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Evaluation of clinical and laboratory findings of pediatric COVID-19: A single-center experience

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Abstract
There is limited data regarding the features of SARS-CoV-2 in children despite the worldwide spread. We aimed to elucidate a better understanding of the clinical and laboratory features of SARS-CoV-2 infection in children. Clinical data about presenting symptoms, exposure history, age, gender, presence of comorbidities, laboratory data, radiological findings including chest radiographs, modalities of treatment, need for hospitalization and clinical classification of disease severity, length of admission were extracted from the medical records. A total of 27 pediatric patients with COVID-19 were included in this study. There were 15 boys, 55.5%. The mean age of children was 6.3 years (range= 2 months-17 years). Six children were hospitalized (22.2%), Hematological abnormalities were present in 15 out of 27 (55.5%) children. All patients got CXRs and 7 out of 27 had abnormal findings (25.9%). There may be differences in presenting symptoms and clinical features between children from different regions and countries. This pediatric clinical report adds data from the epicenter of pandemic in Turkey, Istanbul, discussing symptomatology and radiological findings in children.

Keywords: Coronavirus; 2019 novel coronavirus disease; Pediatric COVID-19; SARS-CoV2

Introduction
Human Coronaviruses cause a significant percentage of all acute respiratory tract infections in children and can be isolated from 4-8%.[1,2] The 2019 novel coronavirus, Severe Acute Respiratory Syndrome (SARS)-CoV-2, often causes an asymptomatic or less severe disease course in children than adults [1, 4]. Virus can be transmitted directly from person to person by respiratory droplets and contact routes [1, 2, 5, 6]. It is speculated that most children with COVID-19 have less severe disease than adults because of higher levels of antibody against the virus, healthier respiratory tracts, fewer comorbidies or the characteristics of their developing immune systems [2, 7].
The first confirmed pediatric case of SARS-CoV-2 infection, an asymptomatic child aged 10 years was reported on January 20 from China [6]. The World Health Organization (WHO) declared a worldwide pandemic in March 2020. Based on the Center for Disease Control (CDC) COVID-19 Response Team report, 1.7% (2572/149,082) of the COVID-19 cases reported as of April 2, 2020, occurred in pediatric patients aged under 18 years, with an hospitalization rate of 5.7% among all pediatric patients [8]. By July 10, there were 12,102,328 confirmed COVID-19 cases globally, and total deaths were 551,046 worldwide [9]. Turkey detected the first adult case on March 11, 2020 [10]. Based on unpublished COVID-19 Surveillance data from Turkish Republic Ministry of Health, there were 117 pediatric cases (117/11535), 1% of the total cases, by 30.03.2020, in Turkey [7]. As of 28.06.2020, among all confirmed cases, 14,388 were children under 15 years of age (7.3%), 27,199 people were aged between 15 to 24 years (13.7%).[11] By July 10, total confirmed cases from Turkey were 210,965 [12].
Although this disease is thought to have a milder clinical course on the pediatric population, there is still limited data regarding the features of SARS-CoV-2 in children despite the worldwide spread.[8] We aimed to elucidate a better understanding of the clinical and laboratory features of SARS-CoV-2 infection in children.

Material and Methods
This cross-sectional study included laboratory-confirmed COVID-19 children from the

pediatric clinics of University of Health Sciences, Zeynep Kamil Maternity and Children's Hospital from March 11 to June 15, 2020. A positive test result for SARS-CoV-2, using real-time reverse transcription–polymerase chain reaction, testing from a respiratory specimen, was defined as a laboratory-confirmed COVID-19 case.

Only children aged between 1 months-18 years old were included; newborns, patients with negative PCR results were excluded from the study. A review of the demographics, clinical, laboratory, radiographic, treatment and outcomes data were recorded. Clinical data about presenting symptoms, exposure history, age, gender, presence of comorbidities; laboratory data including white blood count (WBC), lymphocytes, neutrophil counts, platelets, C-reactive protein(CRP), Creatine Kinase-MB (CK-MB), D-Dimer, troponin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, electrolytes, lactate dehydrogenase (LDH) results; radiological findings including chest radiographs (CXR); modalities of treatment (antibiotic, antiviral, other treatment regimens), need for hospitalization, pediatric intensive care unit (PICU) admission, and outcomes data about mortality, length of admission were extracted from the medical records.

Nasopharyngeal swabs from suspected children were obtained for detection of SAR-CoV-2 RNA. Real-time PCR diagnostic kits were transported to the laboratories that are authorized by the central General Directorate of Public Health (GDPH) Microbiology Reference Laboratory.[10] Clinical classification was based on Chinese experts'consensus statement [13].

Threshold values were determined according to the literature to make comparisons consistently. Leukocyte count below 5,500/ mm^3, lymphocyte count < 1,200/mm^3 was regarded as leukopenia, lymphopenia, respectively [14, 17]. Thrombocyte count below 150,000/mm^3 and neutrophil count < 1,500/mm^3 is considered as thrombocytopenia and neutropenia, respectively.

The study was approved by Ministry of Health of Turkey and the ethics committee of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital (Approval date: 08.07.2020).

Statistical analyses were performed using SPSS version 17 (IBM SPSS Statistics, Chicago, IL). Categorical data were expressed as a number and percentage. A correlation analysis was conducted using Spearmans' analyses. A subgroup analysis was performed on clinical severity by age group. A p-value ≤0.05 was considered statistically significant.

Results

A total number of 145 children were tested for SARS-CoV-2 and only laboratory-confirmed 27 cases were included in this retrospective analysis. The number of confirmed COVID-19 pediatric cases were as follows; 1 in March, 10 in April, 5 in May, 11 cases by June 15. The increase in the number of cases in June may be attributable to the ending of the house confinement of children.

Demographics & Clinical data

There were 15 boys, 55.5%. The mean age of children was 6.3 years (range= 2 months-17 years). Only three children were under 1-year-old. 26 out of 27 of the children had known exposure with a COVID-19 positive adults, mostly parents or close relatives. Only 1 patient had no known contact, he was in-hospital for esophageal dilatation in pediatric surgery clinic.

Most common presenting symptoms were fever and cough (Table 1). Although SARS-CoV-2 testing result was positive, 3 were asymptomatic without any clinical symptoms and signs or imaging findings. Six children were hospitalized (22.2%), two had co-morbidities; a 7-years old girl with epilepsy and an infant with Tetralogy of Fallot and also he was operated for esophageal atresia. The range for length of hospital stay was 4-13 days (median= 5). Patients who were discharged were isolated at home for at least 14 days, they were monitored by telephone.

Table 1: Characteristics and symptoms among 27 laboratory-confirmed pediatric COVID-19 patients

Characteristic	n	%
Gender		
Female	12	44.4
Male	15	55.5
Symptoms		
Fever	18	66.6
Cough	10	37.0
Difficulty in breathing	4	
Fatigue/Myalgia	3	11.1
Dizziness	2	7.4
Headache	2	7.4
Rhinorrhea	2	7.4
Ageusia	2	7.4
Sore throat	2	7.4
Congestion in eyes	1	3.7
Hoarseness	1	3.7
Sweating	1	3.7
Asymptomatic	3	11.1
Treatment		
Out-patient	21	77.7
Hospitalized	6	22.2
Contact history	26	96.3
Co-morbidities	4	14.8
Diabetes mellitus	1	3.7
Epilepsy	1	3.7
Tetralogy of Fallot & esophageal atresia	1	3.7
Asthma	1	3.7

Clinical classification was as follows; asymptomatic 3 (11.1%), acute upper respiratory tract infection (URTI) 16 (59.2%), mild pneumonia 8 (29.6%). Age distribution of children is at Table 2. There was no severe pneumonia or critical patient in our cohort. Mortality rate and PICU admission was 0%.

Table 2: Age distribution of pediatric COVID-19 cases based on Clinical classification. n, % are given

Age (years)	Asymptomatic	Acute URTI	Mild Pneumonia
<1	1, 3.7	1, 3.7	1, 3.7
1-<6	1, 3.7	5, 18.5	3, 11.1
6-18	1, 3.7	10, 37	4, 14.8

Laboratory & Radiologic data

Hematological abnormalities were present in 15 out of 27 (55.5%) children. Leukopenia, lymphopenia, neutropenia, thrombocytopenia and leucocytosis were present in 8 (29.6%), 3 (11.1%), 3 (11.1%), 3 (11.1%) and 1 (3.7%) children, respectively. Two of the children had both

leukopenia and lymphopenia and one child had leukopenia and neutropenia at the same time. D-Dimer, Troponin, CK-MB, urea, creatinine, electrolytes and LDH levels were within the reference ranges. Only one patient with Diabetes Mellitus had hyperglycemia.

CRP was >0.8 mg/dl in 7 children (25.9%). AST>50 IU/L and ALT>45 IU/L were present in two and four children, respectively.

All patients got CXRs and 7 out of 27 had abnormal findings (25.9%). Abnormal finding included bilateral patchy infiltrates, multiple small patchy shadows and interstitial changes.

Treatment data

Therapeutics included general support, monitoring of lung, liver, kidney, and myocardial functions, control over high fever, antibiotics (18, 66.6%), oseltamivir (6, 22.2%) and hydroxychloroquine (3, 11.1%) as needed. Mostly drugs were used in combinations, eight out of 27 were given no drugs.

Hydroxychloroquine was given by oral route, 5 mg/kg/day (max dose 400 mg) twice daily for five days (l). Patients were monitored for QT interval prolongation. No special treatments (Lopinavir-ritonavir, immunoglobulin, interferon) were administered.

Discussion

Turkish Republic Ministry of Health provided a standardized approach all over the country by establishing a Scientific Committee within the GDPH [10]. First versions of "COVID-19 Risk Assessment", "COVID-19 Guideline" and "Case Report Form" were published on January 2020, on the website of the Ministry of Health and constantly revised as new information accumulates [10, 18].

Based on unpublished COVID-19 Surveillance data from Turkish Republic Ministry of Health, pediatric cases had a contact history by 48.7%. Most of the children were male, 53%, with a mean age of 8 years (1 day–17 years) and the 13.6% of cases were <1 year [7]. Only 0.8% of pediatric cases had severe disease. Pediatric ICU hospitalization rate was 4.27% and 80% of admissions were under one year of age.[7] A pediatric referral and tertiary care hospital in Izmir, Turkey had 55 confirmed COVID-19 pediatric cases as of May 12 [19]. Clinical and laboratory data of these children were not available. In this study, we analyzed also symptoms, CXR results and treatment regimens other than demographics in detail.

In a systematic review of 2914 pediatric patients with COVID-19, data from China, United States, Iran, and Spain were analyzed [14]. Mean percentage of males was 56% (range= 33 to 100) [14, 15, 17]. The age range was 1 day to 17 years with a composite mean age of 7.9 years, median age was 11 [8, 14]. Percentage of laboratory-confirmed pediatric cases was 11.2% (41/365) and 12.3% (171/1391) from Madrid and Wuhan, respectively [16, 20]. In present study, test positivity was higher, 18.6% (27/145), in Turkey we ordered PCR tests according to the COVID-19 guideline.[10,18] For a child to get a test done, epidemiological properties and symptoms were evaluated, some criterias were applied such as either he should be symptomatic with fever, tachypnea or cough; 2 or more members of the same household diagnosed with COVID-19; infants of COVID-19 mothers under 9-months old [18].

Lu *et al*. [16] reported that 90.1% of pediatric cases were within family clusters. A cohort of 36 children reported that 89% of transmissions were by close contact with family members [21]. In present study, 96.3% of children had parents/relatives with confirmed COVID-19 living at the same house. Household transmission seems to be more likely than community transmission for pediatric patients since education had been suspended at schools and there was a restriction in the form of a curfew to those who are under the age of 20 during this period [10].

Pediatric patients were asymptomatic with an average of 14.9% [14]. The most common presenting signs and symptoms were cough (48.1%, range=11.1-100), fever (46.8%, range=26.8-100), upper respiratory symptoms as sore throat or pharyngitis, rhinorrhea, sneezing, nasal congestion (42.3%, range=6.5-46.2), fatigue or myalgia (30.6%, range=2.5-22.7). Other symptoms included headaches (24.3%, range=8.3-27.8), shortness of breath, respiratory distress, or tachypnea (15.7%, range=0-50), diarrhea (10.1%, range=0-22.2), vomiting/nausea (7.8%, range=0-10.7), abdominal pain (6%, range=3-8) [8, 14, 17, 20, 22]. Pediatric anosmia or dysgeusia was not reported in any of these studies [4, 8, 14, 17, 20, 22, 23]. In this study, there were children presenting with dizziness and ageusia, two symptoms were rarely reported in pediatric population.

Parri *et al*. [4] reported 130 confirmed children from 28 centers in Italy, 75.4% were asymptomatic or had mild disease. Presence of COVID-19 positive relatives was 51.5% [4]. Fever was the most common symptom, 51.5%. Comorbidities was present in 21% (range= 8.7 to 50), asthma, immunosupression, and cardiovascular disease were the most common diseases [8, 14, 15, 20, 22]. Italian data revealed 26.2% comorbidities mostly consisting of chronic diseases of respiratory, cardiac or neuromuscular systems [4]. The Chinese CDC data from January 16 to February 8, 2020, included 728 laboratory confirmed pediatric cases [24]. Regarding the severity of confirmed cases, 12.9% and 43.1% of cases were diagnosed as asymptomatic and mild disease, respectively.[24] Based on clinical severity, most of the children in present study were diagnosed as acute URTI (59.2%).

The laboratory findings of children were hard to interpret because the reference values lack consistency. Increases in AST > 50 U/L and ALT > 45 U/L were reported in 11/60, 18.3% and 8/68, 11.8%, respectively [4]. Data from China revealed increase in ALT >40 U/L in pediatric population [14, 16, 23]. with a percentage of 25% [23]; lymphopenia 31% [21]; leucopenia 19%.[21] A low WBC of $<5.5\times10^9$/L was present with an average of 31.5% [14, 17]. Lymphopenia (lymphocyte count of$<1.2\times10^9$/L) was present in 20 out of 220 patients with a mean percentage of 9.1%.[14-17] Leucopenia and lymphopenia were detected in 36.8% and 15.7% of Italian cases, respectively [4]. Lymphocyte counts were normal in 70% and elevated in 10% of cases while lymphopenia was reported in 4 of 20 (20%) cases [23]. Hematological abnormalities were also common in this cohort in accordance with the literature.

Abnormal CXR findings were reported in 57.1% of children [14, 15]. Pneumonia or bronchiolitis were given as final clinical diagnosis with an avarege of 53.8%, ranging from 12.9% to 68.0% [14, 16, 20, 22]. Hospitalization rates of pediatric cases were between 19.7% to 60.1%.[8,20] Of the studies with age specific hospitalization data available, 27.0% of patients were children<1 years old (ranging from 0% to 40.1%) [8, 14, 17]. Pediatric ICU admission rate was 6.8% and 2.1% of

hospitalized children needed intubation [5, 8, 14, 17, 20, 22]. Twenty in-hospital children had an average stay of 12.9 days (8-20 days) [23]. All of the children presented with subpleural lesions on CT [23].

CDC reported three pediatric deaths, but no details were given [8]. The mortality rate of children who were hospitalized with COVID-19 was 0.0018% [14]. Lu *et al*. [16] reported three out of 171 children needed intensive care support and mechanical ventilation, all with serious coexisting conditions [16]. Mortality was reported, as of March 8, in a 10-month-old child with intussusception and multiorgan failure [16]. Eghbali *et al*. [15] reported an 11 years old boy with underlying aplastic anemia who died due to respiratory failure. According to COVID-19 Situation Report, Turkey, 10 pediatric deaths; 5 boys and 5 girls under 15 years of age have been confirmed by June 28 [11].

BCG vaccination is routine in our country and applied to all children at the end of 2nd months of age. A study about BCG vaccination policies from BCG World atlas and the correlation of COVID-19 cases reported that countries with long-standing BCG vaccination were less severely affected and also in BCG-vaccinated European countries the mean of deaths per population ratio is found to be lower than BCG-non-vaccinated countries [25, 26].

There are no controlled clinical trials and no high quality evidence for the use of any drug in treatment of pediatric COVID-19. Antibiotics (azithromycin), hydroxychloroquine, antivirals (lopinavir-ritonavir, oseltamivir), immunoglobulin, interferon, systemic corticosteroid treatments were reported in pediatric patients [2, 14, 15, 17, 22]. None of the studies showed efficacy of one treatment regimen over the others. Influenza test was not available in our institution so patients were treated with oseltamivir at the beginning of pandemic. Treatment regimens were tailored according to Pediatric COVID guideline [18] but since there was no standart suggestion for pediatric care, we may have over-treated patients especially with high rate of antibiotic usage.

This study adds clinical data for pediatric COVID-19 from the epicenter of pandemic in 216 Turkey, Istanbul, discussing symptomatology and radiological findings. This study has some limitations as we did not have data about coinfections with other pathogens such as Influenza and did not include consecutive SARS-CoV-2 test results and also lenght of days from exposure to onset of symptoms. Also we do not have CT in our institution, CXR may not exclude pulmonary lesions in every case, even though the child is asymptomatic. Children may not meet all the criteria required in the suspected case definition, tests could be false negative at an early stage so many children may be underdiagnosed during the study period. This data do not represent the whole pediatric population.

In conclusion, most pediatric COVID-19 cases appear to have a milder clinical course and have better outcomes. Special care may be needed for younger children and children with comorbidities. Effective usage of personal protective equipment may not be possible in pediatric patients. Milder disease or asymptomatic nature of the infection in children necessitates extensive testing and isolation of children for infection control.

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