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Original Article

COVID-19 in Turkey: A tertiary center experience

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Abstract ***Background*:** Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a serious epidemic in our country and all over the world since December 2019 and has become a global health problem. The disease caused by the SARS-CoV-2 virus has been named as coronavirus disease 19 (COVID-19).

***Methods*:** We report on the epidemiological and clinical features of 37 children diagnosed with COVID-19.

***Results*:** The median age was of the children was 10 years and 57.1% were male. In addition, 78.3% of the children had a history of contact with adult patients who had been diagnosed with COVID-19, and 27.0% had coexisting medical conditions. We found that 40.5% of our patients had mild infection, while 32.4% had moderate infection, and 27.1% had developed severe or critical illness. The most common abnormal laboratory findings in our patients were decreased lymphocytes (45.9%) and increased D-dimer values (43.2%), while abnormal radiological findings were detected in 56.7% of the children. In addition, 64.8% of the children had received azithromycin, 59.4% had received oseltamivir, and hydroxychloroquine was used in combination with azithromycin in 35.1% of the children. Non-invasive mechanical ventilation was required in 27.0% of the children.

***Conclusions*:** Although COVID-19 infection is usually mild in children, severe illness can be seen in children with comorbidities, or even in children who were previously healthy.

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

Coronavirus is one of the viral pathogens that affect the human airway. Before 2019, coronaviruses such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and Middle-East respiratory syndrome-CoV, which cause acute respiratory distress and threaten public health, had been identified.[1] However, on January 7 2020, Chinese authorities declared that a number of cases of severe pneumonia were clustered in the Wuhan region of China, and when these patients were examined it was determined that they had been in contact with animal markets.[2] The disease, which was caused by severe acute SARS-CoV-2, then spread rapidly to other countries and became a global health problem. The World Health Organization (WHO) described the disease, which was caused by SARS-CoV-2, as coronavirus disease 2019 (COVID-19). The COVID-19 disease was declared a pandemic on 11 March 2020.

The first case in Turkey was reported on 11 March 2020.[3] By early May 2020, the WHO had reported more than 3.5 million definitive cases and 247 503 deaths worldwide.[4] SARS-CoV-2, which is mainly transmitted through respiratory droplets and contact routes, is an enveloped positive stranded RNA virus. Based on the current epidemiological data, the incubation period of the infection from SARS-CoV-2 ranges from 1 to 14 days and the most common initial symptoms include fever, cough, sore throat, headache, myalgia, and sometimes gastrointestinal symptoms.[5] Clinical manifestations range from mild upper respiratory infections to pneumonia or acute respiratory distress syndrome (ARDS). Most of the patients infected by the SARS-CoV-2 have chronic underlying diseases, mainly cardiovascular and cerebrovascular diseases and diabetes.[6] Although children are known to have clinically milder cases of the disease, it has been reported that some children have had severe respiratory failure and needed hospitalization in intensive care units (ICUs).[7] In addition, it was reported that SARS-CoV-2 may trigger diseases such as Kawasaki Disease, so it appears that more information about COVID-19 in children is needed. Here, we report on the epidemiological and clinical features of 37 children diagnosed with COVID-19 in a university hospital in İstanbul.

Methods

Study population

We collected the epidemiological and clinical data from the medical records and included all pediatric patients (aged 0–18 years). This study was approved by the Istanbul University Cerrahpaşa-Cerrahpaşa Medical Faculty ethics committee. Every patient who applied with complaints of fever, cough or other upper/lower respiratory tract symptoms was considered as a possible case and was evaluated. The combined nasopharyngeal-oropharyngeal real time polymerase chain reaction

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(RT-PCR) swab samples, blood counts, biochemical examinations, and D-dimer examinations were obtained from these patients. Chest radiographs were performed in all patients suspected to have mild or severe pneumonia. Computed tomography (CT) was performed in patients with suspicious findings on chest radiography or whose respiratory distress could not be explained by chest radiography findings.

We defined patients as having COVID-19 according to whether they met one of the following two criteria:

- Patients who had positive, combined nasopharyngeal-oropharyngeal RT-PCR swab samples.
- Patients whose samples were negative but whose clinical and radiological features were compatible with COVID-19.

Definitions of clinical types

We divided the patients who had been diagnosed with COVID-19 into three groups, according to the categories described by Dong *et al*[8] mild, moderate and severely or critically ill.

Mild disease

- Upper respiratory symptoms (e.g., pharyngeal congestion, sore throat and fever) for a short duration or asymptomatic infection.
- Positive RT-PCR tests for SARS-CoV-2.
- No abnormal radiographic nor septic presentation.

Moderate disease

- Mild pneumonia
- Symptoms such as fever, cough, fatigue, headache, and myalgia.
- No complication nor manifestation related to severe conditions.

Severe disease

Mild or moderate clinical features, plus any manifestations that suggested disease progression.

- Rapid breathing (≥70 breaths per minute for infants aged <1 year; ≥50 breaths per minute for children aged >1 year).
- Hypoxia.
- Lack of consciousness, depression, coma, and convulsions.
- Dehydration, difficulty feeding. and gastrointestinal dysfunction.
- Myocardial injury.
- Elevated liver enzymes.
- Dysfunction in coagulation, rhabdomyolysis, and any other manifestations that suggested injuries to vital organs.

Critical disease

- Rapid disease progression, plus any other conditions.
- Respiratory failure with need for mechanical ventilation (e.g. ARDS and persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or masks).
- Septic shock.
- Organ failure that needs monitoring in the ICU.

All hospitalized patients were followed up in the isolation section of the general pediatric ward or ICU. We followed up all children who had a mild disease without hospitalization and all of them regularly received a call from a trained physician and questioned about their symptoms and medications on the 1st, 3rd, and 7th days. Children who were asymptomatic or had mild disease were -up without treatment. We gave azithromycin treatment to all diagnosed patients, except those who had mild clinical conditions. We added hydroxychloroquine to the treatment of those who had abnormal findings in CT scans or who had a severe/critical illness. Critically ill patients with ARDS received favipiravir.

Statistical analyses

Statistical analyses were made between patient groups in terms of laboratory data. SPSS statistics package, version 20.0 (IBM, Armonk NY, USA) was used for analysis. For all statistical analysis, $P < 0.05$ was considered significant. ANOVA test *P*-values were considered for test significance. One-way ANOVA test was used to evaluate the statistical difference between laboratory parameters of patient groups.

Results

A total of 326 children who had respiratory symptoms, fever, or had had contact with a patient with a definitive COVID-19 diagnosis applied to our hospital between March 1 and May 1 2020, and 37 of these children who had been confirmed as having COVID-19 were retrospectively enrolled in our study. The age of our patients range from 7 months to 17,75 years (median: 10 years). Most of our patients (40.5%) were over 11 years of age, while 35.1% of them were 1 to 6 years old, and 21.6% were 6 to 11 years old, with only 2.8% of the children under 1 year old. Except for two asymptomatic patients with malignancy, the duration of the patients' symptoms at the time of admission varied between 1 and 7 days (median: 2 days). Twenty (57.1%) of our patients were male. Twenty nine (78.3 %) of the patients had a history of contact with an adult patient who had been diagnosed with COVID-19. None of the patients had a history of traveling abroad in the last 2 weeks, and all of them were Turkish citizens. Tables 1 and 2 show all the clinical features of our patients.

Ten (27%) children had a comorbid disease. (genetic disorder, 1; neurological disease, 1; endocrine disorder, 2; metabolic disease, 1; rheumatological disease 1; malignancy, 3;

Table 1 Epidemiologic and clinical characteristics of children with SARS-CoV-2 (n=37)

	Age†	Gender‡	RT-PCR	Exposure	Comorbidity§	Duration	Fever	Faigue	Rhinorrhea	Headache	Muscle pain	Cough	Vomiting	Diarrhea	Dyspnea	Sore throat
1	1.4	*M*	+	+	–	4	+	–	+	–	–	+	+	+	–	–
2	1.1	*M*	+	+	–	1	+	–	+	–	–	–	+	–	–	–
3	10	*F*	+	+	–	1	+	–	–	–	–	+	–	–	–	–
4	2	*F*	+	+	–	2	+	–	–	–	–	+	–	–	–	+
5	5	*F*	+	+	–	1	+	–	–	–	–	–	+	–	–	+
6	2.7	*F*	+	+	–	2	–	–	+	–	+	+	–	+	–	–
7	4.6	*M*	+	+	–	1	+	–	–	+	–	+	–	–	–	–
8	2.6	*M*	+	+	–	5	+	+	+	–	–	–	–	–	–	–
9	17	*M*	+	+	–	1	+	+	+	+	–	+	–	–	–	–
10	2.6	*M*	+	+	–	1	–	+	+	–	–	+	–	–	–	–
11	14	*M*	+	+	–	2	–	+	+	–	+	+	–	+	–	–
12	6	*F*	+	+	–	2	+	+	–	–	+	–	–	–	–	–
13	15	*F*	+	+	–	7	–	+	–	+	+	+	+	–	–	–
14	11	*F*	+	+	–	5	+	–	–	–	–	–	–	–	–	+
15	16	*M*	+	+	–	1	–	+	+	+	+	+	–	–	–	–
16.	11	*F*	+	+	–	1	+	+	–	–	–	–	–	–	–	–

	Total Leukocyte Count	Lymphocyte Count	CRP (mg/dL)	Pct (ng/mL)	D-dimer (mg/L)	Platelet Count	Creatine (mg/dL)	Ck (IU/L)	LDH (IU/L)	Radiological finding	Treatment¶
1	13 800	3,700	4.6	0.11	0.57	345 000	0.25	55	349	+	AZT+OMV
2	8,700	2,200	2.4	0.08	0.9	360 000	0.42	51	728	–	–
3	3,600	1,800	5.1	0.06	0.82	277 100	0.5	76	174	–	–
4	5,000	3,000	2.5	0.14	0.63	221 000	0.55	65	152	–	
5	5,400	3,500	16.7	0.43	0.47	224 000	0.39	183	289	–	
6	12 300	5,200	2.5	0.02	0.44	368 000	0.36	118	518	–	
7	5,000	3,000	0.75	0.01	0.1	362 000	0.45	52	190	–	–
8	6,100	1,300	12.6	0.11	0.66	280 000	0.25	85	307	–	–
9	5,900	2,600	23.2	0.02	0.93	184 000	0.87	45	985	+	AZT+OMV
10	6,700	3,300	3.08	0.03	0.35	193 000	0.43	157	727	–	–
11	4,900	1,800	3.6	0.09	0.19	232 000	0.85	65	157	–	–
12	8,000	1,500	6.5	0.07	0.19	235 000	0.44	101	330	+	AZT+OMV
13	5,300	1,900	2.9	0.02	0.19	355 000	0.76	43	187	–	–
14	7,600	2,500	0.47	0.02	0.3	293 000	0.54	63	269	+	AZT+OMV
15	6,500	1,300	0.7	0.02	0.19	204 000	0.89	57	211	–	–
16.	6,300	3,100	0.49	0.03	0.21	283 000	0.76	90	187	–	–

	Age†	Gender‡	RT–PCR	Exposure	Comorbidity§	Duration of symptoms	Fever	Faigue	Rhinorrhea	Headache	Muscle pain	Cough	Vomiting	Diarrhea	Dyspnea	Sore throat
17	12.6	F	+	+	+	3	–	–	–	–	+	–	–	–	–	–
18	2.3	M	–	–	–	2	+	+	–	–	–	+	–	–	+	–
19	6.5	M	–	–	–	2	+	+	–	–	–	+	–	–	+	–
20	4.3	M	–	–	–	2	+	+	–	–	–	+	+	–	+	–

Table 1 *Continued*

	Age†	Gender‡	RT−PCR	Exposure	Comorbidity§	Duration of symptoms	Fever	Faigue	Rhinorrhea	Headache	Muscle pain	Cough	Vomiting	Diarrhea	Dyspnea	Sore throat
21	7.7	F	+	+	+	2	+	+	−	−	+	+	−	−	−	−
22	16	M	+	+	−	1	−	+	−	+	+	+	−	+	−	−
23	15.8	M	+	+	−	7	+	+	−	+	+	+	−	−	+	+
24	17	F	+	+	+	7	+	+	−	+	−	+	−	−	+	+
25	1.2	F	+	+	+	2	+	−	+	−	−	+	−	−	+	−
26	15.2	M	+	−	−	1	+	−	+	+	+	+	+	−	+	−
27	11	F	+	+	+	0	−	−	−	−	−	−	−	−	−	−
28	14.7	F	−	−	+	2	+	+	−	−	+	+	+	−	+	+
29	15.3	M	−	−	+	3	+	+	−	+	+	+	+	−	+	_
30	15	F	+	+	−	2	−	+	+	−	+	+	−	−	+	+
31	4,2	F	+	−	+	0	−	−	−	−	−	−	−	−	−	−
32	4.8	M	−	+	−	1	+	−	−	−	−	+	−	−	+	−
33	15.2	M	+	+	−	5	−	−	−	−	+	+	−	−	−	−
34	16,7	M	+	+	−	2	+	+	+	+	+	+	−	−	−	−
35	17.9	M	+	+	−	2	+	+	+	+	−	+	−	−	−	−
36	9	M	−	+	+	2	−	−	−	−	−	−	−	−	+	−
37	0.7	F	−	−	+	7	−	−	−	−	−	−	−	−	+	−

	Total Leukocyte Count	Lymphocyte Count	CRP (mg/dL)	PCT (ng/mL)	D−dimer (mg/L)	Platelet Count	Creatine (mg/dL)	CK (IU/L)	LDH (IU/L)	Radiological findings	Hospitalization (day)	Treatment¶
17	8,100	2,300	0.56	0.03	0.65	301 000	0.48	81	274	−	−	−
18	10 800	1,100	14.2	0.08	0.24	266 000	0.5	93	237	+	7	AZT,OMV,HQ NIV−3 days
19	8,200	900	19	0.21	0.7	161 000	0.5	170	252	+	10	AZT,OMV,HQ NIV−3 days
20	14 800	1,400	3.6	0.08	0.63	345 000	0.39	172	302	+	10	AZT,OMV,HQ NIV−3 days
21	4,500	3,000	1.6	0.09	0.66	240 000	0.48	98	287	+	4	AZT,OMV
22	7,600	1,000	7.9	0.06	0.37	193 000	1.6	96	181	+	7	AZT,OMV,HQ
23	4,800	800	53	0.6	3.2	313 000	0.61	74	399	+	14	AZT,OMV,HQ, FAV NIV−6 days
24	7,200	700	100	0.18	2.72	266 900	0.62	63	482	+	14	AZT,OMV,HQ, FAV NIV 7days Plasmapheresis
25	5,600	1,100	3.76	0.07	0.19	227 400	0.27	64	326	+	11	AZT,OMV
26	5,800	2,500	4.4	0.09	0.35	257 000	0.54	125	232	+	6	AZT,OMV
27	7,200	800	0.69	0.1	0.52	92 000	0.5	39	225	−	5	AZT
28	14 700	1,600	17	0.3	1.7	499 000	0.4	39	409	+	8	AZT,OMV,HQ NIV− 5 days
29	13 300	1,400	284	7.1	1.1	25 000	0.43	67	683	+	17	AZT,OMV,HQ NIV−5 day plasmapheresis
30	7,200	840	2.8	0.04	0.21	229 000	0.57	72	165	+	5	AZT,OMV,HQ O2 support−3 days
31	5,300	100	1.2	0.01	1	270 000	0.3	29	244	−	7	AZT
32	5,800	2,900	0.42	0.02	0.31	289 000	0.38	85	269	+	5	AZT,OMV,HQ MV−1 day
33	4,600	1,500	0.97	0.02	0.3	281 000	0.54	125	239	+	5	AZT,OMV,HQ
34	5,600	1,300	2.8	0.05	0.2	179 000	0.77	81	128	+	5	AZT,OMV,HQ

Table 1 *Continued*

	Total Leukocyte Count	Lymphocyte Count	CRP (mg/dL)	PCT (ng/mL)	D−dimer (mg/L)	Platelet Count	Creatine (mg/dL)	CK (IU/L)	LDH (IU/L)	Radiological findings	Hospitalization (day)	Treatment[¶]
35	5,600	1,100	3.7	0.07	0.19	152 000	0.9	64	242	−	6	AZT,OMV
36	11 500	400	188	3.6	1.87	89 000	0.38	11	268	+	*	AZT,HQ,OMV FAV NIV−9 days plasmapheresis
37	13 300	2,100	31.2	3	0.09	414 000	0.15	129	419	+	7	AZT,HCQ,OMV

*still hospitalized

†Age: Years + months

‡Gender: F:female M:male

§Comorbidities: Patient 17:Juvenil Idiopathic Arthritis, 21: Metabolic Disorder, 24: Obesity, 25:Genetic Disorder, 27: Medulloblastoma, 28: Hodgkin Lymphoma, 29: Diabetes 31: Neuroblastoma 36: Tuberous sclerosis, intracranial lesion, hydrocephalus 37: Immune Deficiency.

¶Treatment: AZT, Azithromycin; CK, Creatine kinase; CRP, C- reactive protein; LDH, Lactate dehydrogenase; HQ, Hydroxychloroquine; MV, invasive mechanical ventilation; NIV, Non invasive mechanical ventilation; OMV, Oseltamivir; PCT, Procalcitonin; RT-PCR, Real-time polymerase chain reaction.

Table 2 Baseline characteristics of children infected with SARS-CoV-2 (n=37)

	n (%)
Age group	
<1 year	1 (2.8)
1 to <6 years	13 (35.1)
6 to <11 years	8 (21.6)
>11 years	15 (40.5)
Sex	
Male	20 (57.1)
Female	17 (42.9)
Severity of illness	
Mild	15 (40.5)
Moderate	12 (32.4)
Severe and critical	10 (27.1)
Exposure	
Yes	29 (78.3)
No	8 (21.7)
Symptoms	
Cough	28 (75.6)
Fever	26 (70.2)
Fatigue	18 (48.6)
Myalgia	13 (35.1)
Rhinorrhea	12 (32.4)
Headache	11 (29.7)
Sore throat	10 (27)
Vomiting	8 (21.6)
Diarrhea	4 (10.8)
Radiological finding	
Yes	21 (56.7)
No	16 (43.2)
Comorbidities	
Malignancy	4 (10.8)
Endocrine disorder	2 (5.4)
Rheumatological disease	1 (2.7)
Genetic disorder	1 (2.7)
Immunodeficiency	1 (2.7)
Metabolic disorder	1 (2.7)
RT-PCR	
Positive	29 (78.3)
Negative	8 (21.7)

n, number of children; RT-PCR, real time polymerase chain reaction.

and immune deficiency, 1) Five children with an underlying disease were hospitalized in the ICU.

Among the pediatric patients included in our study, 15 (40.5%) had a mild infection while 12 children (32.4%) had a moderate infection. A total of 10 (27.1%) children were classified as severely or critically ill. Twenty-nine (78.3%) patients had a positive combined nasopharyngeal-oropharyngeal RT-PCR swab sample, while the other eight (21.7%) patient samples were negative; however, the clinical and radiological findings were compatible with COVID-19. RT-PCR tests for upper respiratory tract infections were performed for a second time in all patients with negative PCR results, and these tests were also negative. We did not send samples from the lower respiratory tract because of the risk of transmission. Among eight patients whose RT-PCR test results were negative, two

had a history of household contact. We followed up the remaining six patients after discharge, and after COVID-19 serology we found the immunoglobulin G tests to be positive.

While 17 (45.9%) of the patients were followed up without hospitalization, 10 children (27%) were admitted to the ICU. The remaining 10 (27%) children were hospitalized in a general pediatric ward.

If we examine the initial symptoms of our patients, the most common was dry cough that was recorded in 28 (75.6%) patients, followed by fever, which was seen in 26 (70.2%) children, fatigue in 18 (48.6%), and shortness of breath in 13 (35.4%) children. Less common symptoms were headache in 11 children (29.7%), sore throat in 10 (27%), rhinorrhea in 12 patients (32.4%), diarrhea in four (10.8%), and vomiting in eight patients (21.6%).

Table 3 shows the results of laboratory examinations. The most common abnormal laboratory findings in our patients were decreased lymphocytes (17, [45.9%]), and increased D-dimer values (16 [43.2%]). Total leukocyte count was high in six (16.2%) patients, while it was low in only one patient. On admission, lactate dehydrogenase (LDH) values were above the normal range in three (8.1%) patients. Only one of our patients had high creatine kinase (CK) value. Troponin levels in all patients were within normal limits. While C-reactive protein (CRP) was high in 14 (37.8%) patients, procalcitonin (PCT) was above the normal limit in five (13.5%) patients. Only one patient had a high creatine value, which returned to normal after fluid replacement. We detected thrombocytopenia in two patients and thrombocytosis in one patient.

When the laboratory parameters were compared, there were no statistically significant differences between laboratory parameters of three different patient classes except for the D-dimer value. The D- dimer value was significantly high in the moderate patient group as shown in Table 4 ($P < 0.05$).

Of the 21 (56.7%) patients in whom we found abnormal findings in radiological imaging, 17 were followed up in the ICU or general pediatric ward, while four were followed up without hospitalization.

Twenty-four (64.8%) patients received azithromycin while 22 (59.4%) patients received oseltamivir. We used favipiravir in three (8.1%) patients. Hydroxychloroquine was used in combination with azithromycin in 13 (35.1%) children all of whom were hospitalized. Non-invasive mechanical ventilation support was required in eight patients (21.6%). One patient was given oxygen support with a nasal cannula, while the other one received invasive ventilation for 1 day. Therapeutic plasma exchange was used in three (8.1%) children. While one of these patients was diagnosed with diabetes, the other had a neurological disorder and hydrocephalus. The third patient who received plasmapheresis treatment was a previously healthy adolescent girl, except for obesity. The median duration of hospitalization was 7 days (range, 4–17 days), except for a child who is still in a general pediatric ward.

Table 3 Laboratory findings of children infected with SARS-CoV-2 (n=37)

Laboratory parameters	Number of patients without normal laboratory limits (%)
Creatine median: 0.48 (0.12–1.06 mg/dL)	High: 1 (2.7)
Creatine kinase median: 72 (26–174 IU/L)	High: 1 (2.7)
CRP median: 3.6 (0–5 mg/L)	High: 14 (37.8)
D-dimer median: 0.44 (0–0.5 mg/L)	High: 16 (43.2)
LDH: median: 269 (105–615 IU/L)	High: 3 (8.1)
Procalcitonin median: 0.07 (0.5 ng/mL)	High: 4 (10.8)
Total leukocyte count median: 6,500	
6–12 months: 6–12.5 x 10^9/L	Low: 1 (2.7)
1–2 years: 6–17.5 x 10^9/L	
2–4 years: 6–17 x 10^9/L	High: 6 (16.2)
4–6 years: 5–8 x 15.5^9/L	
6–8 years: 5–14.5 10^9/L	
8–16 years: 4.5–13.5 x 10^9/L	
16 −18 years: 4.5–13 x 10^9/L	
Lymphocyte count median: 1,800	
6–12 months: 4–13.5 x 10^9/L	Low: 17 (45.9)
1–2 years: 4–10.5 x 10^9/L	
2–4 years: 3–9.5 x 10^9/L	
4–6 years: 2–8 x 10^9/L	High: 0 (0)
6–10 years: 1.5–6.8 x 10^9/L	
10-16 years: 1.5–6.5 x 10^9/L	
16–18 years: 1.2–5.2 x 10^9/L	
Platelet count: median: 270 000 (150–400 x 10(9)/L)	Low: 2 (5.4) High: 1 (2.7)

CRP, C-reactive protein; IU/L, international unit/liter; LDH, lactate dehydrogenase; mg/dL, milligram/deciliter; ng/mL, nanogram/milliliter; PCT, procalcitonin.

Discussion

While COVID-19 has spread rapidly around the world, a large amount of data have been published about the adult patient group, but publications and information about children have been relatively limited. COVID-19 disease has some different and some similar aspects among adults and children. In the literature, the prevalence of COVID-19 in children ranges from 1% to 5%, with a large proportion reported to be under the age of 10. In a study conducted by Dong *et al.*,[8] the median age of patients was 7 years and 65.1% of patients were <10 year, while 34.9% of patients over the age of 10. According to a report by the Centers for Disease Control and Prevention in the US, the median age of 2,572 COVID-19 pediatric patients was 11 years and 59.0% of the patients were over 10 years of age.[9] By March 30 2020, 117 pediatric cases confirmed in Turkey and 49.5% of the patients were over 10 years of age. The median age was 8 years.[10] In our study, similar to these reports, we found that the median age of patients was 10 years (range, 7 months to 17 years 9 months) and 40.5% of them were over 11 years old.

Table 4 Statistical analysis of laboratory data

Parameters	Severity of illness	*P*-value of total leukocyte count
Total leukocyte count	Mild Moderate Severe/critically	0.162
Neutrophil count	Mild Moderate Severe/critically	0.123
Lymphocyte count	Mild Moderate Severe/critically	0.583
C- reactive protein	Mild Moderate Severe/critically	0.259
Procalcitonin	Mild Moderate Severe/critically	0.928
D-dimer	Mild Moderate Severe/critically	0.019
Creatine kinase	Mild Moderate Severe/critically	0.713
Creatine	Mild Moderate Severe/critically	0.527
Lactate dehydrogenase	Mild Moderate Severe/critically	0.784

According to recently published literature, which described demographic and clinical characteristics of 44 672 adult patients in China, COVID-19 has infected both men and women equally (male to female ratio = 1.06:1).[11] We have found slightly more boys than girls (57.1% vs 43.3%) in our study, which is similar to the other studies of the disease epidemiologically in children.[8,12]

In recent studies, it was reported that the rate of COVID-19 in children is similar to the general population, although children are less likely to have severe symptoms and understanding the role of pediatric population in transmission dynamics of SARS-CoV-2 is very important.[13,14] On the other hand, infected adults who have close contact with children are important sources of infection for children, as stated in many studies.[12,15] According to Lu *et al.*,[12] 90.1% of pediatric patients were reported as having a household contact. Similar to other studies, we found 78.3% of our patients had a close contact with infected adults.

Although the effect of comorbid conditions on the severity of the disease in children is not as clearly defined as adults, a current study reports that the most common underlying conditions among 345 children are chronic lung disease (including asthma), cardiovascular disease, and immunosuppression.[9] All infected children with a comorbid disease, except one, were hospitalized in our study. The exception was a child with a diagnosis of juvenile idiopathic arthritis who was managed as an outpatient. Two asymptomatic patients who were diagnosed with neuroblastoma and medulloblastoma and found positive after the contact history, were transferred from the pediatric oncology department to a general pediatric ward. These two patients received azithromycin treatment and were discharged without any deterioration in their clinical condition. Unlike these two patients, the disease was more severe in an adolescent patient diagnosed with Hodgkin lymphoma. Patients in the moderate and severe groups had similar rates in terms of comorbid diseases. In the mild patient group, only one patient had a comorbid disease.

In a report from a liver transplant center in Italy, no severe pneumonia was reported in any of the cases found to be immunosuppressed and SARS-CoV-2 positive. It was concluded that there is no serious risk of complications in immune-suppressed children and adults compared to the general population.[16] In our experience, patients with immune suppression may have severe or mild illness and we do not yet have sufficient data. Therefore, we should pay more attention to these children and further investigations need to be done on specific patient groups.

Severe clinical manifestations may develop in SARS-CoV-2-infected children without underlying diseases. Five of our patients in ICU had no comorbidities. Two patient groups (Patients 17, 18, and 19 were siblings who were previously known to be healthy. Similarly, patients number 23 and 24 were siblings), who were followed up in ICU and required non-invasive ventilation (NIV) support among previously healthy children were siblings. Similarly, a report from Iran describes fatal cases of COVID-19 in three brothers with no underlying disease, suggesting genetic predisposition to COVID-19 in some individuals.[17]

In several studies,[8,15] SARS-CoV-2 infected children were classified into groups, according to the severity of their symptoms: 94.0% of the pediatric patient group was reported to have asymptomatic, mild, or moderate COVID-19 infection.[8] Among the pediatric patients in our study, we found 72.9% of patients having mild or moderate infection, while 27.1% of them were severely or critically ill, which is a higher rate than in similar studies.[8,18] This may be related to the presence of a large pediatric ICU, where a large number of patients are followed in our hospital. This study was performed in a tertiary university hospital located in İstanbul. It is a referral hospital with 106-bed capacity, containing 20 pediatric ICU beds. During the process, a physically separate part of the ICU was allocated to COVID-19 positive patients. We also have a 14-bed pediatric isolation ward, where patients who do not require ICU admission are followed.

The clinical symptoms of COVID-19 in children are nonspecific: cough, fever, sore throat, fatigue, myalgia, headache, vomiting, and diarrhea can be seen. In several studies, the most common symptoms on admission were fever and cough.[12,15] Similarly, we found cough (75.6%) and fever (70.2%) as the most common symptoms in our study. We found rhinorrhea in 32.4% of our patients, which seems higher than in adult studies[9] and may be related to co-infections, which are common in children. While the rate of diarrhea was 9.0% in Parri *et al.*'s[18] study and 8.8% in Lu *et al.*'s[12] study, similarly in our study,

diarrhea was detected in 10.0% of our patients. If we compare the clinical characteristics of the patient groups in our study, the mild and moderate groups mostly presented with upper respiratory tract complaints, whereas patients in the severe group also presented with respiratory distress.

Laboratory investigations of SARS-CoV-2 infected patients, are usually non-specific. Aminotransferase levels, prothrombin time, creatine, D-dimer, CK, and LDH values may be high in relation to the severity of infection. Additionally, lymphopenia is a common finding.[19,20] In a meta-analysis that involved predominantly adult patients, the most common laboratory findings were hypoalbuminemia (75.8%), high CRP (58.3%), high LDH (57.0%), lymphopenia (43.1%), and a high erythrocyte sedimentation rate (41.8%).[21] In our study, the CRP value was high in 14 (37.8%) patients and LDH was high in three (8.1%) patients. While D-dimer levels were high in 43.2% of our patients, Wang *et al.*[22] showed that D-dimer increased in 6.5% of 31 children. Lymphopenia is claimed to be an effective and reliable indicator of severity and need for hospitalization in COVID-19 patients.[23] In a meta-analysis in which 66 pediatric patients were examined, only 3.0% of patients had lymphopenia, and this low rate was thought to be due to the small number of critically ill children.[24] However, lymphopenia was detected in 45.9 % of our patients, which would be related to our high rate of critically ill children, but there was no statistically significant difference in the rate of lymphopenia between the patient groups in our study.

Typical radiological findings seen in COVID-19 disease are ground-glass opacity and consolidation, especially in the lower lobes and subpleural areas.[25]

Qui *et al*. found 19 (53%) pediatric patients had pulmonary ground-glass opacities on CT scan, suggesting pneumonia; similarly we found 56.7% of our patients to have positive radiological findings.[15]

Different treatments modalities have been tried in several studies but there is yet no special therapeutic medication for COVID-19 and treatment strategies generally consist of supportive and symptomatic treatment. Interferon alfa and lopinavir-ritonavir were used in one study[15] while azithromycin, hydroxychloroquine, remdesivir, and tocilizumab were used in critically ill children who were hospitalized in ICU in another.[26] We used azithromycin for patients who were classified as moderately, severely or critically ill and added hydroxychloroquine to treatment for severely and critically ill children. In addition, four children who had a moderate disease received hydroxychloroquine. Three of them were over 15 years old and had CT findings, compatible with COVID-19. The other patient was an infant with suspected immune deficiency. In a recent publication that included 48 children who were admitted to ICU, 44% of patients received hydroxychloroquine, while 17% received azithromycin, similar to our study. Unlike our study, remdesivir and tocilizumab were reported to be used in this study, but favipiravir was not used.[26]

Generally, NIV is not recommended for SARS-CoV-2 infected patients because of the potential risk for aerosolization.[27] On the other hand, patients with severe respiratory distress in whom NIV was used benefited clinically, and these patients were discharged without the need for intubation. We used personal protective equipment such as N95 respirators, goggles, face shields, and disposable gowns, both in ICU and the general pediatric ward to protect healthcare workers. Also, a physically separate part of the ICU was allocated to COVID-19-positive children to protect other non-COVID-19 patients.

Our study has several limitations. Its single center nature and small sample size are the main limitations. Second, we could not evaluate other viral infections such as influenza or respiratory syncytial virus, which could provide more information about interactions between SARS-CoV-2 and other respiratory viruses. Although this issue is important, the focus of this study was SARS-CoV-2.

Conclusions

COVID-19 is rapidly spreading around the world and children are at similar risk to adults. The main source of infection in children is usually their household contacts and most common symptoms are fever and cough. Although COVID-19 infection is mostly mild in childhood, severe disease can be observed in previously healthy children and there may be an underlying genetic predisposition. D-dimer elevation and lymphopenia can be detected, not only in adults, but also in children.

Disclosure

The authors declare no conflict of interest.

Author contributions

P.Ö., A.A.K., F.A., C.D., and H.Ç. designed the study, and collected and analyzed data. C.D. contributed to the concept and design of this work. P.Ö. and A.A.K wrote the manuscript. A.A.K., F.A., and H.Ç. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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