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Covid-19 in pediatric patients: Data from a training and research hospital

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Abstract
Aim: Coronavirus Disease-19 (COVID-19), caused by severe acute syndrome coronavirus 2 (SARS-CoV-2), has become a worldwide emergency. It is known that the course of the disease in pediatric COVID-19 is milder, with a better prognosis and lower rate of deaths. However, epidemiological and clinical data on children with COVID-19 are still scarce. The aim of this study is to describe the demographic, clinical and laboratory findings of children with COVID-19.
Material and Methods: Medical records of patients aged under 18 years who had polymerase chain reaction (PCR) test for SARS-CoV-2 between March 15, 2020 and September 14, 2020 were examined retrospectively.
Results: Of the 108 children infected with SARS-CoV-2, 52 (48.1%) were female, 56 (51.9%) were male, and the median age was 9 years (0-17 years). The most common presentation symptoms included fever (54.6%), fatigue or myalgia (32.4%), and cough (30.5%). Of all patients, 63.9% (n=53) had lymphopenia. Seventy (67.3%) cases with COVID-19 had a contact history. The median time from symptom onset to diagnosis was 1 (0-8) day. Posteroanterior chest X-ray was ordered in 80.5% (n=87) of the SARS-CoV-2 PCR positive patients, and only 5.7% (n=5) had findings in favor of infiltration. Chest computed tomography was ordered in four (3.7%) children, and one (25%) of them had findings consistent with COVID-19. Eight patients were hospitalized, one of whom was followed-up in the intensive care unit, and no patients died.
Discussion: A better understanding of the clinical and laboratory characteristics of COVID-19 infection in children is very important in developing influential strategies to manage the disease.

Keywords
Children, COVID-19, SARS-CoV-2

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Introduction

COVID-19, which has become the first epidemic of the 21st century, can be seen in all age groups, mostly adults. The initial data from China at the beginning of the epidemic showed that children younger than the age of 18 accounted for only 2.4% of all reported cases [1]. In the early days of COVID-19 epidemic, it has been suggested that children were not susceptible to COVID-19 infection; however, later it became clear that children could also become infected with COVID-19, although less frequently [2]. The largest cohort study on the characteristics of laboratory confirmed COVID-19 in European children showed that the disease was most prevalent in children <1 year of age [3]. However, data reanalyzed in China, indicated that children represent 12% of the cases [4]. As of June 2021, 12.4% of all cases in the United States of America were children, and the incidence of the disease in children has increased approximately 7.5 times when compared with the previous year (available at : https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm).

The number of people infected by the virus is increasing globally day by day, and according to the WHO as of June 10, 2021, the number of cases worldwide was 174.061.995, while 3.758.560 people died (available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports).

Although children are susceptible to SARS-CoV-2 infection, rather than the potential effects of the infection on this group, it was focused on their potential roles to prevent community transmission [5]. The view that COVID-19 has a mild course on children is also common; although the reasons for this are not fully established, several theories have been proposed, including thymic function in children, immune system differences such as cross-reactive immunity against common cold coronaviruses and the differences in the expression of angiotensin-converting enzyme-2 (ACE2), which is the entry receptor of the virus [6]. However, this view has also been questioned recently due to the reports of children who presented with a very severe hyperinflammatory syndrome called multisystem inflammatory syndrome in children (MIS-C) [2]. Although the number of children affected by COVID 19 has increased, data relating the situation in children are still limited [3].

The aim of this study was to report the findings obtained from pediatric patients evaluated with a suspicion of COVID-19 in a training and research hospital in the North of Turkey.

Material and Methods

In this descriptive study, medical records of pediatric patients aged under 18 years who were evaluated with a pre-diagnosis of COVID-19 in the pediatrics clinic of our hospital between March 15, 2020 and September 14, 2020 were examined retrospectively. Ethics approval was received from the Clinical Researches Ethics Committee of our hospital (Date: 28/04/2020, Number: 139).

In line with the guideline prepared by the Coronavirus Scientific Advisory Board in Turkey on SARS-CoV-2, suspicious cases were diagnosed and evaluated. Combined naso-oropharyngeal swabs were taken for the reverse transcriptase-polymerase chain reaction (RT-PCR) test from the patients who met the criteria specified in the guideline. Suspected cases found positive for reverse transcriptase-polymerase chain reaction were accepted as confirmed COVID-19 cases (available at: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID- 19_Rehberi.pdf). The patient information flowchart is shown in Figure 1.

Patients' demographic characteristics such as age and gender, and clinical characteristics including, referral presentation time, symptoms and findings, history of exposure comorbidities (e.g. congenital heart disease, chronic lung disease, immunodeficiency, hematological disease), time from the onset of complaints to the confirmation of diagnosis, laboratory findings such as complete blood count, C-reactive protein (CRP) and blood biochemistry, chest X-ray and computed tomography (CT) images were examined retrospectively from the medical records of the hospital.

Statistical Analysis

Statistical analysis was conducted with SPSS version 21.0 (Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) package program. For descriptive statistics, categorical data are expressed as frequency (n) and percentage (%), while continuous data are expressed as mean, standard deviation and median, minimum-maximum.

Results

A total of 18.680 children presented to the pediatric emergency service of our hospital during the study period. Samples were taken from 697 (3.7%) children with suspected COVID-19. Of these children, 320 (45.9%) were females, and 377 (54.1%) were males. The mean age of the children was 8.1 ± 5.5 years. Of the patients who underwent COVID-19 PCR test, 529 (75.9%) tested negative, and 108 (15.5%) were positive for COVID-19. Sixteen (2.3%) samples could not be evaluated since they were not suitable, and 44 (6,.3%) due to system problems and the problems experienced while carrying the samples. Fifty-two (48.1%) positive cases were female, and 56 (51.9%) were male. The mean age of children with COVID-19 was 8.8 ± 5.2 years. A posteroanterior chest X-ray was ordered in 87 (80.5%) of the 108 children with positive PCR for SARS-CoV-2 positive. On the X-ray images, only 5 (5.7%) children were found to have infiltration findings. Thoracic computed tomography (CT) was performed in four (3.7%) children who had posteroanterior chest X-ray and one (25%) was found to have CT findings consistent with COVID-19. The most common presenting symptom of patients with a positive SARS-CoV-2 PCR result was fever. Seventy (64.8%) patients with COVID-19 had a contact history. Characteristics and symptoms of COVID-19 positive patients are shown in detail in Table 1. Apart from these symptoms, three children presented with nasal congestion, three children with chest pain, and three children with complaints of loss of smell and taste. Of these patients, only the SARS-CoV-2 PCR samples of the children who had loss of taste and smell were found as positive.

It was found that PCR samples were taken from the children after a mean of 1 (0-8) day. While August was the month when the highest number of samples was taken, the highest positivity rate (30%) was found in July. The number of samples taken by month and positivity is shown in Figure 2.

Blood tests were ordered in 83 (76.8%) of the 108 cases whose COVID-19 PCR samples were found positive. Blood test results were evaluated considering the normal limits of age groups and

shown in detail in Table 2.

One hundred (92.5%) of the positive cases were followed up as outpatients, while eight (7.5%) were hospitalized. Of the hospitalized patients, only one (12.5%) patient was hospitalized in the pediatric intensive care unit, while the remaining seven (87.5%) patients were followed up in the pediatric wards. Detailed information about hospitalized positive cases is shown in Table 3.

Table 1. Characteristics of SARS-CoV-2-infected children

Characteristic	Total (n)	Percentage (%)
Sex		
Female	52	48.1
Male	56	51.9
Age (years)		
Mean ± SS / median	8.8 ± 5.2 / 9	
Age groups		
≤1 year	14	13
1-5 years	19	17.6
<5-10 years	28	25.9
<10-18 years	47	43.5
Symptoms		
Fever	59	54.6
Fatigue+myalgia	35	32.4
Cough	33	30.5
Exposure to SARS-CoV-2		
Yes	70	64.8
Unknown	38	35.2

Table 2. Laboratory results of COVID-19 cases

Parameter	Low		Normal		Hight	
	n	%	n	%	n	%
Hemoglobin (g/dL)	12	14.5	71	85.5	0	0
Leukocytes (109/L)	19	22.9	62	74.7	2	2.4
Neutrophils (109/L)	9	10.8	71	85.5	3	3.6
Lymphocytes (109/L)	53	63.9	28	33.7	2	2.4
Platelets (109/L)	4	4.8	72	86.8	7	8.4
LDH (U/L)	5	7.6	28	42.4	33	50
CRP (mg/L)			67	80.7	16	19.3
Ferritin (µg/L)	23	33.8	45	66.2	0	0
AST (U/L)			68	82.9	14	17.1
ALT (U/L)			79	96.3	3	3.7

LDH= lactate dehydrogenase; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase

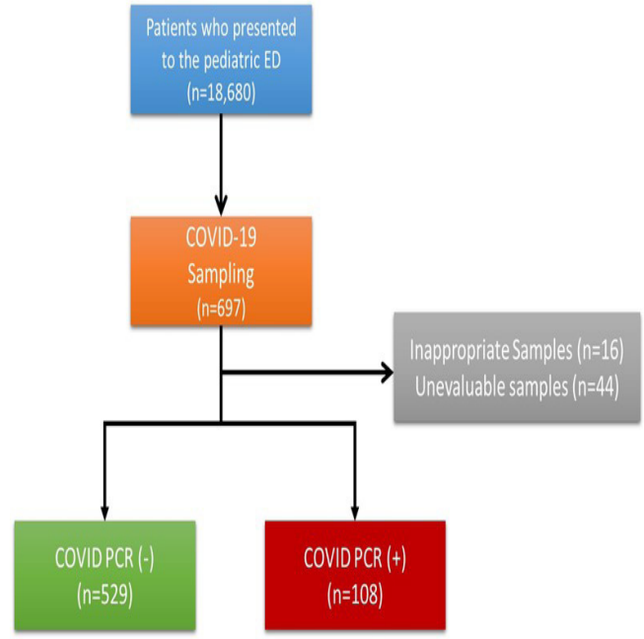


Figure 1. Flowchart of the patients included in the study

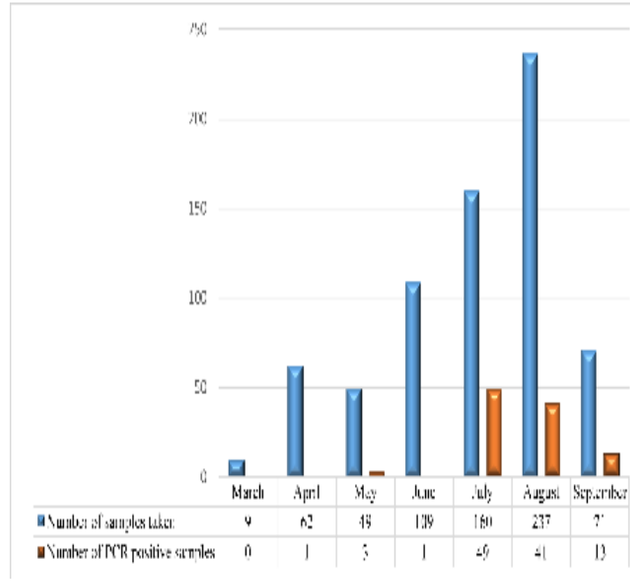


Figure 2. The number of samples taken by months and positivity. Blood tests were ordered in 83 (76.8%) of the 108 cases whose COVID-19 PCR samples were found positive. Blood test results were evaluated considering the normal limits of age groups and shown in detail in Table 2.

Table 3. Characteristics of hospitalized COVID-19 patients

Patient	Unit	Sex	Age (years)	Symptoms	Chronic disease	Exposure	CXR / finding	Chest CT / finding
1	PC	M	1	Cough	No	Yes	Yes / yes	Yes / yes
2	PC	M	8	Fever	No	Yes	Yes / no	No
3	PC	M	1	Fever, cough, fatigue	No	Yes	Yes / no	No
4	PC	F	6	Fever	No	Yes	Yes / no	No
5	PC	M	3	Fever, cough	No	U	Yes/ yes	Yes/ yes
6	PC	M	15	Fever, sore throat, fatigue, headache	No	Yes	Yes / no	No
7	ICU	M	5	Respiratory distress, diarrhea	No	U	Yes / yes	No
8	PC	F	1	None (baby of a mother with COVID-19)	No	Yes	No	No

PC: pandemic service; ICU: intensive care unit; M: male; F: female; COVID-19 = coronavirus disease 2019; U; unknown; CXR= chest X-ray; CT= computed tomography

Discussion

Although there has been an increase in published data on pediatric patients from the beginning of COVID-19 pandemic up to today, it can be seen that most of the studies still include data of adult patients.

At the beginning of the pandemic, it was known that the number and death risk of pediatric COVID-19 patients were lower compared to adults [7]. On February 25, 2020, the first data from China, where the virus originated, showed that the incidence of cases was 0.9% and death rate was 0% in children younger than 10 years of age, while these rates were 1.2% and 0.2% (1 death), respectively in children between 10 and 19 years of age [8]. The April 10, 2020 dated weekly report of CDC about COVID-19 in the USA stated that 1.7% of the cases were children younger than 18 years old and there were 3 deaths among the pediatric cases included in this analysis (available at https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm). In a study conducted in China at the beginning of the epidemic, SARS CoV-2 positivity was reported in 171 (12.3%) of 1391 children, and it was reported that one of these children died [9]. In a study by Korkmaz et al. from Turkey, SARS CoV-2 positivity was found in 21.5% of the children evaluated with a suspicion of COVID-19 and all of the evaluated patients were reported to be recovered [10]. In another study with 581 children, the positivity rate was reported as 14.6% with one death [11]. In the present study, the rate of children infected with SARS CoV-2 was 15.5% and no patients died. Differences in SARS CoV-2 positivity rates of our study and those of the study by Korkmaz et al. might be caused by differences in the technique of taking naso-oropharyngeal swabs, keeping and carrying the samples, amounts of viral load and virus kinetics.

It has been reported that children infected with SARS CoV-2 are mostly males [3, 9, 12]. However, there are also epidemiological studies, which report that girls are more commonly affected by the epidemic [11]. In the present study, the rate of SARS CoV-2 positive boys was higher (51.9%). The gene (Angiotensin-converting enzyme-2ACE2), which SARS-CoV-2 uses as an entry to the host cell, is located on the X chromosome. ACE2 levels in circulation are higher in men when compared with women [13]. This may be partially responsible for the higher frequency and severity of the disease in men when compared with women.

A total of 582 pediatric COVID-19 cases reported from 21 European countries including Turkey have been evaluated in a multi-centred cohort study. According to this study, COVID-19 is most common in children younger than two years old and older than 10 years old [14]. In the studies conducted at the beginning of the pandemic in China in which distribution was evaluated according to age groups, it was shown that COVID-19 pediatric cases were more common in children between the ages of six and 15 [9, 12]. In the present study, more than two thirds of SARS-CoV-2 positive children were between the ages of five and 18. According to the CDC data, the mean age of children infected with COVID-19 is 11 years (available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm). In a study conducted on a similar number of patients, Dong et al. found the mean age of children as seven years [12]. In studies conducted in Turkey, Yayla et al. found mean age as eight in a study examining 77 COVID-19 patients [11] and Korkmaz et al. as 9.5 years in a study examining 81 patients [10]. Similarly, in the present study, the median age of the children with COVID-19 was nine years.

Fever and cough are the most common clinical symptoms in children with COVID-19 [3, 9, 14]. In some patients, symptoms such as fatigue, muscle pain, nasal obstruction, runny nose, sore throat, headache, dizziness, vomiting, diarrhea, abdominal pain, loss of taste and smell can also be seen [15]. In addition, there may be patients with only cough or diarrhea without fever as well as asymptomatic carriers [1]. It was reported that the complaints of the first pediatric case with serious lung involvement reported in Wuhan city of China were diarrhea and vomiting [16]. In a systematic review evaluating 38 studies including a total of 1124 COVID-19 cases, the most common symptoms were reported as fever (47.5%) and cough (41.5%), respectively. In a study examining 220 SARS CoV-2 positive pediatric patients in Turkey, the most common three symptoms were reported as fever (40.5%), cough (35.9%) and muscle pain/fatigue (16.4%), respectively. The other complaints reported in the same study included headache, sore throat, diarrhea, shortness of breath, vomiting, loss of taste and smell, redness in the eyes [17]. Similar to the literature, in our study the most common complaints were fever, fatigue, myalgia and cough.

In the present study, the mean time from the onset of symptoms to the diagnosis was one day, and this rate was smaller than the results of other pediatric studies [12, 17]. This result may be due to our national health policy and our hospital's facilities and working conditions. In studies, the rate of contact history is higher than 90% and it is stated that in general the infected person contacted is a family member [1, 3, 9, 17]. In our study, 64.8% of the cases had a contact history. The reason for our lower rate than the literature may be the fact that contact with individuals who were not confirmed was not included in the rate. The highest positivity rate was found in July (30%) within the time period of our study. As of June 1, 2020, travel restrictions and curfews were ended in Turkey. This situation caused the violation of mask, distance and hygiene rules with the arrival of many people from outside Ordu due to reasons such as visiting, holiday and hazelnut harvest and this might have been effective in the significant increase in positivity rate in July.

Leukopenia, lymphopenia and increased inflammatory markers (erythrocyte sedimentation rate, C-reactive protein or procalcitonin) are the most frequently reported laboratory findings in children and adolescents with COVID-19 [18]. In addition, although the data are limited when compared with adults, lymphopenia, high C-reactive protein, procalcitonin, D dimer and creatine kinase myocardial isoenzyme (CK-MB) levels are laboratory findings associated with more serious disease [19]. When the laboratory results in our study were examined, a remarkable finding was lymphopenia seen in more than half of the patients (63.9%).

Chest X-ray, lung ultrasonography, and high resolution lung tomography (HR-CT) are used in COVID-19 patients as imaging techniques [7]. However, chest X-ray is not recommended as the first imaging option since it does not give normal imaging results in the early stages of the disease [20]. In the present study, chest X-ray was ordered in 80.5% of the patients, but infiltration was found only in 5.7%. Findings consistent with

COVID-19 were seen only in one of the four patients who underwent thoracic CT. The fact that we had little experience about pediatric COVID-19 patients during the study period and the risk of radiation exposure during CT scanning in children continued to be a big concern, which might have affected our choice of imaging methods. We believe that more specific radiological studies are needed to diagnose children with COVID-19.

Weekly COVID-19 hospitalization survey data show an increase in hospitalization rates in children, although these rates are still low when compared with adults (available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). In a small study from Madrid, it was reported that four (10%) of the 41 children with SARS-CoV-2 infection were taken to the intensive care unit [21]. In another study, intensive care was required in only three of the 220 patients [18]. In the current study, only eight (7.5%) patients were followed-up in the hospital, with one admitted to the intensive care unit. All patients hospitalized in the intensive care unit, including a 5-year-old patient who was hospitalized due to respiratory distress, were discharged with recovery after follow-up and completion of treatment.

Conclusion

A better understanding of clinical, laboratory and radiological findings of pediatric COVID-19 cases will contribute to a better understanding of the epidemiological features of SARS-CoV-2 infection, and therefore, taking effective measures to prevent the disease and develop management strategies.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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