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COVID-19 disease in children presenting to the pediatric emergency department: A multicenter study with 8886 cases from Turkey

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ABSTRACT

Background: The aim was to evaluate the epidemiological, clinical, laboratory, and radiologic data of children with SARS-CoV-2 positivity by polymerase chain reaction (PCR) together with treatment strategies and clinical outcomes and to evaluate cases of multisystem inflammatory syndrome in children (MIS-C) in this population.
Methods: This was a multicenter retrospective observational cohort study performed in the pediatric emergency departments of 19 tertiary hospitals. From March 11, 2020, to May 31, 2021, children who were diagnosed with

Abbreviations: COVID-19, Coronavirus disease 2019; WHO, World Health Organization; MIS-C, Multisystem inflammatory syndrome in children; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; PCR, Polymerase chain reaction; CRP, C-reactive protein; BNP, Brain natriuretic peptide; IL-6, Interleukin-6; CT, Computed tomography; EF, Ejection fraction; SD, Standard deviation; IQR, Interquartile ranges; RSV, Respiratory syncytial virus; PICU, Pediatric intensive care unit; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; LDH, Lactate dehydrogenase; PT, Prothrombin time; INR, International normalized ratio.

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confirmed nasopharyngeal/tracheal specimen SARS-CoV-2 PCR positivity or positivity for serum-specific antibodies against SARS-CoV-2 were included. Demographics, presence of chronic illness, symptoms, history of contact with SARS-CoV-2 PCR-positive individuals, laboratory and radiologic investigations, clinical severity, hospital admissions, and prognosis were recorded.

Results: A total of 8886 cases were included. While 8799 (99.0%) cases resulted in a diagnosis of SARS-CoV-2 with PCR positivity, 87 (1.0%) patients were diagnosed with MIS-C. Among SARS-CoV-2 PCR-positive patients, 51.0% were male and 8.5% had chronic illnesses. The median age was 11.6 years (IQR: 5.0–15.4) and 737 (8.4%) patients were aged <1 year. Of the patients, 15.5% were asymptomatic. The most common symptoms were fever (48.5%) and cough (30.7%) for all age groups. There was a decrease in the rate of fever as age increased ($p < 0.001$); the most common age group for this symptom was <1 year with the rate of 69.6%. There was known contact with a SARS-CoV-2 PCR-positive individual in 67.3% of the cases, with household contacts in 71.3% of those cases. In terms of clinical severity, 83 (0.9%) patients were in the severe-critical group. There was hospital admission in 1269 (14.4%) cases, with 106 (1.2%) of those patients being admitted to the pediatric intensive care unit (PICU). Among patients with MIS-C, 60.9% were male and the median age was 6.4 years (IQR: 3.9–10.4). Twelve (13.7%) patients presented with shock. There was hospital admission in 89.7% of these cases, with 29.9% of the patients with MIS-C being admitted to the PICU.

Conclusion: Most SARS-CoV-2 PCR-positive patients presented with a mild clinical course. Although rare, MIS-C emerges as a serious consequence with frequent PICU admission. Further understanding of the characteristics of COVID-19 disease could provide insights and guide the development of therapeutic strategies for target groups.

1. Introduction

Coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, has been the first pandemic of the 21st century [1,2]. Exerting unprecedented pressure on the health facilities of all affected countries in addition to posing a threat to the patient's life, the COVID-19 pandemic has become both a logistic challenge and a medical issue [3].

Pediatric patients were reported to represent 3.7% of all known COVID-19 cases [4]. Although COVID-19 occurs in all age groups, it has been consistently shown that pediatric cases typically have less severe symptoms than adult cases [5-7]. However, with the progression of the pandemic worldwide, severe and life-threatening manifestations of the disease have emerged in pediatric cases, including multisystem inflammatory syndrome in children (MIS-C) [8,9]. It also remains to be fully understood whether children show different clinical presentations [4]. Despite the worldwide spread, the epidemiological and clinical patterns of pediatric COVID-19 still particularly remain unclear. The unique clinical features, complications, and outcomes of COVID-19 disease among pediatric cases warrant special consideration in epidemiologic, management, and prevention studies [5].

In the present study, it was aimed to evaluate the epidemiological, clinical, laboratory, and radiologic data of children found positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by polymerase chain reaction (PCR) and/or serum-specific antibodies against SARS-CoV-2 as well as treatment strategies and clinical outcomes and to evaluate patients diagnosed with MIS-C.

2. Materials and methods

2.1. Study design

This was a multicenter retrospective observational cohort study performed in the pediatric emergency departments of 19 tertiary hospitals in Turkey. The study protocol was approved by the Institutional Review Board of the Dokuz Eylul University Faculty of Medicine (approval number: 2020/12–19).

From March 11, 2020, the time when the first COVID-19 PCR-positive case was announced in Turkey, to May 31, 2021, in light of the guidelines published by the Turkish Ministry of Health's Scientific Committee on COVID-19 [10] and the criteria for MIS-C of the US Centers for Disease Control and Prevention [11], children aged 0 to 18 years who were diagnosed with confirmed PCR positivity of nasopharyngeal/tracheal specimens for SARS-CoV-2 and/or serum-specific antibodies against SARS-CoV-2 were included. The International Classification of Diseases codes for COVID-19 and MIS-C were used to identify patients. Data were obtained from computer databases, electronic medical records, and medical charts and were recorded on case forms sent to each participating center. Cases with insufficient data were excluded from the study.

Demographics, presence of chronic illness (chronic health conditions, both chronic illnesses and chronic physical disabilities were defined as those conditions that last >12 months and are severe enough to create some limitations in usual activity), symptoms, history of contact with other SARS-CoV-2 PCR-positive patients, time from contact to onset of symptoms, presence of any complaints among the contacted people, and the presence of any individual in quarantine, hospitalized in a ward/intensive care unit, or having died among the individuals living with the patients were recorded. Because symptoms of sore throat or loss of smell and taste cannot be described in infancy and preschool age, sore throat was recorded for those who were older than 3 years of age and loss of smell and taste for those older than 5 years. Cases were divided into four age groups as ≤1 year, 1–6 years, 6–10 years, and > 10 years. Clinical features, laboratory data, and results of radiologic investigations were recorded. Levels of C-reactive protein (CRP), procalcitonin, D-dimer, troponin, brain natriuretic peptide (BNP), and interleukin-6 (IL-6) were divided into two groups according to laboratory cut-off values as being equal to/lower than the cut-off value or higher for each hospital. Lymphopenia was reported in the event of a lymphocyte count of $<1500/mm^3$. If applicable, fever was recorded and cases of fever were divided into four groups as follows: <37.6 °C, 37.6–38.0 °C, 38.1–39.0 °C, and > 39.0 °C.

The testing of nasopharyngeal/tracheal swabs for other common human respiratory tract viruses and, if so, presence and type of co-infection were recorded. Chest X-ray findings were grouped as normal, bronchovascular changes, hyperinflation, consolidation, diffuse patchy involvement, and other findings. Thorax computed tomography (CT) findings were grouped as normal, ground-glass opacities, lobar consolidation, subpleural consolidation, and other findings. When echocardiograms were available, the presence of coronary abnormality or left ventricle dysfunction was recorded and cases were divided into three groups according to ejection fraction (EF) values of >55%, 31%–55%, and < 31%.

In terms of clinical severity, SARS-CoV-2 PCR-positive cases were classified into five groups as asymptomatic, mild, moderate, severe, or critical as previously described [5]. Asymptomatic, mild, and moderate cases were defined as Group 1 and severe and critical cases as Group 2. Requirements for respiratory support, treatment strategies, admission to the ward or pediatric intensive care unit (PICU), length of hospital stay, and prognosis were recorded.

2.2. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 22.0 for Windows (IBM Corp., Armonk, NY, USA). Categorical variables were reported as frequencies and percentiles and continuous variables as means with standard deviations (SDs) or medians with interquartile ranges (IQRs). To compare nonparametric data, the Mann-Whitney *U* test was used, while for parametric data, Student's *t*-test and one-way analysis of variance (ANOVA) were used. Chi-square tests were used to evaluate differences of categorical variables. Values of $p < 0.05$ were considered statistically significant.

3. Results

During this research period, 8886 cases were included in the study. Of them, 8799 (99.0%) resulted in a confirmation of SARS-CoV-2 PCR positivity and 87 (1.0%) resulted in a diagnosis of MIS-C. Among the 87 cases of MIS-C, 65 (64.4%) were negative by SARS-CoV-2 PCR but positive for serum-specific antibodies against SARS-CoV-2, 9 (8.9%) were positive by both SARS-CoV-2 PCR and testing for serum-specific antibodies against SARS-CoV-2, and 13 (12.9%) were positive by SARS-CoV-2 PCR but negative for serum-specific antibodies against SARS-CoV-2.

Among those with confirmed SARS-CoV-2 PCR positivity, 4490 (51.0%) patients were male. The median age was 11.6 years (IQR: 5.0–15.4). The most common age group was >10 years with 5014 (57.0%) patients while there were 737 (8.4%) patients aged <1 year (Table 1). There was male predominance among patients aged ≤10 years, but among those aged >10 years, we found a female predominance ($p < 0.05$).

A total of 719 (8.5%) patients had chronic illnesses; the most common was asthma at a rate of 20.4%, followed by hematologic-oncologic diseases at a rate of 19.6%. There was a statistically significant difference between age groups in terms of chronic diseases, the most commonly affected group being those aged 6–10 years at a rate of 10.5% (p: 0.001).

Among the patients, 1360 (15.5%) were asymptomatic. Comparing the age groups, the rate of asymptomatic cases differed ($p < 0.001$); the most commonly asymptomatic age group was 1–6 years at a rate of 18.4%, followed by 6–10 years at a rate of 17.7%. Among symptomatic cases, the most common symptoms were fever (48.5%) and cough (30.7%) for all age groups, followed by fatigue (23.8%) and sore throat (20.3%) among those aged >10 years and followed by runny nose (16.3%) and diarrhea (11.8%) among those aged ≤10 years. There was a decrease in the rate of fever as age increased ($p < 0.001$); the most common age group for fever was <1 year at a rate of 69.6%. There was also a difference in terms of sex; fever was more common among males (51.2%) than females (45.7%) ($p < 0.001$). The degree of fever was available for 7629 cases as presented in Table 1. The rate and degree of fever were both higher among patients aged <1 year and lower among those aged >10 years ($p < 0.001$).

There was a contact with a SARS-CoV-2 PCR-positive individual in 5926 (67.3%) of the cases, being household contact in 71.3% of them. The presence of a contact was more common among patients aged 1–6 years (74.7%), while those aged >10 years had the lowest rate of such contact among all age groups at 64.3% ($p < 0.001$). As age increased, there was a decrease in the rate of contact with a SARS-CoV-2 PCR-positive individual. The median time to onset of symptoms after contact was 4.0 (IQR: 2.0–5.0) days. There were symptoms in 80.1% of the cases involving contact. The rate of hospital admission was higher among those who had contact with a symptomatic individual compared

Table 1
Demographics, clinical features, laboratory results, and treatment strategies of cases of SARS-CoV-2 PCR positivity.

Variable	n: 8799
Age group, n (%)	
0–1 year	737 (8.4)
1–6 year	1822 (20.7)
6–10 year	1226 (13.9)
>10 year	5014 (57.0)
Body temperature of children (°C), n (%)	
<37.6	4495 (58.9)
37.6–38.0	1652 (21.7)
38.1–39.0	1342 (12.6)
>39.0	140 (1.8)
Laboratory results	
White blood cell count/mm^3, median (IQR)	6480.0 (5030.0–8677.0)
Lymphocyte count/mm^3, median (IQR)	2030.0 (1300.0–3150.0)
Neutrophil count/mm^3, median (IQR)	3140.0 (2060.0–4730.0)
Hemoglobin (g/dL), mean ± SD (min-max)	12.8 ± 1.6 (11.9–13.9)
Platelet count/mm^3, median (IQR)	255,000.0 (209,000.0–311,000.0)
Prothrombin time (s), median (IQR)	12.4 (11.7–13.4)
Activated partial thromboplastin time (s), median (IQR)	27.8 (25.0–31.0)
International normalized ratio, median (IQR)	1.0 (1.0–1.1)
Fibrinogen (mg/dL), median (IQR)	2.8 (2.4–3.5)
BNP (pg/mL), median (IQR)	52.0 (27.5–183.5)
Ferritin (ng/mL), median (IQR)	
Alanine aminotransferase (U/L), median (IQR)	28.0 (21.0–39.0)
Aspartate aminotransferase (U/L), median (IQR)	17.0 (12.0–25.0)
Albumin (g/dL), mean ± SD (min-max)	4.4 ± 0.5 (1.3–6.6)
Total protein (g/dL), mean ± SD (min-max)	6.9 ± 0.7 (3.3–9.1)
Creatine kinase (U/L), median (IQR)	90.0 (64.0–128.0)
Lactate dehydrogenase (U/L), median (IQR)	251.0 (204.0–312.0)
Lymphopenia, n (%)	1232 (30.6)
C-reactive protein higher than the reference, n (%)	1137 (29.5)
Procalcitonin higher than the reference, n (%)	384 (16.0)
D-dimer higher than the reference, n (%)	613 (32.3)
Troponin higher than the reference, n (%)	79 (3.8)
Respiratory swabs for other infections, n (%)	980 (11.1)
Co-infection, n (%)	67 (6.8)
Rhinovirus	16 (23.9)
RSV	5 (7.5)
Coronavirus	1 (1.5)
Metapneumovirus	1 (1.5)
Influenza virus	1 (1.5)
Mycoplasma	1 (1.5)
Not defined	41 (61.2)
Diagnosis, n (%)	
Upper respiratory tract infection	6173 (70.1)
Lower respiratory tract infection	616 (7.0)
Acute gastroenteritis	450 (5.1)
Acute abdomen	27 (0.3)
Neurologic disease	23 (0.3)
Sepsis	15 (0.2)
Shock	2 (0.0)
Cardiopulmonary arrest	1 (0.0)
Other	132 (1.5)
Treatment strategies, n (%)	
Antibiotics	1618 (18.4)
Oseltamivir	73 (0.8)
Hydroxychloroquine	112 (1.3)
Favipiravir	201 (2.3)
Steroid	67 (0.8)
IVIG	22 (0.3)
LMWH	101 (1.1)
Vasopressors	14 (0.2)
Immunomodulatory therapy	9 (0.1)
Plasmapheresis	4 (0.0)
ECMO	90 (1.0)

SD: Standard deviation, IQR: interquartile range, PCR: polymerase chain reaction, MIS-C: multisystem inflammatory syndrome in children, RSV: respiratory syncytial virus, IVIG: intravenous immunoglobulin, LMWH: low-molecular-weight heparin, ECMO: extracorporeal membrane oxygenation.

to those having contact with an asymptomatic individual (13.5% versus 7.5%, p: 0.001). In terms of PICU admissions, however, there was no difference regarding the symptoms of the contacted person. The households of 89.6% of the children were in quarantine, with 5.1% having a household member admitted to the intensive care unit, 4.8% having a household member admitted to the ward, and 0.5% having a household member who died.

Laboratory tests were obtained for 4075 (46.3%) cases, being the most common in the age group of <1 year (72.0%) (Table 1). There was a reduction in obtained laboratory tests as age increased ($p < 0.001$). Among the cases for which data were available, 29.5% had CRP, 16.0% had procalcitonin, 32.3% had D-dimer, 3.8% had troponin, and 22.0% had ferritin levels higher than the reference values. Lymphopenia was detected in 30.6% of the cases. For 81 patients, the IL-6 level was obtained, and for 88.9% of them, that value was higher than the reference value. For 980 (11.1%) of the cases, test results of nasopharyngeal/tracheal swabs for other common human respiratory tract viruses were available and the age group that most commonly received such testing was <1 year (14.0%); there was a decrease in tests obtained as age increased ($p < 0.001$). Co-infections were detected in 67 (6.8%) patients but there was no difference in terms of co-infection rates among the age groups. The most commonly detected co-infecting virus was rhinovirus with 16 (23.9%) cases, followed by respiratory syncytial virus (RSV) in 5 (7.5%) cases. Influenza virus was co-detected in only one (1.5%) case (Table 1).

For 4698 (53.4%) patients, radiologic investigations were conducted, being chest radiography in 4629 (52.6%) and chest CT in 478 (5.4%) cases. Among the obtained chest radiographs, 86.0% were normal; consolidation was reported for 6.9% of the patients, bronchovascular changes for 5.8% of patients, diffuse patch involvement for 0.7% of patients, and hyperinflation for 0.3% of patients. Among the performed chest CTs, 61.9% had normal findings, 27.2% had peripheral ground-glass appearance, and 7.4% had consolidation. Pleural effusion was detected in 0.3% of these patients.

Among these cases, the most common diagnosis was upper respiratory system infection (70.1%), followed by lower respiratory tract infection (7.0%) and acute gastroenteritis (5.1%). The most common treatment regimen was antibiotics, which were started for 18.4% of the patients, followed by favipiravir (2.3%). Detailed information about treatment strategies is shown in Table 1. There were 236 (2.7%) patients who needed respiratory support; among them, 78.4% received oxygen by a simple face mask, 9.5% underwent high-flow nasal cannula oxygen therapy, 4.2% underwent noninvasive ventilation, and 5.0% underwent intubation. There was a statistically significant difference among the age groups in terms of the rate of respiratory support; the group most commonly receiving respiratory support was the group of <1 year at a rate of 4.5%. Echocardiograms were obtained for 93 (1.1%) patients; EF was <55% in 7 (7.6%) cases and left ventricle dysfunction was found in 3 (3.3%) cases.

In terms of clinical severity, 83 (0.9%) patients were in Group 2, the severe-critical group. There was no difference for gender or age between Groups 1 and 2 and no difference in terms of the rate of cases in Group 2 among the age groups (Table 2). Cases in Group 2 had a higher rate of underlying diseases ($p < 0.001$). Rates of fever, cough, respiratory distress, and chest pain were higher while rates of headache, sore throat, and runny nose were lower in Group 2 than Group 1 ($p < 0.05$). Comparing the degree of fever, 19.2% of patients in Group 1 had fevers of >38.0 °C while this rate was 47.4% for Group 2 ($p < 0.001$). There was no difference in rates of co-infection with another respiratory virus between these two groups. Patients in Group 2 had higher rates of elevated CRP, procalcitonin, D-dimer, and troponin levels and higher rates of lymphopenia according to the cut-off values for each center ($p < 0.05$) (Table 3). Patients in Group 2 also had lower platelet count, hemoglobin, albumin, and total protein levels and higher white blood cell, neutrophil, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, lactate dehydrogenase (LDH), prothrombin time (PT), fibrinogen, ferritin, and BNP levels than patients in Group 1 ($p < 0.05$). When we evaluated cases according to age groups, among the considered laboratory parameters, only albumin and ferritin levels differed between Groups 1 and 2 ($p < 0.05$). To prevent effects of underlying conditions, we also divided each age group into two subgroups in terms of the presence of any chronic disease. Among those without any chronic disease, in the age group of 1–6 years, albumin was still lower for patients in Group 2 than in Group 1 (p: 0.010). For those aged <1 year and > 10 years, patients in Group 2 still had lower albumin and higher ferritin levels ($p < 0.05$).

Hospital admission was necessary for 1269 (14.4%) patients, with 106 (1.2%) of them admitted to the PICU. The median length of stay in the PICU was 4.0 days (IQR: 2.0–8.0) while median length of stay in the hospital was 5.0 days (IQR: 4.0–8.0). In terms of hospital admissions, there was a statistically significant difference among the age groups ($p < 0.001$). The age group most commonly admitted to the hospital and PICU were patients aged <1 year (hospital admissions: 27.0%, PICU admissions: 2.6%). There was no difference in gender for children admitted or not admitted to the PICU, but those who were admitted to the PICU were younger in age (p: 0.048). Patients who were admitted to the PICU had more chronic diseases than those without PICU admission ($p < 0.05$) but there was no difference in terms of the presence of asthma between these groups. Patients admitted to the PICU also had higher rates of elevated CRP, procalcitonin, D-dimer, and troponin levels according to the cut-off values for each center ($p < 0.05$), although there was no difference in terms of the presence of lymphopenia. Patients with PICU admission had higher white blood cell, neutrophil, AST, ALT, LDH, PT, fibrinogen, ferritin, and BNP levels and lower hemoglobin, albumin, and total protein levels than those who were not admitted ($p < 0.05$). During the study period, a total of 8 (0.1%) patients died, all but one of whom were male and had chronic diseases; 3 of them had hematologic diseases, 2 of them had genetic disorders, one of them had endocrinologic disease and for one patient, there was no information about the type of chronic disease.

Evaluating the 87 patients diagnosed with MIS-C, there was a male predominance with 53 (60.9%) male patients and the median age was 6.4 years (IQR: 3.9–10.4) with the most common age group being 1–6 years with 32 (46.0%) cases. Nine (10.3%) patients had chronic diseases. In terms of body temperature, the most common finding was a fever of 38.1–39 °C, seen in 54 (73.0%) cases. Thirty-seven (42.5%) patients presented with fatigue, 35 (40.2%) with rash, 29 (33.3%) with nausea/vomiting, and 27 (31.0%) with diarrhea as the most common symptoms.

Among the patients, 12 (13.7%) presented with shock. There was no difference for gender or age between those who presented with or without shock, but patients with shock had lower rates of rash and diarrhea, higher rates of elevated troponin levels, and higher PT, international normalized ratio (INR), and ferritin levels ($p < 0.05$). Echocardiograms were obtained in 57 cases and 3 (5.3%) of them revealed an EF <55%. Coronary abnormality was found in one (2.3%) case and left ventricle dysfunction in 6 (14.0%) cases. Hospital admission was necessary in 78 (89.7%) cases, with 26 (29.9%) being admitted to the PICU. Antibiotics were started in 67 (89.3%) of these cases, intravenous immunoglobulin in 53 (70.7%), steroids in 49 (65.3%), and low-molecular-weight heparin in 33 (44.0%) as the most common treatment strategies. Finally, 2 (2.3%) cases, those of a 6.5-year-old girl with hematologic disease and a previously healthy 15-year-old boy, ended in death.

4. Discussion

To the best of our knowledge, this is the largest pediatric study of cases of COVID-19 from Turkey to date and one of the largest such studies globally.

Evaluating SARS-CoV-2 PCR-positive cases, our data revealed a slight male predominance, supporting the current literature [5,12-15]. We found that the most common age group was that of >10 years

Table 2
Demographics, clinical features, and management of SARS-CoV-2 PCR-positive patients according to age groups.

Variable, n (%)	0–1 year (n: 737)	1–6 years (n: 1822)	6–10 years (n: 1226)	>10 years (n: 5014)	p*	All cases (n: 8799)
Male gender	398 (54.0)	963 (52.9)	650 (53.0)	2479 (49.4)	0.007	4490 (51.0)
Chronic diseases	49 (6.6)	180 (9.9)	124 (10.1)	366 (7.3)	0.001	719 (8.5)
Contact with a SARS-CoV-2-positive individual	528 (71.6)	1350 (74.1)	869 (70.9)	3179 (63.4)	<0.001	5926 (67.3)
Household contact	444 (60.2)	1079 (59.2)	637 (52.0)	2063 (41.1)	<0.001	4223 (71.3)
Symptoms						
Fever	511 (69.6)	1097 (60.5)	644 (52.8)	2000 (40.0)	<0.001	4252 (48.5)
Cough	260 (35.6)	520 (28.9)	306 (25.3)	1619 (32.3)	<0.001	2705 (30.7)
Fatigue	62 (8.5)	194 (10.8)	196 (16.2)	1191 (24.0)	<0.001	1643 (18.9)
Sore throat	–	102 (11.4)	173 (15.2)	945 (20.2)	<0.001	1220 (18.2)
Headache	–	54 (3.2)	132 (11.6)	774 (16.6)	<0.001	968 (11.8)
Runny nose	120 (16.4)	213 (11.9)	85 (7.0)	367 (7.4)	<0.001	785 (9.0)
Loss of taste/smell	–	3 (0.8)	27 (2.3)	492 (10.0)	<0.001	522 (8.0)
Myalgia	–	81 (4.5)	105 (8.7)	828 (16.7)	<0.001	1029 (11.8)
Diarrhea	86 (11.8)	160 (8.9)	63 (5.2)	259 (5.2)	<0.001	568 (6.5)
Nausea/vomiting	59 (8.1)	157 (8.7)	117 (9.7)	417 (8.4)	>0.05	750 (8.6)
Abdominal pain	10 (1.5)	103 (6.1)	113 (9.9)	254 (5.4)	<0.001	480 (5.9)
Respiratory distress	39 (5.3)	68 (3.8)	63 (5.2)	579 (11.7)	<0.001	749 (8.6)
Chest pain	–	37 (2.1)	33 (2.7)	189 (3.8)	0.001	273 (3.1)
Arthralgia	–	9 (0.5)	10 (0.8)	69 (1.4)	>0.05	90 (1.0)
Rash	10 (1.4)	28 (1.6)	19 (1.6)	163 (3.3)	<0.001	220 (2.5)
Conjunctivitis	11 (1.5)	25 (1.4)	13 (1.1)	52 (1.0)	>0.05	101 (1.1)
Nasal congestion	7 (0.6)	5 (0.3)	7 (0.6)	20 (0.4)	>0.05	39 (0.4)
Seizure	8 (1.1)	14 (0.8)	3 (0.2)	8 (0.2)	>0.05	33 (0.3)
Anorexia	16 (2.2)	16 (0.9)	3 (3.2)	10 (10.2)	>0.05	45 (0.5)
Dizziness	–	1 (0.1)	–	16 (0.3)	>0.05	17 (0.1)
Pain in the back/waist	–	–	2 (0.2)	12 (0.2)	>0.05	14 (0.1)
Restlessness	19 (2.6)	6 (0.3)	1 (0.1)	4 (0.1)	>0.05	30 (0.3)
Laboratory tests obtained	531 (72.0)	1016 (55.8)	555 (45.3)	1973 (39.3)	<0.001	4075 (46.3)
Radiologic investigations						
Chest X-ray	507 (68.8)	999 (54.9)	614 (50.1)	2510 (50.4)	<0.001	4629 (52.6)
Chest CT	23 (3.1)	65 (3.6)	46 (3.8)	344 (6.9)	<0.001	478 (5.4)
Clinical severity						
Asymptomatic/mild/moderate	724 (98.2)	1805 (99.1)	1216 (99.2)	4971 (99.1)		1362 (15.5)
Severe/critical	13 (1.8)	17 (0.9)	10 (0.8)	43 (0.9)	0.116	6691 (76.0)
Hospital admission	199 (27.0)	358 (19.6)	163 (13.3)	549 (10.9)	<0.001	1259 (14.4)
PICU admission	19 (2.6)	24 (1.3)	11 (0.9)	52 (1.0)	0.003	106 (1.2)

* Compared between age groups. CT: Computed tomography, PICU: pediatric intensive care unit.

(57.0%), followed by 1–6 years (20.7%). In a study evaluating 1156 cases from Turkey, the majority of the patients were reported to be 6–12 years of age [16]. In a meta-analysis by Ding et al., the majority of patients were aged >5 years [14].

We found a history of contact with a SARS-CoV-2 PCR-positive individual in 67.3% of these cases, being household contact in 71.3%. This percentage is slightly lower than the rates previously reported in the literature. Hoang et al. (15) reported 75.6% and Ding et al. [14] reported

Table 3
Demographics, clinical findings, and laboratory results of SARS-CoV-2 PCR-positive patients according to clinical severity groups.

Variable	Asymptomatic/mild/moderate (n: 8716)	Severe/critical (n: 83)	p
Male gender, n (%)	4444 (51.0)	46 (55.4)	0.717
Age in years, median (IQR)	12.0 (4.9–16.0)	11.1 (3.8–15.0)	0.265
Underlying disease, n (%)	672 (8.0)	47 (58.0)	<0.001
Asthma, n (%)	145 (1.7)	1 (1.4)	0.670
History of fever, n (%)	4193 (48.3)	59 (71.1)	<0.001
Fever of >38 °C, n (%)	1446 (19.2)	35 (47.4)	<0.001
Cough, n (%)	2664 (30.9)	41 (49.4)	<0.001
Fatigue, n (%)	1607 (18.7)	18 (26.1)	0.164
Nausea/vomiting, n (%)	733 (8.6)	11 (15.9)	0.049
Diarrhea, n (%)	558 (6.5)	3 (4.3)	0.627
Respiratory distress, n (%)	707 (8.2)	42 (50.6)	<0.001
Chest pain, n (%)	266 (3.1)	7 (8.4)	0.006
Headache, n (%)	965 (11.9)	3 (3.6)	0.008
Sore throat, n (%)	1214 (18.3)	6 (9.5)	0.044
Runny nose, n (%)	783 (9.1)	2 (2.4)	0.016
Ferritin (ng/mL), median (IQR)	44.3 (26.4–82.0)	276.0 (105.0–761.0)	<0.001
Albumin (g/dL), mean ± SD (min-max)	4.4 ± 0.4 (1.3–9.6)	3.8 ± 0.8 (2.0–8.8)	<0.001
Lymphopenia, n (%)	1199 (30.4)	33 (40.7)	0.033
C-reactive protein higher than the reference, n (%)	1074 (28.5)	63 (77.8)	<0.001
Procalcitonin higher than the reference, n (%)	353 (15.1)	31 (44.3)	<0.001
D-dimer higher than the reference, n (%)	557 (30.5)	56 (78.9)	<0.001
Troponin higher than the reference, n (%)	66 (3.3)	13 (25.5)	<0.001
Abnormal chest X-ray, n (%)	591 (13.0)	57 (75.0)	<0.001
Abnormal chest CT, n (%)	147 (33.6)	35 (85.4)	<0.001

SD: Standard deviation, IQR: interquartile range, PCR: polymerase chain reaction.

86.4% of children being exposed to a SARS-CoV-2 PCR-positive household member. This difference could be related to the increased number of adolescents in our study, which was the most common age group. However, household contact and exposure still remain important issues for the spread of COVID-19 in the pediatric population [5,13]. In South Korea, it was reported that 11.8% of household contacts developed COVID-19 compared to 1.9% of non-household contacts, which underlies the transmission dynamics of SARS-CoV-2 within households. [17]. In addition, age may be an important factor in the dynamics of interactions among children, but adequate data for risk stratification by age are still lacking [18].

Of our patients, 8.5% of had chronic diseases, with the majority being asthma, followed by hematologic-oncologic diseases; the rate of underlying conditions was higher among severe/critical cases. Karbuz et al. [16] found 12.9% of their patients to have underlying conditions and the most common was again asthma. In another analysis, asthma was reported as the most commonly diagnosed underlying condition, supporting our data [19]. Kompaniyets et al. [19] showed a higher risk for severe disease among children with underlying conditions. The highest risk for severe disease was reported for those with type 1 diabetes, followed by cardiac and circulatory congenital anomalies and epilepsy and/or convulsions. They also reported that type 1 diabetes being a risk factor for severe disease could be partially explained by complications of type 1 diabetes in the setting of COVID-19 disease or indirect pandemic-related effects such as delays in diagnosis or seeking care [19]. A previous study of 454 patients aged <21 years found asthma to be a risk factor for hospitalization and respiratory support but not critical care [20]. However, the role of asthma in disease severity for both children and adults remain unclear [19]. Physicians should consider the potential need for close observation and cautious clinical management of those with underlying conditions and COVID-19.

Asymptomatic cases were seen among 15.5% of all patients in our study, consistent with the findings of Hoang et al. [15], who reported asymptomatic cases at a rate of 19.2%. Asymptomatic carriage and milder clinical presentation may result in declined requirements for testing; for this reason, attention should be paid to the possibility that the pediatric population may remain a source of continued transmission, the magnitude of which remains unexplored [21,22]. In our study, among 980 patients for whom the results of nasopharyngeal/tracheal swabs for other common human respiratory tract viruses were available, there was co-infection in 67 (6.8%) cases. Rhinovirus was co-detected in 16 and RSV in 5 cases as the most common two pathogens, while influenza virus was co-detected in only one case in our study. In contrast, in the review conducted by Hoang et al. [15], among 1183 samples, influenza virus was the most common respiratory viral pathogen with 8 cases, followed by RSV with 7 cases. The possible explanation for this decline in viral pathogens could be the reduction in respiratory system infections due to COVID-19 mitigation strategies and social isolation.

In terms of clinical severity, 0.9% of our patients were in the severe-critical group, in accordance with the recent findings in the literature. In previous reports on 2141 and 2228 children with COVID-19 disease, severe and critical cases were identified at respective rates of 3.1% and 0.6% [5,23]. This could be related to the incomplete development of innate immunity, which may lead to lower functioning of the adaptive immune system in pediatric cases and which may also explain the milder clinical course in children. Elevated levels of inflammatory markers should point toward more severe disease. In a review, it was reported that elevated levels of transaminases, D-dimer, and LDH with prolonged PT might be indicative of more severe disease [24]. These observations were reported to be explained by three mechanisms. First, the virus may cause organ damage by attaching to ACE2 receptors, which are commonly expressed by the heart, lungs, arteries, intestines, and kidneys. The second mechanism is systemic hyperinflammation caused by the cytokine release mediated by the innate immune system; systemic hyperinflammation affects all tissues and might also explain the increased expression of markers of disseminated intravascular coagulation. The third mechanism is hypoxia resulting from respiratory failure [25-28].

Pediatric data reflect a low incidence of hospitalization and PICU admission [29]. In a study from Italy, the rate of hospitalization was reported as 13.0% while 3.5% of the patients were admitted to the PICU [30]. Similarly, our hospitalization rate was 14.4% while the rate of PICU admission was lower at 1.2%. Other studies in the literature reported higher hospitalization rates reaching up to 68% [29]. This discrepancy may be related to differences in testing eligibility or overestimations of the percentage of patients who need hospitalization between different health facilities. Another reason may be the increased awareness of possible severe disease with the use of hospitalization as an observational means [29]. In previous studies, PICU admission rates were reported between 0.5% and 2% [29,30], in accordance with our finding of 1.2%. Factors associated with PICU admission were reported as male gender, underlying medical conditions, signs or symptoms of lower respiratory system infection at presentation, viral co-infection, and radiologic changes suggestive of pneumonia or acute respiratory distress syndrome [29-33]. In the present study, there was no difference for gender, but those who were admitted to the PICU were younger in age. Patients admitted to the PICU also had more chronic diseases and higher rates of elevated CRP, procalcitonin, D-dimer, and troponin levels according to the cut-off values for each center. In a retrospective cohort study evaluating PICU-admitted children, the presence of comorbidities, low platelet counts, elevated procalcitonin, and circulatory compromise were associated with in-PICU mortality [28]. Among the 8799 SARS-CoV-2 PCR-positive cases in our study, there were 8 (0.1%) deaths. Our findings are supported by Castagnoli et al. [34], who included 1065 patients in their study and reported only one (0.09%) death. Hoang et al. similarly found 7 (0.09%) deaths among 7780 cases [15].

Most patients with COVID-19 have an uneventful course in general but an inflammatory scenario, MIS-C, may be identified within 2–6 weeks after COVID-19 infection. Its incidence was reported as 0.14% in a previous study [15]. There was male predominance of 60.9% in the present study, consistent with previous reports; for example, a review including 1415 cases reported male predominance of 62.0% [35,36]. Fatigue, rash, nausea/vomiting, and diarrhea were the most common symptoms among our patients. Although reports evaluating MIS-C cases present a wide variety of clinical signs, most cases are reported to involve gastrointestinal symptoms and cardiac dysfunction; gastrointestinal symptoms appear as the predominant presenting features of MIS-C in the literature [35-37]. An association between severe disease and several inflammatory markers including CRP, ferritin, and D-dimer was recently reported [38,39]. Another report declared that hepatitis and acute kidney injury were associated with disease severity [35]. In the present study, patients who presented with shock had less presence of rash and diarrhea, higher rates of elevated troponin levels, and higher PT, INR, and ferritin levels.

Among our 87 patients with MIS-C, coronary abnormality was found in one (2.3%) case and left ventricle dysfunction in 6 (14.0%) cases, rates lower than those previously reported in the literature. In a review, coronary involvement was reported in 13% of cases, and the same study found that 36% of cases had cardiac dysfunction, with 46% of those involving an EF of <55% [35]. In another report, coronary artery aneurysms were detected in 13% and left ventricle dysfunction in 42% of cases [40]. These discrepancies may be related to the low number of patients in our study and to the fact that these examinations were recorded at presentation; progressive EF values were not available. The mortality rate, however, was consistent with the literature; mortality was found to be low in previous research, reported at <2% and most commonly occurring in conjunction with severe comorbidities [35].

We acknowledge limitations of the present study. First, this was a multi-center study and some data were missing. Second, for patients diagnosed with MIS-C, inclusion of antibody-positive children may

represent an overestimate of acute infection; possibly recovered from COVID-19 but have other illness leading to symptoms at presentation.

In conclusion, most of the SARS-CoV-2 PCR-positive cases presented here had a mild clinical course. Although rare, MIS-C has emerged as a serious consequence with frequent PICU admission and immunomodulatory therapy required. Further understanding of the characteristics of COVID-19 disease could provide insights and guide the development of therapeutic strategies for target groups. The situation is constantly changing and further pediatric studies are needed.

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CRediT authorship contribution statement

Murat Duman: Conceptualization. **Nihan Şık:** Writing – original draft. **Özlem Tekşam:** Data curation, Writing – review & editing. **Halise Akça:** Data curation. **Funda Kurt:** Data curation. **Ayla Akca Çağlar:** Data curation. **Leman Akcan Yıldız:** Data curation. **Medine Ayşin Taşar:** Data curation. **İlknur Fidancı:** Data curation. **Burcu Ceylan Cura Yayla:** Data curation. **Durgül Yılmaz:** Formal analysis. **Emre Güngör:** Data curation. **Şule Demir:** Data curation. **Haluk Çokuğraş:** Data curation. **Sinem Oral Cebeci:** Data curation. **Pınar Önal:** Data curation. **Eylem Ulaş Saz:** Data curation. **Ali Yurtseven:** Data curation. **Metin Uysalol:** Data curation. **Raif Yıldız:** Data curation. **Süheyla Gümüş:** Data curation. **Alkan Bal:** Data curation. **Semra Şen Bayturan:** Data curation. **Neslihan Zengin:** Data curation. **Sinem Atik:** Data curation. **Dilek Yılmaz Çiftdoğan:** Data curation. **Emel Berksoy:** Data curation. **Alper Çiçek:** Data curation. **Sabiha Şahin:** Data curation. **Mahmut Can Kızıl:** Data curation. **Yalçın Kara:** Data curation. **Hurşit Apa:** Data curation. **Emel Ulusoy:** Data curation. **Aybüke Akaslan Kara:** Data curation. **Edanur Yesil:** Data curation. **Meltem Erdem:** Data curation. **Caner Turan:** Data curation. **Sertac Arslanoglu:** Data curation. **Muhterem Duyu:** Data curation. **Gulser Esen Besli:** Data curation. **Gazi Arslan:** Data curation. **Ayşe Tolunay Oflu:** Data curation. **Mehmet Çeleğen:** Data curation. **Ebru Buldu:** Data curation. **İbrahim Etem Pişkin:** Data curation. **Hakan Kardeş:** Data curation. **Hayri Levent Yılmaz:** Data curation. **Dinçer Yıldızdaş:** Data curation. **Gamze Gökulu:** Data curation. **Pınar Çay:** Data curation. **Utku Özer:** Data curation. **Okşan Derinöz Güleryüz:** Data curation. **Özlem Çolak:** Data curation, Writing – review & editing. **Songül Tomar Güneysu:** Data curation.

Declaration of Competing Interest

The authors declare no conflict of interest.

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