

Evaluation of COVID-19 Pneumonia in Children According to the Original Strain, Alpha, Delta and Omicron Variants

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ABSTRACT

Objective: As known, COVID-19, stemming from the SARS-CoV-2 virus, exhibits distinct clinical patterns across various variants. This research endeavors to comprehensively analyze the variations in clinical presentations between these variants and the original strain, particularly in pediatric COVID-19 pneumonia cases.

Materials and Methods: Patients diagnosed with COVID-19 pneumonia who were admitted to Mersin City Research and Training Hospital between June 2020-2022, were included in the study. Clinical and laboratory data of the patients were evaluated according to their variant status.

Results: 56% (n=62) of 110 pediatric patients were female, and their average age was 11±5.9 (median 13). 31%(n=34) of the patients were infected with the original strain, 20% (n=22) were alpha, 40% (n=44) were delta, and 9% (n=10) were omicron variant. 6% (n=7) of the patients were asymptomatic, 11% (n=12) were mildly symptomatic, 76% (n=83) were moderate (respiratory distress), and 7% (n=8) were severe clinical patients requiring mechanical ventilation. Fever and shortness of breath were most frequently seen in delta, and cough in alpha variant (p=0.0001;p=0.014;p=0.039,respectively). The most severe disease detected in omicron was alpha, delta and original virüs (p=0.001). No relationship detected between the laboratory values of the patients and the variant status (p>0.05). When patients were compared based on radiological severity, no significant differences were found between the variants (p=0.214). However, when cases were classified according to pneumonia severity, regardless of the variant status, higher levels of ferritin (p=0.0001) and CRP (p=0.037) were observed, while lymphocyte count (p=0.009) decreased with increasing pneumonia severity. It's noteworthy that no patient fatalities occurred.

Conclusion: In our study, the most severe clinical picture was shown in the omicron variant, followed by the alpha variant. But, omicron cases were limited, and it is important to examine variants in a larger population.

Keywords: Children, COVID-19, pneumonia. Alpha, Beta, Omicron

Research Article

Received 02-10-2023

Accepted 10-10-2023

E-Pub: 11-10-2023

Issue Publication: 30-10-2023

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INTRODUCTION

COVID-19, which started in China's Wuhan province, has caused a pandemic affecting the whole world. SARS-CoV-2, like other viruses, can transform into different genotypes through mutations over time. Although most mutations do not cause clinical differences, in some cases new variants may cause changes in the clinical picture. These are named as variants of concern (VOC); which can cause rapid spread and increase the clinical severity of the disease. Each variant has various names under which it is used due to different phylogenetic classification systems. The World Health Organization (WHO) has created a terminology indicating VOC based on the Greek alphabet (1). Apart from this, there are also terminology systems created by institutions such as Pango and Nextstrain (2).

According to these terminology systems, alpha (B.1.1.7 according to the Pango system), which was the first VOC named after the original Wuhan type SARS-CoV-2 virus, started to appear in the United Kingdom in September 2020 and showed predominance in December 2020-June 2021. The delta variant (B.1.617.2) was detected in our country on June 29, 2021, and showed predominance worldwide between July 2021 and December 2021. The most mutated Omicron variant (B.1.1.529) was classified as VOC in November 2021 (3). It continues to show predominance from January 2022 to the present (2,4).

Variant genomic surveillance is currently carried out in the world. Accordingly, there are studies on the distribution of variants and variant detection times in our country in the early period of the pandemic, between March-September 2020, and it is thought that the timing of occurrence in Europe and our country is parallel (5).

COVID-19 generally causes milder clinical findings in pediatric cases. As age increases, the patient's clinical symptoms may worsen. It is known that the frequency of pneumonia, especially in the adolescent age group, can be as severe and aggressive as adult COVID-19 disease. In a study conducted in the United States, in a review of 82,798 children under the age of 18 with laboratory evidence who applied between March 2020 and December 2021; 66% of patients are asymptomatic, 27% have mild COVID-19 symptoms and signs, 5% have moderate symptoms (COVID-19-associated pneumonia, gastroenteritis, dehydration) and 2% have severe symptoms and signs (conditions requiring intensive care unit and/or mechanical ventilation) (6). In a separate study evaluating COVID-19 symptoms across different variants, it was found that during the Omicron variant period, nasal congestion, headache, sneezing, and sore throat were more prevalent compared to the Delta variant (7). In a different study conducted with alpha (n=1153), gamma (n=122), delta (n=808) variants, no difference was seen in terms of hospitalization, intensive care admission, and death (8).

It is known that in COVID-19, risk factors such as advanced age, obesity, diabetes mellitus, or chronic diseases are correlated with the risk of disease severity (9). However, some of the VOCs have been shown to cause more severity, especially in children. Studies are showing that delta and omicron variants lead to more hospitalizations (10). COVID-19 treatment is generally a symptomatic support approach such as antipyretics and hydration. Anticoagulants can be added if there is a risk of venous thromboembolism, and antibiotics can be added in the presence of bacterial co-infection (11). Drugs such as corticosteroids, remdesivir, tocilizumab, and favipiravir have been used for treatment according to the schedules designed for pediatric patients' treatment (12).

This study aimed to categorize the clinical, laboratory, and radiological findings of patients hospitalized for COVID-19 pneumonia in the COVID-19 pandemic wards of a tertiary training and research hospital, based on different variants.

MATERIAL and METHODS

Clinical, laboratory and radiological findings of 110 children aged between 1 and 215 months who were followed up due to COVID-19 pneumonia in the children's pandemic wards of ...

City Training and Research Hospital between June 2020 and June 2022, and detected positive for SARS-CoV-2 PCR in their respiratory viral panel samples. Radiological findings were retrospectively examined using hospital information management system files. Clinical symptoms, including fever, cough, shortness of breath, comorbidity status, and whether patients had relatives who had been hospitalized or lost due to COVID-19, were assessed. Signs of respiratory distress such as tachypnea, retraction, hypoxemia, and cyanosis were noted. Oxygen intake status and duration time were noted. Total leukocyte, neutrophil, lymphocyte, platelet values (/mm³), C-reactive protein (CRP), D-dimer and ferritin values were evaluated among laboratory values.

From the nasopharyngeal swab samples of the patients, Bio-Speedy SARS-CoV-2 Variant Plus and Emerging Plus RT-qPCR detection kit (Bioeksen, Istanbul, Turkey) and Coronagen RT-qPCR SARS-CoV-2 (Gensutek, Ankara, Turkey) Variants Detection Kits were studied. Test positivity and variant detection were performed simultaneously using the process. Patient samples with a Cycle Threshold (Ct) value of 20 and below determined in positive patients were forwarded to the General Directorate of Public Health, Department of Communicable Diseases and Early Warning (Ankara) for verification under appropriate conditions. In cases with COVID-19 pneumonia but in which VOC could not be detected, the variants that were mostly seen in the circulation at that time were considered. The timing of the variants was decided according to the VOC detection dates specified in the Variant Genomic Surveillance tracking system of the American Center for Disease Prevention and Control (CDC) (4,13). Accordingly, according to the dominance periods, June-November 2020 was accepted as the period when the original virus dominated, December 2020-June 2021 as Alpha, July-December 2021 as Delta, and January-June 2022 as the Omicron period.

The term obesity was used for cases with a body mass index \geq 95th percentile for age and gender.

Patients were classified into four groups as; asymptomatic, mildly symptomatic (symptoms such as fever, cough, but no signs of respiratory distress), moderately symptomatic (with markers of respiratory distress such as tachypnea, retraction, cyanosis, hypoxemia) and severe symptomatic (need for mechanical ventilation or intensive care unit hospitalization).

Pneumonia was detected in routine imaging for control purposes in asymptomatic and mildly symptomatic SARS-CoV-2 PCR positive cases.

Pneumonia classification was indicated radiologically using chest X-ray, thorax computed tomography (CT), or chest x-ray and CT methods. For radiological classification, the classification system introduced by Chung was used (14). Accordingly, the involvement in each lobe of the lung, which was divided into five lobes, was scored as one point if it was 0-25%, two points if it was 25-50%, 3 points if it was 50-75%, and four points if it was 75-100%. Scores were collected as 1-6 points, 7-11 points and 12 and above and evaluated as mild, moderate and severe involvement (14,15).

Medical and specific COVID-19 treatments were determined in accordance with the guidelines outlined in the Ministry of Health's COVID-19 Management Guidelines (16).

Prognoses were divided into four groups: discharged with recovery within the first 14 days, discharged with recovery after 14 days, and discharged with sequelae or death.

Statistical analysis

After the data were taken from the patients' electronic files, they were recorded with SPSS. Descriptive statistics are given as mean, standard deviation, median, minimum and maximum. In comparing the data, "Paired Samples T Test" was used for variables that showed normal distribution in the dependent groups, and "Non-parametric Wilcoxon test" was used for variables that did not show normal distribution. Comparisons between similar variables in independent groups were conducted using the "Independent Samples T-Test" for normally distributed variables and the "Mann-Whitney U Test" for non-normally distributed variables. The "Kruskal-Wallis Analysis" was employed when analyzing non-normally distributed variables with more than one variable, while the "One-way ANOVA" was utilized for comparing multiple normally distributed variables. Chi-square test was used for categorical variables. In statistical comparisons, the significance level was determined as $p < 0.05$.

RESULTS

Of the 110 COVID-19 pneumonia pediatric cases followed for two years between June 2020-2022, 56% ($n=62$) were female and their average age was 11 ± 5.9 (median 13 years, range 1-215 months). The first attack was the original Wuhan type strain ($n=34$, 31%) in the cases admitted between June and November 2020. The VOCs was detected and confirmed in 82% ($n=62$) of the remaining 69% ($n=76$) cases admitted after December 2020 whom tests' referred to Ankara (capital of Turkey) Sanitation Institute. 31% ($n=34$) of all cases were original SARS-CoV-2 virus, 20% ($n=22$) were alpha variant, 40% ($n=44$) were delta variant, 9% ($n=10$) were the omicron variant. None of the cases had COVID-19 vaccinations. Among the patients, 25% ($n=27$) had a hospitalized parent due to COVID-19, and 4% ($n=4$) experienced the loss of a relative due to COVID-19.

The most comorbid diseases were obesity (6%), asthma (4%), untreatable neurological diseases (4%), diabetes mellitus (2%), metabolic diseases (2%) and immune deficiencies (2%). The most common symptom was cough (86%), followed by fever (77%) and shortness of breath (47%). The total of 84% of the patients did not have any comorbid diseases. There were no signs of respiratory distress in 17% of the cases ($n=19$), 72% ($n=79$) had only tachypnea, and 11% had tachypnea and other respiratory distress findings such as retraction, nasal flaring and cyanosis.

Six percent ($n=7$) of the cases were asymptomatic, 11% ($n=12$) were mildly symptomatic, 76% ($n=83$) were moderate, and 7% ($n=8$) were severe clinical patients requiring mechanical ventilation.

Sixteen percent of the cases ($n=18$) required oxygen for an average of 1.7 ± 6.3 days. Radiological diagnosis was made by both chest radiography and thorax CT in 76% ($n=83$) of the cases, by chest radiography alone in 22% ($n=25$), and by CT alone in 2% ($n=2$). Imaging findings were bilateral in 67% ($n=74$) and unilateral in 33% ($n=36$). 71% ($n=78$) of radiological involvement was mild, 24% ($n=27$) was moderate, and 5% ($n=5$) was severe.

No statistically significant difference was observed between the variant status and age of the cases ($p=0.130$). Comparison of the variant status of the cases and some clinical and demographic data is mentioned in Table-1. As stated in **Table-1**, it was observed that the symptoms of fever, cough, and shortness of breath showed statistically significant differences between the strains ($p=0.0001$; $p=0.039$; $p=0.014$, respectively). Fever was most frequently observed in cases of Delta variant pneumonia, followed by Alpha, Omicron, and the original virus, respectively. Cough was most frequently reported in Alpha variant cases, followed by Delta, the original virus, and the Omicron variant, respectively. Shortness of breath was most frequently seen in the delta variant, followed by omicron, alpha and original virus, respectively. When examining the relationship between the variant status of the cases and disease severity, a statistically significant difference was observed (**Table-2**; $p=0.001$). According to the severity of the disease; the most severe strain was omicron, followed by alpha, delta variants and the original virus, respectively. Asymptomatic and mild pneumonia was observed more frequently in the original strain other than VOCs. No statistically significant difference was detected between radiological severity and variant status ($p=0.214$). When the variant status of the cases and laboratory data were compared, there was no statistically significant difference between the original strain, alpha, delta and omicron variants and laboratory findings (D-dimer, ferritin, leukocyte, neutrophil, lymphocyte count, platelet and CRP; $p=0.190$; $p=0.687$; $p=0.083$; $p=0.148$; $p=0.530$; $p=0.211$; $p=0.555$ respectively).

When cases are classified according to pneumonia severity; ferritin ($p=0.0001$) and CRP ($p=0.037$) values were found to be higher, and lymphocyte count ($p=0.009$) was lower in the group with severe pneumonia compared to mild and moderate pneumonia (**Table-3**). No significant difference was detected in D-dimer, total leukocyte and neutrophil counts (**Table-3**).

Respiratory multiplex PCR was sent to 10% of the cases ($n=11$). Factors other than SARS-CoV-2 were detected in four of them (36%). Parainfluenza type 3 was shown in two of the causative agents, adenovirus was shown in one, and Human Bocavirus and Streptococcus pneumoniae co-infection were shown in one patient. In two of the cases, sputum cultures showed multidrug-resistant Acinetobacter baumannii bacterial coinfection. These 6 (5%) cases in which bacterial or viral co-infection was detected had moderate and severe symptomatic clinics.

Forty-six percent of the cases did not require any medication, while the remaining patients were monitored with combinations of specific treatments, including 39% receiving favipiravir, 30% receiving corticosteroids, 2% receiving remdesivir, and 2% receiving tocilizumab. Low molecular weight heparin was used in 31% of the cases. No thromboembolic complications were observed. There was no statistically significant difference between the initiation of treatment and the variant status ($p=0.63$).

Ninety six percent of the cases were discharged within the first 14 days, and 3% were discharged after 14 days. When the relationship between the variant status of the cases and prognosis, the worst prognosis was in the omicron group, delta and alpha variants had equal prognosis, and the best prognosis was in the original SARS-CoV-2 virus, but this was not statistically significant ($p=0.059$). One percent ($n=1$) case (original SARS-CoV-2) was discharged with sequelae due to the persistence of oxygen need and no longer needed oxygen during follow-up. Control tomography was not performed in 99% of the cases. One patient who underwent control CT who was discharged with sequelae of oxygen need. The control CT scan revealed atelectasis, and COVID-19-related consolidations had completely resolved. No patients were lost.

Table-1: Comparison of demographic data of cases with COVID-19 pneumonia according to variant distribution

	Original (n=34) n, %	Alpha (n=22) n, %	Delta (n=44) n, %	Omicron (n=10) n, %	p
Sex (F)	18, 53%	15, 68%	23, 52 %	6, 60 %	0.623
Comorbidities (none)	29, 85%	17, 77%	38, 86%	8, 80%	0.472
Fever	16, 47%	19, 86%	42, 95%	8, 80%	0.0001
Cough	26, 76%	21, 95%	41, 93%	7, 70%	0.039
Shortness of breath	9, 26%	10, 45%	28, 64%	5, 50%	0.014
Oxygen intake	3, 9%	4, 18%	10, 22%	1, 10%	0.382

Table-2: Comparison of variant status and clinical severity of cases with COVID-19 pneumonia.

	Original (n=34) n, %	Alpha (n=22) n, %	Delta (n=44) n, %	Omicron (n=10) n, %	p
Asymptomatic	7, 21%	0	0	0	0.001
Mildly symptomatic	7, 21%	1, 5%	4, 9%	0	
Moderately symptomatic	17, 50%	19, 86%	38, 87%	9, 90%	
Severely symptomatic	3, 8%	2, 9%	2, 4%	1, 10%	

Table-3: Evaluation of laboratory data of cases with COVID-19 pneumonia according to radiological severity.

	Mild (71%, n=78) (Mean±SD)	Moderate (24%, n=27) (Mean±SD)	Severe (5%, n=5) (Mean±SD)	p
Total leukocyte (/mm ³)	6961±3627	5682±3855	7278±4479	0.288
Neutrophil (/mm ³)	3776±2987	3840±3471	5402±3928	0.536
Lymphocyte (/mm ³)	2385±1371	1586±941	1394±631	0.009
Platelet (10 ³ x/mm ³)	269±92	227±128	264±91	0.185
CRP* (mg/dl)	2.9±8.8	3.6±7.2	13.2±12	0.037
D-dimer (mcg/ml)	4.1±12	1.7±3.1	1.4±1.4	0.532
Ferritin (ng/ml)	72±92	294±453	338±314	0.0001

*CRP: C-reactive protein.

DISCUSSION

It is known that COVID-19 disease may progress severely or with complications in adults with elderly age, diabetes mellitus, hypertension, neurological diseases or chronic conditions. Although there is a misconception that the disease progresses with insignificant symptoms in pediatric cases. But both in the literature and increasing experience in this subject, it is seen that pneumonia and intensive care admissions can occur in children. Although the pandemic seems to be decreasing, it can be predicted that complications may occur again with new VOCs. Therefore, sharing the experiences of centers that follow many patients like in our study, will contribute to the literature.

In our study, as in similar studies, the most common findings were fever and cough (17). In addition, it was noteworthy that the average age of the pneumonia cases was adolescence and that they had comorbidities such as obesity. There was no comorbid disease in 84% of our patients, also obesity, asthma, and chronic neurological diseases were the main comorbidities. It is known that the disease may have a severe course in case of risk factors (18).

In another study in which cases with COVID-19 were compared according to pneumonia status, the CRP value was found to be statistically significantly higher, similar to our study (17). In this study, when laboratory values were compared according to variant status, total leukocyte and lymphocyte values were found to be higher in the omicron variant than in the alpha and delta variant, and CRP and ferritin were found to be lower, and no difference was found in our study (8). Contrary to our study, it was determined that the oxygen requirement was less in omicron, whereas in breakthrough infection, the oxygen requirement was found to be higher in omicron patients (8). Since the patients in our study were not vaccinated, no comments can be made on this issue.

In a study conducted within the pediatric population, it was demonstrated that the alpha variant group had higher rates of ICU admissions, mortality, and the need for mechanical ventilation compared to the delta and omicron variants (10). Especially during the omicron period, as the society got used to the pandemic process, there was a significant decrease in hospital admissions, and mild pneumonias may not have been included in the study for this reason. This interpretation may suggest that the number of patients was less in the omicron period, there were more applications with more severe clinical conditions, and therefore the most severe clinical condition was in the omicron period.

In our study, detailed data about the gamma variant is not given. One of the reasons for this is that it does not show long-term dominance like other alpha, delta and omicron variants. Another reason is that gamma variants were not detected in our study. In addition, in a similar study conducted in our country, the gamma variant was found at a rate as low as 1% among other strains (19).

Although the original SARS-CoV-2 cases in our study had radiological findings of pneumonia, their subclinical complaints were another striking feature.

The productive cough and persistent, sick/septic-looking state expected in typical bacterial pneumonia were generally not observed in our cases. However, there were also cases whose complaints were minimal and who presented with a decrease in oxygen saturation. This can be regarded as a significant clinical feature that sets COVID-19 pneumonia apart from other types of pneumonia. When evaluated according to radiological involvement, bilateral involvement and mild radiological involvement were frequently detected, as in a similar study (20).

In our study, pneumonia severity was found to be correlated with elevated ferritin, CRP, and low lymphocyte levels. In a similar study, as the severity of pneumonia increased, lymphocyte levels were found to be low, and ferritin and CRP were found to be high ($p=0.007$; $p<0.001$; $p<0.001$, respectively), similar to our study (21). Unlike our study, leukocyte, platelet, and D-dimer values were observed to increase according to the pneumonia severity in that study (21).

CONCLUSION

In our study, the Omicron variant of SARS-CoV-2 was found to be the most severe, although the number of patients in this group was relatively small. It was followed by the Alpha variant. It is important to investigate COVID-19 pneumonia and variants in the pediatric population. It will be possible to obtain more data on the clinical follow-up and findings of the cases in multi-center studies where clinical cases are collected with current variant surveillance.

Acknowledgements: none

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions: EY designed and directed the study. Data collection: BÖÖ coordinated data collection and assisted with data interpretation at their sites. EY, MY provided critical feedback and edited the manuscript. EY, MY analysis and interpretation of results: EY, MY, BÖÖ wrote the final draft of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study. 2023/630 numbered and 09/20/2023 dated ethics committee approval is taken from Mersin University ethics committee. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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