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Original Article

Clinical characteristics of pediatric coronavirus disease 2019 and predictors of polymerase chain reaction positivity

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Abstract ***Background*:** To identify the clinical findings and outcomes of children with coronavirus disease 2019 (COVID-19) and factors predicting reverse transcription polymerase chain reaction (RT-PCR) positivity.

***Methods*:** The data were analyzed retrospectively for suspected and confirmed pediatric COVID-19 patients between March 20 and May 31, 2020.

***Results*:** There were 404 children, of them, 176 (43.6%) patients were confirmed to have COVID-19, and 228 (56.4%) were considered suspected cases. Confirmed cases were less symptomatic on admission (67.6%-95.6%). Cough (44.9%), fever (38.1%), sore throat (18.5%), and smell-taste loss (12.7%) were the most common symptoms. Confirmed cases had a 92.6% identified history of contact with COVID-19. Close contact with COVID-19 positive family members and sore throat increased the RT-PCR positivity 23.8 and 5.0 times, respectively; while positivity decreased by 0.4 times if fever was over 38 °C. Asymptomatic and mild cases were categorized as "group 1" (n = 153); moderate, severe, and critical cases as "group 2" (n = 23) in terms of disease severity. Group 2 cases had higher C-reactive protein (40.9%–15.9%) and procalcitonin (22.7%–4.9%) levels and had more frequent lymphopenia (45.5%–13.1%). Out of 23 cases, 19 had abnormal chest radiograph findings; of them, 15 patients underwent chest computed tomographies (CTs), and all had abnormal findings. However, 26.0% of them needed respiratory support, and no patient required invasive ventilation.

***Conclusions*:** Children with COVID-19 have a milder clinical course and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rarely causes severe disease in children. Contact history with COVID-19 and sore throat are the most important predictors for RT-PCR positivity. Consequently, the role of asymptomatic children in the contamination chain must be fully established and considered for the control of pandemic.

Key words children, clinical characteristics, COVID-19, SARS-CoV-2.

In December 8, 2019, an acute respiratory disease, soon named coronavirus disease 2019 (COVID-19), occurred in Wuhan, China.[1,2] As of January 19, 2021, more than 57 million cases and over 1.3 million deaths have been reported globally due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.[3]

The first confirmed case in Turkey was detected on March 11, 2020. Since then, the number of cases has increased and reached over 2.4 million. The initial data focused on the symptoms of severe respiratory failure that were being seen predominantly in adults, but information about COVID-19 in pediatric patients remained insufficient. The first infections of SARS-CoV-2 in children were reported in Shenzen on January 20.[4] Following a small number of case series, more data from pediatric patients in China and Italy, and a systemic review including 7,780 children with confirmed COVID-19 were published recently.[5–7] It is currently known that pediatric patients with COVID-19 are less likely than adults to develop severe disease[8] but the clinical spectrum of COVID-19 in pediatric patients remains unclear. Moreover, few data are available on the management methods of COVID-19 in children.[9,10] However, patients manifesting with severe multisystem inflammation associated with COVID-19 raise concerns about the pediatric population. Nucleic acid amplification tests (NAAT), performed with a reverse transcription polymerase chain reaction (RT-PCR) assay, to detect viral RNA from the respiratory tract, are the gold standard diagnostic test for COVID-19.[11] The accuracy and predictive values of RT-PCR tests have not been systematically evaluated. False negativity ranges from 5% to 40%, but these data are limited because there is no perfect reference standard for comparison.[12,13] In this study, the

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epidemiological and clinical features, the laboratory and imaging findings, and the treatment options and clinical outcomes of suspected pediatric COVID-19 cases were identified, and the incidence and predictors of SARS-CoV-2 RT-PCR positivity were determined.

Methods

Study design and data collection

Our study was designed as a single-center, retrospective, descriptive, and observational study using cross-sectional data from suspected COVID-19 patients admitted to and treated in the emergency room, inpatient clinic, or pediatric intensive care unit of a tertiary hospital in Turkey. Children between 1 month and 18 years of age were included. Suspected cases were diagnosed according to national guidelines, which have been revised intermittently according to the recommendations of the Coronavirus Scientific Advisory.[14] During the study period, our cases were defined as suspected if a child had contact with a confirmed COVID-19 case, lived in an epidemic area where a COVID-19 case was reported, or had any family member hospitalized due to a respiratory infection or experiencing symptoms such as cough, fever, or shortness of breath in the previous 2 weeks, and if the children had respiratory or gastrointestinal symptoms. Suspected cases who tested positive for nasopharyngeal swab specimens with SARS-CoV-2 RT-PCR assays were defined as confirmed cases.

The diagnoses and severity of cases for all suspected patients were defined based on clinical features, laboratory testing, and imaging and included asymptomatic infection and mild, moderate, severe, and critical cases. The diagnostic criteria were as follows:[5]

1. Asymptomatic infection: Any signs and symptoms. Imaging is normal, if performed.
2. Mild: Symptoms and signs of upper respiratory system infection, including fever, cough, sore throat, rhinorrhea, and pharynx congestion. Some cases have only gastrointestinal symptoms such as vomiting and diarrhea. Imaging is normal if performed.
3. Moderate: Symptoms with fever and cough, some may have wheezing but without shortness of breath and hypoxemia. Cases without signs and symptoms but who have abnormal imaging findings.
4. Severe: Respiratory and gastrointestinal system symptoms such as cough, fever, vomiting, and diarrhea. The disease usually progresses, and dyspnea, shortness of breath, and hypoxemia occur.
5. Critical: Patients have acute respiratory failure and may also have encephalopathy, shock, heart failure, acute renal failure, and coagulopathy.

In our study, asymptomatic and mild cases were categorized as "group 1" and moderate, severe and critical cases as "group 2," in terms of disease severity.

Statistical analysis and ethical statement

All confirmed, and suspected cases were included in the analysis. Data sets were recorded from the medical records. Information retrieved included epidemiological and clinical data, contact history, underlying disease, laboratory and imaging results, treatments used, severity of disease and outcomes. Symptoms such as sore throat and smell-taste loss cannot be described at infancy and pre-school age; sore throat was assessed for children over 3 and smell-taste loss over 5 years of age. Demographic and clinical characteristics, laboratory and imaging findings, treatments and outcomes were summarized with standard descriptive statistics for all cases. Chi-squared tests and Fisher's exact tests were used for categorical variables and categorical and continuous variables were reported as frequencies and percentiles and means with standard deviations (SD) or medians with interquartile ranges (IQRs). The Mann–Whitney *U*-test was used to compare non-parametric variables and Student's *t*-test was performed for parametric data. Multivariate regression analysis was used to determine the risk factors for SARS-CoV-2 RT-PCR positivity and the severity of disease. All data obtained were analyzed using an IBM SPSS V22.0 program and P-values ≤ 0.05 were considered significant for all comparisons. Ethics committee approval was received from the Ethics Committee of University of Health Sciences, Derince Research and Training Hospital (Ethics Committee No: 2020-45). The study was approved by the Turkey Ministry of Health.

Results

During the study period, 404 children were admitted to the emergency department and tested for COVID-19 by RT-PCR test. In line with the decision of the local health authority, all suspected patients were hospitalized and followed until RT-PCR results were received. Of these patients, 176 (43.6%) patients were confirmed to have COVID-19, and 228 (56.4%) were considered suspected cases. Table 1 shows the epidemiological and clinical differences between confirmed and suspected cases. The median age of the confirmed cases (55.7% male) was 79 (IQR 34–149) months. The confirmed patients were less symptomatic on admission (67.6–95.6%) than the suspected cases, and the most common symptoms were cough (44.9%), fever (38.1%), sore throat (18.5%), and smell-taste loss (12.7%). Among all the patients, exposure to SARS-CoV-2 was detected in confirmed and suspected cases, at 92.6% and 23.2%, respectively.

Lymphocyte counts were lower for confirmed cases, but no statistically significant difference was found between the confirmed and suspected cases in terms of lymphopenia by age ($P = 0.463$). The confirmed cases had lower procalcitonin (6.8%) and C-reactive protein (CRP) levels (16.4%) than the suspected cases. An examination of the radiological findings showed that the confirmed cases had lower abnormalities on chest radiographs. Chest computed tomography (CT) was performed in 19 of 176 (10.7%) confirmed cases who had

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Table 1 Epidemiologic characteristics and clinical features of 404 children with suspected COVID-19 (n=404)

Characteristics	RT-PCR Positive (n = 176)	RT-PCR Negative (n = 228)	P value
Age			
Month - Median (IQR)	79 (34–149)	30.5 (9–82)	
Distribution – no. (%)			
<1 year	20 (11.4)	82 (36)	0.001
1–6 years	63 (35.8)	72 (31.6)	
6–10 years	27 (15.3)	32 (14)	
10–18 years	66 (37.5)	42 (18.4)	
Sex – no. (%)			
Male	98 (55.7)	135 (59.2)	0.479
Female	78 (44.3)	93 (40.8)	
Days from symptom onset to diagnosis			
Mean (SD)	4.1 (±1.4)	5.8 (±2.2)	<0.001
Underlying disease – no. (%)	3 (1.7)	27 (11.8)	0.001
Symptomatic on admission – no. (%)	119 (67.6)	218 (95.6)	<0.001
Fever, or cough or shortness of breath – no. (%)	104 (59.1)	210 (92.1)	<0.001
Symptoms and findings – no (%)			
Cough	79 (44.9)	144 (63.2)	<0.001
Shortness of breath	6 (3.4)	43 (18.9)	<0.001
Fatigue	9 (5.1)	24 (10.5)	0.066
Sore throat (no:249)	25 (18.5)	11 (9.6)	0.069
Rhinorrhea	3 (1.7)	28 (12.3)	0.001
Nausea or vomiting	11 (6.3)	30 (13.2)	0.030
Diarrhea	13 (7.4)	25 (11)	0.235
Smell-taste loss (no:213)	15 (12.7)	2 (2.1)	0.004
Tachypnea on presentation	2 (1.1)	36 (15.8)	<0.001
Tachycardia on presentation	3 (1.7)	20 (8.8)	0.002
Oxygen saturation <%92	3 (1.7)	18 (7.9)	0.006
Crackle	18 (10.2)	68 (29.8)	<0.001
Rhonchus	5 (2.8)	63 (27.6)	<0.001
Clinical severity of patients – no. (%)			
Asymptomatic	59 (33.5)	10 (4.4)	<0.001
Mild	94 (53.4)	119 (52.2)	
Moderate	22 (12.5)	91 (39.9)	
Severe	0 (0.0)	5 (2.2)	
Critical	1 (0.6)	3 (1.3)	
Exposure to SARS-CoV-2 – no. (%)	163 (92.6)	53 (23.2)	<0.001
Clinical condition of the contact – no. (%)			
Quarantine	15 (9.2)	17 (32.1)	<0.001
Hospitalized	141 (86.5)	36 (67.9)	
ICU	6 (3.7)	–	
Died	1 (0.6)	–	

pneumonia clinically, and the most common findings were bilateral ground glass opacity (36.8%), unilateral ground glass opacity (26.3%), lobar consolidation (10.5%), and diffuse infiltration (10.5%). Chest CTs were found to be normal in four patients who were clinically considered to have pneumonia. Seven patients in the suspected group had abnormal findings. Of those, only one patient had ground glass opacity on chest CT, and the other six patients had atypical abnormalities for COVID-19.

Among all the patients, being asymptomatic and experiencing a mild clinical course were more common in confirmed cases (88.9–56.6%; $P < 0.001$). Out of 176 confirmed cases, only one patient who had underlying primary hemophagocytic lymphohistiocytosis and immunosuppression developed mild acute respiratory distress syndrome and needed non-invasive ventilation. There was no significant difference statistically for length of stay ($P = 0.180$) between confirmed and suspected cases, and no mortality was seen in either group.

A logistic regression analysis was performed to determine the predictive factors for SARS-CoV-2 RT-PCR positivity among all patients (Table 2). Close contact with COVID-19 family members and sore throat increased the SARS-CoV-2 RT-PCR positivity 23.8 and 5.0 times, respectively; on the other hand, positivity decreased by 0.4 times if their fever was over 38 °C.

Among all the patients enrolled, three were diagnosed with multisystemic hyperinflammatory syndrome in children (MIS-C) and were treated effectively with intravenous immunoglobulin, corticosteroid, and supportive care. One of them was positive for SARS-CoV-2 RT-PCR, but the other two were positive for serology. Table 3 shows the clinical, laboratory, and immunological findings and treatments of patients diagnosed with MIS-C.

Regarding the severity of the disease among confirmed cases, there were 153 (86.9%) patients in group 1 (asymptomatic + mild) and 23 (13.0%) patients in group 2 (moderate + severe + critical) (Table 4). The median age of the patients in group 2 was significantly higher than those in group 1 ($P = 0.009$). A severe clinical course was most common in patients over 10 years of age (65.2%). All patients in group 2 had at least one symptom on admission, including cough, fever, or shortness of breath ($P < 0.001$). No clinical deterioration occurred in any patient who was asymptomatic on admission.

Table 5 shows the laboratory and radiological findings, diagnoses, treatments, and outcomes of COVID-19 patients in terms of severity. Lymphopenia was more common in group 2 (47.8% to 13.7%), and they had higher CRP (39.1–13.1%)

Table 2 Predictive factors related SARS-CoV-2 RT-PCR positivity with logistic regression analysis (n=176)

Risk factors	P	OR	95% CI for OR	
			Lower	Upper
Gender	0.253	1.7	0.69	4.01
Cough	0.334	1.6	0.63	3.85
Shortness of breath	0.136	0.2	0.03	1.56
Rhinorrhea	0.983	0.9	0.10	8.88
Smell-taste loss	0.167	4.6	0.52	40.48
Sore throat	0.018	5.0	1.31	19.01
Positive contact history	<0.001	23.8	8.97	63.05
Fever > 38 °C	0.039	0.4	0.17	0.95

Dependent variable: Positive RT-PCR. Categorical variables: Gender, cough, shortness of breath, sore throat, rhinorrhea, smell-taste loss, positive contact, and fever > 38 °C.

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Table 3 Clinical, laboratory and immunological findings of patients diagnosed with MIS-C

Characteristics	Case 1	Case 2	Case 3
Age	6	9	7
Gender	Male	Male	Female
Signs and symptoms	Fever, abdominal pain, vomiting, diarrhea, cough, tachycardia	Fever, diarrhea, cough, dyspnea, tachycardia, tachypnea, increase capillary refill time	Fever, abdominal pain, fatigue, tachycardia,
Exposure to SARS-CoV-2	Yes	Yes	Yes
SARS-CoV-2-RT-PCR	Positive	Negative	Negative
SARS-CoV-2 Serology	Negative	Positive	Positive
Ejection fraction on echocardiography	52%	45%	60%
C-reactive protein (mg/L)	152	214	75
Procalcitonin (ng/mL)	2.4	3.1	2.6
Troponin-I (ngr/L)	422	550	380
Pro-BNP (pg/mL)	9,250	15 250	8,890
Treatments	IVIG, Corticosteroid, LMWH, Inotrope, Diuretics	IVIG, Corticosteroid, LMWH, Inotrope, Diuretics	IVIG, Corticosteroid, LMWH, Diuretics

IVIG, intravenous immunoglobulin; LMWH, low-molecule-weighted-heparin.

and procalcitonin (21.7–4.6%) levels. Out of 23 group 2 cases, 19 (82.6%) patients had abnormal chest radiograph findings; of these, 15 patients underwent chest CTs, and all had abnormal findings. In the group 2, only 27.3% of patients needed respiratory support, and no patient required invasive ventilation. The length of hospital stays was significantly longer in group 2 ($P < 0.001$), and no mortality was seen in either group.

Discussion

Since COVID-19 was first reported in China, most of the studies published included information about adult patients. In the presence of this novel infection, the identification of different clinical spectrums in children is essential to guide surveillance methods and treatment strategies. The surveillance definitions and diagnostic criteria change during a pandemic, and the data from different countries vary. According to the Chinese Center for Disease Control and Prevention less than 2% of the COVID-19 cases were under 10 years of age in the review of 72 314 cases.[15] In a study from Italy, Statista Research found only 1.6% of all patients were under 18 years of age. In the USA, children under 18 years account for approximately 8%–10% of the laboratory-confirmed cases reported by Centers for Disease Control and Prevention (CDC).[16] As of October 25, 2020, 6.3% of COVID-19 cases were under 15 years of age in Turkey according to the Ministry of Health.[17] Reverse transcription polymerase chain reaction positivity rates vary among suspected pediatric cases in different studies; Dong *et al.*, Xiaoxia *et al.*, Zachariah *et al.*, and Ceyhan *et al.* reported rates of 34.1%, 12.3%, 15%, and 8.6%, respectively.[5,6,18–20] Our rate (43.6%) was higher due to testing asymptomatic family members of SARS-CoV-2 positive patients according to Turkish National pandemic policy. This condition should explain the difference.

The sensitivity and specificity of SARS-CoV-2 RT-PCR have not been well established. They are highly specific tests but have high analytic sensitivity only in ideal settings. False positive results are rare but reported false negative rates range from 5% to 40%.[21,22] The sensitivity of these tests likely depends on the type and quality of the specimen obtained, the duration of illness and the specific assay. Lower respiratory tract specimens and tests obtained 5–8 days after exposure (days 1–3 of illness) may be more likely to yield positive results.[23] For these reasons, we could not exclude RT-PCR negative cases and considered them as suspected cases, and we found that low degree fever, positive contact history and sore throat were factors predicting RT-PCR positivity among all patients.

The clinical findings of COVID-19 are similar but the frequency of symptoms varies in children. In addition, pediatric patients with COVID-19 appear to have a favorable clinical course; thus, their symptoms may be unrecognized before diagnosis.[18,24,25] Cough and fever are the most common reported symptoms in children.[6] In a review published recently including 7,780 pediatric cases, 59.1% had fever, 55.9% had cough, 11.7% had shortness of breath and 19.1% were asymptomatic.[7] Although sore throat was not defined as a common symptom according to previous data, we found that the presence of a sore throat especially in older children who can identify it, significantly predicts the RT-PCR positivity. Nausea, diarrhea, rhinorrhea, and fatigue were also reported rarely in previous studies.[7,20] Fever, cough, or shortness of breath were more common in adult patients (93% reported at least one of these). World Health Organization (WHO) and the CDC emphasize fever and respiratory symptoms in the criteria

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Table 4 Epidemiologic characteristics and clinical features of confirmed COVID-19 patients in terms of severity (n=176)

Characteristics	Group 1† (*n* = 153)	Group 2‡ (*n* = 23)	*P* value
Age - Month - Median (IQR)	72 (33–144)	147 (49–188)	0.009
Distribution – no. (%)			
<1 year	18 (11.8)	2 (8.7)	0.031
1–6 years	59 (38.6)	4 (17.4)	
6–10 years	25 (16.3)	2 (8.7)	
10–18 years	51 (33.3)	15 (65.2)	
Sex – no. (%)			
Male	86 (56.2)	12 (52.2)	0.786
Female	67 (43.8)	11 (47.8)	
Underlying disease – no. (%)	1 (0.7)	2 (8.7)	0.045
Symptomatic on admission – no. (%)	96 (62.7)	23 (100.0)	<0.001
Fever, shortness of breath, or cough – no. (%)	96 (62.7)	23 (100.0)	<0.001
Temperature – no. (%)			
≤38 °C	116 (75.9)	9 (39.1)	0.007
38.1–39 °C	34 (22.2)	11 (47.8)	
>39 °C	3 (2.0)	3 (13.0)	
Symptoms and findings – no. (%)			
Cough	58 (37.9)	21 (91.3)	<0.001
Shortness of breath	2 (1.3)	4 (17.4)	0.003
Fatigue	3 (2.0)	6 (26.1)	<0.001
Sore throat (no: 135)	19 (16.2)	6 (33.3)	0.103
Rhinorrhea	3 (2.0)	0 (0.0)	1.000
Nausea and vomiting	9 (5.9)	2 (8.7)	0.639
Diarrhea	12 (7.8)	1 (4.3)	1.000
Smell and taste loss (no: 118)	11 (10.9)	4 (23.5)	0.228
Tachypnea on presentation	0 (0.0)	2 (8.7)	0.016
Tachycardia on presentation	0 (0.0)	3 (13.0)	0.002
Oxygen saturation <% 92	0 (0.0)	3 (13.0)	0.002
Crackle	0 (0.0)	18 (78.3)	<0.001
Rhonchus	1 (0.7)	4 (17.4)	0.001
Clinical condition of the contact – no. (%)			
Quarantine	15 (9.8)	0 (0.0)	0.701
Hospitalized	125 (81.6)	16 (88.9)	
ICU	4 (2.6)	2 (11,1)	
Died	1 (0.7)	0 (0.0)	
Exposure to SARS-CoV-2 – no. (%)	145 (94.8)	18 (78.3)	0.016

†Group 1. Asymptomatic and mild cases.
‡Group2. Moderate, severe and critical cases.

for suspected cases. In our study, only 59.1% of the confirmed cases had fever, cough or shortness of breath similar to the previous studies.[19,24,26,27] As many children are considered to be asymptomatic or to have mild cases, they may not be tested as often as adults, which leads to undiagnosed infected children and increased transmission of the virus.

Although studies show that SARS-CoV-2 causes severe disease in adult patients with underlying disease,[28–30] factors predicting severe disease in children are poorly described. Most pediatric patients appear to be asymptomatic or have mild disease; however, severe disease may also present in children who have underlying disease. According to Dong *et al*., 5.9% of the pediatric patients had severe and critical disease, and only one child died among 2,135 patients.[5] Lu *et al*. reported in another study that three patients who had underlying conditions required intensive care support.[6] Among 345 confirmed pediatric cases in the USA, 23% had an underlying condition and hematological disorder; chronic kidney disease on hemodialysis, chronic liver disease, and neurological problems are significant reasons for severe disease. Our results showed that children who had underlying disease did not have increased susceptibility to SARS-CoV-2. This might have been achieved by better isolation of children with chronic disease.

Elevated inflammatory markers (i.e., procalcitonin, CRP, ferritin, D-dimer, IL-6) and lymphopenia are potential markers of severe disease and are associated with worse outcomes.[19,31] Guan *et al*. demonstrated 96.1% of adult COVID-19 patients had lymphopenia, especially in severe cases. In our study, lymphopenia found in only 18.2% in the confirmed cases, while the rate was 47.8% in severe cases. Previous pediatric studies have shown that lymphopenia was reported in 12.9% of confirmed cases.[27,32] Lymphopenia may not therefore be a reliable sign for COVID-19 but should be a significant predictor of the severity of the disease in children.

During the study period, most of these confirmed cases (92.6%) were likely to have close contact with SARS-CoV-2 positive family members. This is because the Turkish government closed all schools and imposed a curfew on people under 20 and over 65 years of age in the early stages of pandemic.[33] This clearly represents person-to-person transmission within family members. This transmission pattern has also been reported from studies on adult and pediatric patients.[4,5,28,34] With this transmission pattern and children infected with SARS-CoV-2 presenting as mostly asymptomatic and with a milder clinical course, children's role in the contamination chain is precisely established and considered.

Since the majority of adult COVID-19 patients had chest CT findings, chest CT are proven to be an important diagnostic method.[35] Moreover, some reports have suggested a chest CT may be a better diagnostic tool in adult COVID-19 patients;[36] pediatric COVID-19 patients tend to show fewer abnormalities on chest CTs.[37] However, most pediatric patients have a milder clinical course, and fewer have typical imaging features, thus; due to radiation protection considerations, only clinically highly suspected and severe pediatric patients who have negative RT-PCR tests should undergo chest CTs.

Although the clinical course is mild in children, hyperinflammatory syndrome overlapping features of Kawasaki disease has caused concern. Reports from the UK and Italy emphasized a significant increase in hyperinflammatory syndrome in children positive or even negative for SARS-CoV-2 RT-PCR.[38–40] In the UK, eight children presented with high fever, abdominal symptoms, rash, and conjunctivitis. All of the patients had elevated levels of procalcitonin, CRP, ferritin,

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Table 5 Laboratory and radiological findings, and outcomes of COVID-19 patients in terms of severity (n=176)

Characteristics	Group 1[†] (n = 153)	Group 2[‡] (n = 23)	P value
Lymphopenia – no./total no (%)	21 (13.7)	11 (47.8)	0.001
Lymphocyte count ($\times 10^9$/L) Mean (SD)	2,984.9 (±1639.2)	1,926.0 (±1487.6)	<0.001
Procalcitonin (ng/mL) – Median (IQR)	0.01 (0.01–0.02)	0.02 (0.01–0.05)	0.008
Elevated procalcitonin – no. (%)	7 (4.6)	5 (21.7)	0.011
C-reactive protein (mg/dL) – Median (IQR)	2.0 (2.0–2.0)	4.8 (2.0–16.8)	<0.001
Elevated C-reactive protein – no. (%)	20 (13.1)	9 (39.1)	0.004
Abnormal findings on X-ray – no. (%)	0 (0.0)	19 (82.6)	<0.001
Abnormal findings on CT – no./total no. (%)	0/4 (0.0)	15 /15 (100.0)	0.001
Length of stay – days. Mean (SD)	4.5 (±1.29)	10.3 (±3.28)	<0.001
Admitted to ICU – no. (%)	0 (0.0)	1 (4.3)	0.131
Survived – no. (%)	153 (100.0)	23 (100.0)	1.000

[†]Group 1. Asymptomatic and mild cases.
[‡]Group2. Moderate, severe, and critical cases.

and troponin, and required respiratory assistance and vasopressor agents. Five of the patients had ventricular dysfunction on echocardiography, and one of them required extracorporeal membrane oxygenation.[41] In a study from Italy, the investigators described 10 children with MIS-C. Those patients manifested with fever (n = 10), diarrhea (n = 6), and cardiac findings on echocardiography (n = 6).[42] In our cohort, three patients had fever over 5 days, gastrointestinal symptoms, fatigue, tachycardia, and diagnosed MIS-C. Due to significant cardiac complications, prompt diagnosis and treatment are needed, with the aim to preventing coronary artery aneurysms.

This study has some limitations. First, we were not able to identify any other pathogens; as a result, we could not determine the exact infectious microorganism in the RT-PCR-negative group or the coinfection rates in the RT-PCR-positive group. Second, the data included only one hospital; further national and worldwide research is needed to understand COVID-19 in the pediatric population. The strength of this study is that it is the first pediatric study to determine predictive factors for RT-PCR positivity.

Conclusion

Most of the pediatric COVID-19 cases have a favorable clinical course and SARS-CoV-2 rarely causes severe disease in children. Our findings indicate that the predictors of RT-PCR positivity in suspected cases are the presence of contact history and sore throat in terms of symptoms. Fever, cough, or shortness of breath, which are the most common symptoms in adults, may also not be seen in pediatric patients. The role of asymptomatic children in the contamination chain must therefore be fully established and considered for the control of the pandemic. Consequently, larger studies are needed to determine the factors predicting RT-PCR positivity and disease severity in children.

Disclosure

The authors declare no conflict of interest.

Author Contribution

G.A. and H.A. designed the study. G.A., H.A., and M.D. collected and analyzed the data. G.A. and M.D. wrote the manuscript. All authors read and approved the final manuscript.

References

1 Huang C, Wang Y, Li X *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497–506.
2 Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. *JAMA* 2020; **323**: 707–8.
3 World Health Organization (WHO). *COVID-19 Weekly Epidemiological Update*. [Internet]. [Cited 22 Nov 2020.] Available from URL: https://www.who.int/publications/m/item/weekly-epidemiological-update---19-january-2021
4 Chan JF, Yuan S, Kok K *et al*. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514–23.
5 Dong Y, Mo X, Hu Y *et al*. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020; **145**: e20200702.
6 Lu X, Zhang L, Du H *et al*. SARS-CoV-2 infection in children. *N. Engl. J. Med.* 2020; **382**: 1663–5.
7 Hoang A, Chorath K, Moreira A *et al*. COVID-19 in 7780 pediatric patients: a systematic review. *EClinicalMedicine.* 2020; **24**: 100433.
8 Wang E, Brar K. COVID-19 in children: an epidemiology study from China. *J. Allergy Clin. Immunol. Pract.* 2020; **8**: 2118–20.
9 Shekerdemian LS, Mahmood NR, Wolfe KK *et al*. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr.* 2020; **174**: 868–73.
10 Shen K, Yang Y, Jiang R *et al*. Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition). *World J. Pediatr.* 2020; **16** (3): 232–9.
11 Centers for Disease Control and Prevention. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak — United States. December 31, 2019 - February 4, 2020. [Cited 29 October 2020.] Available from URL: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6905e1-H.pdf

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12 Weissleder R, Lee H, Ko J, Pittet M. COVID-19 diagnostics in context. *Sci. Transl. Med.* 2020; **12**: eabc1931.
13 Long D, Gombar S, Hogan C *et al*. Occurrence and timing of subsequent severe acute respiratory syndrome coronavirus 2 reverse-transcription polymerase chain reaction positivity among initially negative patients. *Clin. Infect. Dis.* 2020; ciaa722. https://doi.org/10.1093/cid/ciaa722
14 Sağlık Bakanlığı TC. Halk Sağlığı Genel Müdürlüğü, COVID-19 Epidemiyoloji ve TanıRehberi. Haziran, 2020. [Cited 30 November 2020.] Available from URL: https://covid19.saglik.gov.tr/Eklenti/39551/0/covid-19rehberigenelbilgilerepidemiyolojivetanipdf.pdf
15 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239–42.
16 Stokes EK, Zambrano LD, Anderson KN *et al*. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. *Morb. Mortal. Wkly Rep.* 2020; **69**: 759–65.
17 Republic of Turkey Ministry of Health. COVID-19 Weekly Situation Report. Available from URL: https://covid19.saglik.gov.tr/TR-68443/covid-19-durum-raporu.html
18 Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy. *N. Engl. J. Med.* 2020; **383**: 187–90.
19 Zachariah P, Johnson CL, Halabi KC *et al*. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. *JAMA Pediatr.* 2020; **174** (10): e202430.
20 Cura Yayla BC, Özsürekçi Y, Aykaç K *et al*. Characteristics and management of children with COVID-19 in Turkey. *Balk. Med. J.* 2020;**37**:341–347. https://doi.org/10.4274/balkanmedj.galenos.2020.2020.7.52
21 Nalla AK, Casto AM, Casto AM *et al*. Comparative performance of SARS-CoV-2 detection assays using seven different primer-probe sets and one assay kit. *J. Clin. Microbiol.* 2020; **58**: e00557.
22 Lieberman LA, Pepper GNaccahce SM, Huang ML, Jerome KR, Greninger AL. Comparison of commercially available and laboratory developed assays for in vitro detection of SARS-CoV-2 in clinical laboratories. *J. Clin. Microbiol*. 2020; **58**: e00821–20.
23 Wang W, Zu Y, Gao R *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; **323**: 1843–4.
24 Choi SH, Kim HW, Kang JM, Kim DH, Cho EY. Epidemiology and clinical features of coronavirus disease 2019 in children. *Clin. Exp. Pediatr.* 2020; **63**: 125–32.
25 Petra Z, Nigel C. Coronavirus infections in children including COVID-19. *Pediatr. Infect. Dis. J.* 2020; **39**: 355–68.
26 Parri N, Magistà AM, Marchetti F *et al*. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. *Eur. J. Pediatr.* 2020; **179**: 1315–23.
27 De Souza TH, Nadal J, Nogueira RJN, Pereira RM, Brandao MB. Clinical manifestations of children with COVID-19: a systematic review. *Pediatr. Pulmonol.* 2020; **55**: 1892–9.
28 Wang D, Hu B, Hu C *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061–9.
29 Zheng Z, Peng F, Xu B *et al*. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J. Infect.* 2020; **81**: e16–25.
30 Zhou F, Yu T, Du R *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054–1062.
31 Chao JY, Derespina KR, Herold BC *et al*. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. *J. Pediatr.* 2020; **53**: 14–9.
32 Guan W, Ni Z, Hu Y *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 2020; **382**: 1708–1720.
33 Ministry of Interior of the Republic of Turkey. Available from URL: https://www.icisleri.gov.tr/sehir-giriscikis-tebirleri-ve-yas-sinirlamasi
34 Phan LT, Nguyen TV, Luong QC *et al*. Importation and human-to-human transmission of a novel coronavirus in Vietnam. *N. Engl. J. Med.* 2020; **382**: 872–4.
35 Duan Y, Zhu Y, Tang L, Qin J. CT features of novel coronavirus pneumonia (COVID-19) in children. *Chinese J. Radiol.* 2020; **54**: 1–7.
36 Fang Y, Zhang H, Xie J *et al*. Sensitivity of chest CT for COVID-19: comparison to RT-PCR Yicheng. *Radiology* 2020; **296**: E115–7.
37 Du W, Yu J, Wang H *et al*. Clinical characteristics of COVID - 19 in children compared with adults in Shandong Province, China *Infection* 2020; **48**: 445–52.
38 Ramcharan T, Nolan O, Lai C *et al*. Paediatric inflammatory multisystem syndrome : temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK Tertiary Paediatric Hospital. *Pediatr. Cardiol*. 2020; **12**: 1–11.
39 Harahsheh AS, Dahdah N, Newburger JW *et al*. Missed or delayed diagnosis of kawasaki disease during the 2019 novel coronavirus disease (COVID-19) pandemic. *J. Pediatr.* 2020; **222**: 261–2.
40 Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. *Lancet* 2020; **395**: 1741–3.
41 Riphagen S, Gomez X, Gonzalez-martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395**: 1607–8.
42 Verdoni L, Mazza A, Gervasoni A *et al*. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; **395**: 1771–8.

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