

# Clinical Manifestations of COVID-19 in Children at a Pediatric Tertiary Center in Turkey

Pediatric COVID-19 Vakalarının Klinik Değerlendirilmesi: 3. Basamak Tek Merkez Deneyimi

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## Abstract

Limited studies have been published on practices and management of coronavirus disease-2019 (COVID-19) in children from the beginning of the pandemic. With this study, we aimed to share the clinical and epidemiological characteristics of infection in pediatric patients and our experiences. COVID-19 Polymerase Chain Reaction (PCR) test positive pediatric patients we followed up in our hospital between March to December 2020 were included in the study. The epidemiological, laboratory, radiological, and clinical data of the patients were analyzed retrospectively. During the study period, 246 test positive pediatric patients were admitted. The median age was 9 years (2 months-17 years), girls accounted for 53,7%, and 76 (31%) patients were asymptomatic. The cough was the predominant symptom (48%), followed by fever (43%) and sore throat (15%). There was a household contact in 199 (81%) of all cases and 32 (12%) patients had comorbidity and chronic illness. The most common laboratory findings; lymphopenia (26%), eosinopenia (21%), monocytosis (18%), high C-reactive protein (20%). Distribution according to case classes; asymptomatic (32,2%), mild (52,4%), moderate (13,8%), severe (1,2%), critical (0,4%). Of all cases, 48 (19,5%) were inpatients and 11 (4,5%) were in intensive care. Chest tomography was performed in 25 (10%) patients and 10 (4%) were abnormal. As a treatment, 22 (8%) patients received favipiravir, 1 (0,4%) lopinavir-ritonavir, 16 (6%) antibiotics, 4 (1,6%) methylprednisolone and 3 (1,2%) low molecular weight heparin. COVID-19 is often asymptomatic and mild in children, it may rarely have a severe course. More caution should be exercised in children under 1 year of age and patients with comorbidities.

**Keywords:** COVID-19, child, pandemics

## Özet

Pandeminin başlangıcından itibaren çocuklarda COVID-19 tanı, klinik bulguları ve yönetimi hakkında sınırlı sayıda çalışma yayınlanmıştır. Bu çalışma ile çocuk hastalarda COVID-19 enfeksiyonunun klinik ve epidemiyolojik özelliklerini ve deneyimlerimizi paylaşmayı amaçladık. Mart 2020 -Aralık 2020 tarihleri arasında hastanemizde takip ettiğimiz COVID-19 polimeraz zincir reaksiyon testi pozitif çocuk hastalar çalışmaya dahil edildi. Hastaların epidemiyolojik, laboratuvar, radyolojik ve klinik verileri geriye dönük olarak incelendi. Çalışmaya 246 çocuk hasta kabul edildi. Hastaların, %53'ü kızdı ve ortanca yaşı 9'du (2 ay-17 yıl) ve 76'sı (%31) asemptomatikti. En sık semptomlar, öksürük (%48), ateş (%43) ve boğaz ağrısıydı (%15). Olguların 199'unun (%81) ailesinde temas öyküsü mevcuttu ve 32'sinin (%12) kronik hastalığı vardı. En sık görülen laboratuvar bulguları; lenfopeni (%26), eozinopeni (%21), monositoz (%18), yüksek C-reaktif protein (%20) di. Vakaların %32'si asemptomatik, %52'si hafif, %14'ü orta, %1,2'si şiddetli (%1,2), %0,4'ü kritik sınıftaydı. Hastaların 48'i (%19,5) hastaneye yatırıldı, 11'i (%4,5) yoğun bakımda takip edildi. Hastaların 25'ine (%10) akciğer tomografisi çekildi ve 10'unda (%4) anaormal bulgular mevcuttu. Tedavi olarak 22 (%8) hastaya favipiravir, 1 (%0,4) lopinavir-ritonavir, 16 (%6) antibiyotik, 4 (%1,6) steroid ve %3 (1,2) düşük molekül ağırlıklı heparin verildi. COVID-19, çocuklarda sıklıkla asemptomatik ve hafif olmasına rağmen, nadiren şiddetli seyredebilir. Özellikle bir yaşın altındaki çocuklarda ve komorbiditesi olan hastalarda daha dikkatli olunmalıdır.

**Anahtar Kelimeler:** COVID-19, çocuk, pandemi

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## 1. Introduction

In December 2019, many atypical pneumonia cases were detected in Wuhan, China, and spread rapidly to the World (1). This epidemic has been linked to a new coronavirus called Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19), respectively. On March 11, 2020, the World Health Organization (WHO) announced a COVID-19 Pandemic (2).

The first COVID-19 case in our country was reported on March 11, 2020. In phylogenetic analysis, SARS-CoV-2 is included in the beta coronavirus family with the largest positive-polar RNA genome. (3) Droplets are the most common way for respiratory secretions to transfer pathogens from person to person, with an average incubation period of 1-14 days. It causes symptoms ranging from mild upper respiratory tract symptoms to severe respiratory failure in adult patients. In the early days of the COVID-19 pandemic, there were very few pediatric patients and children were thought not to be susceptible to this infection. A 10-year-old boy living in Shenzhen, China, was reported as the first pediatric case of COVID-19 in the literature on January 20, 2020. (4) Pediatric cases continued to be reported from many centers afterward. The clinical and laboratory manifestations of COVID-19 in children differ from those in adults, and the disease had a mild form in children than in adults. (5) However, it has also been reported that COVID-19 can be severe, especially in children with underlying chronic diseases (6). Despite the numerous studies, the COVID-19 course in children has not been fully elucidated. This study was carried out to shed light on the epidemiology, laboratory, and clinical course of COVID-19 in pediatric patients.

## 2. Materials and Methods

Between March 2020 and December 2020, children with positive COVID-19 PCR test results were enrolled in this study at Eskişehir Osmangazi University Medical Faculty Hospital, Department of Pediatrics. The study was sent for approval to the Ministry of Health's COVID-19 Scientific Research

Assessment Commission and the Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (decision number, 161618). Children aged 0 to 18 years old were included in the study if their combined nasopharyngeal swab sample was positive for COVID-19 PCR (confirmed by our hospital's microbiology and genetic laboratory using the Bio-Speedy Double Gene test kit). The hospital automation system was used to access the details of these patients, and the research was performed retrospectively. Patients who were negative for COVID-19 PCR and whose COVID-19 PCR test was found to be positive in other health institutions were not included in the study. The diagnosis, treatment, and follow-up of the cases were arranged according to the Ministry of Health COVID-19 Pediatric Patient Guide and the World Health Organization data. The data belong to cases; epidemiological and demographic data, age, gender, contact and transmission history, presence of accompanying chronic disease and risk factors, symptoms and signs, laboratory and radiological findings (hemogram, CRP, procalcitonin, erythrocyte sedimentation rate, AST, ALT, urea, creatinine, LDH, triglyceride, D-dimer, INR, ferritin, chest radiography, chest computed tomography), echocardiography findings, service, and intensive care admission history, disease severity (asymptomatic, mild, moderate, severe, critical), treatments (favipiravir, hydroxychloroquine, lopinavir, steroid, antibiotic, oxygen support), treatment duration, disease course, etc. were evaluated. The classification of the disease degree was classified according to the COVID-19 guidelines of the Ministry of Health and the classification made by Dong et al, which is accepted in the literature (6). Patients were divided into 5 groups as asymptomatic, mild, moderate, severe, and critical illness, according to the clinical, laboratory findings, radiological findings, oxygen, and intensive care needs of the patients.

### *Statistical analysis*

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 21.0 software. Numerical properties

were compared with the Mann – Whitney U test, and the relationships between numerical properties were analyzed by correlation analysis. The compatibility of the variables to normal distribution was examined using the Kolmogorov-Smirnov / Shapiro-Wilk tests. Descriptive analysis for normally distributed variables; The mean, standard deviation, and the median (minimum-maximum) for non-normally distributed variables were given. Categorical variables were expressed as "%".  $p < 0.05$  was considered statistically significant.

### 3. Results

Between March 2020 and December 2020, combined nasopharyngeal swab samples were taken from 2225 pediatric patients for suspicion of COVID-19 infection, and 246 (10.2%) patients were found to be positive for COVID-19. In patients with positive COVID-19 PCR test, 132 were girls (53.7%). The median age was 9 years (min: 2 months, max: 17 years). The cases were divided into five age groups, with approximately half of the cases (55%) being children over the age of ten. There was a household contact in 199

(81%) of all cases. A total of 32 cases had comorbid diseases, with the most common being a chronic hematological disease in 6 patients, chronic kidney disease in 4 four patients, chronic lung disease in 3 patients, chronic heart disease in 2 patients, and obesity in 4 patients (Table-1). While 76 of all cases were asymptomatic, the most common symptom was cough (48%), followed by fever (43%), sore throat (15%), shortness of breath (12%), myalgia (11%) (Table 1). Chest X-ray was taken in 66 patients and 6 of them had infiltration and consolidation. Lung tomography was performed in 25 (10.2%) patients, 10 (4.1%) patients had ground-glass opacity, consolidation, and infiltration. In four patients who were found to be normal on chest X-ray, ground-glass opacity and infiltration were found in lung tomography (Table-2). The most common laboratory findings; lymphopenia in 66 (26.8%), eosinopenia in 53 (21.5%), elevated CRP in 48 (20%), monocytosis in 45 (18.3%), leukopenia in 20 (8.1%), leukocytosis in 15 (6.1%) (Table 1). Elevated CRP, LDH, and ferritin levels were prominent in the inpatient group compared to outpatients ( $p: 0.01$ ) (Table-2).

**Table 1.** Demographic and clinical features of patients with COVID-19

Factors	All patients (n:246)(%)	Outpatient (n:198)(%)	Inpatient (n:48)(%)	p
<b>Sex</b>				0,342
Girl	132 (54)	108 (81)	24 (19)	
Boy	114 (46)	90 (79)	24 (21)	
<b>Age (year)</b>	9,4 (2 month-17)	9,7 (2month-17)	8,1(2month-16)	<b>0,006</b>
<1	18 (7)	8 (44)	10 (56)	
1-5	53 (21)	44 (83)	9 (17)	
6-10	37 (15)	32 (87)	5 (13)	
11-15	77 (31)	61 (79)	16 (21)	
>15	61 (24)	53 (87)	8 (13)	
<b>Symptoms</b>				
Asymptomatic	76 (31)	76(100)	0(0)	
Cough	120 (48)	87 (73)	33 (27)	<b>0,002</b>
Fever	107 (43)	64 (60)	43 (40)	<b>0,001</b>
Sore throat	38 (15)	29 (76)	9 (23)	0,300
Shortness of breath	30 (12)	10 (33)	20 (67)	<b>0,001</b>
Myalgia	28 (11)	18 (64)	10 (36)	<b>0,025</b>
Chest Pain	12 (5)	3 (25)	9 (75)	<b>0,001</b>
Vomiting	9 (3,7)	1 (11)	8 (89)	<b>0,001</b>
Headache	9 (3,7)	5 (63)	3 (37)	0,192
Diarrhea	7 (2,9)	5 (71)	2 (29)	<b>0,411</b>
Abdominal pain	4 (1,5)	1 (25)	3 (75)	<b>0,024</b>
Neurological sign	5 (2)	0 (0)	5 (100)	<b>&lt;0,001</b>
<b>Accompanying diseases</b>				<b>0,001</b>
Lung diseases	3 (1,2)	2 (67)	1 (33)	

Congenital heart Disease	2 (0,8)	2 (100)	0 (0)	
Renal disease	4 (1,6)	4 (100)	0 (0)	
Romatological diseases	3 (1,2)	2 (67)	1 (33)	
Hemato-Oncological diseases	6(2,4)	3 (50)	3 (50)	
Gastrointestinal diseases	5 (2)	4 (80)	1 (20)	
Neurological disease	2 (0,8)	0 (0)	2 (100)	
Immun deficiency	2 (0,8)	2 (100)	0 (0)	
Tip-1 DM	1 (0,4)	0 (0)	1 (100)	
Obesity	4 (1,6)	0 (0)	4 (100)	
<b>History of Contact</b>				
Housohold contact	199 (81)	163 (82)	36 (18)	0,300
School contact	6 (4)	5 (83)	1 (17)	
No contact	39 (15)	27 (71)	11 (29)	

**Table 2.** Laboratory and radiological findings of patients with COVID-19

Laboratory	All patients (n:246)(%)	Outpatients (n:198)(%)	Inpatients (n:48)(%)	P
<b>Leucocyt</b>	8162(1310-62910)	1550(1550-17400)	9254(1310-62910)	
Leucocytosis	15 (14,7)	6 (5,9)	9 (8,8)	0,504
Leucopenia	20 (19)	11 (10)	9 (9)	0,500
<b>Lymphocyte</b>	3119 (400-60420 )	2358(400-7420)	4140(410-60720)	
Lymphopenia	66 (64,7)	38(37,3)	28 (27,5)	0,504
<b>Eosinophils</b>	134(0-4700)	98 (0-800)	182(0-4700)	
Eosinopenia	53(52)	27 (26,5)	26(25,5)	0,146
<b>Monocytes</b>	815 (70-2730)	798 (70-1960)	836 (150-2730)	
Monocytosis	45 (43,7)	23 (22,3)	22(21,4)	0,180
<b>CRP</b>	13(1-181)	10 (1-119)	16 (1-181)	
Crp ↑	45(48,4)	23 (24,7)	22 (23,7)	0,184
<b>D-dimer</b>	1,2 (0,1-26)	0,6(0,1-6)	1,7(0,2-26)	
D-dimer ↑	27(40,3)	9 (13,4)	18 (26,9)	<b>0,018</b>
<b>LDH</b>	284 (125-1500)	257(125-780)	324(132-1500)	
LDH ↑	29(34,1)	14(16,5)	15(17,6)	0,117
<b>Ferritin</b>	118(4-857)	68(4-344)	180(28-857)	
Ferritin ↑	7 (13,7)	1(2)	6(11,8)	<b>0,027</b>
<b>ProBNP</b>	251 (8-3671)	86 (10-570)	8 (89)	
ProBNP ↑	5 (20)	2 (8)	3 (12)	0,230
<b>Chest X-ray</b>	66 (26,8)	38(15,4)	28(11,4)	<b>0,001</b>
Normal	60(24,4)	36(14,6)	24 (9,9)	
Consolidation+Infiltration	6 (2,4)	2(0,8)	4 (1,6)	
<b>Chest tomography</b>	25 (10)	13(5,3)	12 (4,8)	<b>0,001</b>
Normal	15 (6,1)	9 (3,7)	6(2,4)	
Abnormal	10(4,1)	4(1,6)	6 (2,4)	
<b>Treatment</b>				
Supportive	221 (89)	188 (76)	33 (13)	<b>0,001</b>
Favipiravir	22(8,9)	8 (3,3)	14(5,7)	<b>0,001</b>
Lopinavir-ritonovir	1 (0,4)	1(0)	1 (0,4)	0,195
Steroid	6 (2,4)	2 (0,8)	4(1,6)	<b>0,004</b>
LMWH	3 (1,2)	0(0)	3 (1,2)	<b>0,001</b>
Antibiotics	16 (6,5)	2 (0,8)	14 (5,7)	<b>0,001</b>
<b>Ventilation support</b>				<b>0,001</b>
Noninvasive ventilation	4 (1,6)	0 (0)	4 (100)	
Invasive ventilation	1(0,4)	0 (0)	1 (18)	

Distribution according to case classes; Asymptomatic 79 (32,2%), mild 129 (52,4%), moderate 34 (13.8%), severe 3 (1.2%), critical

1 (0.4%) patient were observed. Of all cases 198 were followed up as outpatients, 48 as inpatients, and 11 as intensive care patients.

While the morbidity rate was very low in our study, there was no mortality. The mean length of stay in the hospital was 6.9 days (Table-3). Patients who received favipiravir 22(8%), lopinavir-ritonavir 1(0.4%), antibiotics 16(6.5%), methylprednisolone

4(1.6%), and low molecular weight heparin 3(1.2 %). Thirty-nine patients received oxygen therapy via mask and nasal cannula, four received noninvasive ventilation, and one received invasive ventilation (Table-3).

**Table 3.** Treatment and clinical classification of patients with COVID-19

	Asymptomatic	Mild	Moderate	Severe-Critic	Total	P
<b>Age</b>						<b>0,008</b>
<1 age	3 (1,2)	9 (3,7)	5 (2)	1 (0,4)	18 (7,3)	
2-5 age	16 (6,5)	33 (13,4)	4 (1,6)	0 (0)	53 (21,5)	
6-10 age	10 (4,1)	24 (9,8)	3 (1,2)	0 (0)	37 (15)	
11-15 age	28 (11,4)	37 (15)	9 (3,7)	3 (1,2)	77 (31,3)	
>15 age	22 (8,9)	26 (10,6)	13 (5,3)	0 (0)	61 (24,8)	
Total	79 (32,2)	129 (52,4)	34 (13,8)	4 (1,6)	246 (100)	
<b>Treatment</b>						<b>0,001</b>
Favipiravir	0 (0)	1 (0,4)	17 (6,9)	4 (1,6)	22 (8,9)	
Lopinavir-Ritonovir	0 (0)	0 (0)	0(0)	1 (0,4)	1 (0,4)	
Steroid	0 (0)	0 (0)	3 (1,2)	3 (1,2)	6 (2,4)	
DMAH	0 (0)	0 (0)	0 (0)	3 (1,2)	3 (1,2)	
Antibiotics	0 (0)	5 (2)	7 (2,8)	4 (1,6)	16 (6,5)	
<b>Oxygen support</b>						<b>0,001</b>
Noninvasive ventilation	0 (0)	0 (0)	0 (0)	4 (1,6)	4 (1,6)	
İnvazive ventilation	0 (0)	0 (0)	0 (0)	1 (0,4)	1 (0,4)	

#### 4. Discussion

After the World Health Organization declared COVID-19 a pandemic in March 2020, the entire world has struggled to control and treat this pandemic. While data on pediatric patients was limited at the start of the pandemic, data were updated on a daily basis with the participation of all countries and centers. In this study, we looked at the epidemiological, laboratory, and clinical data of 246 COVID-19 PCR positive pediatric patients who were followed up on at our center. Although COVID-19 is seen in children of all ages, it progresses with milder clinical findings than in adults (6,7). In our study, appropriate to the literature, 79 (32,2%) of the cases were asymptomatic and 129 (52,4%) had mild symptoms. Observation of children who have milder symptoms than adults; Children with lower expression of ACE-2 cell receptors and S-proteins involved in coronavirus pathology, as well as a more active natural immune system as a result of previous viral infections, are thought to have a better response to COVID-19 (8-10). In our

study, 53,7 percent of COVID-19 -PCR positive pediatric patients were girls, with median age of 9 years. While the majority of cases were over ten years old, there were only 18 cases that were under than 1-year-old. While the number of cases increased with age, the rate of hospitalization was higher in children under the age of one year. According to Dong et al. boys are more affected than girls. According to the same study, COVID-19 has a more severe course in those under the age of one year and those with concurrent chronic diseases (6). In our study, however, there was no significant difference between boys and girls in terms of both disease onset and progression. The rate of hospitalization was higher in children under the age of one year. This can be explained by the higher number of hospitalizations (unrelated to clinical severity) for follow-up and surveillance in children under the age of one year. In our study, 32 of the cases also had chronic diseases. The most common symptoms of COVID-19 in children in studies

with large case numbers were fever, cough, shortness of breath, chest pain, sore throat, but other system findings such as headache, diarrhea, vomiting, and abdominal pain have also been shown to cause less frequently (6, 11-13). Similar to the literature, the most common symptoms at presentation in our study were cough, fever, sore throat, and shortness of breath. Patients who presented with dyspnea, chest pain, or neurological findings were more likely to be hospitalized. The majority of pediatric cases were infected through household contacts. A study found that this rate was 94 percent (7). There was a history of household contact in 81% of our cases. According to clinical and laboratory findings, COVID-19 positive cases were classified as asymptomatic, mild, moderate, severe, or critical in the study by Dong et al (6). 4.4 percent of the cases were asymptomatic, 50.9 percent were mild, 38.8 percent were moderate, 52 percent were severe, and 0.6 percent were critical. Similarly, in our study, the distribution of cases was as follows: asymptomatic 32,2%, mild 52,4%, moderate 13,8%, severe 1,2%, and critical 0,4%. The number of asymptomatic cases was higher than expected based on the literature. This can be explained by the early screening of parent-positive family members. The most frequently reported laboratory findings were lymphopenia, elevated CRP, elevated LDH, elevated D-dimer, and normal procalcitonin levels (14-16). The most common laboratory findings in our study included lymphopenia, eosinopenia, monocytosis, and elevated CRP levels. D-dimer and ferritin levels were higher in hospitalized patients and moderate-to-severe patients.

Although COVID-19 causes some changes in the lung, such as consolidation, infiltration, and ground-glass opacity, chest radiography may be normal in the early stages of the disease, lung tomography is more sensitive. However, radiation exposure from tomography in childhood should be considered (17-18). Chest radiography was performed on 66 patients in our study, and lung tomography was performed on 25 patients. Consolidation, infiltration, and ground-glass opacity were found in ten of the twenty-five patients who underwent lung

tomography. The frequency of lung tomography was lower than in the literature, and in four patients with normal chest radiography, a ground-glass opacity and infiltration were detected in lung tomography.

There is no established common treatment protocol for COVID-19 in pediatric patients. Supportive therapies, antiviral treatments, antibiotic therapy, oxygen support, steroid low molecular weight heparin, intravenous immunoglobulin, remdesivir, tocilizumab, and plasma therapy are all used (19-27). In our study, 22 patients received favipiravir, one patient received lopinavir-ritonavir, and three patients received low molecular weight heparin treatment. In none of our patients did we use hydroxychloroquine or oseltamivir treatment. Four patients received noninvasive ventilation, while one received invasive ventilation support. Favipiravir is typically used in moderate-to-severe and hospitalized patients, whereas low molecular weight heparin and steroids are typically used in severe and critical cases.

Our study had some limitations, including the use of observational data from a single center with a small sample size. There were only four serious and critical patients in our study. As a result, the small sample size may have prevented some analyses from reaching definitive conclusions. Despite these limitations, this study is important because it is one of the few reports on the characteristics of confirmed pediatric COVID-19 cases in Turkey. The study provides valuable data on pediatric cases because COVID-19 is a novel disease with limited data, particularly in the pediatric population.

As a result; Although COVID-19 is often asymptomatic and mild in children, it should be kept in mind that it can be severe and critical. In children under 1 year of age and patients with comorbidities, more care should be taken in the follow-up of the disease. The vast majority of pediatric patients are infected indoors, so children from families with positive parents should be closely monitored in terms of symptoms and signs. Larger and multi-center clinical studies are needed for the follow-up and treatment of COVID-19 in children.

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