Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.6 (2024). p.517-26; DOI: https://doi.org/10.14238/pi64.6.2024.517-26

Original Article

Comparing clinical, laboratory, and epidemiological features of COVID-19 variants during different pandemic waves among children in Ukraine

Tetiana Harashchenko[1], Tetiana Umanets[1], Tetiana Kaminska[2], Lapshyn Volodymyr[1], Yurii Antypkin[1]

Abstract

Background The SARS-CoV-2 virus, the causative agent of the coronavirus disease (COVID-19), mutated during its replication and spread among the population. These mutations led to new viral variants, which differed in their characteristics and manifestations, contributing to the wave-like progression of the COVID-19. The Centers for Disease Control and Prevention classified variants based on the public health risk include variants of interest such as λ and μ, variants of concern including α, β, γ, δ, o, variants of high consequence, and variants being monitored.

Objective To conduct a comparative analysis of the demographic, clinical, epidemiological, radiological, and laboratory characteristics of hospitalized children with COVID-19 during different waves of the disease.

Methods A cohort study was conducted involved 337 children aged one month to 18 years who were hospitalized with laboratory-confirmed COVID-19 between 2020 and 2023 in Ukraine.

Results During wave 3 (W3), wave 5 (W5) and wave 6 (W6), children under 3 years of age were hospitalized more frequently. The severe course of disease predominantly occurred during W3 period, with 47.3% cases demonstrating severe symptoms such as respiratory failure, bilateral pneumonia, and significant changes in laboratory parameters, including white blood cell count, erythrocyte sedimentation rate, D-dimer, and procalcitonin. One fatal case was reported during W3. The duration of hospitalization was longest for children in the W3 group. A moderate course of the disease was significantly more prevalent among hospitalized children in the first wave (77.78%, $P<0.05$), characterized by interstitial changes in the lungs, elevated C-reactive protein, and platelet levels. Fever and intoxication syndrome were reported with similar frequency during all waves of COVID-19.

Conclusion Our study demonstrates the dynamic changes in manifestations and the progression of the disease across different variants of concern of SARS-CoV-2. The most severe cases of COVID-19 was observed during the third wave which predominated by the δ (delta) strain. **[Paediatr Indones. 2024;64:517-26; DOI: https://doi.org/10.14238/pi64.6.2024.517-26].**

Keywords: *COVID-19; waves; variants; children; SARS-CoV-2*

COVID-19 caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first diagnosed in December 2019 in Wuhan, China, and has since become a global public health crisis. The virus spread rapidly around the world, leading the *World Health Organization* (WHO) to declare COVID-19 a pandemic on March 2020.[1]

Children can be infected by SARS-CoV-2. The severity of the disease in pediatric patients ranges from asymptomatic to severe illness.[2] Systematic reviews indicate that 1% to 6.4% of all SARS-CoV-2 infections worldwide occur in children, and the child mortality rate is lower than that of adults, accounting for only 1% to 6.4% of total deaths.[3,4]

At the beginning of the pandemic, the most common symptoms in pediatric patients included fever (98%), fatigue (96%), dry cough (59.4%), headache (8%), and diarrhea (3%).[2] Laboratory

From the Department of Respiratory Diseases and Allergy in Children, State Institution - Institute of Pediatrics, Obstetrics and Gynecology named after Academician O.M. Lukyanova, National Academy of Medical Sciences of Ukraine[1] and Department of Pediatrics, CNE Kyiv City Children's Clinical Infectious Disease Hospital[2], Kyiv, Ukraine.

Corresponding author: Tetiana Harashchenko, MD. State Institution - Institute of Pediatrics, Obstetrics and Gynecology named after academician O. Lukyanova of the NAMS of Ukraine. Platona Mayborody st., 8, Kyiv, 04050, Ukraine. Fax: (044) 483-90-94. Email: tatti.my@gmail.com.

Submitted January 12, 2024. Accepted December 9, 2024.

findings reported lymphopenia (11.4%) and elevated C-reactive protein (CRP) levels (18.6%).[5] Over the course of the pandemic, the clinical, epidemiological, and laboratory characteristics of COVID-19 in children began to diverge due to genetic changes in the virus.

The SARS-CoV-2 virus, a single-stranded RNA virus belonging to the Coronaviridae family and Betacoronavirus genus, has mutated during its replication and spread in the population.[6,7] As a result of these mutations, new viral variants have emerged, each with different clinical manifestations and laboratory characteristics. To categorize the SARS-CoV-2 variants, a group of WHO experts proposed a classification system using Greek letters: α, β, γ, δ, ε, ζ, η, θ, ι, κ, λ, μ and ο.[8] The *Centers for Disease Control and Prevention* (CDC), in collaboration with the SARS-CoV-2 Interagency Group (SIG), has developed a classification system for SARS-CoV-2 variants based on their public health risk. The groups idenstified include variants of interest (VOI), such as λ (lambda) and μ (mu), Variants of Concern (VOC), including α (alpha), β (beta), γ (gamma), δ (delta), ο (omicron), variants of high consequence (VOHC), and variants being monitored (VBM).[9]

The omicron variant is characterized by rapid mutation and higher transmissibility compared to other SARS-CoV-2 strains, leading to the emergence of several subvariants (BA.1, BA.2, BA.3, BA.4 and BA.5). Scientists have also identified numerous recombinant subvariants of this strain, such as XBB, XBD and XBF, were also found during the Omicron period. Each of the subvariants and recombinant subvariants differs in clinical manifestations and characteristics.[10,11]

New strains of the virus have caused wave-like patterns in the spread of COVID-19 worlwide.[9] During each wave, specific variants of the virus have prevailed. The timing of these waves varies by country, depending on the speed at which new variants spread globally. Ukraine was no exception, after the first reported case of COVID-19 on March 3, 2020, peaks in incidence began to emerge, leading to a wave-like progression of the pandemic.[12] The first wave (W1) occured from September to December 2020, dominated by the α variant, while the third wave (W3) took place from September to December 2021, primarily involving the δ variant. The highly transmissible omicron strain dominated during two waves: the fifth wave (W5) from September to December 2022, with the predominance of Omicron BA.5 (VOC), and the sixth wave (W6) from January to February 2023, marked by the Omicron XBB.1.5 (VOC) strain. This study aimed to conduct a comparative analysis of demographic, clinical, epidemiological, radiological, and laboratory characteristics of hospitalized children with COVID-19 during different waves of the disease in Ukraine.

Methods

This cohort study involved 337 children aged one month to 18 years who were hospitalized at the Kyiv City Children's Clinical Infectious Diseases Hospital, Ukraine, with laboratory-confirmed COVID-19. Diagnosis was made using real-time nasopharyngeal and oropharyngeal reverse transcription polymerase chain reaction (RT-PCR) from September to December 2020, 2021, and 2022, and January to February in 2023. These periods were selected to exclude the influence of seasonality on the study results and correspond with the first, third, fifth, and sixth waves of COVID-19 in Ukraine, during which the highest number of hospitalized children were observed. Notably, the α, δ, and omicron strains circulated during these times, including omicron subvariants BA.5 and XBB.1.5. The children were divided into four groups according to the COVID-19 waves in Ukraine.

Demographic data such as age and gender, duration of hospitalization, source of infection, clinical characteristics (including symptoms and severity), comorbidities, complications, results of laboratory, and chest X-ray were collected from patient medical histories. These data were then entered into a standardized electronic database for further statistical analysis. All patients were tested for SARS-CoV-2 nucleic acid in the hospital laboratory certified by the Ministry of Health of Ukraine. The date of diagnosis was recorded as the date of a positive test result.

Children were categorized by age based on widely accepted developmental stages: infants (1 month - 1 year), toddlers (1-3 years,) preschoolers (3-5 years), middle childhood (6-12 years), and adolescence (13-18 years).[13] Fever was defined as

a body temperature of ≥38°C, according to the CDC guidelines, while disease severity was assessed according to WHO criteria. Upon admission to the hospital, all children underwent a complete blood count to assess white blood cell (WBC), lymphocyte, platelet counts, and erythrocyte sedimentation rate (ESR). Additionally, a biochemical blood test was performed to measure levels of C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, as well as the concentration of D-dimer and procalcitonin (PCT) in the serum. Chest X-rays were also performed for all hospitalized children.

Baseline characteristics such as symptoms, comorbidities, disease course, and results of instrumental methods and laboratory tests were reported as frequencies (percentages), while age and duration of hospitalization were presented as median (range). Categorical variables were analyzed using chi-square or Fisher's exact test, and the Kruskal-Wallis test was applied for continuous variables. Statistical significance was set at 95%, with $P<0.05$ considered valid. All of the statistical analysis was performed using *SPSS IBM version 21.0*. Ethical approval for the study was granted by the bioethics committee of the State Institution "Institute of Paediatrics, Obstetrics and Gynecology named after Academician O.M. Lukyanova, National Academy of Medical Sciences of Ukraine". Informed consent was obtained from patients and parents.

Results

The demographic characteristics of patients hospitalized between September 2020 and February 2023 are shown in **Table 1**. Among all of subjects , there were 54% boys and 46% girls. During the W3, W5, and W6 periods, children under three years of age were hospitalized more frequently, with a predominance of infants in the W5 (49.2%) and W6 groups (63%), and the toddlers group (29.7%) in the W3, while during W1, school-aged children (ages 6-18 years) were hospitalized more often (67.2%).

The main characteristics of the surveyed group of children are shown in **Table 2**. Notably, there were no recorded deaths during this wave. It is also worth noting that children in the W3 group were more likely to exprerience respiratory failure (RF) and to require oxygen support compared to children in the other groups ($P<0.05$). According to the epidemiological data, the frequency of SARS-CoV-2 infection was the highest among family members during W3 (74.3%) compared to others period. During W6, it was statistically more often impossible to identify the source of infection. Among all of subjects, 54.6% had at least one comorbidity. Children with comorbidities were significantly more likely to be hospitalized during W3. The most common comorbidities included chronic tonsillitis, atopic dermatitis, allergies, neurological disorders, obesity, and asthma. Children with recurrent respiratory illnesses (RRI), i.e., those with more than six episodes of viral infections per year, were more likely to be hospitalized during W3, with 38 children diagnosed with recurrent bronchitis. During other waves of COVID-19, there was no statistical

Table 1. Demographic characteristics of patients during four waves of COVID-19 in Ukraine

Characteristics	W1 (n=171)	W3 (n=74)	W5 (n=65)	W6 (n=27)	Total (N=337)	P value
Gender, n(%)						
Boys	85 (49.7)	45 (60.8)	36 (55.4)	16 (59.3)	182 (54)	0.739
Girls	86 (50.3)	29 (39.2)	29 (44.6)	11 (40.7)	155 (46)	0.656
Age distribution, n(%)						
Infants (1 month - <1 year)	20 (11.7)	21 (28.4)	32 (49.2)	17 (63)*	90 (26.7)	0.000*
Toddlers (1-3 years)	25 (14.6)	22 (29.7)*	9 (13.8)	2 (7.4)	58 (17.2)	0.001*
Preschool (3-5 years)	11 (6.4)	17 (22.8)	12 (18.5)	3 (11.1)	43 (12.7)	0.007
Middle Childhood (6-12 years)	61 (35.7)*	9 (12.7)	8 (12.3)	5 (18.5)	83 (24.6)	0.000*
Adolescence (13-18 years)	54 (31.6)*	5 (6.7)	4 (6.2)	0 (0.0)	63 (18.7)	0.000*

*statistically significant

Table 2. The main characteristics of patients during four waves of COVID-19 in Ukraine

Variables	W1 (n=171)	W3 (n=74)	W5 (n=65)	W6 (n=27)	Total (N=337)	P value
Mean hospital duration (SD), days	9.5 (1.6)	15.1 (1.5)*	7.2 (1.2)	6.9 (1.5)	9.6 (1.4)	0.000*
Primary source of infection, n(%)						
Family members	101 (59.1)	55 (74.3)*	40 (61.5)	10 (37)	206 (61.1)	0.006*
Children's team	19 (11.1)	6 (8.1)	5 (7.7)	3 (11.1)	33 (9.8)	0.316
None	51 (29.8)	13 (17.6)	20 (30.8)	14 (51.9)*	98 (29.1)	0.000*
COVID-19 severity, n(%)						
Moderate	133 (77.8)*	39 (52.7)	46 (70.8)	18 (66.7)	236 (70)	0.003*
Severe	38 (22.2)	35 (47.3)*	19 (29.2)	9 (33.3)	101 (30)	0.017*
Oxygen support, n(%)	1 (0.6)	9 (12.2)*	3 (4.6)	2 (7.4)	15 (4.4)	0.000*
Respiratory failure, n(%)	12 (7)	17 (23)*	10 (15.4)	4 (14.8)	43 (12.7)	0.036*
Fatal, n(%)	0 (0)	1 (1.35)	0 (0)	0 (0)	1 (0.3)	0.245
Comorbidities (abs.), n(%)	88 (51.5)	57 (77)*	27 (41.5)	12 (44.4)	184 (54.6)	0.031*
RRI	89 (52)	48 (64.8)*	25 (38.5)	6 (22.2)	168 (49.8)	0.000*
Chronic tonsillitis	20 (11.7)	25 (33.8)*	15 (23.1)	1 (3.7)	61 (18.1)	0.000*
Atopic dermatitis	9 (5.2)	15 (20.8)*	5 (7.7)	4 (14.8)	33 (9.8)	0.006*
Anemia	11 (6.4)	10 (13.5)	5 (7.7)	4 (14.8)	30 (9)	0.141
Neurological disorder	8 (4.7)	12 (16.3)*	7 (10.7)	2 (7.4)	29 (8.6)	0.058*
CMV	11 (6.4)	5 (6.7)	11 (16.9)*	0 (0.0)	27 (8)	0.025*
Allergy	7 (4.1)	12 (16.2)*	4 (6.1)	4 (14.8)	27 (8)	0.012*
Gastrointestinal diseases	5 (2.9)	9 (12.1)	5 (7.7)	1 (3.7)	20 (6)	0.061*
Asthma	4 (2.3)	9 (12.1)*	3 (4.6)	1 (3.7)	17 (5)	0.020*
Obesity	5 (2.9)	9 (12.2)*	1 (1.53)	1 (3.7)	16 (4.7)	0.008*
Epilepsy	5 (2.9)	6 (8.1)	2 (3.1)	0 (0.0)	13 (3.8)	0.168
Oncological disease	2 (1.17)	1 (1.35)	0 (0)	0 (0.0)	3 (0.9)	1.000

RRI=recurrent respiratory infection; CMV=cytomegalovirus; *statistically significant

significance regarding prevalence of comorbidities.

A comparison of the predominant symptoms during all waves of COVID-19 is shown in **Figure 1**. Fever and intoxication syndrome, such as general malaise and headache, were recorded with equal frequency across all waves of the disease among children in Ukraine. In W3, respiratory complaints like wheezing (41.9%), cyanosis (27%), and dyspnea (23%) were more common compared to W1, W5 and W6 ($P<0.05$). During W5, cough (89.2%), rhinitis (81.5%), loss of appetite (55.4%), nausea/vomiting (43.1%), and seizures (4.6%) were statistically more prevalent ($P<0.05$). Sore throat (69.6%), myalgia (39.7), and anosmia (13.5) were symptoms reported during W1. It is also noteworthy that diarrhea was nearly equally common in W1 and W5 at 31.6% and 32.3%, respectively.

A chest X-ray examination was conducted for all hospitalized children, with the results summarized in **Table 3**. In W3 and W5, pneumonia was identified as the most common X-ray finding in the lungs, compared to W1, interstitial changes were statistically more prevalent, whereas in W6, no significant pathological changes were observed on the chest X-ray. Notably, among children in group W3, cases of bilateral pneumonia with pleurisy were predominant. Bronchitis was observed during all waves. In total, 25.2% showed no changes in their chest X-rays.

The laboratory test results are shown in **Table 4**. In W1, changes confirmed by laboratory tests included thrombocytosis and an increase in CRP, both of which were statistically significant. Results of W3 indicated a higher frequency of the following features: ESR, D-dimer concentration, PCT, and leukocytosis. Increased ALT, AST, lymphocytosis and leukopenia were common among hospitalized children in group W5. In contrast, lymphopenia was more common in group W6, affecting 70.4% of the children. No statistically significant differences were found among the four study groups regarding thrombocytopenia and creatinine levels.

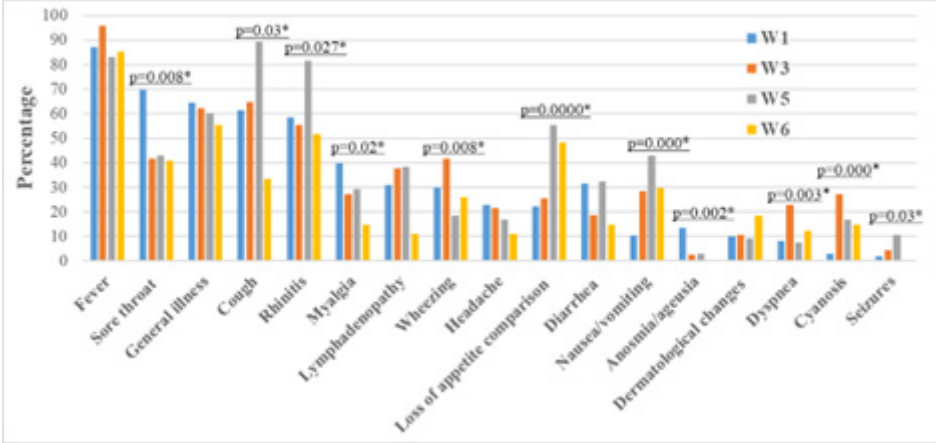

Figure 1. Comparison of symptoms reported at admission among COVID-19 cases during four waves in Ukraine

Table 3. X-Ray Findings of Children With COVID-19 during four waves in Ukraine

X-ray findings	W1	W3	W5	W6	Total
Pneumonia (total), n(%)	34 (19.9)	32 (43.2)	28 (43.1)	6 (22.2)	100 (29.7)
Unilateral pneumonia	21 (12.3)	13 (17.5)	15 (23.1)	6 (22.2)	55 (16.3)
Bilateral pneumonia	13 (7.6)	19 (25.6)*	13 (20)	0 (0.0)	45 (13.3)
Interstitial changes, n(%)	87 (50.9)*	21 (28.4)	10 (15.4)	8 (29.6)	126 (37.4)
Bronchitis, n(%)	10 (5.8)	1 (1.3)	5 (7.7)	1 (3.7)	16 (4.74)
Pleurisy, n(%)	2 (1.2)	6 (8.1)	1 (1.5)	0 (0.0)	9 (2.7)
None, n(%)	38 (22.2)	14 (18.9)	21 (32.3)	12 (44.4)*	85 (25.2)

*statistically significant

Table 4. Distribution of subjects with abnormal laboratory test results during four waves in Ukraine

Parameter	Reference values	W1 (n=171)	W3 (n=74)	W5 (n=65)	W6 (n=27)	Total (N=337)	P value
WBC, n(%)	<5.5x10^9 cells/L	38 (22.2)	9 (12.2)	22 (33.8)*	8 (29.6)	77 (22.8)	0.009*
	>12x10^9 cells/L	32 (18.7)	22 (29.7)*	9 (13.8)	4 (14.8)	67 (19.9)	0.04*
Lymphocytes, n(%)	<45%	117 (68.4)	40 (54.1)	29 (44.6)	19 (70.4)*	205 (60.8)	0.04*
	>65%	12 (7)	11 (14.8)	19 (29.2)*	1 (3.7)	43 (12.7)	0.000*
PLT, n(%)	<150x10^{12} cells/L	30 (17.5)	5 (6.7)	6 (9.2)	0 (0.0)	41 (12.2)	0.09
	>450x10^{12} cells/L	40 (23.4)*	9 (12.2)	3 (4.6)	2 (7.4)	54 (16)	0.001*
ESR, n(%)	>10 mm/h	16 (9.3)	19 (25.7)*	3 (4.6)	3 (11.1)	41 (12.1)	0.000*
CRP, n(%)	>3 mg/L	91 (53.2)*	34 (45.9)	18 (27.7)	5 (18.5)	148 (43.9)	0.02*
ALT, n(%)	>40 IU/L	17 (9.9)	1 (1.3)	16 (24.6)*	3 (11.1)	37 (11)	0.000*
AST, n(%)	>40 IU/L	42 (24.5)	21 (28.4)	34 (52.3)*	17 (63)	114 (33.8)	0.002*
Creatinine, n(%)	>50 mmol/L	46 (26.9)	22 (29.7)	16 (24.6)	7 (25.9)	91 (27)	0.793
D-dimer, n(%)	>0.5 g/L	18 (10.5)	69 (93.2)*	12 (18.4)	14 (51.8)	113 (33.5)	0.000*
PCT, n(%)	0.5-2.0 µg/L	18 (10.5)	24 (32.4)*	10 (15.4)	0 (0.0)	52 (15.4)	0.002*
	2.0-10 µg/L	1 (0.58)	3 (4.05)	0 (0.0)	0 (0.0)	4 (1.2)	0.18

*statistically significant; WBC=white blood cells; PLT=platelets; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; ALT=alanine transaminase; AST=aspartate transferase; PCT=procalcitonin test

Discussion

Our study demonstrates dynamic changes in the manifestations and course of SARS-CoV-2 VOC variants - α, δ, and Omicron BA.5 and XBB.1.5 - during 2020 to 2023 in Ukraine, confirming continuous mutation of the virus, which cause the alteration of its characteristic manifestations. When assessing the demographic characteristics of the subjects, we found that during W3, W5, and W6, children aged 3 years and younger were hospitalized more frequently. In contrast, during W1, the highest hospitalization rates were observed in the school-age group, accounting for 67.2%. During W5 and W6, when Omicron and its subvariants were prevalent, children under one year of age were statistically more likely to be hospitalized, while the number of children in the 13-18 age group significantly decreased. A large population-based study in the United Kingdom also observed a higher hospitalization rate among younger children during the Omicron waves (W5, W6), which aligned with findings from a study in South Korea.[15-17] This trend may be related to compliance with epidemiological measures in schools and the implementation of COVID-19 vaccination among older school-age children. Vaccination for children aged 12-17 began in Ukraine in October 2021 and for children aged five years and older in the fall of 2022.

Assessment of the duration of inpatient treatment indicated that during W3, the longest treatment lasted 15.1 (SD 1.5) days, while in W6, when the Omicron XBB.1.5 strain circulated, the average duration of inpatient treatment was 6.9 (SD 1.5) days, the shortest among the four waves. This reduction may suggest a milder course of the disease during this period, improved treatment protocols, and a higher vaccination rate among Ukraine's pediatric population.[15,18,19] Analysis of the epidemiological characteristics revealed an association between the δ strain and SARS-CoV-2 virus infection from family members. A similar association was reported in a study in the United Kingdom.[19]

When comparing symptoms among hospitalized children during the four waves of COVID-19 in Ukraine, we found some patterns. Fever and signs of intoxication syndrome (such as general malaise and headaches) were the most common symptoms and occurred consistenly during all four waves of COVID-19, indicating that these symptoms are typical for children with this infection. Our conclusion align with findings from researchers in other countries.[20, 21] Symptoms such as sore throat, myalgia, and anosmia/ageusia were significantly more common in children during W1, when the α strain dominated, compared to the other three waves. This observation is likely due to the older age of hospitalized children in this group, as younger children might not have been able to describe or report such symptoms.

A similar pattern was described in a study in Colorado, US.[22] During W5, when the Omicron BA.5 strain dominated, there was a higher incidence of seizures among hospitalized children with COVID-19 compared to the other three groups (10.81% *vs.* 4.62% *vs.* 1.92% *vs.* 0%). This difference may be attributed to the distinct hyperthermic syndrome associated with COVID-19, as well as the age distribution of hospitalized children, as more children aged two months to one year were admitted during this wave. It is known that the frequency of febrile seizures is higher in this age group.[23] Multicenter studies indicate that 31% hospitalized children with COVID-19 during the Omicron period experienced seizures, highlighting these as typical manifestations of this SARS-CoV-2 variant.[24] Moreover, our results align with findings from Japanese researchers, who reported increased frequency of seizures among children infected with the Omicron strain and its subvariant BA.5.[25] Some researchers suggest that this manifestation of the Omicron virus strain may result from its ability to penetrate the central nervous system through the nasal mucosa and blood-brain barrier, potentially leading to seizures in patients.[26,27]

We also found that during W5, symptoms such as cough and rhinitis were significantly more common, while anosmia and ageusia were less frequently reported. This pattern may be explained by the Omicron strain's predisposition to upper respiratory tract infections, as reported by researchers from Iraq and China.[28,29] Furthermore, children in the W5 group had significantly more gastrointestinal complaints, including diarrhea, nausea, vomiting, and loss of appetite, compared to children hospitalized during other waves of COVID-19.

During W3, respiratory symptoms such as wheezing, cyanosis, and dyspnea were significantly more common. This is understandable, as children

during this period more frequently experienced respiratory failure and required oxygen therapy. This trend can be attributed to the fact that the δ variant penetrates the lung cells faster and has a higher affinity for the mucous membrane.[30,31] The typical manifestations of the δ variant include lesions in the lower respiratory tract, which explains the increased prevalence of pneumonia, particularly bilateral pneumonia with pleurisy, among hospitalized children during W3.

When comparing laboratory test values in hospitalized children across the four waves of COVID-19, we observed distinct differences. The α variant was characterized by elevated levels of CRP and platelets. Previous researches indicate that viral infections can lead to thrombocytosis due to the actibation of various inflammatory cytokines, including IL1, IL6, IL8, and TNF-a, which are responsible for platelet elevation.[32,33] Among the different variants of SARS-CoV-2, the α strain was characterized by thrombocytosis, as also reported in study conducted in France.[34] It is widely recognized that thrombocytosis correlates with an increase in CRP levels during viral infections, explaining the higher CRP and platelet levels observed during W1.[34,35] During W3, an elevated concentration of D-dimer emerged as a typical laboratory finding.

Literature indicates that the "cytokine storm" can lead to intravascular coagulation, thereby increasing D-dimer levels. Moreover, this "cytokine storm" is associated with the development of pneumonia and the severe progression of COVID-19.[36] Our results are consistent with this pattern, as children with severe and bilateral pneumonia were significantly more prevalent during W3. Thus, D-dimer can be considered a marker of lung damage and severe COVID-19 progression.[37] Important to note that during W3, laboratory parameters indicative of bacterial complications, such as PCT and WBC, were statistically higher. An increase in PCT is known to correlate with the presence of pneumonia and serves as a biomarker for bacterial complications in lower respiratory tract infections, similar to WBC.[38] Given the higher incidence of pneumonia, particularly bilateral pneumonia, during W3, we can infer a possible bacterial etiology. During W5, among laboratory parameters, there was a notable increase in liver function tests, such as ALT and AST.

The spike protein of the SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE2), facilitating the virus entry into the cells, replication, and intercellular transmission.[39] ACE2-receptors are predominantly expressed in cholangiocytes and minimally in hepatocytes. Consequently, SARS-CoV-2 infection affects liver function through direct cytotoxicity due to the continuous replication of the virus in these cells.[40,41]

Similar to findings in the adult population and limited pediatric studies,[15,22,42] our results confirm that the clinical course of COVID-19 during W3, while the δ strain was prevalent, was more severe than in W1, W5, W6. This is supported by the number of hospitalized children with severe course of the disease (47.3%), the frequency of respiratory failure, the need for respiratory support, the duration of hospitalization, the prevalence of bilateral pneumonia, and increased WBC, D-dimer, and PCT during this wave of COVID-19. Also in our study, one fatal case was recorded exactly during W3.

Our study had some limitations. First, the sample size of patients was small. Second, the timeframes of COVID-19 waves related to specific virus variants were determined based on the periods when each variant accounted for at least 50% of the circulating strain in the population. Since we did not conduct genetic analysis, it is possible that children hospitalized during each period may have been infected with different SARS-CoV-2 variants than those that were dominant at that time. Despite these limitations, our study provides important data on the changes in epidemiological, laboratory, radiological, and clinical characteristics of COVID-19 among pediatric patients across the four waves in Ukraine.

In summary, our study provides additional information regarding the continuous evolution of symptoms and severity of COVID-19 among children. It is probable that the virus will continue to mutate and change, underscoring the importance of ongoing research into the evolving clinical characteristics of SARS-CoV-2. This research is crucial for understanding the trends in the epidemiological process and for predicting the course of the disease in pediatric patients during future waves of COVID-19.

Conflict of interest

None declared.

Funding acknowledgment

This research was funded by the NRFU to "Investigate the importance of medical, biological and sociological factors in the spread of coronavirus infection among women and children in Ukraine" with state registration no. 0120U104508 and "Develop a personalised prognosis of COVID-19 in children based on markers of hereditary predisposition" with state registration no. 0123U102780.

References

1. World Health Organization (WHO). Coronavirus Disease (COVID-19) Situation Reports. Geneva: World Health Organization; 2020. [cited 2023 Nov 2]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public?adgroupsurvey={adgroupsurvey}&gclid=CjwKCAiA-vOsBhAAEiwAIWR0Ta3u9u4X1Dzz03Op0gvuk9DG9f8LLHLk8GPHMILN9k2nAl7FHAUDiRoCuSQQAvD_BwE
2. Wu L, Zhang XF, Yang Y, Yi XY, Jiang XP, Han HY, *et al.* Clinical Characteristics of Pediatric Cases of COVID-19 in Hunan, China: A Retrospective, Multi-Center Case Series. Front Pediatr. 2021;9:665377. DOI: https://doi.org/10.3389/fped.2021.665377
3. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109:1088-95. DOI: https://doi.org/10.1111/apa.15270
4. United Nations International Children's Emergency Fund (UNICEF). Child survival. [cited 2023 Nov 2]. Available from: https://data.unicef.org/topic/child-survival/covid-19/
5. Qi K, Zeng W, Ye M, Zheng L, Song C, Hu S, *et al.* Clinical, laboratory, and imaging features of pediatric COVID-19: A systematic review and meta-analysis. Medicine (Baltimore). 2021;100:e25230. DOI: https://doi.org/10.1097/MD.0000000000025230
6. Antypkin YG, Lapshyn VF, Umanets TR, Kaminska TM, Banadyha NV, Koloskova OK, *et al.* Analysis of the COVID-19 prevalence among children in Ukraine during the first year of the pandemic. Child's Health. 2023;18:1-5. DOI: https://doi.org/10.22141/2224-0551.18.1.2023.1551
7. Makulo JR, Wumba R, Mandina MN, Mbala P, Aziza AA, Nlandu YM, *et al.* SARS-CoV2 mutations and impact on mortality: observational study in a sub-saharan Africa hospital. Virol J. 2023;2056. DOI: https://doi.org/10.1186/s12985-023-02014-1
8. Callaway E. Coronavirus variants get Greek names - but will scientists use them? Nature. 2021;594:162. DOI: https://doi.org/10.1038/d41586-021-01483-0
9. Mahilkar S, Agrawal S, Chaudhary S, Parikh S, Sonkar SC, Verma DK, *et al.* SARS-CoV-2 variants: Impact on biological and clinical outcome. Front Med (Lausanne). 2022;9:995960. DOI: https://doi.org/10.3389/fmed.2022.995960
10. Chatterjee S, Bhattacharya M, Nag S, Dhama K, Chakraborty C. A detailed overview of SARS-CoV-2 omicron: its sub-variants, mutations and pathophysiology, clinical characteristics, immunological landscape, immune escape, and therapies. Viruses. 2023;15:167. DOI: https://doi.org/10.3390/v15010167
11. Parums DV. Editorial: The XBB.1.5 ('Kraken') subvariant of omicron SARS-CoV-2 and its rapid global spread. Med Sci Monit. 2023;29:e939580. DOI: https://doi.org/10.12659/MSM.939580
12. Gankin Y, Nemira A, Koniukhovskii V, Chowell G, Weppelmann TA, Skums P, *et al.* Investigating the first stage of the COVID-19 pandemic in Ukraine using epidemiological and genomic data. Infect Genet Evol. 2021;95:105087. DOI: https://doi.org/10.1016/j.meegid.2021.105087
13. Centers for Disease Control and Prevention (CDC). Child Development Basics. Available from: https://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/index.html
14. Raniszewska A, Górska E, Kotuła I, Stelmaszczyk-Emmel A, Popko K, Ciepiela O. Recurrent respiratory tract infections in children - analysis of immunological examinations. Cent Eur J Immunol. 2015;40:167-73. DOI: https://doi.org/10.5114/ceji.2015.52830
15. Marks KJ, Whitaker M, Agathis NT, Anglin O, Milucky J, Patel K, *et al*; COVID-NET Surveillance Team. Hospitalization of infants and children aged 0-4 years with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 2020-February 2022. MMWR Morb Mortal Wkly Rep. 2022;71:429-36. DOI: https://doi.org/10.15585/mmwr.mm7111e2
16. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, *et al.* Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet. 2022;399:1303-12. DOI: https://doi.org/10.1016/S0140-6736(22)00462-7

17. Han MS, Kim KM, Oh KJ, Chang JY, Lee SY, Choi JE, *et al.* Distinct clinical and laboratory features of COVID-19 in children during the pre-delta, delta and omicron wave. Pediatr Infect Dis J. 2023;42:423-28. DOI: https://doi.org/10.1097/INF.0000000000003872
18. Shi DS, Whitaker M, Marks KJ, Anglin O, Milucky J, Patel K, *et al.* Hospitalizations of children aged 5-11 years with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 2020-February 2022. MMWR Morb Mortal Wkly Rep. 2022;71:574-81. DOI: https://doi.org/10.15585/mmwr.mm7116e1
19. Allen H, Vusirikala A, Flannagan J, Twohig KA, Zaidi A, Chudasama D, *et al.* Household transmission of COVID-19 cases associated with SARS-CoV-2 delta variant (B.1.617.2): national case-control study. Lancet Reg Health Eur. 2022;12:100252. DOI: https://doi.org/10.1016/j.lanepe.2021.100252
20. Di Chiara C, Boracchini R, Sturniolo G, Barbieri A, Costenaro P, Cozzani S, *et al.* Clinical features of COVID-19 in Italian outpatient children and adolescents during parental, delta, and omicron waves: a prospective, observational, cohort study. Front Pediatr. 2023;11:1193857. DOI: https://doi.org/10.3389/fped.2023.1193857
21. Harashchenko T, Umanets T, Podolskiy V, Kaminska T, Marushko Y, Podolskiy V, *et al.* Epidemiological, clinical, and laboratory features of children with SARS-CoV-2 in Ukraine. J Mother Child. 2023;27:33-41. DOI: https://doi.org/10.34763/jmotherandchild.20232701.d-23-00012
22. Jelic M, Silveira L, Lang S, Curran-Hays S, Boyer S, Carter B, *et al.* Children and COVID-19 in Colorado study. Changing characteristics of children with COVID-19 in Colorado admitted during different variant periods. Pediatr Infect Dis J. 2023;42:679-84. DOI: https://doi.org/10.1097/INF.0000000000003944
23. Mayo Clinic. Febrile seizure. [cited 2023 Nov 2]. Available from: https://www.mayoclinic.org/diseases-conditions/febrile-seizure/symptoms-causes/syc-20372522
24. Cloete J, Kruger A, Masha M, du Plessis NM, Mawela D, Tshukudu M, *et al*. Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B.1.1.529) variant wave in South Africa: a multicentre observational study. Lancet Child Adolesc Health. 2022;6:294-302. DOI: https://doi.org/10.1016/S2352-4642(22)00027-X
25. Ikuse T, Aizawa Y, Yamanaka T, Hasegawa S, Hayashi T, Tamura T, *et al.* Comparison of clinical characteristics of children infected with coronavirus disease 2019 between omicron variant BA.5 and BA.1/BA.2 in Japan. Pediatr Infect Dis J. 2023;42:503-9. DOI: https://doi.org/10.1097/INF.0000000000003894
26. Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, *et al.* Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci. 2021;24:168-75. DOI: https://doi.org/10.1038/s41593-020-00758-5
27. Burks SM, Rosas-Hernandez H, Alejandro Ramirez-Lee M, Cuevas E, Talpos JC. Can SARS-CoV-2 infect the central nervous system via the olfactory bulb or the blood-brain barrier? Brain Behav Immun. 2021;95:7-14. DOI: https://doi.org/10.1016/j.bbi.2020.12.031
28. Nori W, Ghani Zghair MA. Omicron targets upper airways in pediatrics, elderly and unvaccinated population. World J Clin Cases. 2022;10:12062-5. DOI: https://doi.org/10.12998/wjcc.v10.i32.12062
29. Jiang J, Yang M, Li DY, Qiao LN, Zhang HY. Clinical characteristics of children with omicron variant infection in Chengdu area, China]. Zhongguo Dang Dai Er Ke Za Zhi. 2023;25:849-54. Chinese. DOI: https://doi.org/10.7499/j.issn.1008-8830.2302147
30. Dhawan M, Sharma A, Priyanka, Thakur N, Rajkhowa TK, Choudhary OP. Delta variant (B.1.617.2) of SARS-CoV-2: Mutations, impact, challenges and possible solutions. Human Vaccines & Immunotherapeutics. 2022;18:2068883. DOI: https://doi.org/10.1080/21645515.2022.2068883
31. Samieefar N, Rashedi R, Akhlaghdoust M, Mashhadi M, Darzi P, Rezaei N. Delta variant: the new challenge of COVID-19 pandemic, an overview of epidemiological, clinical, and immune characteristics. Acta Biomed. 2022;93:e2022179. DOI: https://doi.org/10.23750/abm.v93i1.12210
32. Lee FE, Walsh EE, Falsey AR, Lumb ME, Okam NV, Liu N, *et al*. Human infant respiratory syncytial virus (RSV)-specific type 1 and 2 cytokine responses ex vivo during primary RSV infection. J Infect Dis. 2007;195:1779-88. DOI: https://doi.org/10.1086/518249
33. Zheng SY, Xiao QY, Xie XH, Deng Y, Ren L, Tian DY, *et al.* Association between secondary thrombocytosis and viral respiratory tract infections in children. Sci Rep. 2016;6:22964. DOI: https://doi.org/10.1038/srep22964
34. Vassallo M, Manni S, Klotz C, Fabre R, Pini P, Blanchouin E, *et al*. Patients Admitted for Variant Alpha COVID-19 Have Poorer Outcomes than Those Infected with the Old Strain. J Clin Med. 2021;10:3550. DOI: https://doi.org/10.3390/jcm10163550
35. Yadav D, Chandra J, Sharma S, Singh V. Clinicohematological study of thrombocytosis. Indian J Pediatr. 2010;77:643-7. DOI: https://doi.org/10.1007/s12098-010-0091-4

36. Gürsoy B, Sürmeli CD, Alkan M, Satıcı C, Altunok ES, Kamat S, *et al*. Cytokine storm in severe COVID-19 pneumonia. J Med Virol. 2021;93:5474-80. DOI: https://doi.org/10.1002/jmv.27068
37. Chen YE, Ren FL, Gu X, Zhang HJ, Li WJ, Yang H, Shang FQ. Clinical value of platelets and coagulation parameters in predicting the severity of delta variant SARS-CoV-2. Pathobiology. 2023;90:241-50. DOI: https://doi.org/10.1159/000528318
38. Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. Clin Infect Dis.2011;52:S346-50. DOI: https://doi.org/10.1093/cid/cir050
39. Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect. 2020;53:425-35. DOI: https://doi.org/10.1016/j.jmii.2020.04.015.
40. Warner FJ, Rajapaksha H, Shackel N, Herath CB. ACE2: from protection of liver disease to propagation of COVID-19. Clin Sci (Lond). 2020;134:3137-58. DOI: https://doi.org/10.1042/CS20201268
41. Cichoz-Lach H, Michalak A. Liver injury in the era of COVID-19. World J Gastroenterol. 2021;27:377-90. DOI: https://doi.org/10.3748/wjg.v27.i5.377
42. Lin L, Liu Y, Tang X, He D. The disease severity and clinical outcomes of the SARS-CoV-2 variants of concern. Front Public Health. 2021;9:775224. DOI: https://doi.org/10.3389/fpubh.2021.775224