



Evaluation of Children Hospitalized for COVID-19

COVID-19 Nedeniyle Hastaneye Yatırılan Çocukların Değerlendirilmesi

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Abstract

Objective: As the COVID-19 pandemic continues, childhood data changes daily. This study aimed to determine the epidemiological, clinical, and laboratory features of hospitalized pediatric patients with COVID-19.

Material and Methods: We retrospectively collected the medical records of hospitalized pediatric patients aged <18 years, diagnosed with COVID-19 between March 2020 and October 2021. Demographic characteristics, clinical features, and laboratory findings were recorded. The management and clinical course of the disease were also examined.

Results: A total of 123 pediatric patients were included in the study. Sixty-eight (55.3%) were males, with a mean age of 95.94 ± 72.20 months. Comorbidity was present in 30 (24%) patients; asthma (n= 9, 7.3%) was the most common underlying condition. Length of hospital stay-in median range was 5.09 days (1-14 days). Thirty-two (26%) patients had severe disease, and five (4.1%) patients had PICU admission. C-reactive protein (CRP) and ferritin values were found to be higher in the severe disease group ($p < 0.05$), and no relationship was found with lymphopenia and neutrophil/lymphocyte ratio (NLR) in terms of disease severity. Neutropenia was significant in patients younger than five years of age ($p < 0.05$).

Conclusion: The rate of severe disease in hospitalized pediatric patients was not low. CRP and ferritin were essential in determining the prognosis. There was a tendency for neutropenia which was benign and transient in under five years old patients.

Keywords: COVID-19, children, disease severity, laboratory findings, neutropenia

Öz

Giriş: COVID-19 pandemisinin devam etmesiyle birlikte, çocukluk verileri de değişmektedir. Bu çalışmada, COVID-19 nedeniyle hastanede yatan çocuk hastaların epidemiyolojik, klinik ve laboratuvar özelliklerini belirlemeyi amaçladık.

Gereç ve Yöntemler: Mart 2020-Ekim 2021 tarihleri arasında hastanede yatan, COVID-19 tanısı alan <18 yaş çocuk hastaların tıbbi kayıtlarını retrospektif olarak topladık. Hastaların demografik özellikleri, klinik özellikleri ve laboratuvar bulguları kaydedildi. Hastalığın seyri ve tedavi yönetimleri incelendi.

Bulgular: Çalışmaya toplam 123 çocuk hasta dahil edildi. Altmış sekizi (%55.3) erkekti ve yaş ortalaması 95.94 ± 72.20 aydı. Otuz (%24) hastada komorbidite mevcuttu, astım (n= 9, %7.3) en sık altta yatan durumdu. Hastanede kalış süresi medyan aralığı 5.09 gündü (1-14 gün). Otuz iki (%26) hastada ciddi hastalık vardı ve beş (%4.1) hasta yoğun bakım ünitesinde izlendi. C-reaktif protein (CRP) ve ferritin değerleri ağır hastalığa sahip grupta daha yüksek bulundu ($p < 0.05$), lenfopeni ve nötrofil/lenfosit oranı (NLO) ile hastalık şiddeti arasında ilişki saptanmadı. Nötropeni beş yaşından küçük hastalarda belirgindi ($p < 0.05$).

Sonuç: Hastanede yatan çocuk hastalarda ciddi hastalık oranı düşük değildi. CRP ve ferritin prognozu belirlemede önemli yer teşkil etti. Beş yaşın altındaki hastalarda iyi seyirli ve geçici olan nötropeni eğilimi olduğu saptandı.

Anahtar Kelimeler: COVID-19, çocuk, hastalık ciddiyeti, laboratuvar bulguları, nötropeni

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Introduction

A novel coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan, China, in December 2019 (1). The World Health Organization (WHO) defined the Coronavirus disease-2019 (COVID-19) outbreak as an international public health emergency on January 30, and the first case of COVID-19 was reported on March 11, 2020, in Türkiye (2). As of March 06, 2022, over 433 million confirmed cases and over 5.9 million deaths had been reported by WHO (3).

Children account for 1-5% of diagnosed COVID-19 cases (4). Majority of the reports have demonstrated that pediatric cases are asymptomatic or with a mild clinical course. Compared to adults (18.5%), asymptomatic, mild, and moderate infections comprise over 90% of all children who have tested positive for COVID-19, with fewer severe and critical cases (5.9%) (5). Fever (50%) and cough (38%) are the most common symptoms in children (6). Children are more likely to have upper respiratory symptoms than lower respiratory symptoms and recover in a short time. In childhood, immune response to the SARS-CoV-2 virus than adults, properties of respiratory tracts, interaction with the other common viruses in the mucosa of the respiratory system, and differences in ACE-2 expression age by age have been suggested as the most important factors that play a role in the mild course of the disease (7,8). With the continuation of the pandemic, the number of pediatric cases has increased, and it has been observed that the disease can have a more serious course, especially in cases with an underlying disease and under one year of age. Also, some infected children may develop multisystem inflammatory syndrome (MIS-C), a rare but serious complication of COVID-19 (9).

This report aimed to determine the demographic, clinical, and laboratory characteristics of pediatric patients hospitalized for COVID-19.

Materials and Methods

Pediatric cases aged 0-18 years diagnosed with COVID-19 and hospitalized between March 15, 2020, and October 15, 2021, were included. The diagnosis was confirmed by nasopharyngeal and oropharyngeal polymerase chain reaction (PCR). The patient's medical records were collected retrospectively. Demographic characteristics (age, sex, comorbidities), clinical features (duration and severity of symptoms) laboratory findings [biochemical test, complete blood count, levels of inflammatory markers as C-reactive protein (CRP), procalcitonin, ferritin, radiological evaluation with X-ray or computerized chest tomography (CT)] were examined. Management (antiviral therapy, antibiotics, steroid therapy, anticoagulant therapy, respiratory support), length of hospital stay, pediatric

intensive care unit (PICU) admission, and the disease outcome were also determined.

Neutropenia was defined as absolute neutrophil count (ANC) less than $1500/\text{mm}^3$, lymphopenia was defined as absolute lymphocyte count (ALC) less than $1500/\text{mm}^3$, neutrophil-to-lymphocyte ratio (NLR) was calculated from a complete blood count (CBC) test by dividing the ANC by the absolute lymphocyte count (10,11).

Disease severity was defined according to the clinical features and laboratory results (including chest radiograph imaging). Patients were divided into two groups; mild disease was defined in patients with signs of upper respiratory tract infection and/or pneumonia who had fever, pathological findings on lung auscultation without oxygen requirement. In this group, some patients' chest radiography or tomography showed signs of infection and lung lesions.

Severe disease was defined in patients with pneumonia who had hypoxemia and oxygen requirement. Chest radiography or tomography showed obvious pathological findings and respiratory support (invasive/non-invasive) was given in some patients in this group.

Statistical analysis was performed with SPSS statistical package (version 25 for Windows). Data were expressed as either mean \pm SD or percentages. Median, range [interquartile range (IQR)], mean, standard deviation, number, and percentage were used as descriptive statistics, according to the normality of distribution. Comparisons of categorical variables were made using the Chi-square test. Comparisons of laboratory parameters between the two groups were made using t-test for independent samples or Mann-Whitney U test depending on the normality of distribution. Level of significance was considered as $p < 0.05$.

Results

A total of 123 pediatric hospitalized patients with COVID-19 were included in the study. Fifty-five (44.7%) were females and 68 (55.3%) were males with a mean age of 95.94 ± 72.20 months. Of the patients, 18 (14.6%) were under one year old, there were 31 (25.2%) patients aged 1-5 years, 53 (43.1%) patients aged 5-15 years, and 21 (17.1%) patients over the age of 15. Comorbidity was present in 30 (24%) patients; asthma in nine (7.3%), neurometabolic and neurogenetic disorders in eight (6.5%), obesity in six (4.8%), cardiopathy in four (3.2%), and immunodeficiency in three (2.4%) patients. The most common symptom of the patients was fever (74%) ($n = 91$) for a median of two days (IQR= 1-4 days). Other common symptoms were sore throat ($n = 77$, 62.6%), cough ($n = 50$, 40.6%), myalgia ($n = 41$, 33.3%), dyspnea ($n = 28$, 22.8%), gastrointestinal symptoms ($n = 15$, 13%), headache ($n = 7$, 5.6%) and nasal discharge ($n = 5$, 4%). Length of hospital stay-in median range

Table 1. Characteristics of the hospitalized patients

Characteristics of the patients	n (%)
Age (mean) (months)	95.94 ± 72.20
Age groups (years)	
0-1 yr	18 (14.6%)
1-5 yrs	31 (25.2%)
5-15 yrs	53 (43.1%)
>15 yrs	21 (17.1%)
Sex	
Female	55 (44.7%)
Male	68 (55.3%)
Comorbidities	
Asthma	30 (24%)
Neurometabolic-	9 (7.3%)
Neurogenetic disorders	8 (6.5%)
Obesity	6 (4.8%)
Cardiopathy	4 (3.2%)
Immunodeficiency	3 (2.4%)
Symptoms	
Fever	91 (74%)
Sore throat	77 (62.6%)
Cough	50 (40.6%)
Myalgia	41 (33.3%)
Dyspnea	28 (22.8%)
Gi symptoms	15 (13%)
Headache	7 (5.6%)
Nasal discharge	5 (5.4%)
Severity	
Mild	91 (74%)
Severe	32 (26%)
Treatment	
Hydroxychloroquine	4 (3.2%)
Antibiotic treatment	50 (40.6%)
Favipiravir	2 (1.6%)
Corticosteroid	17 (13.8%)
Salbutamol	33 (26.8%)
Anticoagulant	11 (8.9%)
Length of hospital stay (day)-median (range)	5.09 (1-14)
PICU admission	5 (4.1%)
Mortality	0 (0%)

GI: Gastrointestinal, PICU: Pediatric intensive care unit.

was 5.09 days (1-14 days) (Table 1). Thirty-two (26%) patients had signs of lower respiratory tract infection requiring oxygen therapy, and these patients were considered to have severe disease. In contrast, patients with milder symptoms and those who did not need oxygen support were supposed to have mild disease, and the patients were thus divided into two groups. In the severe group, five (4.1%) patients had PICU admission; high-flow oxygen therapy was given to two patients,

and bilevel positive airway pressure (BPAP) support was given to one patient; none required intubation in the follow-up. Ninety-one (74%) patients had mild disease. When these two patient groups were compared, it was found that the underlying condition, radiological involvement, and admission to the intensive care unit were higher in the severe disease group and were found to be statistically significant ($p < 0.05$) (Table 2). There was no difference in terms of age and sex (Table 2). When the two groups were compared in terms of laboratory findings, C-reactive protein and ferritin values were found to be higher in the severe disease group compared to the other group and were statistically significant ($p < 0.05$). Lymphopenia was detected in 21 (17.1%) patients and neutropenia in 33 (26.8%) patients; there was no significant difference between the two groups. Also, when the neutrophil/lymphocyte ratio (NLR) was compared, no significant difference was found between the two groups ($p = 0.23$) (Table 3). Although there was no relationship between the severity of the disease and lymphocyte, neutrophil, and NLR, it was noted that there were differences in age groups. When the patients were divided into two groups under five years old and over five years old, we determined that all lymphopenic patients were in the group over five years old; no lymphopenia was found in the group under five years old ($p < 0.05$). In terms of neutropenia, the rate of neutropenia in the group under five years old ($n = 22$, 66.6%) was higher than those in the group above five years old ($n = 11$, 33.4%), and it was statistically significant ($p < 0.05$) (Table 4).

Chest X-ray was performed on 113 patients. Seventy-one (62.8%) had normal results among these patients, while 42 (37.7%) had pathologic findings. CT was performed on 58 patients. Of these patients, 24 (41.3%) had normal results. Thirty-four (58.6%) patients had pathologic findings on CT. Among all hospitalized patients, radiological involvement on CT (specific findings due to COVID-19 as glass opacities, etc. was detected in 34 (27.6%).

Antibiotic treatment was given to 50 (40.6%) patients; ampicillin sulbactam is used in 19 (15.4%) patients, ceftriaxone is used in 31 (25.2%) patients, ceftriaxone + clarithromycin is used in 20 (16.2%) patients, clarithromycin is used alone in 11 (8.9%) patients, azithromycin is used in 10 (8.1%) patients, ceftriaxone + vancomycin is used in six (4.8%) patients, meropenem used in four (3.2%) patients, piperacillin-tazobactam is used in three (2.4%) patients, ciprofloxacin used in one (0.8%) patient.

Four patients (3.2%) over 15 years of age were treated with hydroxychloroquine, and two (1.6%) patients were treated with favipiravir. Steroid therapy was administered to 18 (14.6%) patients, and low molecular weight heparin therapy was administered to 11 (8.9%) patients.

Table 2. Demographic and laboratory characteristics of the mild and severe COVID-19 patient groups

	Mild	Severe	p
Age (mean) (months)	87.89 ± 69.94	121.1 ± 72.58	0.647
Sex	Male 49 (53.8%)	Male 17 (58.6%)	0.653
Comorbidity	12 (13.2%)	18 (62.1%)	0.000
PICU admission	1 (1.1%)	4 (13.8%)	0.003
Radiological involvement	14 (15.4%)	18 (62.1%)	0.000
Antibiotic use	74 (81.3%)	28 (96.6%)	0.045
Antiviral therapy	0 (0%)	2 (7.7%)	0.009
Steroid therapy	1 (5.9%)	16 (94.1%)	0.000
Neutropenia (<1500/mm ³)	23 (24.2%)	10 (31%)	0.462
Lymphopenia (<1500/mm ³)	15 (16.5%)	6 (20.7%)	0.604
Increased CRP (>5 mg/L)	10 (11%)	12 (41.4%)	0.000

CRP: C-reactive protein, PICU: Pediatric intensive care unit.

Table 3. Laboratory characteristics of the mild and severe COVID-19 patient groups

Laboratory parameters, median (IQR)	Mild	Severe	p
WBC/mm ³	6800 (4995-8995)	7230 (4065-10560)	0.879
ANC/mm ³	2570 (1450-4375)	3550 (1165-7045)	0.405
ALC/mm ³	2330 (1825-3795)	2000 (1475-3185)	0.134
Hb, g/dL	12.1(11.4-13.1)	12.9 (11.6-13.6)	0.410
PLT/mm ³	258.000 (213.500-308.000)	271.000 (185.500-361.500)	0.550
CRP, mg/L	0.3 (0.1-1.4)	3.1 (0.6-8)	0.000
Ferritin, µg/L	51 (39-66.2)	141.5 (43.2-283.7)	0.035
D-dimer, µg/L	158.5 (101.7-263)	274 (134.5-434)	0.089
NLR	1.04 (0.49-1.93)	1.19 (0.53-26.1)	0.23

ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, CRP: C-reactive protein, Hb: Hemoglobin, NLR: Neutrophil-to-lymphocyte ratio, PLT: Platelet count, WBC: White blood cell.

Table 4. Distribution of lymphopenia and neutropenia by age groups

	Patients, n= 123	p
Lymphopenia (<1500/mm ³)	n= 21 (17%) 0-5 yrs, 0 (0%) >5 yrs, 21 (17%)	0.000
Neutropenia (<1500/mm ³)	n= 33 (26.8%) 0-5 yrs, 22 (17.8%) >5 yrs, 11 (8.9%)	0.001

Discussion

Our study presented our single-center experience, including 123 pediatric patients hospitalized for COVID-19. Most of the patients (n= 74, 60.1%) were over five years old, and male (n= 68, 55.3%). Male cases have been reported slightly more than female cases in most studies (12-16). Similar to our study, Ding et al. reported that most pediatric patients with COVID-19 were older than five years (12).

There are many publications on the effects of comorbidity on the course of the disease. According to the CDC-MMWR, 23% of the pediatric patients had underlying conditions. The most common underlying conditions were chronic lung disease (including asthma), followed by cardiovascular disease and immunosuppression (13). We also found comorbidity in 24% of the patients; asthma, neurometabolic-genetic disorders, and obesity were the most common underlying conditions. In Türkiye's most extensive pediatric data reported on COVID-19, the underlying disease was present in 12.9% of patients; the most common were asthma and lung disease (14).

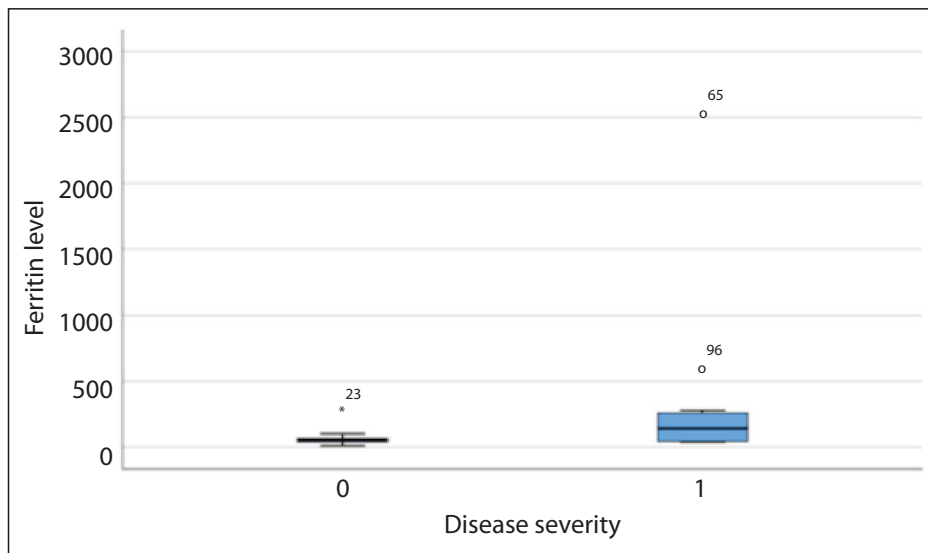


Figure 1. Ferritin levels between mild (0) and severe (1) group.

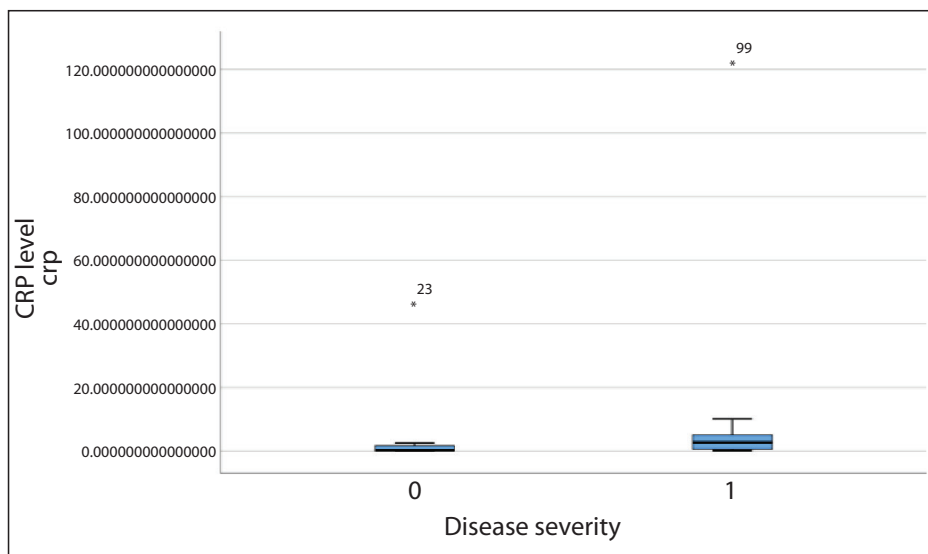


Figure 2. CRP levels between mild (0) and severe (1) group.

The most common symptom of the patients was fever (74%, for a median of two days), which was followed by sore throat (62.6%) and cough (40.6%) in the study. In the current literature, fever and cough are emphasized as the most common symptoms in childhood (14-16).

At the beginning of the pandemic, a less severe clinical course of COVID-19 in children compared to adults was emphasized. The lower maturity and function of angiotensin-converting enzyme II (ACEII) in children, a receptor for SARS-CoV-2, is one of the hypotheses (17). Specific regulatory mechanisms in the respiratory, and immune systems and the immaturity of children’s immune systems may explain the lower potential to develop exaggerated immune response

and cytokine storm (18). On the other hand, severe cases in various age groups of children with COVID-19 have been reported with the continuation of the pandemic. Chinese data suggest the highest incidence of critical patients in infants (10.6%), and children 1-5 years old (7.3%), with decreasing prevalence in older age groups (19). Also, we detected a severe course of COVID-19 disease requiring O2 support in 26% of our patients. Similar to our study, Karbuz et al. have also found moderate-severe illness in 25.2% of their patients (14). In another study, moderate-to-severe disease was reported in 25.1% of pediatric patients (16). There is still no clear data on how the disease will progress in children and the risk factors for severe disease.

In our study, we examined whether there was a difference between the severity of the disease and the laboratory findings; patients with mild and severe illness were compared, and we determined that there was no difference between the two groups in terms of age, sex, lymphopenia, neutropenia, and NLR. C-reactive protein and ferritin values were higher in the severe disease group than in the other group and were statistically significant ($p < 0.05$). There are publications with data showing that elevated CRP, ferritin, and fibrinogen values are correlated with severe disease (15,16). A study, including pediatric cases, evaluated the demographic characteristics and laboratory findings of confirmed COVID-19 instances according to the degree of illness severity and did not show statistical differences in the median age and sex between the groups (15). There were also no statistical differences in the mean WBC, ANC, ALC, Hb, PLT, MPV, D-dimer, NLR, PCT, and NT-pro BNP values between the groups. Mean values of CRP and fibrinogen were statistically higher in severe (moderate to critical) patients than in nonsevere (asymptomatic to mild) patients. In adults, leukopenia and thrombocytopenia are associated with disease severity (19,20). Similarly, in a study including pediatric COVID-19 patients, they have demonstrated that the patients with leukopenia had a longer length of hospitalization and also had a higher need for PICU admission (21).

A recent study has shown that nearly one-third of children with COVID-19 have abnormal findings on their initial complete blood count (21). Still, the prognostic significance of these hematologic abnormalities has not yet been well defined. In our study, neutropenia was detected in 26.8% of the patients. When the patients were analyzed according to age groups, we found more neutropenia in those under five years old ($p = 0.001$) and lymphopenia in those above five years old ($p = 0.000$). Similarly, Karbuz et al. have reported that leukopenia (12.6%) and lymphopenia (44.1%) were more common in older groups (patients who were ≥ 15 years of age) (14). Folino et al. have reported that 12.63% of the patients with documented SARS-CoV-2 infection were neutropenic, had mild clinical manifestations, and were discharged without sequelae (22). They have mentioned that neutropenia does not emerge as a potential negative prognostic factor in pediatric COVID-19, and it was like transient benign neutropenia associated with other common viral infections. Similarly, our study found that neutropenia was associated with mild disease findings and resolved spontaneously. Venturini et al. have reported two infants with mild COVID-19 and severe neutropenia with a low-grade fever and mild respiratory symptoms (23). Severe neutropenia was noted on the fifth day, but neutrophil values improved without clinical complications. They have mentioned that postinfectious transient neutropenia had been associated with many other viral infections in infancy, which

might share pathogenic mechanisms. This finding in neonates and infants could be another manifestation of the age-related different immunologic response to SARS-CoV-2 infection.

Among all hospitalized patients, radiological involvement on CT was detected in 34 (27.6%) patients who had pneumonia findings clinically. Unlike adult practice, we have taken radiological examinations as an absolute necessity for our population, which we try to protect from the possible harmful effects of radiation. Because of the less severe character of the disease in childhood, it may be a more accurate approach to evaluate patients with chest X-rays at admission and perform CT according to the clinical course.

Antibiotic treatment was given to 40.6% of the patients; since secondary bacterial infection could not be excluded, antibiotic treatment was prescribed for those with a severe clinical course, those who needed respiratory support, those with elevated CRP, and those with clinical and laboratory (including radiological) deterioration. Antiviral therapy was given to a small number of selected patients, as there is no approved treatment option in cases under 15 years of age. Dexamethasone IV treatment was beneficial in patients with severe pneumonia.

In conclusion, our study revealed that a significant proportion of children hospitalized for COVID-19 might develop severe illness and pneumonia requiring substantial oxygen support and asthma was the most common comorbidity. Ferritin and CRP were found to be markers that could be used to predict disease severity. Our study did not find a relationship between lymphopenia and poor prognosis, which is frequently emphasized in adult studies. The number of patients who developed neutropenia was higher than lymphopenia. It was remarkable that neutropenia was detected mainly in children under the age of five, had a temporary benign course and was not associated with the severity of the disease. Although a single-center experience and retrospective nature are limiting factors of our study, we think different prognoses may develop in childhood with varying variants. Future studies and more data sharing are needed to understand the effects and consequences of COVID-19 on children.

Ethics Committee Approval: This study was approved by Ege University Rectorate Medical Research Ethics Committee (Decision no: 22-4T/6, Date: 07.04.2022).

Informed Consent: Patient consent was obtained.

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