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ANALYSIS OF *MTHFR* AND *VDR* GENE VARIANTS AND OXIDATIVE/NITROSATIVE STRESS MARKERS IN THE DEVELOPMENT AND COURSE OF COVID-19 IN CHILDREN FROM THE POLTAVA REGION: APPROACHES TO PERSONALIZED THERAPEUTIC AND PREVENTIVE STRATEGIES

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Summary.

Analysis of gene variants, oxidative and nitrosative stress markers, and their interrelationships may facilitate the development of personalized approaches to the prevention and treatment of coronavirus disease 2019 (COVID-19) and other infectious diseases, particularly in regions affected by environmental pollution. The present study was conducted to evaluate the influence of MTHFR (rs1801133, rs1801131) and VDR (rs731236) gene variants, as well as oxidative and nitrosative stress markers, on the course of COVID-19 in children residing in the Poltava region, with consideration of nitrate and fluoride pollution.

Methods. *The study included 40 children diagnosed with COVID-19 and 17 age-matched children in the comparison group. The following parameters were assessed: variants of the MTHFR and VDR genes; urinary concentrations of nitrates, nitrites, malondialdehyde (MDA), and sialic acids; and residence in territories with elevated fluoride and nitrate pollution.*

Results. *In children with COVID-19, a significantly higher frequency of the AA genotype of the rs1801131 variant was observed. Elevated urinary levels of nitrites, MDA, and sialic acids were identified as significant pathogenic factors associated with the disease. Among children living in fluoride- and nitrate-polluted areas, correlations were found between MTHFR gene variants and serum concentrations of bilirubin, creatinine, and MDA. Betaine-arginine supplementation was identified as a potential strategy for personalized prevention and treatment in pediatric COVID-19.*

Conclusion. *Associations were established between MTHFR gene variants and increased susceptibility to COVID-19. The influence of fluoride- and nitrate-polluted environments was confirmed, key pathogenic factors (nitrite, MDA, and sialic acid levels) were delineated, and betaine-arginine supplementation was proposed as a potential preventive and therapeutic intervention.*

Keywords: *COVID-19; MTHFR; Nitrosative Stress; Oxidative Stress; VDR*

Introduction

Environmental conditions exert a substantial influence on the development and progression of infectious diseases. Air pollution increases susceptibility to respiratory infections, while climate change and global warming promote the emergence and dissemination of novel pathogens, altering their geographic range and extending epidemic periods. Urbanization and loss of biodiversity further erode natural barriers between humans and zoonotic agents, thereby elevating the risk of pandemics [1].

In children, environmental exposures play a critical role in modulating immune development [2]. Air pollution compromises the barrier integrity of the respiratory mucosa, rendering pediatric populations more vulnerable to respiratory pathogens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). Environmental toxicants can impair immune maturation, thereby diminishing host defence against infections. Chemical contamination of drinking water and food, particularly in densely populated urban settings, adversely affects overall health in children and heightens the risk of severe complications from infectious diseases.

During the first wave of the COVID-19 pandemic in Ukraine, dominated by the Alpha variant, the disease in children was predominantly asymptomatic, mild, or moderately severe. The most common clinical manifestations included fever, cough, tonsillopharyngitis, and diarrhea. In the second wave (Beta variant), older children more frequently developed pneumonia, severe intoxication, and respiratory failure, with a marked rise in complication rates. The third wave was characterised by upper respiratory tract involvement and pneumonia predominantly in younger children and infants, underscoring distinct patterns of disease progression [3]. These variations are likely attributable not only to the emergence of successive viral variants but also to region-specific environmental influences.

Nitrate contamination of water and food constitutes a major health hazard for children, particularly in the setting of infectious diseases. Upon absorption, nitrates are converted to nitrosamines, which impair immune function and compromise host resistance to infection [4]. Nitrates also interfere with tissue oxygenation, exacerbating hypoxia during respiratory infections. Chronic nitrate exposure induces persistent inflammation, thereby aggravating disease course and increasing the probability of severe complications.

Fluoride contamination of drinking water and food products similarly poses a significant risk to pediatric health. Elevated fluoride levels can result in chronic intoxication, which suppresses immune competence [5]. Under such conditions, susceptibility to respiratory infections increases owing to diminished pathogen clearance capacity. Fluorides also promote oxidative stress and impair antioxidant defences, thereby complicating the

clinical course of diseases such as COVID-19 and elevating the risk of adverse outcomes.

Ecogenetics, an essential discipline within medical genetics, examines the interplay between genetic traits and environmental exposures. Ecogenetic investigations focus on how genetic predispositions modulate an organism's response to environmental agents such as toxins, nutritional factors, or stressors. This framework elucidates inter-individual and inter-group differences in susceptibility to disease or environmental insults. Ecogenetic testing is instrumental in optimising health outcomes when environmental exposures cannot be eliminated; such testing informs the design of targeted therapeutic and preventive interventions, including metabolic modulation during viral pandemics.

In Ukraine, the absence of mandatory food folate fortification contributes to prevalent folate deficiency states, which are associated with compromised immune function and heightened susceptibility to infections [6]. The *MTHFR* gene encodes methylenetetrahydrofolate reductase, an enzyme central to folate metabolism. This enzyme catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cofactor required for the remethylation of homocysteine to methionine. Nitrates can interfere with folate metabolism, thereby exacerbating folate deficiency and elevating homocysteine concentrations [7]. The most extensively studied and prevalent *MTHFR* variants are rs1801131 and rs1801133, both of which reduce methylenetetrahydrofolate reductase activity [8]. The **rs1801131** variant (or A1298C), located in exon 7 of the *MTHFR* gene, results in a glutamate-to-alanine substitution at codon 429 within the C-terminal regulatory domain that binds S-adenosylmethionine, an allosteric inhibitor of methylenetetrahydrofolate reductase. It has been suggested that rs1801131 may alter S-adenosylmethionine binding affinity, leading to diminished enzymatic activity [9]. The rs1801133 variant (or C677T) in exon 4 of the *MTHFR* gene results in the substitution of alanine with valine at codon 222 in the N-terminal catalytic domain, leading to increased thermolability and decreased enzyme activity [10]. Prior investigations have suggested associations between these *MTHFR* gene variants and severe manifestations of COVID-19 [11, 12].

The *VDR* gene encodes the vitamin D receptor, which is critical for modulating immune responses, given the essential role of vitamin D in immune homeostasis. Fluoride and nitrate pollution can impair vitamin D metabolism [13]. Fluorides, for instance, interfere with metabolic processes required for vitamin D activation, thereby decreasing its bioavailability. The rs731236 variant is among the most common in the VDR gene and involves a T>C transition, producing a synonymous change at codon 352 in exon 9 [14]. Located in the 3′-untranslated region, this variant influences mRNA stability. The T allele has been associated with enhanced transcriptional activity, enhanced mRNA stability, and elevated circulating levels of active vitamin D (1,25(OH)2D3) [14]. This *VDR* variant, when linked to vitamin D insufficiency, has been correlated with increased severity and mortality of COVID-19, particularly in Ukrainian cohorts [15, 16].

Investigation of the *MTHFR* and *VDR* gene variants through the lens of ecogenetics provides insight into gene-environment interactions that influence pediatric health outcomes. Genetically determined impairments in detoxification pathways may hinder viral clearance [17]. Examination of gene variants, phenotypic expressions of oxidative and nitrosative stress, and their interrelationships supports the development of individualized strategies for the prevention and management of COVID-19 and other infectious diseases, particularly in settings with environmental pollution.

Objective of the study: to evaluate the effects of *MTHFR* (rs1801133, rs1801131) and *VDR* (rs731236) genes variants, together with oxidative and nitrosative stress markers, on the clinical course of COVID-19 in children from the Poltava region, taking into account nitrate and fluoride pollution, with a view to informing the development of therapeutic and preventive interventions.

Materials and Methods

Study population.

The study included 40 children aged up to 16 years who were hospitalised with confirmed COVID-19 between 2019 and 2023. Given the extended duration of enrolment, participants were drawn from different pandemic waves. The first wave, dominated by the SARS-CoV-2 Alpha variant, was characterised predominantly by asymptomatic or mild disease in children, with fever reported in 40-56% of cases, cough in 50%, tonsillopharyngitis in 40%, and diarrhea in 33%. The second wave, driven by the Delta variant, primarily affected older children and featured pneumonia in 36.1% of cases, along with severe intoxication, respiratory failure, and increased complication rates. The third wave, associated with the Omicron variant, accounted for the highest number of paediatric hospitalisations, predominantly involving younger children and infants, with upper respiratory tract infections as the main presentation and pneumonia occurring in only 6% of cases.

Inclusion criteria comprised laboratory-confirmed severe COVID-19 and provision of parental informed consent. Exclusion criteria were congenital developmental anomalies and parental refusal to participate. The comparison group consisted of 17 age-matched children without COVID-19. Demographic and clinical characteristics of the study groups are summarised in Table 1. All participants were hospitalised for the first time with this diagnosis, regardless of subsequent disease severity. None of the children had received COVID-19 vaccination, and medical record review confirmed no prior SARS-CoV-2 infection in any participant.

The study protocol was approved by the Ethics Committee on Biomedical Ethics of Poltava State Medical University (protocol No. 184, dated 25 June 2020). Written informed consent was obtained from the parents or legal guardians of all participating children. The study adhered to the principles of the World Medical Association Declaration of Tokyo, the Declaration of Helsinki on human rights, the Council of Europe Convention on Human Rights and Biomedicine, and the Ethical Code of Physicians of Ukraine.

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Table 1

Distribution of children by gender, age, and age subgroups

Parameter		Main group (n=40)	Comparison group (n=17)
Gender	male	23 (57.5%)	10 (58.8%)
	female	17 (42.5%)	7 (41.2%)
Age, years		3,0 [1.0; 6.0]	4,0 [3.0; 8.0]
Age subgroups	≤3	23(57.5%)	8 (47.1%)
	3,1-6	9 (22.5%)	4 (23.5%)
	≥6,1	8 (20.0%)	5 (29.4%)

Fluoride and nitrate pollution.

Data on the administrative-territorial distribution of geochemical provinces in the Poltava region with respect to mobile fluoride and nitrate levels in decentralized drinking water sources were obtained from the State Institution «Poltava Regional Center for Disease Control and Prevention of the Ministry of Health of Ukraine» and the Department of Hygiene and Ecology at Poltava State Medical University.

Nitrate concentrations in water were determined using a photometric method based on the reaction of nitrates with sodium salicylate in the presence of sulfuric acid, yielding a yellow sodium-salicylate complex whose absorbance was measured photometrically.

Fluoride content was quantified by a photometric method in which fluoride ions form a soluble violet-blue triple complex with lanthanum and alizarin complexone. The colour intensity was measured photometrically.

Genotyping of MTHFR and VDR Gene Variants.

Genomic DNA was extracted from buccal epithelial cells. Samples were collected using single-use sterile brushes and stored/transported in tubes containing DNA/RNA Shield™ stabilization solution by Zymo Research, USA. DNA isolation was performed using Zymo Research Quick-DNA MiniPrep Plus Kit. Genotyping of *MTHFR* and *VDR* gene variants was conducted by polymerase chain reaction followed by restriction fragment length polymorphism analysis and allele-specific polymerase chain reaction, according to previously published protocols [18, 19].

Markers of oxidative and nitrosative stress.

Oxidative and nitrosative stress was assessed by measuring urinary concentrations of nitrates, nitrites, malondialdehyde (MDA), and sialic acids [20]. All determinations were performed using spectrophotometric methods in urine samples from the study groups.

Methodology for Determining Nitrates and Nitrites.

Nitrite concentration was quantified by reaction with sulfanilic acid and α-naphthylamine (Griess-Ilosvay reagent), yielding red-coloured derivatives. Nitrate concentration was determined indirectly by measuring the increase in nitrite levels following reduction with hydrazine sulfate.

Methodology for Determining Free MDA Concentration.

Free MDA concentration was measured based on its reaction with 1-methyl-2-phenylindole in a methanol-acetonitrile mixture, resulting in an orange chromogen.

Methodology for Determining Sialic Acids.

Sialic acids were released from urinary glycoproteins by hydrolysis and quantified by the formation of a coloured complex upon heating with an acetic-sulfuric acid reagent (Hess reaction). Concentrations were determined from a calibration curve of absorbance versus concentration.

Statistical analysis.

Statistical analysis was conducted using SPSS version 27 software. Normality of data distribution was assessed with the Shapiro-Wilk test. Categorical variables were expressed as absolute numbers and frequencies. Continuous variables were presented as mean ± standard deviation if normally distributed, or as median [Q1; Q3] if non-normally distributed.

Comparisons of categorical variables between groups or subgroups were performed using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Associations between genetic variants and investigated biochemical markers were evaluated with Spearman's rank correlation. Statistical power exceeding 80% was required for significance consideration. Differences were considered statistically significant at $p < 0.05$.

Results

Data on nitrate and fluoride concentrations in decentralized drinking water sources in the Poltava region were evaluated. Territories with nitrate levels exceeding 50 mg/L and fluoride levels exceeding 1.5 mg/L were classified as polluted.

The study groups were compared with respect to the frequency distribution of genotypes for the investigated genetic markers and levels of biochemical markers. The results of this analysis are presented in Table 2.

Genotype frequencies for the investigated gene variants were consistent with Hardy-Weinberg equilibrium. In the main study cohort of children with COVID-19, a significantly higher frequency of the AA genotype of the rs1801131 variant of the *MTHFR* gene was observed, suggesting a potential association between this genotype and increased disease risk. In the same group, lower urinary concentrations of nitrites, nitrates, and sialic acids were detected. These findings may reflect phenotypic manifestations of oxidative and nitrosative stress that alter immune responses and intensify inflammatory processes. Additionally, children with COVID-19 exhibited a markedly higher upper quartile for malondialdehyde (MDA) levels, indicating greater variability in MDA concentrations and its contribution to the distinctive clinical course of the infection in pediatric patients.

Table 2

Genetic, biochemical, and environmental characteristics of the study groups

Parameter		Main group (n=40)	Comparison group (n=17)	p
MTHFR *rs*1801133	CC	12 (33.3%)	8 (50.0%)	0.21*
	CT	18 (50.0%)	8 (50.0%)	
	TT	6 (16.7%)	0 (0.0%)	
MTHFR *rs*1801131	AA	25 (69.4%)	6 (37.5%)	0.038*
	AC	10 (27.8%)	7 (43.8%)	
	CC	1 (2.8%)	3 (18.8%)	
VDR rs731236	TT	15 (41.7%)	6 (37.5%)	0.79*
	TC	14 (38.9%)	8 (50.0%)	
	CC	7 (19.4%)	2 (12.5%)	
Nitrite levels, nmol/L		1.22 [0.91; 1.90]	2.13 [1.82; 2.43]	0.03
Nitrate levels, nmol/L		2.74 [1.82; 3.75]	4.26 [3.65; 4.56]	0.03
MDA levels, nmol/L		2.98 [1.24; 9.06]	3.83 [2.59; 5.85]	0.99
Sialic acid levels, nmol/L		0.16 [0.08; 0.44]	0.53 [0.34; 0.94]	0.001
Living in fluoride-polluted territory		34 (85.0%)	14 (82.4%)	0.54
Living in nitrate-polluted territory		11 (27.5%)	6 (35.3%)	0.55

**the lowest value of the «p» is provided.*

To evaluate the contribution of oxidative and nitrosative stress markers to the development of the COVID-19-associated infectious process, binary logistic regression was applied to construct a predictive statistical model. The model incorporated all studied parameters and utilised the Wald forward variable selection method (Table 3).

Table 3

Predictive model for the formation of pathophysiological changes in the development of COVID-19 in children due to oxidative and nitrosative stress

Parameter	B	Standard Error	Wald	df	Significance	Exp (B)
Nitrite level	-1.619	0.648	6.239	1	0.012	0.198
MDA level	0.559	0.208	7.194	1	0.007	1.749
Sialic acid level	-6.283	2.168	8.402	1	0.004	0.002
Constant	4.071	1.344	9.174	1	0.002	58.602

Analysis revealed that elevated urinary nitrite, malondialdehyde (MDA), and sialic acid levels constituted significant pathogenic factors contributing to the development and phenotypic expression of COVID-19 in children.

Correlation analysis was performed between genetic variants, biochemical markers of oxidative and nitrosative stress, and clinical parameters, stratified by the child's region of residence with respect to drinking water pollution. In the subgroup of patients from the fluoride-polluted territories, a significant correlation was observed between the rs1801133 variant of the *MTHFR* gene and the total bilirubin concentration (r_s=0.51, p=0.011). Carriers of the TT genotype exhibited higher median total bilirubin levels: 11.9 [11.9; 14.9] nmol/L.

In the subgroup of patients from nitrate-polluted territories, significant correlations were identified as follows: between the rs1801133 variant of the *MTHFR* gene and MDA levels (rs = 0.79, p = 0.034), with higher median MDA concentrations in TT genotype carriers (9.2 [8.7; 10.8] nmol/L); and betweeb the rs1801131 variant of the *MTHFR* gene and creatinine levels (rs = 0.73, p = 0.027), with the lowest median creatinine concentration observed in AA genotype carriers (41.0 [39.0; 57.0] μmol/L).

In children residing in territories polluted with fluoride and nitrates, *MTHFR* gene variants showed significant associations with total bilirubin, creatinine, and MDA levels. Given the established role of *MTHFR* polymorphisms in predisposing to folate-dependent disorders and impairing antioxidant capacity, together with the observed correlation with hepatic and renal function markers in this cohort, betaine-arginine dietary supplementation (1 g betaine, 1 g arginine, and citrate ions per dose) was proposed as an adjunct to standard nutrition. This supplement was selected based on its capacity to support folate metabolism and mitigate phenotypic consequences of oxidative and nitrosative stress in the context of viral infection.

To evaluate the potential effects of this supplement, a subgroup of children with severe COVID-19 was selected from the overall cohort. The supplement was administered in addition to standard therapy (following parental consent) at a dose of one sachet daily. The median age of supplemented children was 5.0 [3.0; 7.0] years. The comparison subgroup of clinically healthy children at the time of assessment had a median age of 4.0 years [3.0; 8.0], which did not differ significantly from the severe COVID-19 subgroup. The supplement was not administered to children with mild disease (median age 1.0 year [0.8; 3.0]).

Dynamic monitoring of oxidative and nitrosative stress markers was performed in the described subgroups. Concentrations of nitrites, nitrates, MDA, and sialic acids were re-determined on day 14 after disease onset (Table 4).

Table 4

Comparison of oxidative and nitrosative stress indicators and their temporal dynamics in the examined children, stratified by infection status and betaine-arginine supplementation

Parameter	Children with severe COVID-19, supplement administered (n=17)		Children with mild COVID-19, no supplement (n=17)		Clinically healthy children (n=17)
	1 day	14 day	1 day	14 day	1 day
Nitrites	2.12 [1.37; 3.50]	1.82 [1.52; 3.12]	0.91 [0.91; 1.37'	1.22 [0.61; _]	2.13 [1.82; 2.43]
Nitrates	3.95 [2.74; 7.30]	3.95 [3.04; 6.08]	2.13 [1.82; 2.74]	2.43 [1.22; _]	4.26 [3.65; 4.56]
MDA	9.23 [7.09; 13.11]	8.44 [4.00; 9.90]	1.35 [1.07; 2.19]	2.36 [1.91; _]	3.83 [2.59; 5.85]
Sialic acids	0.16 [0.10; 0.63]	0.40 [0.20; 0.95]	0.08 [0.05; 0.33]	0.08 [0.07; _]	0.53 [0.34; 0.94]

Comparison of biomarkers measured on day 1 of illness between the subgroup of children with severe COVID-19 who received betaine-arginine supplementation and the clinically healthy comparison group revealed no significant differences in urinary nitrite or nitrate concentrations. In contrast, MDA levels were significantly elevated in the severe COVID-19 subgroup on both day 1 ($p = 0.0001$) and day 14 ($p = 0.021$) compared with the healthy group. Urinary sialic acid concentration on day 1 was significantly lower in the severe subgroup ($p = 0.041$); by day 14, mean sialic acid levels no longer differed between the supplemented severe subgroup and the healthy group, consistent with a potential beneficial effect of the supplement.

In the severe COVID-19 subgroup receiving supplementation, median nitrite concentration decreased over time, whereas nitrate levels remained unchanged. Notably, mean MDA concentration declined and mean sialic acid concentration increased by day 14 in this subgroup Dynamic assessment on day 14 was not feasible in the mild COVID-19 subgroup due to early withdrawal from the study. However, mean biomarker values on day 1 in the mild subgroup differed significantly from those in the comparison group, a difference most likely attributable to age disparity rather than disease severity.

Discussion

Large-scale genome-wide association studies (GWAS) conducted under the COVID-19 Host Genetics Initiative, encompassing millions of participants, have identified multiple genetic loci associated with COVID-19 severity. Notable associations involve genes implicated in immune response, including IFNAR2, IL10RB, TYK2, and HLA loci [21]. While these findings have advanced understanding of the genetic architecture of COVID-19 susceptibility and severity in predominantly adult populations, pediatric-specific data remain limited. The present study extends this body of evidence by examining the role of oxidative and nitrosative stress, together with gene-environment interactions, in the pathogenesis and clinical course of COVID-19 in children.

Oxidative and nitrosative stress represent key mechanisms in COVID-19 pathogenesis, contributing to cellular and tissue injury that may precipitate severe disease progression and complications. Oxidative stress arises from an imbalance between reactive oxygen species (ROS) generation and antioxidant defence capacity. In COVID-19, excessive ROS production is driven by the host inflammatory response and tissue hypoxia, resulting in peroxidation of lipids, oxidation of proteins, and DNA damage. Nitrosative stress is mediated by overproduction of reactive nitrogen species, particularly nitric oxide (NO) and peroxynitrite. Although NO production may initially represent an anti-inflammatory or antiviral response, excessive peroxynitrite formation leads to protein nitration and subsequent cellular dysfunction.

The interaction between oxidative and nitrosative stress exacerbates cellular damage through the formation of highly reactive intermediates, thereby amplifying inflammation, endothelial dysfunction, and coagulopathy – hallmarks of severe COVID-19. Urinary metabolites such as nitrates, nitrites, MDA,), and sialic acids serve as established biomarkers of these processes Elevated concentrations of these markers reflect impaired antioxidant capacity and excessive accumulation of ROS and reactive nitrogen species. Increased levels of these biomarkers have been consistently associated with COVID-19 severity and inflammatory burden.

Nitrates enter the human body primarily via drinking water and food in regions affected by agricultural runoff or industrial contamination [22]. Approximately 75% of ingested nitrates are excreted unchanged in urine [23], rendering urinary nitrate concentration a reliable indicator of systemic exposure. Nitrates may also serve as an additional source of nitric oxide; however some nitrates can be reduced to nitrites, leading to the formation of potentially carcinogenic N-nitroso compounds [24].

The present findings demonstrate a significant influence of environmental nitrate contamination on metabolic pathways in children with COVID-19, particularly on biomarkers of antioxidant status, hepatic function, and renal function. The observed correlations between *MTHFR* gene variants and metabolite levels indicate a gene-environment interaction that may heighten vulnerability of children to oxidative damage in polluted regions. Elevated urinary nitrite and nitrate concentrations were identified as significant biochemical markers in pediatric COVID-19 cases, consistent with prior observations in adults [25, 26]. These levels correlated with clinical severity, underscoring the contribution of nitrosative stress to disease progression in children.

SARS-CoV-2 infection triggers a robust inflammatory cascade that markedly increases reactive oxygen species (ROS) production, thereby inducing oxidative stress. Lipid peroxidation damages cell membranes and elevates MDA concentrations, a widely used biomarker of oxidative damage. Multiple studies in adults with COVID-19 have consistently demonstrated elevated MDA levels,

particularly in severe cases, correlating with greater tissue injury, heightened inflammation, and disease progression [25]. In the present pediatric cohort, however, no significant difference in MDA concentrations was observed between children with COVID-19 and the comparison group. Nevertheless, the logistic regression coefficient identified elevated MDA as an independent predictor of increased COVID-19 risk. This apparent discrepancy may reflect the existence of threshold MDA concentrations required to drive clinically relevant pathophysiological effects, or interactions with other oxidative/nitrosative stress parameters that modulate the overall risk profile in children.

Sialic acids, particularly on the cell surface, have been implicated in facilitating SARS-CoV-2 attachment to host cells. Although ACE2 serves as the primary entry receptor, additional factors, such as sialic acids may enhance initial viral binding to cells. The interaction of the SARS-CoV-2 spike (S) protein with sialic acids on cell-surface glycoproteins and glycolipids may facilitate initial viral attachment to host cell membranes prior to engagement of the primary ACE2 receptor. The level of ACE2 expression in epithelial cells is recognised as a determinant of susceptibility to SARS-CoV-2 infection [27, 28]. Sialic acid homeostasis may further modulate COVID-19 progression. Dysregulation of sialic acid balance in tissues can alter immune responses and promote inflammation, a hallmark of severe disease [29]. Sialic acids are therefore regarded not only as potential biomarkers but also as modulators of viral–host interactions, with relevance to COVID-19 diagnosis and pathogenesis. Elevated sialic acid concentrations have been reported in patients with severe COVID-19 [30]. The divergent findings in the present study may be attributable to age-related physiological differences. Children exhibit distinct patterns of sialic acid synthesis and catabolism compared with adults. Moreover, prior observations of elevated sialic acids predominantly derive from critically ill adults requiring intensive care, whereas the paediatric participants in this cohort presented with mild to moderate disease managed in inpatient settings These results suggest that sialic acid levels may initially decrease during the early phase of infection in children, followed by an increase during immune hyperactivation and progression to severe disease.

Fluoride contamination represents a relevant environmental determinant of COVID-19 severity. A strong positive correlation has been reported between groundwater fluoride concentrations and COVID-19 mortality rates [31]. High fluoride exposure disrupts endocrine function [32], thereby influencing metabolic pathways and the biosynthesis of biomolecules, including sialic acids. Excess fluoride also induces oxidative stress [33]. These mechanisms may contribute to the association between fluoride exposure and increased COVID-19 severity. In the present study, a significant correlation was identified between the rs1801133 variant of the *MTHFR* gene variant and total serum bilirubin concentration, indicating a gene-environment interaction in the development and course of COVID-19, providing evidence of gene-environment interaction that exacerbates metabolic derangements and organ dysfunction in children with COVID-19 residing in areas with contaminated drinking water.

Certain *MTHFR* gene variants have been shown to impair the efficiency of oxidant detoxification [33]. In polluted environments, oxidative stress is amplified [34], thereby promoting chronic inflammation, reducing immune effectiveness, and increasing vulnerability to infections. Endothelial barrier function is also compromised, facilitating pathogen entry into the bloodstream [33]. Prior research has linked *MTHFR* variants to severe COVID-19, thromboembolic complications, and increased mortality [11, 12]. The current findings corroborate a significant association between *MTHFR* gene variants and COVID-19 risk. This effect appears modulated by co-exposure to fluoride and nitrate contamination. Notably, the rs1801133 variant reduces enzyme activity, leading to impaired methylation and homocysteine accumulation [12]. Under such conditions, reduced detoxification capacity may potentiate the toxic effects of fluoride, further aggravating oxidative burden and weakening immune surveillance against SARS-CoV-2.

No significant association was detected between the rs731236 variant of the VDR gene and COVID-19 risk in this cohort. Similarly, stratification by fluoride and nitrate exposure did not reveal differential effects. Although preliminary reports have suggested a role for this variant in COVID-19 susceptibility and severity, particularly within Ukrainian populations, the absence of association in the present study may be attributable to widespread prophylactic vitamin D supplementation among Ukrainian children. Adequate vitamin D status could mitigate potential adverse consequences of the rs731236 polymorphism on vitamin D receptor function and immune regulation.

Development of targeted adjunctive therapies in the management of COVID-19 stress remains a critical priority, particularly in paediatric populations. Betaine-arginine supplementation has demonstrated favourable effects on metabolic and immunological pathways, including attenuation of oxidative stress, improvement of endothelial function, normalisation of homocysteine concentrations, and restoration of antioxidant balance [35]. This combination is approved for use in children aged 3 years and older and may serve as a supportive intervention in COVID-19 treatment protocols. Clinical evidence supports the use of arginine in COVID-19, where it has been associated with improved outcomes [36]. Similarly, reduced circulating betaine levels have been linked to poorer prognosis in COVID-19 [37]. In the present study, favourable changes in biochemical markers were observed following betaine-arginine supplementation in children with COVID-19, consistent with attenuation of oxidative stress. The findings indicate that COVID-19 risk and progression are associated with *MTHFR* gene variants, consistent with a folate-dependent pathology that necessitates targeted preventive and personalized treatment approaches. Further large-scale studies are required, incorporating detailed genetic and metabolic profiling, with particular emphasis on nitrosative stress pathways, which remain underexplored.

Conclusions

The present study identified significant associations between MTHFR gene variants and increased risk of COVID-19 in children. Key biochemical markers – urinary nitrate, nitrite, sialic acid, and malondialdehyde (MDA) concentrations – were implicated in disease pathogenesis. These associations, together with observed gene-environment interactions, indicate that COVID-19 in children residing in regions with fluoride and nitrate contamination of drinking water constitutes a folate-dependent condition, particularly in the Poltava region. Oxidative and nitrosative stress were confirmed as central pathogenic mechanisms driving disease development and progression, as evidenced by the corresponding biomarker profiles. Administration of betaine-arginine supplementation was associated with favourable changes in these biomarkers, suggesting potential utility as an adjunctive component of preventive or personalized therapeutic strategies for paediatric COVID-19.

Prospects for further research. The prospect for further research is search and study of new biochemical and genetic markers of COVID-19 severity in children.

Contribution of co-authors to the preparation of materials for the scientific article: V. Pokhylko – concept and design of the study, collection and processing of materials, analysis of the obtained data; Yu. Cherniavska – analysis of the obtained data, writing the text; S. Tsvirenko – concept and design of the study, collection and processing of materials; O. Shevchenko – concept and design of the study, analysis of the obtained data; Z. Rossokha – concept and design of the study, analysis of the obtained data, collection and processing of materials; O.Popova – collection and processing of materials, analysis of the obtained data; L. Fishchuk – analysis of the obtained data, writing the text.

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References:

1. Guo CY, Zhang WX, Zhou YG, Zhang SS, Xi L, Zheng RR, et al. Dynamics of respiratory infectious diseases under rapid urbanization and COVID-19 pandemic in the subcenter of Beijing during 2014-2022. Heliyon. 2024;10(9): e29987. DOI: http://doi.org/10.1016/j.heliyon.2024.e29987 PMID: 38737278; PMCID: PMC11088252.

2. Hong JY, Medzhitov R. On developmental programming of the immune system. Trends Immunol. 2023;44(11):877-89. DOI: http://doi.org/10.1016/j.it.2023.09.004 PMID: 37852863.

3. Seriakova I, Yevtushenko V, Kramarov S, Palatna L, Shpak I, Kaminska T. Clinical course of COVID-19 in hospitalized children of Ukraine in different pandemic periods. Eur Clin Respir J. 2022;9(1):2139890. DOI: http://doi.org/10.1080/20018525.2022.2139890 PMID: 36325478; PMCID: PMC9621244.

4. Ward MH, Jones RR, Brender JD, de Kok TM, Weyer PJ, Nolan BT, et al. Drinking Water Nitrate and Human Health: An Updated Review. Int J Environ Res Public Health. 2018;15(7):1557. DOI: http://doi.org/10.3390/ijerph15071557 PMID: 30041450; PMCID: PMC6068531.

5. Zhu S, Wei W. Progress in research on the role of fluoride in immune damage. Front Immunol. 2024;15:1394161. DOI: http://doi.org/10.3389/fimmu.2024.1394161 PMID: 38807586; PMCID: PMC11130356.

6. Mikkelsen K, Apostolopoulos V. Vitamin B12, folic acid, and the immune system. In: Mahmoudi M, Rezaei N, editors. Nutrition and Immunity. Cham: Springer; 2019. p. 95-112. DOI: http://doi.org/10.1007/978-3-030-16073-9_6

7. Danishpajooh IO, Gudi T, Chen Y, Kharitonov VG, Sharma VS, Boss GR. Nitric oxide inhibits methionine synthase activity in vivo and disrupts carbon flow through the folate pathway. J Biol Chem. 2001;276(29):27296-303. DOI: http://doi.org/10.1074/jbc.M104043200 PMID: 11371572.

8. Fan Y, Wu L, Zhuang W. Methylenetetrahydrofolate Reductase Gene rs1801133 and rs1801131 Polymorphisms and Essential Hypertension Risk: A Comprehensive Analysis. Cardiovasc Ther. 2022;2022:2144443. DOI: http://doi.org/10.1155/2022/2144443 PMID: 35284002; PMCID: PMC8888071.

9. Zhang HZ, Wu JH, Huang Q, Yang Q, Sima Q, Chen KY, et al. Associations of methylenetetrahydrofolate reductase gene (MTHFR) rs1801131 and rs1801133 polymorphisms with susceptibility to vitiligo: A meta-analysis. J Cosmet Dermatol. 2021;20(7):2359-68. DOI: http://doi.org/10.1111/jocd.13857 PMID: 33219596.

10. Alam NF, Ahmed R, Mahmud Z, Tamanna S, Shaon MA, Howlader MZH. Genetic association and computational analysis of MTHFR gene polymorphisms rs1801131 and rs1801133 with breast cancer in the Bangladeshi population. Sci Rep. 2024;14(1):24232. DOI: http://doi.org/10.1038/s41598-024-75656-y PMID: 39414907; PMCID: PMC11484754.

11. Moness H, Mousa SO, Mousa SO, Adel NM, Ibrahim RA, Hassan EE, et al. Thrombophilia genetic mutations and their relation to disease severity among patients with COVID-19. PLoS One. 2024;19(3): e0296668. DOI: http://doi.org/10.1371/journal.pone.0296668 PMID: 38507367; PMCID: PMC10954113.

12. Bagheri Hamidi A, Namazi N, Mohammad Amoli M, Amani M, Gholami M, Youssefian L, et al. Association of MTHFR C677T polymorphism with elevated homocysteine level and disease development in vitiligo. Int J Immunogenet. 2020;47(4):342-50. DOI: http://doi.org/10.1111/iji.12476 PMID: 32064757.

13. Jhamb JA, Rampal S, Jaiman A, Sinniah A, Tong JB, Jaiman A. Worsening air pollution: an unfamiliar cause of low vitamin D levels – a systematic literature review. J Clin Med Kaz. 2023;20(5):4-8. DOI: http://doi.org/10.23950/jcmk/13760

14. Lei W, Tian H, Xia Y. Association Between the TaqI (rs731236 T>C) Gene Polymorphism and Dental Caries Risk: A Meta-analysis. Genet Test Mol Biomarkers. 2021;25(5):368-75. DOI: http://doi.org/10.1089/gtmb.2020.0263 PMID: 33960841; PMCID: PMC8140352.

15. Fishchuk L, Rossokha Z, Pokhylko V, Cherniavska Y, Tsvirenko S, Kovtun S, et al. Modifying effects of TNF-α, IL-6 and VDR genes on the development risk and the course of COVID-19. Pilot study. Drug Metab Pers Ther. 2021;37(2):133-9. DOI: http://doi.org/10.1515/dmpt-2021-0127 PMID: 34860474.

16. Regina da Silva Correa da Ronda C, Berlofa Visacri M, Tiemi Siguemoto J, Motta Neri C, Crispim Lopo de Abreu M, de Souza Nicoletti A, et al. Single-nucleotide polymorphisms related to vitamin D metabolism and severity or mortality of COVID-19: A systematic review and meta-analysis. Gene. 2024;906:148236. DOI: http://doi.org/10.1016/j.gene.2024.148236 PMID: 38316264.

17. Kaidashev I, Shlykova O, Izmailova O, Torubara O, Yushchenko Y, Tyshkovska T, et al. Host gene variability and SARS-CoV-2 infection: A review article. Heliyon. 2021;7(8): e07863. DOI: http://doi.org/10.1016/j.heliyon.2021.e07863 PMID: 34458641; PMCID: PMC8382593.

18. Murzina A, Rossokha Z. Polymorphic variants of the VDR gene in children with psoriasis. Dermatol Venerol. 2020;3(89):8-15. DOI: http://doi.org/10.33743/2308-1066-2020-3-8-15

19. Fishchuk L, Rossokha Z, Pokhylko V, Cherniavska Y, Popova O, Tsvirenko S, et al. Associations of variants of folate cycle genes with features of the clinical course of severe intraventricular hemorrhages in premature infants. J Neonatal Perinatal Med. 2022;15(3):545-51. DOI: http://doi.org/10.3233/NPM-210962

20. Kovalova O, Pokhylko V, Cherniavska Y, Tsvirenko S, Rossokha Z, Davydenko A. Peculiarities of metabolism (by level of nitrates, nitrites, malondialdehyde and sialic acids) in 6- to 9-month-old infants born to mothers with metabolic syndrome who had hypoxic-ischemic encephalopathy in the early neonatal period. Neonatol Surg Perinat Med. 2024;4(54):56-64. DOI: http://doi.org/10.24061/2413-4260.XIV.4.54.2024.8

21. D'Antonio M, Nguyen JP, Arthur TD, Matsui H; COVID-19 Host Genetics Initiative; D'Antonio-Chronowska A, Frazer KA. SARS-CoV-2 susceptibility and COVID-19 disease severity are associated with genetic variants affecting gene expression in a variety of tissues. Cell Rep. 2022;39(11):110968. DOI: http://doi.org/10.1016/j.celrep.2022.110968 PMID: 35705058; PMCID: PMC9195561.

22. Bowles EF, Burleigh M, Mira A, Van Breda SGJ, Weitzberg E, Rosier BT. Nitrate: «the source makes the poison». Crit Rev Food Sci Nutr. 2025;65(24):4676-702. DOI: http://doi.org/10.1080/10408398.2024.2395488 PMID: 39213282.

23. Wu Z, Tian T, Ma W, Gao W, Song N. Higher urinary nitrate was associated with lower prevalence of congestive heart failure: results from NHANES. BMC Cardiovasc Disord. 2020;20(1):498. DOI: http://doi.org/10.1186/s12872-020-01790-w PMID: 33238887; PMCID: PMC7690024.

24. Ward MH, Jones RR, Brender JD, de Kok TM, Weyer PJ, Nolan BT, et al. Drinking Water Nitrate and Human Health: An Updated Review. Int J Environ Res Public Health. 2018;15(7):1557. DOI: http://doi.org/10.3390/ijerph15071557 PMID: 30041450; PMCID: PMC6068531.

25. Bastin A, Abbasi F, Roustaei N, Abdesheikhi J, Karami H, Gholamnezhad M, et al. Severity of oxidative stress as a hallmark in COVID-19 patients. Eur J Med Res. 2023;28(1):558. DOI: http://doi.org/10.1186/s40001-023-01401-2 PMID: 38049886; PMCID: PMC10696844.

26. Lorente L, Gómez-Bernal F, Martín MM, Navarro-Gonzálvez JA, Argueso M, Perez A, et al. High serum nitrates levels in non-survivor COVID-19 patients. Med Intensiva (Engl Ed). 2020;46(3):132-9. DOI: http://doi.org/10.1016/j.medin.2020.10.003 PMID: 33293102; PMCID: PMC7654288.

27. Sun XL. The role of cell surface sialic acids for SARS-CoV-2 infection. Glycobiology. 2021;31(10):1245-53. DOI: http://doi.org/10.1093/glycob/cwab032 PMID: 33909065; PMCID: PMC8600286.

28. Kaminskyi V, Vorobei L, Zhdanovych O, Korniienko S, Kolomiichenko T, Fastovets O. Clinical and genetic determinants of severe course of COVID-19 in pregnant women. Reprod Endocrinol. 2022;65:38-43. DOI: http://doi.org/10.18370/2309-4117.2022.65.38-43

29. Wielgat P, Rogowski K, Godlewska K, Car H. Coronaviruses: Is Sialic Acid a Gate to the Eye of Cytokine Storm? From the Entry to the Effects. Cells. 2020;9(9):1963. DOI: http://doi.org/10.3390/cells9091963 PMID: 32854433; PMCID: PMC7564400.

30. Haroun RA, Osman WH, Eessa AM. Evaluation of serum total sialic acid in moderate COVID-19 patients with and without gastrointestinal tract manifestations. Tissue Cell. 2022;74:101679. DOI: http://doi.org/10.1016/j.tice.2021.101679 PMID: 34801789; PMCID: PMC8598396.

31. Bhat D, Priya S, Bharath SV, Manohar B. Relationship between COVID-19 severity and fluoride levels of drinking water among children in Karnataka state, India: an epidemiological study. Int J Appl Dent Sci. 2022;8(4):33-7. DOI: http://doi.org/10.22271/oral.2022.v8.i4a.1623

32. Skórka-Majewicz M, Goschorska M, Żwierełło W, Baranowska-Bosiacka I, Styburski D, Kapczuk P, et al. Effect of fluoride on endocrine tissues and their secretory functions – review. Chemosphere. 2020;260:127565. DOI: http://doi.org/10.1016/j.chemosphere.2020.127565 PMID: 32758781.

33. Kirmit A, Yesilnacar MI, Calısır M, Bayhan I, Celik H. Oxidative stress, DNA damage and apoptosis levels in those who use borderline high level fluoride content drinking water. J Contemp Med. 2020;10(1):45-50. DOI: http://doi.org/10.16899/jcm.690968

34. Daiber A, Münzel T. Organic Nitrate Therapy, Nitrate Tolerance, and Nitrate-Induced Endothelial Dysfunction: Emphasis on Redox Biology and Oxidative Stress. Antioxid Redox Signal. 2015;23(11):899-942. DOI: http://doi.org/10.1089/ars.2015.6376 PMID: 26261901; PMCID: PMC4752190.

35. Rossokha Z, Fishchuk L, Sheyko L, Medvedieva N, Gorovenko N. Positive effect of betaine-arginine supplement on improved hyperhomocysteinemia treatment in married couples with reproductive disorders. Georgian Med News. 2020;309:22-8. PMID: 33526724.

36. Trimarco V, Izzo R, Lombardi A, Coppola A, Fiorentino G, Santulli G. Beneficial effects of L-Arginine in patients hospitalized for COVID-19: New insights from a randomized clinical trial. Pharmacol Res. 2023;191:106702. DOI: http://doi.org/10.1016/j.phrs.2023.106702 PMID: 36804278; PMCID: PMC9928676.

37. Israr MZ, Ibrahim W, Salzano A, Sarmad S, Wilde MJ, Cordell RL, et al. Association of gut-related metabolites with respiratory symptoms in COVID-19: A proof-of-concept study. Nutrition. 2022;96:111585. DOI: http://doi.org/10.1016/j.nut.2021.111585 PMID: 35131599; PMCID: PMC8730784.

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АНАЛІЗ ВАРІАНТІВ ГЕНІВ MTHFR ТА VDR І МАРКЕРІВ ОКСИДАТИВНОГО/НІТРОЗАТИВНОГО СТРЕСУ В РОЗВИТКУ ТА ПЕРЕБІГУ COVID-19 У ДІТЕЙ З ПОЛТАВСЬКОЇ ОБЛАСТІ: ШЛЯХИ РОЗРОБКИ ПЕРСОНАЛІЗОВАНИХ ТЕРАПЕВТИЧНИХ ТА ПРОФІЛАКТИЧНИХ ЗАХОДІВ

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Резюме.

Аналіз варіантів генів, маркерів оксидативного та нітрозативного стресу може допомогти в розробці персоналізованих стратегій профілактики та лікування COVID-19 та інших інфекційних захворювань, особливо в контексті існуючого забруднення навколишнього середовища.

Мета. Метою дослідження було оцінити вплив варіантів генів *MTHFR* (rs1801133, rs1801131) та *VDR* (rs731236), маркерів оксидативного та нітрозативного стресу на перебіг COVID-19 у дітей з Полтавської області, враховуючи забруднення нітратами та фтором.

Матеріали і методи. У дослідженні взяли участь 40 дітей з COVID-19 та 17 дітей в групі порівняння. Були проаналізовані такі ключові показники: варіанти генів *MTHFR* та *VDR*; рівень нітратів, нітритів, малонового діальдегіду (МДА) та сіалових кислот у сечі; а також проживання на території, забрудненій фтором та нітратами. Відповідно до рішення комісії з біоетики Полтавського державного медичного університету № 184 від 25.06.2020, матеріали наукового дослідження відповідають етичним вимогам гуманного поводження з пацієнтами, визначеним Токійською декларацією Всесвітньої медичної асоціації, Гельсінкськими міжнародними рекомендаціями, Загальною декларацією прав людини, Конвенцією Ради Європи про права людини та біомедицину, а також чинним законодавством України, наказами МОЗ і положеннями Кодексу етики лікаря України. Усі батьки дали згоду на обстеження. Статистичний аналіз проводили за допомогою програмного забезпечення SPSS версії 27. Дослідження виконано в рамках науково-дослідної роботи кафедри педіатрії № 1 із неонатологією Полтавського державного медичного університету № 0120U102856 «Розробити клініко-лабораторні критерії, методи прогнозування та запобігання метаболічних порушень у дітей раннього віку».

Результати. У групі дітей з COVID-19 спостерігалася значна поширеність генотипу AA варіанту rs1801131 гену *MTHFR*. До вагомих патогенних факторів захворювання належали рівні нітритів, МДА та сіалових кислот усечі. У дітей, які проживають на територіях, забруднених фтором та нітратами, спостерігалася помітна кореляція між варіантами гена *MTHFR* та рівнями білірубіну, креатиніну та МДА. Крім того, дослідження підкреслило потенційну користь харчових добавок з бетаїн-аргініном як профілактичної та персоналізованої стратегії лікування дітей з COVID-19.

Висновок. У результаті проведеного дослідження було виявлено зв'язки між варіантами гена *MTHFR* та підвищеним ризиком COVID-19, підкреслено вплив середовища, забрудненого фтором та нітратами, визначено ключові патогенні фактори, такі як рівні нітритів, МДА та сіалових кислот у сечі. Харчова добавка з бетаїн-аргініном може бути розглянута як потенційний профілактичний та лікувальний варіант у дітей з COVID-19.

Ключові слова: COVID-19; *MTHFR*; нітрозативний стрес; оксидативний стрес; *VDR*.

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