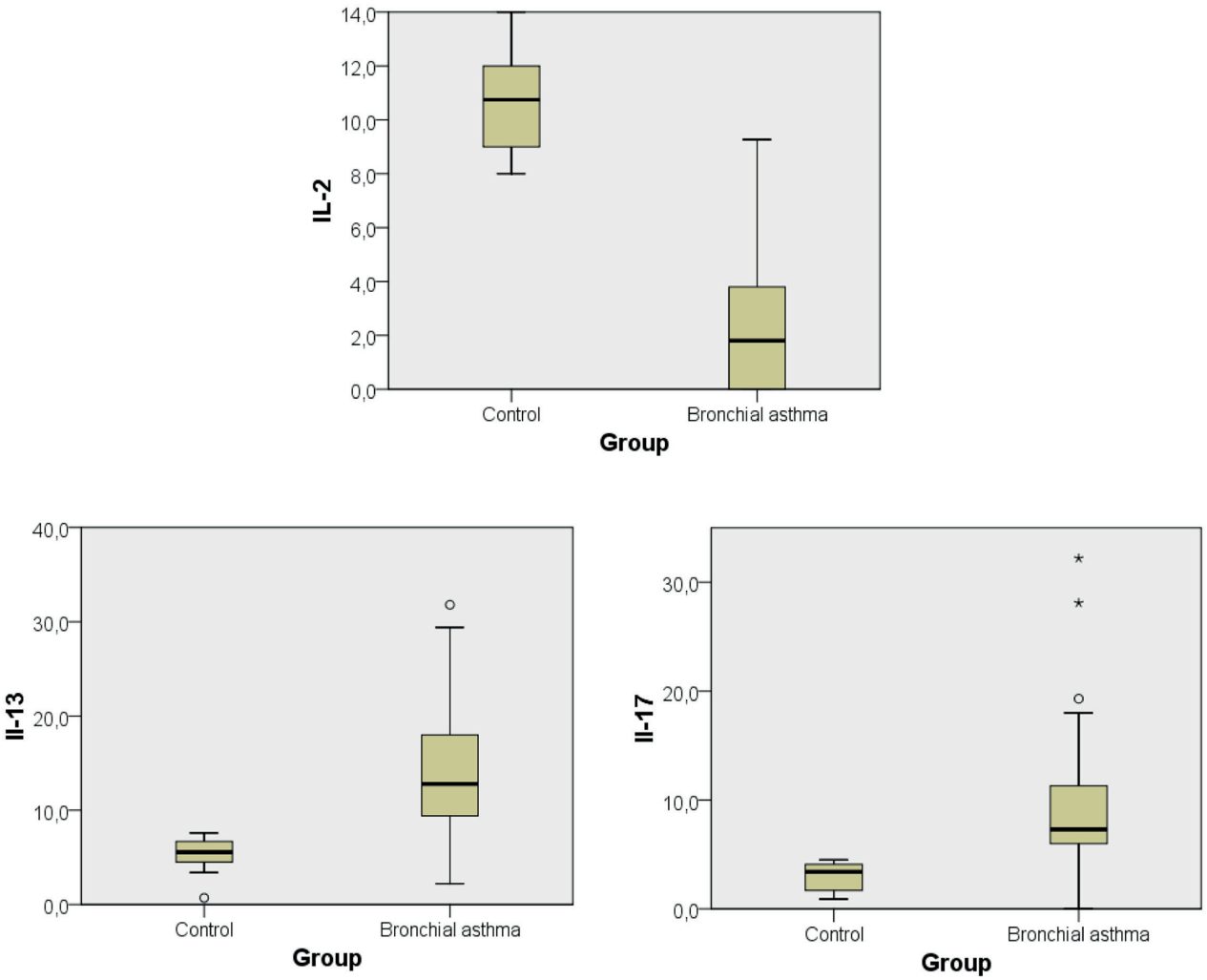
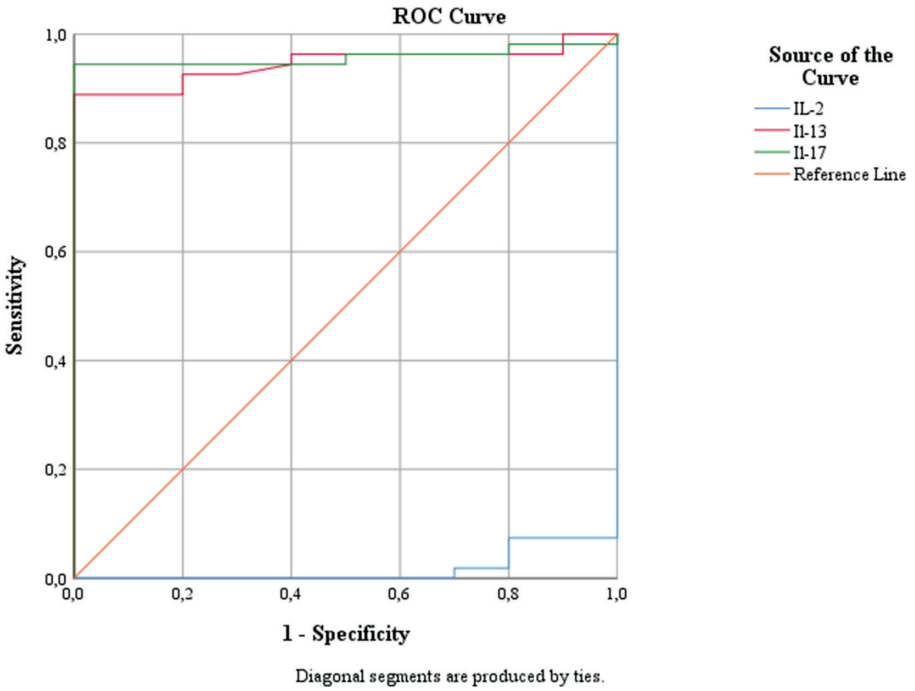


Figure 2. Comparative evaluation of anti- and pro-inflammatory cytokines in children with bronchial asthma.



Area Under the Curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% CI	
				Lower Bound	Upper Bound
IL-2	0.017	0.013	0.000	0.000	0.043
IL-13	0.945	0.028	0.000	0.891	1.000
IL-17	0.957	0.025	0.000	0.907	1.000

Figure 3. Evaluation of the informativeness of cytokine indicators in children with atopic bronchial asthma.

the ROC curve for IL-2 was 0.017 ± 0.013, with a 95% CI ranging from 0.000 to 0.043. This result was statistically significant ($p < 0.001$).

These are the results obtained from the comparison of pro-inflammatory cytokine indicators. The area of the ROC curve of IL-13 is 0.945±0.028; 95% CI upper and lower limits 0.891 – 1.0; $p < 0.001$, along with this the area of the ROC curve of the IL-17 indicator is 0.957±0.025; 95% CI upper and lower limits 0.907 – 1.0; $p < 0.001$.

The results of the ROC analysis demonstrate that pro-inflammatory cytokines are statistically significant diagnostic markers with high accuracy in identifying atopic bronchial asthma, playing a predictive role in its early diagnosis and reflecting their involvement in the disease pathogenesis.

Cut-off points of IL-2 < 7.45, sensitivity 92.6±3.6%, cut-off points of IL-13 - < 7.65, sensitivity 88.9±4.3%, cut-off points of IL-17 - < 4.8, the sensitivity was 94.4±3.1%. Specificity was assessed at 100% for all three indicators.

The general diagnostic value (GDV) for indicators was 93.8±3.0% in IL-2, 90.6±3.6% in IL-13, and 95.3±2.6% in IL-17. In order to study the practical application of this indicator, the negative and positive evaluation efficiency was calculated and the accuracy ratio for IL-2 and IL-17 was "excellent" in both "+" and "-" results, and "+" accuracy ratio for IL-13 was "excellent", and the "-" truth attitude was evaluated as "good" (Table 1).

Thus, statistically significant results were obtained between vitamin D and cytokines. One of the study's

Table 1. Evaluation of cytokine sensitivity, specificity and GDV in children with atopic bronchial asthma.

Indicators	IL-2	IL-13	IL-17
N	64	64	64
Bound	< 7.45	> 7.65	> 4.8
n_+	54	54	54
++	50	48	51
Sensitivity	92.6	88.9	94.4
±mp	3.6	4.3	3.1
n-	10	10	10
--	10	10	10
Specificity	100	100	100
±mp	0	0	0
GDV	60	58	61
%	93.8	90.6	95.3
±mp	3	3.6	2.6
Predictive positive value (pPV)	100	100	100
±mp	0	0	0
Predictive negative value (nPV)	71.4	62.5	76.9
±mp	12.1	12.1	11.7
LR_+	Excellent	Excellent	Excellent
LR-	Excellent	Good	Excellent

Table 2. Assessment of the correlation between vitamin D and cytokines.

		IL-2	IL-13	IL-17
VitD	ρ (Rho)	0,363*	-0,247*	-0,340*
	P	0,003	0,049	0,006

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

key findings is the significant vitamin D deficiency observed in children with atopic bronchial asthma. The imbalance in cytokines during the deficiency of this vitamin has compensatory character and can lead to an exacerbation of the allergic inflammatory process and its transition to a chronic form (Table 2).

Therefore, in addition to examining the function of vitamin D as a potential biomarker in the diagnosis of these patients, assessing vitamin D levels should be regarded as essential for optimizing treatment adjustments for these conditions.

Discussion

The results of this research indicate a notable correlation between vitamin D deficiency and modified cytokine profiles in pediatric patients suffering from atopic bronchial asthma. The average serum 25(OH)D concentration in asthmatic children was found to be 17.4±0.9 ng/ml, reflecting a moderate deficiency of vitamin D, whereas the control group exhibited levels of 45.3±2.2 ng/ml, which are considered optimal. This significant disparity ($p < 0.001$) is consistent with earlier studies that have documented reduced vitamin D levels in asthmatic children, implying that vitamin D may play a crucial role in the regulation of immune responses and the management of airway inflammation (27).

Our analysis of cytokines revealed a significant decrease in the anti-inflammatory cytokine IL-2 among asthmatic children suffering from vitamin D deficiency when compared to healthy controls (2.5±0.3 pg/ml versus 10.8±0.7 pg/ml, $p < 0.001$). IL-2 plays a crucial role in the development of T regulatory cells, and its reduction may hinder immune tolerance mechanisms associated with asthma (28). Conversely, the increased concentrations of the pro-inflammatory cytokines IL-13 (13.8±0.8 pg/ml) and IL-17 (9.4±0.8 pg/ml) in these patients highlight the involvement of Th2 and Th17 pathways in the process of allergic airway inflammation (29).

The ROC curve analysis confirmed the diagnostic utility of these cytokines. Both IL-13 (AUC = 0.945) and IL-17 (AUC = 0.957) exhibited excellent sensitivity and specificity, supporting their value as potential biomarkers in atopic asthma. The AUC for IL-2 is very low (0.017), indicating limited diagnostic utility; however, its observed inverse relationship with vitamin D may suggest a potential immunomodulatory role that requires further investigation in future studies.

Moreover, significant correlations were observed between vitamin D levels and cytokine profiles. Vitamin D levels were positively correlated with IL-2 ($r = 0.363$, $p = 0.003$) and inversely correlated with IL-13 ($r = –0.247$, $p = 0.049$) and IL-17 ($r = –0.340$, $p = 0.006$). While these correlations are statistically significant, their moderate strength indicates that vitamin D deficiency is likely one of several factors influencing

cytokine regulation in pediatric asthma. These findings are in agreement with previous literature suggesting that vitamin D may modulate immune responses by downregulating Th17 activity and promoting regulatory T cell function (30).

In addition to these immunological effects, several factors influence vitamin D status in children with asthma. Geographic location, sun exposure, skin pigmentation, dietary intake, obesity, and seasonal variation have all been shown to affect vitamin D levels, thereby modulating asthma severity and control (31, 32). For example, limited sunlight exposure in higher latitudes and winter months often leads to lower vitamin D synthesis, exacerbating deficiency risks in asthmatic populations (33). Obesity, which is prevalent among some pediatric asthma cohorts, may also sequester vitamin D in adipose tissue, reducing its bioavailability (34). These multifactorial influences further complicate the relationship between vitamin D levels and immune function in asthma, underscoring the need for personalized supplementation strategies. Understanding these factors is essential for designing effective vitamin D supplementation strategies tailored to improve clinical outcomes in asthmatic children.

Taken together, our findings and the existing body of research emphasize the importance of monitoring and potentially correcting vitamin D deficiency as part of comprehensive asthma management, particularly in pediatric patients. Further longitudinal and interventional studies are needed to clarify causality and optimize vitamin D-based therapeutic approaches.

The identification of IL-13 and IL-17 as reliable biomarkers with high diagnostic accuracy offers promising potential for clinical application. These cytokines could be included in screening protocols to identify children at increased risk of severe or poorly controlled asthma. In addition, monitoring their levels could help in risk stratification and the development of individualized treatment plans, ultimately improving disease management and patient outcomes. However, integration into routine clinical practice requires further validation through larger prospective studies.

These results indicate that monitoring vitamin D levels along with related cytokine profiles may improve personalized asthma management for children. Subsequent studies should aim to confirm these biomarkers in larger groups and investigate vitamin D supplementation as a specific therapeutic approach to enhance immune regulation and clinical results.

Conclusion

This study supports the hypothesis that vitamin D deficiency contributes to immune dysregulation in pediatric patients with atopic asthma, primarily through altered cytokine profiles. Vitamin D deficiency was associated with decreased levels of the anti-inflammatory cytokine IL-2 and increased levels of the pro-inflammatory cytokines IL-13 and IL-17, indicating a shift towards a pro-inflammatory state. This immune imbalance may contribute to chronic airway inflammation and increase the risk of asthma exacerbations.

Significant correlations between vitamin D status and cytokine levels highlight the potential of IL-2, IL-13, and IL-17 as biomarkers of disease severity and therapeutic targeting. These results suggest that routine assessment and correction of vitamin D deficiency should be considered an integral part of childhood asthma management. Incorporating vitamin D assessment into personalized treatment strategies may help optimize immune regulation and improve clinical outcomes.

However, this study has certain limitations. The relatively small sample size and the retrospective design based on medical records may affect the generalizability of the findings. Additionally, since all asthmatic participants had undergone prior therapy, the potential influence of treatment on cytokine profiles and vitamin D levels cannot be entirely ruled out. These factors should be considered when interpreting the results and designing future prospective studies with larger, treatment-naïve cohorts.

At the same time, this study offers valuable directions for future research. The use of retrospective medical records and the fact that participants had received some prior treatment present opportunities to consider additional aspects in subsequent studies. Larger-scale and prospective approaches may further deepen the understanding in this area and enhance its practical applications.

Despite these constraints, the study offers important insights and a foundation for future research. The potential utility of IL-2, IL-13, and IL-17 as biomarkers not only for diagnosis but also for monitoring treatment response and predicting disease progression warrants further investigation in larger, longitudinal studies.

The identified moderate, albeit significant, correlations indicate that vitamin D deficiency is one of several factors contributing to immune dysregulation in pediatric asthma, underscoring the need for further research into other underlying mechanisms.

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Authors Contribution: NS: experiment, review, AJ, RK, MO: investigation, methodology, editing, resources, writing, data curation. GI: statistical calculation, visualization. All authors contributed to the article and approved the submitted version.

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Correspondence:
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Rana J. Karimova
Department of Modeling of Pathological Processes,
Experimental Surgery and Therapy,
Scientific Research Center, Azerbaijan Medical University
Samad Vurgun street 163, AZ1022, Baku, Azerbaijan,
E-mail: dr.renakerimova@mail.ru
ORCID: 0009-0004-4323-9625