MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine
e-mail: eumj@med.sumdu.edu.ua
eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite / Як цитувати статтю: Pavlyshyn H, Labivka O. Micronutrient status in children infected with the SARS-COV-2 virus. *East Ukr Med J*. 2024;12(4):788-797

DOI: https://doi.org/10.21272/eumj.2024;12(4):788-797

ABSTRACT

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MICRONUTRIENT STATUS IN CHILDREN INFECTED WITH THE SARS-COV-2 VIRUS

The coronavirus disease (COVID-19) caused by SARS-CoV-2 has raised significant public health concerns, leading to varying degrees of respiratory illness. Vitamins A, D, B6, B9, and B12 are essential for immune responses to viral infections, including COVID-19, while homocysteine, regulated by B vitamins, may affect inflammatory reactions and vascular complications.

This study aimed to assess the levels of these micronutrients and homocysteine in children with COVID-19, exploring potential links to disease severity.

Materials and Methods: The study, included 112 children with COVID-19 and 23 healthy controls. Serum levels of vitamins A, D, B6, B9, B12, and homocysteine were measured using the enzyme-linked immunosorbent assay.

Results showed that children with mild COVID-19 had higher vitamin A levels (456.10 ng/ml) than those with moderate (347.30 ng/ml) and severe cases (242.90 ng/ml) ($p < 0.05$). Vitamin D and B6 levels also decreased with increased severity, from 30.91 ng/ml and 56.80 ng/ml in mild cases to 22.42 ng/ml and 39.41 ng/ml in severe cases, respectively ($p < 0.05$). Vitamin B9 was lower in severe cases (3.90 ng/ml) compared to mild (4.78 ng/ml) ($p < 0.05$), while B12 showed no significant differences.

Conclusions: vitamins D, B6, and B9 appear to play a significant role in reducing COVID-19 severity in children, while vitamin A has a smaller effect, and B12 shows no notable influence. These findings suggest the importance of maintaining adequate vitamin levels during the COVID-19 pandemic to potentially mitigate disease severity.

Keywords: COVID-19, children, vitamins, homocysteine.

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РЕЗЮМЕ

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СТАТУС МІКРОЕЛЕМЕНТІВ У ДІТЕЙ, ІНФІКОВАНИХ ВІРУСОМ SARS-COV-2

Коронавірусна хвороба (COVID-19), спричинена SARS-CoV-2, викликала серйозні проблеми у сфері громадського здоров'я, що призвело до респіраторних захворювань, різного ступеня важкості. Вітаміни A, D, B6, B9 і B12 є важливими для імунної відповіді на вірусні інфекції, включаючи COVID-19, тоді як гомоцистеїн, який регулюється вітамінами групи B, може впливати на запальні реакції та судинні ускладнення.

Метою цього дослідження було оцінити рівень цих мікроелементів і гомоцистеїну у дітей з COVID-19, досліджуючи можливі зв'язки зі ступенем тяжкості хвороби.

Матеріали та методи: дослідження включало 112 дітей із COVID-19 та 23 здорових контрольних осіб. Рівні вітамінів A, D, B6, B9, B12 та гомоцистеїну в сироватці крові вимірювали за допомогою імуноферментного аналізу.

Результати: результати показали, що діти з легкою формою COVID-19 мали вищий рівень вітаміну A (45.61 нг/мл) порівняно з тими, хто мав середню (347.30 нг/мл) та важку форму (242.90 нг/мл) ($p < 0.05$). Рівні вітамінів D і B6 також знижувалися зі збільшенням тяжкості: від 30.91 нг/мл і 56.80 нг/мл при легкій формі до 22.42 нг/мл і 39.41 нг/мл при важкій формі відповідно ($p < 0.05$). Вітамін B9 був нижчим у випадках важкої форми (3.90 нг/мл) порівняно з легкою (4.78 нг/мл) ($p<0.05$), тоді як вітамін B12 не показав значних відмінностей.

Висновки: вітаміни D, B6 і B9, ймовірно, відіграють значну роль у зменшенні тяжкості COVID-19 у дітей, тоді як вітамін A має менший ефект, а вітамін B12 не виявляє суттєвого впливу. Ці результати вказують на важливість підтримки достатнього рівня вітамінів під час пандемії COVID-19 для потенційного зниження тяжкості захворювання.

Ключові слова: COVID-19, діти, вітаміни, гомоцистеїн.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has become the most significant public health crisis in recent history [1]. SARS-CoV-2 leads to acute respiratory illness with varying severity across different age groups, though the disease tends to be relatively mild in children [2]. International pediatric data show lower rates of severe disease in children (up to 4.4% of cases) [3] and higher rates of asymptomatic infection (up to 94% of cases) [4,5]. However, there is a need for a deeper understanding of the factors that may influence the severity of the disease in children, which remains essential.

COVID-19 is marked by an initial stage of immunosuppression (mild symptomatic period), followed by a second stage of hyperinflammation (severe symptomatic period) [6, 7]. A well-coordinated immune response promotes recovery, while an uncontrolled systemic inflammatory response leads to complications and death [6]. Depletion and a decrease in the number of lymphocytes, particularly T-regulatory lymphocytes, are found in patients with a severe course of COVID-19, which can lead to a loss of regulatory functions and a cytokine storm [8, 9]. The release of cytokines disrupts the integrity of the alveolar-capillary barrier, which leads to acute respiratory distress syndrome (ARDS), large microthrombi formation, and multiple organ failure [6].

Recently, there has been increasing interest in the role of micronutrients in supporting the immune system and their impact on the course of infectious diseases.

Micronutrients are crucial for influencing and maintaining every stage of the immune response. Their deficiency can affect both innate and adaptive immunity, causing immunosuppression and thus increasing susceptibility to infections [10].

Vitamins such as A, D, B6, B9, and B12 support children's immune function, normal development, and general health [11, 12]. Vitamin A is known for its effect on the barrier function of epithelial tissues and the immune response [13]. Vitamin D regulates the immune system and reduces inflammatory processes [14, 15]. B vitamins (B6, B9, and B12) are involved in metabolic processes, DNA synthesis, and nervous system functioning [12]. It follows that adequate levels of trace elements are necessary to ensure the practical work of each component of the immune system, and their insufficiency can lead to a weakening of the immune response, increasing vulnerability to infections [13], including COVID-19 [12]. Vitamins B6, B9, and B12 are essential for homocysteine metabolism, and their deficiency can lead to elevated levels of this amino acid, increasing the risk of complications. In COVID-19, elevated homocysteine levels may heighten the risk of thrombosis and cardiovascular issues, potentially worsening the course of the disease [16].

The purpose of the study is to evaluate the level of vitamins A, D, B6 (pyridoxine), B9 (folic acid), B12 (cobalamin), and homocysteine in children with COVID-19 and their relationship with the severity of the disease.

Research materials and methods: A total of 112 children, aged one month to 18 years, diagnosed with COVID-19 (confirmed by the polymerase chain reaction (PCR) of nasal swabs and positive serological tests for IgM and IgG, or IgM alone) were included in the study, along with 23 healthy children of similar age, without clinical signs or medical history indicating any acute or chronic infectious or somatic conditions. Additionally, these children had no underlying factors that could influence vitamin levels, such as specific dietary restrictions or chronic diseases. The children with COVID-19 were admitted to the infectious disease department of the Ternopil City Children's Hospital between March 2021 and May 2023.

The severity of COVID-19 was determined by medical recommendations [17], which considered factors such as the severity of clinical symptoms (i.e., cough, weakness, sore throat, shortness of breath during physical exertion), body temperature, and respiratory rate, confirmation of pneumonia via computed tomography, blood oxygen saturation (SpO2) levels, and C-reactive protein level in blood serum. Based on these criteria, the patients were divided into three groups: Group I – 57 children with a mild course of the disease; Group II – 43 children with a moderately severe course; and Group III – 12 children with a severe course.

Ethical Statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). *The Bioethics Commission of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine (Protocol No 78, dated August 18, 2024) approved the study.* Individual informed consent for this study was obtained from all children`s caregivers.

Serum levels of vitamins A, D, B6, B9, and B12 were determined by the colorimetric enzyme-linked immunosorbent assay. The levels of vitamins A, B6, B9, B12, and homocysteine were measured using the Elabscience test system, while vitamin D level was determined by the Monobind test system. The criteria for assessing vitamin status are shown in Table 1.

*Table 1 – **Criteria for assessing vitamin status***

Vitamin A (ng/ml)	Vitamin D (ng/ml)	Vitamin B6 (ng/ml)	Vitamin B9 (ng/ml)	Vitamin B12 (pg/ml)
≥ 300 ng/ml	30–100 ng/ml	>5 ng/ml	>6 ng/ml	200–900 pg/ml
200~300 ng/ml	29–20 ng/ml	< 5 ng/ml	3–6 ng/ml	<200 pg/ml
< 100 ng/ml	< 20 ng/ml		< 3 ng/ml	

A sufficient level of homocysteine was defined as 5–15 μmol/L. Levels between 16 to 30 μmol/L were classified as moderately elevated, 31–100 μmol/L was considered intermediately elevated, and values above 100 μmol/L as severe hyperhomocysteinemia.

Statistical analysis was performed using the "Stat Plus" program. The 95% confidence interval (95% CI) was calculated for the mean values, and quantitative indicators were presented as Me (25%; 75%), where Me represents the median, 25% is the first quartile, and 75% is the third quartile. Qualitative measurements were displayed as numbers (n) and percentages (%). The Kruskal–Wallis test (H-test) was used to assess the equality of medians across multiple samples. Correlation analysis was conducted by calculating the Spearman rank correlation coefficient to determine relationships between the investigated variables. Statistical significance was set at p<0.05. A multiple linear regression model was used to analyze the effect of vitamin levels on the severity of COVID-19, a multiple linear regression model was used, where the severity of the disease was the dependent variable, and the levels of vitamins A, D, B6, folate, and B12 were the independent variables.

Research results. The average age of children examined was 5.95 ± 0.7 years (95% CI 5.25 to 6.65). Of these, 92 were boys (52.57%), and 83 were girls (47.43%), with no statistically significant differences by gender (p < 0.001).

The children were divided into three groups based on the severity of COVID-19. In 57 children, the disease was mild, with an average age of 6.73±5.77 years (95% CI 5.23−8.23). In 43 children, the disease was moderately severe, with an average age of 7.9±5.75 years (95% CI 6.16−9.64). In 12 children with severe disease, the average age was 7.31±6.22 years (95% CI 3.36−11.26) (Fig. 1). The average age of children in the control group was 6.92±5.72 years (95% CI 4.45−9.39).

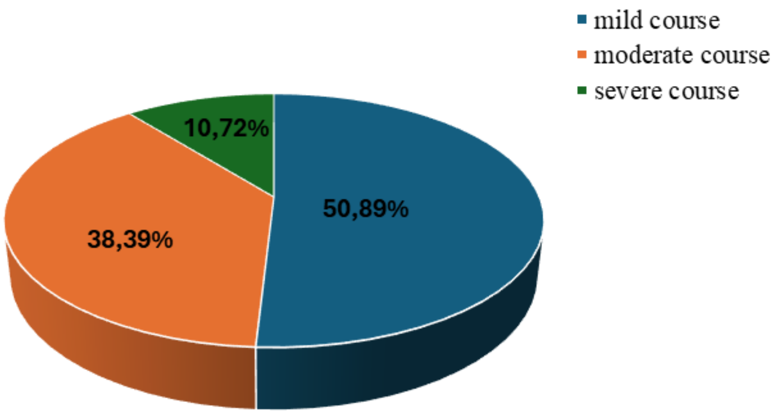

Figure 1 - Degrees of severity of COVID-19

Analysis of vitamin levels revealed that the level of vitamin A in children with a mild course of the disease was 456.10 ng/ml, which was significantly higher than in children with moderate disease (347.30 ng/ml) (p<0.05) and those with severe course of the disease (242.90 ng/ml) (p<0.05) (Table 2). Also, children with moderate and severe SARS-CoV-2 infection had a significantly lower level of this vitamin than uninfected individuals of the control group (p<0.05). At the same time, vitamin A levels in patients with mild COVID-19 did not differ from the control group (p > 0.05).

It was established that the concentration of vitamin D in children with a mild course of COVID-19 was 30.91 ng/ml; in children with a moderate course – 29.10 ng/ml, and in children with a severe course – 22.42 ng/ml (Table 2). The vitamin D level in the control group was significantly higher than in patients with moderate and severe disease (p < 0.05).

The vitamin B6 level in children with mild disease was 56.80 ng/ml, significantly higher than in the moderate group (48.97 ng/ml) (p < 0.05) and the severe group (39.41 ng/ml) (p < 0.05). Vitamin B6 levels were notably lower in patients with severe SARS-CoV-2 infection compared to those without infection (p < 0.05). However, the levels of vitamin B6 in patients with mild and moderate COVID-19 did not differ significantly from the control group (p > 0.05) (Table 2).

The concentration of vitamin B9 in children with a mild course of COVID-19 was measured at 4.78 ng/ml, while those with a moderate course had levels of 4.22 ng/ml, and children with a severe course recorded levels of 3.90 ng/ml (Table 2). The level of vitamin B9 in the control group was significantly higher than in patients with moderate (p<0.05) and severe courses of the disease (p<0.05).

In contrast, vitamin B12 levels did not show significant differences among patients with mild, moderate, and severe COVID-19 (Table 2). However, patients with severe SARS-CoV-2 infection had lower vitamin B12 levels compared to uninfected individuals (p<0.05).

Notably, a majority of children with mild (85.96%) and moderate (67.44%) disease severity had sufficient vitamin A levels. In contrast, 58.00% of children with a severe course of COVID-19 exhibited vitamin A deficiency. Furthermore, vitamin A deficiency was significantly more prevalent in patients with a severe course of COVID-19 (25.00 %) compared to mild (12.28 %) and moderate severity (6.98 %) (Table 3).

*Table 2 – **Vitamin Concentration Relative to Disease Severity***

Disease Severity	Vitamin A (ng/ml)	Vitamin D (ng/ml)	Vitamin B6 (ng/ml)	Vitamin B9 (ng/ml)	Vitamin B12 (pg/ml)
Mild course (1)	456.10 (394.00; 566.00)	30.91 (21.50; 42.45)	56.80 (49.86; 61.40)	4.78 (3.36; 6.36)	369.10 (270.20; 484.10)
Moderate course (2)	347.30 (279.60; 503.10)	29.10 (21.25; 37.68)	48.97 (35.60; 57.67)	4.22 (3.19; 6.23)	365.40 (288.50; 442.40)
Severe course (3)	242.90 (203.25; 272.55)	22.42 (18.99; 30.50)	39.41 (37.90; 43.72)	3.90 (2.27; 5.10)	310.90 (255.55; 410.85)
Control group (4)	487.00 (430.50; 653.90)	37.90 (34.60; 43.25)	57.56 (43.50; 64.69)	5.47 (4.76; 7.03)	461.10 (374.10; 615.70)
Kruskal-Wallis criterion	H=30.18; *P* <0.001*	H=14.34; *P*=0.003*	H=23.90; p<0.001*	H=10.70; p=0.014*	H=9.69; p=0.022*
	P_{1-2}, P_{1-3}, P_{2-4}, P_{3-4}	P_{2-4}, P_{3-4}	p_{1-2}, p_{1-3}, p_{3-4}	p_{2-4}, p_{3-4}	p_{3-4}

*Table 3 – **Vitamin A, D, B6, B9, and B12 Status in Children with COVID-19***

Indicator status	**COVID-19 Groups**						**Control Group**	
	Mild course		Moderate course		Severe course			
	n	%	n	%	n	%	n	%
Vitamin A (ng/ml)								
Sufficient level	49	85.96	29	67.44	2	16.67	23	100.00
Insufficient level	1	1.75	11	25.58	7	58.33	0	0
Deficiency	7	12.28	3	6.98	3	25.00	0	0
χ^2=47,85; p<0,001								
Vitamin D (ng/ml)								
Sufficient level	20	55.56	12	42.86	3	25.00	13	86.67
Insufficient level	9	25.00	11	39.29	4	33.33	2	13.33
Deficiency	7	19.44	5	17.86	5	41.67	0	0
χ^2=14,41; p=0,013								
Vitamin B6 (ng/ml)								
Sufficient level	15	26.32	23	53.49	11	91.67	7	30.43
High level	42	73.68	20	46.51	1	8.33	16	69.57
χ^2=21.56; *p*<0.001								
Vitamin B9 (ng/ml)								
Sufficient level	16	28.07	11	25.85	1	8.33	11	47.83
Insufficient level	30	52.63	23	53.49	7	58.33	11	47.83
Deficiency	11	19.30	9	20.93	4	33.33	1	4.35
χ^2=9.04; *p*=0.171								
Vitamin B12 (pg/ml)								
Sufficient level	55	96.49	41	95.35	12	100.00	22	95.65
Deficiency	2	3.51	2	4.65	0	0	1	4.35
χ^2=5.90; *p*=0.435								

The majority of children with mild (55.56%) and moderate (42.86%) COVID-19 had a sufficient level of vitamin D. At that time, vitamin D deficiency was more typical for children with severe cases (41.67%) (Table 3).

The study found that children with a mild course (73.68%) and children from the control group (69.57%) had a higher level of vitamin B6 compared to patients with a severe illness (8.33%) (Table 3).

In children with a mild (52.63%), moderate (53.49%), and severe course of COVID-19 (58.33%), vitamin B9 deficiency was observed. At the same time, vitamin B9 deficiency is more characteristic for children with a severe course of the disease (33.33%) compared to mild one (19.30%) (Table 3).

Most children with mild (96.49%), moderate (95.35%) and severe (100.00%) disease had sufficient levels of vitamin B12. At the same time, vitamin deficiency was determined in a small percentage of children (3.51%) with a mild course of the disease and in children with a moderately severe course (4.65%) (Table 3).

When analyzing the correlations between the levels of vitamins, different degrees of connection between them were established. From the analysis of correlation coefficients, it was established that most vitamins have a weak or moderate correlation with each other. We observe the strongest positive correlation between vitamins A and B6 (r=0.498) and the strongest negative correlation between vitamins D and B6 (r=-0.533). These correlations may indicate that the levels of these vitamins are interrelated and may influence each other (Table 4).

*Table 4 – **Correlation Analysis of Vitamins A, D, B6, B9, and B12 in Blood Serum of Children with COVID-19***

	Vitamin A (ng/ml)	Vitamin D (ng/ml)	Vitamin B6 (ng/ml)	Vitamin B9 (ng/ml)	Vitamin B12 (pg/ml)
Vitamin A (ng/ml)	-	0.178	0.498	-0.303	-0.007
Vitamin D (ng/ml)	0.178	-	-0.533	-0.256	0.334
Vitamin B6 (ng/ml)	0.498	-0.533	-	-0.167	-0.316
Vitamin B9 (ng/ml)	-0.303	-0.256	-0.167	-	-0.368
Vitamin B12 (pg/ml)	-0.007	0.334	-0.316	-0.368	-

Vitamin B6, B9 (folate), and B12 levels significantly affect blood homocysteine levels, with higher concentrations of these vitamins being associated with lower levels of homocysteine.

In our study, the levels of homocysteine measured in children were as follows: 9.89 μmol/L in those with a mild course of COVID-19, 11.20 μmol/L in those with a moderate course, and 13.59 μmol/L in those with a severe course. Notably, homocysteine levels were significantly higher in patients with a severe form of COVID-19 compared to healthy children ($p<0.05$).

It was also investigated that a high level of vitamin B6 is associated with a lower level of homocysteine in the blood ($r=-0.993$), and a high level of vitamin B12 is also associated with a lower level of homocysteine ($r=-0.911$) (Table 5).

*Table 5 – **Correlation analysis of vitamins B6, B9, B12 and homocysteine in blood serum in children with COVID-19***

	Vitamin B6, ng/ml	Vitamin B9, ng/ml	Vitamin B12, pg/ml	Homocysteine, μmol/l
Vitamin B6, ng/ml	-	0.894	0.819	-0.993
Vitamin B9, ng/ml	0.894	-	0.951	-0.911
Vitamin B12, pg/ml	0.819	0.951	-	-0.870
Homocysteine, μmol/l	-0.993	-0.911	-0.870	-

When analyzing correlations between vitamins and some blood parameters, it was established that vitamin D has a weak positive correlation with lymphocytes (r=0.316), which may indicate a possible connection between the level of vitamin D and immune cells (Table 6). The correlation between B vitamins, vitamin A, and indicators of general blood analysis, such as CRP, leukocytes, neutrophils, lymphocytes, and ESR, is relatively weak or absent (Table 6).

The resulting multiple linear regression coefficients indicate how changes in the levels of each vitamin affect the predicted severity of the disease. Notably, folate (β=−0.0257, p = 0.02) and vitamin D (β=−0.0087, p = 0.01) showed the most significant negative impact on the course of the disease, which suggests that increasing their levels may be associated with a less severe course of COVID-19. Vitamin B6 (β=−0.0164, p = 0.03) also showed a significant effect, while vitamin A (β=−0.0017, p = 0.05) had a less pronounced effect. Vitamin B12 (β=−0.0003, p = 0.12) did not reveal a statistically significant impact on the severity of the disease (Table 7, Figure 2).

*Table 6 – **Correlation analysis of levels of vitamins A, D, B6, B9, B12 and indicators of general blood analysis in children with COVID-19***

	Vitamin A, ng/ml	Vitamin D, ng/ml	Vitamin B6, ng/ml	Vitamin B9, ng/ml	Vitamin B12, pg/ml
CRP, mg/l	-0.462	0.127	0.131	0.173	0.156
Leukocytes, 10^9/l	-0.462	0.037	0.209	0.240	0.231
Neutrophils, %	-0.463	-0.054	0.177	0.213	0.221
Lymphocytes, %	0.037	0.316	0.182	0.094	0.133
ESR, mm/h	-0.310	0.013	0.091	0.224	0.237

*Table 7 – **Multiple linear regression: coefficients and p-values for vitamin levels in children with COVID-19***

Vitamins	Coefficient β	p-value
Vitamin A	-0.002	0.05
Vitamin D	-0.009	0.01
Vitamin B6	-0.016	0.01
Vitamin B9	-0.026	0.02
Vitamin B12	-0.0	0.12

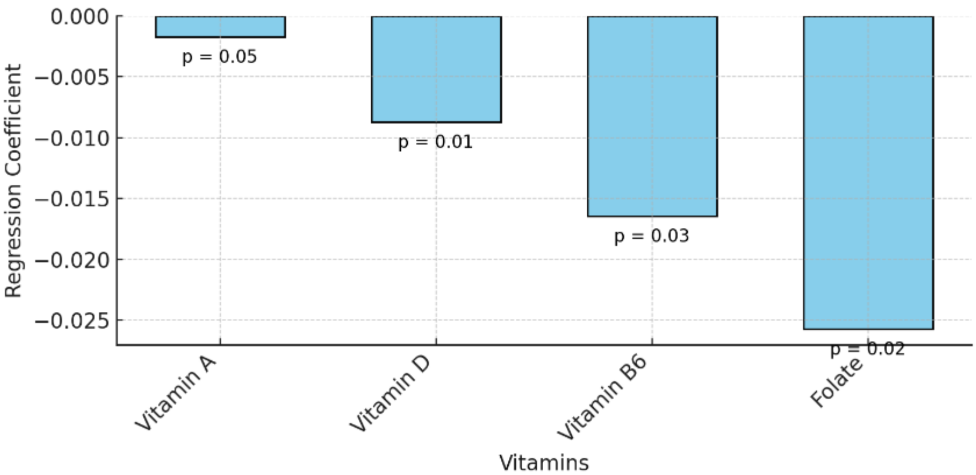

Figure 2 – Graphical Visualization of Regression Coefficients and p-values

Discussion. The importance of studying the effect of vitamins on the course of COVID-19 in children is emphasized by their crucial role in supporting the immune system [13–15]. Our results show significant correlations between the levels of specific vitamins and the severity of the course of the disease.

Our study found that levels of vitamins, particularly A, D, B6, B9, and B12, are associated with the course of COVID-19 in children. These findings are consistent with the results of other studies that emphasize the importance of micronutrients for the immune response to infections, including COVID-19 [15, 18–19].

Insufficiency of vitamin A increases the risk of pathogen penetration and severe course of COVID-19 due to a reduced immune response [11, 12]. Vitamin A levels in children with mild disease were higher than in children with severe disease, which may indicate a relationship between vitamin A levels and the severity of infection. This is confirmed by studies that show that vitamin A plays a vital role in maintaining the integrity of epithelial barriers and the functioning of the immune system [20].

Vitamin D levels also emerged as a significant factor. Vitamin D deficiency can enhance the inflammatory response, thereby increasing the risk of a severe course of COVID-19 [12, 13]. Children with mild disease exhibited average vitamin D levels, while those with moderate and severe cases had significantly lower levels. Thus, our results support previous studies indicating its importance in regulating the immune response and reducing the risk of severe respiratory infections, including COVID-19 [20–23].

Insufficiency of B vitamins can weaken the immune response and the body's ability to fight infections, including SARS-CoV-2, and increase the risk of a severe course of COVID-19 [12–14]. The elevated levels of vitamin B6 observed in children with mild disease correlate with studies showing that this vitamin is vital for supporting immune system functions, including cytokine and antibody production [24–26]. Our data confirm that vitamin B6 deficiency is associated with more severe forms of COVID-19 in children.

The lack of vitamin B9, especially in children with a severe disease course, corresponds to the studies emphasizing its role in maintaining the immune response and preventing immunosuppression [27, 28]. Folic acid deficiency can increase susceptibility to infections and complications, particularly in the case of COVID-19.

Regarding vitamin B12, our results are consistent with international data highlighting its role in maintaining immune system health and preventing severe respiratory infections [29–31]. Vitamin B12 deficiency has been associated with a severe course of COVID-19, confirming the importance of adequate vitamin B12 levels for an optimal immune response.

Additionally, it is well-documented that a deficiency in B vitamins can lead to elevated levels of homocysteine in the blood, which is associated with a higher risk of complicated COVID-19 cases in children [32,33]. Our study observed elevated homocysteine levels in children with severe disease, which negatively correlated with vitamins B6 and B12.

Conclusions. The study found that vitamins D, B6, and folate had the most pronounced protective effects in children with COVID-19. Higher levels of folate and vitamin D were associated with a significantly reduced risk of severe COVID-19, while vitamin B6 also showed a notable protective effect. In contrast, vitamin A had a less pronounced effect, and vitamin B12 did not show a statistically significant impact on the severity of the disease.

A strong correlation between vitamin deficiency and disease severity was observed, with children suffering from severe COVID-19 having significantly lower levels of vitamins A, D, and B6 compared to those with mild or moderate cases.

The study suggests that targeted vitamin supplementation, particularly with vitamins A, D, and B6, could reduce the risk of severe COVID-19 in children. Pediatricians might focus on dietary guidelines to ensure children get enough of these vitamins naturally, while screening programs could help detect deficiencies early in high-risk children. Additionally, seasonal vitamin supplementation, especially during winter, may further protect children's immune health.

AUTHOR CONTRIBUTIONS

(I) Conception and design: Halyna Pavlyshyn; Oksana Labivka;
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(III) Provision of study materials or patients: Oksana Labivka, Halyna Pavlyshyn;
(IV) Collection and assembly of data: Oksana Labivka, Halyna Pavlyshyn;
(V) Data analysis and interpretation: All authors;
(VI) Manuscript writing: All authors;
(VII) Final approval of manuscript: All authors.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Received 09.10.2024
Accepted 08.11.2024

Одержано 09.10.2024
Затверджено до друку 08.11.2024

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